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Medico-social aspects of hepatocellular carcinoma

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Abstract

Oncological diseases are one of the leading health problems both in the world and in Kazakhstan, second only to cardiovascular diseases. Hepatocellular carcinoma occupies the 8th place in the structure of oncopathologies, has an unfavorable prognosis and an unfavorable course. According to the WHO, more than 1.3 million people die each year from hepatocellular carcinoma (HCC). The incidence rate of HCC in Kazakhstan is up to 5.5 cases per 100 thousand of the population, and the mortality rate remains high (about 1000 people annually). In 2017, 82.3% of HCC patients died before the end of the year. Five-year survival in HCC does not exceed 18%, and postoperative recurrence is about 50%.

Key words: social, hepatocellular carcinoma, incidence, healthcare

Introduction

The study of epidemiology of hepatocellular carcinoma in Kazakhstan is a relevant task, which will allow to predict the volume of innovative treatment.

The modern approach in treatment of hepatocellular carcinoma is interventional oncoradiology - it is a radical method of radiofrequency ablation of the liver, however its use is possible at early stages of primary liver cancer.

Detection of early stages of hepatocarcinoma is possible by liver ultrasound, but an important component at this stage is the qualification of the doctor.

The use of radiofrequency ablation of the liver will improve the quality of life of patients with hepatocellular carcinoma, as this method extends their life expectancy.

Objective: To identify the epidemiology of hepatocellular carcinoma and innovative methods of its treatment in the world.

Material and methods

Research methodology: desk method. PICO method. P - patients with primary liver cancer, I - intervention, use of modern methods of treatment, C - comparison with other methods of treatment of patients with hepatocellular carcinoma, O - comparison of patients' quality of life at late stages of hepatocellular carcinoma diagnosis.

Modern methods of treatment of primary liver cancer is radiofrequency ablation of the liver, which is possible only in the early stages of detection. Cancer diseases take second place in the structure of the population's total mortality after circulatory system diseases. Hepatocellular carcinoma (HCC) is a representative of primary liver cancer [1,2]. In recent years, in Kazakhstan, there has been an increase in the incidence of hepatocellular carcinoma (HCC) which was 3.3% in 2018, while mortality, in the same period was 4.5% [3]. The five-year survival rate is 23.7% [4].

HCC is characterized by an aggressive course and, in most cases, by an unfavorable prognosis. According to the world data, the five-year survival rate in HCC does not exceed 18%, and postoperative relapse - 50% [5-7]. In Kazakhstan, analysis of epidemiology of primary liver cancer will allow to develop measures aimed at the improvement of prevention, diagnostics and treatment of HCC [8].

According to the World Health Organization, more than one million people die of HCC annually. According to the International Agency "Cancer Incidence in the Five Continents" [9], the highest standardized incidence rates of liver cancer in men are in Korea, ranging from 44.9 to 50.0 per 1,000 population. Indicators above 300 are registered in Thailand, Japan, and China. Minimal rates are established in Algeria, India, Belgium, and the Netherlands. At the same time, in women - the rates are much lower [10].

According to the World Health Organization, 9.6 million people died of cancer worldwide in 2018. About 70% of cancer deaths occur in low- and middle-income countries. In 2018, neoplasms ranked fourth among the causes of death in Kazakhstan (8.8%). Early detection of cancer at I-II stages is 60.5% [11].

Currently, worldwide, primary liver cancer poses a serious public health problem. The relevance of the problem is due to unsatisfactory results of treatment of patients, namely late diagnostics, oncological care and life expectancy [12].

Current realities of HCC are problems that are related to late diagnosis in 75% of cases, patients metastasize, which complicates and limits the choice of treatment. As a result, in some cases, chemotherapy remains the treatment of choice for patients with primary liver cancer. At the same time, the results of late treatment remain insufficiently satisfactory, and the effectiveness rate of various chemotherapy regimens is low, ranging from 12.0 to 36.0% [13].

HCC is the fifth most common disease in men and the ninth most common disease in women. HCC is mostly advanced, highly aggressive, and has a low survival rate and life expectancy. In the structure of cancer mortality, primary liver cancer occupies the second place and makes 9.6 % of all cancer deaths [14-15].

Currently, liver cancer is a complex section of abdominal oncology, which attracts more and more attention of surgeons, oncologists and radiologists. HCC is the most common epithelial malignancy of the liver and its incidence is 8.5 per 10,000 population. The age profile is presented on the life period of the working-age population - from 40 to 50 years old. Predisposing factors are liver cirrhosis in 80-90% of cases induced by viral hepatitis B and C [16].

More than 564,000 new cases of liver cancer are reported worldwide each year, including 398,000 in men and 166,000 in women. Liver cancer in men tends to be detected at 2-4 times higher rates than in women [17].

The annual incidence of liver cancer in high-risk countries may occur at a young age of up to 20 years, whereas in low-risk regions liver cancer occurs rarely before the age of 50 years. The incidence of liver cancer is increasing in several developed countries, including the United States, and the increase is likely to continue for several decades. The trend is the result of a cohort effect associated with hepatitis B and C virus infection, which peaked in the 1950s and 1980s [18].

The incidence of liver cancer has decreased in some regions of several developing countries, possibly as a result of the use of hepatitis B virus vaccination and improved food quality. The geographic variability in the incidence of liver cancer is largely due to the distribution of hepatitis B and C viruses and aflotoxins.

Over the past ten years worldwide, including Kazakhstan, the incidence of malignant neoplasms tends to increase and occupy one of the leading positions among the main causes of death. Morbidity is more widespread in the female population in the age group "60 years and older". According to averaged data, every year the number of malignant neoplasms increased by 578 cases and the average annual growth rate was 1.84%. In turn, the morbidity rate of malignant neoplasms in Kazakhstan was also unstable. From 2005 to 2014, the incidence rate increased slightly, from 192.5 per 10,000 population to 198.8. The average annual growth rate of morbidity increases by 0.36% [19].

In 2011, the National Screening Program for early detection of malignant neoplasms was introduced in Kazakhstan. Analysis of the situation of the State Program of Health Development "Densaulyk" for 2016-2019 for the period of implementation of the program "Salamatty Kazakhstan" noted the low effectiveness of the National screening program (detection rate is 3.4% among adults, 16.4% - among children). A possible reason is low monitoring of screening efficacy [20]. According to the program of development of oncological care in Kazakhstan for 2012-2016, the main goal is to increase the life expectancy and quality of life of Kazakhstanis by reducing mortality from cancer. The incidence of malignant neoplasms in 2013 for HCC was 285.0, which is higher than in 2012 (282.9) by 0.7%. The increase in morbidity is due to the aging of the population, the development of preventive screening medical examinations and increased detectability [21].

According to a rough estimate, more than 500,000 new cases of liver cancer are registered annually in the world, and 85% of them occur in countries with a high degree of hepatitis B infection (South-East Asia, Central Africa). Among European and U.S. populations, the incidence rate is 2-7 per 100,000 people. In Russia, the incidence of liver cancer is 4.9 in men and 2.2 in women, but it also varies greatly depending on the region. The incidence of liver cancer in South Kazakhstan region is 6.7 per 100,000 people and ranks 6th among malignant diseases (about 140 patients are detected per year). With I-II stages 16,1 % of patients are revealed, with III - 47,1 %, with IV - 36,8% of patients. Up to 90% of patients are men. The one-year mortality rate is 57-60%, which is determined by the absence of a wide introduction of liver surgery in our region. With the introduction of endovascular interventions into the everyday practice of the South Kazakhstan regional oncologic dispensary the possibility of regional chemotherapy for liver cancer has appeared [22].

The structure of medical care for cancer patients with HCC is at the stage of development. Only some clinics have experience in interventional radiological interventions for locally disseminated processes and conduct drug therapy. Rapid and significant reduction in mortality is possible if multidisciplinary approach to diagnosis and treatment of HCC is widely implemented based on active intra- and interclinical collaboration of different specialists: surgeons, transplantologists, interventional radiologists, chemotherapists, hepatologists, diagnosticians at all stages of tumor process development [23].

Multidisciplinary approach, including new methods of treatment, one of which is interventional oncology, is necessary to improve the effectiveness of the treatment of oncologic patients. Interventional oncoradiology has proven highly effective in the treatment of many malignant neoplasms, including liver cancer in addition to surgery, chemotherapy and radiation therapy. In addition to interventional oncology, immuno-oncology, which allows tumor control at the molecular level, is widely implemented in oncology [24-27]. The advantages of interventional oncoradiology are the effect directly on the tumor, excluding systemic effects of chemo medication, accompanied by fewer side effects, as well as good tolerability of the procedure [28-30]. When assessing the effectiveness of the procedure, the main endpoints are evaluated: overall survival, time without disease progression, and time to progression [31,32].

Overall survival is a key criterion for assessing treatment efficacy [33]. Thus, according to the overall survival rate it is possible to evaluate the advantage of techniques for the treatment of cancer patients [32].

In Kazakhstan, 36,272 new cases of malignant neoplasms were detected in 2019, along with nonmelanoma skin cancer (2018 - 35,758), including 426 primary multiple MNs (377) or 1.2% and 663 postmortem cases (752) or 1.8%. The number of cases detected increased by 514 or 1.4%. Liver cancer in 2018 in the structure of causes of death from malignant neoplasms in the population of both sexes shifted from 10th to 9th place

with a specific weight of 4.6% (2018 - 4.1%), the mortality rate was 3.40. In East Kazakhstan and West Kazakhstan regions (6.9 each), Pavlodar region (4.3), Zhambyl region (3.5) and Shymkent city (3.5) liver cancer mortality is higher than the national average. Aktobe (2.3), Kyzylorda (2.4) and Almaty (2.5) regions have the lowest rates [34].

Liver cancer in 2018 in the structure of causes of death from malignant neoplasms of both sexes moved from 9th to 10th place, with a share of 4.1/4.0 (2017), the mortality rate per 10,000 population was 3.2/3.3. In East Kazakhstan - 4.9, Karaganda - 4.8, West Kazakhstan - 4.1, Pavlodar - 4.1, Mangistau - 3.7, Zhambyl - 3.6, Turkestan - 3.6 regions, and in Astana city - 3.7 liver cancer mortality is above the national average [35].

According to the indicators of the national oncological service for 2020 there is a decrease in mortality from cancerous diseases of various localizations. The mortality rate for 2020 was 75.5 per 100 thousand people. The specific weight in the mortality structure was 0.7%.

In the structure of mortality lung cancer was in the first place (16.4%), stomach cancer in the second place (11.5%), colorectal cancer in the third place (10.7%) and breast cancer (7.8%) [36].

In execution of the order of the Head of the state, voiced in the Address to the people of Kazakhstan "New opportunities for development in the conditions of the fourth industrial revolution", a draft Comprehensive Plan to combat cancer in Kazakhstan for 2018-2022 was developed. The aim of the Comprehensive Plan is to reduce the burden of malignant neoplasms. The Comprehensive Plan provides for the establishment of the National Scientific Oncological Center in Astana, which will play a coordinating role in cancer care. The main objectives of the Center will be 1) to provide cancer care in accordance with international standards; 2) to conduct research in the field of oncology; 3) to develop and implement personalized methods of prevention, early diagnosis and treatment [37].

Conclusion

The results of the literature review showed that worldwide, there is an increase in cancer pathology and primary liver cancer (hepatocellular carcinoma) has a rapidly progressing course.

For screening of primary liver cancer in the world, the effectiveness of liver ultrasound has been proven, but under an important condition - the qualification of a doctor.

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Adnexal masses associated with pelvic pain: A review and commentary on the evidence

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Abstract

Pain in relation to the menstrual cycle is representative of Endometriosis. It has been reported that Endometriosis can be easily confounded with neoplasia. In the clinical practice of Gynecologic Oncology we find with relative frequency patients who are unknown carriers of endometriosis who present and are operated on because they resemble a picture of gynecological cancer, predominantly of the ovary. It has been reported that Endometriosis can be easily confounded with neoplasia. Endometriomas form part of the differential diagnosis alongside various ovarian cystic formations.

On the other hand, ovarian tumors are very common in women of reproductive age. Most are benign, but malignant ovarian tumors are a leading cause of cancer death in women.

In women with endometriosis, the risk of developing ovarian cancer has been estimated to be up to 50% higher than in the general population. The aim of our concise review was to establish the current state of knowledge regarding adnexal tumors associated with pelvic pain.

Key words: endometrioma, tumor-associated pain, differential diagnosis

Introduction

Endometriosis affects approximately one in ten women at some point in their lives [1], mainly during reproductive age since it is an estrogen-dependent disease, and who will manifest pain in relation to their menstrual cycles, either as dyspareunia, dyschesia, dysmenorrhea or chronic pelvic pain with or without the presence of infertility. Different theories have been proposed regarding its pathogenesis.

Among the most accepted theories are the predisposition due to genetic factors, increased secretion of cytokines and other inflammatory mediators, in utero exposure to estrogens or potent environmental toxins, or the widely accepted retrograde menstruation secondary to subtle anatomical alterations. However, its appearance has been reported even among patients who underwent an adnexal-sparing hysterectomy or in Mayer-Rokitansky-Küster-Hauser syndrome [2] where there is congenital absence of the uterus as part of the syndromatic procession.

In our clinical practice of Gynecology Oncology we find with relative frequency patients who are unknown carriers of endometriosis who present and are operated on because they resemble a picture of gynecological cancer, predominantly of the ovary. It has been reported that Endometriosis can be easily confounded with neoplasia.

Therefore, the objective of our review presented here was to establish the current knowledge and intertwine the current state of the art with our experience in managing clinical situations regarding adnexal tumors associated with pelvic pain.

Ovarian endometriosis as a cause of pelvic pain

What is happening in endometriosis is that the endometrial tissue, both the stroma and glands, is actually located outside of the uterus. This entity can be detected clinically in approximately one in ten of patients during reproductive age, up to 50 % of them present infertility associated with chronic pelvic pain [3,4,5].

The incidence of endometriosis in infertile women is about 50% and it is estimated that around 190 million young women and adolescents worldwide suffer from the disease, although it can also occur in menopausal women [6]. As for adolescents diagnosed with endometriosis, it is estimated that 70-93% present some discomfort associated with menstruation, as well as being associated with a higher risk of depression and anxiety [7]; therefore, this condition affects the quality of life not only the woman who suffers it, but also the partner or relatives [6].

The appearance of endometriosis at earlier ages is associated with a delay in diagnosis [7]. The diagnosis is usually made 8-12 years on average from the onset of symptoms [6]. Therefore, it is of great importance for the clinician to keep in mind the prevalence of this disease as well as manage a high index of suspicion.

Ovarian endometriomas

Endometriosis can have different forms of clinical presentation [8]. The most common form of presentation in 20-25% of patients with endometriosis are ovarian cysts (endometriomas) [9]; ovarian endometriomas (OMAs) are associated with pain that usually goes from moderate to severe. However, severe pain may be associated with concomitant "deep infiltrating endometriosis" (DIE) [10].

Other forms of endometriosis are "superficial endometriosis" commonly found in the peritoneum, characterized by the endometrial tissue being found on the surface of the subserosal soft tissue of the peritoneum or visceral organs [3,8,11] or as "DIE" which measures more than 5mm [8,11] reaching the muscle layer and is commonly located in the recto-vaginal septum, bladder wall, diaphragm or other organs [3,11]; it usually causes significant pain and also gastrointestinal and/or urological abnormalities that do not respond to medical treatment, most cases ending in surgical management [3] (Figure 1).
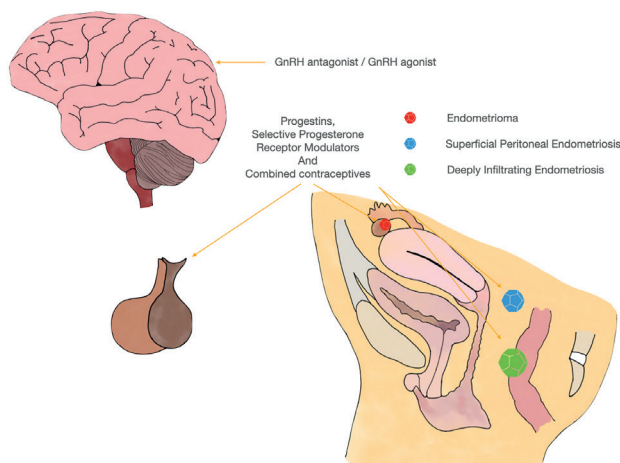

Figure 1 - The most common forms of endometriosis: The ovarian endometrial cyst (red mark) followed by superficial peritoneal endometriosis (blue mark) and deeply infiltrating endometriosis (green mark). GnRH agonist/antagonist exert an effect over the CNS. Progestins, SPRMs and combined contraceptives exert an effect over the hypophysis and directly over the endometrial lesions.

Endometriosis-associated risk factors

There are some risk factors that have been related to the disease, including genetic factors (family history), exposure to endogenous estrogens for long time, as happens with early menarche, late menopause and short menstrual cycles, heavy menstrual bleeding, outflow tract obstruction (Müllerian alterations) and exposure to to diethylstilbestrol in utero [5,7]. It is believed that among the genetic factors, chromosomal alterations in 7p15.2 and 10q26 may be involved, as well as the ARID1A and PIK3CA genes in ovarian cancer in patients with endometrial ovarian cysts [8].

Causes of endometriosis

There have been proposed some theories as cause of endometriosis, like Samson's theory, which consists of a retrograde menstruation, that is, menstrual bleeding that can reach the peritoneal cavity after passing through the tubes; however, 90% of normal women may present retrograde menstruation without problems [5]. More recent studies have shown that endocrine, immunological, pro-inflammatory and pro-angiogenic processes must be present concomitantly with retrograde menstruation [8] The GE theory (genetic and epigenetic changes) suggests that a series of GE changes can occur during cell division, causing the endometrial tissue to develop characteristics of cancer cells [12]. Another theory includes the generation of a coelomic metaplasia in which there is a transformation of the mesothelium to a glandular endometrium or lymphatic or hematogenous metastasis [8].

The reflux of endometrial tissue by itself contributes to the progress of pain and development of infertility; for the evolution of OMAs the presence of hormonal fluctuations and ovulation during menstruation are essential [10]. The endometrial tissue forms an ovarian cyst in the ovary that gives rise to a hematoma [5]. The formation of endometrioma causes ovarian reserve levels to decrease and favor the adhesions between the tubes and the broad ligament with the ovary [9]. Ectopic endometrial tissue results in inflammation which causes or promotes pain, dyspareunia, dysmenorrhea, and infertility [5].

Symptoms of endometriosis

The most common reported symptom among patients with endometriosis is dysmenorrhea. This symptom is the result of the prostaglandin production within the pelvic cavity, which causes endometrial hypertonia and secondary ischemia [10]; in a third of cases, ovarian endometriosis is bilateral [5]. The ectopic endometrium causes a chronic estrogen-dependent inflammatory reaction, triggering pain secondary to compression of the adjacent nerves and/or an increase in the prostaglandin production [7]. We can find in the peritoneal fluid of patients with endometriosis the presence of IL-10, IL-6, IL-8, COX-2, VEGF and TNF-α [13].

Characteristically, endometrial lesions have an increased expression of ER beta, which promotes the growth of lesions by inhibition of TNF-alpha by increasing interleukin Iß which improves cell adhesion and proliferation [8]; high levels of estradiol in turn causes PR to decrease [14]. Type A and B PR change during the menstrual cycle in response to the variation of ovarian steroids, their maximum expression occurs in the middle of the cycle [15]. Progesterone triggers the PR beta during the luteal phase, which promotes the transcription of the 17-ß-hydroxysteroid dehydrogenase (17ß-HSD) -2, which transforms estradiol-E2 into E1, which is a less potent form of estradiol [14,16]. However, ectopic endometrial tissue has an ER-alpha lower expression, and increased ER-beta, compared to the endometrium [16]; instead, PR expression may be decreased or even absent [17], which gives rise to resistance to progesterone [16]. COX-2 and aromatase are also responsible for stimulating the synthesis of E2 [18].

Endometriosis-related pain

The characteristics of the pain depend on the location [19]. When endometriosis is found in the peritoneum or in the pelvic wall, the pain is usually of somatic type. Pain is usually more localized, supposedly because to the high density of sensory nerve fibers in the parietal peritoneum. Later, macrophages colonize the nerve fibers [8,20] increasing the intensity of pain [20]; these macrophages have an increased expression of IGF-1, which in endometrial cells prevents apoptosis, and in stromal cells increases the expression of the ER beta [21]. Patients with endometriosis present an increase in neurotransmission from the anterior insula to the medial prefrontal cortex, promoting chemical changes which alter brain functions, increasing pain intensity, and increasing the risk of cross-organ sensitization due to the convergence of neuronal pathways [8]; interestingly, this central sensitization effect may explain coexisting chronic syndromes, irritable bowel syndrome, bulbodynia, or painful bladder syndrome [10].

On the other hand, the pain is usually of visceral type when endometrial lesions are found in the uterus, bladder or intestine, making the pain less localized and more spasmodic [19]. "DIE" usually develops other symptoms depending on the site where the condition is found. For example, when the lesions are rectovaginal, it usually causes dyschetia, stool irregularities, and constipation; lesions located in the bladder usually cause cyclic dysuria or even hematuria when the urethra is involved and/or the bladder is infiltrated.

In women suffering from endometriosis, nerve growth factor (NGF) has been found elevated in the peritoneal fluid, which gives rise to acyclic neurological inflammation causing pain resistance to NSAID's and hormonal therapy that in the long term can generate depression and somatoform disorders [19].

Adnexal causes of pelvic pain

Endometriosis can occur during a woman's reproductive life as frequently as 5 to 15% [20]. When this common gynecological condition becomes symptomatic, it can manifest with chronic pelvic pain, dyspareunia, or dysmenorrhea [21]. Therefore, the appearance of any pelvic pain during reproductive life represents a significant diagnostic challenge.

The local inflammatory reaction caused by endometriotic implants triggers, in turn, formation of adhesions which will produce fibrosis and a modified pelvic anatomy. This progressive sequence of changes can lead to pelvic organ dysfunction, with the onset of infertility and chronic pelvic pain.

The most frequent location of endometriotic implants is the ovary. This diagnosis should be considered, along with cancer, cystadenomas, tuboovarian abscesses, hemorrhagic cysts, and cystic adenomyoma, within the differential diagnoses. Ultrasound is particularly useful for identifying the "typical" endometrioma in premenopausal women, as it can easily identify unilocular cysts with echogenicity of ground-glass content, poor vascularity on color Doppler evaluation, and debris/polar clots.

The clinical diagnosis, however, is sometimes not easy, particularly when there are multiple cysts, since they can make it difficult to distinguish the adnexal endometrioma from some different masses, as mucinous cystadenomas (Figure 2). When there is intracystic vascularization, its presence can lead the clinician to suspect the presence of cancer (endometrioid adenocarcinoma or a borderline tumor of the ovary) [22] since 1% of these masses presumably suspected as endometriomas will result in a clear neoplasia.
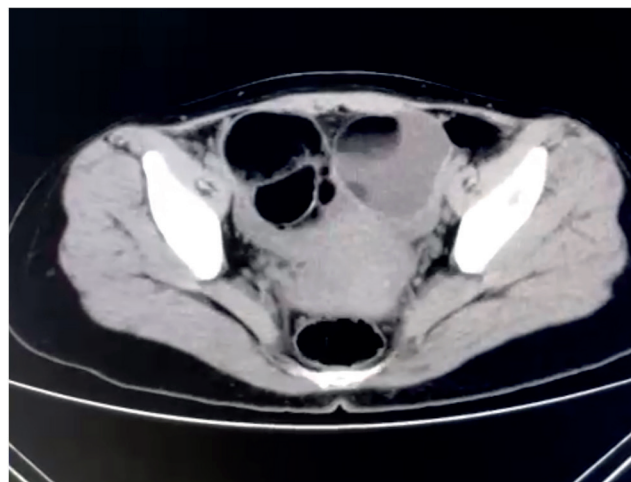
Figure 2A - Case of surgically and pathologically confirmed endometrioma. CT images showing a large lesion in the pelvis in which the significant perilesional inflammatory reaction is evident.
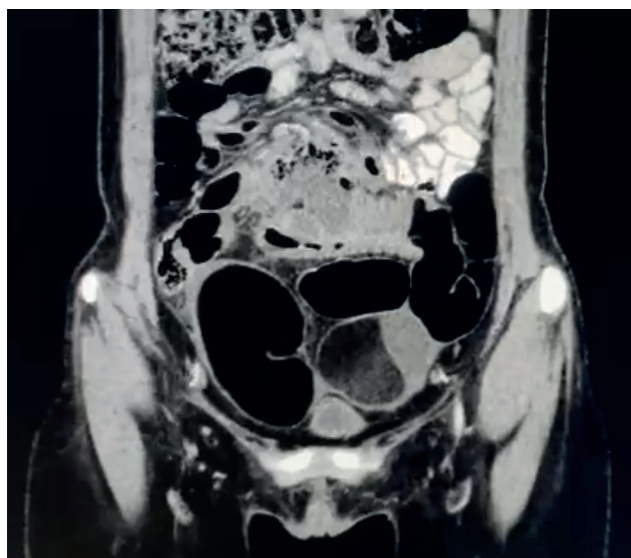
Figure 2B - Case of surgically and pathologically confirmed endometrioma. CT images showing a large lesion in the pelvis in which the significant perilesional inflammatory reaction is evident.

Pain evolution in endometriosis

The onset of pain is caused by biochemical signaling caused by the production of some pro-inflammatory molecules, as TNF-alpha, PGE2 and interleukin [8,10], which increase sensitivity and become a neuronal sign (peripheral sensations). This type of pain is usually well controlled with NSAIDs and hormonal therapy (by decreasing the release of inflammatory mediators) [19]. Estradiol has been identified as the main mediator of macrophages, as well as some chemoattractants such as IL-8, which causes neutrophil infiltration in the peritoneal fluid. It has been observed that macrophages invade the ectopic endometrium in greater numbers than the normal endometrium, activating NF-kB that promotes the expression of pro-inflammatory toxins and COX-9, which with the expression of pro-inflammatory cytokines such as IL-6, IL-1beta and TNF-alpha [23], stimulates cell proliferation, angiogenesis, inflammation and production of adhesion molecules of the endometrial tissue [13].

Bleeding within the pelvic cavity from the ectopic endometrial tissue trigger the secretion of pro-inflammatory and pro-oxidants factors, producing free iron and reactive oxygen

species (ROS) [11,16]. Iron overload activates the transcription of NF-kB in the endometrial stromal cells [11,24] causing overexpression of the divalent metal transporter I (DMTI), which promotes oxidative stress [24] giving rise to macromolecular oxidative damage [11]. In addition to this, oxidative stress and pro-inflammatory factors interrupt the function of PR, causing resistance to progesterone [16] and, concomitantly, there may be an alteration in the ROS elimination pathway, which increases chronic inflammation [11]. Adaptive immunological mechanisms are also involved in the development of pain. IL-10 has been identified in the peritoneal fluid, which has been related to an increase in the severity of the disease, and IL-17 is believed that contributes to the progression of endometriosis, as well as the stimulation of cytokines which induce angiogenesis and inflammation [23].

In severe dysmenorrhea, pain is initially regulated at the spinal level; however, in cyclic dysmenorrhea it triggers a process in which the release of neurotransmitters is altered, causing spinal hyperalgia [19]. Studies in mice with endometriosis have shown a significant increase in COX-2 and TNF-alpha in the spinal cord and brain [25] The pain can be so severe that can trigger vegetative reactions (nausea, vomiting), and patient adopts different positions in order to relieve pain. At the same time this can cause contraction of pelvic muscles which, in the long term, leads to dysfunction of the pelvic floor [19].

Overview of ovarian tumors

Ovarian tumors can frequently develop in women of reproductive age. Most are benign tumors, but malignancies are a leading cause of cancer death in women. Due to the complexity of the different tissues of origin, there is a variety of patterns and types of ovarian tumors, so most of the time a certain preoperative diagnosis will not be possible, except in very few patients. Screening among women with no family history, has not demonstrated an impact in the reduction of ovarian cancer mortality.

Most women with early-stage ovarian tumors are mainly asymptomatic; some other may experience mild gastrointestinal symptoms. In case of a palpable abdominal mass, patients frequently present other data such as ascites, pressure on pelvic or abdominal organs, and sometimes pain.

Ultrasound is useful for making a differential diagnosis of ovarian masses among themselves or with extraovarian masses, and between those that are benign and those that have a greater malignant potential. However, US has low sensitivity used as screening in the low-risk group of patients.

Once a pelvic mass is detected, it should first of all be categorized by the clinician. In terms of malignancies, the age of women is of crucial importance as a predictive factor, since in patients over 35 years of age the possibility of carrying a malignant epithelial tumor increases exponentially. In underage women, this possibility decreases enormously, being replaced by benign or borderline epithelial tumors, or by malignant tumors of germinal lineage, much rarer and that should receive conservative management.

Other relevant predictive factors to consider are ultrasound findings, serum CA 125 level, whether the ovarian mass is single or bilateral, its size, and whether or not there is pain. Simple cyst less than 8 cm in size is mostly benign, especially if accompanied by pain. Most ot these simple cysts will undergo regression and resolve spontaneously; they should be just monitored with no surgical intervention. If the mass is symptomatic, surgical exploration is warranted. Likewise, an invasive procedure should be indicated if the mass did not change in size on repeated ultrasound evaluation. A clear advantage of using transvaginal over abdominal ultrasound has not been demonstrated, but patient preference, especially the discomfort of bladder filling required for abdominal ultrasound, should always be an important consideration by the clinician.

If the mass is 10 cm in diameter or larger, a surgical procedure is warranted, especially if accompanied by pain. If the content of the cyst on ultrasound is considered hemorrhagic, with debris inside and is accompanied by significant abdominopelvic pain, especially cyclical, monthly repetitive, the diagnosis of endometrioma should be considered as a strong possibility, regardless of the data of suspicion of papillae or calcifications in the patient with less than 35 years, as well as a determination of serum CA 125 that reports levels < 200 units. In the case of a benign neoplasm, unilateral oophorectomy or even tumor excision is usually performed. If malignancy were suspected, the evaluation must be carried out by an oncologist.

For early stage ovarian cancer, you will have to decide the surgical approach depending on the patients' age. For patients over 35 years of age, the standard therapy should be surgical staging including hysterectomy and bilateral salpingo-oophorectomy with omentectomy, selective lymphadenectomy in some cases, and appendectomy in the case of mucinous tumors; all of this considering an epithelial ovarian cancer as the first possibility.

Aggressive removal of all visible tumor, seeking to achieve an optimal residual for intra-abdominal disease, would improve the survival in the case of more advanced disease. In these women, adjuvant or postoperative chemotherapy is indicated, especially the combination of Carboplatin with Paclitaxel, rescuing up to two thirds of these patients.

In the case of patients less than 35 years with a rare germline cancer, a conservative surgical management is imposed, respecting pelvic organs and fertility, with the administration of postoperative chemotherapy, which will be curative in these patients and will rescue the vast majority of women.

Endometriosis mimicking adnexal tumors

In our clinical practice of Gynecology Oncology not infrequently we find patients who are unknown carriers of endometriosis who present and are operated on because they resemble a picture of gynecological cancer, predominantly of the ovary. Endometriosis is often easily misdiagnosed as a malignancy [26].

In addition, the diagnosis of a pelvic neoformative process, particularly if it is a non-cystic malignancy, is favored by the macroscopic appearance of the lesion. These unusual cases represent greater difficulties in management even in experienced centres. The frozen-section pathological examination is a very useful intraoperative analysis that helps to make a surgical decision, increasing sensitivity and specificity for the risk classification [27].

In the differential diagnosis, neither the clinical presentation nor the age of presentation of endometriosis can be taken into account, which are largely similar to the other diagnoses.

The presentation of endometriosis is often retroperitoneal, close to the uterus (i.e., paracervical and parametrial) [28]. We have to include in the differential diagnosis the presence of a lateral spread of cervical cancer [29]. We have found endometrioid adenocarcinomas arising from an endometriotic cyst located in the broad lateral ligament, in proximity to the pelvic wall, in apposition to the ureter. Broad ligament endometriosis can also infiltrate medially into paracervical tissues, and in many cases even appear as a solid mass [30]. In contrast, frank retroperitoneal cystic endometriosis is not common [26].

Endometriosis-associated ovarian cancer

A 1.4 to 1.9% risk of developing ovarian cancer throughout life has been reported among patients with endometriosis, compared to the general population [31,32].

Epithelial ovarian cancer

Endometriosis is tightly related to some subtypes of epithelial ovarian cancer (EOC), particularly ovarian clear cell carcinoma (OCCC) and endometrioid ovarian carcinoma (EnOC) [33].

This association between endometriosis and EOC subtypes has been confirmed by detecting mutations in cancer-associated genes using molecular pathology [35,36]. The first time they were reported in the literature, in 1925, they were described as endometriosis-associated endometrioid ovarian carcinoma [34].

It is known that, despite this, patients with endometriosis will spend years suffering from this benign disease but will never develop cancer related to endometriosis; it is also known that OCCC and EnOC that can occur in younger women, most of them in the range between 35 and 55 years of age, are directly related to endometriosis. EnOC's constitute 10% of EOC's and, similarly, prevalence of OCCC's is between 5-12% [33].

Ovarian germ cell neoplasm

A less frequent group of malignant neoplasms, ovarian germ cell malignancies (OGCM's) most usually present in women under the age of 30. The most frequent symptom in this group of very low-incidence tumors is abdominal pain accompanied by a mass, abdominal or pelvic, in 85% [37]. The disease manifests clinically with pain as the first symptom in 64% of patients and abdominal distension as the first sign in 26% of cases [38]. Transvaginal bleeding and ascites are also reported. In a much smaller percentage of patients it can present acutely with symptoms due to ovarian torsion. The median age of OGCM patients at diagnosis is 24 years [38].

Definitive diagnosis

The definitive diagnosis depends to a great extent on the findings in the ultrasonogram (US). In this study, endometriomas are frequently observed as thick-walled unilocular masses with regular margins that are often bilateral and multiple, with homogeneous content and fine internal echoes that result in an echogenic "ground glass" appearance, caused by the blood cells flaking off the walls [39].

Ovarian endometriomas constitute an important differential diagnosis of a large number of ovarian cystic lesions such as benign cystic teratomas or dermoid cysts, and hemorrhagic luteal cysts. The US is important to detect the characteristics of the lesion, variable in each case. The edges may be serrated; they can be infiltrated by the surrounding tissues. Most disease deposits demonstrate vascularization on color Doppler.

In the absence of a conclusive US or with suspicion of ovarian cancer, a CAT or MRI scan is recommended [40]. Tumor markers must be interpreted in a prudent and judicious manner, maintaining an important consideration of the context, with the decision being made according to the age of the patient.

Conclusion

Benign or malignant tumors can resemble and be diagnosed as Ovarian Endometrioma. These cases represent greater difficulties in management even in experienced centres. The clinical presentation is generally not very helpful in the differential diagnosis. The intraoperative frozen-section analysis is of great help in making a surgical decision. Tumor markers must be interpreted in a prudent and judicious manner, maintaining an important consideration of the context, with the decision being made according to the age of the patient. In the case of a malignant neoplasm, it will always be recommended that the person responsible for performing the surgical evaluation and making the surgical decision be a gynecologic oncologist.

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Burden of respiratory morbidity amongst survivors of COVID-19 infection in Lagos, Southwest Nigeria

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Abstract

Background: COVID-19 disease is associated with long-term effects in some survivors. There exists dearth of information about the burden of respiratory morbidity among COVID-19 survivors in Nigeria. This study was designed to identify the common respiratory symptoms of long COVID-19 to educate and increase index of suspicion of healthcare practitioners caring for such patient for optimal care.

Material and methods: This is a cross-sectional survey that took place at the adult pulmonology clinic of Lagos State University Teaching Hospital Ikeja. The individuals who were treated for PCR confirmed COVID-19 infection referred for unresolved symptoms 4 weeks following discharge that consented were recruited. A proforma was used to obtain information on socio-demographic characteristics, medical history, and comorbidities. The degree of dyspnea was assessed using MRC(Medical Research Council) dyspnea scale while the functional capacity of patients was assessed using Six-minute walk test (6mwt). The analysis of the data collected was done using descriptive statistics, and chi-square was used to test for association.

Results: Ninety-four subjects participated. The mean age of participants was 49.48±17.8 years, with male: female ratio of 1:1.1. The median duration of admission due to COVID-19 infection was 10.0 (7.0-15.8) days. The common symptoms were fatigue (85.1%), loss of smell (71.3%), dyspnea 53(56.4%), and Cough (62.8%). Dyspnea was present in 62.8% using the MRC dyspnea scale, while the 6-minutes walk test showed inadequate functional capacity in 61.7%, and both showed significant association. (X^2=18.606, P=0.001*)

Conclusion: Respiratory morbidity remains a significant post covid condition. There is a need to raise awareness amongst healthcare workers, particularly within the primary healthcare setting for early identification and referral of COVID-19 survivors with prolonged respiratory symptoms to pulmonology clinics for optimal care. There is also a need for further research on predictors of post COVID syndrome and treatment modalities.

Key words: post covid syndrome, Long covid, post covid disease

Introduction

Infection with SARS COV2 virus causing COVID-19 disease is associated with long-term effects in some survivors [1]. These clinical conditions have been referred to in the literature as long COVID, long haul COVID, post-acute sequelae of SARS-CoV-2 infection (PASC), long-term effects of COVID, and chronic COVID [1]. Post-COVID-19 Syndrome includes persistent symptoms related to residual inflammation, organ damage, non-specific effects from the hospitalization or prolonged ventilation (post-intensive care syndrome), social isolation, or impact on pre-existing clinical condition [1]. The multi-systemic clinical sequelae associated with COVID-19 are similar to post-acute viral syndromes described in survivors of other virulent coronavirus epidemics previously [2]. These symptoms include fatigue, dyspnea, cough, chest pain, sleep abnormalities, and mood disorders [3-5].

As of September 2022, the global pandemic caused by coronavirus disease 2019 (COVID-19) has affected more than 605, 000 000 people and caused more than 6,400 000 deaths in over 215 countries or regions worldwide [3,6]. There were a large number of patients

who had been cured and discharged from the hospitals all over the world. Presently, about 265,000 people have been treated for COVID-19 infection in Nigeria [6-8]. In Lagos State, 103,957 cases have been treated so far with 814 currently on admission and 102,372 discharged.

The clinical profile, treatment and prognosis of COVID-19 infection have been extensively studied. As a result, we are now more able to effectively optimize the treatment of patients with acute infection and prognosticate the outcome compared with the beginning of the pandemic. However, the prevalence, nature, duration and risk factors of sequelae in COVID-19 survivors have not been extensively reported in Nigeria. There exists dearth of information about the clinical sequelae, particularly pertaining to burden of respiratory morbidity among COVID-19 survivors in Nigeria. To bridge this gap, this study was thus designed to describe the clinical sequelae of COVID-19 infections amongst a group of COVID-19 survivors in Lagos, Southwest Nigeria to educate and increase index of suspicion of healthcare practitioners about the common respiratory symptoms of long COVID-19 for optimal care of survivors with delayed recovery. This study identified various respiratory manifestations as well as other systemic symptoms following acute infection with sarscov2. The implication of this is the need for follow-up of COVID survivors by a multidisciplinary team including pulmonologists for early identification of prolonged symptoms that could predict pulmonary morbidity which may be addressed or salvaged to improve the quality of life of such patients.

Material and methods

This study took place at Lagos State University Teaching Hospital (LASUTH), a 600-bed tertiary center with a 20-bed isolation center for attending to active COVID-19 patients. The teaching hospital was not a COVID-19 treatment center during the first wave and post-COVID-19 disease was largely unrecognized. The Covid-19 management was coordinated by the family and community physicians as well as internist consultation on request. The service was supported by a specialist pulmonology clinic that in addition receives referrals from other public and private centers managing COVID-19 in Lagos. The clinic is manned by three pulmonologists in the service of Lagos State. Most patients were referred on account of persistent respiratory symptoms and abnormal imaging following COVID-19 disease management. However, following the relaxation of lockdown, the respiratory unit clinic experienced increased referral at the outpatient and in-patient of cases of COVID-19 pneumonia with residual symptoms and abnormal imaging.

We recruited patients with PCR confirmed COVID-19 managed at LASUTH isolation center or any of the isolation centers in Lagos State referred to our respiratory clinic on account of symptoms lasting more than four weeks after discharge or with abnormal imaging who consented to participate in the study.

We excluded symptomatic patients with positive COVID-19 PCR, individuals with no proven evidence of positive PCR but with abnormal imaging and also dyspnea associated (like COPD, and severe heart failure) illnesses prior to COVID-19 infection.

Ethical approval was gotten from Lagos State University Teaching Hospital Ethics and Review Committee. Written informed consent was obtained from individual participants.

The calculated sample size was 92 using the Cochran formula (N = Z^2pq/d^2 where, N = sample size, Z = standard normal deviation, usually set at 1.96, which corresponds to the 95% confidence interval, p = mean prevalence of adults at high risk of Covid 19 in Nigeria = 40 % [9], q = (1 — p), and d =

degree of accuracy desired, usually set at 0.10) [10]. A proforma comprising of two sections was used to obtain needed information. Section A dealt with the socio-demographic characteristics (age, sex, occupation, duration of diagnosis, symptoms etc), medical history, comorbidities and MRC dyspnea scale.

MRC dyspnea scale

The MRC dyspnoea scale is a simple questionnaire that allows patients to indicate the extent to which their breathlessness affects their mobility. It is used to measure dyspnea in various conditions like COPD, bronchial asthma, restrictive disease, pulmonary fibrosis, occupational lung disease, and various heart conditions such as heart failure. It comprises of five statements that measure the degree of disability that breathlessness poses on day-to-day activities on a scale from 0 to 4: 0, no breathlessness except on strenuous exercise; 1, shortness of breath when hurrying on the level or walking up a slight hill; 2, walks slower than people of same age on the level because of breathlessness or has to stop to catch breath when walking at their own pace on the level; 3, stops for breath after walking ~100 m or after few minutes on the level; and 4, too breathless to leave the house, or breathless when dressing or undressing [11,12]. The questionnaire was administered by the researcher. The score is the number that best fits the patient's level of dyspnea with activity [11,12].

Six minutes walk test

The six-minute walk test (6mwt) aids in assessing the functional capacity of patients with cardiopulmonary disease [13,14]. The patients were instructed to walk as far as possible on a straight track of 100 feet in length. Patients were advised to walk on their own pace and pause to rest, if needed, but should resume walking as soon as they were able. The timer for the test continued throughout the 6 minutes period even during the times patients paused to rest. The total distance walked (six-minute walk distance) was obtained. The scoring involved figuring out the distance that a person has covered by multiplying the number of lengths by the distance of the track. The score range for healthy adults was set at 400–700 m. The higher a person's score, the better their exercise tolerance. A low score correlates with lower function. The estimation of arterial oxygen saturation by pulse oximetry was collected pre-test, at intervals during the test and at the end of test [13,14].

Statistical analysis

Continuous variables were described using mean with standard deviation (SD) or median while categorical variables were expressed as percentage. The correlation between MRC dyspnea scale with saturation levels of patients at rest and after a 6 minutes-walk test was assessed using spearman's test. The comparison between MRC dyspnea scale and adequacy of distance covered during 6 minutes-walk test was done using the Chi-square test. The conventional level of statistical significance of 0.05 was used for all the analyses. Statistical analyses was performed using SPSS Version 21.0.

Results

There were ninety four participants with mean age of 49.48±17.8, and male: female ratio of 1:1.1. The median duration of illness of the participants during the acute infection was 10.0(7.0-15.8). Seventy six (80.6%) of the participants have never smoked previously. Other socio-demographic characteristics is shown in Table 1. Common comorbidities

Table 1	Demographic and clinical characteristics of participants	
Variable	**Frequency (n=94)**	**Percentage**
Age		
<40	39	41.5
41-60	25	26.6
>70	30	31.9
Mean±SD	49.48±17.8	
Gender		
Male	45	47.9
Female	49	52.1
Year of COVID diagnosis		
2020	41	43.6
2021	53	56.4
COVID variant		
Delta	9	9.6
Omicron	13	13.8
Unknown	72	76.6
Median duration of illness (Days)	10.0 (7.0-15.8)	
Comorbidities		
Hypertension	58	61.7
Diabetes	32	34.0
Obesity	16	17.0
Asthma	9	9.6
Heart failure	2	2.2
Renal failure	2	2.2
OSA	1	1.1
COPD	1	1.1
Connective tissue disease	1	1.1
Cancer	1	1.1
Sickle cell disease	1	1.1
Coronary heart disease	1	1.1
GERD	1	1.1
None	22	23.4
Smoking status		
Never	76	80.9
Previous smoker	11	11.7
Current smoker	7	7.4

The table shows the socio-demographic characteristics of the participants as well as the distribution of comorbidities.

amongst the participants are hypertension 58(61.7%), diabetes 31 (34.0%), and obesity 16(17.0%). Frequent respiratory symptoms experienced include fatigue 80(85.1 %), loss of smell/ taste 67(71.3%), dyspnea 53(56.4%), and Cough 59 (62.8%). Non–respiratory symptoms include headache 2(2.1%), GIT symptoms 5 (5.3%) and depression 5(5.3%) as shown in Figure 1.
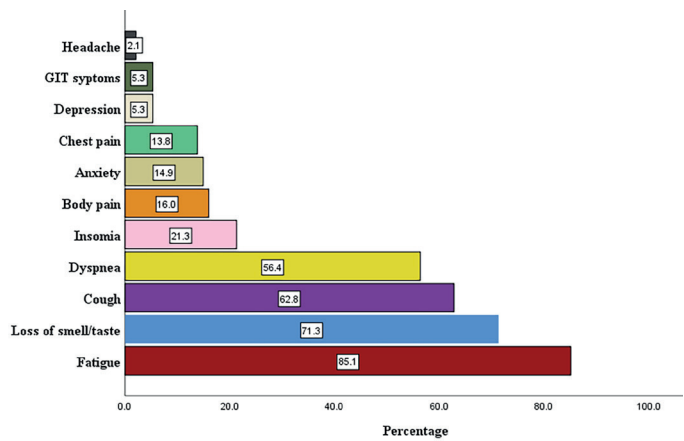
Figure 1 - Prevalence of respiratory symptoms post COVID
The figure is a histogram chart showing the distribution of post covid symptoms

Treatment received by patients include multivitamins 94 (100%) and Zinc 93 (98.9%) taken by all. Other treatment modalities used includes Ivermectin, dexamethasone, antipyretic and oxygen used by 71 (75.5%), 50(53.2%), 48 (51.1%) and (48.4%) respectively. This is shown in Table 2.

Table 2	Treatment modalities during Acute infection phase	
Variable	**Frequency (n=94)**	**Percentage**
Pulmonary rehabilitation	16	17.0
Anticoagulant	16	17.0
Multivitamin	94	100.0
Zinc	93	98.9
Antipyretic	48	51.1
Ivermectin	71	75.5
Dexamethasone	50	53.2
Colchicine	16	17.0
Proning	19	20.2
CPAP	12	12.8
Oxygen administration	47	50.0

The table shows the distribution of various treatments received by the participants during acute infection.
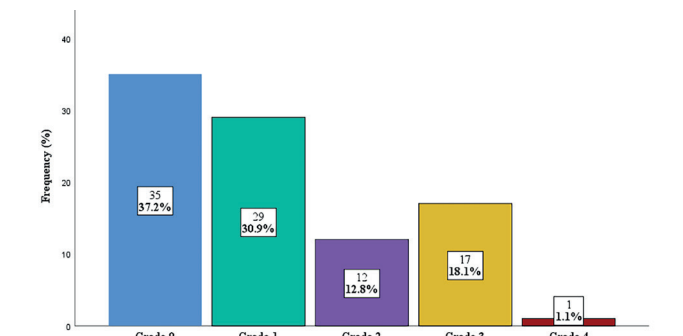
Figure 2 - MRC DYSPNEA scale among participants
The figure is a bar chart showing the number of participants with different grades of dyspnea.
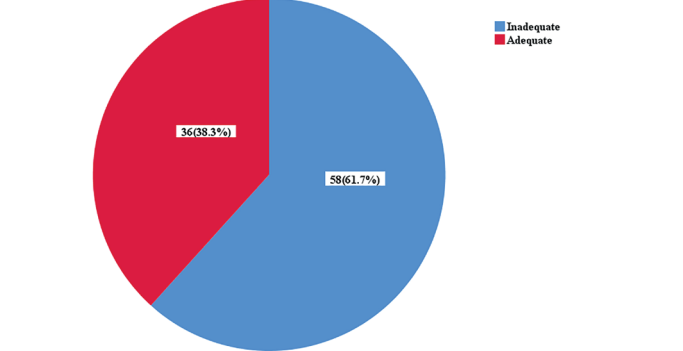
Figure 3 - 6-minutes walk test
The figure is a pie chart showing the adequacy of six minutes walk test among the participants (N = 94)

Table 3	Association between 6-meter walk test and MRC DYSPNEA scale among participants			
	6-minutes walk test		**χ^2**	**p-value**
	Inadequate	**Adequate**		
MRC DYSPNEA scale			18.606	0.001*
Grade 0	12(34.3)	23(65.7)		
Grade 1	21(72.4)	8(27.6)		
Grade 2	10(83.3)	2(16.7)		
Grand 3	14(82.4)	3(17.6)		
Grade 4	1(100.0)	0(0.0)		

Dyspnea was present in 62.8% using the MRC dyspnea scale: Grade 1 was present in 30.9%, Grade 2 in 12.8%, Grade 3 in 18.1% while 1.1% had grade 4 as shown in Figure 2. The mean baseline saturation was 95.92±20.0 while the mean post 6 minutes walk test saturation was 94.55±29. The mean total distance covered during the test was 402.07±110.5. The functional capacity assessed using 6-minutes-walk test was adequate only in 36 (38.3%) of participants as shown Figure 3. There was negative correlation between MRC dyspnea scale with baseline saturation and end of test saturation (correlation coefficient: -0.733 and p <0.001, correlation coefficient: -0.765 and p< 0.001 respectively). Table 3 shows a significant association between functional capacity using 6-meter walk test and respiratory disability using MRC Dyspnea scale (x^2=18.06, p=0.001), implying that with increase in proportion of patients with inadequate functional capacity there is increase in the grade of respiratory disability.

Discussion

Post-COVID-19 syndrome is now a clinical condition well recognized and includes new or worsening abnormalities in physical, cognitive and psychiatric domains after critical illness [15]. This study described the burden of respiratory morbidity as a clinical sequelae of COVID-19 infection amongst a group of COVID-19 survivors in Lagos, Southwest Nigeria. Our results are consistent with the findings by Yong et al who noted in a literature review of possible pathophysiology, risk factors, and treatments in long COVID that the common symptoms of long COVID reported in many studies include fatigue and dyspnoea that last for months after acute COVID-19 [16]. The study reported other persistent symptoms that include cognitive impairments, chest pains, joint pains, palpitations, myalgia, smell with taste dysfunctions, cough, headache, and gastrointestinal and cardiac issues [16].

The possible pathophysiologic explanation for the long COVID includes long-term tissue damage, pathological inflammation, immune dysregulation, and autoimmunity [16].

Raveendran et al in another review mentioned fatigue, cough, chest tightness, breathlessness, palpitations, and myalgia as symptoms reported in long COVID [17]. The implication of this is that patients with treatment for COVID could have prolonged symptoms which may be quite disturbing or debilitating after the acute infection. Hence, there is a need for follow up of such patients.

The common comorbidities reported in our study include hypertension, diabetes and obesity and these were similar to the findings in a prospective cohort study of COVID-19 survivors in Moscow where pre-existing hypertension was associated with post COVID-19 conditions at 12 months [18]. This is also similar to the findings in another cross-sectional study of COVID-19 survivors using hospital based where the main determinants of the persistent post-COVID-19 symptoms included hypertension, and chronic pulmonary disorders [19].

Conversely, Carvalho-Schneider et al reported that the presence of initial symptoms during acute infection(chest pain, dyspnoea, fever, anosmia, ageusia), gender or number of comorbidities did not predict post-COVID syndrome in a descriptive study where 150 patients with noncritical COVID-19 confirmed by real-time reverse transcriptase PCR at Tours University Hospital were followed up to two months post discharge [20]. This may suggest that there are still inconsistency in specific risk factors for developing and determining the severity of Long COVID. Hence, there is a need for more research on this subject.

Our findings revealed varying respiratory disabilities using MRC dyspnea scale and 6 minutes walk test in about two third of patients and this is similar to the findings of Ceurci Claudio et al who characterized pulmonary function and disability status of Covid survivors in a crossectional observational study and reported severe respiratory disability, and difficulty to perform 6-MWT with poor results in majority of the participants [21]. Similarly, Anastasio et al evaluated COVID survivors in Europe and reported that lung damage during COVID-19 correlates to the reduction of pulmonary function 4 months after acute infection [22]. However, Xiaojun in a prospective, cohort study in China among patients admitted to hospital for severe COVID-19 who did not require mechanical ventilation who were prospectively followed up at 3 months, 6 months, 9 months, and 12 months after discharge reported improved dyspnoea scores and exercise capacity over time [23]. Although, in a subgroup of patients at 12 months they still found evidence of persistent physiological and radiographic changes [23].

Our study is limited by our inability to carry out spirometry and further assess lung physiology. Inclusion of these data may have helped us to ascertain whether there is a correlation between altered physiology, physical performance, and reported persistent symptoms. The use of recall to assess presence of persistent symptoms may be subjected to recall bias.

Conclusion

Long COVID-19 is another public health crisis following the COVID-19 pandemic. Respiratory morbidity remains a significant post covid condition. There is a need to raise awareness amongst healthcare workers, particularly within the primary healthcare setting for early identification and referral of COVID-19 survivors with prolonged respiratory symptoms to pulmonology clinics for optimal care. There is also a need for further research on predictors of post COVID syndrome and treatment modalities.

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Prevalence and determinants of vitamin D deficiency amongst patients in Erbil, Kurdistan region of Iraq

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Abstract

Aim: This study aims at calculating the prevalence of Serum Vitamin D deficiency and determining risk factors associated with deficiency amongst patients in Erbil, Kurdistan Region of Iraq.

Material and methods: This was a prospective cross-sectional study conducted on 424 patients from September to November 2021 in the Outpatient Department of Kurdistan Cardiac Center – Surgical Specialty hospital.

Results: Results showed that study population consisted of adults aged 30 years and above, 171 (40.3%) females and 253 (59.7%) males. The majority of the study population (51.9%) were Serum Vitamin D deficient, 27.6% were Serum Vitamin D insufficient and 20.5% had normal Vitamin D levels. Serum Vitamin D deficiency was seen more frequently among female gender, increased BMI, previous infection of COVID 19, Diabetes Mellitus and those with abnormal lipid profiles.

Conclusion: There is a high prevalence of Serum Vitamin D deficiency in Erbil, Kurdistan Region of Iraq. In addition, there were associations between Serum Vitamin D deficiency and many other diseases. Therefore, medical practitioners should consider more education of patients regarding importance of vitamin D status in the body.

Key words: vitamin D, prevalence, deficiency, risk factors, prospective cross-sectional study

Introduction

Vitamin D is a fat-soluble vitamin that has a remarkable role in homeostasis of phosphorus and calcium [1]. Like so many other vitamins, it has an essential role in human health and wellbeing. The two main existing forms of Vitamin D are D2 (Ergocalciferol) and D3 (Cholecalciferol). Ergocalciferol is acquired from sources of plant, while cholecalciferol is acquired from exposure to sunlight and animal derivates [2].

When ultraviolet B (UVB) radiation of wavelength 290-315 nm hits the skin, 7-dehydrocholesterol gets converted to pre-vitamin D3, and vitamin D3 is produced upon its isomerization. However, the amount of vitamin D produced can vary depending on the individual's age, skin complexion, day time, sunscreen product usage, latitude, and seasonal changes [3].

Due to its long half-life, serum concentration of 25-hydroxyvitamin D [25(OH)D] is considered the main indicator of vitamin D status, which reflects total vitamin D in the human body [4]. In today's world, there is a widespread prevalence of vitamin D deficiency that is primarily caused by under-appreciation of the important role of moderate sun exposure in supplying vitamin D for humans [5]. Furthermore, the amount of vitamin D found naturally in food is very limited, and foods that contain vitamin D are insufficient to meet an individual's needs [6]. The prevalence of Vitamin D deficiency appears to be highest in countries such as Asia, the Middle East, Africa, and amongst immigrants residing in regions of higher latitudes [7].

Vitamin D has long been known for its impact on bone and muscle health. However, it is becoming

increasingly evident that vitamin D is essential for overall wellbeing and has a role in conditions other than its main role in the musculoskeletal system [8]. It has been noticed that it may also have extensive regulatory effects on both innate and adaptive immune cells and contributes to inflammation in the body [9]. Vitamin D status has also been linked to diabetes mellitus [10] as it appears to have a direct influence on insulin sensitivity and resistance [11]. It also possesses regulatory roles in cardiovascular diseases [12], chronic kidney disease [13], and different types of cancer [14]. Furthermore, deficiency in vitamin D has been linked to obesity as a cause and consequence through direct and indirect mechanisms [15].

Since vitamin D has an important role in maintaining the homeostasis of the body, it is essential to have sufficient data of vitamin D status among the population and its correlations with different diseases. Having said that, in the Kurdistan region of Iraq, there is limited studies and investigations implemented regarding the status of vitamin D amongst the population. Thereby, this study was conducted to inspect prevalence of vitamin D and its association with various conditions in the body.

Material and methods
Study population and design of the study

Prospective cross sectional study conducted amongst 424 male and female patients of different regions in Iraq, seeking medical consultation in outpatient department in Kurdistan Cardiac Center- Surgical department.

Collection of blood samples
A total of 424 blood samples were collected from participants. The serums were used for the measurement of: serum gamma glutamyl transferase (S. GGT), total cholesterol, serum high density lipoprotein (S.HDL), serum low density lipoprotein (S.LDL), serum very low-density lipoprotein (S. VLDL), serum triglyceride (S.TG), S. 25 OH vitamin D, creatinine, and C reactive protein (CRP).

Inclusion and exclusion criteria
Both genders, adults aged 30 years and above attending the medical outpatient department due to any medical reason were included.

Exclusion criteria involved those on vitamin D or multivitamin supplements and/or calcium supplementation taken within 12 months before interview was conducted. Cancer patients (undergoing regular treatment and/or diagnosed with malignancies), those with chronic kidney disease (stage 3 Renal failure or higher), liver dysfunction (including viral hepatitis, cholestasis jaundice) and ischemic or hemorrhagic stroke during 12 months before interview was conducted.

Study timeline
The present study was carried out from 15th of September 2021 to the 15th of November 2021 at the outpatient department of SSH/Cardiac Center- Erbil/ Iraq.

Statistical analysis
All statistical data were analyzed using SPSS Statistics 26 (SPSS Inc., Chicago, IL, USA)

Questionnaire form design
Data was collected through direct administration of a face-to-face questionnaire that was pretested with modifications made before its use in the study. Along with access to medical records or records which contain intimate personal information, and are individually identifiable and not publicly available. The questionnaire included demographic variables (name, age, gender, home address, time of administration, date and socioeconomic status), clinical risk factors of the patient, family history, and smoking habitual of the patient.

Ethical considerations
Ethical approval was obtained from the ethics committee of Hawler Medical University. Verbally informed consent was taken from each patient. A complete explanation of the nature and aim of the study was given to each participant and reassured about the confidentiality of the data and their anonymity.

Laboratory Parameters:

Cholesterol	mg/dL Good: <200 Borderline: 201-239 High: >240
TG	mg/dL Good: <159 Borderline: 160-199 High: >200
HDL cholesterol	mg/dL 30-55
LDL cholesterol	mg/dL Good: <100 Borderline: 101-130 High: >130
S. VLDL	mg/dL Good: 2-30 Borderline: 30-40 High:>40
Serum creatinine	Normal: 0.6-1.2 mg/dL High: >1.3 mg/dL
Vitamin D	ng/mL Risky: >100 Normal: 30-100 Insufficient: 21-29 Deficient: <20
CRP	Mg/Dl Normal: <5 High: >6
GGT	IU/L Normal: 0-30 Abnormal: >30

Results
This was a cross sectional prospective study with a sample size of 424 cases. The study population consisted of 171 (40.3%) females and 253 (59.7%) males. According to age, the majority of the population were between the age group 60-69 (32.2%) and 50-59 (30.2%), followed by the 40-49 age group (21.9%), >70 age group (11.3%) and lastly the <39 age group which consisted of only 4.2% of the population (Table 1).

Concerning the BMI of the cases, the majority of them were overweight (37.7%) and obese class I (36.8%) followed by normal weight (15.3%), obese class II (7.5%) and obese class III (2.6%) (Table 1).

Among the study population, 207 (48.8%) of them had a previous history of COVID-19 infection (Table 1).

According to the serum vitamin D levels, the study population was divided into three categories: those with serum vitamin D deficiency (<20 ng/ml), serum vitamin D insufficiency (21-29 ng/ml), and those with normal serum vitamin D levels (30-100 ng/ml).

Table 1	Distribution of age, gender, BMI class and previous COVID 19 infections in the sample

Characteristic	Frequency	Percentage (%)
Age Group		
<39	18	4.25
40-49	93	21.93
50-59	128	30.2
60-69	137	32.3
>70	48	11.32
Gender		
Males	253	59.7
Females	171	40.3
*BMI		
Normal weight	65	15.33
Overweight	160	37.73
Obese Class I	156	36.8
Obese Class II	32	7.54
Obese Class III	11	2.6
Previous COVID-19 Infection		
Yes	207	48.8
No	217	51.2

*BMI: Body Mass Index

The majority (51.9%) were vitamin D deficient, (27.6%) were insufficient and (20.5%) had normal vitamin D levels (Figure 1).
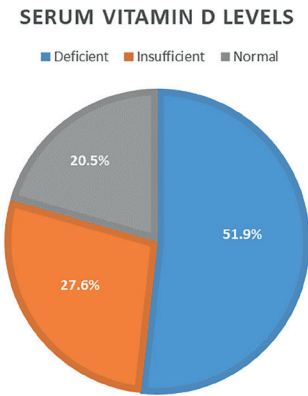
SERUM VITAMIN D LEVELS

Figure 1 - The distribution of serum Vitamin D levels amongst patients

Upon comparing the serum vitamin D levels between the different sexes, the following findings were observed: amongst the female participants (55.5%) were vitamin D deficient, (20.5%) were vitamin D insufficient and (24%) had normal levels.

Amongst the males; (49.4%) were vitamin D deficient, (32.4%) were vitamin D insufficient and (18.2%) had normal levels of vitamin D.

This slightly higher level of deficiency seen among the females was statistically significant with a (P = 0.02) (Table 2).

Concerning the incidence deficiency amongst the different BMI classes: (41.5%) of the normal-weight, (48.8%) of the overweight, (55.1%) of the obese class I, (65.6%) of the obese class II and (72.7%) of the obese class III were vitamin D deficient, respectively.

Table 2	Association between gender and serum vitamin D status

Serum Vitamin D levels	Gender	
	Females n (%)	Males n (%)
Deficient	95 (55.5%)	125 (49.4%)
Insufficient	35 (20.5%)	82 (32.4%)
Normal	41 (24%)	46 (18.2%)
P Value	0.021	

This rising percentage of deficiency associated with increasing BMI was statistically significant (P = 0.004) (Table 3).

Upon analyzing the existence of a relationship between a previous COVID-19 and Vitamin D deficiency, it was discovered that (45.9%) of those with a previous COVID-19 had vitamin D deficiency, while (25.6%) had insufficiency and (28.5%) had normal Vitamin D levels. In contrast, amongst those without a previous COVID-19 infection, (57.6%) of patients had deficiency, (29.5%) of them had insufficiency and only (12.9%) had normal levels. This was a highly significant association with a P value <0.001 (Figure 2).

Among the study population, (35.4%) were considered diabetic while (64.6%) were not. The proportion of adults with diabetes were more common among participants with deficient and insufficient Vitamin-D, (61.3%) and (20.7%) respectively. This difference was significant with a P value of 0.013 (Table 4).

Regarding a previous percutaneous coronary intervention (PCI) performed on the population, (29.5%) of patient had undergone the procedure. Results showed that 88% of patients who had a previous PCI had either insufficient or deficient Vitamin-D levels. This was also statistically significant (P = 0.016) (Table 5).

When investigating the relation between serum Vitamin D deficiency and serum lipid levels, the following categories were defined. High cholesterol (> 200 mg/dl) was found in (37.7%) of the patients. Similarly, (39.2%) of the cases had high values of TG, 20% had high VLDL levels, 38.7% had high LDL levels and 33% had low HDL levels (Figure 3).

Aside from the lipid levels; CRP, creatinine and GGT blood levels were also measured. Only 20 out of the 424 patients (4.7%) presented with high creatinine levels. Cases of high CRP were more abundant amongst the patients (21.9%). GGT elevation was found in (38.2%) of the patients (Figure 3).

Table 3	Association of serum vitamin D levels with BMI class

Serum Vitamin D levels	*BMI				
	Normal weight n (%)	Overweight n (%)	Obese Class I n (%)	Obese Class II n (%)	Obese Class III n (%)
Deficient	27 (41.54%)	78 (48.8%)	86 (55.1%)	21 (65.6%)	8 (72.7%)
Insufficient	14 (21.54%)	53 (33.1%)	41 (26.3%)	9 (28.1%)	0 (0%)
Normal	24 (36.92%)	29 (18.1%)	29 (18.6%)	2 (6.3%)	3 (27.3%)
P Value	0.004				

*BMI: Body Mass Index

Table 4   Association between Serum Vitamin D levels and Diabetes.

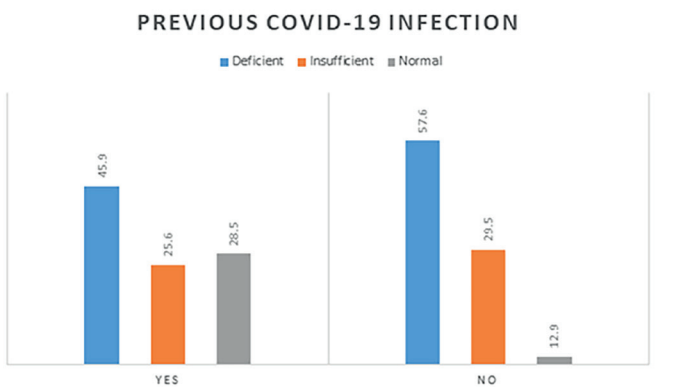| Diabetes	Serum Vitamin-D level				P-value
	Deficient n (%)	Insufficient n (%)	Normal n (%)	Total n (%)	0.013
Yes	92 (61.3%)	31 (20.7%)	27 (18.0%)	150 (100%)	
No	128 (46.7%)	86 (31.4%)	60 (21.9%)	274 (100%)	
Total	220	117	87	424	

Figure 2 - Relationship between previous COVID-19 infection and Vitamin D amongst patients

Table 5   Vitamin D levels amongst patients who had undergone previous PCI or not

Previous PCI	Serum Vitamin-D level				p-value
	Deficient	Insufficient	Normal	Total	
Yes	72(57.6%)	38(30.4%)	15(12.0%)	125	0.016
No	148(49.5%)	79(26.4%)	72(24.1%)	299	
Total	220	117	87	424	

Table 6   Association of serum vitamin D levels with cholesterol and triglycerides

Serum Vitamin D levels	Serum Cholesterol		Serum Triglyceride	
	Normal n (%)	High n (%)	Normal n (%)	High n (%)
Deficient	124 (47%)	96 (60%)	130 (50.4%)	90 (54.2%)
Insufficient	76 (28.8%)	41 (25.6 %)	65 (25.2%)	52 (31.3%)
Normal	64 (24.2%)	23 (14.4%)	63 (24.4%)	24 (14.5%)
P value	0.015		0.038	

Table 7   Association of serum vitamin D levels with LDL, HDL and VLDL.

Serum Vitamin D levels	Serum *LDL		Serum *VLDL		Serum *HDL		
	Normal n (%)	High n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)
Deficient	132 (50.77%)	88 (53.7%)	171 (50.44%)	49 (57.6%)	80 (57.1%)	140 (50%)	0 (0%)
Insufficient	74 (28.46%)	43 (26.2%)	90 (26.55%)	27 (31.8%)	41 (29.3%)	73 (26.1%)	3 (75%)
Normal	54 (20.77%)	33 (20.1%)	78 (23.01%)	9 (10.6%)	19 (13.6%)	67 (23.9%)	1 (25%)
P value	0.84		0.04		0.018		

*LDL: Low Density Lipoprotein
*VLDL: Very Low Density Lipoprotein
*HDL: High Density Lipoprotein

Table 8   Association of serum vitamin D levels with creatinine, GGT and CRP.

Serum Vitamin D levels	Serum Creatinine		Serum *CRP		Serum *GGT	
	Normal n (%)	High n (%)	Normal n (%)	High n (%)	Normal n (%)	High n (%)
Deficient	204 (50.49%)	16 (80%)	160 (48.3%)	60 (64.5%)	133 (50.8%)	87 (53.7%)
Insufficient	115 (28.47%)	2 (10%)	105 (31.7%)	12 (12.9%)	76 (29%)	41 (25.3%)
Normal	85 (21.04%)	2 (10%)	66 (19.9%)	21 (22.6%)	53 (20.2%)	34 (21%)
P Value	0.032		0.001		0.704	

Gamma-Glutamyl Transferase
*CRP: C-Reactive Protein
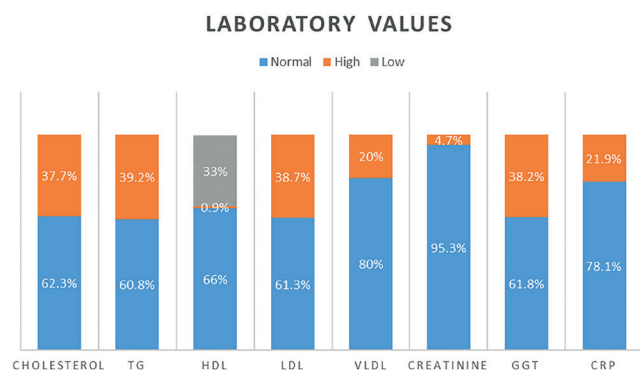
LABORATORY VALUES

Figure 3 - The relationship between Serum Vitamin D levels amongst different laboratory parameter

Results had shown that 60% of patients with high serum cholesterol levels were vitamin D deficient and 25.6% were insufficient. Patients with normal serum cholesterol levels were vitamin D deficient only in 47% of the cases and insufficient in 28.8%. The calculated P value for serum cholesterol and serum vitamin D relationship was 0.015 (Table 6).

As for the serum TG levels, 54.2% of those with high serum TG levels were found to be deficient, and 50.4% of patients with normal serum TG levels lacked sufficient vitamin D (Table 6).

Of the 20% of patients with high serum VLDL levels, 57.6% were Vitamin D deficient and 31.6% were insufficient. For the patients with normal serum VLDL levels, 50.4% of them were deficient (Table 7).

Although connection was implied between high serum TG (p = 0.038), serum VLDL (p = 0.040) and serum vitamin D levels, the results for serum LDL levels didn't appear significant. Amongst those patients with high serum LDL levels, 53.7% were found serum vitamin D deficient, while 50.8% of patients with normal serum LDL presented with deficiency as well (Table 7).

While 57.1% of patients with low serum HDL levels were simultaneously serum vitamin D deficient, only 50% of patients with normal serum HDL had shown Serum Vitamin D deficiency (Table 7).

Regarding the serum CRP and creatinine levels, 80% of patients with high serum creatinine were found to be deficient in vitamin D, while 64.5% of those with high serum CRP levels were deficient. These findings were both significant with P values of 0.032 and 0.001, respectively (Table 8).

Concerning the serum GGT levels, 53.7% of those with high serum GGT levels were Serum Vitamin D deficient. For those without serum GGT elevation, deficiency was described in 50.8%. However, the P value was 0.704 and therefore the result was not statistically significant (Table 8).

Discussion

Out of the 424 participants that were included in the study, it was noted that (55.6%) females and (49.4%) males were serum vitamin D deficient, similar results were shown in Jinzhong city, China whereby (75%) of women and (69%) of men had inadequate level of vitamin D [16]. Also, (51.9%) were vitamin D deficient, (27.6%) were insufficient and (20.5%) had normal vitamin D levels. Likewise, prevalence of vitamin D deficiency was (50,8%) and vitamin D insufficiency was (19.6%) among 1111 visitors of single consultation outpatient clinic in Isfahan City, Iran [17]. According to our results, BMI was inversely proportional to vitamin D deficiency, which was in accordance with a meta-analysis of 23 articles, suggesting a positive association between vitamin D deficiency and BMI

[18]. A suggested cause for that may be due to extra body fat retaining vitamin D metabolites, and that body fat sequesters cholecalciferol taken from diet or produced through the skin is partly before it is hydroxylated by the liver [19].

Vitamin D has a host of extra skeletal effects. Studies have showed that vitamin D plays a pivotal role in preserving the function of islet cells. Low vitamin D levels have repeatedly been shown to be associated with increased risk of diabetes mellitus (DM) [20]. From the 424 participants involved in the study it was evident that there was a significant correlation between vitamin D levels amongst those patients diagnosed with DM. The proportion of adults with diabetes were more common among participants with deficient levels (51.9%) and insufficient levels (27.6%). A study conducted in the Babylon governorate of Iraq claimed that DM as well as hypertension is the most common reported chronic non-communicable diseases that correlated significantly with serum vitamin D inadequacy [21].

As one of the stages of Vitamin D synthesis takes place in the liver, GGT levels were taken into consideration when searching for the risk factors of vitamin D deficiency. Clinical studies have reported a relationship between chronic liver diseases and lowering of serum Vitamin D levels [22]. Vitamin D insufficiency was even described as a biomarker in chronic liver diseases [23]. However, among samples included in this study, no significant correlation was found in those with high serum GGT levels and those with serum Vitamin D deficiency.

When comparing the vitamin D levels in patients with high and normal serum creatinine, the results were seemingly significant. Up to (80%) of the patients with high creatinine levels presented with vitamin D deficiency. This would contradict the results of clinical study conducted in the Jawaharlal Institute of Postgraduate Medical Education and Research in India. According to the study, the total serum Vitamin D levels were not affected by chronic kidney disease [24]. Similar results were found in children with steroid sensitive nephrotic syndrome in the Institute of Child Health in Kolkata, India [25].

As there were only (4.7%) patients with high creatinine levels in this study, it is possible that the results were solely due to insufficient number of samples. To confirm the relationship additional research would be required.

Furthermore, the study showed significant associations between serum vitamin D deficiency and dyslipidemia. Low serum HDL, high serum cholesterol and high serum TG were significantly associated with a higher incidence of serum vitamin D deficiency and insufficiency [26]. This is similar to a study done by Jiang X conducted in Northern China which found a strong association between vitamin D levels and dyslipidemia. Specifically, serum Vitamin D was inversely correlated with LDL cholesterol and triglycerides levels, and positively correlated with HDL cholesterol level [27].

In contrast, a study done by Zittermann A conducted in North-easter Brazil showed no relation between serum vitamin D level and serum cholesterol [28].

It was also noted that there was no significant association between serum vitamin D levels and serum LDL, which was in contrast to the study conducted by Han YY in Taiwanese population which showed higher levels of serum LDL in vitamin D deficient cases [29]. The relationship between serum vitamin D levels and lipid profile can be explained by the lipid lowering actions of vitamin D through its effects on calcium metabolism and parathyroid hormone regulation [30].

A study done by Jin D showed that serum vitamin D levels and normal lipid profiles were directly related. Furthermore, this same study showed an inverse relationship between serum

Vitamin D levels and serum CRP, which was consistent to our own results [31].

Several studies, including our own, showed a clear link between serum vitamin D levels and serum CRP [32-34]. This obvious association can be explained by vitamin D's immunological and anti-inflammatory actions. Vitamin D plays a key role in reducing inflammation by acting on the innate and adaptive immune systems [35].

Limitations

All measures in the study were self-reported and subject to recall bias. Data collection only included individuals who were attending the outpatient department of Cardiac center and results collected from Cardiac center lab.

The samples were taken over a two-month period and were collected in the Autumn season in Erbil. Furthermore, 25(OH) D, has a relatively long circulating half-life (approximately 3 weeks) and is considered a good biomarker, but serum vitamin D levels may change throughout the day and season of the year. A single measurement of vitamin D may not reflect lifetime status.

The sample size included patients with chronic diseases such as diabetes mellitus, chronic kidney disease and liver dysfunction which might disrupt Vitamin D levels in the body.

Vitamin D levels were not determined in a control group of healthy individuals for the purpose of comparative analysis.

Recommendation

Based on our findings, practitioners should consider more education of patients regarding importance of vitamin D status in the body. Additionally, Vitamin D deficiency should be corrected using supplements, correct diet and safe sun exposure.

Further researches need to be conducted regarding prevalence of Vitamin D as well as causes of low Vitamin D and associated conditions among Kurdistan Region population. Future studies could include Calcium status and use of sunscreen products, with a bigger and more equivalent number of people involved in all parts of Kurdistan Region throughout all four seasons of the year.

Conclusion

Vitamin D deficiency is a prevalent condition in the Kurdistan Region of Iraq, with a large number of people suffering from its implications. Several factors proved to be associated with serum vitamin D deficiency, including a previous infection of COVID-19, female gender, increased BMI, diabetes mellitus, the presence of atherosclerotic heart disease, or other inflammatory processes.

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A bibliometric analysis study on Chlamydia trachomatis

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Abstract
Aim: *Chlamydia trachomatis,* is one of the most important sexually transmitted disease (STD) pathogens on a global scale. In this study we aimed to analyze the publication developments with bibliometric methods on *C.trachomatis* by examining the research articles published between January 1970–December 2021.

Material and methods: Herein, a bibliometric design was used to achieve the developments in *C. trachomatis* research. Research articles published in the Web of Science (WoS) database between January, 1970–December, 2021 were included in the study. The keywords selected for the search were '*Chlamydia trachomatis, Chlamydia,* and *C. trachomatis*'.

Results: The search of the WoS database for *C. trachomatis* research articles from 1970 to 2021 yielded 8133 results. Of the documents, 5696 were articles. 95.769% were published in Science Citation Index Expanded (SCI-EXPANDED) indexed journals. Most were published in English (94.803%). The articles were mostly from the Infectious Diseases (33.251%) research area. Most of the articles were from the USA. About 51% of the studies had funding organizations, with the United States Department of Health and Human Services provided the most financial support. Most of the articles (n=346, 6.074%) were published in the Journal of Sexually Transmitted Diseases. Although the number of publications seems to be irregular, it has not fallen below 80 articles per year, especially since 1980. The articles were cited 147,672 times (25.93 times per article) and the H-index was 133.

Conclusion: STDs are still an important public health problem in almost all parts of the world. We have found that the number of published articles and citations to articles on C. trachomatis has increased rapidly, especially in recent years. However, although the number of publications in developed countries has increased, the number of publications in developing and underdeveloped countries is below the expected level. Since C. trachomatis is a global public health problem, countries with a lower number of publications should be supported financially.

Key words: *Chlamydia* trachomatis, publications, bibliometric analysis, sexually transmitted diseases

Introduction

Chlamydia trachomatis is a gram-negative obligate intracellular bacterium. Humans are the only natural hosts for *C. trachomatis* [1]. The principal etiological agents of avoidable blindness (serovars A to C), the most frequent bacterial sexually transmitted diseases (STDs) globally (serovars D to K), and lymphatic system infections (serovars D to K) are all chlamydial serovars (serovars L1 to L3) [1,2].

Chlamydia trachomatis is a common cause of urethritis in men and cervicitis in women [3]. The largely asymptomatic reservoir of infections provides a constant source of disease transmission, as well as the ability to spread the disease silently [4]. Moreover, this disease is predicted to be the most expensive non-viral sexually transmitted illness due to these outcomes [5]. This infection has become more common in the last 20 years. In recent years, novel features of *C. trachomatis*

infections have emerged, such as lymphogranuloma venereum proctitis in men who have sex with males and a variety with a deletion in the cryptic plasmid [6]. Screening programs that are well-organized are thought to play a key role in preventing the spread of the disease and its long-term effects [6].

The use of statistical tools to examine a wide range of literature in order to determine the historical evolution of a field of research, as well as qualitative and quantitative investigation of publications, is referred to as bibliometrics. The bibliometric method can also be used to determine the importance given to a topic and possible research areas by examining a field of scientific research [7–10]. In various fields of medicine, bibliometric research has been conducted. Web of Science (WoS), Scopus, and PubMed are often utilized in the international scientific literature for the bibliometric analysis of medical publications. Bibliometric analysis, on the other hand, evaluates the overall (absolute) number of publications while calculating relative indicators, their dynamics through time, and the amount of research funding. Content analysis, which involves recognizing research trends, is one of the topics of bibliometric analysis [8–10]. However, no similar study on *C. trachomatis* was found in the available literature.

In this study, it was aimed to analyze the developments in publications *C. trachomatis* by examining the research articles published between 1970 and 2021. We aimed to reveal the scientific map on this subject by examining many bibliometric parameters such as the distribution of publications by years, the countries with the most publications, the journals with the most publications, the authors with the most publications, the institutions with the most publications, the distribution of citations over the years, the institutions that fund scientific publications, scientific partnerships between institutions and countries.

Material and methods

Herein, a bibliometric design was used to achieve the developments in *C. trachomatis* research. The following search strategy was used:

Selected database: The Web of Science database

The keywords and search methodology: *Chlamydia trachomatis*, *Chlamydia*, *and C. trachomatis* were used in the Title section of the WOS database' search engine.

Document type: Articles

Timespan: January 1970–December 2021

Editions: Web of Science Core Collection [Science Citation Index Expanded (SCIE), Social Sciences Citation Index (SSCI), Arts & Humanities Citation Index (AHCI), Emerging Sources Citation Index (ESCI), Book Citation Index (BKCI) and Conference Proceedings Citation Index (CPCI)].

Data source

The keywords *Chlamydia trachomatis*, Chlamydia, and *C. trachomatis*, were used in the search. Only research articles were included in the study. On February 13th, 2022, all electronic searches were completed, and the year 2022 was excluded from the study because complete data for that year was unavailable.

Data collection

The WoS database was used to evaluate the bibliographic records. The authors' names, publication year, published journal, institution, country, and citation frequency were all retrieved for each publication. These were used to look into the worldwide knowledge domain of *C. trachomatis* research development patterns.

Visualization and mapping

The Vosviewer visualization tool (VOSviewer version 1.6.18) was used for visualizations. Thus, an international collaboration network map, citation network visualization map between links, and keyword visualization map of articles and authors with at least 5 publications and 100 citations were investigated.

Results

The search of the WoS database for *C. trachomatis* research articles from 1970 to 2021 yielded 8,133 results. Of these documents, 5,696 were articles. Moreover, 95.769% were published in Science Citation Index Expanded (SCI-EXPANDED) indexed journals. Most were published in English (94.803%). French (1.966%), German (1.141%), and Spanish (1.053%) were the other most preferred languages. While the number of research articles on *C. trachomatis* continued to increase from 1970 to 1985, it was determined that it did not decrease below 100 articles from 1986 onwards, except in 1995 and 2004. In other words, although the number of publications appears to be irregular, it has not fallen below 80 articles per year, especially since 1980 (Graphic 1).
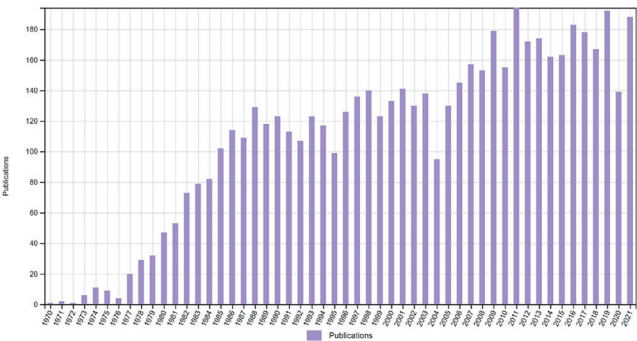
Graphic 1 - The number of articles according to the years between 1970-2021.

Table 1	Research fields	
Research Fields	**n = 5,696**	**%**
Infectious Diseases	1,894	33.251
Microbiology	1,531	26.879
Immunology	1,129	19.821
Obstetrics Gynecology	564	9.902
General Internal Medicine	402	7.058
Public Environmental Occupational Health	372	6.531
Biochemistry Molecular Biology	308	5.407
Science Technology Other Topics	226	3.968
Pharmacology Pharmacy	219	3.845
Pathology	180	3.160
Research Experimental Medicine	163	2.862
Reproductive Biology	154	2.704
Pediatrics	118	2.072
Urology Nephrology	117	2.054
Cell Biology	115	2.019
Dermatology	108	1.896
Biotechnology Applied Microbiology	94	1.650
Tropical Medicine	81	1.422
Parasitology	72	1.264
Medical Laboratory Technology	60	1.053
Oncology	56	0.983
Genetics Heredity	53	0.93
Rheumatology	51	0.895
Virology	51	0.895
Ophthalmology	48	0.843

*Showing 25 out of 82 entries: 3 record(s) (0.053%) did not contain data in the field being analyzed.

The articles were mostly from the fields of Infectious Diseases (33.251%), Microbiology (26.879%), and Immunology (19.821%) (Table 1).

The articles were from 136 countries globally. Most of the articles were from the USA (38.29%). Canada ranked 3rd. Apart from the USA and Canada, the top 7 countries were all European countries. China ranked 9th. India ranked 13th and Japan 14th. Brazil ranked 16th (Table 2).

Table 2	Top 20 countries on Chlamydia research		
Ranking	**Countries/Regions**	**n**	**%**
1	USA	2,181	38.290
2	England	635	11.148
3	Canada	318	5.583
4	Sweden	312	5.478
5	Netherlands	302	5.302
6	France	258	4.529
7	Germany	252	4.424
8	Australia	225	3.950
9	China	215	3.775
10	Denmark	159	2.791
11	Italy	150	2.633
12	Finland	123	2.159
13	India	121	2.124
14	Japan	116	2.037
15	Switzerland	107	1.879
16	Brazil	88	1.545
17	Scotland	77	1.352
18	Norway	67	1.176
19	Iran	65	1.141
20	Spain	62	1.088

*Showing 20 out of 136 entries: 24 record(s) (0.421%) did not contain data in the field being analyzed.

Nearly 51% of the studies had funding agencies. *The United States Department of Health and Human Services and the National Institutes of Health* funded most of the articles (21.752%, and 20.681%, respectively) (Table 3).

Most of the articles (n = 346, 6.074%) were published in the *Journal of Sexually Transmitted Diseases* (Table 4).

Table 3	Top 10 funding agencies on Chlamydia research		
Funding Agencies		**n**	**%**
United States Department of Health Human Services		1,239	21.752
National Institutes of Health USA		1,178	20.681
National Institute of Allergy Infectious Diseases		906	15.906
European Commission		223	3.915
National Eye Institute		120	2.107
National Institute of General Medical Sciences		87	1.527
United Kingdom Research Innovation		87	1.527
Welcome Trust		86	1.510
Medical Research Council United Kingdom		85	1.492
Eunice Kennedy Shriver National Institute of Child Health Human Development		82	1.440

*Showing 10 out of 1.690 entries: 3.370 record(s) (59.164%) did not contain data in the field being analyzed

Citing analysis

The articles were cited 147,672 times (25.93 times per article) and the H-index was 133. The number of citations has increased over the years (Graphic 2).

Table 4	Journals publishing the most articles on C. trachomatis	
Journals	**n = 5,696**	**%**
Sexually Transmitted Diseases	346	6.074
Infection And Immunity	323	5.671
Journal of Clinical Microbiology	287	5.039
Sexually Transmitted Infections	185	3.248
International Journal of STD Aids	142	2.493
Journal of Infectious Diseases	127	2.230
PloS One	114	2.001
Journal of Bacteriology	87	1.527
Genitourinary Medicine	74	1.299
American Journal of Obstetrics and Gynecology	73	1.282
Antimicrobial Agents and Chemotherapy	61	1.071
Journal of Medical Microbiology	61	1.071
BMC Infectious Diseases	57	1.001
European Journal of Clinical Microbiology Infectious Diseases	53	0.930
Diagnostic Microbiology and Infectious Disease	50	0.878
Journal of Immunology	50	0.878
Journal of Clinical Pathology	46	0.808
Obstetrics and Gynecology	46	0.808
FEMS Microbiology Letters	45	0.790
Molecular Microbiology	44	0.772
British Journal of Venereal Diseases	42	0.737
Human Reproduction	40	0.702
Fertility and Sterility	39	0.685
Clinical Infectious Diseases	38	0.667
Journal of General Microbiology	38	0.667

*Showing 25 out of 986 entries
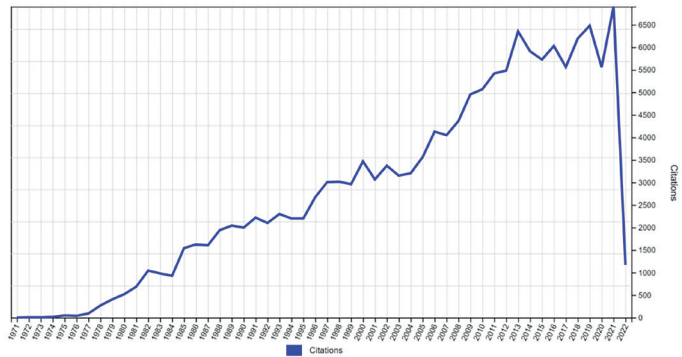
Graphic 2 - Number of citations by year.

Discussion

STDs are among the important public health problems that are increasing rapidly and in need of solutions worldwide. *C. trachomatis* is the bacteria with the highest prevalence among STDs. The USA has the highest prevalence of STDs among developed countries. *C. trachomatis* is the most common STD agent in the USA with an estimated 1.8 million cases annually [11–13]. Due to the fact that the disease poses a serious threat to the USA as well as all over the world, a treatment guide has been published by the Centers for Disease Control and Prevention (CDC) covering the approach to these patients, their treatments, preventive measures for patients and their partners, risky behaviors related to diseases, and preventive measures from diseases [3, 14, 15]. In this bibliometric analysis, it is not surprising that the USA is the country that publishes the most articles on *C. trachomatis* (38.29%) and provides the most support to research it, due to the widespread prevalence of this disease and its economic power. The USA is followed by England (11.148%). Canada ranked 3rd. Apart from the USA and Canada, the top 7 countries were all European countries. China ranked
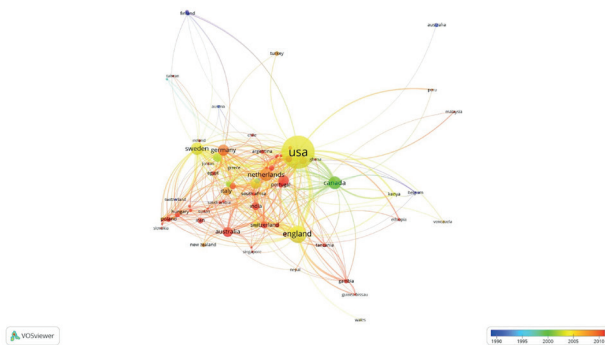
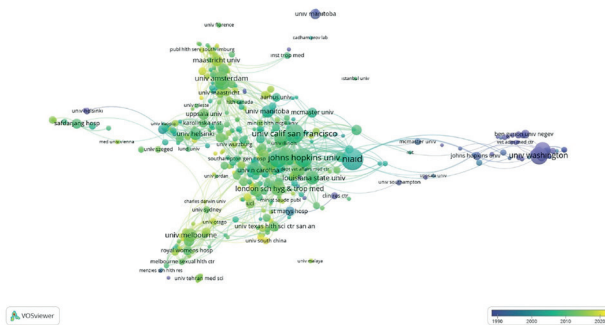**Figure 1** - International collaboration network map.

Figure 2 - Citation network visualization map among affiliations with at least 5 publications
**Collaboration is shown with lines linking institutions. Stronger cooperation is indicated by
thicker lines. Countries with a bigger circle or text size had a higher level of international
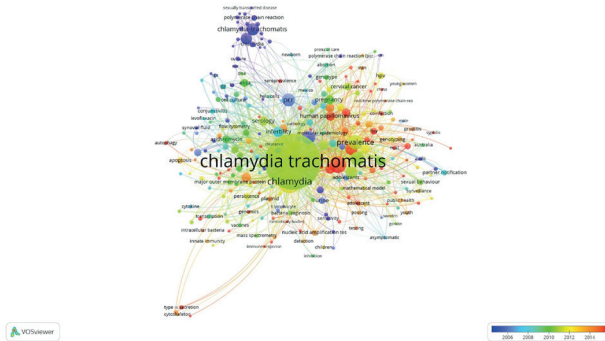cooperation.

Figure 3 - Keyword visualization map of articles with at least 5 occurrences.
**Connecting lines are indicative of occurrence relations in the articles. Keywords represented by a larger circle size or font size had a relatively higher occurrence in the articles.
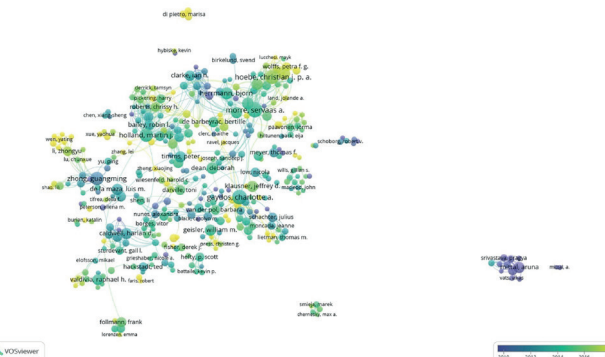

Figure 4 - Authors with at least 5 publications and 100 citations are shown on the map.
**Citations are shown by lines linking the authors. Authors with a greater circle size or font size had a higher number of citations.

9th. India ranked 13th and Japan 14th. Brazil ranked 16th. Iran, a developing country, ranked 19th. Nearly 51% of the studies had funding agencies. Most of the financial support to research article institutions was the *United States Department of Health Human Services and the National Institutes of Health USA*. In addition, it was determined that research cooperation between countries and continents was carried out comprehensively with the participation of 136 countries. To summarise in general, the USA and European countries took the lead in the number of publications.

C. trachomatis is the most reported sexually transmitted bacterial infection in the USA. According to the PubMed database search herein, it was detected that the first reports were in 1969. However, there were no similar bibliometric studies on *C. trachomatis*. In this study, 5,696 articles on *C. trachomatis* were identified and published between 1970-2021 by using the WoS database. While the number of research articles on *C. trachomatis* continued to increase from 1970 to 1985, it was determined that it did not decrease below 100 articles from 1986 onwards, except in 1995 and 2004. The increasing number of papers published and citations since its identification shows that *C. trachomatis* is still an important issue for humans and a topic of interest for researchers [16, 17].

In order to understand the biology of infectious diseases, it is necessary to examine the host-pathogen relationship and their interaction with the environment, as well as to characterize the characteristics of the agent. Using epidemiology, immunology, and genomic tools helps to examine the biology of infectious diseases. Lots of research has been done on the epidemiology, immunology, and genomics of *C. trachomatis* [11, 18–25]. In this study, it was shown that the studies on *C. trachomatis* were mostly related to the disease in the fields of Infectious Diseases, Microbiology, and Immunology.

The H-index is frequently used today to measure the quality and impact of scientific research by researchers, countries, institutions, and journals [7, 9, 10]. In a previous study [10], researchers analyzed the articles published on gonorrhea, one of the STD agents, with a similar approach. In this article, like our study, the USA ranked first in the ranking of published articles and the average H-index of the articles was determined as 117. In current study, the average H-index of the articles was determined as 133. *C. trachomatis* is the most common infectious disease, especially in the USA according to CDC case reports, and it is a public health crisis because it threatens reproductive health, especially in young women [3, 26]. Also, studies on the involvement of *C. trachomatis* in the etiology of cancer have revealed the severity of the disease; therefore, vaccine studies continue to be conducted [11, 26]. Therefore, the high number of citations of the publications may be related to the public health importance of *C. trachomatis* infection. In our study, despite the number of citations seeming to be irregular, there has been a rapid increase since the 1980s, and especially since 2010, it has not fallen below 5,000 citations per year.

The term "keyword co-occurrence analysis" describes the number of works where they co-occur and how often they do so. It may be easier for researchers to notice research hotspots and trends in a field and perhaps get the idea for a new research project if two keywords co-occur often in a single publication since they may have a tighter link to one another than other terms [27]. Figure 3 shows the keyword visualization map of articles mentioned at least five times. Accordingly, words related to the prevalence of the disease, other concomitant STDS (e.g. Human Papilloma Virus), treatment, and diagnosis were the most preferred keywords. The largest circles in Figure 3 indicate the highest number of occurrences.

Co-authorship analysis is the process of determining how closely related different products are by counting the number of papers they have in common. For instance, author co-authorship analysis exposes collaborative relationships among authors, which may assist new researchers in better understanding current collaborations and locating future colleagues in a field [27]. Figure 1 shows a map of the international cooperation network and reveals that the USA cooperates closely with European countries. The largest circle shows the largest number of publications and the thickest line the largest number of collaborations. In addition, the same colors indicate the links between the cooperating countries.

Conclusion

STDs continue to be an important public health problem almost everywhere in the world. Research on the subject is important in controlling STDs, which are increasing in frequency. As a result of this bibliometric analysis, we found that the USA is the country that publishes the most articles and supports the most research on *C. trachomatis*. It was observed that the number of articles published on *C. trachomatis* increased over the years and the citations to the articles increased rapidly. Our study showed that although the number of publications from developed countries increased, the number of publications from developing and underdeveloped countries was low. Since *C. trachomatis* continues to be a growing global public health problem, it is necessary to support all countries, especially those countries where the number of cases is increasing, scientifically on issues such as prevention, spread, and vaccination studies.

Limitations

In this study, only the WOS database was selected as the bibliometric database and only articles were selected as the document type. Since other databases were not selected, this study may not reflect the entire scientific literature. This may have caused a bias. Different databases and comparisons can be made in the future. This is only an initial bibliometric study on *C. trachomatis*. Therefore, our study is valuable. It can also guide the next bibliometric researchers.

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Evaluation of the shock index and different scores in predicting the mortality in upper gastrointestinal bleeding

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Abstract

The upper gastrointestinal bleeding (UGIB) is one of the most common causes of the adult emergency admissions. In the UGIB, scoring systems are used to predict the need for clinical intervention or provide insight into prognosis. In this study, we investigated the potential of the shock index to predict 30 day-mortality in comparison with GBS, Rockall Score and AIMS65 score.

Material and methods: This is a retrospective and single-center study conducted in the emergency department. The study included the patients, who admitted to the emergency service due to GIS bleeding complaints, with confirmed diagnosis of upper bleeding, who had endoscopy. The data of the admissions between 01.01.2016 and 01.01.2020 have been used.

Results: There were a total of 141 patients with upper gastrointestinal bleeding. The number of women was 34 (24.1%) and man was 107 (75.9%). The median value of the shock index was 1.6 (1.5 to 1.8). Glasgow Blatchford score median value was 8.0 (6.0 to 11.0). Rockall score median value was 4.0 (2.0 to 5.0). The area under the curve of the receiver operating characteristic curve (AUC ROC) values of Glasgow Blatchford and Rockall score were 0.63, 0.79 (respectively) for short-term mortality.

Conclusion: We have found that the shock index failed to predict short-term mortality in patients with UGIB. Until more powerful new scoring systems are developed, the Glasow Blatchford and Rockall scoring systems are effective for UGIB patients.

Key words: Glasgow Blatchford bleeding score, Rockall score, AIMS65 score, shock index

Introduction

The upper gastrointestinal bleeding (UGIB) refers to the intraluminal bleeding between the upper esophageal sphincter and Treitz's ligament of proximal duodenum. It was reported to be responsible for 85% of upper GI bleeding and to have an annual incidence of approximately 67/100.000 [1]. Common causes of UGIB are peptic ulcer (55-74%), esophageal varices (5-14%), mallory-weis tears (2-7%), tumors (2-5%) and other malformations like arteriovenous (2-3%) [2]. Peptic ulcer disease including gastric, duodenal, esophageal and stomach ulcers is among the most common causes for the UGIB [3]. Acute upper gastrointestinal (GI) bleeding is one of the most common causes of the adult emergency admissions. Mainly, endoscopic and angiographic methods are used in diagnosis and treatment. It has high mortality rate [4]. This rate is 8% in patients below 60 years of age,

while it is 13% in patients above 60 years of age. The admission and clinical course of the patients with upper gastrointestinal bleeding include various stages from a sub-clinical asymptomatic bleeding to abundant bleeding, from chronic anemia to acute hypovolemic shock. During the evaluation, the medical history search, physical examination, diagnosis and treatment options should be initiated concurrently, and according to the clinical data, the patient should be resuscitated and stabilized [5,6].

In the UGIB evaluation, scoring systems are used to predict the need for clinical intervention or provide insight into prognosis. The most commonly used scoring systems are Glasgow Blatchford Bleeding Score (GBS) and Rockall Score [7]. GBS is a scoring system applied by using the basic clinical and laboratory variables without use of any endoscopic data. It is evaluated to predict the need for clinical intervention [8]. Rockall score has pre-

endoscopic and endoscopic components and was developed to provide insight into mortality [9]. On the other hand, AIMS65 scoring system was developed to determine the prognosis of the patients with UGIB. Compared to the other scores, AIMS65 has the advantage of being simple to apply in case of an emergency [10,11].

The Shock Index was developed to predict blood transfusion and prognosis in the patients with trauma. Past studies have demonstrated that Shock Index predicted the need for endoscopic intervention [12]. It was suggested to include pre-shock index in the pre-endoscopic scoring systems [13].

In this study, we investigated the potential of the shock index to predict 30 day-mortality in comparison with GBS, Rockall Score and AIMS65 score.

Material and methods

This is a retrospective and single-center study conducted in the emergency department of the University of Health Sciences, İstanbul Şişli Hamidiye Etfal Training and Research Hospital. The data of the admissions between 01.01.2016 and 01.01.2020 have been used. Approval was taken from the Ethics Committee of the Hospital (no 191-02/12/2020).

| Table 1 | Rockall risk scoring system |

Parameters	Score
A. Age	
≥ 80	2
60-79	1
< 60	0
B. Shock	
Hypotension, systolic blood pressure <100 mmHg	2
Tachycardia, systolic blood pressure ≥ 100 mmHg and heart rate > 100/min.	1
No shock, systolic blood pressure ≥ 100 mmHg and heart rate < 100/min.	0
C. Comorbid Disease	
Kidney failure, liver failure, common malignity	3
Cardiac failure, ischemic heart disease, other major comorbid disease	2
No major comorbid disease	0
D. Endoscopic Diagnosis	
Upper gastrointestinal cancer	2
All the other diagnoses	1
No lesion, no new bleeding finding, Mallory-Weiss lesion	0
E. Major New Bleeding Finding	
Upper gastrointestinal system bleeding, adherent clot, visibly or gushingly bleeding vein	2
Normal or only dark point lesion	0
Pre-endoscopy score: A+B+C. Total score: A+B+C+D+E. Minimum score: 0 Maximum score: 11	

| Table 2 | Glasgow-Blatchford scoring |

Parameters	Score
A. Blood urea nitrogen(mg/dL)	
≥ 70	6
≥28- < 70	4
≥22,4- < 28	3
≥18,2- < 22,4	2
<18,2	0
B. Hemoglobin (g/dL)	
< 10 g/dL in male and female	6
10- < 12 male, only	3
10- < 12 female, 12- <13 male	1
≥ 12 female, ≥13 male	0
C. Systolic Blood Pressure (mmHg)	
<90	3
90-99	2
100-109	1
≥ 110	0
D. Other markers	
Cardiac failure	2
Liver disease	2
Presentation with Syncope	2
Presentation with Melena	1
Heart rate ≥ 100/min.	1
Total score: A+B+C+D Minimum score: 0 Maximum score: 23	

| Table 3 | AIMS65 scoring system |

Risk factor	Score
Albumin<3.0 mg/dL	1
INR > 1.5	1
Mental status change	1
Systolik blood pressure < 90 mmHg	1
Age > 65	1
Minimum score:0 Maximum score:5	

The study included the patients, who admitted to the emergency service due to UGIB bleeding complaints, with confirmed diagnosis of upper bleeding, who had endoscopy. The patients who are below 18 years of age, pregnant, have lower upper GI bleeding and incomplete data were excluded.

The admission complaints, demographic characteristics, comorbid diseases, laboratory values of the patients, drugs used by them, their vital parameters and endoscopy results were searched through the hospital's electronic patient recording system. Based on the data obtained, shock index (heart rate divided by systolic blood pressure), Rockall (Table 1), Glasgow Blatchford (Table 2) and AIMS65 (Table 3) Scores were calculated. 30-day mortality results were taken from the hospital's electronic information system or national death notification system.

Table 4 Baseline characteristics of the enrolled patients and their comparison between the survivor and non-survivor groups

Variables	Total n = 145	Survivor n = 99 (70%)	Non-Survivor n = 42 (30%)	P
Age (25th-75th percentiles)	56.0 (41.0 to71.0)	49.0 (34.5 to 65.5)	69.5 (57.5 to 81.8)	0.001
Gender				
Female (%)	34 (24.1)	21 (21.2)	13 (31.0)	0.307
Male (%)	107 (75.9)	78 (78.8)	29 (69.0)	
Symptoms				
Syncope (%)	5 (3.5)	2 (2.0)	3 (7.1)	0.314
Hematemesis (%)	31 (22.0)	16 (16.2)	15 (35.7)	0.019
Hematochezia (%)	3 (2.1)	2 (2.0)	1 (2.4)	1.000
Melena (%)	83 (58.9)	63 (63.6)	20 (47.6)	0.114
Other (%)	17 (12.1)	15 (15.2)	2 (4.8)	0.147
Comorbidities				
History of gastrointestinal bleeding (%)	9 (6.4)	5 (5.1)	4 (9.5)	0.537
Heart disease (%)	7 (5.0)	4 (4.0)	3 (7.1)	0.725
Malignancy (%)	3 (2.1)	2 (2.0)	1 (2.4)	1.000
Cirrhosis (%)	22 (15.6)	10 (10.1)	12 (28.6)	0.012
Hypertension (%)	28 (19.9)	17 (17.2)	11 (26.2)	0.319
Chronic obstructive pulmonary disease (%)	12 (8.5)	10 (10.1)	2 (4.8)	0.478
Diabetes mellitus (%)	22 (15.6)	13 (13.1)	9 (21.4)	0.323
Vital parameters				
Systolic blood pressure (mm/hg) (25th to 75th percentiles)	110.0 (95.0 to 120.0)	110.0 (99.5 to 120.0)	106.5 (90.2 to 121.5)	0.517
Diastolic blood pressure (mm/hg) (25th to 75th percentiles)	69.0 (60.0 to 80.0)	70.0 (60.0 to 80.0)	63.5 (53.2 to 75.2)	0.29
Pulse rate	91.0 (81.0 to 99.0)	88.0 (81.0 to 96.0)	92.5 (81.2 to 100.0)	0.279
Mean arterial pressure (mm/hg) (25th to 75th percentiles)	82.7 (70.0 to 91.7)	83.0 (73.3 to 90.8)	77.3 (67.4 to 92.5)	0.311
Laboratory parameters				
International Normalized Ratio (25th to 75th percentiles)	1.1 (1.1 to 1.3)	1.1 (1.0 to 1.2)	1.2 (1.1 to 1.4)	0.001
Hemoglobin (g/dL) (25th to 75th percentiles)	9.1 (7.6 to 11.0)	9.2 (8.0 to 11.0)	8.1 (7.2 to 9.8)	0.039
Albumin (g/dL) (25th to 75th percentiles)	3.3 (3.0 to 3.8)	3.5 (3.1 to 3.8)	3.0 (2.4 to 3.4)	0.001
Scores				
Glasgow-Blatchford Scoring (25th to 75th percentiles)	8.0 (6.0 to 11.0)	8.0 (4.5 to 9.5)	9.0 (6.2 to 12.8)	0.013
Rockall Scoring system (25th to 75th percentiles)	4.0 (2.0 to 5.0)	3.0 (1.5 to 4.0)	5.0 (5.0 to 6.8)	0.001
Aims65 Scoring system (25th to 75th percentiles)	1 (1.0 to 2.0)	1 (1.0 to 3.0)	1 (1.0 to 2.0)	0.829
Shock Index (25th to 75th percentiles)	1.6 (1.5 to 1.8)	1.6 (1.5 to 1.8)	1.6 (1.5 to 1.9)	0.551

Table 5 The area under the receiver operating characteristic curve values

Scores	Cut-off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
Rockall Scoring System	5	78.57%	75.76%	57.89%	89.29%	0.79
Glasgow-Blatchford Scoring	11	40.48%	80.81%	47.22%	76.19%	0.63
Aims65 Scoring system	2	92.93%	14.29%	71.88%	46.15%	0.49
Shock index	1.6	49.49%	54.76%	72.06%	31.51%	0.47

Abbreviation; AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value.

In the statistical analysis, SPSS 22.0 for Windows program was used. Distribution of data was analyzed by Shapiro-Wilk test. Descriptive statistics using numbers and percentages were used for the categorical data. The mean, standard deviation, median were used for the numerical variables. Since they do not meet the normal distribution requirement, the Numerical variables were compared to Mann Whitney U Test. The parametric test requirement was not fulfilled between the numerical variables. Spearman Correlation Analysis was performed. Cut off value was investigated by receiver operating characteristic curve (ROC) Analysis. Statistical alpha significance level was accepted as p<0,05.

Results

Total 184 patients were evaluated in the study. 43 patients were excluded due to insufficient data. The final study included 141 patients. Among the patients, 24.1% were female and 75.9% were male. The mean age of the patients was 56 (41.0 to 71.0). In our study cohort, mortality was 30%. The bleeding causes of the patients in our study were due to varicose causes in 8 (5.6%) patients and non-varicose causes (peptic ulcer 113 (80.1 %), tumors 18 (12.7 %), mallory-weis tears 2 (1.4 %)) in 133 patients.

The most common comorbidity was hypertension with the rate of 19.9%. It was followed by diabetes mellitus (15.6%) and liver cirrhosis (15.6%). There was no significant difference
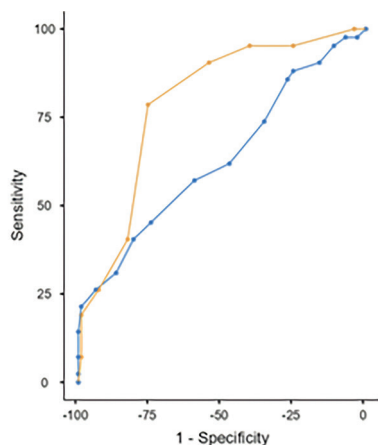
Figure 1 - The receiver operating characteristic curve of Glasgow Blatchford and Rockall

between the groups in comorbid diseases. In admissions, the most common symptom was observed to be melena with the rate of 58.9%. The second most common symptom was hematemesis (22.0%). Melena also did not cause a significant difference between the groups, but the hematemesis ratio was significantly higher in the survivor group (35.7%) (p= 0.019). Among the vital parameters, the systolic blood pressure median value was 110.0 mm/hg (95.0-120.0). Albumin (g/dL) values were significantly lower in the non-survivor group with 3.0 g/dL (2.4 to 3.4) (p=0.001). Glasgow Blatchford score median value was 8.0 (6.0 to 11.0). It was significantly higher in the non-survivor group with 9.0 (6.2 to 12.8) p= 0.013. Rockall score median value was 4.0 (2.0 to 5.0). It was 5.0 (5.0 to 6.8) in the non-survivor group, which was statistically significant (p=0.001). AIMS65 score median value was 1 (1.0-2.0). No significant difference was observed between the groups. Shock index median value was 1.6 (1.5 to 1.8) and it caused no significant difference between the groups (p=0.551). Baseline characteristics of the enrolled patients and their comparison between the survivor and non-survivor groups are presented in Table 4. The area under the curve of the receiver operating characteristic curve (AUC ROC) values of Glasgow Blatchford and Rockall score were 0.63, 0.79 (respectively) for short term mortality. The maximum Cut-off point of Glasgow Blatchford score in predicting prognosis was 11 points. The maximum Cut-off point of Rockall score in predicting prognosis was 5 and it had a sensitivity of 78.57%, 75.76% specificity, a positive predictive value of 57.89% and negative predictive value of 89.29% (Table 5).

Discussion

In our study, we investigated 145 patients who admitted to emergency department due to upper GI bleeding complaints, diagnosed with UGIB and had endoscopy. The relation between the short-term mortality and Glasgow Blatchford, Rockall, AIMS65 scores, shock index of the patients was investigated. Glasgow Blatchford and Rockall scores have significantly predicted the short-term mortality of the patients. No significant relation was observed between AIMS65, shock index and the short-term mortality of the patients.

The risk of mortality and recurrent bleeding is high in the UGIB [14]. Early diagnosis and triage of the patients increase the care effectivity and help the clinicians in taking the outcome decision (referring to service, taking into intensive care unit or discharge from emergency department) Besides, it is indicative for early discharge of low-risk patients and safe outpatient treatment. Any scoring to be used in the emergency department should be easily calculated and predict, with high accuracy, the

result desired to be predicted or exclude it [15].

Glasgow-Blatchford score was provided in 1997 upon evaluation of the Scotch population. It is commonly used for the UGIB and has been validated by many studies. It uses medical history of the patient, Vital parameters and hemoglobin results [16]. It is not based on the endoscopy result. In a study carried out on 3012 patients, Stanlet at el reported that Glasgow Blatchford score has high accuracy in predicting hospital intervention and survey [17]. In our study, GBS significantly predicted mortality. GBS scores the patient's laboratory parameter and comorbid diseases. This is an advantage of this score because comorbid diseases are one of the most important factors that affect prognosis in the UGIB. The comorbid diseases are known to adversely affect tissue oxygenation, wound healing and coagulation mechanism [18]. The majority of deaths in patients over 60 years of age occur in those with serious comorbid diseases such as serious heart disease, cancer, kidney failure. Another important factor for monitoring, prognosis and treatment management of the patients who admitted due to UGIB symptoms is the hemoglobin value obtained from the tests during the first admission of the patient [19]. The severity of the bleeding, pre-bleeding anemia and prolongation of hospital admission have effect on the admission hemoglobin level [20]. Since GBS scores the hemoglobin value that has effect on comorbid diseases and mortality, we suggest to use it in the patients with UGIB.

RS is commonly used in scoring the patients with upper GI bleeding. RS needs endoscopic data for calculation [21]. This is a disadvantage of this score. Taslıdere et al suggested quick SOFA scoring instead of RS since RS predicts the patient's survey, but there is no endoscopy intervention in some emergency departments [22]. In our study, we detected that RS significantly predicted short term mortality. Considering the necessity of endoscopy results in calculation of the score, we note that this makes it difficult to use this score in emergency departments.

Shock index is a good indicator of the fluid loss and left ventricular dysfunction [23]. It is recommended in critical patient monitoring. Saffouri et al reported that Shock Index had low accuracy in predicting the AUC ROC value, post UGIB major clinical end points compared to the existing pre-endoscopy scores. They concluded that Shock Index was not clinically useful in predicting the results in UGIB [13]. In our study, shock index failed to predict survey of the patients as well. We believe that this is associated with the partially good heart rate and systolic blood pressure results, which are among the vital parameters, of the patients during admission. In the upper GI bleeding admissions, the most common complaint is melena. Since the patients immediately admitted to hospital after occurrence of melena, many patients have vitals intact at the time of admission. Since the change in vitals will occur not at the time of admission, but after continuity of bleeding for some time, we believe that the shock index and mean arterial pressure (MAP) at the time of admission will not predict mortality with sufficient accuracy.

AIMS65 was developed to predict the hospitalization time, survey, and cost for the patients with acute UGIB. It is based on the age of the patient, the systolic blood pressure, mental status and laboratory data [24]. Various studies have shown that AIMS65 predicts the mortality in UGIB. However, in our study, it did not achieve this. This may be associated with the fact that at the time of admission, the blood parameters such as INR and albumin and the systolic blood pressure values did not change to an extent to predict the mortality.

In our study, we detected the mortality rate as (n=42) 29.8%. Despite the developments in medical and endoscopic

treatments, the mortality rate in UGIB is 5-15%. The mortality rate was reported as 1.8% in a study carried out by Bryant et al, as 4.8% in a study conducted by Stanley et al, while Dicu et al reported the mortality rate as 18.7% in a study they carried out [25–27]. In our study, we calculated the mortality rate higher than those in the studies of Bryant et al, Stanley et al and Dicu et al. The high mortality rate may be associated with the fact that our patient group had a low hemoglobin level according to literature studies [28]. This patient group represents the group that has high value in scoring of upper GI bleeding and is predicted to have higher mortality compared to the other groups. Moreover, we believe that the other factor that affect this result is the analysis of a smaller number of patients than the other studies [25–27].

Limitation

The limitation of our study is that it is a retrospective, single-center study and the number of the patients included in the study is low. One of the reasons of this is that the albumin test request calculated under AIMS65 score is not among the routine tests requested in the emergency department. The second disadvantage is that our patient cohort consisted of the patients that had endoscopy. This patient group is known to have high mortality in upper GI bleeding. Additionally, our patients had a high rate of comorbid diseases. In our opinion, we concluded mortality rates higher than those in the literature for this reason.

Conclusion

In our study, we found that the shock index and AIMS65 failed to predict short-term mortality in patients with UGIB. Until new scoring systems that are more useful are developed, the Glagow Blatchford and Rockall scoring systems are effective for UGIB patients.

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Accessing disease information via smartphones: A senile macular degeneration investigation in over-65-year-old patients

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Abstract

Aim: To investigate how frequently over-65-year-old senile macular degeneration (SMD) patients use smartphones and the Internet for disease information, as well as to evaluate website readability and information quality.

Material and methods: There were 400 SMD patients who were followed up on at a retina clinic. SMD was defined as the presence of >5 hard drusen or >1 125 μm soft drusen in the macula, and scar or subretinal fluid compatible with SMD. Face-to-face interviews were used to gather demographic data, including age, gender, educational level, smartphone use, and whether patients researched SMD in Google, YouTube, or other websites. Two experienced ophthalmologists blindly evaluated 32 Google websites and 37 YouTube videos using Ateşman and Bezirci-Yilmaz readability formulas, as well as JAMA and DISCERN indexes.

Results: The average age of the patients was 75.0±6.6 years, and 37.3% owned a smartphone. Legally blind patients (40.5%) used smartphones less frequently for Internet searches (p<0.001). As educational level increased, patients became more active in searching diseases electronically. The JAMA score in texts was 0.8±0.4, while it was 0.7±0.6 in videos (p=0.654). The DISCERN score was 35.1±6.2 and 33.2±10.3 in texts and videos, respectively (p=0.347). Smartphone use decreased with age (OR=0.896, 95% CI: 0.859-0.934), but not with legal blindness (OR=0.756, 95% CI: 0.458-1.245).

Conclusion: Improved quality and reliability of internet websites and video information, more emphasis on informative audio recordings and videos for people with low vision, and easily readable Internet websites could all have a positive impact on patients' adherence to treatment.

Key words: google, information, internet, readability, senile macular degeneration, smartphones, youtube videos

Introduction

Over the last decade, smartphones, personal computers, laptops, tablets, and other information and communication technology-related devices have grown in popularity and use. This has allowed people to accomplish a variety of tasks more quickly and safely [1,2]. Indeed, studies on eliminating health disparities are being conducted as a result of these innovations [3]. While the devices used in the health system were previously designed to be used by health professionals, technological advancements have brought the use of technology to the forefront in order to obtain information about people's health and conduct necessary research [4].

The elderly population in the USA is expected to exceed 72 million by 2030, and the global elderly population is expected to reach 1.6 billion by 2050, implying that health problems will become more prevalent as the population ages [5,7]. A significant proportion of the elderly population is gradually embracing technology, and smartphone use among the elderly is on the rise [8]. It is anticipated that the elderly, who are thought to have difficulty accessing health services, will attempt to obtain health information via smartphones in the future. Given the increasing use

of smartphones, the potential for internet use to improve the health of older adults is quite high, particularly given projected population growth.

Many studies have been conducted to determine the readability of text on websites that appear on the screen based on Google searches [9,10], which patients rely on as the most popular internet search engine for information [11]. Moreover, YouTube, the second most visited website on the Internet, is gaining traction as an information source [12]. In 2020, 2.1 billion users watched over one billion hours of video on YouTube, and more than 500 hours of new videos were uploaded every minute [13]. Parallel to all of this, 74% of adults in the USA use YouTube [14], with its popularity owing to the fact that it is free to use on devices such as laptops and smartphones, with the latter accounting for 70% of all visits [15]. Matter of fact, numerous ophthalmology studies analyzing YouTube videos have been published [16,17].

This study aimed to determine how frequently senile macular degeneration (SMD) patients over the age of 65 use smartphones and the Internet for disease information, as well as which websites they frequently use as a source of information. It also aimed to investigate the readability and information quality of Internet websites, as well as to evaluate the data in terms of demographics such as age, gender, educational level, and frequency of smartphone use.

Material and methods
Study design and data collection

This study followed the ethical principles outlined in the Declaration of Helsinki and was approved by the Afyonkarahisar Health Sciences University Ethics Committee Institutional Review Board, with the approval code and date 2022/315. It included SMD patients who were being monitored in the retina clinic of a tertiary hospital by two experienced ophthalmologists (MD and IEA). SMD was defined as the presence of >5 hard drusen or >1 125 μm soft drusen in the macula, as well as scar or subretinal fluid compatible with SMD.

Face-to-face interviews were used to collect data about the patients' age, gender, education level, and smartphone use when they came in for examination. Data was also collected about whether or not patients searched the Internet for SMD information and, if so, which Google, YouTube, or other websites they visited

Inclusion and exclusion requirements

The inclusion criteria were that the patients' cognitive level be at a level where they could come to the ophthalmology clinic independently or with a relative and be examined and answer the questions asked. Those with severe dementia and difficulties understanding the questions were barred from participating in the study. SMD patients with a visual acuity of <20/200 in the well-sighted eye were regarded legally blind [18].

Readability formulas

The Ateşman readability formula takes into account factors such as the number of words in sentences and the number of syllables in words before calculating a score [19]. Scores of a) 90-100 indicate that the text is readable with as little as four years of education, b) 80-89 between 5th-6th grades, c) 70-79 between 7th-8th grades, d) 60-69 between 9th-10th grades, e) 50-59 between 11th-12th grades, f) 40-49 between 13th-14th grades, and g) 30-39 indicate that the text is readable with 16th grade education. The Bezirci-Yilmaz formula, on the other hand,

directly determines which education level the text is readable for [20]. The text is readable for primary school if 1-8 points are present, high school if 9-12 points are present, and undergraduate education if 12-16 points are present.

Internet website readability level assessment

The study included the first 50 websites that appeared on the screen after the search term "senile macular degeneration" was entered into the Google search engine on July 01, 2022. Duplicate websites or websites with information in a different language were not studied. The Ateşman [19] and Bezirci-Yilmaz [20] readability formulas, which are two distinct readability formulas with established validity and reliability in Turkish, were used to assess the information on 32 websites.

YouTube video information quality assessment

The first 50 videos that appeared on the screen after entering "SMD" into the YouTube search bar were included in the study. Again, duplicate videos and content broadcast in a different language were excluded from the study, leaving 37 videos for assessment. Two experienced ophthalmologists (MD and IEA) blindly evaluated the first 32 Google internet websites and 37 YouTube videos using the Journal of the American Medical Association (JAMA) [21] and DISCERN [22] indexes, which are used to measure the quality of health-related information on the Internet. The following parameters were investigated: a) broadcasting duration (the number of days the videos have been broadcast since their upload), b) views count, c) viewing rate (the number of views divided by the broadcasting duration), d) video duration, and e) likes and comments count.

JAMA index

The JAMA index is used to evaluate health-related website content. This index calculates a general score by assigning 0 or 1 points for authorship, bibliography, patent rights, and timeliness.

DISCERN index

The DISCERN scoring system was developed to objectively assess the quality of health-related publications by patients, physicians, and internet information providers. It contains a clear statement of the information's objectives, a list of sources, balanced and unbiased information, and an overall scoring table on the advantages and disadvantages of treatments (Table 1). Each question is assigned a score of 0 to 5, and the total DISCERN score ranges from 16 to 80. A score of 63-80 is considered excellent, 51-62 good, 39-50 moderate, 27-38 poor, and 16-26 very poor.

Data analysis

SPSS (PAWS Statistics, Version 18, Chicago IL) was used to conduct the statistical analysis. Categorical variables are shown as percentages and frequencies in descriptive statistics results, while continuous variables are shown as mean and standard deviation. The chi-square test was used to compare categorical variables. The conformity of continuous variables to normal distribution was assessed using skewness and kurtosis values, and it was discovered that they exhibited normal distribution characteristics. To compare normally distributed continuous variables, the Student's t test was employed. The inter-rater reliability analysis employed the intraclass correlation

Table 1	The DISCERN scoring system	
1.	Are the objectives of the information provided clear?	1-5
2.	Does the information provided achieve its objectives?	1-5
3.	Is the information provided relevant to the objectives?	1-5
4.	Is it clear which sources of information were used to provide the information?	1-5
5.	Is it clear when the information used or reported in the publication was produced?	1-5
6.	Is the information provided balanced and unbiased?	1-5
7.	Does it contain details of information sources?	1-5
8.	Does the information given refer to areas of uncertainty?	1-5
9.	Is it explained how each treatment works?	1-5
10.	Are the benefits of each treatment explained?	1-5
11.	Are the risks and side effects of each treatment explained?	1-5
12.	Is it explained what will happen if no treatment is given?	1-5
13.	Is the impact of treatment options on overall quality of life explained?	1-5
14.	Is it explained that there may be more than one possible treatment option?	1-5
15.	Does the information provided provide support for joint decision making?	1-5
16.	Assess the overall quality of the publication based on the responses to all questions.	1-5

coefficient (ICC). An excellent fit was defined as an ICC value greater than 0.80. Comparisons were made in the statistical analysis using the evaluators' average scores. After statistical analysis, the Multinominal Logistic Regression test was used to evaluate variables and confounding variables that revealed statistically significant differences. Logistic regression results are presented as odds ratio (OR) and 95% confidence interval (95% CI). Statistical significance level was accepted as $p<0.05$.

Results

There were 194 (48.5%) females and 206 (51.6%) males. The mean age was 75.0 ± 6.6 years. 64% of the participants had only completed primary school. 40.5% were legally blind. There were 37.3% of the smartphone users. 11.8% of participants used smartphones to search for SMD-related information, with 9% using Google to search for Internet websites and 2.8% watching YouTube videos (Table 2).

Table 2	Demographic characteristics of the patients.
Parameters	n (%)
Educational level	
Illiterate	71 (17.7)
Primary school	256 (64.0)
High school	33 (8.3)
University	40 (10.0)
Legal blindness	
Absent	238 (59.5)
Present	162 (40.5)
Smartphone use	
No	251 (62.7)
Yes	149 (37.3)
Information source	
Never searched	353 (88.2)
Google	36 (9.0)
YouTube	11 (2.8)
Total	400 (100.0)

n=Number of participants, %=Percent

Legally blind SMD patients had significantly lower frequency of smartphone use and a history of SMD-related Internet searching ($p<0.001$). Patients were more active in searching their disease on the Internet as their educational level increased (Table 3).

The readability level of 32 SMD-related Internet websites was 11-12, with an average of 54.1 ± 6.8 points, according to the Ateşman readability formula. The Bezirci-Yilmaz formula determined that the websites were readable with an education level of 11-12 years, corresponding to an average of 11.7 ± 2.1 points. The website written in the easiest to read format was readable after 7 years of education, while the website written in the most difficult to read format was readable after 17 years of education.

The average duration for SMD-related YouTube videos was 453 ± 547, with 136 ± 317 likes and 5.4 ± 12.7 comments. The average broadcasting duration, view count, and viewing rate were 1548 ± 1011 days, 21079 ± 51841, and 17.8 ± 40.2, respectively.

The correlation between the JAMA (ICC=0.824) and DISCERN (ICC=0.994) scores for the websites and YouTube videos of both ophthalmologists was determined to be "excellent." The JAMA score in written text on websites was 0.8 ± 0.4, while in YouTube videos it was 0.7 ± 0.6 ($p=0.654$). The DISCERN score in written text on websites was 35.1 ± 6.2 points and 33.2 ± 10.3 points in YouTube videos ($p=0.347$). Longer videos received high JAMA and DISCERN index scores, and factors such as likes, comments, and view count were found to be unrelated to the JAMA and DISCERN scores.

The logistic regression analysis revealed that smartphone use decreased with age (OR=0.896, 95% CI: 0.859-0.934). Legal blindness, on the other hand, was not associated with smartphone use (OR=0.756, 95% CI: 0.458-1.245). As educational levels rose, so did the use of smartphones (Table 4).

Discussion

Access to information in medicine has made significant progress since the 1990s, thanks to advances in information technology [23]. In fact, the term "e-health" first appeared at that time, and access to health-related information in the electronic environment has grown in popularity ever since [24]. Several studies on the use of smart technology products show that the elderly are becoming more adaptable to changing technology [25,26].

Furthermore, the aging population and widespread use of smartphones are widely acknowledged to be becoming increasingly important in general society. The elderly's use of smartphones and similar devices increases their possibility of benefiting from smartphones in getting disease information, given that they are more likely to experience many health problems as they age. In medicine, it is a critical issue based on health literacy that the elderly population, which is bombarded with information from a variety of sources, particularly the physicians they are examined by, access accurate information about their diseases while their treatments continue. After all, research on the use of smartphones in this field has been conducted in order to assess treatment compliance and symptoms, to aid in treatment management, and to determine health literacy [27,28].

The current study has a high power with 400 SMD patients, and the findings can be generalized globally. Smartphones were used by 37.3% of the patients, and 11.8% searched the Internet for SMD-related information. While 9% of the patients used Google, 2.8% searched the Internet and attempted to obtain SMD-related information via YouTube videos. A small

Legal blindness and educational status in relation to smartphone use and Internet search

Legal blindness		Educational level				Total	P value
		Illiterate n, (%)	Primary school n, (%)	High school n, (%)	University n, (%)	n, (%)	
				Smartphone use			
No	No	27 (84.4)	93 (61.2)	4 (18.2)	7 (21.9)	131 (55.0)	<0.001
	Yes	5 (15.6)	59 (38.8)	18 (81.8)	25 (78.1)	107 (45.0)	
Yes	No	36 (92.3)	73 (70.2)	6 (54.5)	5 (62.5)	120 (74.1)	0.015
	Yes	3 (7.7)	31 (29.8)	5 (45.5)	3 (37.5)	42 (25.9)	
			Senile macular degeneration-related Internet search				
No	No	31 (96.9)	139 (91.4)	16 (72.7)	15 (46.9)	201 (84.5)	<0.001
	Yes	1 (3.1)	13 (8.6)	6 (27.3)	17 (53.1)	37 (15.5)	
Yes	No	39 (100.0)	100 (96.2)	8 (72.7)	5 (62.5)	152 (93.8)	<0.001
	Yes	0 (0.0)	4 (3.8)	3 (27.3)	3 (37.5)	10 (6.2)	

n=Number of participants, %=Percent

Logistic regression analysis of smartphone use by age, legal blindness, and educational level.

Parameters	B	S.E.	Wald	P value	OR	95% CI for EXP (B)	
						Lower	Upper
Age (Years)	-0.110	0.021	27.070	0.000	0.896	0.859	0.934
Legal blindness present (Reference: no legal blindness)	-0.280	0.255	1.209	0.272	0.756	0.458	1.245
Educational level (Reference: illiterate)			35.762	0.000			
Primary school	1.314	0.412	10.175	0.001	3.721	1.660	8.342
High school	2.593	0.554	21.915	0.000	13.365	4.514	39.572
University	2.741	0.533	26.412	0.000	15.499	5.449	44.080
Constant	7.860	1.576	24.867	0.000	2590.587		

proportion of SMD patients used the Internet to learn about their diseases.

As patients' educational levels rise, so does their use of smartphones, and they become more active in searching their disease on the Internet. Expectedly, SMD patients with legal blindness had significantly lower rates of smartphone use and a history of searching their disease on the Internet. In contrast, the logistic regression analysis revealed that legal blindness was unrelated to smartphone use, and that smartphone use increased gradually as education level increased. Even if they were legally blind, patients with a high educational level were just as effective at using smartphones as those with good vision but low education. These patients appeared to benefit from smartphones, which allow them to listen to a text aloud while also enlarging the image to some extent. After all, education seems to be a powerful tool for overcoming a wide range of challenges, including legal blindness.

When the readability level of 32 SMD-related Internet websites was assessed, the Ateşman readability formula revealed that it required an education level of 11th to 12th grade with an average of 54.1±6.8 points. Furthermore, Internet websites were readable with an education level of 11-12 years, corresponding to an average of 11.7±2.1 points in the Bezirci-Yilmaz formula. In one study, the readability level and information quality of 12 frequently clicked websites containing SMD information were evaluated using JAMA scoring, revealing that the websites were readable with 11-12 years of education and the information quality was low [29]. Despite being for Internet websites in a different language, these results were comparable to ours. The JAMA and DISCERN scores for the current study also indicated low quality information, putting it in line with the literature.

Longer videos had higher JAMA and DISCERN index scores, and it was revealed that factors such as the number of likes and comments, as well as view count, were unrelated to the JAMA and DISCERN index scores. This demonstrated that expert-approved videos containing more accurate information were unrelated to patient-favored videos. Patients are unable to select videos with more accurate information. Thus, it appears that patients are very likely to receive incorrect information since broadcasting on YouTube does not require expertise.

To our knowledge, no research on SMD videos on YouTube has been published. We can assume that many people use YouTube to learn more about this particular disease, based on the fact that the videos in the current study were viewed by an average of 21079±51840 people. Despite this, the JAMA and DISCERN scores indicated that the information in these videos was of poor quality. As a result, both text on Internet websites and YouTube videos may not be regarded as platforms where patients could obtain healthy and reliable information about SMD. Even if adults over the age of 65 with SMD use these websites as a source of information infrequently today, we anticipate that smartphone use among the elderly will increase in the future. Conducting relevant studies in this area, as well as preparing high-quality videos and written texts for the public's access to healthy and reliable information by various non-governmental medical organizations, particularly ophthalmological societies, could be beneficial in increasing patients' adherence to treatment.

Medicine can no longer be limited to simply examining patients and providing disease information. Depending on where they practice, physicians should be partly or entirely responsible for providing accurate information to patients through medical associations or individually through the Internet. Otherwise,

since no specialized knowledge is required to publish videos or prepare informational texts in this field, increased viewing of videos created by unqualified individuals who may mislead patients in order to generate advertising revenue by generating a large number of clicks and who promise healing with unlikely treatments may become a public health issue.

Our study has a significant limitation in that patients were asked if they had done direct Internet searches for information on their own. It should be noted that patients' relatives, particularly those younger than themselves, might well be researching the disease and inadvertently passing on incorrect information to the elderly patients. Furthermore, despite the fact that the current study included 400 patients and the results were evaluated using power analysis generalizable to the global population, it was conducted with Turkish patients using Turkish-written materials. Large-scale multi-racial and multi-lingual studies conducted in different geographic locations may yield more clinically and ethically significant results.

Conclusion

As the elderly population grows, so does smartphone use. As a result, the elderly who have been diagnosed with SMD are expected to use the Internet more frequently for disease information. Therefore, the Internet websites should be easy to read; more emphasis should be placed on informative audio recordings and videos for individuals with low vision; and, if necessary, the quality and reliability of the information on these websites should be improved by having it prepared by experts. Otherwise, patients' adherence to treatment may be jeopardized, and improperly prepared Internet websites and YouTube videos may become a public health issue.

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Systemic inflammation response index and systemic immune-inflammation index are associated with severity of acute pancreatitis

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Abstract

Aim: Acute pancreatitis (AP) is a disease with inflammation, and patients present with severe acute upper abdominal pain in emergency departments. AP can result in higher mortality as its clinical severity increases. Therefore, in this study, we want to investigate the clinical utility of the systemic inflammation response index (SIRI) and systemic immune-inflammation index (SII) in showing the severity of AP.

Material and methods: Among the patients admitted to our emergency department between January 2020 and December 2022, 201 patients diagnosed with AP were included in the study. These patients were divided into two groups according to the severity of the disease as mild and severe AP (MAP and SAP). Demographic data and laboratory data of the patients (white blood cell count, such as SIRI, SII and C-reactive protein, SIRI, SII and C-reactive protein) were recorded. Differences between groups of AP patients divided according to disease severity were analyzed.

Results: 165 (82.1%) patients had MAP and 36 (17.9%) patients had SAP. 52.8% of the patients were male. The mean of the SAP group was significantly higher than the SII MAP group (3165.71±3058.42 vs.1043.31±849.15; p<0.001). In addition, SII levels were significantly higher in the SAP group compared to MAP (11.19±6.27 vs. 3.12±3.01; p<0.001). In regression analysis, CRP, SIRI and SII was found to be able to predict SAP in patients with AP. The power of SIRI and SII were found to be higher in predicting SAP [AUC for SIRI: 0.890; [AUC for SII: 0.859].

Conclusion: High SII and SIRI are useful markers that can show the severity of AP.

Key words: acute pancreatitis severity, SII, SIRI, biomarker

Introduction

Acute pancreatitis (AP) is a condition that can cause with severe inflammation-related reactions, and patients often present to the emergency department (ED) with severe acute upper abdominal pain [1,2]. AP is clinically categorized as mild acute pancreatitis and severe acute pancreatitis (SAP), and SAP patients described by multi-organ failure are associated with high mortality [3]. In recent years, there are many studies concentrating on cytokine activation, macrophage-mediated reaction response in SAP patients. Early diagnosis and treatment of SAP patients reduce the rate of mortality and morbidity [4].

Although scorings such as Ranson criteria, Atlanta, and BISAP have been created to demonstrate the severity of AP, it requires the collection of several parameters that may affect the prediction. Ranson criteria from these scoring systems are frequently used. The Ranson criteria are a reliable indicator of the clinical severity and prognosis of acute pancreatitis. Ranson score ≥ 3 is defined as severe pancreatitis. For this explanation, it can cause problems in timing in AP patients for whom early diagnosis and diagnosis are critical [5,6]. Therefore, there is a need for biomarkers that can predict SAP patients quickly and effectively. Many biomarkers, including C-reactive protein (CRP), neutrophil or platelet to lymphocyte ratio (NLR, PLR), and immature granulocyte (IG), have been used effectively by clinicians to define the severity of AP [2,7,8]. Systemic inflammatory response index (SIRI) has been characterized in the literature as an inflammatory marker that can be estimated by the combination of routine whole blood parameters such as neutrophils, monocytes, and lymphocytes [9]. The systemic immune-inflammation index (SII), another inflammatory marker consisting of a combination of neutrophils, platelets, and lymphocytes, has been similarly reported [4]. Recently many studies showed that the prognostic utility of SIRI and SII in

oncological diseases, and gastrointestinal system conditions such as appendicitis, cholecystitis, and cardiovascular system diseases [10,11]. However, there are insufficient studies on whether SIRI and SII can predict the clinical projection of AP. Therefore, in this study, we wanted to show the clinical utility of SIRI and SII in patients with AP.

Material and methods
Patients
This study consists of patients analyzed with AP patient between January 2020- December 2022 after local ethics committee approval. The study protocol adhered to the Declaration of Helsinki's ethical principles and received full approval from the institutional review boards of Antalya Training and Research hospital Ethical Committee with approval ID: 2022/348. In our study, patient data were inspected retrospectively from electronic information processing systems. The investigation population consisted of patients aged ≥18 years who presented to the tertiary hospital (Health Science University Antalya Training and Research Hospital, Antalya, Turkey) ED with abdominal pain, whose clinical, symptom, imaging, and laboratory tests were assessed and were compatible with AP. Typical abdominal ultrasonography and tomography findings in the routine imaging of the patients were accepted as AP. The exclusion criteria in our study were patients <18 years of age, those with exacerbation due to chronic diseases such as patients with hematological or oncological disorders, pregnant women, patients with insufficient data, patients, those guided to an external center, and additional physical examination, examination and imaging findings specified as patients with an infectious disease. Patients were then grouped according to the Atlanta acute disease classification. These were MAP and SAP (including moderate/severe pancreatitis). The MAP group consisted of patients without organ failure and (peri-)pancreatic necrosis, and another group, the SAP group, consisted of patients with permanent or transient organ failure and/or sterile-infected (peri-)pancreatic necrosis. Demographic and clinical characteristics were investigated from the hospital data processing system.

Laboratory tests
CRP, hemoglobin, platelet and white blood cell count (WBC), neutrophil, lymphocyte, monocytes, IG values, amylase, lipase, glucose, liver function tests, and lactate dehydrogenase (LDH) levels of the patients were documented. SIRI calculated in this form: neutrophil count, monocyte count/lymphocyte count, and SII calculated in this formula: platelet count was found by the ratio of neutrophil count/lymphocyte count.

Statistical analysis
In our study, SPSS 21.0 was used in the analysis of the data, and mean ± standard deviation was used for continuous variables. While frequency and percentage (%) were used for categorical data, Pearson chi-square and Fischer's precision test were used in the analysis of categorical variables. Student's t-test was used for normally distributed variables and Mann-Whitney U test was used for non-normally distributed variables in the analysis of groups for AP severity. Parameters with P<0.20 in univariate analysis were entered into a backward multivariate logistic regression analysis. Receiver operating characteristic (ROC) analysis was performed for AP severity (WBC, CRP, SIRI, and SII) and a statistically significant P<0.05 was considered.

Results
Our analysis included 201 patients, including 165 (82.1%) OAB and 36 (17.9%) SAP. 106 (52.8%) of the patients were male. The patients were divided into two groups as MAP and SAP according to the severity of AP, and when they were evaluated between genders according to the severity of AP, it was found that 49.7% of the patients in the MAP group and 66.7% of the patients in the SAP group were male, and there was no significant difference between the groups (p=0.069). When the patients were evaluated according to age groups, the mean age was found to be significantly higher in the severe AP group than in the MAP group (52.69±16.08 vs. 61.78±15.81; p<0.003). Mean WBC, neutrophil, CRP, LDH, and glucose levels were significantly higher in SAP patients compared to the MAP group; lymphocyte levels were found to be significantly lower. While the mean SIRI levels were 3165.71±3058.42 in SAP patients, it was 1043.31±849.15 in MAP patients. Mean SIRI levels were discovered to be significantly higher in SAP patients. While the mean SII levels were 11.19±6.27 in SAP patients, it was 3.12±3.01 in MAP patients. Mean SIRI levels were discovered to be significantly higher in SAP patients. Demographic data and laboratory values of the study population are compared in Table 1.

| Table 1 | Demographics and laboratory findings in patients with acute pancreatitis |

	MAP N=165	SAP N=36	P value
Age (years)	52.69±16.08	61.78±15.81	0.003
Gender (Male);n(%)	82 (49.7)	24 (66.7)	0.069
Laboratory tests			
WBC count (×103/mm3)	8.69±3.32	12.79±5.74	**0.013**
Neutrophil	6.48±3.11	12.23±4.80	<0.001
Lymphocyt	1.78±0.85	1.17±0.64	0.001
Platelet	225.47±80.88	204.08±76.11	**0.845**
CRP (mg/dL)	67.58±8.91	132.9±14.84	**0.017**
ALT (U/L)(IQR)	109 (212.5)	126 (193.5)	0.434
Amylase (U/L)(IQR)	239.5 (436.2)	358 (610)	0.395
Lipase(U/L)(IQR)	335 (875.2)	586 (1061)	0.600
Glucose (mg/dl)	107.03±49.35	139.38±99.21	0.009
LDH(U/L)	241.06±139.06	252.48±85.71	0.035
SII	1043.31±849.15	3165.71±3058.42	<0.001
SIRI	3.12±3.01	11.19±6.27	<0.001

Abbreviation: WBC: White blood cell count; CRP: C-reactive protein; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index

Table 2	Predictors of severe acute pancreatitis on multivariate logistic regression analysis

Multivariate logistic regression			
Variable	**OR**	**95% CI**	**P-value**
Age	2.24	1.090-5.108	0.053
Sex(male)	2.04	1.049-4.316	0.068
WBC count	1.094	1.002-1.196	**0.046**
Neutrophil	1.314	1.161–1.488	**0.024**
Glucose (mg/dl)	1.703	1.008-2.877	**0.046**
LDH(U/L)	2.64	1.162-2.554	**0.034**
CRP (mg/dL)	3.17	1.51-6.735	**0.003**
SIRI	8.04	1.137-16.38	**0.020**
SII	6.59	1.13-8.24	**0.035**

Abbreviation: WBC: White blood cell count; CRP: C-reactive protein; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index

Figure 1 - Receiver operating characteristic curves of systemic inflammation response index (SIRI) and systemic immune-inflammation index (SII) to predict the severity of acute pancreatitis

Table 3	The receiver operating characteristic curves for severe acute pancreatitis prediction

	Cut-off	AUC (95% CI)	Sensitivity (%)	Specificity (%)	P
WBC(×103/mm3)	10.27	0.719 (0.532-0.906)	63.6	51.8	0.03
SIRI	4.83	0.890 (0.837-0.943)	83.8	80	<0.001
SII	1288.2	0.859 (0.798-0.920)	83.3	73.3	<0.001
CRP (mg/dL)	32.7	0.647 (0.476-0.872)	63.6	58.8	0.086

Abbreviation: AUC: Area under the curve; CI: Confidence interval WBC: White blood cell; NLR: Neutrophil lymphocyte ratio ; IGC: Immature granulocyte count; IG%: Immature granulocyte percentage; CRP: C-reactive protein

In regression analysis, CRP, SIRI and SII was found to be able to predict SAP in patients with AP (Table 2). The efficiency of WBC, SIRI, SII, and CRP parameters in determining MAP and SAP was estimated by plotting ROC curves (Figure 1). The effectiveness of WBC, SIRI, and SII in predicting SAP were statistically significant. The power of SIRI and SII was found to be higher [AUC for SIRI: 0.890; sensitivity 83.8, specificity 80 p<0.001]; [AUC for SII: 0.859, sensitivity 83.3, specificity 73.3; p<0.001] (Table 3).

Discussion

In this study, we examined the association between inflammatory markers such as SIRI and SII and the severity of AP. According to the data in our investigation, we found that SIRI and SII were associated with the severity of AP. Accordingly, we think that SIRI and SII may be helpful in the early recognition of SAP patients in the emergency department.

Studies have shown that AP is associated with many systems and organs. It can lead to serious disorders ranging from simple clinical symptoms to severe discomfort and multiorgan failure [12]. The severity of AP continues to be a severe problem for physicians for years. Although the mortality and morbidity rates in patients with AP tend to lower with the developing medical requirements, it still maintains its clinical importance due to the high incidence of SAP [13]. It should be noted that although patients with AP initially progress with an aseptic inflammation, they may show peritonitis, multi-organ failure, and shock in advanced stages [14]. Clinicians used scoring systems such as Ranson's criterion, BISAP score, Harmless acute pancreatitis score, Organ failure-based scores as well as imaging methods such as CT severity index to determine the prognosis and severity of pancreatitis [15,16]. Although these scorings are widely used by clinicians, quick and simple assessment markers become important because they contain many clinical data and difficulties that may occur in calculations [17]. In recent years, fast and simple new types of violence such as NLR, PLR, and IG, and methods that help predictive assessment have been used [2,18]. In this study, we found that SIRI and SII were associated with AP severity.
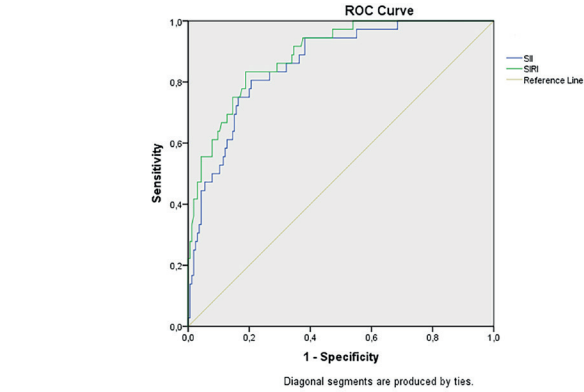
It has been established that SIRI can be a prognostic marker of many gastrointestinal and cardiovascular diseases, especially oncological conditions. Chao et al. A study by SIRI has highlighted that SIRI is a prognostic index and a potential marker that has significant benefits in patients with treatable cervical cancer [19]. In a study by Dziedzic et al., SIRI was found to be significantly higher in cardiac conditions such as acute coronary syndrome and stable coronary artery disease [20]. Li et al. It has been reported that high SIRI levels are associated with poor survival in patients on peritoneal dialysis due to renal failure [21]. A comprehensive study by Zhang et al. found an association between higher SIRI values and mortality, sepsis, and higher stroke severity [22]. Jin et al. In a study they conducted, it was reported that SIRI could be predictive with low sensitivity and high specificity in patients with rheumatoid arthritis [23]. In our study, we also showed that there is a significant relationship between high SIRI values and SAP.

The systemic immune-inflammation index (SII) has also been reported as a prognostic marker in many conditions such as SIRI [4]. In a study by Li et al., it is used as a potential marker for the poor prognosis of patients with acute/subacute CVST in the pregnant population and men [24]. Trifan et al. In a study by Supratentorial spontaneous intracerebral hemorrhage, early LII is an independent predictor of poor outcome at hospital discharge [25]. Hu et al. emphasized that SII may be associated with circulating tumor cells in patients with hepatocellular carcinoma and may be a strong prognostic marker in patients with hepatocellular carcinoma [26]. Topçuoğlu et al. showed that increased SII values were associated with an improvement in the incidence of symptomatic ICH associated with intravenous thrombolysis [27]. Pedro Silva-Vaz et al., reported 117 patients with AP, found SIRI levels to be significantly higher in severe AP [28]. In another study by Pedro Silva-Vaz et al., for the first time, of SIRI as a new prognostic tool for AP severity [29]. In our study, we exhibited that SII can be a marker for AP severity.

One of the most significant limitations of our study is that our study was created retrospectively. Another limitation of ours is the inability to determine the time from physical examination findings, symptoms, and complaints to sample collection. In

accumulation, SII and SIRI were estimated at a one-time point only. Intermittent measurements to catch changes in these parameters over time and during baseline may contribute to more accurate outcomes. Prospective multicenter studies are required.

Conclusion

It is a useful indicator that can indicate high SII and SIRI AP severity. However, our results should be further estimated using prospective studies with more extended follow-ups.

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Evaluation of carotid intima-media thickness and cardiovascular risk factors in benign prostatic hyperplasia patients

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Abstract

Objective: To assess the carotid intima-media thickness and cardiovascular risk factors in patients with benign prostatic hyperplasia.

Material and methods: This was a prospective observational study conducted over two years in 100 patients who presented with benign prostatic hyperplasia (BPH). IPSS questionnaire was used to evaluate the symptomatology of BPH. Patients were examined for cardiovascular risk factors. All patients underwent echocardiographic examination for left ventricular function. A single experienced sonographer, blinded to all clinical information, assessed the common carotid artery.

Results: The patients mean age was 69.32 years. The mean BMI was 28.91 kg/m². Of the total mild symptom score cases, 75 % (N=6) cases had Grade I prostatomegaly (26 – 40 cc). 98.38 % (N=61) cases had Grade II prostatomegaly (41 – 60 cc), 93.33 % (N=28) cases had Grade III prostatomegaly (>60cc). A mean carotid intima-media thickness (IMT) of 0.56 mm was found in cases having mild IPSS scores (Score 1-7), 0.73 mm was found in cases having moderate IPSS score (Score 8-19), 0.92 mm was found in cases having severe IPSS scores (Score 20-35). Significant association was present between mean BMI, diabetes mellitus, hypertension, hyperlipidemia, smoking and mean Carotid IMT with IPSS as p-value was <0.05. Significant association was present between total cholesterol, HDL, LDL and prostate volume with p-value <0.0001.

Conclusion: This study found that prostatic tissue had a strong relationship with carotid IMT and cardiovascular risk factors in BPH patients. These data suggest a possible link between carotid IMT and cardiovascular risk factors and BPH.

Key words: benign prostate hyperplasia, carotid, diabetes mellitus, hypertension, intima-media thickness, sonography

Introduction

BPH (benign prostatic hyperplasia) is a significant health problem that affects more than half of all men in their sixties [1]. Despite the fact that BPH is common, the cause of the ailment is unknown. Other than age and sex steroid hormones, evidence suggests that BPH has modifiable risk factors. Diabetes, obesity, metabolic syndrome, smoking, and high blood pressure are all risk factors for BPH [2-4].

The unregulated growth of connective tissue, smooth muscle, and glandular epithelium inside the prostatic transition zone is a histological feature of BPH [1]. Prostate tissue and the prostatic utricle have a similar embryologic genesis to the uterus and upper

vaginal canal. These are derived from the Müllerian duct's joined ends [5]. Female uterine leiomyomas are the most often seen benign tumours [6]. Uterine leiomyoma has been associated with cardiovascular risk factors such diabetes, hypertension, obesity, and smoking [7-9]. Furthermore, a recent study found a link between carotid intima-media thickness (IMT) and the occurrence of uterine leiomyoma [10].

As a result, we were interested in studying carotid IMT and cardiovascular risk factors in BPH patients.

Objective: To assess the carotid intima-media thickness and cardiovascular risk factors in patients with benign prostatic hyperplasia.

Material and methods

This was a prospective observational study conducted over two years in 100 patients who had presented to the department of urology.

Inclusion criteria were all patients above 45 years who presented with benign prostatic hyperplasia associated symptoms to the department of urology and who were willing to give consent for this study. Exclusion criteria were patients below 45 years of age, Patients who were not willing to give consent for this study. The institutional ethics committee gave its approval to the project. After receiving written informed permission, patients were enrolled (correctly outlining the objectives, procedures, anticipated advantages, and any risks important for choosing to take part in the study).

The IPSS questionnaire was utilised to assess the BPH symptomatology. The IPSS is a quick and simple self-administered questionnaire used to evaluate BPH in patients. An eight-question written screening test called the IPSS questionnaire is used to quickly diagnose, monitor, and prescribe treatment for BPH. It is based on responses to one quality of life question and seven questions on urinary symptoms. The patient can select one of six options for each question about urinary symptoms, with the answers representing the increasing severity of that specific symptom. The solutions are given scores ranging from 0 to 5. Consequently, the final score might be between 0 and 35 (asymptomatic to very symptomatic). Patients are rated on their quality of life, from wonderful to terrible (0-6) [11]. Questions about urine symptoms include: incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. The IPSS classifies symptoms as follows: Mild (symptom score 1–7), Moderate (symptom score 8–19), and Severe (symptom score range 20-35).

Routine demographic information, personal history including smoking and alcohol addiction history, physical examination including digital rectal examination (DRE), haematological data such as complete blood profile, biochemical data such as renal function test and lipid profile, and transabdominal ultrasonography for the urinary system and carotid intima-media thickness of patients were recorded in an Excel sheet. The patients' cardiovascular risk factors were investigated. Age, BMI, diabetes mellitus (known diabetes treated with diet, drugs, or both, or a fasting serum glucose of more than 126 mg/dL), hypertension (known hypertension treated with antihypertensive drugs, two or more blood pressure recordings higher than 140/90 mm Hg), and hyperlipidemia with one or more factors (known case and treated with drugs, high fasting or non-fasting serum cholesterol concentrations) were all recorded. Current cigarette smoking was defined as actively smoking cigarettes within the past 12 months. The prostatic volume was measured by transabdominal ultrasonography (in

cc). For a cardiac status and left ventricular function evaluation, echocardiography was performed on all patients. All patients had B-mode ultrasonographic exams using a 7.0-MHz linear array transducer (HD 11XE; PHILIPS Ultrasound). One skilled sonographer who was unaware of any clinical details checked the common carotid artery. The previously described technique was used to quantify the intima-media thickness (IMT) of the common carotid artery [12]. A lengthy axis of the common carotid artery, 10 mm from its bifurcation, was examined. At the conclusion of diastole, the IMT was measured in the posterior wall from the B-mode screen to a location inside the 10 mm section close to the bifurcation of the common carotid artery. During carotid scanning, both the right and left common carotid arteries were examined. Additionally determined was the average carotid intima-media thickness (IMT). To compare the clinical characteristics, cardiovascular risk factors, and mean carotid IMT, patients were divided into three IPSS categories: mild symptom group (Score range 1-7), moderate symptom group (Score range 8-19), and severe symptom group (Score range 20-35). They were also divided into three prostatic volume grades: Grade I (26 cc - 40 cc), Grade II (41 cc - 60 cc), and Grade III (>60 cc) [13].

Statistical analysis

To compare clinical features, cardiovascular risk factors, and mean carotid IMT, patients were classified into three IPSS groups and three prostatic volume grades. The following variables were analysed statistically: age, hypertension, diabetes mellitus, smoking, total cholesterol levels, LDL levels, HDL levels, BMI and mean carotid IMT. Continuous values were reported as mean standard deviation, and categorical variables as a percentage. To test the association between the groups, the Pearson chi-square test was used. Using the ANOVA (Analysis of Variance) test, the mean difference between the three groups was examined. The statistical analysis was carried out utilising IBM SPSS version 24.0. (SPSS Inc, Chicago, IL). In all tests, statistical significance was defined as a P value 0.05.

Results

A total of 100 cases of BPH were included in this study from January 2019 to December 2020. They were evaluated based on International Prostate Symptom Score (IPSS) and prostate volume done by transabdominal ultrasonography. Cardiovascular risk factors and carotid IMT were also noted in all the cases.

As the IPSS symptom score increased from mild to severe, grades of BPH also increased. Of the total mild symptom score cases, 75 % (N=6) cases had Grade I BPH (26 – 40 cc). Of the total moderate symptom score cases, 98.38 % (N=61) cases had Grade II BPH (41 – 60 cc). Of the total severe symptom score cases, 93.33 % (N=28) cases had Grade III BPH (>60cc) (Table 1).

The patients mean age was 69.32 years. As the age of patients increased, IPSS grading also increased. The mean BMI was 28.91 kg/m². 33.3% (N=2) hypertension cases and 16.7% (N=1) hyperlipidemia cases were having a mild IPSS score (Score 1-7). A mean carotid IMT of 0.56 mm was found in cases having mild IPSS scores (Score 1-7). 69.2% (N=45) diabetes mellitus cases, 46.2% (N=30) hypertensive cases, 53.8% (N=35) hyperlipidemia cases and 64.6% (N=42) smokers had moderate IPSS (Score 8-19). Mean carotid IMT of 0.73 mm was found in cases having moderate IPSS score (Score 8-19). 89.7% (N=26) diabetes mellitus cases, 75.9% (N=22) hypertensive cases, 93.1% (N=27) hyperlipidemia cases and 82.8% (N=24) smokers

Table 1   Association between International Prostatic Symptom Scores subgroups and prostatic volume subgroups

International Prostate Symptom Score (IPSS)	Prostate Volume (in cc)				P value*
	Grade I (26-40 cc) (N=8)	Grade II (41-60cc) (N=62)	Grade III (>60 cc) (N=30)	Total cases (N= 100)	
Mild Symptom score Cases (%) (Score 1-7)	75% (N=6)	0 % (N=0)	0% (N=0)	6% (N=6)	
Moderate Symptom score Cases (%) (Score 8-19)	25% (N=2)	98.38% (N=61)	6.66% (N=2)	65% (N=65)	P<0.0001
Severe Symptom score Cases (%) (Score 20-35)	0% (N=0)	1.61% (N=1)	93.33% (N=28)	29% (N=29)	
Total cases	(N=8)	(N=62)	(N=30)	(N=100)	

*(<0.05 significant) Pearson ChiSquare Test

Table 2   Association between Demographic, Anthropometric, Cardiovascular parameters and International Prostatic Symptom Scores subgroups

Demographic, Anthropometric & Cardiovascular parameters	International Prostate Symptom Score (IPSS)				P value*
	Mild Symptom score cases (Score 1-7) (N=6)	Moderate Symptom score cases (Score 8-19) (N=65)	Severe Symptom score cases (Score 20-35) (N=29)	Total Cases (N=100)	
Mean Age (years)	67.17±7.223	68.94±8.968	70.62±6.444	69.32±8.201	0.531 (ANOVA)
Mean BMI (kg/m²)	26.81 ± 0.854	27.79 ± 2.00	31.87 ± 3.18	28.91 ± 3.02	<0.0001 (ANOVA)
Diabetes Mellitus (%)	0.0% (N=0)	69.2% (N=45)	89.7% (N=26)	71.0% (N=71)	<0.0001 (CHI SQUAR E)
Hypertension (%)	33.3% (N=2)	46.2% (N=30)	75.9% (N=22)	54% (N=54)	0.016 (CHI SQUAR E)
Hyperlipidemia (%)	16.7% (N=1)	53.8% (N=35)	93.1% (N=27)	63.0% (N=63)	<0.0001 (CHI SQUAR E)
Smoking (%)	0.0% (N=0)	64.6% (N=42)	82.8% (N=24)	66.0% (N=66)	<0.0001 (CHI SQUAR E)
Mean Carotid IMT (mm)	0.56 ± 0.02	0.73 ± 0.06	0.92 ± 0.06	0.78 ± 0.11	<0.0001 (ANOVA)

*(<0.05significant) Pearson ChiSquare / ANOVA test

Table 3   Association between Lipid Profile parameter and prostatic volume subgroups

Lipid Profile	Prostate Volume (in cc)				P value*
	Grade I cases (26-40 cc) (N=8)	Grade II cases (41-60cc) (N=62)	Grade III cases (>60 cc) (N=30)	Total cases (N= 100)	
Mean Total Cholesterol (TC) (mg/dl)	171.25 ± 42.90	227.33 ± 55.23	336.73±46.22	255.67± 75.53	<0.0001
Mean High Density Lipoproteins(HDL) (mg/dl)	43.75 ± 5.84	37.58 ± 6.66	26.97 ± 4.45	34.89 ± 8.09	<0.0001
Mean Low Density Lipoproteins (LDL) (mg/dl)	90.38 ± 26.20	122.00 ± 39.66	192.77 ± 36.63	140.70 ± 51.53	<0.0001

*(<0.05 significant) (ANOVA test)

had severe IPSS (Score 20-35). A mean carotid IMT of 0.92 mm was found in cases having severe IPSS scores (Score 20-35). Overall for 100 cases, the mean carotid IMT was 0.78 mm (Table 2).

A significant association was present between mean BMI, diabetes mellitus, hypertension, hyperlipidemia, smoking and mean Carotid IMT with IPSS as p-value was <0.05 (Table 2).

As age increased (from 67.88 years to 70.93 years), grades of BPH increased (from Grade I to Grade III) and hence, the prostate volume also increased.

As mean BMI increased (from 25.89 kg/m² to 32.15 kg/m²), grades of BPH increased (from Grade I to Grade III) and hence, the prostate volume also increased.

Of the total Grade II BPH cases, 71% (N=44) had diabetes mellitus (DM). Of the total Grade III BPH cases, 90% (N=27) had diabetes mellitus. A significant association was present between DM and prostate volume.

Of all the Grade I, Grade II, Grade III BPH cases, 25% (N=2) cases, 46.8% (N=29) cases and 76.7% (N=23) cases had hypertension respectively. A significant association was present between hypertension and prostate volume.

The mean total cholesterol level was 255.67 mg/dl. The mean HDL level was 34.89 mg/dl. The mean LDL level was 140.70 mg/dl. A significant association was present between total cholesterol, HDL, LDL and prostate volume (Table 3).

Out of the total 100 cases, 66% (N=66) were smokers. A significant association was present between smoking and prostate volume.

The mean carotid IMT was 0.78 mm. Grade I, Grade II and Grade III prostate cases had 0.56mm, 0.73mm, and 0.92mm mean carotid IMT respectively. A significant association was present between mean Carotid IMT and prostate volume.

Discussion

BPH and cardiovascular diseases commonly occur in elderly men. The coexistence of these two diseases in the same patient is not by chance alone but indicates a shared common pathophysiologic process [14]. The exact mechanism of atherosclerosis is still unknown despite the great understanding of its pathophysiology. Several studies have suggested a link between atherosclerosis and cardiovascular risk factors and prostatic hyperplasia [15-17].

Studies have proven that baseline prostate size can be considered a strong indicator of BPH progression. Also, prostate volume as a risk factor for acute urinary retention (AUR) has also been proven [18].

The role of IPSS to assess symptom severity of LUTS in BPH patients is already proven as the majority of men with BPH present with LUTS [11,19]. In the present study, 100 BPH patients were assessed for symptoms with IPSS grading. Awaisu M et al. in a prospective correlational study in 290 patients of BPH demonstrated that as the grades of IPSS increase, prostate volume and the severity of BPH increases [20]. In his study, there was a strong positive association between prostate volume and IPSS (r=0.179, p=0.002), and the majority of the patients reported moderate symptoms on the IPSS (55%) with a mean IPSS value of 16.41±7.43 [20]. In the present study also, 65% (N=65) of BPH cases had moderate symptom scores on IPSS. Also, a similar significant correlation was present between IPSS score and prostate volume. As IPSS score increased, grades of BPH also increased, hence the severity of BPH also increased. In contrast to patients in the normal group, Yelsel K et al. found a strong correlation between grades on the IPSS and overweight and obesity (P 0.001). In comparison to the overweight group, the obese group's IPSS levels were considerably greater (P = 0.010) [21].

In the present study also, as the mean BMI increased, grades of IPSS increased. There was a positive correlation between IPSS and body mass index (BMI) as the p-value was <0.0001. In this study, mean BMI is 26.81kg/m², 27.79kg/m² and 31.87kg/m² in mild, moderate and severe IPSS score cases respectively, thus corresponding with the positive association of overweight and obesity with higher grades of IPSS. Ponholzer A et al. investigated the association between vascular risk factors like diabetes mellitus, hypertension, hyperlipidemia, nicotine use and LUTS in both sexes. In men, the IPSS score was identical in those with no vascular risk factor and one

vascular risk factor but increased to in those with two or more risk factors (p=0.01) [22]. A substantial positive link between a number of cardiovascular risk variables, including smoking, hypertension, hyperlipidemia, diabetes mellitus, and IPSS scores, was discovered in the current study as well. In 2014, Lee et al. examined in 799 men the association between carotid artery plaque and the international prostate symptom score (IPSS). They found a significant (P=0.002) correlation between the maximal intima-media thickness (max IMT) and the IPSS voiding subscore. They noticed a strong correlation between the severity of the voiding score and plaque severity (P=0.003) [23]. In the current study also, the mean carotid IMT is different between the three IPSS groups and is highest (0.92 mm ± 0.06 mm) for a severely symptomatic group with an IPSS score between 20-35. Previous studies have demonstrated as grades of IPSS increase, prostate volume and the severity of BPH increase [20]. In this study also, maximum mean carotid IMT of 0.92 mm was present in severely symptomatic IPSS group and higher grades of IPSS was associated with higher grades of BPH, thus proving that as carotid IMT increases, grades of BPH and severity of BPH increases. The association between carotid IMT and IPSS was significant (P-value<0.0001).

Liu CC et al. in 2007 demonstrated a significant positive correlation of age with BPH especially with prostate volume (r=0.309, P<0.001) [24]. In the present study also, as mean age increased, grades of BPH increased corresponding to increased prostate volume but the association was not significant as p=0.424. This may be due to the fewer cases in the present study.

In 2008, YD Kim et al. examined the relationships between anthropometric and metabolic variables and prostate volume. After doing a bivariate study, the researchers discovered a positive link between prostate volume and body weight, height, and body mass index (BMI) [25]. There is a role of obesity as an etiological factor for BPH due to its influence on metabolic factors and obesity-related endocrine changes. The development of benign prostatic hyperplasia and the severity of urinary obstructive symptoms are both known to be influenced by abdominal obesity, which raises the oestrogen to androgen ratio and may enhance sympathetic nerve activity. BPH risk was shown to be highly correlated with body mass index (BMI), a measure of general obesity, and waist to hip ratio (WHR), a marker of abdominal obesity [26]. According to research by Hammarsten et al., obesity is a risk factor for developing BPH since it is positively correlated with measures of obesity like BMI [12,27]. In the present study also, higher BMI values were associated with increasing grades of BPH, thus corresponding to an increase in the severity of BPH which was significantly correlated (p=<0.0001).

Diabetes and BPH become more common as people become older. Several research have revealed a link between BPH and diabetes [28]. Hammarsten J et al. from Sweden showed in a series of early cross-sectional investigations that diabetes was strongly related with an enlarged prostate size consistent with BPH. Men with diabetes had a bigger prostate gland than men without diabetes among LUTS patients (78 mL vs. 45 mL, respectively; P=0.006), according to the researchers [12,16,27,29]. Men with diabetes had a two-fold increased risk of having an enlarged prostate (40 mL), as determined by MRI, whereas men with excessive fasting glucose had a three-fold increased risk [30]. Nandeesha H also found a positive association with diabetes mellitus and BPH [28]. Even though process by which diabetes causes BPH is unknown, previous research has revealed that vascular damage caused by type 2 diabetes can exacerbate BPH It has been suggested that detrusor

hypoxia can play a role in the aetiology of BPH. By affecting angiogenesis, hypoxia can hasten the growth of the prostatic gland. The transcription factor hypoxia-inducible factor 1 (HIF-1) as well as growth factors like vascular endothelial growth factor (VEGF), fibroblast growth factors 2 and 7 (FGF-2 and FGF-7), transforming growth factor-b (TGF-b), and cytokines like IL-8 can all be expressed more when there is hypoxia. By gradually subjecting the prostate stroma to greater growth factor levels, chronic hypoxia may accelerate prostate development and contribute to the pathogenesis of BPH. As a result, BPH treatment may be affected if tissue hypoxia is reduced by boosting oxygen supply with proper diabetes control [28]. In this study also, of 100 patients of BPH, 71 patients (71%) had statistically significant diabetes mellitus, thus correlating with findings of other studies and signifying the association of diabetes with BPH. Men's age-related illnesses including BPH and hypertension are quite common and put a significant strain on the world's healthcare systems. Twenty to thirty percent of individuals with benign prostatic hyperplasia experience arterial hypertension. Recent epidemiological studies have demonstrated that men with hypertension are more likely than age-matched controls to receive surgical intervention for BPH-related irritative voiding symptoms. According to this research, noradrenergic nerves, which control vascular tone, also contribute to the functional aspect of bladder outlet blockage brought on by BPH [28]. Nandeesha H also concluded hypertension as a risk factor for BPH [28]. Guo LJ et al. discovered hypertension in 128 BPH patients (30.3 percent) in a retrospective investigation of 423 BPH cases, and substantial positive associations were established among prostate volume and duration of hypertension [31]. It has been found that the time of incidence of BPH and the requirement for surgical intervention was sooner with in hypertensive group than in the normal blood pressure group [31]. Furthermore, the prevalence of urine retention and haematuria was shown to be greater in BPH patients linked with hypertension, showing that primary hypertension might influence the onset and clinically progression of BPH [31]. The sympathetic nervous system's activity has been the common pathological mechanism that connects BPH with hypertension. A recent study by Achari R et al. backs up this theory [32]. In the current study also, of the total grade III and grade II BPH cases, 76.7% cases and 46.8% cases had hypertension respectively, thus signifying hypertensive patients have more prostate volume corresponding to severe grades of BPH. Of the total BPH patients, 54% of patients had hypertension, which was significantly correlated with a p-value of 0.006, thus corroborating with other studies.

Hyperlipidemia was found in 50.2 percent of BPH patients in a Chinese retrospective investigation by Li PJ et al [31]. In several studies, Hammarsten J et al. hypothesised that dyslipidemia, particularly low levels of HDL cholesterol, is in fact a risk factor for the onset of BPH [12,27]. In comparison to males with slow-growing BPH, they discovered decreased HDL cholesterol levels in men with fast-growing BPH (p=0.021). The rate of yearly BPH development was adversely linked with HDL cholesterol (rs=-0.22; p=0.001) [27]. When compared to controls, BPH patients had considerably higher total cholesterol, lower HDL cholesterol, and higher LDL cholesterol, according to Nandeesha H et al [33]. The inhibitory effect of testosterone on HDL cholesterol levels helps to explain low HDL cholesterol levels in BPH. Low amounts of HDL cholesterol can increase LDL cholesterol synthesis, modify LDL cholesterol by oxidation, and activate Protein C kinase, which leads to aberrant prostate cell growth and BPH [28]. In the present study also, patients with BPH had higher total cholesterol 255.67 mg/dl, low HDL cholesterol 34.89 mg/dl and high LDL cholesterol 140.70 mg/dl as found in other studies, thus proving lipids role in BPH (Table 3).

According to research by EA Platz et al., current cigarette smoking is positively associated with BPH [34]. In the present study also, of the total grade III and grade II BPH cases, 83.3% cases and 66.1% cases were smokers respectively. The association between smoking and prostate volume was found to be significant. Thus, smoking was associated with a severe grade of BPH corresponding to the severity of BPH.

Very few studies have evaluated prostatic hyperplasia with carotid IMT. Erbay et al. objectively assessed carotid IMT in BPH patients. The study comprised 123 participants who were examined for the existence of BPH with concomitant symptoms. They found that in BPH patients, carotid IMT was significantly associated with prostatic volume (beta coefficient: 0.628; confidence interval: 37.02–60.1; P=.001) [35]. According to Lee et al., there is a strong correlation between the IPSS voiding subscore and the maximal carotid IMT (p=0.002) and the severity of the plaque as it grows (p=0.003). They also discovered that, after correcting for age and metabolic syndrome factors, there is a greater chance of having a higher IPSS voiding subscore as plaque severity increases [23]. Previous studies have already established the association of higher IPSS grades with prostate volume and severity of BPH [20]. Hence, there is a higher likelihood of association of carotid IMT and plaque size to prostate volume and severity of BPH. In the present study, mean Carotid IMT is different in three groups of prostate volume, showing an increasing trend in ascending order, as lowest carotid IMT (0.55mm±0.03mm) for Grade I BPH cases to highest carotid IMT (0.92mm±0.05mm) for Grade III BPH cases. The mean carotid IMT was 0.78mm±0.11mm for total cases of BPH. There was a significant correlation between mean carotid IMT and prostate volume (p-value<0.05). Although a link between atherosclerosis and BPH has previously been demonstrated, the specific mechanism behind the association between BPH and carotid IMT remains unclear and requires clarification. Previous studies have discovered a connection between the onset of BPH and non-insulin-dependent diabetes mellitus, hypertension, and dyslipidemia, suggesting that systemic as opposed to local factors may be to blame [35,36]. Hypoxia, neovascularization, oxidative stress, and eventual vascular damage are further theories put out to explain the connection between atherosclerosis and BPH. These factors lead to a decrease in blood flow to the prostatic tissue [15,37]. According to Berger et al., people with severe vascular disease have much worse prostatic tissue perfusion than healthy people. Persistent ischemia brought on by vascular damage may aid in the development of BPH [15]. Carotid IMT was utilised to assess the prostate volume and BPH because there is a positive correlation between atherosclerosis and BPH and because it is a proxy marker for atherosclerosis. These two associated histologic abnormalities (carotid IMT and BPH) share the same risk factors for smooth muscle proliferation, which are increasing age and an unspecific genetic make-up. Therefore, the discovery of a relationship between BPH and carotid IMT in terms of smooth muscle proliferation was not unexpected. Unexpectedly, a connection between uterine leiomyoma, carotid IMT, and cardiovascular risk factors has been established [10]. Similar pathophysiologic pathways are thought to be involved in atherosclerosis, BPH, and uterine leiomyoma since the prostatic and uterine tissues are both descended from the Müllerian duct. These putative pathophysiologic mechanisms lead to the discovery that smooth muscle cells from atherosclerotic plaques and uterine leiomyomas have monoclonal origins and

perform similarly in cell culture [38]. Age-related prevalences of diseases including atherosclerosis, prostatic hyperplasia, and uterine leiomyomas support the idea that pathophysiologic mechanisms connected to smooth muscle cell proliferation may exist. Carotid IMT is a well-recognized sonographic marker for early atherosclerosis, and intima-media complex thickening indicates generalised atherosclerosis. Cardiovascular risk factors and BPH are associated with atherosclerosis [39]. BPH is linked to prostate volume and the IPSS. IPSS and prostate volume are also linked with carotid IMT. As a result, it suggests that there is a direct association between carotid IMT and cardiovascular risk factors and BPH.

The study's limitation was the small number of patients, as more patients would result in a more accurate evaluation and correct conclusion. Another restriction was that, despite the fact that carotid IMT was assessed by a single observer, some differences in measurement might occur by the same observer, altering the value of carotid IMT. Few studies have linked carotid IMT to BPH, and additional study is needed in the future to strongly indicate and conclude carotid IMT as a marker of BPH.

Conclusion

This research found a substantial link between prostatic tissue and carotid intima-media thickness and cardiovascular risk factors in BPH patients. These findings point to a probable relationship between carotid intima-media thickness, cardiovascular risk factors, and BPH.

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The impact of periodontitis on the risk of preterm birth: Systematic review and meta-analysis

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Abstract

Background: Preterm birth (PTB) is one of the most prevalent and serious adverse pregnancy outcomes (APOs) and major health risk for pregnant individuals and their children during pregnancy and throughout their lifespan. Periodontitis has long been regarded as a silent pandemic which happens to favor the pregnant women due to the physical and hormonal changes during pregnancy. Understanding of the association underscores the importance of keeping oral diseases under check and control to predict and even reduce the risk. The aim is to evaluate the association between periodontitis during pregnancy and preterm birth.

Material and methods: A screening and analysis was conducted on studies with comparison data about periodontal infection diseases during pregnancy and preterm birth. The databases include Scopus, PubMed, Elibrary, local databases and the Cochrane library and were searched up to November 20, 2022. The selected studies were included in a random-effects meta-analysis after evaluation of the methodological quality. The summary odds ratios (ORs) with 95% confidence intervals (CI) were calculated with Review Manager software.

Results: The review finally included 29 studies involving 2606589 pregnant women. Compared with healthy oral status in pregnancy, periodontitis was associated with preterm birth [OR=1.81, CI=1.60 to 2.03; p<0.001; I2 = 95%].

Conclusion: Periodontitis as one of the important factors is associated with increased risks of preterm birth. It is important to put the disease under control before and during pregnancy to reduce the preterm birth outcome.

Key words: pregnancy, preterm birth (PTB), periodontitis

Introduction

Preterm birth is a serious medical condition and remains one of the most intransigent research problems in obstetrics and gynecology in the world. According to the statistics, there were 1 in 10 babies born preterm, of these, 80% were born in Asia and Africa [1]. In Kazakhstan, this figure was 8.8 % and increased to 15.2% in 2017 [2]. According to experts of the Statistics Committee of the Ministry of National Economy in the country, despite the

fact that the overall infant mortality rate in the country has decreased, these figures are still disappointing. In the Atyrau, Almaty and Aktobe regions, infant mortality is still high. In one center of the country alone, about 350 children are treated annually. About 200 of them were born prematurely.

The sequelae of preterm birth for the children ranging from significant morbidity such as mental retardation, vision impairment and cerebral palsy, to

mortality of the offsprings [3]. In the long term, preterm birth increased risk for cardiovascular disease, diabetes and cancer as an adult [3,4]. For the mother, delivering preterm increases her risk of a subsequent preterm delivery [4].

To date, advances in maternal prenatal care, increased public awareness and progress has been made in identifying the factors that may be connected with prematurity, as well as ruling out certain treatments that have not been shown to be effective [5]. Infection and host inflammatory response has long been associated with adverse pregnancy outcomes, including PTB [6]. Periodontitis has long been regarded as a silent pandemic which happens to favor pregnant women due to the physical and hormonal changes. It reported that periodontitis occurs about 2 to 3 times more often than genitourinary tract infections [7]. The role of periodontitis as one of the causation of adverse pregnancy outcomes such as pre-eclampsia, gestational diabetes, preterm delivery, low birth weight infants has been extensively evaluated from observational evidence [8]. Periodontitis is a preventable and treatable disease, and it is thus necessary to identify the most common and representative predisposing factors among pregnant women may have a contribution to update a prenatal and perinatal oral health care protocol. Thus a better understanding of the nature of this association will assist in treatment planning to reduce adverse pregnancy outcomes.

This review considers whether the maternal periodontitis as a potential risk factor for preterm birth while there have been more and more recent studies reported conflicting results.

Material and methods

The study was conducted according to PRISMA guidelines [9]. The research question was generated as whether there was a higher risk of preterm birth among periodontitis affected pregnant population compared to the one with healthy periodontium. The databases include Scopus, PubMed, Elibrary, local databases and the Cochrane library and were searched up to November 20, 2022. Medical Subject Headings (MeSH) terms and keywords set as "Periodontal disease OR Periodontitis" AND "pregnancy". Two authors screened the titles and abstracts after searching the databases and involved studies for final evaluation. All of the full text available articles evaluating oral health status during pregnancy and maternal and infant outcomes that met the following inclusion criteria were scrutinized and selected: observational study; population included pregnant people; Oral health status were evaluated with periodontal examination; comparisons included pregnant women with periodontitis versus those without periodontitis or with controlled status; outcomes included preterm birth. Reviews, Meta analyses, case reports, case series and abstracts were excluded from the study.

The following data was extracted from the studies included: author with year of publication, design of the study, the number of participants included in the study, definition of the oral diseases including periodontitis. The characteristics of the included studies are described in Table 1. Newcastle–Ottawa Scale was used to assess quality of the studies (Table 2).

Statistical analysis

Review Manager 5.4 was used to analyze the data extracted from the included studies. The associations between oral diseases and preterm birth and low birth weight were assessed and measures of effect were presented as odds ratios (ORs) with 95% confidence intervals (CIs). The heterogeneity between studies was assessed with I2 statistics. The analysis was considered significant when P<0.05.

Results

The search strategy resulted in 1487 potentially relevant citations. 1304 initially searched studies excluded from further analysis after screening the title and abstract. The PRISMA Flow Diagram (Figure 1) summarizes the process of literature search and selection of studies. After screening the titles and abstracts, we read 67 full-text papers and included 29 studies with comparable outcomes [10-38].

Among the 2606589 pregnant participants, 827223 of them with maternal periodontitis and 1779366 unaffected pregnant controls assessed the oral infection on preterm birth in this study, compared with pregnant women without periodontitis, the pregnant women with periodontitis regardless of the diagnostic criteria and other factors were at higher risk of experience preterm birth [OR =1.81, CI = 1.60 to 2.03; p<0.001; I2=95%] (Figure 2). A funnel plot was plotted and egger's test was conducted to assess the presence of potential publication bias (Figure 3). There was no potential publication bias found (Table 3).

Discussion

Periodontal disease and other oral health problems have been supposed to be a risk factor for preterm birth in many literatures [2,8]. This systematic review and meta-analysis focuses on the most common and severe oral disease namely periodontitis with one of the adverse pregnancy outcomes, preterm birth. Our result found maternal periodontitis during pregnancy is associated with preterm birth compared with periodontal healthy pregnancies. This finding suggests that the health care system should adopt effective strategies to keep oral diseases under check and control to predict and even reduce the risk of exhibiting pregnancy related adverse outcomes.

Although several previous systematic review and meta-analysis regards the periodontitis and adverse pregnancy outcomes reported positive correlation between periodontitis and preterm birth [8], all of the studies showed the need for updating evidence while the number of well-designed publications from observational to experimental studies on this topic have been increased along with time.

The present study was based on the last global and local data, with more observed outcomes. As our results, the 29 individual studies included in the present investigation, which can be considered conflicting, since several of them indicate that there is no association between two health conditions. Another findings of our data searching and screening the methodological quality and design of the original data showed that local or neighbor studies from Central Asia on the aspect of oral health and its relation to maternal and child health is scarce. Well-designed evidence with clear diagnostic criteria of diseases with consideration of confounding factors are needed for contributing to the international database, while regional, genetic, dietary, hygiene, and health care differences contribute to different risks.

In accordance with the previously published systematic reviews, Our meta-analysis also suggests that the periodontitis during the pregnancy is one of the risk factors for occurrence of the preterm birth while the disease is multifactorial in nature. The mechanisms underlying the association could be explained by the theory that set as the periodontal pathogens may trigger an inflammatory response leading to elevated inflammatory cytokines level which would influence the degradation of the extracellular matrix of the fetal membranes and cervix [6,7]. It also could be explained as the periodontal pathogens, such as Fusobacterium nucleatum, migrates to the fetal-placental

| | Table 1 | | | | | Characteristics of the included studies | | |

Study	Country	Design	Blind	Participants Control/case	Age	Examination	PD definition	Conclusion
2022 Iqbal A	India	Retrospective	NA	4/100,7/100	23-24	Before delivery	NA	No association, p=0.189
2022 Pockpa ZAD	Ivory Coast	Prospective	Yes	12/137,50/201	15-50	Before delivery	2018 EFP/AAP	Positive association,OR = 3.62
2022 Lee YL	Taiwan	Retrospective	Yes	97447/ 825399,93589/ 728643	20-45	Before delivery	AAP	OR=1.09
2022 Trivedi P	India	Prospective	Yes	143/1897,37/ 80	24.6	Before delivery	Irritation, redness, and swelling of the gums.	OR= 11.4
2022 Shaggag LM	Sudan	Case-control	Yes	115/250,50/ 80	22-36	After delivery	EFP/AAP	OR=2.05
2021 Choi SE	USA	Retrospective	Yes	105346 / 731081,2935/ 15979	27.8/31.6	Before delivery	Treatment pre pregnancy	OR=1.15
2021 Márquez-Corona ML	Mexico	Case-control	NA	6/32,10/79	18–42	Before delivery	CDC-AAP	Positive
2021 Uwambaye P	Rwanda	Case-control	Yes	31/260,154/ 295	16-35	After 1 to 5days Delivery	EFP/AAP	OR=6.36
2020 Micu IC	Romania	Case-control	Yes	54/156,20/38	18-43	within the first 72 h after delivery	AAP	OR=2.18
2020 Nikolić L	Serbia	Cross sectional	NA	19/68,37/44	17-41	within 48 hours following delivery	1999	Positive
2020 Moncunill-Mira J	Spain	Case-control	Yes	28/82,32/64	18-45	the first 2 days of the postpartum	AAP	OR= 7.49
2020 Novák T	Hungary	Case-control	Yes	44/165,33/77	29.3/	3 days post-par- tum.	PD ≥4 mm found at least at one site, and BOP ≥50% of the teeth.	OR=1.95
2020 de Oliveira LJC	Brazil	Prospective	Yes	299/ 2239,39/362	20-34	Before delivery	AAP	OR=1.93
2020 Erchick DJ	Nepal	Prospective	Yes	113/ 840,84/554	15-40	Before delivery	BOP ≥10% and/or PD ≥4 mm	OR=1.07
2020 Taniguchi-Tabata A	Japan	Prospective	Yes	1/21,4/23	34.1	first or early second trimester.	EM	Positive
2019 Pérez-Molina JJ	Mexico	Case-control	NA	114/522,229/ 507	23.8 /23.2	first 24 hours of the NB delivery	EM	CDC–AAP OR 2.95
2019 Kopycka-Kedzierawski DT	USA	Retrospective	NA	18292/ 211966,6231/ 77247	27.7/27.3	After delivery	Bleeding swollen gum	OR=0.950 No association
2018 Lafaurie GI	Colombia	Case control	NA	51/296,22/69	NA	After delivery	CPI index	OR=2.04
2018 Gesase N	Tanzania	Cross sectional		79/958,31/ 159	18-46	the time of admission to the labour and delivery area	CPI index	OR=2.7
2018 Montenegro DA	Colombia	Case control	NA	30/91,52/105	24,24.1	before or up to 8 hours after the delivery	AAP	OR=1.99
2017 Govindasamy R	India	Cross sectional	NA	653/1556,747/ 1944	18-35	within 3 days of delivery	AAP	OR=0.72
2016 Khan NS	Pakistan	Case Control	NA	31/89,49/71	18–35	within the first 48 hours	EM	OR =3.173
2015 Blanc V	Spain	Case Control	Yes	18/29,18/28	24	24 h from delivery	EM	No
2015 Basha S	India	Prospective	NA	17/181,20/126	18-28	After delivery	EM	OR= 4.54
2014 Macedo JF	Brazil	Case-control	NA	58/250,16/46 42/222,32/74	18-40	within the first 48 h after delivery	EM	OR=1.98
2013 Ashok Kumar	India	Prospective		24/132,23/61	20-35	at 14–20 weeks	CPI index	OR=2.72
2013 Wang YL	Taiwan	RCT	Yes	11/149,11/62	22-40	<5 months gestation	AAP	No
2013 Santa Cruz	Spain	Prospective	NA	3/116,2/54	NA	Before delivery	EFP	No
2012 Tejada	Switzerland	Case-control	Yes	50/304,34/125	NA	cwithin 24–72 h following delivery	AAP	Positive

NA means not available.
CAL clinical attachment loss, PD probing depth
CDC-AAP: absent: PD<3mm and CAL<2mm; mild: PD≥3mm or CAL≥2mm; moderate: two or more sites with PD ≥ 5mm and two or more sites with CAL≥2mm; and severe: four or more sites with PD≥5 mm and four or more sites with CAL≥2 mm.
EFP/AAP classification, interdental CAL at two non-adjacent teeth with buccal/oral CAL≥3 mm, with pocketing >3 mm
CPI index: Clinical attachment loss and probing depth □4 mm in one or more site
EM: least four teeth with one or more sites with a probing depth of ≥4 mm and with clinical attachment loss of ≥3 mm [41]

Table 2	Assessment of quality of the included studies using Newcastle-Ottawa Scale.			
Study	Selection	Comparability	Exposure/ outcome	Total
2022 Iqbal A	***	*	**	6
2022 Pockpa ZAD	***	**	***	8
2022 Lee YL	***	**	***	8
2022 Trivedi P	**	**	**	6
2022 Shaggag LM	***	**	**	7
2021 Choi SE	***	**	***	8
2021 Márquez-Corona ML	**	*	**	5
2021 Uwambaye P	***	*	**	6
2020 Micu IC	***	**	**	7
2020 Nikolić L	**	*	***	6
2020 Moncunill-Mira J	***	**	**	7
2020 Novák T	***	*	***	7
2020 de Oliveira LJC	***	**	***	8
2020 Erchick DJ	***	*	**	6
2020 Taniguchi-Tabata A	*	**	**	5
2019 Pérez-Molina JJ	***	**	**	7
2019 Kopycka-Kedzierawski DT	****	**	**	8
2018 Lafaurie GI	***	*	**	6
2018 Gesase N	***	*	**	6
2018 Montenegro DA	***	**	**	7
2017 Govindasamy R	***	*	**	6
2016 Khan NS	***	*	**	6
2015 Blanc V	**	**	**	6
2015 Basha S	***	*	**	6
2014 Macedo JF	**	**	**	6
2013 Ashok Kumar	***	**	***	8
2013 Wang YL	****	**	***	9
2013 Santa Cruz	***	*	**	6
2012 Tejada	**	**	**	6

Study or Subgroup	Periodontitis Events	Total	Healthy Events	Total	Weight	Odds Ratio M–H, Random, 95% CI	Year
Tejada 2012	34	125	50	304	3.5%	1.90 [1.15, 3.12]	2012
Ashok Kumar 2013	23	61	24	132	2.3%	2.72 [1.38, 5.38]	2013
Santa Cruz I 2013	2	54	3	116	0.4%	1.45 [0.23, 8.93]	2013
Wang YL 2013	11	62	11	149	1.5%	2.71 [1.11, 6.62]	2013
Macedo JF 2014	16	46	58	250	2.3%	1.77 [0.90, 3.46]	2014
Basha S 2015	20	126	17	181	2.2%	1.82 [0.91, 3.63]	2015
Blanc V 2015	18	28	18	29	1.1%	1.10 [0.37, 3.23]	2015
Khan NS 2016	49	71	31	89	2.3%	4.17 [2.14, 8.11]	2016
Govindasamy R 2017	747	1944	653	1556	7.9%	0.86 [0.75, 0.99]	2017
Gesase N 2018	31	159	79	958	3.9%	2.69 [1.71, 4.25]	2018
Lafaurie GI 2018	22	69	51	296	2.8%	2.25 [1.25, 4.05]	2018
Montenegro DA 2018	52	105	30	91	2.8%	1.99 [1.12, 3.57]	2018
Kopycka–Kedzierawski DT 2019	6231	77247	18292	211966	8.8%	0.93 [0.90, 0.96]	2019
Pérez–Molina JJ 2019	229	507	114	522	6.1%	2.95 [2.25, 3.87]	2019
de Oliveira LJC 2020	39	362	299	2239	5.0%	0.78 [0.55, 1.12]	2020
Erchick DJ 2020	84	554	113	840	5.6%	1.15 [0.85, 1.56]	2020
Micu IC 2020	20	38	54	156	2.1%	2.10 [1.02, 4.30]	2020
Moncunill–Mira J 2020	32	64	28	82	2.3%	1.93 [0.99, 3.77]	2020
Nikolić L 2020	37	44	19	68	1.3%	13.63 [5.19, 35.82]	2020
Novák T 2020	33	77	44	165	2.9%	2.06 [1.17, 3.64]	2020
Taniguchi–Tabata A 2020	4	23	1	21	0.3%	4.21 [0.43, 41.14]	2020
Choi SE 2021	2935	15979	105346	731081	8.7%	1.34 [1.28, 1.39]	2021
Márquez–Corona ML 2021	10	79	6	32	1.0%	0.63 [0.21, 1.90]	2021
Uwambaye P 2021	154	295	31	260	4.0%	8.07 [5.20, 12.52]	2021
Iqbal A 2022	7	100	4	100	0.8%	1.81 [0.51, 6.38]	2022
Lee YL 2022	93589	728643	97447	825399	8.8%	1.10 [1.09, 1.11]	2022
Pockpa ZAD 2022	50	201	12	137	2.3%	3.45 [1.76, 6.76]	2022
Shaggag LM 2022	50	80	115	250	3.3%	1.96 [1.17, 3.28]	2022
Trivedi P 2022	37	80	143	1897	3.7%	10.55 [6.59, 16.91]	2022
Total (95% CI)		827223		1779366	100.0%	1.81 [1.60, 2.03]	
Total events	104566		223093				

Heterogeneity: Tau² = 0.04; Chi² = 558.99, df = 28 (P < 0.00001); I² = 95%
Test for overall effect: Z = 9.73 (P < 0.00001)

Figure 2 - Forest plots of summary crude odds ratios (ORs) and 95% confidence intervals (CIs) for the periodontitis and preterm birth.
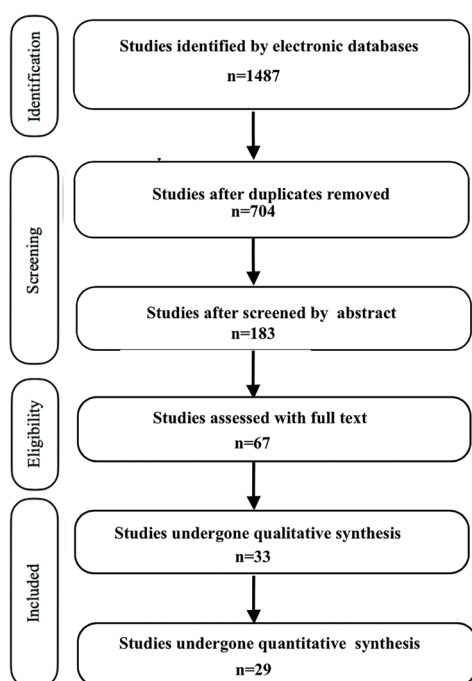
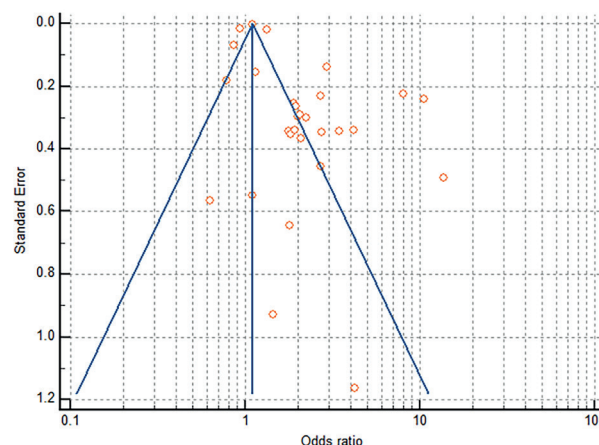**Figure 1** - Flow diagram of the study search and identification.

Figure 3 - Funnel plot for assessment of potential publication bias.

Table 3	Egger's test for potential publication bias in the included studies

Egger's test	
Intercept	2.2885
95% CI	0.6757 to 3.9013
Significance level	P = 0.0071

sections of the mother hematogenously, while these pathogens have been isolated from the placenta and amniotic fluid of preterm cases [39]. A most recent Israel study found that the high level of Gal-GalNAc, also known as Thomsen Friedenreich antigen during pregnancy mediates the placental colonization by Fusobacterium nucleatum [40].

Our study is limited by the inconsistent research design, as the includ studies regardless of the prospective and retrospective cohort and case control studies. Secondly, the unequal baseline of the sample in studies, such as geographic distribution, age, socio economic factors may also have influenced the heterogeneity of the studies, since most of the studies were carried out in the developed western countries. In addition, both health conditions share some major confounding factors, which may bias the estimates. In an attempt to minimize the possibility of publication bias, more databases were selected to search the original evidence. Furthermore, the diagnostic criteria for the periodontitis in the studies are difficult to standardize, while there are several diagnostic criteria presented in these studies and evaluated the association according to the definition used. In this sense, it is necessary to standardize criteria for determining periodontitis for pregnant women, which aims at greater methodological homogeneity between studies and a more consistent direction for the clinical practice of dental professionals. Further validation or substantiation about the association needs to collect more robust data.

Conclusion

Periodontitis during pregnancy must be considered as one of the important factors which is associated with increased risks of preterm birth. It is important to put the disease under control before and during pregnancy while it is preventable and treatable. It may be important to reduce the preterm birth outcome.

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Post-COVID-19 fatigue: A cross-sectional study

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Abstract

Aim: To evaluate the prevalence of post-infection fatigue (PVFS) over one year after COVID-19.

Material and methods: 165 people who had COVID-19 more than a year ago were interviewed. A Fatigue Assessment Scale was used to assess the degree of fatigue. Chemiluminescent analysis was carried out to detect antibodies to Epstein-Barr Virus (EBV) antigens. For statistical analysis Fisher's exact test and Spearman correlation were conducted.

Results: Among people with PVFS, there were 4.1 times more women than men (80.4% vs. 19.6%), people over 45 years old (76%), and people who needed hospitalization for COVID-19 (76%). The average fatigue duration was 573±18,3   days. Among individuals without PVFS, there were significantly more individuals under the age of 45 compared with the group of individuals with PVFS (40% and 24%, respectively, p=0.007) and there were significantly more individuals who did not need hospitalization compared with the group of individuals with PVFS (52% vs. 24%, p=0.005). EBV reactivation was determined in almost half of the individuals with PVFS (48%), while none of the individuals without PVFS had EBV reactivation. A statistically significant negative mean correlation was found between the duration of PVFS and the severity of PVFS (r=-0.357, p=0.007). A statistically significant negative correlation was found between the PVFS duration and the PVFS severity (r=-0.357, p=0.007).

Conclusion: PVFS is a prevalent symptom after COVID-19. The duration of PVFS can reach and not be limited to 1.5 years. PVFS is more typical of women, people over 45 years of age and people who have had moderate and severe COVID-19. Over time, the severity of PVFS decreases.

Key words: COVID-19, post-infection fatigue, Epstein-Barr virus

Introduction

The COVID-19 pandemic, which lasted almost two years and, according to WHO, affected more than 659 million people and claimed more than 6.6 million lives worldwide as of early January 2023 [1], left many unresolved issues, primarily associated with post-COVID sequels. A feature of long COVID is the presence of a wide range of symptoms of varying severity, including general symptoms such as fatigue, post-exercise malaise and fever, as well as groups of symptoms related to disorders in the functioning of various organs and systems [2-4].

There is currently no long-term evidence base to help determine how long the current effects seen after SARS-CoV-2 infection last. The term "post-covid syndrome" has been agreed to mean that the acute phase of the disease has ended, but the patient has not yet recovered.

Today, a distinction is made between prolonged fatigue (PF), chronic fatigue (CF), idiopathic chronic fatigue (ICF), and systemic exertion intolerance disease (SEID) exercise intolerance syndrome, also referred to as chronic fatigue syndrome (SCF) or myalgic encephalomyelitis (ME), which is isolated as a separate nosology. At the same time, in the spectrum of post-COVID disorders, researchers report the predominance of chronic fatigue, the signs of which developed during or immediately after COVID-19 and can be regarded as post-viral fatigue (PVFS) [5-8]. Corresponding criteria are formulated for each type of fatigue [9, 10]. To

identify fatigue, researchers usually use various questionnaires to identify feelings of mental and/or physical fatigue, as well as the fatigue effect on the respondent's quality of life [7, 11-16].

To date, researchers have shown that one of the main symptoms of long COVID is fatigue, which can be present in a patient for 6 months or more after COVID-19 [13, 17, 18]. However, the issue of the duration of this post-COVID symptom and its characteristics in a longer period has not yet been sufficiently studied.

This study is devoted to the study of the prevalence of PVFS in the period of more than one year after COVID-19.

Material and methods

The study was conducted at the Asfendiyarov Kazakh National Medical University, Kazakhstan, Almaty in October 2022.

Study design

Cross-sectional study of COVID-19 survivors over a year ago to assess long-term PVFS prevalence.

Study population

For the study, 200 individuals of both sexes with a history of PCR-confirmed COVID-19 more than one year ago were selected from the medical information system of the Ministry of Health of the Republic of Kazakhstan "Damumed", regardless of the disease severity and the fact of hospitalization during the infection acute period. A telephone call was made to these individuals, during which 165 people were interviewed. Of these, three groups were formed: individuals who indicated the post-COVID symptoms absence (n=87), individuals with PVFS (n=55) and individuals with post-COVID symptoms who did not indicate the fatigue presence (n=23). Nine individuals from the PVFS group refused to participate in the study. Thus, a study group was formed, consisting of 46 people who were examined using the Fatigue Assessment Scale (FAS) and laboratory methods. For the formation of the control group, 50 participants were randomly selected from fully recovered COVID-19 patients (Figure 1).

Inclusion Criteria

The study included people of both sexes aged 18-80 who had been ill with confirmed COVID-19 more than one year ago.

Exclusion Criteria

A history of chronic diseases: oncological, autoimmune and others, which may be manifested by fatigue and / or require treatment with cytostatics, immunosuppressive drugs, including genetically engineered biological products, as well as psychotropic drugs.

Fatigue assessment

The presence and level of fatigue was assessed using FAS. This scale was developed by Michielsen et al [19], is recommended for use and has been widely used to assess fatigue in various study cohorts since 2003 [7, 20-23]. FAS consist of 10 items. Each FAS item is scored on a five-point Likert-type scale ranging from 1 (never) to 5 (always). Items 4 and 10 are evaluated in reverse order. The score ranges from 10, indicating the lowest fatigue level, to 50, indicating the highest level of respondent fatigue.

Ethical aspects

The study was approved by the Ethics Committee of the Asfendiyarov Kazakh National Medical University (Minutes No.1 (124) of 01/26/2022).

Informed consent was obtained from all study participants after a full explanation of the purpose and methods of the study, confirmation of the confidentiality of the data obtained, and notification that they can refrain from the study at any time without explanation.

Antibodies to Epstein-Barr virus (EBV) antigens were determined by immunochemiluminescence analysis using test kits for IgM to the capsid antigen (CA), IgG and IgA to the early antigen (EA) and core antigen (NA) EBV (Maglumi, China).

The simultaneous seropositivity of IgM for EA (IGM-EA) and IgG for NA (IgG-EBNA-1) was considered a marker of EBV reactivation [24].

Statistical analysis

All statistical analyzes were performed using IBM SPSS Statistics v29.0 and statistical significance was considered $p < 0, 05$. Descriptive statistics are presented as mean with error of mean and minimum/maximum value. We analyzed the intergroup differences between individuals with PVFS compared with those without it using Fisher's exact test. In the correlation analysis according to the data, the Spearman correlation coefficient was used.

Results

Comparative characteristics of individuals with PVFS (PVFS+) and those without it (PVFS -) are presented in Table 1.

When comparing the main characteristics in individuals with and without PVFS, a slight predominance of men in the group with no PVFS was revealed, compared with the group with PVFS (32% vs. 20%). At the same time, among individuals without PVFS, there were significantly more individuals under the age of 45 compared with the group of individuals with PVFS (40% and 24%, respectively, p=0.007). Also, significant differences were found between the compared groups in terms of the severity of COVID-19.

Table 2	Study group characteristic with PVFS (n=46)		

№	Parameters		Amount, n	%
1	Sex	Male	9	20
		Female	37	80
2	Age (years)	26-44	11	24
		45-59	22	48
		60-74	9	20
		75-80 ≥	4	8
3	BMI	<18.5	1	2
		≥18.5 до < 25	22	48
		≥25	23	50
4	Required inpatient treatment for COVID-19	No	11	24
		Yes	35	76
5.	Fatigue degree*	Mild	32	70
		Moderate	9	20
		Severe	5	10
6	Average duration of fatigue at the time of the survey M±m (max/min)	573±18,3 (856/370)	-	-

* The severity of PVFS was determined according to the questionnaire:
Mild – 22-28 points
Moderate – 29-34 points
Severe – above 35 points

Table 1 — Comparative characteristics of PVFS+ and PVFS – groups

Parameters		PVFS+ N=46	PVFS – N=50	P
Sex	Male	9 (20%)	16 (32%)	0,166
	Female	37 (80%)	34 (68%)	
Age (years)*	26-44	11 (24%)	20 (40%)	**0,007**
	45-59	22 (48%)	12 (24%)	
	60-74	9 (20%)	18 (36%)	
	75-80 ≥	4 (8%)	0 (0%)	
BMI**	<18.5:	1 (2%)	2 (4%)	0,770
	≥18.5 до < 25	22 (48%)	26 (52%)	
	≥25	23 (50%)	22 (44%)	
Required inpatient treatment for COVID-19	No	11 (24%)	26 (52%)	**0,005**
	Yes	35 (76%)	24 (48%)	
EBV reactivation	No	24 (52%)	50 (100%)	**<0,001**
	Yes	22 (48%)	0 (0%)	

* Age criteria were determined in accordance with WHO criteria
* BMI criteria were determined in accordance with the WHO classification

Table 3 — Group's characteristic with different degrees of PVFS

Parameters	M±m	Mild (22-28 points), n=32 (100%)	Moderate (29-34 points), n=9 (100%)	Severe (above 35 points), n=5 (100%)
Sex				
Male (n=9)	28,11±1,79	5 (16%)	2 (22%)	2 (40%)
Female (n=37)	26,97±0,80	27 (84%)	7 (78%)	3 (60%)
Age				
26-44 (n=11)	27,36±1,76	8 (25%)	2 (22%)	1 (20%)
45-59 (n=22)	27±1	15 (47%)	5 (56%)	2 (40%)
60-74 (n=9)	27,44±1,60	7 (22%)	1 (11%)	1 (20%)
75-80 ≥ (n=4)	27,25±3,01	2 (6%)	1 (11%)	1 (20%)
BMI				
<18.5 (n=1)	-	0 (0%)	1 (11%)	0 (0%)
≥18.5 до < 25 (n=22)	26±1	18 (56%)	3 (33%)	1 (20%)
≥25 (n=23)	28,04±1,03	14 (44%)	5 (56%)	4 (80%)
Needed COVID-19 inpatient treatment				
No (n=36)	27,69±1,75	26 (81%)	7 (78%)	3 (60%)
Yes (n=10)	27±0,76	6 (19%)	2 (22%)	2 (40%)

Table 4 — Correlation analysis results between PVFS duration, age, body mass index with PVFS severity

Parameters	Spearman's correlation coefficient	P-value
Duration of PVFS after COVID-19 (days)	-0,357	0,007
Age	0,069	0,325
BMI	0,135	0,186

Thus, in the group with no PVFS, there were significantly more individuals who did not need hospitalization compared with the group of persons with PVFS (52% vs. 24%, p=0.005).

EBV reactivation was determined in almost half of the individuals with PVFS (48%), while none of the individuals without PVFS had EBV reactivation.

The main characteristics of individuals with PVFS lasting more than 1 year after COVID-19 are presented in Table 2.

Among individuals with PVFS, there were 4.1 times more women than men (80.4% versus 19.6%). At the same time, PVFS was more common in people older than 45 years (76%). Half of those with PVFS were overweight. At the same time, 76% of individuals required hospitalization for COVID-19.
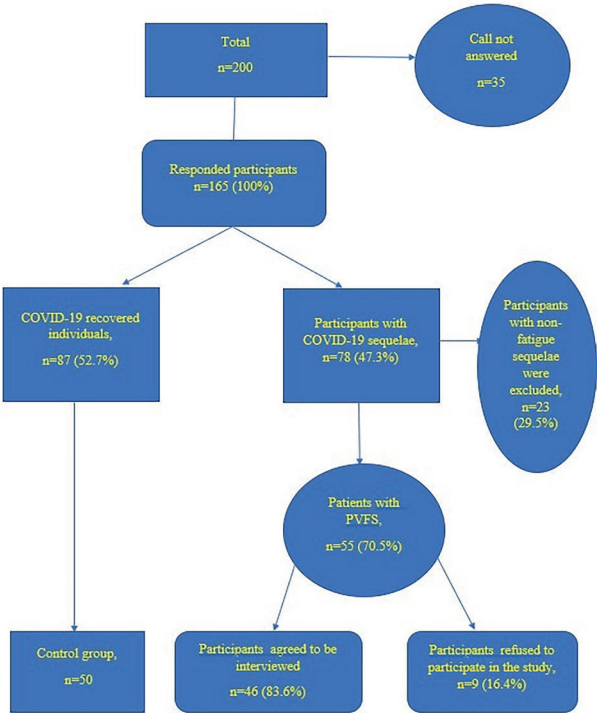
Figure 1 - Flow chart of study population
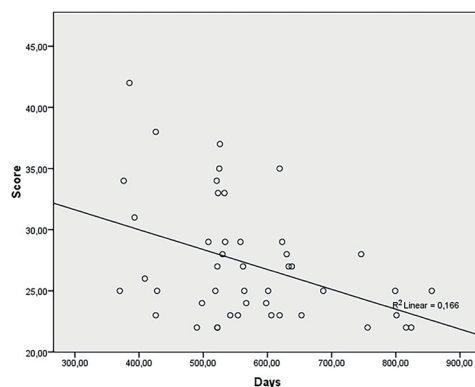
Figure 2 - Association between PVFS duration and PVFS severity
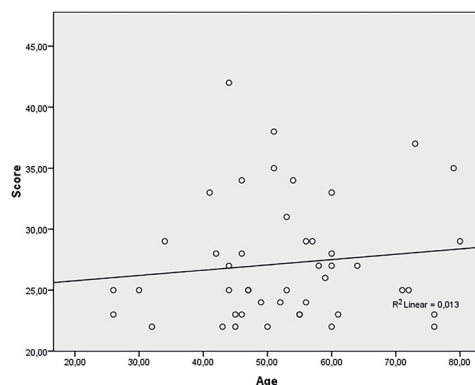
Figure 3 - Association between age and PVFS severity
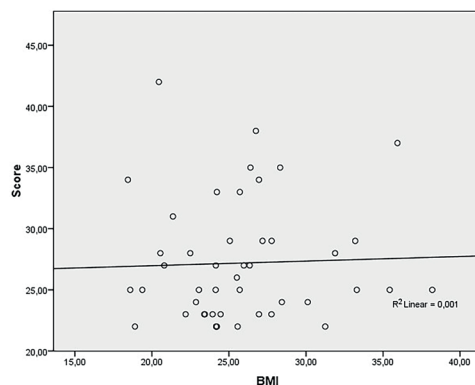
Figure 4 - Association between BMI and PVFS severity

However, 70% of individuals noted a mild degree of PVFS, while severe PVFS was observed in only 5% of individuals. The average duration of fatigue was 573 days.

Severe PVFS prevailed in women compared to men (60% versus 40%, respectively). Severe PVFS was found in 80% of overweight individuals. At the same time, a mild degree of PVFS prevailed in those who did not need hospitalization (81%) (Table 3).

The results of the correlation analysis between the duration of PVFS, age and BMI with the PVFS severity are presented in Table 4.

A statistically significant negative correlation was found between the duration of PVFS and the severity of PVFS (r=-0,357, p=0,007). A positive, non-significant weak correlation was found between age, BMI and PVFS severity (r=0,069, p=0,325 and r=0,135, p=0,186, respectively) (Figures 2-4).

Discussion

One of the main issues in the COVID-19 post-pandemic stage is how long post-COVID manifestations are and what their mechanism is.

To date, studies on the post-COVID effects duration are limited to a period of just over 1 year [25-28]. In our study, we covered a later period of 1 to 2 years. At the same time, we focused only on the PVFS manifestations, since this symptom is one of the most common sequalae of COVID-19 [29, 30], but, at the same time, due to unexpressed symptoms, it often falls out of the sight of clinicians.

In our study, it was found that in almost half of the people who had COVID-19, after 1 year, various manifestations of post-COVID complications persist, while chronic fatigue is the predominant symptom (70.5%). These data significantly exceed data on the prevalence of both idiopathic chronic fatigue (ICF) and chronic fatigue syndrome (CFS) in the adult population [31-33]. In a previously conducted pilot study of the prevalence of fatigue in the Kazakhstan population in 2018, we conducted a survey of 1000 respondents using FAS. According to this study results, pathological fatigue was found in 432 (43.2%) and no fatigue in 568 (56.8%) respondents. In the group of people with fatigue, 62.4% were women and 37.6% were men. Since we excluded individuals with comorbid conditions that may contribute to the development of chronic fatigue from the study, we can assume that this fatigue is a post-COVID consequence.

In our group of PVFS individuals, there was a predominance of women, people over 45 years old, and people who needed COVID-19 inpatient treatment, that is, people with a more severe COVID-19. Moreover, severe PVFS was observed in women 1.5 times more often than in men. These data are consistent with the results of studies by other authors in the earlier post-COVID period [25, 34].

It is assumed that the prevalence of women in the group with chronic fatigue is associated with both psychological and physiological characteristics of women, such as a lower tendency to mask symptoms, as well as neurohormonal characteristics [35].

A comparative analysis of the indicators of PVFS individuals and those without PVFS also confirmed these data, showing significant differences in age and COVID-19 severity. Interestingly, some authors noted the presence of fatigue in the earlier post-COVID period, even with mild COVID-19 [36]. At the same time, the results of our study suggest that in mild cases of COVID-19, PVFS rarely lasts more than 1 year. Even if people who recovered easily from COVID-19 noted fatigue after 1 year, this fatigue is not expressed according to our data.

The propensity to reduce the PVFS severity over time is also confirmed by the data of the correlation analysis, which revealed a significant negative relationship between the duration of PVFS and the severity of PVFS. A similar association has also been found in earlier studies [37]. We also found a weak positive relationship between age and BMI and the severity of PVFS. We believe that the lack of significant differences in our study in these parameters is due to the small sample size, which is a limitation of our study. An additional limitation is the lack of data on other potential risk factors for fatigue in the post-COVID-19 period. At the same time, the median duration of PVFS in our cohort was 573 days, suggesting that PVFS may continue for at least 1.5 years after COVID-19.

In our study, 48% of PVFS individuals had EBV reactivation. Earlier studies have shown that EBV reactivation can occur both with COVID-19 and in the post-COVID period [25, 38-41]. Since our study is cross-sectional, we cannot

identify the timing of the onset of EBV reactivation and be sure that this reactivation is associated with COVID-19. However, the prevalence of EBV reactivation in our focus group with PVFS exceeds the prevalence of EBV in risk groups associated with EBV reactivation [42, 43]. In this regard, we believe that more in-depth studies are needed to study the causes of EBV reactivation in the long-term period after COVID-19.

Conclusion

PVFS is the predominant symptom one year after COVID-19 (70.5%), which exceeds its frequency in the pre-COVID period (43.2%). The duration of PVFS has not been determined and may continue beyond 1 year after the acute phase. The average duration of PVFS was 537 days. PVFS for a period longer than 1 year persists to a greater extent in women and persons over 45 years of age. PVFS was detected in those who had COVID-19 in moderate and severe forms and received inpatient treatment. Over time, the intensity of PVFS decreases. At the same time, serological markers of EBV reactivation were detected in 48% of individuals with PVFS.

However, additional studies are needed to confirm the hypotheses put forward and to identify factors associated with the prolonged fatigue formation in the late post-COVID period.

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Nurses' compliance with standard precautions during COVID-19 pandemic

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Abstract

Aim: Nurses are healthcare professionals who work at the forefront of healthcare delivery during the Covid-19 pandemic. Pandemic conditions have brought many difficulties for nurses. On the one hand, nurses working 24 hours a day, seven days a week to meet the severe health care needs of patients infected with Covid-19, on the other hand, are struggling against the risk of virus transmission. This study was conducted in a descriptive manner to determine the nurses' compliance with standard precautions during the Covid-19 pandemic process.

Material and methods: This study was carried out at Dr. Ersin Arslan Training and Research Hospital between September and December 2021. The population of the study consisted of nurses working in the hospital during the pandemic process, and 219 nurses who agreed to participate in the study without any sampling method formed the sample of the study. The study data were collected by the researcher by face-to-face interview technique with the "Socio-demographic Information Form" and "Scale of Adaptation to Standard Precautions" created by the researchers.

Results: 57.5% of the nurses participating in the study were women and 63.9% were single. The age of the participants in the study is between 18-65 and 31.5% of them are between 26-35 years old. 23.7% of the nurses participating in the study work in the intensive care unit, and 32.9% of them work between 26-30 years. The mean score of the Nurses' Compliance with Standard Precautions Scale was 14.48±2.80.

Conclusion: As a result of the study, the compliance score of nurses to standard precautions in the Covid-19 pandemic was found above the average. In addition, it has been determined that the characteristics of nurses such as age, gender, professional experience are factors that affect their compliance with standard precautions.

Key words: Covid-19, nurse, standard precautions

Introduction

Nurses are the health professionals who are at the forefront of health service delivery during the Covid-19 pandemic [1]. Nurses working at the bedside 24 hours a day, seven days a week to meet the severe health care needs of patients infected with Covid-19 are struggling against the risk of virus transmission [2,3]. The International Council of Nursing (ICN) has reported that there are over 90 thousand Covid-19 infected healthcare professionals worldwide [1]. The most basic precautions to be taken against Covid-19 are personal hygiene, isolation and social distancing. In the literature, the precautions to be taken at the social level against Covid-19 are limited to these three topics, and it has been reported that the precautions to be taken for nurses, who provide care to Covid-19 infected patients in hospitals and are one of the high-risk occupational groups, should be examined in more detail [4,5]. In a meta-analysis study in which 119.219 patients infected with Covid-19 were analyzed; 10% of the patients were reported to be healthcare professionals [6]. The percent of healthcare professionals in Covid-19 cases are reported to be 14.5%

in the UK, 12.9% in the USA, and 10.6-20% in Italy [7-10]. In Turkey, it was announced that 10.9% of infected patients were healthcare professionals until February 2021; 216 of them died due to Covid-19 [11]. In a study conducted in the People's Republic of China (2020) with 2431 healthcare professionals who worked during the pandemic; it was reported that 60% of the employees were nurses and 30% were physicians [12].

Isolation methods known as standard precautions in the hospital environment are considered as a whole for patients and healthcare professionals. Standard precautions are the ones taken on the assumption that each individual is potentially infected and/ or colonised with a pathogen that may cause infection. Isolation is the precautions taken by the health personnel and the patient against the known route of transmission of the infection in addition to the standard precautions [13]. The main objective of the standard precautions for healthcare professionals is to prevent the transmission of all pathogenic microorganisms from patient blood, urine and stool, secretions and mucous membranes [14]. During the pandemic process, nurses' compliance with standard precautions due to their close contact with patients infected with Covid-19 is extremely important in terms of infection control [15]. Standard precautions that nurses should apply in the fight against Covid-19 include ensuring the continuity of hand hygiene, effective use of PPE and management of wastes that are properly eliminated [16]. Standard precautions taken for healthcare professionals for Covid-19 include the use of PPE to prevent the transmission of microorganisms from body fluids such as blood, urine, stool, and environmental waste management [14]. Standard precautions must always be applied. Hand hygiene and respiratory hygiene are the most basic precautions. Hand washing and the use of alcohol-based antiseptics are the most effective and simplest ways to prevent the spread of respiratory infections [17]. Rational, consistent and correct use of PPE is essential to prevent the spread of pathogens. The effectiveness of PPE is largely dependent on regular and adequate supplies, adequacy of staff training, proper hand hygiene and appropriate individual behaviour [18]. Patients should cover their mouth and nose with a napkin or elbow when sneezing or coughing. Hands hygiene should be maintained before and after touching a patient, before any aseptic procedure is performed, after contact with body fluid, after touching the patient's environment, before and after putting on PPE [17,19]. Hand hygiene should be provided with soap and water for at least 20 seconds or with 60-95% alcohol-based hand sanitisers. If there is no visible contamination, alcohol-based disinfectants should be preferred. If there is visible contamination, hands should be washed with soap and water [19].

Isolation precautions taken in hospitals have been determined by institutions with competence in global standards such as CDC, ECDC (European Centre for Disease Prevention and Control) [20]. In Turkey, these standards are carried out by "Infection Control Committees" established by the relevant persons in hospitals under the Ministry of Health [21]. Compliance of healthcare professionals with infection control methods is important in terms of minimizing nosocomial infections [22].

Material and methods
Aim
It was a descriptive and cross-sectional study to determine the nurse' compliance with standard precautions during Covid-19.

Place and date
The study was conducted between September and December 2021 at a training and research hospital, a tertiary healthcare institution in Gaziantep city centre and serving in two separate buildings. The total number of beds in hospital is 840. The hospital has internal and surgical inpatient wards, general intensive care, internal and surgical intensive care, neonatal intensive care wards.

Population and sample
The study population consisted of 896 nurses. The sample size was calculated as 270, which was determined by power analysis with a significance level of 0.05, a confidence interval of 0.95, an effect size of 0.5, and a 95% representativeness of the universe. The 12 nurses who were on leave during the data collection period, 25 nurses who did not want to participate in the study and 14 nurses who collected incomplete data forms were excluded from the study and the study was completed with 219 nurses. In the study, simple random sampling method was used.

Inclusion criteria
- Volunteering for the study
- Being in the nursing profession during the pandemic

Exclusion criteria
- Not working in the hospital where data is collected during the pandemic
- Not volunteering
- Failure to complete data forms in full

Data collection
The data were collected online. After the data collection forms were created from Google form, the executive nurses were contacted. Necessary explanations about the study were made. E-mail addresses or mobile phone numbers of the nurses were obtained. The link to the data collection forms was shared with the nurses to be included in the study. The necessary explanation about the study and consent for participation in the study were added to the data collection form.

Descriptive characteristics form
In this form, which was prepared by the researcher by examining the relevant literature, there are 5 questions including descriptive characteristics of the nurses such as age, gender, marital status, duration of professional experience and the unit of employment.

Compliance with Standard Precautions Scale (CSPS)
The Compliance with Standard Precautions Scale (CSPS) is a scale that aims to reveal the compliance of healthcare professionals with standard protective precautions, which are evaluated within the scope of precautions to be taken for infection control. In other words, it is a measurement tool in which healthcare professionals make self-assessments to determine whether they exhibit protective and safe behaviours in infection control and prevention [23]. The scale was developed by Simon Ching Lam in 2011 based on the international protective precautions published by the CDC [24]. The Turkish validity and reliability study of the scale was conducted by Samur et al. in 2020. The one-dimensional and four-point Likert scale is graded as "1=never", 2=rarely", "3=sometimes", "4=always". In the evaluation of the scale, the "always" response to the positively scored items (items 1, 3, 5, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19 and 20) is coded with "1 point" and the other responses are coded with "0 points". The "never" response to the negatively scored items in the scale (items 2, 4, 6 and 15) is coded as "1 point" and the other responses are coded as "0 points". The total score that can be obtained from the scale varies between "0 - 20". Cronbach's alpha value of the original scale is 0.73. Cronbach's alpha value in this study was found to be 0.86.6.

Data evaluation

The evaluation of the data was carried out using SPSS 22 programme. Frequency and percentage calculations were used in the evaluation of data related to descriptive characteristics, mean and standard deviation values, ANOVA test, t-test and Mann Whitney-U test were used for the analysis of the nurses' level of compliance with standard precautions.

Ethical dimension of the study

Before starting the study, the necessary approvals were obtained and the principle of "Informed Consent" was fulfilled by explaining the purpose of the study to the nurses included in the study, the principle of "Confidentiality and Protection of Confidentiality" by stating that the information obtained would be kept confidential, and the principle of "Respect for Autonomy" was fulfilled by voluntary participation of all nurses.

Results

Table 1 shows the nurses' socio-demographic characteristics and 57.5% were female and 63.9% were married. 31.5% of the nurses were between 26-35 years of age, 23.7% of them were working in intensive care unit and the working years of 32.9% were between 26-30 years. It was determined that 63.5% of the nurses believed that standard precautions were protective and 63.9% did not experience any negative effects of standard precautions. In our study, it was determined that 79% of the nurses were not diagnosed with Covid-19, 92.7% did not lose any relatives due to Covid-19, and 73.5% did not live with a Covid-19 risk individual (Table 1).

The mean total score of the Standard Precautions Scale of the nurses participating in the study was found to be 14.48±2.80, which was above the literature and the average (Table 2).

The comparison of the socio-demographic characteristics of the nurses and the mean scores of the standard precautions compliance scale is given in Table 3. When the mean scores of the scale of compliance with standard precautions according to the age groups of the nurses are analyzed in the table, the mean scale score of those in the 56-65 age group was 16.25±0.95, which was higher than the other age groups, and the statistically significant difference was found (p<0.05). The mean score (15.18±3.64) of nurses with chronic disease on the scale of compliance with standard precautions is higher than the mean score (14.25±2.82) of nurses without chronic disease and the statistically significant difference was found (p<0.05). The mean scale score of the nurses working in the Intensive Care Unit (14.94±2.09) was higher than the mean score of the nurses working in other units and the difference was statistically significant (p<0.05). The mean scale score of nurses working 40 hours or less per week (15.22±2.32) was higher than the mean scale score of nurses working 41 hours or more (14.21±2.92) and the statistically significant difference was found (p<0.05).

Discussion

Isolation precautions taken in hospitals have been determined by institutions with competence in global standards such as CDC, ECDC (European Centre for Disease Prevention and Control) [20]. In Turkey, these standards are carried out by "Infection Control Committees" established by the relevant persons in hospitals under the Ministry of Health [21]. In the literature, factors affecting compliance with standard precautions are reported as age, gender, educational status, frequency of managerial controls. It has also been reported that compliance with standard precautions increases with effective training provided within the organizations themselves [25].

The mean total score of the Standard Precautions Scale of the nurses participating in the study was found to be 14.48±2.80, which was above the literature and the average (Table 2). In a study conducted by Pereira et al. (2021), it was reported that the average compliance of nurses with standard precautions in the Covid-19 pandemic was 12.8 [5]. We think that the differences in the Covid-19 pandemic are due to the fact that the process is managed and monitored with different practices in different countries.

Table 1	Distribution of Nurses' Socio-demographic Characteristics (N=219)		
	n=219		**%**
Gender			
Female	126		57,5
Male	93		42,5
Marital Status			
Single	79		36,1
Married	140		63,9
Age			
18-25	32		14,6
26-35	69		31,5
36-45	47		21,5
46-55	67		30,6
56-65	4		1,8
Education Status			
High school	33		15,1
Associates Degree	82		37,4
Bachelor's Degree		91	41,6
Master's Degree	13		5,9
Chronic Disease			
Yes	55		25,1
No	164		74,9
Worked Unit			
Surgical service	40		18,3
Internal Medicine service	37		16,9
Intensive care unit	52		23,7
Operating room	26		11,9
Covid-19 unit	31		14,2
Emergency	33		15,1
Weekly Working Hours			
40 hours and less	59		26,9
41 hours and more	160		73,1
Year in the Profession			
1-5 year	63		28,8
6-10	34		15,5
11-15	14		6,4
16-20	14		6,4
21-25	22		10,0
26-30	72		32,9
Belief in the protection of standard precautions			
Yes	139		63,5
No	80		36,5
Negative effect of standard precautions (dermatitis, allergy, etc,)			
Yes	79		36,1
No	140		63,9
Receiving education about Covid-19			
Yes	119		54,3
No	100		45,7
Diagnosed with Covid-19			
Yes	46		21,0
No	173		79,0
Lost of relatives due to Covid-19			
Yes	16		7,3
No	203		92,7
Living with person in Covid-19 risk			
Yes	58		26,5
No	161		73,5

Table 2	Average of Nurses' Compliance with Standard Precautions Scale Total Scores

	Min.	Max.	X±SS
Standard Measures Scale Total Score	0	20	14,48±2,80

Pereira et al. (2021) reported in their study that the compliance of nurses with higher education level with standard precautions was higher than nurses with lower education level [5]. In this study, there is no significant difference between compliance with standard precautions and educational status. Similarly, the results of the study conducted by İkbal and Özdemir are in parallel with our study [26]. It is thought that training can increase awareness, improve behaviour and create changes in practices. Considering that the education levels of the participants in both studies were similar, we think that the differences may be due to the courses taken during the training sessions and the courses given during Covid-19.

According to Table 3, the mean score of compliance with standard precautions scale of female nurses (14.30±2.90) was lower than that of male nurses (14.73±2.66) and the difference was not statistically significant (p>0.05). In the literature, it has been reported that there is a relationship between the mean scores of compliance with standard precautions and the mean scores of gender [14,25]. Cruz et al. (2020) reported that male student nurses showed higher compliance with standard precautions than females [25]. Pereira et al. reported that women were more likely to comply with standard precautions than men [5]. In our country, especially in the Covid-19 process, we think that the fact that nursing practices are expected to be performed by each nurse in accordance with the standards, regardless of gender, is the reason why no relationship was found between compliance with standard precautions and gender

When the compliance with standard precautions according to the age groups of the nurses participating in our study is analyzed, it was found that the mean scale score of nurses in the 56-65 age group was (16.25±0.95) and higher than the other age groups, the mean age of nurses with the lowest mean score (14.09±2.88) was 18-25 and there was a statistically significant relationship between age and mean scale score (p<0.05). In terms of Covid-19, it has been reported that individuals over 65 years of age who are in the risk group have higher compliance with protective precautions/standard precautions compared to younger individuals [26,27]. We assume that this difference between the age of the nurses participating in the study and their compliance with standard precautions is related to the fact that they are not in a risky age group in terms of Covid-19.

When the mean scores of compliance with standard precautions according to the units in which nurses work were analyzed, The mean scores of the nurses working in the emergency department (14.87±2.76) were higher than those working in other units and the difference was statistically significant (p<0.05). We believe that the main source of this difference is that emergency departments undertook important tasks in identifying and isolating patients, preventing in-hospital infections and informing public health authorities during the Covid-19 outbreak.

In the literature, there are studies indicating that compliance with standard precautions increases with increasing clinical experience [14,28]. In this study, unlike the literature, no significant difference was found between occupational working time and compliance with standard precautions scores.

Global health organizations such as WHO and CDC have identified risk groups where the disease can cause serious illness

Table 3	Comparison of Nurses' Socio-Demographical Characteristics and Mean Scores of the Scale of Compliance with Standard Precautions

	Scale of Compliance with Standard Measures		
	X±SS	Test and p	
Gender			
Female	14,30±2,90	t=5356,5	p=,274
Male	14,73±2,66		
Medeni Durum			
Single	14,68±2,70	t=5,347	p=,682
Married	14,37±2,86		
Age			
18-25	14,09±2,88		
26-35	14,30±3,13	t=4,072	p=,036
36-45	14,38±2,62		
46-55	14,82±2,58		
56-65	16,25±0,95		
Education Status			
High school	14,72±2,38		
Associate's degree	14,32±2,88	t=6,051	p=,109
Bachelor's Degree	14,74±2,88		
Master's Degree	13,00±2,48		
Chronic Disease			
Yes	15,18±3,64	t=3673,5	p=,038
No	14,25±2,82		
Worked Unit			
Surgical Service	14,82±2,62		
Internal Medicine Service	14,48±3,12		
Intensive care unit	14,94±2,09		
Operating room	13,61±3,22	t=6,032	p=,033
Covid-19 unit	13,58±3,15		
Emergency	14,87±2,76		
Weekly Working Hours			
40 hours and less	15,22±2,32	t=3874,5	p=,040
41 hours and more	14,21±2,92		
Year in the Profession			
1-5 year	13,82±3,19		
6-10	14,79±2,77		
11-15	14,50±2,06	t=9,780	p=,082
16-20	13,07±3,17		
21-25	15,18±2,57		
26-30	14,97±2,42		
Belief in the protection of standard precautions			
Yes	14,40±3,00	t=5407,5	p=,733
No	14,62±2,42		
Negative effect of standard precautions (dermatitis, allergy, etc,)			
Yes	14,59±3,08	t=5178,0	p=,431
No	14,21±2,64		
Receiving education about Covid-19			
Yes	14,45±3,09	t=2,245	p=,135
No	14,52±2,42		
Diagnosed with Covid-19			
Yes	14,67±2,59	t=1,412	p=,236
No	14,43±2,86		
Lost relatives due to Covid-19			
Yes	15,12±2,70	t=1423,5	p=,407
No	14,43±2,81		
Living with person in Covid-19 risk			
Yes	14,84±2,98	t=1,144	p=,775
No	14,35±2,73		

*ANOVA test, t-test and Mann Whitney-U

while combating Covid-19. Some of these groups are; being over 65 years of age, having a chronic disease [20]. In the literature, it is reported that people with chronic diseases show more compliance with preventive precautions/standard precautions [17,27]. In this study, the mean score of nurses' compliance with standard precautions with chronic disease was higher than those without chronic disease and the difference was found significant statistically.

Strength and limitation

The limitation of this study is that the study data were not collected during the pandemic process and the nurses could not spare enough time.

Conclusion and recommendations

According to the results, the level of compliance of the participants with standard precautions is above the average value. In order to carry out the Covid-19 fight against the pandemic more effectively, it is recommended to increase training, counselling, monitoring and supervision activities aimed at further increasing the level of compliance with standard precautions, with priority to nurses working in clinics.

As a result of the study, the recommendations are as follows:
• Provision of the minimum materials required in the working environment, especially and primarily in terms of standard protective precautions (apron, mask, etc.),
• Making standard protective precautions and safety training part of orientation programmes,
• Mandatory and regular training of nurses on the use of protective equipment
• Evaluation of nurses' protective use through observations and improvement with feedbacks.

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Stratifying breast cancer patients by baseline risk of cardiotoxic complications linked to chemotherapy

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Abstract

A majority of modern antitumor pharmaceuticals are accompanied by cardiotoxicity. The **study aims** to present practical approaches to stratifying the baseline risk of antitumor therapies' cardiotoxicity in patients newly diagnosed with breast cancer started on anthracyclines and/or trastuzumab.

Material and methods: Stratifying the risks of antitumor therapy was carried out according to the European Society of Cardiology recommendations. A therapist examined all patients for existing cardiovascular diseases and risk factors detection. The blood levels of glucose, cholesterol, creatinine, cardiac troponin I, and brain natriuretic peptide were determined. Electrocardiography and echocardiography with an assessment of the myocardium global longitudinal strain were performed.

Results: In total, 128 breast cancer patients with a mean age of 54.3±11.0 years were included in the study. Of them, 84.4% had tumor stages I and II, and 21.1% were HER2-positive. Chronic heart failure and ischemic heart disease were detected in 2.3%. Among the risk factors, the most common were arterial hypertension (51.6%), obesity (29.7%), age 65-70 years (18%), significant smoking history (15.6%), and diabetes mellitus (11.7%). Elevated cardiac troponin I and brain natriuretic peptide baseline levels were present in 5.5% and 7.0% of patients, respectively. To a high-risk group for cardiotoxic complications, 7.8% were allocated, 35.7% were assigned to the moderate-risk group, and 54.7% had low risk. High/very high and moderate-risk patients (43.5%) were referred to a cardiologist. Cardioprotective treatment was started immediately in high/very high-risk patients.

Conclusion: All revealed differences between the cardiovascular risk groups were related to age, cardiovascular system condition, and the severity of comorbid pathologies. The baseline stratification of patients into risk groups is a crucial step in preventing the cardiotoxicity of anticancer therapy. Comprehensive assessing the patient's condition before and during chemotherapy allows for avoiding the development of fatal cardiovascular complications in at-risk patients.

Key words: cardiotoxicity, chemotherapy, breast cancer, cardiovascular risks

Introduction

Over the past decades, owing to achievements in early diagnosis of the tumor process and the introduction of effective antitumor therapies into clinical practice, the prognosis of cancer patients improved drastically [1]. At the same time, numerous studies have demonstrated various side effects caused by chemotherapy and radiation therapy, among which cardiotoxicity has the most significant prognostic value [2,3]. Clinical manifestations of antitumor therapies' cardiotoxicity vary widely from asymptomatic subclinical changes recorded only by special imaging techniques such as global longitudinal strain measurement (GLS) and 3D-Echocardiography (EchoCG) to severe clinical

symptoms evidencing heart failure and requiring emergency hospital admission [4]. Cardiotoxicity, or, according to the current definition, cancer treatment-related cardiovascular disease (CTRCD), can develop both during antitumor therapy and in the first year or even years after chemotherapy completion [5]. CTRCD may be irreversible due to myocardial injury (type 1) and reversible due to myocardial dysfunction (type 2). Type 1 CTRCD is associated with anthracyclines and often manifests as heart failure (HF) and arrhythmias [6]. Trastuzumab, vascular endothelial growth factor (VEGF) inhibitors, checkpoint and/ or proteasome inhibitors are responsible for the development of type 2 CTRCD, manifesting as HF, arrhythmias, arterial hypertension (AH), and myocardial ischemia [7-9]. Myocarditis, pericarditis, ischemic heart disease (IHD), valvular disease, conduction disorders, and thoracic aorta calcification (porcelain aorta) are more common after radiotherapy [10].

CTRCD can occur in the treatment with anthracyclines (1-26%), trastuzumab (2-28%), tyrosine kinase inhibitors (0.005-11%), or high doses of cyclophosphamides (7-28%) [11].

When managing cancer patients, there are three essential periods. The first period commences after the diagnosis of a tumor disease. Determining the baseline risk of cardiotoxic complications before initiating antitumor treatment is necessary. There are very-high, high, intermediate, and low-risk categories. Allocation into risk groups is based on assessing existing cardiovascular diseases (CVD) and CV risk factors, an objective examination focused on the CV system, measurement of blood pressure, ECG, EchoCG, laboratory blood tests, and performing the tests on cardiac troponin I (cTnI) and brain natriuretic peptide (BNP). In addition, the previous anticancer therapy must be considered [12,13].

An individual monitoring program for cardiotoxic complications is being created for each risk category. Patients at very high and high risk of such complications are started with preventive cardioprotective treatment. The next step involves monitoring at planned intervals (depending on baseline risk) for the onset of symptoms or signs of CTRCD, focusing on detecting early preclinical signs. The final stage begins when the anticancer treatment is completed. This period includes monitoring patients who experienced CTRCD and the entire cohort of cancer patients, as late CV complications may still occur [14].

The study **aims** to demonstrate practical approaches to baseline CTRCD risk stratification in patients with breast cancer (BC) who are administered anthracyclines and/or trastuzumab.

Material and methods

In total, 128 women newly diagnosed with BC and started antitumor chemotherapy with doxorubicin and/or trastuzumab at the University's Medical Center from September 2021 to August 2022 were enrolled in the study. The eligible patients were those with verified BC of any stage, at age ≥18 years, and started on mentioned antitumor therapy. Exclusion criteria: Simpson left ventricular ejection fraction (LVEF)≤40%; decompensation of any comorbid pathology. The study was approved by the Bioethics Committee of the West Kazakhstan Medical University (Ref. No. 5, 13/05/2020) and registered in the international registry of clinical trials ISRCTN, ID 12628444. The study protocol was published [15]. Figure 1 displays the research design.

We assessed the tumor's clinical, molecular-genetic subtypes in BC patients. We established the presence of existing CV diseases and risk factors, such as stable angina pectoris, previous myocardial infarction, myocardial revascularization in history, AH, chronic heart failure (CHF), atrial fibrillation,
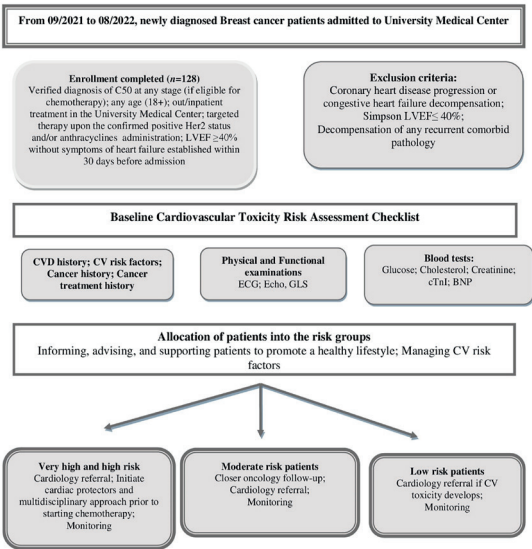
Figure 1 - Study flowchart

diabetes mellitus (DM), and obesity. Besides, we detected the baseline levels of glucose, cholesterol, creatinine, cTnI, and BNP [16]. The glomerular filtration rate was calculated using the CKD-EPI formula. Patients underwent computerized ECG using the Poly-Spectrum-8 device (Neurosoft, Russia).

| Table 1 | An example of patients stratifying according to baseline cardiovascular toxicity risk (by Heart Failure Association-International Cardio-Oncology Society). |

Baseline CV toxicity risk factors	Anthracycline-based chemotherapy	Patient's code: 17
Previous cardiovascular diseases		
Heart failure or cardiomyopathy	Very high	0
Severe valvular heart disease	High	0
Myocardial infarction or previous coronary revascularization (PCI* or CABG**)	High	0
Stable angina	High	0
Cardiac imaging		
Baseline LVEF <50%	High	0
Borderline LVEF 50–54%	Medium 2	0
Cardiac biomarkers		
Elevated baseline cardiac troponin	Medium 1	0
Elevated baseline natriuretic peptides (BNP/ NT- proBNP)	Medium 1	0
Age and cardiovascular risk factors		
Age ≥80 years	High	0
Age 65–79 years	Medium 2	2
Arterial hypertension	Medium 1	1
Chronic kidney disease	Medium 1	1
Diabetes mellitus	Medium 1	1
Previous exposure to		
Anthracycline-based chemotherapy	High	0
Radiotherapy to left chest or mediastinum	High	0
Non-anthracycline-based chemotherapy	Medium 1	0
Lifestyle risk factors		
Current smoker or significant smoking history	Medium 1	0
Obesity (BMI>30 kg/m2)	Medium 1	1
Summary M 6 - High risk		
*PCI - Percutaneous Coronary Intervention **CABG - Coronary Artery Bypass Grafting		

EchoCG was performed on a GE Vivid 9 machine (GE Healthcare). Measurement of LVEF was carried out by the biplane method, according to Simpson. GLS measurement was performed from the apical 3-chamber (3C), 4-chamber (4C), and 2-chamber (2C) positions. The apical positions were taken so that the myocardial wall's thickness along the entire length of the left ventricle fell into the study area.

Table 2   Descriptive and comparative statistics of BC patients allocated into risk groups.

Parameters	Total, n=128	High risk, n=10	Moderate risk, n=48	Low risk, n=70	p
Age, years	54,3±11.0	68,3±5.4	58.8±8.9	49,3±9.8	**<0.001**
Ethnicity: Asian, n (%)	89(69.5)	3(30.0)	27(56.3)	59(84.3)	
European, n (%)	39(30.6)	7(70.0)	21(43.7)	11(15.7)	**<0.001**
Heredity, n (%)	16(12.5)	3(30.0)	3(6.3)	10(14.3)	0.094
Menopause, n (%)	87(68.0)	10(100.0)	42(87.5)	35(50.0)	**<0.001**
Localization: Right	56(43.7)	5(50.0)	16(33.3)	35(50.0)	
Left	70(54.7)	5(50.0)	31(64.6)	34(48.6)	
Both sides	2(1.6)	-	1(2.1)	1(1.4)	0.193
Clinical stage: I, n (%)	6(4.7)	-	3(6.3)	3(4.3)	
IIA, n (%)	44(34.4)	4(40.0)	17(35.4)	23(32.9)	
IIB, n (%)	58(45.3)	3(30.0)	24(50.0)	31(44.3)	
IIIA, n (%)	5(3.9)	1(10.0)	1(2.1)	3(4.9)	
IIIB, n (%)	10(7.8)	2(20.0)	2(4.2)	6(8.6)	
IV, n (%)	5(3.9)	-	1(2.1)	4(5.7)	0.706
Tumor histotype, n (%) Invasive carcinoma, unspecified;	89(69.5)	9(90.0)	33(68.8)	47(67.1)	
Invasive ductal carcinoma;	34(26.6)	4(40)	15(31.3)	15(21.4)	
Invasive lobular cancer;	4(3.1)	1(10.0)	1(2.1)	2(2.9)	
Angiosarcoma	1(0.78)	-	1(2.1)	-	0.286
*Breast cancer types, n (%) 1 - Nodular cancer	106(82.8)	8(80.0)	44(91.6)	54(77.1)	
2 - Mastitis-like cancer	2(1.6)	-	-	2(2.8)	
3 - Edematous-infiltrative	10(7.8)	1(10.0)	3(6.3)	6(8.6)	
4 - Paget disease of BC	1(0.78)	-	-	1(1.4)	
5 - Armor-like cancer	9(7.0)	1(10.0)	1(2.1)	7(10.0)	
6 - Erysipelas-like	-	-	-	-	
7 - Diffuse forms - other	-	-	-	-	0.630
Imminohistochemistry, n(%) 1 - Triple negative (TNBC);	23(18.0)	2 (20.0)	10(20.8)	11(15.7)	
2 - Luminal A type;	35(27.3)	2(20.0)	15(31.3)	18(25.7)	
3 - Luminal B (positive);	18(14.1)	1(10.0)	7(14.6)	10(14.3)	
4 - Luminal B (negative);	43(33.6)	5(50.0)	14 (29.2)	24(34.3)	
5 - Her2-positive	9(7.0)	-	2(4.2)	7(10.0)	0.826
Smoking, n(%)	20(15.6)	1(10.0)	9(18.7)	10(14.3)	0.708
IBM, kg/m2	27.0(23.3;30.9)	29.5(27.4;34.6)	30.8(26.6;35.3)	23.6(22.3;28.4)	**<0.001**
**SBP, mmHg	120±17.5	122±14.0	130±17.6	113±14.6	**<0.001**
DBP, mmHg	75±9.6	74±6.7	80±9.6	72±8.5	**<0.001**
Heart rate	76(70;80)	76(74;88)	76(68;80)	76(72;80)	0.449
Charlson Comorbidity index, points	5(3;6)	6.5(5;7)	5(4;6)	4(3;5)	**<0.001**
Hb, g/L	124.2±13.5	123.5±14.4	126.5±13.6	122.7±13.4	0.398
Creatinine, μmol/L	67.8(59.6;77.2)	68.2(55.0;70.5)	68.4(60.9;79.0)	66.9(58.8;76.5)	0.543
eGFR, mL/min/1,73m2	90.1±17.5	82.0±13.2	84.8±16.3	95.0±17.6	**0.003**
Glucosae, mmol/L	5.2(4.7;5.6)	5.8(5.2;6.0)	5.2(4.7;5.6)	5.1(4.6;5.4)	**<0.001**
Cholesterol, mmol/L	5.2±1.0	4.9±0.6	5.2±1.1	5.2±1.0	0.645
Baseline LVEF, %	59.7±3.9	55.8±4.5	58.8±3.5	60.8±3.6	**0.001**
Baseline GLS, %	18.2±3.0	16.2±4.1	17.8±3.1	18.8±2.5	**0.028**
Baseline cTnI, ng/mL	0.10(0.10;0.27)	0.23(0.10;0.40)	0.10(0.10;0.29)	0.10(0.10;0.22)	0.240
Baseline BNP, pg/mL	54.9(36.1;86.7)	109.0(93.8;124.8)	53.3(37.8;72.8)	49.7(35.2;74.6)	**<0.001**
***6MWT, m	398.0(322;448.0)	363.0(313.0;407.0)	358.0(298.5;408.5)	432.0(354.0;469.0)	**<0.001**

*According to BC types clinical classification adopted in our country.
**SBP, DBP - systolic, diastolic blood pressure.
***6 Minute Walk Test.

We accepted the normal GLS value at (-)18%. All obtained information was entered into particular forms developed by the European Society of Cardiologists (ESC) experts for stratifying the CV risk of future therapy with anthracyclines and/or trastuzumab. All risk factors for CV complications included in the forms are evidence-based or have been discussed by experts [17]. An example of a filled-in form is presented in Table 1.

The statistical data analysis was carried out using the software package Statistica (StatSoft, Inc., Tulsa, OK, USA, v. 10). The Kolmogorov-Smirnov test was used to check the normality of the quantitative variables distribution. A comparison of three groups (very high/high, intermediate, and low risk) was performed using the Kruskal-Wallis H-test. Accordingly, the critical value of the significance level was set at $p<0.017$ (given the three groups of pairwise comparisons under analysis). As we tested the three statistical hypotheses, we used a smaller critical significance level of p. This level was calculated using the formula $1-0.95^{1/3} = 0.017$ [18,19]. To analyze the differences between groups regarding qualitative and rank variables, the Pearson criterion χ^2 was applied.

Results

The average age of participants was 54.3±11.0 years. Summarized patients' data are presented in Table 2.

Table 2 shows no statistically significant differences between the CV risk groups regarding the tumor clinical staging or biological features. All revealed differences were related to age, CV system condition, and the severity of comorbid pathologies.
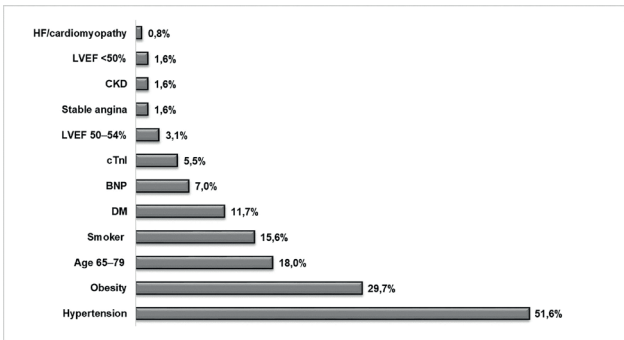
Figure 2 - Baseline cardiovascular toxicity risk factors
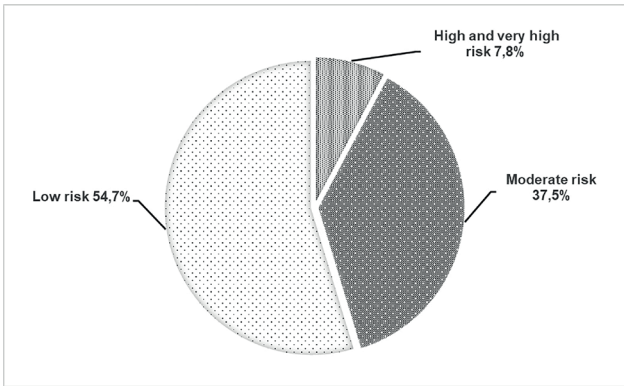
Figure 3 - Baseline cardiovascular toxicity risk stratification

The occurrence of significant CV diseases and risk factors before the start of chemotherapy is shown in Figure 2. At baseline, three patients (2.3%) had CVD; two had a history of stable angina Class II, and one suffered from CHF with a permanent form of atrial fibrillation. Among the risk factors for CVD, AH was the most common (66 individuals out of 128), then obesity (BMI> 30 kg/m2) - 38 (29.7%), age 65-70 years

- 23 (18%), active smoker or significant smoking history - 20 (15.6%), and DM - 15 (11.7%). After EchoCG and determining blood biomarkers, four patients were assigned to the moderate-risk group, receiving two points each for LVEF lower than 54%. For elevated baseline levels of cTnI, seven (5.5%), and nine patients (7.0%) for elevated BNP, received one point each and were also assigned to the moderate-risk group.

Patients were stratified into risk groups, as shown in Figure 3. Overall, 70 out of 128 were identified as low-risk patients, 48 were counted as patients at moderate risk, and ten were referred to the high- and very high-risk groups. Almost half (45.3%) of patients were assigned to very high/high and moderate-risk groups, according to points calculation for comorbidities and other risk factors, as demonstrated in Table 1.

We united very-high and high-risk patients; they were ten (7.8%). But, for clarity, only one was referred to the very-high-risk group, and the rest nine were high-risk patients. They were those who received the highest points, according to Table 1. As mentioned above, three (2.3%) had a history of cardiovascular disease. So, the only patient, M., 58 years old, referred to the very-high-risk group developed atrial fibrillation due to stable angina II before enrollment in the study. According to ESC Guidelines, cardioprotective therapy was administered immediately after the diagnosis and before she started chemotherapy. Patient M. has been prescribed, except for routine cardiac medications, Mineralocorticoid Receptor Antagonists (MRA), Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors, and oral anticoagulants. So, M. received Enalapril 5 mg x 2 times per day; Bisoprolol 5 mg; Eplerenone 50 mg; Dapagliflozin 10 mg; and Dabigatran 150 mg twice a day. Afterward, after three months of observation, LVEF fell from 51% to 41%, and anthracycline therapy was canceled at a summary dose of 260 mg/m2 due to the deterioration of her condition. Anticancer treatment was continued with Tamoxifen and courses of radiation therapy.

All ten high- and very-high-risk patients have been prescribed Angiotensin-converting enzyme inhibitors / Angiotensin-receptor blockers (ACE-I/ARBs); Beta-blockers were additionally administered to nine of them, and eight of them were provided by statins.

Out of 48 patients at moderate risk, 40 (83.3%) were provided with cardioprotectors before chemotherapy started, according to indications. As most of them suffered from arterial hypertension (40 from the moderate risk group out of total 66 with AG), they were provided with appropriate antihypertensive medications.

Chemotherapy of BC patients, given the tumor process and the risk of cardiotoxic complications, is displayed in Figure 4. An overwhelming majority of patients (85.9%) started on an anthracycline-based regimen. In this cohort, the cumulative effect of anthracyclines and the possible development of irreversible type 2 CTRCD should be expected.

During the present study, we faced a case of classic acute cardiotoxicity. Patient Sh., 46 years old, ST IIB T3NxM0, had no CV diseases in history and revealed risk factors. Baseline LVEF 64%, GLS 22.4%, cTnI 0.1 ng/ml; BNP 43.8 pg/ml. The initial risk of forthcoming anthracycline therapy seemed to be low. After the first dose of doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2, the patient experienced two episodes of asystole at Holter monitoring, 9327 msec, and 4051 msec, respectively (Figure 5).

This case proves the necessity of scrutinizing and constantly monitoring patients undergoing chemotherapy with potentially cardiotoxic agents, particularly anthracyclines having cumulative effects.
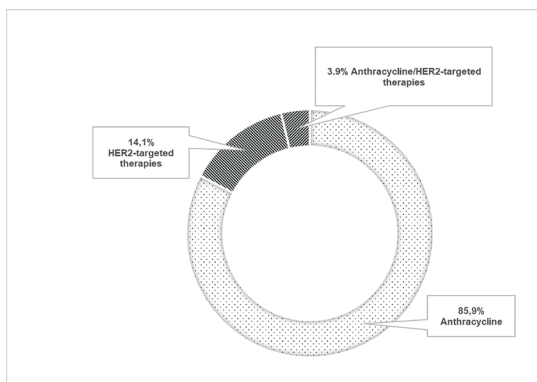
Figure 4 - Cancer treatment groups

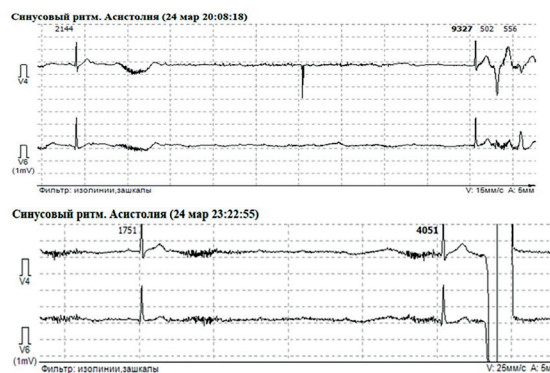**Figure 5** - A fragment of Holter monitoring in patient Sh., 46 years old, with acute anthracycline-induced cardiotoxicity

Discussion

As stated above, the baseline risk of cardiotoxic complications was very-high/high in 7.8% and moderate in 37.5% of BC patients. Anthracyclines, associated with the most severe and irreversible cases of CTRCD, have been administered to 85.9% of patients. Thus, the study identified groups of patients who would benefit the most from a multidisciplinary approach. In very high and high-risk patients, the predicted risk of antitumor therapy cardiotoxic complications fluctuates from 10% to 19%, i.e., CTRCD can develop in each fifth patient. In the presence of 2 to 4 moderate risk factors, the predicted risk of cardiotoxic complications is 2-9%; if there are no risk factors or one moderate risk factor, then the risk is defined as low, <2% [20]. In our cohort of patients, the following diseases and conditions, such as HF/cardiomyopathy, stable angina, and LVEF<50%, were associated with a very high and high risk of CTRCD. However, the majority of patients, 60%, were assigned to this group as they scored more than five moderate risk points. The most common moderate risk factors were AH, obesity, age 65+ years, active smoking, DM, and high baseline BNP and cTnI (Figure 2). Baseline risk stratification should be performed quickly without delaying antitumor treatment. Cardiology referral is recommended in high-risk, very high-risk, and moderate CV toxicity risk patients before chemotherapy. Anticancer therapy can be paused/changed by the decision of an interdisciplinary team consisting of an oncologist and a cardiologist only in patients at high and very high risk of CV complications. Patients should be informed of the risk of CV complications and may be involved in the treatment choice. All patients with a very high and high risk of CT complications should start primary prevention, including treatment of existing CV diseases, proper control of CV risk factors, scheduling optimal antitumor therapy, and the most appropriate chest radiation regimen [21]. If surgical treatment is required, patients undergo a preoperative risk assessment for surgical intervention.

The next stage is regular monitoring of CTRCD development during anticancer treatment. CTRCD is a continuous event that begins with damage to myocardial cells and then manifests as a progressive decrease in LVEF and overt HF. Suppose we evaluate the symptoms of HF (dyspnea, fatigue, orthopnea, cardiac asthma attacks, weight gain) and signs of CV insufficiency (galloping rhythm, tachycardia, tachypnea, crackles in the lungs, jugular vein swelling, peripheral edema, pleural effusion, liver enlargement, ascites). In that case, cardiotoxicity was detected late. If we focus on a decrease in LVEF, we can see cardiotoxicity a few months after the process starts. We can catch subclinical cardiotoxicity if we assess the degree of damage to myocardial cells using GLS technology and biomarkers like troponin and natriuretic peptides [22].

Thus, only comprehensive monitoring of echoCG parameters and biomarkers allows for revealing myocardial dysfunction at the preclinical stage. The frequency of monitoring depends on the patient's risk group. For very high and high-risk patients, echoCG is recommended every two cycles of chemotherapy and within three months after treatment completion. In patients at moderate to low risk of cardiotoxic complications, echoCG is recommended after a cumulative dose of ≥250 mg/m2 of doxorubicin or equivalent. In high and very high-risk patients, monitoring of cTnI and natriuretic peptides (BNP, NT-proBNP) is recommended before every cycle during anthracycline chemotherapy and 3 and 12 months after therapy completion. In moderate- and low-risk patients receiving a cumulative dose of ≥250 mg/m2 of doxorubicin or equivalent, cTn and NP monitoring should be considered every two cycles during anthracycline chemotherapy and within three months after therapy completion [23]. During echocardiography, the preferred method for assessing LVEF is 3D-echoCG (2D-LVEF if 3D is unavailable); also, GLS should be evaluated [24]. During the examination, systolic and diastolic function, the state of the heart valves, the pericardium, the right ventricle, the right atrium, and the inferior vena cava should be assessed. The criterion for subclinical myocardial dysfunction is a decrease in LV GLS ≥15% from baseline, confirmed by repeat imaging after two weeks [25]. In such a clinical situation, it is necessary, together with the oncologist, to discuss the possibility of modifying anticancer therapy to reduce its cardiotoxicity and proceed with CHF secondary drug prevention.

In a study by Cardinale et al., 2625 patients who received anthracyclines were followed up for a median value of 5.2 (2.6–8) years, and 226 (9%) developed CTRCD. In 98% of cases, cardiotoxicity developed one year after the chemotherapy completion (median 3.5 months). During cardioprotective therapy with enalapril and beta-blockers (carvedilol or bisoprolol), 82% had partial or complete recovery of LV systolic function. Cardiotoxicity in this study was associated with LVEF at the end of chemotherapy (RR 1.37, 95% CI 1.33;1.42) and doxorubicin dose per 50 mg/m2 (RR 1.09, 95% CI 1.04;1.15) [26].

The meta-analysis by de Baat et al. showed that dexrazoxane in anthracycline patients demonstrated cardioprotective effects; in three studies, n=417 (RR 0.37, 95% CI 0.24;0.56), and in two studies, n=534 (RR 0.46, 95% CI 0.33;0.66) dexrazoxane reduced the risk of cardiotoxicity [27]. Meta-analysis of randomized clinical trials revealed the benefit of ACEI/ARBs and beta-blockers in patients on trastuzumab- and anthracycline-associated cardiotoxicity [28]. Anthracycline infusion for more than 6 hours or longer reduces the risk of clinical and subclinical cardiotoxicity and is also considered a potential cardioprotective

strategy [29]. According to another meta-analysis, liposomal doxorubicin reduced the development of HF without changing antitumor efficacy and overall survival - OR 0.34 (0.24;0.47) [30]. If LVEF falls below 40% or any symptom of heart failure is present, treatment with anthracyclines and trastuzumab should be discontinued [31].

In general, acute, subacute, and chronic cardiotoxicity can occur during anthracycline therapy. Acute and subacute myocardial injury is a rarer type of cardiotoxicity; it can happen within a week after taking an anthracycline drug and appears as arrhythmia, myocarditis, pericarditis, or acute left ventricular failure [32].

We have presented the above case with patient Sh., acute cardiotoxicity that occurred less than a week after the first administration of 60 mg/m2 doxorubicin. As the patient developed rhythm disturbances as asystole, we prolonged observation after the relief of acute episodes. Holter data came to normal values a week after the event. She has been prescribed Trimetazidine at a dose of 80 mg. After a year of observation, LVEF decreased from 64% at baseline to 58%, GLS from [-22.4%] to [-15.3%], and reduction was 31.7%. Nonetheless, Sh. successfully completed the courses of anthracycline therapy at a summary dose of 455 mg/m2. Of note, the patient was not transferred to other risk groups as there were no indications of allocation to the high- or very high-risk, or moderate-risk group. This case is critical to understand the nuances of patients' baseline allocation into risk groups. Episodes of acute or subacute cardiotoxicity can occur in patients at any time, irrespective of their baseline risks.

The final stage occurs after the chemotherapy treatment completion. Meticulous monitoring is required for patients who have developed cardiotoxic complications or have potential risk factors, such as a total dose of doxorubicin ≥250 mg/m2, an amount of radiation therapy ≥30 Gy, and treatment with HER2-targeted agents. Patients treated due to the onset of CTRCD conditions require long-term follow-up. Educating and supporting cancer patients to make appropriate healthy lifestyle choices is strongly recommended. Cancer patients should also receive education on recognizing CVD's early signs and symptoms. Regular exercise for at least 150 minutes per week and a healthy balanced diet must be included in the list of recommendations.

In asymptomatic high-risk patients, echoCG and cardiac serum biomarkers are recommended at 3 and 12 months after completion of antitumor therapy. In asymptomatic moderate and low-risk patients, echoCG and cardiac serum biomarkers should be considered within 12 months after the therapy completion. Annual CV risk assessment, including ECG and natriuretic peptides (BNP; Pro-BNP), and CV risk factors management is recommended in cancer survivors (CS) treated with potentially cardiotoxic cancer medications or radiotherapy. CV toxicity risk restratification is recommended for five years after therapy to arrange long-term follow-up. EchoCG at years 1, 3, and 5 after completion of cardiotoxic cancer therapy and, subsequently, every five years, should be considered in asymptomatic very high- and early high-risk adults (CS). Echocardiography may also be considered every five years in asymptomatic moderate-risk adult CS [23].

Patients diagnosed with cardiotoxic events, irrespective of the time passed from the event, should be treated and followed up by a cardiologist for as long as necessary.

Conclusion

We found no statistically significant differences between the CV risk groups regarding the tumors' clinical staging or biological features. All revealed differences were related to age, CV system condition, and the severity of comorbid pathologies.

Thus, the baseline stratification of patients into risk groups is a key step in the primary prevention of anticancer therapy cardiotoxicity. In our cohort of BC patients, 43.5% had a baseline very high/high risk and a moderate risk of cardiotoxic complications. These patients should have an opportunity to be examined by a cardiologist to monitor and manage cardiovascular complications in a cancer treatment division under the conditions of a multifunctional hospital. In the long run, every multifunctional hospital should be provided with a specialist in cardio-oncology.

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The association between insulin resistance, sleep disorders, and inflammation in obese children

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Abstract

Aim: Both obesity and sleep disorders cause chronic subclinical inflammation. Inflammation is a significant factor in triggering insulin resistance. This study aimed to analyze the association between sleep disorders, inflammation, and insulin resistance in obese/overweight children.

Material and methods: In this cross-sectional study, 150 overweight/obese children were included. Sleep disorder was measured by using the Sleep Disturbance Scale for Children. The homeostasis model of assessment for insulin resistance (HOMA-IR) was calculated according to fasting glucose and insulin results. Logistic regression models and Spearman Rank Correlation Coefficients were used to estimate associations between parameters.

Results: A statistically significant raising was found in insulin resistance and C-reactive protein levels in those with sleep disorders ($p<0.05$). However, no correlation was found between sleep disorders and the HOMA-IR, C-reactive protein, and neutrophil-to-lymphocyte ratio levels. On the other hand, HOMA-IR was weak positively correlated with neutrophil-to-lymphocyte ratio ($r=0.222$, $p=0.006$), and CRP ($r=0.390$, $p<0.001$).

Conclusion: Although we did not detect the association between sleep disorders and insulin resistance and C-reactive protein levels, we revealed that children with sleep disorders had higher insulin resistance and C-reactive protein levels than those without.

Key words: sleep, insulin resistance, children, obesity, neutrophil-lymphocyte ratio, C-reactive protein

Introduction

Obesity is an important clinical problem worldwide that is increasingly prevalent among both children and adults [1]. It is estimated that 17% of children and adolescents aged 2 to 19 suffer from obesity [2]. The increasing rate of obesity has been linked with an increase in sleep disorders [3]. Although some studies have shown that obesity contributes to sleep disorders, other studies have also shown that sleep disorders compose a predisposition to obesity [4, 5]. As a result, both clinical disorders are acknowledged to be bi-directionally connected [6, 7].

Obesity and sleep disorders cause chronic low-grade systemic inflammation and independently increase the risk of insulin resistance [6, 8]. Their frequent coexistence has a synergistic effect, contributing to the pathophysiological effects of each other's metabolism. Inflammation is thought to be the most essential mechanism linking these effects [9, 10].

Obesity is defined as an overaccumulation of adipose tissue in the organism. The primary role of adipose tissue is to depot excess energy in the structure of triacylglycerol. Furthermore, adipose tissue secretes many peptides as an endocrine organ. Adipocytes need the anabolic effects of insulin to depot the exceeding

energy. The increased lipid storage need is supplied by the anabolic ability of hyperinsulinemia. Eventually, adipocytes compass a threshold where no further anabolic pressure can be compensated, which puts stress on the adipocytes. Thus, impaired adipogenesis leads to inflammatory cytokine release, necrosis, increased immune cells, and inflammation. Tumor necrosis factor (TNF)-α and interleukin (IL)-6 levels that increase with inflammation may trigger insulin resistance. In addition, C-reactive protein (CRP) levels, an important proinflammatory indicator, increase with obesity [8, 9]. Obesity-induced low-grade inflammation reduces sleep quality and duration. Because this increased TNF-α and IL-6 levels shift from night to morning, causing daytime sleepiness and less slow-wave sleep. As sleep disorders continue, the inflammatory response progresses, causing further TNF-α, IL-6, and CRP levels to increase. On the other hand, chronic-systemic inflammation also induces hyper-stimulation of the central nervous system. And this causes excessive activation of the hypothalamus-pituitary-adrenal (HPA) axis and sympathetic system. Eventually, these mechanisms maintain the vicious circle between inflammation, insulin resistance, and obesity in the body [6, 10, 11].

TNF-α, IL-6, and CRP have been investigated for the potential to be beneficial biomarkers in the diagnosis of sleep disorders and obesity-induced inflammation. CRP is more accessible and less expensive than TNF-α and IL-6 biomarkers. The neutrophil-to-lymphocyte ratio (NLR) has also been reported as a potential inflammatory marker. NLR, like CRP, is inexpensive and more easily accessible than TNF-α and IL-6 [12]. Therefore, we planned to examine the NLR besides the traditional inflammatory parameter CRP while evaluating the relationship between sleep disorders, obesity, and insulin resistance with inflammation.

The present study aimed to analyze the association of sleep disorders, inflammation levels, and insulin resistance in obese/overweight children. We hypothesized that concomitant sleep disorders in obese/overweight patients are associated with increased inflammation (increased CRP, NLR) and insulin resistance.

Material and methods

This study was performed by the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Ankara City Hospital (No: E2-22-2231). All children and/or their parents signed the Consent and Informed Form.

Patients and study design

This prospective and cross-sectional study was performed at the pediatric outpatient of a tertiary care children's hospital. Obese or overweight children aged 6-16 years were included in the study for 5 months after obtaining permission from the ethics committee. This study covered 150 obese or overweight children and adolescents. The limits of overweight and obesity were determined by the World Health Organization (WHO) references. Accordingly, if body mass index (BMI) was more than 2 standard deviations from the median obesity was considered, and if it was more than 1 standard deviation, it was considered overweight [13]. The participant's height and weight measurements were taken by trained pediatric nursing staff, and BMI was calculated by a pediatrician. Children with chronic diseases such as diabetes, rheumatological diseases, liver diseases, or other comorbid sleep disorders (adenoids, insomnia, narcolepsy, and restless legs syndrome), those with acute or chronic infections, and those who use drugs that may affect sleep were excluded.

Sleep disturbance scale

The Children's Sleep Disorder Scale (SDSC) questionnaire was used to detect sleep disorders. [14, 15]. The SDSC is a parents-report measure of children's sleep disorders in the last six months. SDSC included 26 items and six subscales. These are disorders of initiating and maintaining sleep (DIMS), sleep-breathing disorders (SBD), disorders of arousal (DA), sleep-wake transition disorders (SWTD), disorders of excessive somnolence (DOES), and sleep hyperhidrosis (SHY).The scores of the items on this five-point Likert type (1=least severe and 5=most severe) scale supply a total sleep score from 26 to 130. A total score of more than 70 is considered a sleep disorder.

Assessment of insulin resistance, CRP, and NLR levels

Glucose levels were measured automatically by the glucose oxidase method. CRP levels were measured by a latex-enhanced immunoturbidimetric method, and insulin levels were determined via chemoluminescence immunoassays. All three parameters were measured using Atellica Solution Immunoassay & Clinical Chemistry Analyzers (Siemens Healthcare Diagnostics, Erlangen, Germany). Hemograms and accordingly neutrophil/lymphocyte ratio levels were performed using the ADVIA 2120 Hematology System (Siemens Healthcare Diagnostics, Erlangen, Germany). Blood samples were drawn simultaneously, between 08.00-10.00 A.M, .after 10-12 hours of fasting. HOMA-IR was estimated as insulin (μU/ml)x glucose (mg/dl) /405 and HOMA-IR $\geq$ 2.5 was considered insulin resistance [16].

Statistical analysis

Categorical variables were revealed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and median and minimum-maximum where appropriate. Chi-square test was used to compare categorical variables between the groups.

The distribution normality of continuous variables was approved by the Kolmogorov-Smirnov test. For the comparison of continuous variables between two groups, the Student's t-test or Mann-Whitney U test was used depending on whether the statistical hypotheses were fulfilled or not. To evaluate the correlations between measurements, Spearman Rank Correlation Coefficient was used. Logistic regression analysis was performed to determine significant predictors of insulin resistance variable. In univariate analysis, variables significant at the p <0.25 level were entered in backward logistic regression analysis. All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. The statistical level of significance for all tests was considered to be 0.05.

Results

This study enrolled 150 patients with a mean age of 12.1±2.7 years, including 83 (55.3%) boys and 67 (44.7%) girls. All patients had a median BMI of 27.6 (kg/m2) and a median BMI SD of 2.1; 72 (48.0%) were overweight, and 78 (52.0%) were obese.

The children's mean total SDSC questionnaire score was 44.3±13.2 (min: 27.0, max: 113.0). The number of children with total SDSC scores greater than 70, indicating a sleep disorder is 11 (7.3%). The characteristics of the participants with and without sleep disorders are given in Table 1. There was no statistical variation between sleep disorder groups for age, gender, BMI, glucose, and NLR. However, the sleep disorders group was higher HOMA-IR and CRP (p<0.001 and p=0.004,

	Sleep Disorders		p
	No (n=139)	Yes (n=11)	
Age(year)	12.0(7.0-16.0)	13.3(7.6-16.0)	0.997
Gender, n(%)			
Girls	76(54.7)	7(63.6)	0.755
Boys	63(45.3)	4(36.4)	
BMI	27.6(19.2-49.4)	28.7(23.7-38.6)	0.174
Glucose	84.0(68.0-100.0)	87.0(77.0-106.0)	0.261
HOMA-IR	2.9(0.7-15.1)	5.2(4.0-30.0)	<0.001
N/L	1.7(0.7-4.4)	2.3(1.0-4.2)	0.444
CRP	2.0(0.0-19.2)	5.4(0.0-12.1)	0.004

Unless otherwise specified data was expressed as mean±standard deviation, median(min-max).
BMI: Body mass index, NLR: Neutrophil-to lymphocyte ratio, CRP: C-reactive protein, HOMA-IR: Homeostasis model of assessment for insulin resistance, SDSC: Sleep Disturbance Scale for Children

respectively) (Figure 1). Age, BMI, glucose, NLR, and CRP increased significantly with IR (p=0.013, p<0.001, p<0.001, p=0.023, and p=0001, respectively). Although the median SDCD total score did not differ significantly between the insulin resistance groups, all individuals with sleep disorders (n=11) were found to be in the insulin resistance group (p=0.004). There were no significant differences among the insulin resistance group concerning DIMS, SBD, DA, SWTD, DOES, and SHY (p>0.05 for all) (Table 2).

In correlations analysis, HOMA-IR was significantly positively correlated with age (r=0.233, p=0.004), BMI (r=0.359, p<0.001), NLR (r=0.222, p=0.006), and CRP (r=0.390, p<0.001). However, no association was found between SDSC total score and demographic characteristics, inflammation markers, or HOMA-IR (Table 3). The univariate and multiple logistic regression analyses are expressed in Table 4. Multiple logistic regression analysis revealed that independent risk factors for insulin resistance were BMI (OR= 1.13, 95% CI: 1.03-1.25, p=0.009) and CRP (OR= 1.21, 95% CI: 1.03-1.42, p=0.022). Every one unit increase in BMI and CRP resulted in a 13%, and 21% increase in the occurrence of insulin resistance, respectively.

Table 2 Demographic and clinical characteristics according to insulin resistance groups

	Non-IR (HOMA-IR<2.5) (n=59)	IR (HOMA-IR≥ 2.5) (n=91)	
Age(year)	11.3(7.0-16.0)	12.6(7.3-16.0)	0.013
Gender, n(%)			
Girls	35(59.3)	48(52.7)	0.533
Boys	24(40.7)	43(47.3)	
BMI	25.6(21.0-38.9)	28.0(19.2-49.4)	<0.001
Glucose	82.6±5.9	86.1±6.1	<0.001
NLR	1.4(0.7-4.0)	1.8(0.7-4.4)	0.023
CRP	0.8(0.0-12.6)	2.3(0.0-19.2)	0.001
Sleep Disorders			
SDSC total score	42.0(29.0-59.0)	40.0(27.0-113.0)	0.894
Sleep disorders, n (%)			
No	59(100.0)	80(87.9)	0.004
Yes	-	11(12.1)	
DIMS	13.0(8.0-22.0)	13.0(7.0-29.0)	0.879
SBD	4.0(2.0-12.0)	3.0(3.0-15.0)	0.332
DA	4.0(3.0-12.0)	3.0(3.0-15.0)	0.160
SWTD	10.0(6.0-17.0)	9.0(6.0-29.0)	0.657
DOES	7.0(5.0-14.0)	7.0(5.0-25.0)	0.357
SHY	3.0(2.0-10.0)	3.0(2.0-10.0)	0.182

Unless otherwise specified data was expressed as mean±standard deviation or median(min-max). Sleep disorders state as defined by SDSC total score>70 IR: Insulin resistance, HOMA-IR: homeostasis model of assessment for insulin resistance, BMI: Body mass index, CRP: C-reactive protein, NLR: Neutrophil-to lymphocyte ratio, DIMS: Disorders of initiating and maintaining, SBD: Sleep-breathing disorders, DA: Disorders of arousal, SWTD: Sleep-wake transition disorders, DOES: Disorders of excessive somnolence, SHY: Sleep hyperhidrosis.

Table 3 Correlation coefficients

	BMI	N/L	CRP	HOMA-IR	SDSC total score
Age(year)	0.552(<0.001)	0.323(<0.001)	0.072(0.383)	0.233(0.004)	-0.035(0.675)
BMI	-	0.245(0.002)	0.204(0.012)	0.359(<0.001)	-0.034(0.682)
N/L		-	0.251(0.002)	0.222(0.006)	-0.020(0.812)
CRP			-	0.390(<0.001)	0.130(0.112)
HOMA				-	0.071(0.389)
SDSC total score					-

Data was expressed as correlation coefficient and corresponding p-value.
BMI: body mass index, NLR: neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, HOMA-IR: homeostasis model of assessment for insulin resistance, SDSC: Sleep Disturbance Scale for Children

	Univariate		Multiple	
	OR (95%CI)	p	OR (95%CI)	p
Age(year)	1.17(1.04-1.33)	0.012		
Gender(2)	1.31(0.67-2.54)	0.429		
BMI	1.15(1.06-1.26)	0.002	1.13(1.03-1.25)	0.009
N/L	1.77(1.08-2.92)	0.025		
CRP	1.25(1.07-1.46)	0.005	1.21(1.03-1.42)	0.022
SDSC total score	1.02(0.99-1.04)	0.238		

Table 4 Univariate and multiple logistic regression analysis for the prediction of IR

OR: Odds ratio, CI: confidence interval. Nagelkerke R^2=0.136
BMI: body mass index, NLR: neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, HOMA-IR: homeostasis model of assessment for insulin resistance, SDSC: Sleep Disturbance Scale for Children
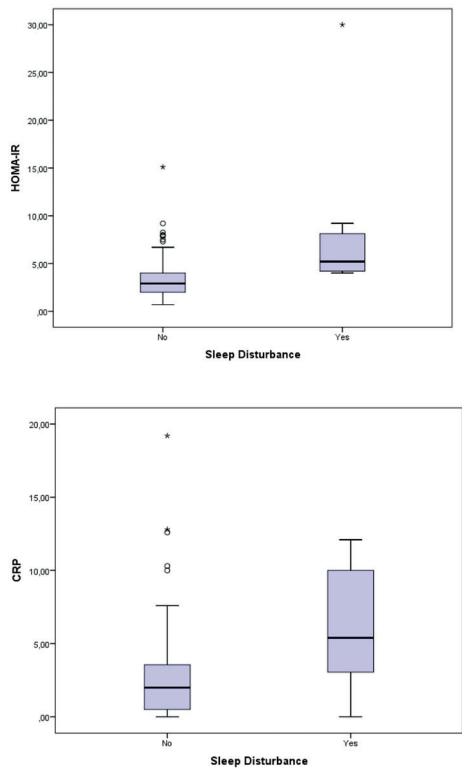
Figure 1 - Distribution of HOMA-IR and CRP according to sleep disturbance groups

Discussion

This study evaluated the association of sleep disorders, inflammatory markers (CRP, NLR), and insulin resistance in obese/overweight children. It is demonstrated that the estimation of insulin resistance via the HOMA-IR formulation in overweight/ obese children is not associated with sleep disorders. However, age, BMI, NLR, and CRP were associated with HOMA-IR. Especially NLR and CRP were detected independently associated with HOMA-IR.

Sleep disorders have been associated with increased inflammatory mechanisms and sustained activation of the HPA axis and sympathetic nervous system. As a result, an increase is observed in cortisol levels, TNF-α, IL-6, CRP, and noradrenaline levels [10, 17]. In this study, we demonstrated that CRP levels are higher in those suffering from sleep disorders. However, they were not associated with each other. NLR, another indicator of systemic inflammation, was higher in those with sleep disorders, but this was not statistically significant. Previous studies have analyzed the relationship between sleep disturbance severity and NLR in patients with obstructive sleep apnea, and conflicting results have been reported [18, 19]. In addition, several studies demonstrated NLR levels are linked to IL-6 [20]. However, while

high levels of IL-6 are commonly detected in sleep disorders, there are conflicting results regarding NLR levels. We suppose that this may be due to the difference in leukocyte glucocorticoid sensitivity emerging in patients with metabolic syndrome [21].

Obesity is also associated with systemic inflammation. Increased intestinal bacterial antigens in the circulation due to increased intestinal permeability, excessive adipokine secretion by hypertrophic adipocytes, relative hypoxia of expanding adipose tissue, and mechanical stress caused by excessive accumulation of triglycerides in adipocytes each trigger the inflammatory cascade [9]. Finally, TNF-α, IL-6, and CRP levels increase in obese [1]. A few studies demonstrated that NLR is also associated with obesity [22] and insulin resistance in obese [23]. In this study, CRP and NLR were correlated with BMI and HOMA-IR.

Studies evaluating the link between sleep disorders and insulin resistance have reported conflicting results. Numerous studies [2, 24, 25] support an association between sleep disorders and insulin resistance while others do not [26-28]. This disagreement may be associated with the different exploration methods for sleep disorders, diverse study populations, and the different accepted HOMA-IR cut-off levels. For instance, Siriwat et al. investigated sleep pathologies via polysomnography in 2- 18 aged obese children. They accepted the cut-off level of HOMA-IR ≥ 3 for insulin resistance [2]. Chen et all used the actigraphy watch to obtain sleep data and considered insulin resistance to be 90th percentile and upper of HOMA-IR for age [25]. In another study involving the 7-16 age group, the questionnaire method was preferred for sleep assessment, and HOMA-IR above 3.16 were accepted as insulin resistance [28]. In our study, insulin resistance was detected in all individuals with sleep disorders, but no statistically significant correlation was detected between these two parameters.

Numerous reports have revealed a direct link between inflammation and insulin resistance [1, 9, 29]. Both sleep disorders and obesity independently trigger inflammation. Besides their independent effects, they can contribute indirectly to inflammation through their bidirectional interaction. For this reason, we suspected that the emerging insulin resistance possibility may increase via the increased inflammatory response in the coexistence of these two clinical pathologies. In this study, we found higher HOMA-IR and CRP levels in obese patients with sleep disorders than in obese patients without sleep disorders. However, there was no significant correlation between these parameters and sleep disorders.

This study has several limitations. It was performed as a single-center study, so the generalizability of the study is limited. Secondly, due to the cross-sectional nature of the study, the sample group with sleep disorders was small. A larger sample size with sleep disorders might suggest more reliable

results. Thirdly, sleep disorder was detected using the parent questionnaires in this study and this method is a subjective evaluation. Finally, we did not use different HOMA-IR cut-off values for children and adolescents.

In conclusion, our findings demonstrated that insulin resistance was associated with CRP and NLR, but not with sleep disorders. The hypothesis that comorbid sleep disturbances in obese children are associated with increased levels of inflammation and insulin resistance has not been confirmed. There were no significant correlations between sleep disorders with HOMA-IR, CRP, and NLR. Nonetheless, CRP and HOMA-IR levels were higher in those with sleep disorders. Considering that metabolic risk may continue from childhood to adulthood, early detection of factors that may facilitate this is important to avoid possible negative effects. Therefore we speculate that future studies with large samples may be helpful to determine whether sleep disorders may increase the risk of insulin resistance in obese/overweight children and which markers may be early indicators of this.

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Spectrum of lower urinary tract symptoms in the women attending gynecological OPD in a tertiary care hospital in Northeast India

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Abstract

Aim: Lower Urinary Tract Symptoms (LUTS) are common conditions seen in women of all ages and by clinicians of nearly all specialties. The prevalence of LUTS has been measured by numerous epidemiological studies around the globe. However, there are insufficient data from India, particularly among women consulting gynecology clinics. This observational study was conducted to determine the proportion of LUTS among women attending the Gynecology OPD.

Material and methods: For the evaluation, a standardized, pretested, structured, and scored Bristol LUTS questionnaire containing sociodemographic information and a clinical history of LUTS symptoms has been utilized. The symptoms of LUTS were classified as storage, voiding, and stress symptoms. Each response received a score between 0 and 4. Patients were categorized into no/minimal LUTS (score1–7), moderate LUTS (score8–19), and severe LUTS (score>20). In our study, 48% of women attending the Gynecological OPD had LUTS. Age and vaginal delivery had a significant influence on the incidence of LUTS.

Results: Despite the high prevalence of LUTS, few patients in our study spontaneously reported symptoms of LUTS. This underreporting may be due to a lack of awareness as well as social stigma. Many consider these symptoms to be a normal part of the ageing process, especially in postmenopausal women.

Conclusion: Although all of the patients we have identified are based on the evaluation of a symptomatic questionnaire, a urodynamic study should be conducted to determine whether or not these women have different types of LUTS.

Key words: lower urinary tract symptoms, Bristol's questionnaire, urodynamic study, LUTS

Introduction

Lower Urinary Tract Symptoms (LUTS) are prevalent conditions that can affect men and women of all ages and clinical specialties. These symptoms have extensive human and social repercussions, causing distress, shame, and loss of self-esteem. In recent years, there has been a growing interest in various LUTS due to improved diagnostic and treatment options, as well as an increased awareness of the symptomatology and its negative influence on daily life. According to current standards recommended by the International Continence Society (ICS), LUTS are divided into three groups: storage, voiding, and post-micturition. The symptoms of excessive storage are an overactive bladder (OAB) and urinary incontinence (UI). The symptoms of voiding include a feeble or sluggish stream, hesitancy, and terminal dribbling. The post-urination symptoms include incomplete voiding and post-urination dribbling. LUTS comprises symptoms related to sexual activity, as well as genital and lower urinary tract pain [1,2]. The prevalence of lower urinary tract symptoms is high and tends to rise with age. Pregnancy, childbirth, and obesity are also major

risk factors. Other risk factors for urinary incontinence include smoking, diabetes, chronic obstructive airway disease and neurological disorders, and previous significant pelvic surgery such as hysterectomy [2].

Menopause has been identified as a risk factor for urinary incontinence. Menopause may have a distinct association with stress urinary incontinence than with urge incontinence, according to available evidence. In one study, the prevalence of urodynamic stress incontinence decreased from 21% to 12% after menopause, while the prevalence of detrusor overactivity increased from 9% to 19% [3]. There has been concern that hysterectomy may be associated with development of urinary incontinence via damage to the pelvic nerves and pelvic support structures [4]. A study found that LUTS appears to be more common following vaginal than abdominal hysterectomy [5].

Consequently, a validated instrument with extended questions for LUTS quantification was added to the Gynae OPD register [6]. However, the majority of prospective studies have failed to discover an association between hysterectomy and subsequent incontinence, whereas several epidemiologic studies have reported an association. Hormone replacement therapy has been extensively used to treat LUTS for many years. In the HERS study, however, it was discovered that urinary incontinence intensifies in older postmenopausal women taking daily estrogen plus progestin therapy compared to those women who were on placebo [7]. The prevalence of LUTS, particularly stress urinary incontinence (SUI) and OAB, increases with pelvic organ prolapse. In many cases, correction of pelvic organ prolapse reduces LUTS symptoms.

Before corrective surgery, it is necessary to have a solid understanding of the co-occurrence of LUTS and pelvic organ prolapse [8]. LUTS impacts women of all ages, and an in-depth study of LUTS is necessary to develop an individualized treatment protocol.

Review of literature

The EPIC study is the world's largest epidemiological investigation to measure the prevalence of UI, OAB, and other LUTS to date. This is the first evaluation of LUTS using the ICS definitions from 2002. LUTS can be divided into storage voiding and post micturition symptoms according to the ICS 2002 definitions. The storage symptoms include urgency, frequency, nocturia, and urinary incontinence (UI); voiding symptoms include slow stream, intermittent stream, hesitancy, straining, and terminal dribble; Over active bladder (OAB) is a recently defined syndrome characterized by the storage LUTS of urgency with or without UI usually with frequency and nocturia [9].

The study found that 66.6% of women had one or more LUTS [9]. Before the introduction of ICS definitions, two other studies evaluated the prevalence of OAB – SIFO study in six European countries between 1997-98 and the National Over Active Bladder Evaluation (NOBLE) Study which was conducted in the United States [10]. In other studies, the prevalence of LUTS in women ranges from 45.2% to 76.3%, and this prevalence was from the outpatient population [11]. Debra et al. reported that storage symptoms are more prevalent in women than voiding or postmicturition symptoms. In the majority of women, nocturia was the most prevalent symptom (54.5%), followed by urgency (12.8%) and OAB (12.8%) [3,12]. In the year 1998-99, in Vienna a health screening survey was conducted using Bristol Female LUTS questionnaire and again those women surviving in the year 2005 were re-interviewed which suggested that the female LUTS is a dynamic condition rather than a progression disorder; This study has tried to analyze the natural history of LUTS in females which postulated that the storage symptoms are more likely to improve with time [13]. Karin et al. from EpiLUTS study evaluated the participants ratings of the frequency and symptom-specific bother of individual LUTS and condition-specific HRQL(health related quality of life), generic health status, anxiety and depression. Most of the women had the lowest levels of HRQL and highest levels of anxiety and depression, 53.3% of women meeting self-reported screening criteria for clinical anxiety (Hospital Anxiety and Depression Scale, HADS, Anxiety > or =8), and 37.6% of women meeting self-reported criteria for clinical depression (HADS Depression > or =8). This indicates that women with LUTS have a high level of anxiety and depression, which is very concerning [9,14].

Numerous studies have identified the risk factors that may contribute to the development of LUTS in women. The factors which are associated with urinary incontinence includes age, parity, obesity, pelvic surgery, pulmonary disease, smoking, alcohol consumption, blood pressure, physical activity diabetes mellitus cardiac diseases [13,15-18]. The EPICONT study surveyed women of Norway between 1996-97 and again in 2006-08, showed a 16% increase in the prevalence of urinary incontinence between two time period with an incidence rate of 18.7% and remission rate of 34.1%.[15]However the prevalence of SUI peaks in the fifth decade of life and thereafter MUI continues to increase [15]. Though many studies have suggested the occurrence of LUTS as an age independent phenomenon, many studies have also confirmed the effect of age related changes leading to LUTS which peaks from 40 years of age and gradually plateau among women between 50-70 years and again its incidence doubles after 70 years of age [9,12,16]. Parity and the use of instruments are also associated with incontinence [17,18,19]. Women with a higher BMI have 12 times more chances of having LUTS as compared to underweight women [19]. Postmenopausal status and longer duration of peri-menopause have also been associated with storage and voiding LUTS, including SUI, nocturia, and a weak stream [20- 25]. In a study it has been suspected that women with adult lower urinary tract symptoms may have a higher prevalence of history of childhood dysfunctional voiding [26]. There are few longitudinal data on LUTS because of the slow progression of the disease, costs of longitudinal designs and difficulties in following a substantial number of individuals over several years; understanding natural history of the disease in women is important due to its high prevalence especially among the elderly [12,13,27].

Aim: The purpose of this study was to determine the prevalence of lower urinary tract symptoms among female patients of our institution's outpatient Obstetrics and Gynecology department.

Objectives: To estimate the proportion of LUTS among women attending the Gynecology OPD.

Material and methods

Type of investigation – observational.

Cross-sectional research design.

The study took place at Agartala Government Medical College AND GB Pant Hospital Agartala, Tripura, India.

This research was conducted over the course of six months, from September 2020 to March 2021.

Females of any age attending the hospital's gynecology outpatient department (OPD) were designated as the study population.

Sample size [8]-

Sample size = z2 x px(1-p)/d2

Z = degree of assurance

P= anticipated frequency or percentage
D= precision
n=3.84X35.9X(100-35.9)/5X5=354
The number of samples is 354.

Inclusion requirements: Women of any age attending the gynecology OPD who were presumably healthy and willing to participate in the study met the inclusion criteria for the study.

Exclusionary standards:
• Female with known kidney disease and undergoing any uro-gynecological procedures;
• Females during the menstrual cycle;
• Females with identified urinary tract abnormalities;
• Those who were expectant;
• Not interested in participating.

For the evaluation, a standardized, pretested, structured Bristol's female LUTS-SF questionnaire containing sociodemographic information and clinical history for LUTS symptoms was utilized. The symptoms of LUTS were classified as storage, voiding, and tension. Each response received a score between 0 and 4. Patients were categorized into no/minimal LUTS(score,1–7), moderate LUTS (score,8–19), and severe LUTS (score,>20).

The data was entered into SPSS version 25 and expressed in frequency and percentage form for analysis.

Statistical analysis: The Chi-Square test and multiple regression analysis will be utilized for qualitative data analysis.

Results and evaluation

354 participants were recruited for the study. The Bristol Female LUTS-SF questionnaire was used to assess LUTS in women who met the study's inclusion criteria. The socio-demographic information is provided in Table 1. Presented data are n (%); N=354. In our investigation, the majority of the population was between the ages of 21 and 40, i.e., between 21 and 40 years old i.e., 161 (46.5%) demonstrated in Figure 1 and Table 3. The participant's average age was 35.5 years.

Table 1	Socio-Demographic characteristics of the participants.
Age Group:	
<20	33 (9.3%)
21-40	161 (46.5%)
41-60	120(33.9%)
60-80	20 (7.1%)
80-100	15(4.2%)
Education:	
Illiterate	56(15.8%)
Primary	156(44.1%)
Secondary	88(24.9%)
Graduation	30(8.5%)
Post graduation	24(6.7%)
Marital Status	
Single	54(15.3%)
Married	204(57.6%)
Divorced	50(14.1%)
Widow	46(13%)
Occupation:	
Housewife	151(42.7%)
Working	149(42%)
Student	30(8.5%)
Retired	24(6.8%)
Others	0
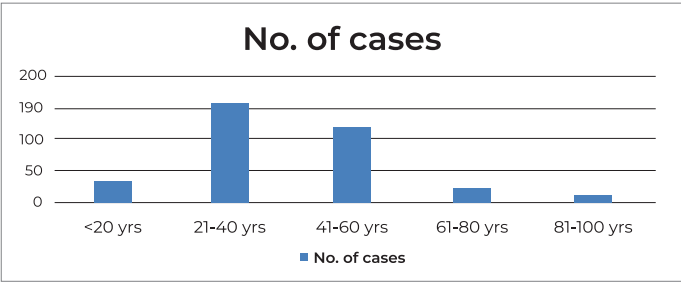
Figure 1 - Number of cases according to age
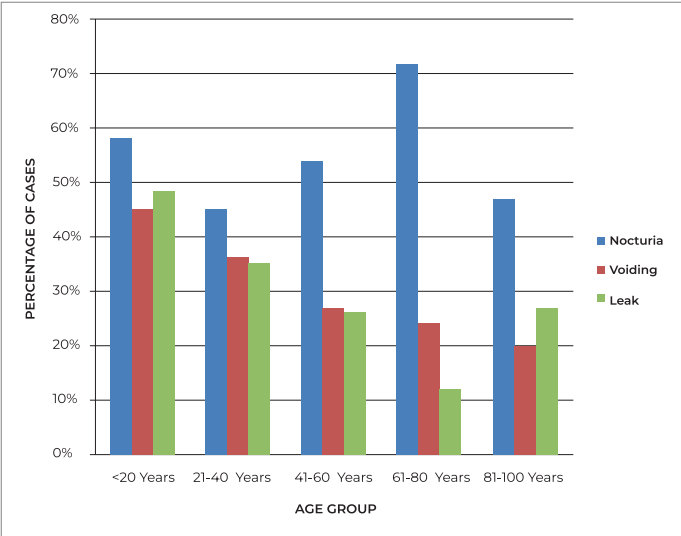
Figure 2 - Percentage of various LUTS

Table 2	Comorbidities in the study population.
Diabetes:	Yes: 54 (15.2%), No:300 (84.8%)
Hypertension:	Yes: 154 (43.5%), No: 200 (56.5%)
Smoking:	Yes: 14 (4%), No:340 (96%)
Abdominal Hysterectomy:	Yes: 4 (1.1%), No:350 (98.8%)

Table 3	Age distribution.
Age Group	No. of cases
<20	33 (9.3%)
21-40	161 (46.5%)
41-60	120(33.9%)
60-80	20 (7.1%)
80-100	15(4.2%)

Table 4	The proportion of LUTS according to severity.
No LUTS	184 (52%)
Mild LUTS	20 (5.6%)
Moderate LUTS	75 (21.2%)
Severe LUTS	75 (21.2%)
Proportion of LUTS	48%

In our study hypertension is the most common comorbidity (43.5%) followed by diabetes mellitus, smoking and hysterectomy respectively demonstrated in Table 2. In our study, the prevalence of LUTS was 48%, with moderate and severe LUTS sharing the same proportion, i.e., 21.2% each (75/170) demonstrated in Table4. The frequency symptoms were seen in 170 (100%), the urination symptoms were seen in 114 (67%), and the leakage symptoms were seen in 110 (64%) as demonstrated in Figure 3.
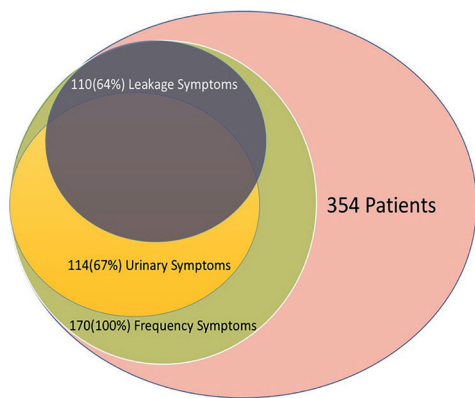
Figure 3 - Proportion of various symptoms of LUTS.

| Table 5 | Demonstrate severity of LUTS with age. |

Age Group	No LUTS	Mild LUTS	Moderate LUTS	Severe LUTS	P -Value
<20 years	31	2	0	0	0.000
21-40 years	153	7	1	0	
41-60 years	0	11	70	39	
61-80 years	0	0	3	22	
81-100 years	0	0	1	14	

| Table 6 | Demonstrates severity of LUTS with parity. |

Parity	No LUTS	Mild LUTS	Moderate LUTS	Severe LUTS	P -Value
Nulliparous	36	0	0	0	0.000
1	108	5	3	1	
2	40	11	27	9	
3	0	4	34	33	
4	0	0	9	12	
5	0	0	2	17	
6	0	0	0	3	

| Table 7 | Relation of LUTS with Mode of Delivery. |

MODE OF DELIVERY	LUTS PRESENT	LUTS ABSENT	Significance (p- value)
VAGINAL	109 (48.6%)	115 (51.4%)	0.000
CS	61 (46.9%)	69 (53.1%)	

| Table 8 | Demonstrates the severity of LUTS with BMI. |

BMI	No LUTS	Mild LUTS	Moderate LUTS	Severe LUTS	P - Value
≤20 kg/m2	114	19	63	17	0.000
21-25 kg/m2	74	1	7	8	
26-30 kg/m2	0	0	5	16	
>30 kg/m2	0	0	0	34	

| Table 9 | Demonstrates the presence of LUTS in Pelvicorgan prolapse. |

Prolapse	LUTS present	LUTS absent	Odd's Ratio
Present	47	14	OR=4.63
Absent	123	170	

In every age group, nocturia is the most prevalent symptom, followed by voiding complaints as demonstrated in Figure 2.The prevalence of nocturia in different age groups is approximately 58% below 20 years, 44% in the age group 21-40 years, 53% in the age group 41-60 years, 71% in the age group 61-80 years, and 48% in the age group 81-100 years as demonstrated in Figure 2. In our study, elderly women were more likely to experience LUTS than their younger counterparts. The prevalence of severe LUTS increased significantly after the age of 41; in the 81-100 age group, 93.3% (14/15) of participants had severe LUTS, 88.0% (22/25) in the 61-80 age group, and 86.4% (70/81) in the 41-60 age group, which is highly significant (p value<0.005) demonstrated in Table 5. While evaluating the parity history, it has been observed that Nulliparous women have no LUTS at all. There were 36(10.2%) women were nulliparous; 117(33.1%) women were with parity =1; 87(24.6%) women were with parity =2; 71(20.1%) women were with parity =3; 21(5.9%) women were with parity = 4; 19(5.4%) women were with parity = 5; and 3(0.8%) women were with parity = 6 as demonstrated in Table 6. The proportion of LUTS were high in women with parity more than >2 (p<0.005). In our study, 63.2% (224/354) of the women had vaginal births. Compared to caesarean section, however, women who delivered vaginally were more prone to develop LUTS (48.6% versus 46.4%) as demonstrated in Table 7. In this study the severity of LUTS increases with increasing BMI. There were 34 women who had BMI >30 and all of them are suffering from severe LUTS. There were 213 women who has BMI <20 Kg/m2 and only 17 had severe LUTS as demonstrated in Table 8. Among all the participants 61 women had pelvic organ prolapse and 47 had LUTS. The Odds Ratio calculated is 4.63 which is statistically significant, demonstrated in Table 9.

Discussion

In earlier studies, the prevalence of LUTS in women in the out-of-hospital population ranged from 45.2% to 76.3% [28]. The EPIC study which was the first largescale, multinational, cross-sectional study estimated the prevalence of LUTS, which is 64.3% in general population using the recent ICS definition (2002) and 66.6% of women were affected by one or more LUTS [9]. The prevalence of LUTS in women in China was 57.7%. Storage symptoms (frequency) were present in all women with LUTS, followed by voiding symptoms in 67% of women and post micturition symptoms in 62% of women [29]. Our study's higher prevalence of storage symptoms is consistent with previous research. In this study, the majority of participants were between the ages of 21 and 40, but the prevalence of LUTS increased significantly after age 41. The relationship between age and LUTS is consistent with many previous studies [9,12,16,27,29]. In some studies, it has been found that LUTS symptoms subside after 65 years of age [27]. The remission of symptoms with increasing age is not well understood. In our study, however, we discovered that as age increases, so do the symptoms, which is statistically significant (p value < 0.005). Our study demonstrates that severe forms of LUTS are more common in people older than 41, with the highest proportion occurring in those aged 81 to 100. Among all of the symptoms of various LUTS, including storage, voiding, and post micturition symptoms, nocturia is the most prevalent, affecting between 44% and 71% of patients across all age categories. This finding of nocturia with or without urgency or frequency indicates a problem with storage LUTS and is the most prevalent symptom, which is consistent with other studies [9,29]. The majority of patients in the younger age group did not have LUTS. This may be attributed to the menopausal

genitourinary changes. According to recent data, 50% of women in the older age group suffer from urinary incontinence [30]. This was primarily contributed by muscle injuries, widening of levator hiatus, diminution of reflex pelvic floor activation on coughing, or increased urethral mobility at stress. In older women, the urethral closing pressure and pelvic denervation decrease. In our study, the presence of pelvic organ prolapses and LUTS has a significant association with an OR of 4.63. Similar results were observed in The Boston Area Community Health Survey or BACH survey, an observational cohort study in which the multivariate adjusted OR for the association between uterine prolapse and the progression of LUTS was 3.05 [31]. This study also demonstrates that LUTS are more prevalent in women with >3 children, and as the number of children increases, so does the severity. However, it has been discovered that LUTS are more prevalent in vaginally-delivered women than in those who have undergone caesarean section. In our study, 63.2% (224/354) of the women had vaginal births. Comparing vaginal delivery to caesarean section, however, women who delivered vaginally were more prone to develop LUTS (48.6% vs. 46.4%). Our study's conclusion regarding the incidence of LUTS in relation to vaginal versus caesarean delivery is statistically significant. In their investigations, Nancy et al. found that women who have had three vaginal births are at a greater risk of developing LUTS [31]. Throughout the literature, caesarean section has been shown to protect against the development of incontinence. In a prospective Cohort study, Erica et al.studied the effects of method of delivery on urinary incontinence and found that Caesarean section is associated with a lower absolute risk of developing incontinence as compared to vaginal delivery in the postpartum period 3 months after delivery; urinary incontinence occurred daily in 3.11 percent of patients following vaginal delivery compared to 0.88 percent following caesarean section [32]. In a number of studies, it was discovered that some degree of LUTS occurs during pregnancy and increases in the postpartum period, but that the symptoms resolve on their own [32-34]. Many researchers have proposed the reversible trauma hypothesis, which may be due to partial recovery of the pelvic floor muscles.

Conclusion

Although LUTS are prevalent in the population, its impact has received less attention. It has evolved into a major issue affecting the quality of life. The majority of investigations on LUTS have focused on the general population. However, we have limited information regarding gynecology OPD patients who may be suffering from LUTS. Few studies have been conducted on the natural history of LUTS in males, while there was few research in the female population. Therefore, establishing a clinical practice of identifying LUTS in the Gynecology OPD will improve the lifestyle outcomes of women attending for other gynecological issues. In our study, we discovered that nearly 48 percent of patients have some degree of LUTS. However, only a small percentage of patients report experiencing LUTS symptoms. This underreporting may be due to a lack of awareness and social stigma in the community. All of the patients we've identified are based on the evaluation of symptomatic questionnaires, but urodynamic testing should be performed to confirm whether these women truly have various types of LUTS.

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Evaluation of the functional outcome following endoscopic decompression of retrocalcaneal bursitis

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Abstract

Introduction: Retro calcaneal bursitis is an inflammation of the bursa located between the posterior surface of the heel bone and the anterior surface of the Achilles tendon. This study was conducted to evaluate the clinical efficacy of endoscopic decompression and debridement in patients with retrocalcaneal bursitis who had not responded to conservative treatment. Our primary objective was to estimate the improvement in American Orthopaedic Foot and Ankle Society (AOFAS) score after surgery, and our secondary objectives were to estimate the average surgical duration and the incidence of post-operative complications.

Material and methods: This was a single-centre intervention study at a tertiary institution's level. Included in the study were all patients who were diagnosed with retrocalcaneal bursitis and who had failed a minimum 6-month trial of conservative treatment. 36 patients (36 heels) underwent endoscopic decompression.

Results: A prospective interventional cohort study was conducted on a total of 36 adult patients (18-70 years) with clinical and radiological findings suggestive of retrocalcaneal bursitis, duration of failed conservative treatment prior to surgery > 6 months, and refractoriness to other forms of non-operative treatment like steroid injections regardless of duration. There were no patients lost to follow-up. The mean duration of follow-up was 6 months [6 months to 2 years]. The average pre-operative AOFAS score was 56.42 ± 6.8, ranging from 44 to 70. The difference between preoperative and postoperative AOFAS scores at 1 week, 2 weeks, 4 weeks, 3 months, and 6 months was statistically significant ($p=0.0001$).

Conclusion: In patients with retrocalcaneal bursitis, arthroscopic decompression is a safe, effective, and simple procedure. Within the first three months, the majority of study participants experienced pain relief and a significant improvement in function.

Key words: retrocalcaneal bursitis, endoscopic decompression, tendo-achilles, tendinitis

Introduction

Retrocalcaneal bursitis is an inflammation of the bursa between the posterior surface of the calcaneus and the anterior surface of the Achilles tendon [1]. The retrocalcaneal bursa is a horseshoe-shaped structure located above and behind the calcaneus [2]. Inflation of this bursa is most frequently associated with excessive prominence of the posterosuperior aspect of the calcaneum, which impinges on the Achilles tendon; this condition was first described by Haglund and is named after him [3]. The most prevalent etiological factors associated with Haglund deformity [4] are repetitive trauma, overuse, and pressure on the area caused by wearing tight-fitting shoes and high heels. Retrocalcaneal bursitis is also associated with gout, rheumatoid arthritis, and other spondyloarthropathies [5,6]. Bursitis typically results in insertional Achilles tendinitis, which is the degeneration of the distal 2 cm of Achilles tendon from its insertion over the calcaneus

[7]. Retrocalcaneal bursitis causes pain and discomfort among patients in posterior part of heel and is usually diagnosed is usually by the lateral view radiograph of the ankle joint that may show postero-superior bony prominence and intra tendinous calcification [3,8]. Ultrasound and MRI are additional imaging methods used to confirm the diagnosis [3]. Conservative treatment, including footwear modification, the use of heel pads, moist heat, stretching exercises, nonsteroidal anti-inflammatory medications, local steroid injections, and extracorporeal shock wave therapy, is the cornerstone of treatment [3,9-12]. Patients who do not respond adequately to nonoperative treatment may require calcaneal osteotomy with or without Achilles tendon debridement, excision of the retrocalcaneal bursa, or endoscopic decompression, which involves debridement of the inflamed retrocalcaneal bursa with/without resection of the postero-superior aspect of the calcaneus [13,14]. When compared to open techniques, minimally invasive procedures, such as endoscopic techniques, provide a superior image of the retrocalcaneal space, have a shorter postoperative recovery period, less postoperative pain, and a lower complication rate [15-19].

This study was conducted to evaluate the clinical efficacy of endoscopic decompression and debridement in patients with retrocalcaneal bursitis who had not responded to conservative treatment. Our primary objective was to estimate the improvement in American Orthopaedic Foot and Ankle Society (AOFAS) score after surgery, and our secondary objectives were to estimate the average surgical duration and the incidence of post-operative complications.

Material and methods

This was an intervention study conducted at a single tertiary centre. Included in the study were all patients who were diagnosed with retrocalcaneal bursitis and who had failed a minimum 6-month trial of conservative treatment. Retrocalcaneal bursitis was suspected based on the senior author's clinical evaluation, which revealed pain and swelling in the retrocalcaneal region for over six weeks, along with difficulty walking and pain in ankle plantar flexion against resistance. Patients who met the aforementioned criteria underwent a clinical examination, a roentgenographic examination of the ankle (axial and lateral views), and an MRI of the heel. On MRI, patients with retrocalcaneal bursitis were included in the study. Excluded from the study were patients with a history of retrocalcaneal steroid injection, hind foot surgery, anatomical foot deformities such as cavus or valgus foot, gout, spondyloarthropathies including rheumatoid arthritis, and infective retrocalcaneal bursae. Additional patients with calcific Tendo Achilles tendinitis detected on lateral ankle X-rays were excluded from the study. Patients who finally met these criteria were enrolled in the study after obtaining their informed consent. 36 patients (36 heels) underwent endoscopic decompression. There were 22 women and 14 men present. The range of ages was 19-53 years, with a mean of 36.19 years. 20 procedures were performed on the right side and 16 procedures were performed on the left. On the patient proforma, the demographic information, medical history, and examination findings were recorded. The presence/absence of Achilles tendon calcification, neurovascular status, American Orthopaedic Foot and Ankle Society (AOFAS) score, and amount of bone to be resected were evaluated preoperatively using the criteria outlined by Kondaredi et al. [4] (Figure 1). To assess bony projection on the posterior aspect of the calcaneum, two parallel pitch lines were drawn. The baseline is formed by the lower line, which extends from the anterior tubercle to the medial posterior tubercle. The upper line is drawn parallel to the
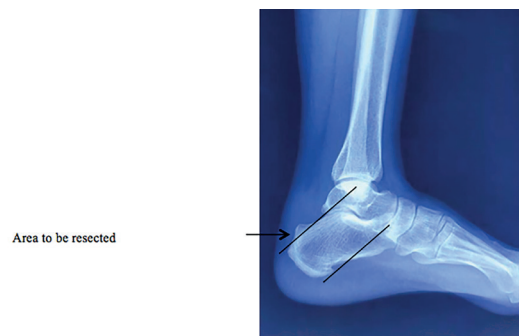
Figure 1 - Radiograph (lateral view) depicting area of calcaneum that requires resection

line above, beginning at the talar articular surface and ending at the posterior tuberosity. The prominence of the bony projection above the upper line necessitates surgical excision.

Operative technique

The patient was placed in a prone position with one foot hanging over the table's edge during the procedure. Utilizing a pneumatic tourniquet with a pressure setting of 270 mm of mercury, the bleeding was controlled. Antibiotics of the third generation were administered 15 minutes prior to surgery as a precaution. A stab incision was made just above the line drawn from the tip of the lateral malleolus to the Achilles tendon insertion and in front of the Achilles tendon to create the lateral portal. A trocar was inserted gently into the retrocalcaneal space. The 4mm 30° arthroscope was developed. For the insertion of an arthroscopic shaver, a spinal needle was inserted on the medial side, directly opposite the lateral side, under direct visualisation. A medial portal was created in front of the Achilles tendon's medial edge. A hemostat was introduced to the arthroscope, and a space was created for the introduction of a shaver. From the medial side, a 4mm arthroscopic shaver was introduced. The retrocalcaneal bursa was observed and resected using a razor (Figures 2 (a), 2 (b).
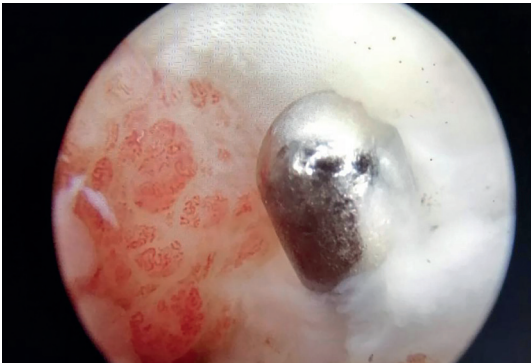
Figure 2 (a) - Shaver resecting inflamed bursa
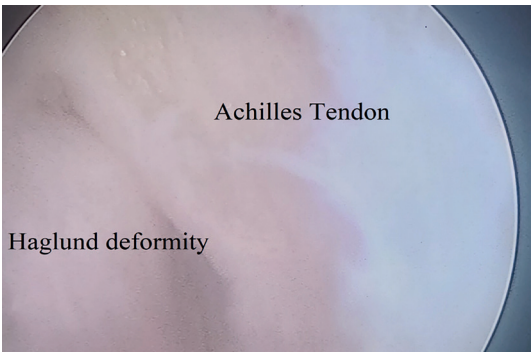
Figure 2 (b) - Endoscope view of retrocalcaneal space

Figure 3 (a) - Preoperative radiograph (lateral view)

Figure 3 (b) - Post Operative radiograph (lateral view) at end of 6th month

The opposite side of the calcaneum from the Achilles tendon was abraded. To prevent tendon injury, the hooded portion of the instruments was kept towards the tendon. For the resection of the posterosuperior aspect of the calcaneum, a burr was introduced. The bone was resected from the posterior to the anterior. The bone was resected up to the Achilles tendon attachment. The margins were smoothed with a curette or an arthroscopic bone file. Under arthroscopic observation, hyperplanterflexion and dorsiflexion of the foot were performed to rule out signs of impingement. The fragments were irrigated with copious quantities of normal saline and then vacuumed. The portal sites were injected with a local anaesthetic. There were no drains used. In relaxed equinus, the portal sites were sutured with 2-0 mattress sutures and a removable below-knee slab was given. Postoperatively, the foot was splinted in relaxed equines, and the patient was advised not to bear weight for ten to fourteen days. The sutures were removed after fourteen days. The splint was then removed and replaced with a walking boot (with a 1-inch heel) for the following two weeks. After four weeks, normal walking was resumed with normal shoes.

Postoperative protocol: All patients followed a similar postoperative protocol. In the second to third week, ankle range of motion and Achilles tendon stretching exercises were initiated. The patient was observed at 1 week, 2 weeks, 4 weeks, 3 months, and 6 months. At each follow-up visit, ankle range of motion, AOFAS Score, and any recurrence or persistence of pain or deformity were recorded. Each visit involved lateral X-rays (Figures 3 (a), 3 (b). The scoring was done by uninvolved surgeon. Each of the 36 patients was monitored. There was no subsequent loss.

Analytical statistics

Using the Kolmogorov-Smirnov test, the normality of the data was examined. Using the Wilcoxon signed rank test, quantitative variables (preoperative and postoperative AOFAS scores) were compared. The Kruskal Wallis test was used to compare the association between outcome and age group, and the Mann Whitney test was used to compare the association between outcome and side. A p value of less than 0.05 was deemed statistically significant. The data were entered into an MS EXCEL spreadsheet, and SPSS version 21.0 was used for analysis.

Results

It was a prospective interventional cohort study conducted on a total of 36 adult patients (18-70 years of age) with clinical and radiological findings suggestive of retrocalcaneal bursitis, duration of failed conservative treatment prior to surgery > 6 months, and refractoriness to other forms of non-operative treatment such as steroid injections regardless of duration. There were no patients lost to follow-up. The mean duration of follow-up was 6 months [6 months to 2 years]. The mean preoperative AOFAS score was 56.42 ± 6.8 with a range of 44 to 70. It increased to 65.56 ± 5.32 at the first week, 73.5 ± 3.26 at the second week, 85.25 ± 3.81 at the fourth week, 93.69 ± 5.09 at the third month, and 95.67 ± 4.85 at the end of the sixth month. The difference between preoperative and postoperative AOFAS scores at 1 week, 2 weeks, 4 weeks, 3 months, and 6 months was statistically significant (p=0.0001). Ten patients with retrocalcaneal bursitis and non-insertional Achilles tendinosis had mean pre-operative AOFAS scores of 51.4 ± 5.98, which improved to 93.1 ± 8.8 at the end of 6 months. In contrast, the mean pre-operative AOFAS Scores of 26 patients with retrocalcaneal bursitis alone increased from 53.15 ± 4.13 at the end of the first week to 96.65 ± 1.05 at the end of the sixth month. Both groups of patients showed significant improvement. The preoperative scores of the two groups did not differ statistically [p=.42], but patients with retrocalcaneal bursitis alone reported better outcomes than those with non-insertional Achilles tendinosis [p=.001]. The mean improvement in AOFAS score at 6 months was 47.89 when preoperative AOFAS scores were <50, 43.75 when preoperative AOFAS scores were between 51-55, 35.11 when preoperative AOFAS scores were between 56-60, 33.83 when preoperative AOFAS scores were between 61-65, and 28.25 when preoperative AOFAS scores were >65. Lesser the preoperative AOFAS score, which is indicative of disease severity, the greater the magnitude of postoperative improvement after arthroscopic decompression. Consequently, there is a positive correlation between disease severity (as measured by low AOFAS scores) and the magnitude of AOFAS score improvement in the postoperative period (Correlation coefficient = -0.946; p value 0.0001). However, no correlation was found between age and disease outcome (p=0.923) or between side of pathology and disease outcome (p=0.867). 1

(2.78%) of 36 subjects experienced persistent pain even after surgery, and the patient complained of pain throughout the entire 6-month follow-up period. Other treatment methods were attempted on the patient, but none were successful. The patient was advised to undergo an MRI and was counselled regarding the need for an open resection, but the patient refused. Four out of thirty-six patients (11.11%) complained of postoperative swelling around the incision site that persisted until suture removal at 14 days and was alleviated by limb elevation, active ankle range of motion exercises, and cold compressions. There were no intraoperative complications, altered sensations at the surgical site, surgical site infections, Achilles tendon ruptures, or neurovascular deficits.

Discussion

The study demonstrates that endoscopic decompression and debridement of the retrocalcaneal space is an effective procedure for the minimally complication-prone management of patients with retrocalcaneal bursitis who have failed adequate conservative treatment. Cases with less severe disease and no insertional tendinitis fared better than those with severe disease or insertional tendinitis, according to additional research.

Retrocalcaneal bursitis is a common condition that causes morbidity in a substantial proportion of patients.

The first line of treatment [4,12] includes the use of analgesics, hot saline fomentation, gastrocnemius and soleus stretching exercises, and the avoidance of tight shoes. If initial conservative treatment fails in certain conditions, steroid injections have also been used, but they cause Achilles tendon rupture [10,20]. In our study, no steroid injections were administered. Leitze et al. [4] reported a 10% failure rate for conservative therapy. In contrast, Sammarco et al. [21] reported a 65% failure rate with conservative treatment. Retrocalcaneal bursitis and Haglund deformity patients who do not respond adequately to non-operative treatment have numerous open surgical options, including calcaneal osteotomy with or without Achilles tendon debridement and retrocalcaneal bursectomy [13,14]. Nonetheless, these extensive open surgical techniques were linked to complications such as skin breakdown, Achilles tendon avulsion, mutilating scars, altered sensation, and joint stiffness [4].

The problems with open surgery led to the rise in popularity of minimally invasive surgeries [15]. Ortmann F.W. et al. performed endoscopic debridement and discovered that the average postoperative AOFAS score significantly increased (97 from preoperative score of 62). There were no intraoperative complications noted. 19 days after surgery, 1 patient developed an Achilles tendon rupture requiring primary repair. 1 patient complained of persistent pain, necessitating reoperation with open decompression and debridement [3]. Similarly, Van Dijk et al. performed 21 Endoscopic Calcaneoplasty procedures on 20 patients who had failed to respond to conservative treatment for at least six months. The mean duration of follow-up was 3.9 years. According to the Ogilvie-Harris score, the study yielded 15 excellent results, 4 good results, and 1 fair result. There were no surgical complications reported [16]. Jerosch J. performed endoscopic calcaneoplasty and discovered excellent results in 84 patients, good results in 71 patients, and fair and poor results in 5 and 4 patients, according to the Oglivie-Harris score. The study found that more than 90% of patients had excellent or good results without any of the complications associated with open procedures, such as wound dehiscence, lesions in the Achilles tendon, scar irritation, transformation to keloid, pain persistence,

and hypesthesia of the skin overlying the scar [22].

Similar to these findings in the literature, we discovered that endoscopic decompression is an effective treatment for retrocalcaneal bursitis in patients.

In a study of 33 heels treated with endoscopic decompression, Leitze et al. found that 9 had excellent results, 5 had good results, 3 had fair results, and 3 had poor results [4]. The average AOFAS score for patients treated with an endoscopic approach was 61.8 pre-op and 87.5 post-op (p=0.001), whereas the average AOFAS score for patients treated with open surgery was 58.1 pre-op and 79.3 post-op (p=0.006). There were no intraoperative complications reported. In the endoscopic group, one patient had a wound infection, one reported sural neuropathy, one reported heel numbness, and one reported symptoms similar to sympathetic dystrophy. Similar to our observation, their study discovered that the greater the severity of disease preoperatively, the greater the magnitude of improvement postoperatively, indicating a correlation between the preoperative score and the magnitude of improvement (0.048). Nonetheless, no correlation was found between age and outcome or postoperative resection angle and outcome, similar to the present study's findings.

Operating time reveals a steep learning curve for endoscopic procedures. The average operating time decreased to 40 minutes from an initial 75 minutes. Patients with retrocalcaneal bursitis alone reported better outcomes than those with non-insertional Achilles tendinosis, as determined by Kondreddi et al. [3].

Leitze et al. discovered a correlation between disease severity (as measured by low AOFAS scores) and the magnitude of improvement in AOFAS score in the postoperative period (Correlation coefficient, -0.946; p value 0.0001) [4]. Similar to the results reported by Leitze et al., we also found no correlation between age and disease outcome (p=0.923) or between the side of pathology and disease outcome (p=0.867).

This study has several limitations, including the absence of a control group for comparison, a relatively short follow-up period of only 6 months, the inability to measure the effect of different angles of calcaneum resection on outcome, the inability to compare calcific and non-calcific degeneration, and the small sample size.

Conclusion

In patients with retrocalcaneal bursitis, arthroscopic decompression is a safe, effective, and simple procedure. Within the first three months, the majority of study participants experienced pain relief and a significant improvement in function. The procedure offers benefits such as minimal blood loss, direct visualisation of the structures, accelerated functional recovery, and a low complication rate. It can be concluded that patients without tendon degeneration benefit more than those with tendon degeneration. Second, a positive correlation has been identified between disease severity (as measured by a low AOFAS score) and the magnitude of improvement at the end of the follow-up period.

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Delta parathormone value as an indicator of postoperative hypocalcemia in patients with parathyroid adenoma

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Abstract

Aim: In primary hyperparathyroidism patients, avoiding hypoparathyroidism and hypocalcemia after surgery is essential. We aimed to evaluate if the delta parathormone percent value (ΔPTH%) can identify patients with an increased risk of developing hypocalcemia after parathyroid surgery for primary hyperparathyroidism.

Material and methods: Eighty patients with parathyroid adenomas who underwent single parathyroidectomy were analyzed, and demographical data, preoperative, and postoperative laboratory data were collected were included in the study. Postoperative hypocalcemia was defined as a corrected calcium value below 8.5 mg/dL calculated from the blood values taken on the first postoperative day. The ΔPTH value was calculated by finding the difference between the preoperative PTH value and the postoperative PTH value, and the percentage of ΔPTH was calculated by dividing the ΔPTH value by the preoperative PTH (ΔPTH = Preoperative PTH – Postoperative PTH, and ΔPTH% = ΔPTH / Preoperative PTH).

Results: Postoperative hypocalcemia developed in 7.5% of the patients. Hypocalcemic patients had higher ΔPTH and ΔPTH% values. The selection of 130.95 ng/L as ΔPTH level cutoff level divided patients with and without postoperative hypocalcemia with 83.3% sensitivity and 62.2% specificity. As for ΔPTH%, a cut-off value of 71.4% had 100.0% sensitivity, 56.8% specificity, and a 16-fold increase in odds of postoperative hypocalcemia.

Conclusion: ΔPTH and ΔPTH% values are helpful predictors of postoperative hypocalcemia after parathyroidectomy and can be used as a guiding tool.

Key words: parathyroid adenoma, postoperative hypocalcemia, parathormone, endocrinology, complication

Introduction

A parathyroid adenoma is a benign tumor that develops in one of the four parathyroid glands. Parathyroid adenomas produce excessive parathyroid hormone (PTH), leading to primary hyperparathyroidism [1]. Hyperparathyroidism can cause various symptoms because of elevated calcium levels, including kidney stones, osteoporosis, fatigue, and depression. Hyperparathyroidism is more commonly diagnosed due to better diagnostic tools, more healthcare provider knowledge, and more widespread use of regular blood calcium tests [2].

The most definitive treatment for a parathyroid adenoma is the surgical removal of the affected gland, and one of the potential complications of parathyroidectomy is postoperative hypocalcemia [1]. In many cases, postoperative hypocalcemia has more than one cause. Reasons include direct damage to the parathyroid gland or inferior thyroid artery, accidental removal of other glands, hemodilution, hungry bone syndrome, and thyrotoxic osteodystrophy [3]. Long-term hypercalcemic suppression of non-adenomatous parathyroid tissue causes the remaining parathyroid tissue to be unable to respond when calcium levels must

be abruptly controlled postoperatively [4]. During this time, a decline in serum calcium can be observed [5].

In parathyroid surgery, avoiding postoperative hypoparathyroidism and hypocalcemia is an essential principle. Significant postoperative morbidity is associated with symptomatic hypocalcemia in individuals receiving parathyroid surgery [6]. 15% to 30% of individuals with primary hyperparathyroidism have transient hypocalcemia after surgery [4, 6]. Most of the postoperative hypocalcemia occurrences are temporary, and just 0.5% to 3.8% of instances are found to be persistent [3].

According to many studies, a substantial decrease in calcium is not seen until the third and fourth postoperative days [6]. Because of this delay, an easily accessible perioperative approach for identifying individuals at risk for hypocalcemia would be advantageous [3]. Our initial objective in this study was to see whether the delta PTH percent value could be utilized to identify postoperative hypocalcemia.

Material and methods

All patients who underwent minimally invasive parathyroidectomy or unilateral parathyroidectomy due to a parathyroid adenoma at the Hitit University Erol Olçok Training and Research Hospital, Department of General Surgery, between 01.01.2017 - 01.10.2022, were found from the archives retrospectively. Patients over 18 years of age, patients without known hematological and oncological diseases, and patients with single parathyroid adenoma in radiologic images were found for the study. Then, patients with multiple parathyroid adenomas, patients with prior parathyroid or thyroid surgery, patients with known additional metabolic diseases, and patients whose pathology reports aren't consistent with an adenoma were excluded from the study. Patients who had parathyroidectomy for reasons apart from primary hyperparathyroidism (secondary and tertiary hyperparathyroidism, parathyroid malignancies) were also excluded from the study and 80 patients were selected for the study.

Age, gender, hospitalization duration, operation duration, preoperative lymphocyte, platelet, neutrophil, hemoglobin, albumin, calcium, parathormone values and postoperative 1st-day lymphocyte, platelet, neutrophil, hemoglobin, albumin, calcium values, and postoperative 1st-hour serum parathormone (PTH) values of 80 patients were recorded and included in the study. Adjusted calcium values were calculated by using patients' post-operative serum calcium and albumin levels. [AdjCa = (Ca + ((4 - Albumin) x 0.8)))]. Postoperative hypocalcemia was defined as a corrected calcium value below 8.5 mg/dL calculated from the blood values taken on the 1st postoperative day. The ΔPTH value was calculated by finding the difference between the preoperative PTH value and the postoperative PTH value, and the percentage of ΔPTH (ΔPTH%) was calculated by dividing the ΔPTH value by the preoperative PTH (ΔPTH = Preoperative PTH − Postoperative PTH, and ΔPTH% = ΔPTH / Preoperative PTH). This study has been approved by the local Clinical Research Ethics Committee (Decision No: 2023-38/ Date: 16.03.2023).

This study is planned retrospectively. All statistical analysis was performed using IBM SPSS Statistics for Windows software (version 26; IBM Corp., Armonk, N.Y., USA). Descriptive statistics were reported as count and percentages for categorical variables, and mean ± standard deviation and median in parentheses for numeric variables. The distribution of data was evaluated by the Shapiro-Wilks test. The relationships between the variables were investigated with the Pearson or Spearman correlation coefficient in accordance with the data distribution. A comparison of numerical measurements for two independent research groups for age, preoperative lymphocyte, platelet, hemoglobin, and postoperative platelet levels was done with student t-test, for hospitalization duration, operation duration, preoperative neutrophil, albumin, calcium, parathormone levels, postoperative lymphocyte, neutrophil, hemoglobin, albumin, calcium, corrected calcium levels, and post-operative 1st hour PTH levels, ΔPTH and ΔPTH percentage levels were evaluated by Mann Whitney U test in accordance with the data distribution. The ratio comparisons of the gender distribution according to the research groups were evaluated using a Chi-square test. A ROC analysis was done to differentiate groups with and without hypocalcemia, and the optimal cut-off values were found using the area under the curve and the Youden index. For these cut-off values, sensitivity, specificity, PPV, NPV, test accuracy, and odds ratio values were calculated. For odds ratio calculations, the Haldane-Anscombe correction technique was used for estimated odds ratios. For statistical significance, $p<0.05$ was accepted.

Results

The mean age of the 80 patients in the study was 58.58±11.02 (58.5) years, and 82.5% of the patients were female. The median length of hospital stay was 4 (3-8.75) days. The mean preoperative calcium level was 11.04±0.86 (11) mg/dL, and after parathyroidectomy, the mean postoperative calcium level was 9.42±0.83 (9.5) mg/dL. The adjusted postoperative calcium mean was 9.34±0.78 (9.31) mg/dL. Patient characteristics and other laboratory values are shown in Table 1.

The median preoperative parathormone level was 154.95 (104-244.75) pg/mL, and the postoperative first-hour parathormone median were found as 41.5 (25.78-69.35) pg/mL, there was a statistically significant decrease in parathormone levels after surgery (p<0.001). The median of the calculated ΔPTH values was 107.65 (70-193.65) pg/mL, and the mean of the ΔPTH% was 0.69±0.20 (0.71).

Comparison of patients with and without postoperative hypocalcemia

Post-operative hypocalcemia developed in 7.50% of the patients (Group 2). There were no statistically significant differences between groups in age, gender, hospitalization duration, and operation duration (p=0.213, p=0.281, p=0.342, p=0.216, respectively). There were no statistically significant differences between the mean preoperative lymphocyte, platelet, neutrophil counts and albumin, calcium levels of postoperative normocalcemic (Group 1) and hypocalcemic patients (Table 1).

The mean preoperative hemoglobin level of postoperative normocalcemic patients was significantly higher than patients with postoperative hypocalcemia (13.1±1.53 (13.05) vs 11.58±2.16 (11.9), p=0.027). Like the preoperative period, the mean of postoperative hemoglobin in normocalcemic patients was statistically significantly higher than in postoperative hypocalcemia patients (12.93±1.88 (13.1) vs 11.03±1.22 (10.7), p=0.012).

The median preoperative parathormone level of postoperative normocalcemic patients was 143.85 (103.75-238.38), and the median of preoperative hypocalcemic patients was 219.9 (146.5-1617), although the mean and median values were higher in the hypocalcemia group, no statistically significant difference was observed (p=0.139).

In an evaluation of postoperative laboratory values, there was no statistically significant difference between the mean of

Table 1	Comparison between patient groups				
Variables		All Patients (n=80)	Postoperative Normocalcemia (n=74)	Postoperative Hypocalcemia (n=6)	Statistical Significance
Age		58.58±11.02 (58.5)	59.01±10.83 (59)	53.17±12.94 (50.5)	0.213
Gender	Male	14 (17.50%)	12 (16.22%)	2 (33.33%)	0.281
	Female	66 (82.50%)	62 (83.78%)	4 (66.67%)	
Hospitalization Duration*		4 (3-8.75)	4 (3-7.5)	7 (3.5-10.25)	0.342
Operation Duration*		78.5 (60-100)	75 (60-100)	90 (78.75-112.5)	0.216
Preoperative	Lymphocyte	2.11±0.68 (2.03)	2.13±0.68 (2.08)	1.89±0.69 (1.73)	0.414
	Platelet	266.83±75.15 (260)	262.64±66.42 (258.5)	318.5±146.12 (291.5)	0.394
	Neutrophil	4.21±1.51 (3.79)	4.23±1.54 (3.79)	3.91±1.06 (3.84)	0.777
	Hemoglobin	12.98±1.62 (13)	13.1±1.53 (13.05)	11.58±2.16 (11.9)	0.027
	Albumin	4.15±0.35 (4.2)	4.14±0.36 (4.2)	4.2±0.24 (4.2)	0.869
	Calcium	11.04±0.86 (11)	11.07±0.87 (11)	10.60±0.61 (10.6)	0.159
	Parathormone*	154.95 (104-244.75)	143.85 (103.75-238.38)	219.9 (146.5-1617)	0.139
Postoperative	Lymphocyte	2.23±0.95 (2.16)	2.26±0.97 (2.26)	1.83±0.46 (1.88)	0.195
	Platelet	271.45±73.15 (271.5)	270.86±72.88 (272)	278.67±83.16 (241.5)	0.803
	Neutrophil	5.05±2.35 (4.6)	5.12±2.39 (4.73)	4.18±1.58 (3.66)	0.261
	Hemoglobin	12.79±1.9 (12.95)	12.93±1.88 (13.1)	11.03±1.22 (10.7)	0.012
	Albumin	4.1±0.46 (4.2)	4.12±0.46 (4.2)	3.73±0.36 (3.75)	0.018
	Calcium	9.42±0.83 (9.5)	9.56±0.67 (9.5)	7.65±0.6 (7.95)	<0.001
	Parathormone*	41.5 (25.78-69.35)	42 (25.93-70.35)	31.85 (8.96-112.92)	0.401
	Corrected Calcium	9.34±0.78 (9.31)	9.46±0.67 (9.33)	7.86±0.61 (8.06)	<0.001
Post-operative Hypocalcemia	No hypocalcemia	74 (92.50%)			
	Post-operative hypocalcemia	6 (7.50%)			
ΔPTH*		107.65 (70-193.65)	95.75 (65.95-182.33)	187.99 (123.23-1363.58)	0.043
ΔPTH Percent		0.69±0.20 (0.71)	0.68±0.20 (0.70)	0.86±0.11 (0.87)	0.020
ΔPTH: Change in PTH level, *: Reported as median value and 25th and 75th percentiles					

lymphocyte, platelet, and neutrophil counts between the two groups (Table 1). The mean postoperative albumin of patients in Group 1 was 4.12±0.46 (4.2), while it was 3.73±0.36 (3.75) in Group 2 (p<0.018). When the corrected calcium values of the two groups were compared, the corrected calcium mean of the postoperative normocalcemic patients was 9.46±0.67 (9.33), and the mean of postoperative hypocalcemia patients was 7.86±0.61 (8.06) (p<0.001).

There were no differences found between the groups in postoperative 1st-hour parathormone levels (42 (25.93-70.35) vs. 31.85 (8.96-112.92), p=0.401). When ΔPTH values were calculated, the median of Group 1 was 95.75 (65.95-182.33) and significantly lower than patients with postoperative hypocalcemia (187.99 (123.23-1363.58), p=0.043). The mean of ΔPTH% was significantly lower in postoperative normocalcemic patients than in the postoperative hypocalcemia group (0.68±0.20 (0.7) vs 0.86±0.11 (0.87), p=0.020).

Evaluation of ΔPTH and ΔPTH percentage as an indicator of postoperative hypocalcemia

To determine the optimal cut-off values of the ΔPTH value for the distinction of postoperative hypocalcemia, a ROC analysis was used (AUC 0.750 (0.091), CI%95 (0.571-0.929), p=0.043). The cut-off value for the ΔPTH was found to be 130.95 with 83.3% sensitivity, 62.2% specificity, 15.2% positive predictive value, 97.9% negative predictive value, and 63.8% test accuracy but when tested with Chi-square analysis there were no statistically significant differences observed and it was found unsuccessful as an independent indicator for postoperative hypocalcemia (OR 8.214, 95%CI 0.912-73.973, p=0.077).

In the ROC analysis for ΔPTH% (AUC 0.786 (0.076), CI95% (0.638-0.934), p=0.020), a value of 0.7140 (71.4%) was found with 100.0% sensitivity, 56.8% specificity, 15.8% positive predictive value, 100.0% negative predictive value, and 60.0% test accuracy (OR 17*, CI 95% 1.023-312.854*, p=0.009) (*: Haldane-Anscombe correction technique). When these diagnostic markers were compared, ΔPTH% was successful in predicting hypocalcemia. A patient whose parathormone level dropped by more than 71.4% at the first postoperative hour compared to the preoperative period was approximately 16 times more likely to belong to the hypocalcemia group than to other patients.

Discussion

Primary hyperparathyroidism has been recognized as a frequent endocrine condition due to its increased accidental diagnosis with regular laboratory testing. Early surgery is often the best course of action when treating parathyroid adenomas. However, one of the significant possible consequences of parathyroid surgery is postoperative hypocalcemia. Hypocalcemia may be either temporary or permanent. Increased risk of postoperative hypocalcemia is associated with the extent of exploration for parathyroidectomy [7]. Only individuals who received minimally invasive parathyroidectomy or unilateral parathyroidectomy were included in the present analysis to control this effect. In a prior meta-analysis, 1.6% of patients had postoperative hypocalcemia after targeted parathyroid investigation, and 13.2% had postoperative hypocalcemia after bilateral exploration [8]. In our study, this ratio was found as 7.5%.

Postoperative deterioration of the blood circulation of the parathyroid glands has also been suggested as one of the hypotheses for postoperative hypocalcemia to occur after bilateral total thyroidectomy and parathyroidectomy. Torer et al. found that secondary hyperparathyroidism patients with

Variables	Cut-Off	Diagnostic Values					ROC Analysis			Odds Ratio		
		Sensitivity	Specificity	PPV	NPV	Accuracy	AUC (SE)	%95 CI	p	OR	%95 CI	p
ΔPTH	130.95	83.3%	62.2%	15.2%	97.9%	63.75%	0.750 (0.091)	0.571-0.929	0.043	8.214	0.912-73.973	0.077
ΔPTH Percent	55.08%	100%	24.3%	9.7%	100%	30%	0.786 (0.076)	0.638-0.934	0.02	4.256*	0.228-79.241*	0.328
	85.28%	50%	75.7%	14.3%	94.9%	73.75%				3.111	0.576-16.795	0.182
	71.40%	100%	56.8%	15.8%	100%	60%				17*	1.023-312.854*	0.009

*Values are calculated and estimated based on Haldane-Anscombe correction, PPV: positive predictive value, NPV: negative predictive value, ROC: receiver operating curve, AUC: area under curve, SE: standard error, CI: confidence interval, p: statistical significance, OR: odds ratio

postoperative hypocalcemia after parathyroidectomy had lower preoperative hemoglobin levels than patients without postoperative hypocalcemia [9]. In our study, we found that both preoperative and postoperative hemoglobin levels of patients with postoperative hypocalcemia were lower than those of other patients. The fact that such a difference was observed between the hemoglobin levels of the two groups in our study could indicate the importance of circulation in the pathogenesis of hypocalcemia after parathyroidectomy.

There was no statistically significant difference between the albumin levels among the patient groups in our study in the preoperative period, but the postoperative albumin levels of the patients with hypocalcemia were significantly lower than the other group. Hemodilution was considered as the reason for the difference in such a short time. A study conducted with patients after total thyroidectomy by Karunakaran et al. observed that the intraoperative fluid volume given was higher in the group with postoperative hypocalcemia [10]. While we did not have the opportunity to monitor intraoperative fluid administration in our study directly, we believe the difference in albumin levels after surgery could be caused by the difference in intraoperative fluid volume given and might be a factor for postoperative hypocalcemia.

In a study conducted by Abdullah et al. on patients after total thyroidectomy, they predicted that the level of parathormone in the early postoperative period alone might be a marker for postoperative hypocalcemia [11]. Similarly, AlQahtani et al. suggested that the postoperative first-hour parathormone level after bilateral total thyroidectomy alone can predict postoperative hypocalcemia [12]. However, in our study, both preoperative and postoperative parathormone levels did not differ significantly between the two groups and could not be used as a single predictor for predicting postoperative hypocalcemia after single parathyroidectomy.

In some studies to predict hypocalcemia after bilateral total thyroidectomy, some authors have found success with a single parathormone measurement [11]. As in our study, studies examining the difference between preoperative and postoperative parathormone levels also report successful results [13, 14]. In a study by Noordzij et al., the percentage of PTH decline in the postoperative 6th hour was successful in predicting postoperative hypocalcemia with a cut-off value of %65 [15]. Chapman et al. reported the optimal cut-off value for 6th-hour parathormone drop lower than Noordzij, at %44 [16]. In another study by Soylu et al., more than a %40.8 decrease in 2nd-hour parathormone levels was predictive of postoperative hypocalcemia after bilateral total thyroidectomy [13]. A study done by Vanderlei et al. was also using the percentage of change between preoperative and postoperative first-hour parathormone levels similar to our study; the authors demonstrated that a 73.5% PTH drop in the first hour after bilateral total thyroidectomy has a sensitivity of 91.6% and a specificity of 87.5% for predicting postoperative hypocalcemia

[17]. In our patient population of primary hyperparathyroidism patients, we found a PTH change of more than 71.4 percent was prognostic for postoperative hypocalcemia with a 100% sensitivity and 56.8% specificity. The fact that the sensitivity was calculated as high as 100% may be due to the small number of postoperative hypocalcemia patients in our study. A patient whose parathormone level dropped by more than 71.4% at the first postoperative hour was approximately 16 times more likely to belong to the hypocalcemia group than to other patients.

According to some studies, calcium and vitamin D supplementation are recommended to all patients after total thyroidectomy. Unfortunately, this strategy causes at least fifty percent of patients to get needless care, which raises healthcare costs [18]. With a more objective assessment of the risk of hypocalcemia, unnecessary treatment and the economic burden it brings can be avoided. As a cheap and easily reproducible way of determining the risk of postoperative hypocalcemia after parathyroidectomy, the ΔPTH% value calculated from preoperative and first-hour parathormone values is a promising tool that can be beneficial to clinicians.

The main limitations of this research were its retrospective approach, relatively small sample size, and absence of intraoperative fluid intake data. Even though there are many studies investigating postoperative hypocalcemia incidence and risk factors after total thyroidectomy, to our knowledge, this study is one of the first studies using parathormone change percentage (ΔPTH%) for predicting postoperative hypocalcemia in patients operated for primary hyperparathyroidism caused by parathyroid adenomas.

Determining the risk of postoperative hypocalcemia following parathyroidectomy in the first few hours after surgery might help avoid a common complication arising from an early hospital release. While preoperative and postoperative parathormone levels could not predict postoperative hypocalcemia after parathyroidectomy for parathyroid adenomas alone, ΔPTH and ΔPTH% are helpful in this prediction. Patients at risk for postoperative hypocalcemia may be recognized and treated sooner using this parameter, leading to decreased morbidity. Larger series from prospective, randomized, multicenter trials are required to prove the relationship between anemia, intraoperative fluid volume, ΔPTH, ΔPTH%, and postoperative hypocalcemia.

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Effectiveness of the modified darn repair method in inguinal hernia repair: 10 years of experience

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Abstract

Aim: We aimed to evaluate the effectiveness of the Modified Darn Repair (MDR) method performed in our clinic for Inguinal Hernia Repair (IHR) and to determine the postoperative complications and recurrence rates of this method.

Material and methods: The records of all patients who underwent IHR with MDR method in our clinic between January 2012 and December 2021 were obtained from the hospital database. Demographic characteristics of the patients, intraoperative findings, hospitalization and return to normal activities, postoperative complications and recurrence rates were retrospectively analyzed.

Results: A total of 892 patients aged between 18 and 85 with a male:female ratio of 14:1 were studied. Of 1011 elective IHRs, 773 were unilateral (right/left: 452/321) and 119 (119 right + 119 left) were bilateral. Hernia types were 667 (66%) indirect, 273 (27%) direct, 71(7%) pantaloon (combined) hernias. All procedures were performed under spinal anesthesia. The mean duration of surgery was 35 (15-75) minutes, hospital stay was 1.1 (1-3) days, and return to normal activities was 12.8 (10-20) days. The postoperative complications were wound infection in 33 (3.26%) patients, hematoma in 11 (1.09%) patients, and abscess/seroma in 15 (1.48%) patients. In addition, suture material reaction developed in 1 (0,12%) patient. Recurrence was observed in 25 (2.4%) patients and no mortality was observed in any patient.

Conclusion: The goal of every surgeon is to have a non-recurring repair in IHR without leaving a foreign body in the patient. Despite the criticism, we believe that the MDR technique is a safe, effective and viable option.

Key words: modified darning, inguinal hernia, repair, recurrence rate, postoperative complications

Introduction

Inguinal hernia repair (IHR) is one of the most frequently performed surgical procedures in our clinic, as it is all over the world [1]. Regardless of the hernia type, the definitive treatment of inguinal hernia is surgery [2]. In inguinal hernia repair, many new techniques have been described since the description of the Bassini technique [3]. Inguinal hernia repair, many new techniques have been described since the description of the Bassini technique [3]. All the techniques described are aimed at reducing the recurrence rate. In most of these repair methods, the cause of recurrence is the wear of the inguinal ligament fibers because of a significant amount of tension [4]. In most of these repair methods, the cause of recurrence is the wear of

the inguinal ligament fibers due to a significant amount of tension [4]. The Darning technique, first introduced by Abrahamson and popularized by Moloney, has been recognized as a relatively tension-free method of tissue-based repair. They described the inguinal canal as connecting the tissues from the pubic tubercle to the inner ring in a tension-free manner to form a lattice, and narrowing to the inguinal ligament (Poupart's ligament) and the tendon conjugate with monofilament nylon up to the pubic tubercle again [5,6]. After all the techniques used in inguinal hernia repair; postoperative pain, time to return to daily activities, recurrence rates and chronic inguinal pain are the main problems [7].

To evaluate the success of any surgery, IHR is evaluated by criteria such as recurrence rate and

complications such as chronic inguinal pain, cost, and time to return to the normal activities. The search for a method that can achieve all the above objectives, preferably without any foreign objects such as knitting, continues. Studies evaluating the netting technique have shown satisfactory results in terms of recurrence and other postoperative complications. Some of these are comparable to the Lichtenstein inguinal hernia repair technique, which has now become the gold standard for open inguinal hernia repair [8,9]. The recurrence rate of traditional sutured hernia repair techniques is reported to be between 0.7% and 9.3% [10]. On the other hand, the recurrence rate of tension-free network repair is less than 1% [11].

This study aims to present our experience with the use of MDR (posterior wall reconstruction and darning on it) technique for inguinal hernia repair in a tertiary hospital in our country. In addition to the demographic characteristics of the patients in our clinic, to evaluate the results in terms of postoperative complications and recurrence rates in the light of the literature. Standardizing any surgical procedure and adopting it as a training curriculum may be the most important key to increasing quality and improving outcomes for this technique.

Material and methods

The records of all patients who underwent IHR with the MDR method in our clinic between January 2012 and December 2021 were obtained from the hospital database. Demographic characteristics, intraoperative findings, postoperative complications and recurrence rates of the patients were analyzed retrospectively. All patients were controlled in the outpatient clinic. The clinical studies of our hospital were approved by the ethics committee (Decision No: 2022/514/223/1 and Date: 13.04.2022).

Incarcerated and strangulated inguinal hernias, recurrent hernias, non-American society of anesthesia (ASA) 1-3, scrotal hernias performed in the emergency were not included in the study. All patients were operated in the supine position and under spinal anesthesia. It was supported by general anesthesia if the spinal anesthesia is insufficient. However, patients who were converted to general anesthesia were not included in the study. The surgical procedure was performed by two specialist surgeons and their team. Hernia type was determined after exploration with standard inguinal incision, sac preparation and herniectomy were performed in indirect hernias. With 1/0 or 0/0 non-absorbable propylene suture, posterior wall reconstruction (plication) is provided starting from the pubic tubercle up to the annulus inguinalis profunda with continuous sutures. The defect between the tendon conjugate and the inguinal ligament was repaired without tension using the darning method with the same suture (Figure 1-4). MDR was not performed for recurrent and scrotal inguinal hernias.

All patients who underwent MDR technique for IHR in our clinic were examined. Information on demographic characteristics (age, gender), hernia type, operation details (anesthesia method and operation time), and postoperative results (hospitalization time, return to daily activities) were obtained. This information was obtained from the hospital archive. The study team followed all patients who underwent MDR up in the outpatient clinic. Post-operative complications; hematoma, surgical site infection and recurrence information were obtained from the outpatient clinic records.

The patients did not have any comorbidities such as chronic liver disease, ascites, immunocompromised, etc. that could affect the outcome. Duration of surgery; it was measured as the time from skin incision to skin closure. Intravenous non-
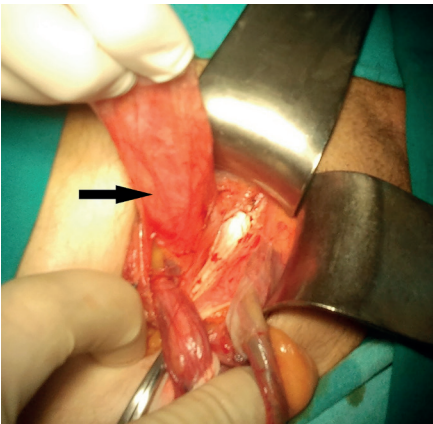
Figure 1 - Prepared direct inguinal hernia (IH) (arrow).
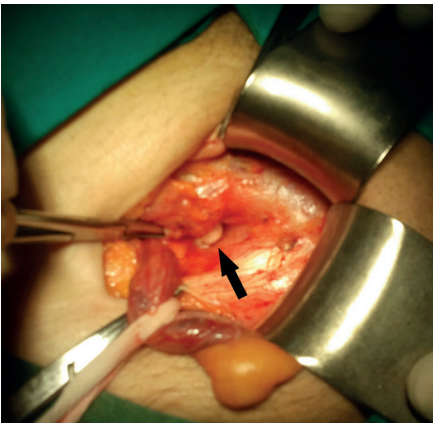
Figure 2 - Reduced inguinal hernia after direct inguinal hernia preparation (arrow).
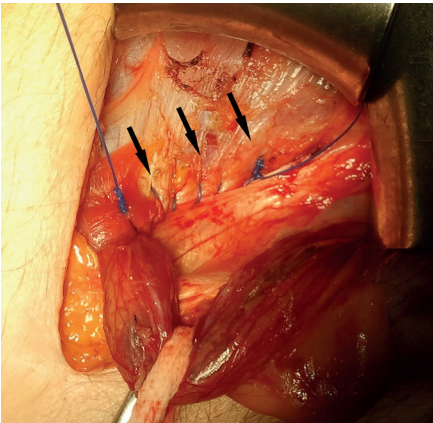
Figure 3 - Posterior wall reconstruction (posterior wall defect plication) (arrows).
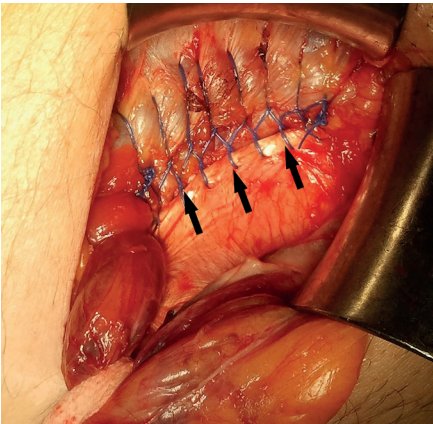
Figure 4 - Modified darning method in inguinal hernia repair (arrows).

steroidal anti-inflammatory drugs (NSAIDs), which is the routine analgesia application of our clinic in the early postoperative period, was used. In addition, patients who were discharged were given oral NSAIDs.

Statistical analysis

Statistical analysis of data was performed using SPSS™ software, version 20. Continuous variables were described as median and normal range. Categorical variables were reported using numbers and proportions. Qualitative data were described using the number and percent. Pearson's chi-square test was used for qualitative data and Student's t-test for quantitative data. All data were expressed as mean (min-max) except when otherwise indicated.

Results

Between January 2012 and December 2021, a total of 7861 patients were operated due to inguinal hernia in the general surgery clinic of our hospital. Unilateral without graft IHR: 773 (9.83%), unilateral grafted IHR: 5318 (67.65%), bilateral without graft IHR: 119 (1.52%), bilateral grafted IHR: 573 (7.3%), laparoscopic totally extraperitoneal (TEP) unilateral IHR was 907 (11.53%), and laparoscopic TEP was bilateral IHR: 171 (2.17%) (Table 1). We included a total of 892 patients who underwent MDR.

Table 1	Distribution according to IHR operation method.

Operation method in IHR	n	%
Without graft (MDR Method), unilateral:	773	9,83
Grafted (Lichtenstein method), unilateral:	5318	67,65
Without graft (MDR Method), bilateral:	119	1,52
Grefted (Lichtenstein method), bilateral:	573	7,30
Laparoscopic TEP, unilateral	907	11,53
Laparoscopic TEP, bilateral	171	2,17
Total:	7861	100

IHR: Inguinal Hernia Repair, MDR: Modified Darn Repair, TEP: Totally extraperitoneal, n:Number

Distribution of inguinal hernias by age
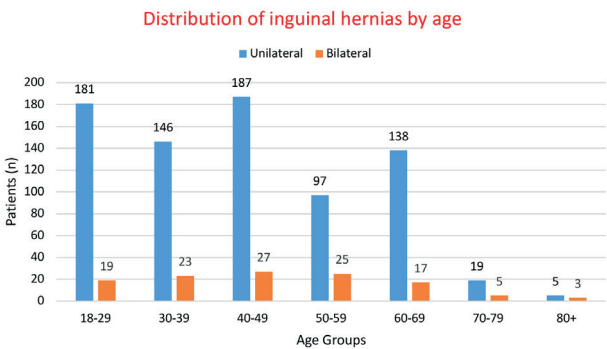
Graphic 1 - Distribution of patients undergoing MDR in IHR by age.

A total of 892 patients, 832 males and 60 females (male/female = 14/1), with a mean age of 49.4 years (18-85), were studied (The distribution of patients by age is as in Graphic 1). Of 1011 elective IHRs, 773 were unilateral (right/left: 452/321=58% right, 42% left) and 119 (119 right + 119 left) were bilateral inguinal hernias. Of the hernias, 667 (66%) were indirect, 273 (27%) were direct, and 71 (7%) were pantaloon (combined) hernias. All procedures were performed under spinal anesthesia. The mean duration of surgery was 35 (15-75) minutes, hospital stay was 1.1 (1-3) days, and return to normal activities was 12.8 (10-20) days (Table 2).

Table 2	Demographic and clinico-pathological features of the patients.			
FEATURES		**RESULTS**	**TOTAL**	**p VALUE**
Gender (n, %)	Male	832 (93.25%)	892	<0,01
	Female	60 (6.75%)		
Age (years)	Median (Interval)	49.4 (18-85)		
Side of Hernia (n, %)	Right	452 (58%)	773	>0,05
	Left	321 (42%)		
	Bilateral		119	
Type of Hernia (n, %)	Direct	667 (66%)	1011	<0,05
	Indirect	273 (27%)		
	Combined (Pantaloon)	71 (7%)		
Duration of Surgery (minutes)	Mean (Interval)	35 (15-75)		
Hospital Stay (days)	Mean (Interval)	1.1 (1-3)		
Return to Normal Activities (days)	Mean (Interval)	12.8 (10-20)		
Follow-up (years)	Mean (Interval)	4.6 (1-10)		

Complications were seen in 59 (5.83%) patients in the early postoperative period. The most commons were hematoma, seroma and wound infection. Patients with early complications were treated in the ward at the bedside or in the outpatient setting. None of these patients were operated on again. The patients were followed up in the outpatient clinic. Late complications were seen in 26 (2.6%) cases. Of the 25 recurrences, 12 were unilateral and 13 were in patients with bilateral IHR. Rejection to the suture material developed in 1 patient (Table 3).

Table 3	Postoperative complications.			
	Complication	**n**	**%**	**Total**
Early	Hematoma	11	1.09	59(%5,83)
	Seroma	15	1,48	
	Wound infection	33	3,26	
Late	Rejection	1	0,12	26 (%2,6)
	Recurrence	25	2,4	

Discussion

Many surgical methods have been described in the IHR and clinical researches have been conducted. These are basically grafted or non-grafted anterior approach and posterior approach methods and laparoscopic methods. Anterior and tension-free repairs are now the most common procedures. The aim of all these types of operations is to achieve lower recurrence and complication rates, earlier return to daily activities and less cost. The mean age of the patients, male:female ratio, operation time, length of hospital stay, hernia types (indirect, direct, pantaloon) were consistent with the literature. All procedures were performed under spinal anesthesia, but when spinal anesthesia was insufficient, general anesthesia had intervened.

The Lichtenstein technique and its modifications have become the most popular and frequently performed methods, but there is a high incidence of chronic inguinal pain following hernia repair and reportedly ranges from 28.7% to 43.3% [12,13]. If inguinal sepsis occurs after graft repair, complete removal of the graft is required to treat sepsis [14]. Potential damage to the

spermatic cord and nerve compression following graft repair due to extensive fibrosis are also concerns raised by this technique [15]. Laparoscopic hernia repairs are costly [16] and have a long learning curve [17]. The anterior approach and open methods without the use of grafts also have disadvantages among themselves. The Shouldice technique, which is considered the gold standard among these methods, has 1-4% recurrence rates in specialized centers [18,19]. Long learning curve, risky dissection of the inguinal floor and insufficient experience; this makes it inaccessible to surgeons working outside specialized centers for this method [20]. IHR with the Darning method has the advantage of a short learning curve [21].

Complications were observed in a total of 59 (5.83%) patients in the early postoperative period. The most common of these was surgical site infection with 33 (3.26%) cases. These cases healed within a week with antibiotics and dressings. Essawy et al. reported 7.5% [22] and a study by Olasehinde et al. reported 4.5% surgical site infection [23]. On the other hand, hematoma developed in 11 (1.09%) cases and seroma developed in 15 (1.48%) cases. The patients recovered spontaneously with anti-edema and scrotal elevation. Essawy et al. 12.5% [22] and Olasehinde et al [23] reported hematoma/seroma in 1.5% of cases in the study. Postoperative early complications are consistent with the literature. In our study, none of these patients required additional surgical intervention.

Late complications were seen in 26 (2.6%) cases. Rejection against the suture material developed in 1 (0,12%) case. The patient, who did not recover with conservative care, was treated in operating room conditions by removing sutures. In our study, recurrence was seen in 25 (2.4%) cases. When the articles published in the IHR using the Darn method are examined in the literature; Essawy et al. [22] 0%, Olasehinde et al. [23], 1.5%, Memon et al. [24] 1.5%, Manzoor et al. [25] 0.8%, Farooq et al. [8] 0.6%, Kamran et al. [26] reported a recurrence rate of 0%. Investigators, reported 0% recurrence, have published articles with short-term follow-up. In addition, these are mostly studies conducted in the direction of early complications and return to normal activities. In our study, the mean follow-up period of the patients was 4.6 years.

In our study, most of the recurrence cases were bilateral IHR. Recurrence was 12/773 (1.6%) in unilateral, whereas it was 13/119 (10.1%) in bilateral IHR. Johansen et al. reported 13% recurrence rate in bilateral inguinal hernia repair in a large series [27]. When bilateral and unilateral IHR are compared; It has been reported that the risk of recurrence is 32 times than more with bilateral IHR [23]. However, the reason for this is not fully specified. Predisposing factors should be investigated in detail in patients with bilateral inguinal hernia and precautions should be taken against possible recurrences. Because of that, some surgeons recommend grafted repair in bilateral IHR [23,27].

The hospital stay was 1.1(1-3) days and the return to normal activity was 12.8 (10-20) days. Memon et al. reported 2-4 days for hospitalization and 14-21 days for return to daily activities [24]. In another graft-free IHR publication, it is stated that return to work takes an average of 8.62 days (6-14) [28]. Although the hospitalization and return to normal daily activities data were different, they were found to be compatible with the literature data.

Our study has advantages as well as disadvantages. The disadvantages are that it is retrospective and not comparable to any other method. The advantages of our study are that all kinds of techniques are performed in IHR in our clinic, the number of patients is very high compared to the literature, and we obtain long-term data. Since pain is a subjective finding, the study was not performed. Local magnetic resonance imaging is required for nerve injury. It was not done because it was an additional cost for the patient. We believe that the study would be more valuable if the patient was evaluated with a visual analog scale (VAS) for chronic pain.

Conclusion

The aim of every surgeon when performing IHR is to repair without recurrence and without leaving a foreign body in the patient. MDR is a procedure that every surgeon can do with an easy learning time. It has a recurrence rate comparable to any other procedure for IHR. MDR technique is a reliable and effective method. Despite the criticism, we believe that the Darn technique is a viable option for inguinal hernia repair. We do not recommend the MDR method in bilateral IHR.

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Splenic infarction associated with Salmonella typhi infection: A rare case report

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Abstract

We described a rare case of a splenic infarction associated with typhoid fever in a 26-year-old Bangladeshi man who returned from a vacation 10 days ago from his home country and presented to the emergency department with fever followed by left hypochondrial pain. Contrast-enhanced computed tomography of the abdomen showed multiple areas of splenic infarction. Salmonella typhi, which was sensitive to ceftriaxone, grew in the blood culture. The patient received intravenous ceftriaxone, analgesics, hydration, antiemetics, and other supportive care. He showed significant clinical improvement and was discharged. The patient was seen at the hospital two months after discharge, he was doing well and no splenic infarction could be detected by sonography.

Key words: typhoid fever, splenic infarction, antibiotics, analgesics

Introduction

Splenic infarction is an infrequent clinical entity that has various etiologies and presents with variable and nonspecific symptoms. Splenic infarction occurs when the splenic artery or any of its branches are occluded, either by distant emboli or by thrombosis in situ [1]. The most common causes of splenic infarction include infiltrative hematologic diseases that cause congestion of the splenic circulation by abnormal cells, or thromboembolic conditions that produce obstruction of larger vessels. Other causes include abdominal trauma, pancreatic disorders, hyper-coagulable states, autoimmune diseases, vascular disorders, and infections [2,3]. Additionally, iatrogenic splenic infarction following various procedures has been reported in the literature [4]. Infections complicated by splenic infarction have been reported in the literature, including the Epstein-Barr virus, cytomegalovirus, malaria, and brucellosis [5-7]. Typhoid fever cases accompanied by splenic infarction are rare; only a few cases have been reported in the literature [8-11]. In this report, we presented a rare case of splenic infarction associated with typhoid fever.

Case presentation

A 26-year-old Bangladeshi man, previously in good health, presented to the emergency department with a 6-day fever followed by rash and left hypochondrial pain. The pain was sharp 7/10 on a scale of 10, increasing with breathing and radiating to left shoulder. He came back from Bangladesh 10 days ago. On examination he appeared ill but conscious and oriented. The temperature was 39.4°C, the pulse rate was 120/minute and the blood pressure was recorded as 110/85 mm Hg. There was a tender enlarged spleen. The rest of the systemic examination was unremarkable.

Initial investigations revealed leukocytes of 13600/ul (mainly neutrophils); hemoglobin 10 g/dl; and platelets 450,000/ul. Blood sugar and kidney function tests were within the normal range. Liver enzymes were elevated (AST 220 u/l and ALT 122 u/l). A malaria parasite smear was negative and the urine dipstick and microscopy were normal. His C-reactive protein was 70 mg/L and blood samples were sent for Gram stain and culture.

Urgent abdominal ultrasound showed an enlarged spleen with irregular hypodense areas within the spleen suggestive of splenic infarctions. Contrast-enhanced computed tomography (CT) of the abdomen also showed findings consistent with splenic infarction (Figure 1). Further testing to determine the causes of the infarction revealed negative results for sickling, antinuclear factor, lupus antigen, and human immunodeficiency virus (HIV) serology, while no vegetations were visible on transthoracic echocardiography. Protein C and S activities were within normal limits and there were no abnormalities in splenic artery and vein Doppler.
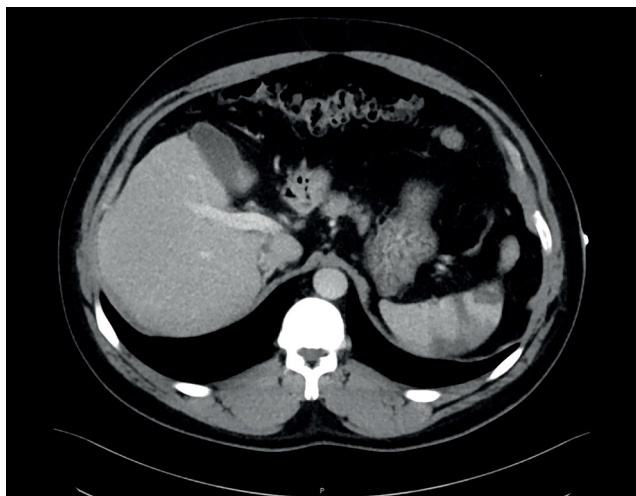
Figure 1 - Contrast-enhanced computed tomography of the abdomen shows hypodense splenic lesions consistent with splenic infarction.

He was admitted to the medical ward and given piperacillin-tazobactam intravenously while the sepsis workup was pending. On the following days, blood culture grew *Salmonella typhi* sensitive to piperacillin–tazobactam, ampicillin, ciprofloxacin, and ceftriaxone. The patient received intravenous ceftriaxone for 2 weeks. He showed significant clinical improvement and was discharged. Two months after discharge, the patient was seen in the clinic, he was asymptomatic and a repeat ultrasound of the abdomen was normal.

Discussion

Splenic infarction as a part of the extraintestinal complication of typhoid fever is rare, only a few cases have been reported worldwide. The exact incidence of splenic infarction in patients with typhoid fever is not well known because the diagnosis is often overlooked due to its nonspecific presentation, which offers no clues or indicators [1]. To the best of our knowledge, this is the first reported case of typhoid fever-associated splenic infarction in Qatar.

The clinical presentation of patients with splenic infarction may include nonspecific abdominal pain of variable intensity, nausea, vomiting, and fever [1-3, 12], probably resembling the symptoms of enteric fever. Therefore, in the setting of infectious diseases such as enteric fever, a splenic infarction may go unnoticed because clinicians are more concerned with determining the cause of the sepsis and frequently start broad-spectrum antibiotics, which can mask the condition. On the hand, presenting with severe abdominal pain and a tender abdomen may prompt physicians to request an abdominal CT scan resulting in the incidental detection of spleen infarction on a radiological test that was not intended to diagnose spleen infarction, as the case in our report.

Since the diagnosis of splenic infarction is based on clinical suspicion and imaging [12], a high index of suspicion is needed when a patient presents with abdominal pain and/or tender splenomegaly in the setting of febrile illness in endemic areas or after returning from an endemic area as in our case. However, between 17% and 20% of patients with splenic infarction reported no abdominal pain [1,2], making diagnosis in such cases challenging or impossible.

Although the precise pathogenesis of splenic infarction is still unknown, several mechanisms, including infection-induced injury to endothelium and nearby tissues, infected embolism, endophlebitis, triggering of the inflammatory cascade, infection-induced red blood cell rouleaux formation, and hypercoagulable state, have been proposed [5,12,13].

Laboratory workups are of no value in the diagnosis of splenic infarction, and contrast-enhanced CT of the abdomen is the imaging modality of choice to identify this clinical entity. Following the diagnosis of splenic infarction, all efforts should be directed towards finding the underlying etiology as these aids in patient management and prognosis [11-13]. We assumed that our patient had a typhoid-associated splenic infarction based on the isolation of Salmonella typhi from the patient's blood and the exclusion of common causes of splenic infarction by the absence of thrombi or vegetations on the echocardiogram, the absence of evidence of sickle erythrocytes, the negative results of antinuclear antibodies, lupus antigen, and human immunodeficiency virus. In addition to the normal splenic artery and vein doppler.

Treatment of splenic infarction in the setting of enteric fever consists primarily of administration of antibiotics, analgesics, hydration, antiemetics, and other supportive measures. There is uncertainty about the role of anticoagulation in the management of these patients. Our patient was treated conservatively with analgesics, analgesics, and antibiotics, with significant improvement.

Conclusion

Splenic infarction is a rare complication of typhoid fever that requires a high index of suspicion. Physicians should be aware that pain in the left hypochondrium that occurs during a febrile illness may be due to splenic infarction. Therefore, abdominal CT is the first option for diagnosis, and treatment consists mainly of the administration of antibiotics, analgesics, hydration, antiemetics, and other supportive measures.

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Benign retroperitoneal cyst – important differential diagnosis of retroperitoneal mass

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Abstract

Retroperitoneal cyst is very rare clinical condition having incidence 1:5750 to 1:250,000. Most of the retroperitoneal lesions are asymptomatic.

We are presenting a case of retroperitoneal cyst in a 65 years old female patient who presented with vague pressure symptoms. Exploratory laparotomy was performed. A large cystic right lumbar retroperitoneal mass displacing overstretched inferior vena cava, abdominal aorta and right psoas muscle seen intraoperative. Intact retroperitoneal cyst filled with its contents was removed.

Large lesion as in our study cause abdominal pain, mass effect on kidney and major vessel consistent. We excised cyst in totocyst preserving vital structure to prevent spillage and avoid further recurrence which is consistent with standard literature.

Retroperitoneal cysts are rare in incidence and asymptomatic. Due to silent nature and critical anatomy multidisciplinary approach is must for management of retroperitoneal cyst.

Key words: benign retroperitoneal cyst, retroperitoneal mass, benign cyst, case report

Introduction

Retroperitoneal cyst is very rare clinical condition having incidence varying from 1:5750 to 1:250,000 [1]. Large retroperitoneal mass may cause pressure symptoms on organs like duodenum, colon, kidneys, aorta, lymphatic or cause renal failure due to ureteric obstruction. Retroperitoneal cyst have embryonic origin, may result from trauma, parasitic infection or arise from lymphatic cell inclusion or inherited genetically like Noonan syndrome or trisomy 21 in cystic lymphangioma. Retroperitoneal mass can be unilocular (epidermoid cyst, mucinous cystadenoma) or multilocular (pseudomyxomas, cystic mesotheloma, perianal mucinous carcinoma) [2,3,4]. On computed tomography scan abdomen, well circumscribed mass containing fluid, adipose tissue and calcification is seen in cystic tertoma, single spot or curvilinear calcification in pseudomyxoma retroperitonei [5], multiloculated cyst lesion with septal calcification in perianal mucinous carcinoma and wall calcification in cystic lymphangioma. We are presenting a case of retroperitoneal cyst in a 65 years old female patient presented with vague pressure symptoms.

Case presentation

A 65 year old female presented with complaint of vague abdominal discomfort, early satiety, and easy fatigability of 3 year duration. She had no other relevant positive history.

On Examination: Patient was vitally stable. On per abdomen examination: vague retroperitoneal mass extending from right hypochondrium to right lumbar region was palpable. Superiorly mass extended below the right costal margin separate from liver. The percussion note was tympanic.

Contrast enhanced computer tomography (CECT) of abdomen showed cystic mass of 12X10X14 cm occupying right retroperitoneal space extending behind duodenum to right lateral side of Aorta. The lesion had non enhancing thin wall without any solid component. The lesion displaced inferior vena cava anteromedially, with anterior displacement of duodenum and uncinate part of pancreas. It abutted the right psoas muscle but maintained its planes with the muscle. No intraosseous extension seen. Impression was suggestive of benign retroperitoneal cyst.
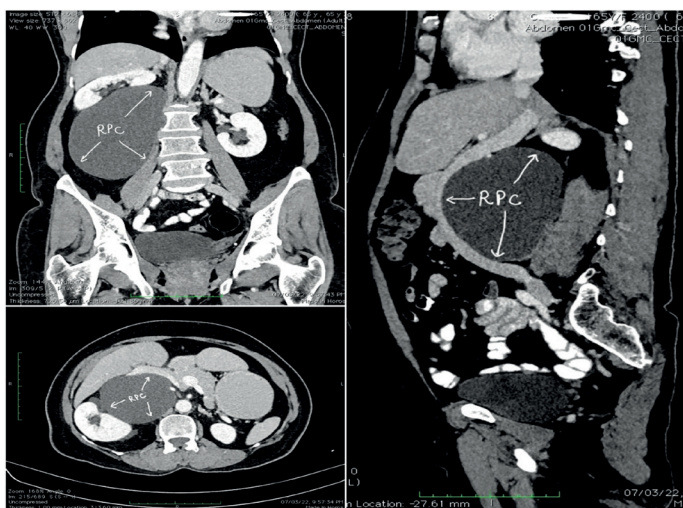
Figure 1 - CECT (Contrast Enhanced Computer Tomography) Abdomen [coronal view (upper left), axial view (lower left), saggital view (right)] showing right retroperitoneal mass in right lumbar region displacing right kidney displacing abdominal aorta and inferior vena cava.

Operative procedure

Exploratory laparotomy was performed by chevron roof top incision. A large cystic retroperitoneal mass noticed in right lumbar region the peritoneal organs in the right hypochondriac and right lumbar regions. Catell–Braasch maneuver was performed to expose retroperitoneal area. Careful dissection done to separate the cyst from displaced and overstretched inferior vena cava, abdominal aorta and right psoas muscle. Intact retroperitoneal cyst filled with its contents was removed.

Intraoperative finding:

• 15x10x15 cm retroperitoneal cystic mass occupying right retroperitoneal space pushing the right kidney and the right ureter along the lateral abdominal wall, stretching inferior vena cava, duodenum and hepatic flexure antero-medially.

• Posteriorly mass was densely adherent to the right psoas muscle, anterior surface of vertebral column and right lateral surface of abdominal aorta.

• Excised cyst contain straw colored fluid and inner layer of cyst studded with fine granules.
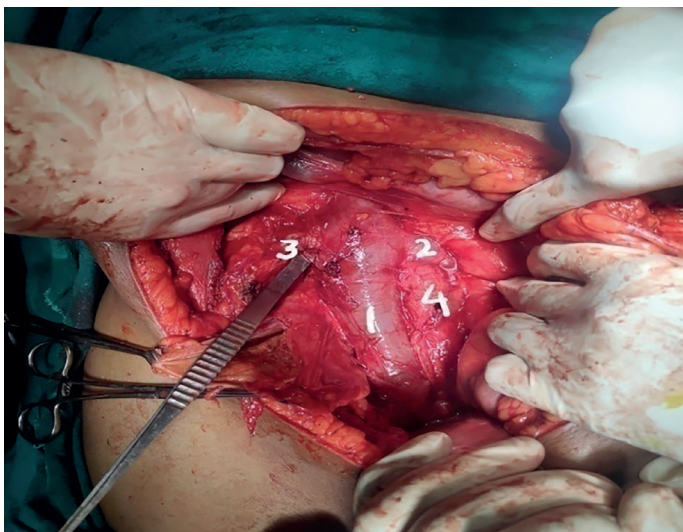
Figure 2 - Intraoperative finding after dissecting of retroperitoneal cyst from surrounding structures (1- inferior vena cava, 2- left renal vein, 3- right renal vein, 4-Aaorta).

Histopathological examination: retroperitoneal benign cyst
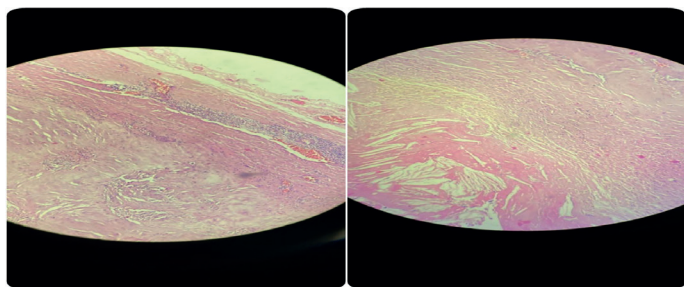
Figure 3 - 5x microscopic image (right) & 40x microscopic image (left)

Postoperative follow-up: Patient tolerated the procedure well. Post-operative period went uneventful and discharged in satisfactory condition after 10 days.

Discussion

Retro peritoneum cystic mass varied from neoplastic lesion to non-neoplastic cyst [6]. Most of the retroperitoneal lesions are asymptomatic [7]. Large lesion as in our study cause abdominal pain, mass effect on kidney and major vessel consistent with finding mentioned in standard data.

Retroperitoneal mass can occur at any age but mainly involve adult population. cyst mesothelioma, presacral tailgut cyst occur in middle age women [8], paraganglioma in third to fifth decade female, perianal mucinous carcinoma found in middle aged male where cystic lymphangioma more common in <2 year male child. Radiologically imaging techniques such as CECT and MRI help to diagnose stage and guide the further management of retroperitoneal mass [9]. Retroperitoneal cystic lesion can be treated by percutaneous interventional drainage where surgical excision considered as treatment of choice. Recurrence of this cyst (up to maximum 25%) depends upon on type, nature and amount of excision of cyst. We excised cyst in toto cyst preserving vital structure to prevent spillage and avoid further recurrence which is consistent with the standard literature.

Conclusion

Retroperitoneal cysts are rare in incidence and asymptomatic. Due to silent nature and critical anatomy detail study of retroperitoneal mass is very important. Multidisciplinary approach involving surgeon, radiologist, pathologist is must for appropriate diagnosis and management of retroperitoneal cyst.

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A clinical case of pityriasis rubra pilaris - juvenile type

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Abstract

Pityriasis rubra pilaris is a rare chronic inflammatory papulo-squamous skin disease, the pathogenesis of which is still unclear. The pathological essence of the disease is associated with a violation of keratinization against the background of hyperactivity of keratinocytes with subsequent inflammation, as well as with vitamin A dysmetabolism and a weakening of the protein-binding fiction of the liver. Unfortunately, treatment is complex with inconsistent improvement from topical therapies, including emollients, keratolytics, corticosteroids, vitamin D analogs, and retinoids. We present a clinical case of the juvenile type of Devergie's disease in a 3-year-old child, which was caused by poisoning.

Key words: pityriasis rubra pilaris, Devergie's disease, juvenile form, systemic retinoids

Introduction

Pityriasis rubra pilaris (PRP) - heterogeneous, chronic, inflammatory papulo-squamous skin disease, which is divided into congenital form has an autosomal dominant type of inheritance, and the acquired (sporadic) form is not genetically determined. Most cases are sporadic, but familial forms of the disease have been described, in particular, those associated with mutations in the gene map [1-3]. Although it is generally accepted that the name and description belong to Alphonse Devergie, the first case was reported in 1828 by Claudius Tarral. He noted isolated scaly rashes pierced in the center by hair, on palpation of which a very dense roughness is felt on the surface of the skin [4-9].

Devergie's disease (DD) is a rare disease accounting for 0.03-1.3% of all skin diseases. Its onset occurs in the first or fifth decade of life. The etiology and pathogenesis of dermatosis is still not fully understood, the opinions of modern authors differ. It is thought to be caused by an abnormal immune response to various antigenic stimuli such as infections, trauma, autonomic and hormonal dysfunctions, hepatosis, vaccination, and malignancy [10,11]. In DD, the epidermis is in a hyperkinetic state with an increase in the turnover of follicular keratinocytes. A pathogenic role has been suggested for vitamin A deficiency or dysfunction [12] or a decrease in serum retinol-binding protein, which is the vitamin A transporter [13], along with some clinical similarities to rhinoderma (a skin manifestation of vitamin A deficiency [14].

In 1980, W. Griffiths described five different types of DD based on clinical characteristics, age of onset, and prognosis [15]. Subsequently, Miralles suggested adding a 6th type associated with HIV infection to this classification [9] (Table 1).

Currently, the classification of DD includes three clinical forms:
1. Classical type.
2. Localized juvenile type.
3. Type associated with HIV infection.

DD is characterized by pronounced clinical polymorphism. The most common clinical features are follicular papules progressing to yellow-orange erythroderma with rounded small patches of normal skin and well-circumscribed palmoplantar keratoderma. Lesions are symmetrical and diffuse and appear first on the extensor surfaces of the limbs, shoulders, and buttocks, usually spreading caudally with possible development of erythroderma. The presence of islands of healthy skin is of great clinical importance for the diagnosis of DD, sometimes being one of the most important differential signs [16]. This symptom is the presence of small patches of healthy-looking skin, coin-shaped, about 1 cm in diameter, scattered on an erythrodermic background in any part of the skin. Peeling has a heterogeneous character: the scales on the upper half of the body are small, on the lower - more often large-lamellar. Localization of follicular hyperkeratosis on the back surface of the I-II phalanges of the fingers in the literature is called "Besnier's symptom". The nail plates are often affected, have a yellowish color,

Types of Devergie's disease by W. Griffiths (1980) augmented by Miralles

Type	Frequency of occurrence (≈%)	Prevalence of rashes	Clinical characteristics	Course and prognosis
I — classical adult	55	Generalized	Follicular papules, erythroderma with "islands of apparently healthy skin", palmoplantar hyperkeratosis, nail changes. Spreads the faucet audibly	In most cases resolved within 3 years
II — atypical adult	5	Generalized	Ichthyosiform changes on the lower extremities, eczema-like rashes and the appearance of diffuse non-scarring alopecia	Chronic
III — classical juvenile	10	Generalized	Similar to type I, develops in children in the 1st-2nd year of life or in adolescence	In most cases resolved within 3 years
IV — circumscribed juvenile	25	Localized	Well-circumscribed plaques with hyperemia, areas of follicular keratosis with clear boundaries, localized on the skin of the elbows and knees	Resolved in late adolescence
V — atypical or nevoid juvenile	5	Generalized	Follicular hyperkeratosis associated with sclera-like changes in the hands and feet develops in early childhood	Chronic
VI — HIV-associated	<5	Generalized	Typical follicular papules with nodular cystic and pustular acneiform features associated with HIV infection. There is a regression of elements during antiviral treatment	Chronic. Unfavorable prognosis

are striated with longitudinal or transverse furrows, subungual hyperkeratosis is often pronounced. In some cases, there is a deformation of the nail plates of the feet and hands, up to onychogryphosis. Clinical diagnosis of the disease is based on characteristic features: osteofollicular papules, forming the symptom of a "grater"; perifollicular erythema, with a tendency to merge; the presence of "islands of healthy skin" against the background of erythroderma; brick red color of the skin; palmar-plantar hyperkeratosis; nail changes; Besnier's symptom.

The classical juvenile type occurs in the 1st or 2nd year of life. Clinically, it manifests itself in the same way as the classic adult type, only the age of patients differs [17,18]. It differs from the adult type in a more frequent (2 times) onset on the lower half of the body and slow spread. Follicular hyperkeratosis may also occur on the phalanges of the fingers. Compared with the classical adult type, the clinical picture is less pronounced.

Treatment of DD is not an easy task, especially in children. Complex therapy is applied. Currently, drugs that affect the processes of keratinization are retinoids. Today, it has been proven that vitamin A is involved in the regulation and proliferation of many cell types from the moment of embryonic laying and throughout life. The most effective among all synthetic retinoids in the treatment of DD is Neotigazon at a dose of 0.5–0.7 mg/kg/day [7–9, 19]. The drugs of first choice are systemic retinoids and methotrixate. According to various authors, alternative methods of treatment may be Prednisolone (15-20 mg / day), Diprospan (2.0 / m once every 10 days № 3) and cytostatics: prospidin (50-100 mg / m daily for a course of 2.0–3.0 g) or methotrexate (15 mg IM once every 7 days) [9, 20]. External treatment while taking retinoids is of no fundamental importance, however, it significantly improves the general

condition of the patient and improves the quality of his life. Both classic ointments and creams and modern dry skin care products are used. To eliminate massive horny layers, ointments with 2–5% salicylic acid, 10% urea, 1–20% malic acid are prescribed. In addition, physiotherapy is used to treat patients with DD. Useful are warm general baths with sea salt, starch baths, followed by the use of keratolytic ointments, phonophoresis of hydrocortisone cream with the addition of aevit. The prognosis for life is favorable, with regard to cure - uncertain [21]. The question of the advisability of using ultraviolet irradiation in such patients has not yet been resolved; the opinions of modern authors are contradictory and require further study [22].

Case presentation

We present a case of the classic juvenile type of Devergie's disease. A married couple with a 3-year-old child came to the Asmo clinic with complaints of skin rashes and itching. The rash was observed in all family members, appeared at about the same time, they associated with poisoning after eating the local dish "shish kebab", although the exact cause was not established. The father of the family had urticarial rashes, acute urticaria was diagnosed, the mother had rashes on the skin of the trunk and extremities in the form of pink spots, 1 cm in diameter, no peeling was observed. She was diagnosed with allergic dermatitis. At the time of treatment, the child had a pronounced dryness of the entire skin, slight hyperemia in the area of the cheeks, upper and lower extremities, and finely lamellar peeling in the area of the folds (Figures 1-3). No concomitant somatic diseases were found in the child. During luminescent diagnostics, no pathological glow was detected in the rays of the Wood's lamp. A diagnosis of Atopic Dermatitis was made.

Figure 1 - Severe dryness, finely lamellar peeling, slight hyperemia in the cheeks, pinpoint excoriations covered with hemorrhagic crusts.

Figure 2 - Salmon color of the skin of the palms, dryness, the presence of deep cracks.

Figure 3 - Finely lamellar peeling on the skin of the scalp.

All three were prescribed desensitizing therapy, enterosorbents, antihistamines, local glucocorticosteroid ointments, and a moisturizing emollient cream. After 10 days, there was a positive dynamic in the treatment - the rashes in the father and mother were resolved, however, in the child, the rashes acquired a generalized character. At the follow-up consultation:

Status localis: Skin - pathological process is subacute, widespread, symmetrical, inflammatory. It is represented by erythematous-squamous elements, multiple follicular small papules without a tendency to merge on the skin of the scalp with a predominant lesion of the skin of the trunk and upper extremities (Figures 1-3). After receiving therapy for "atopic dermatitis", islands of healthy skin appeared. The patient was hospitalized for inpatient treatment at «Asmo clinic». A diagnostic biopsy was recommended to confirm the clinical diagnosis of Devergy's disease.

According to the test results: In the general blood test - leukocytes 11.4 x 10 9/l (↑); neutrophils - 7.1 x 109 (↑); eosinophils - 6%; hemoglobin 109 g/l (↓); ESR - 20 mm/h (↑); IgE - 127.1 IU / ml (N - 0-200.0 IU / ml); In the biochemical analysis of blood - without pathology; 25 OH vitamin D - 78.2 mg / ml - (N - 30-100 adequate level)

The result of the pathomorphological study - There is a pronounced hyperkeratosis with horny invaginations, horny plugs, parakeratosis, pronounced acanthosis with elongation and thickening of the epidermal process, the granular layer of the epidermis is preserved. Perivascular lymphohistiocytic infiltration in the dermis. Skin appendages are preserved. This morphological picture is characteristic of pityriasis rubra pilaris (Devergie's disease) (Figure 4).
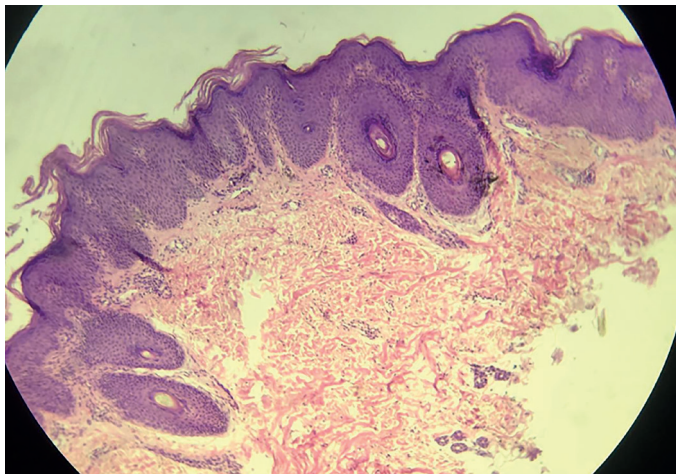
Figure 4 - Histological picture of a biopsy specimen from the skin of the body, stained with Hematoxylin-eosin. Zoom x 100.

Figure 5A and 5B - Condition after treatment.

The patient received the following treatment: sodium chloride solution 0.9% -100.0 + calcium gluconate solution 10% -2.0 i/v № 7; solution of dexamethasone 4 mg -1.0 i/m № 3; Cap. Retinol acetate 33,000 IU, 1 capsule x 2 times a day; Caps. Bifloran Neo 1 capsule x 2 times a day No. 10; Syrup Zodak 2.5 mg x 1 time per day № 10; Dexeryl cream; Cream Mesoderm (Mometasone furoate) - 1 time per day; Physiotherapy - PUVA therapy № 10.

During the treatment, a positive clinical effect was noted in the form of resolution of the majority of rashes, which confirms the correct choice of therapy (Figures 5A and 5B).

Conclusion

This clinical case is of particular interest, since Devergie's disease is a rather rare dermatological disease in pediatric practice. When working with children, a dermatologist should conduct a thorough differential clinical diagnosis with such diseases as seborrheic dermatitis, psoriasis, atopic dermatitis, follicular ichthyosis, lichen planus, lichenoid parapsoriasis, etc., so as not to miss the disease. The number of diseases for differential diagnosis proves the diversity of Devergie's disease.

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