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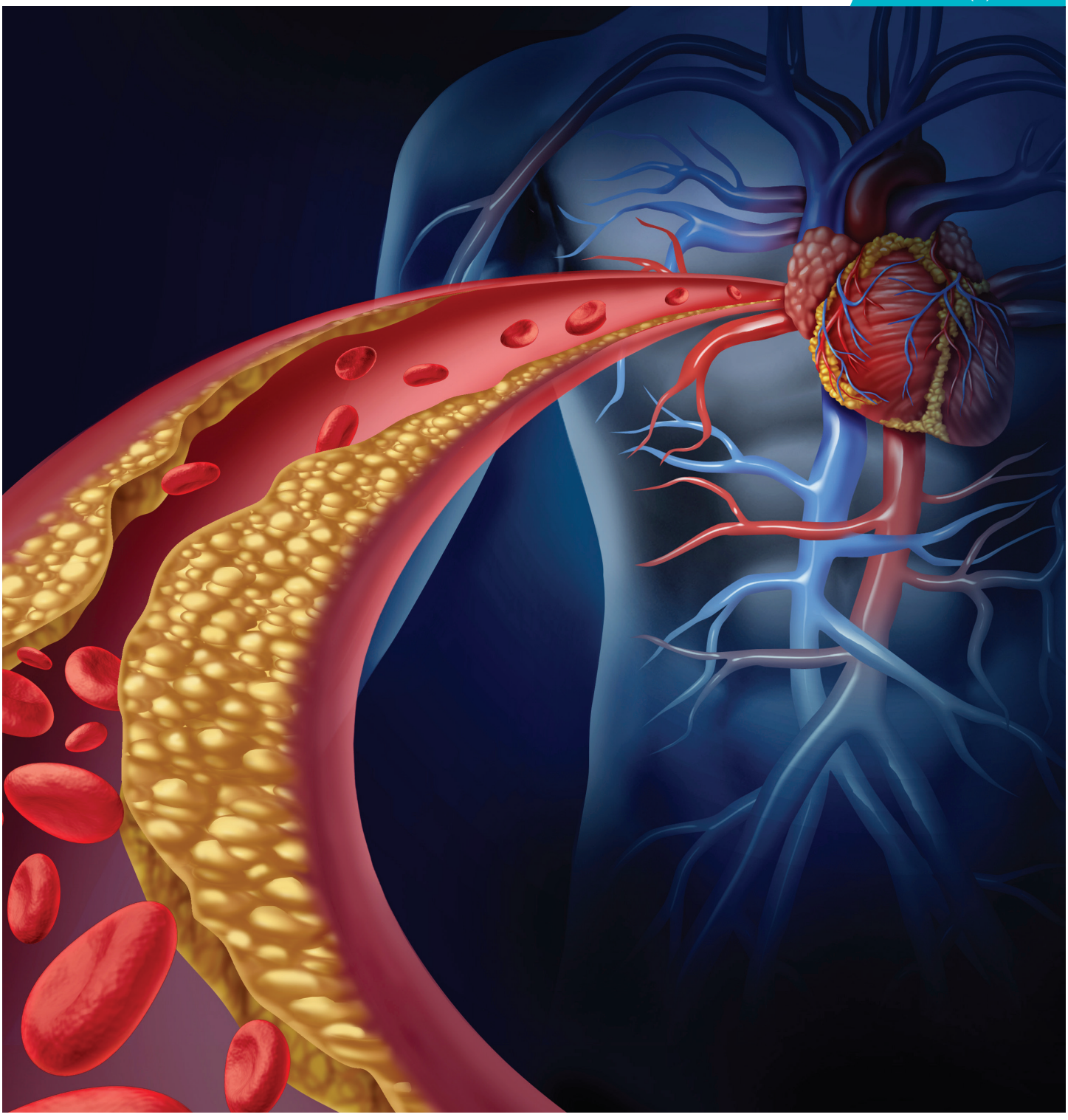

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Evolution of surgery of ventricular septal defect closure

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Abstract

A ventricular septal defect is one of the foremost prevalent congenital heart defects, accounting for around 20% of all congenital heart malformations.

Nowadays, there are three surgical methods for ventricular septal defect: surgical treatment of ventricular septal defect with a heart-lung machine, interventional closure of ventricular septal defect by percutaneous puncture, and hybrid operation (with no heart-lung machine).

Hybrid operation – there is some of the latest evolutions introduced in cardiac surgical treatment practice. This technique is mild, to reduce surgical trauma, and perform not connecting the patient to the heart-lung machine, without X-ray exposure, and there are additional indications than the interventional procedure.

The article reviewed literature sources on the surgical treatments of the ventricular septal defect and the results of the above methods, and also considers more detail especially hybrid operation (without a heart-lung machine).

Key words: congenital heart disease, ventricular septal defect, pediatric cardiac surgery, perventricular closure technique, hybrid method

Introduction

Obstetric violence (OV), is a specific type of violatCongenital heart diseases (CHD) are the most prevalent type of birth defect. The average percentage of live-born, full-term births with CHD is in the range of 0.8% and 1% (8-10 per 1000 for full-term), while this percentage is much higher when it comes to preterm infants, which is 8.3% [1,2].

Even though there are a lot of types of CHD, which include ventricular septal defects (33%), atrial septal defects (18%), and anomalies of the pulmonary valves (10%) [3,4], in my article I will focus on VSDs due to its frequent appearance according to the abovementioned percentages. As it was mentioned before, according to the data, ventricular septal defect (VSD) is the foremost common type of congenital heart malformation. The VSDs can exist in isolation, but also it can be combined with intracardiac abnormalities, such as transposition of the great vessels, complete atrioventricular canal defects, tetralogy of Fallot, and double-outlet right ventricle. Despite the abovementioned combinations, the cause of VSD may be associated with mutations in TBX5 and GATA4 genes [5-7]. In embryonic life, the association of VSD with chromosomal defects is in the range of 10% to 30% considering it's the type and size of the defect. However, the figures can increase considering the situation after birth, depending on anatomical features of defects [8,9].

There are 4 types of ventricular septal defect:

- **Membranous VSD.** These VSDs are located in a specific zone of the upper section of the ventricular septum (a membranous septum), close to the valves. Due to the fact that this type of VSD does not close by itself, usually, it requires an operation.
- **Muscular VSD.** These VSDs are located in the muscular area of the lower section of the ventricular septum. Compared to the previous type of VSD, it is the most common type and it may close spontaneously, which leads to the situation when the operation is not necessary.
- **Atrioventricular canal type VSD.** These VSDs are combined with an atrioventricular canal defect and, there are located under the atrioventricular valves.
- **Conal septal VSD.** These types of VSDs can be considered the most uncommon type, which appears in the ventricular septum underneath the semilunar valve [10-15].

This article is based on the literature from accessible international and local scientific sources and aims to review the surgical treatment methods for isolated ventricular septal defects. Moreover, detailed information and research will be provided on the technique and the results of hybrid operation for VSD (without a heart-lung machine).

The outline of the article will include all types of surgical treatment for VSD:

1. surgical treatment of ventricular septal defect with a heart-lung machine;
2. interventional method of treatment for VSD;
3. hybrid operation for VSD without a heart-lung machine [16,17].

Surgical treatments of the ventricular septal defect

Surgical treatment of ventricular septal defect with a heart-lung machine

There are different types of treatment for VSD, surgical treatment of VSD with a heart-lung machine (HLM) could be considered the most conventional treatment modality last decades [18]. This type of treatment started to consider the gold standard after the operation by Lillehei et al. in 1954 when it VSD was closed by surgery. Although this method is effective for the treatment of VSD, the potential risks after the surgery of sequelae urged doctors and scientists for innovating [19-21]. After making research in this field and better learning of the pathophysiology of complications associated with a heart-lung machine, some improvements in the HLM technique started to appear, consequently, HLM is started to be much safer for infants. Despite the fact that the HLM technique is a satisfactory way to deal with VSD, post-HLM neurologic outcomes cannot be ignored, which would have an impact on one's quality of life, therefore, it needs to be enhanced [18].

Interventional method of treatment for VSD

Currently, with the significant development of technology and, devices surgical treatment of VSD under a heart-lung machine was not the only type of treatment for VSD. The alternative way of treatment for perimembranous and muscular VSDs is interventional closure by a percutaneous puncture. The first surgery of this type of treatment happened in 1988 and was considered a valuable and effective alternative for the selection of patients with VSD [22]. Nevertheless, this method was still linked to some negative outcomes, such as different types of arrhythmias, embolism of the occluder, and vascular complications. However, with enhancements in the device closure technique, the first real off - pump transcatheter device closure of VSD was introduced in animals in 1997 and then applied in patients with muscular VSD (mVSD) in 1998 [23]. In addition, the whole procedure is carried out under constant control fluoroscopy or transthoracic echocardiography while averting sternotomy and connecting a heart-lung machine [24].

Despite the fact this method is used for treating VSDs for relatively two decades, the sequel of prolonged fluoroscopic impact on different organs is not been sufficiently figured out by scientists. However, there are already existing side effects associated with some negative events, including arrhythmia, embolism of the occlude, and vascular complications. Moreover, as its vascular access and technical limitations, this procedure had a few problems while operating on patients with low weight or managing difficult cases, consequently, some complications (intraoperative valves abuse by wire, different types of atrioventricular block, or others) were many times reported in those cases [25].

Hybrid operation for VSD without a heart-lung machine

Initially, it is important to define this method in more detail: hybrid operation for VSD without a heart-lung machine (HLM) – a method that started to be in use only approximately the last two decades in cardiac surgery practice. According to the data published, the importance of this technique is that it allows it to perform without connecting to the HLM, additionally, no X-ray exposure and additional indications than the interventional method can be considered as different items compared to the previous methods, consequently it might minimize surgical trauma [26,27]. With the enhancement of technology and the appearance of new devices, a new type of technique was invented, by some surgeons for closing muscular VSDs [28]. The first real case practice of this surgery by perventricular closure of VSD was fulfilled on animals under the control of transesophageal echocardiography (TEE) in 1997. Based on the experience Amin and his colleagues performed this type of closure of VSD on patients in 1998 [29,30]. Moreover, scientists always tried to find a different way of incision for VSD, consequently, Bacha and his coworkers reported the case when the operation on a patient who had muscular VSD was done with the usage of subxiphoid access in 2003. The abovementioned case was considered the first case when muscular VSD was treated without HLM by subxiphoid access. There was no reported case of hybrid closure of perimembranous VSD without HLM in patients through subxiphoid access before 2006 [31]. In that year, Doctor Li Feng recomended the closure of perimembranous VSDs without HLM in patients by subxiphoid access in China. Even though long-term side-effects have not been reported, it showed a good result in the short period. Important to mention here is that the technique was used in the 12 patients and all cases have finished effectively [32].

In comparison with previous surgical methods - winding track through the blood vessels of the thigh in the interventional method or post-HLM neurologic outcomes after the traditional operation, the last method has more direct access to VSD, without HLM, which is a more secure way for patients [33].

Based on statistics provided by reliable articles reported work average mortality of the hybrid method is lower than that of surgical treatment. For example, the mortality after the hybrid method is 2.6%, this is 3 in 116 cases with isolated mVSD, and also 24.1% of the cases with multiple mVSDs. The mortality after surgical treatment is more than in the above method. This is 3.6% (2 in 56 cases with isolated mVSD) and 17% with multiple mVSDs. Moreover, based on other statistics provided by researchers, comparable mortality was indicated in the interventional method (10.6%, 6 in 55 cases, 22 cases with single mVSD) [34-36].

Furthermore, ventricular dysfunction was a case that should be considered. According to several cohort studies of multiple mVSDs the ventricular dysfunction had more after surgical treatment than the hybrid method. For instance, after five years of follow-up left ventricular dysfunction rate of 30% after a left ventriculotomy (after surgical treatment) [37-39], as the hybrid method had less left ventricular dysfunction, ranging from 7.1% to 12.5%, which was reclaimed after 3 years. Also, the right ventricular dysfunction rate (after surgical treatment) varied from 0% to 22% [41-43], and after hybrid method had not to case about the right ventricular dysfunction [40,44].

As it was mentioned before, there have not been fulfilled long-term studies on this method of surgical treatment, but there are short- and medium-term studies with the conclusion that serious functional problems are limited. Additionally, it was reported that if the treatment was performed at early ages,

quality of life will not have significant changes compared to normal life [45].

Moreover, it is important to report the experience of our medical center – the National Scientific Medical Center, which is located in Nur-Sultan, Republic of Kazakhstan. The hybrid method has been implemented by professor Xiangbin Pan from China in 2016. From 2016 to 2022 operations were performed on more than 400 patients, which is an excellent and leading result among all Kazakhstan's medical centers. Currently, we are doing a retrospective study for evaluating the effectiveness and safety of this method. Further, the results based on these patients will be published in an original research article that will be written by me and my colleagues.

Table 1 Perioperative and postoperative performance indicators of three surgical treatments for VSD [51-53].

Indicators	**Surgical treatment of VSD with a heart-lung machine**	**Interventional method of treatment for VSD**	**Hybrid operation for VSD without a heart-lung machine**
Access	total median sternotomy	vascular access	partial sternotomy
Wound size	depend on the size of the sternum (from 5 cm and more)	0.35-0.5cm	2-4 cm
Optimal body weight for surgical repair	from 4 kg	from 10 kg	from 4 kg
The heart-lung machine time (min)	56.6 ± 13.5	0	0
Aortic occlusion clamping time (min)	39.1 ± 12.3	0	0
Mechanical ventilation time (h)	15.8 ± 4.8	0	10.5 ± 2.8
Intensive care unit time (h)	22.6 ± 5.8	0	13.7 ± 2.5
Radiation	no	yes	no
The average length of surgery (min)	60-100	20-40	30-60
The average length of stay in a hospital (days)	7-10	3	5-7
Complications after surgical repair:			
- residual shunt	2-3%	1-2%	2-3%
- atrioventricular block	0	1%	1-2%
- right bundle branch block	0	1%	1%
-new tricuspid regurgitation	0	1-2%	1-2%
-new aortic regurgitation	0	1-2%	1-2%
-incision complications	2-3%	0	0
-pericardial effusion	2-3%	1%	0
-pneumothorax	1%	0	0

Surgery steps of hybrid method

The technique of the hybrid method is comparable with the interventional method except for its direct access to the defect. The general steps of the hybrid method are described below and in Figure 1 [46-48].

Step 1: Firstly, preoperative assessment, then it is necessary to use general anesthesia. Before the surgery, transesophageal echocardiography (TEE) should be used to evaluate the location and morphology of the VSD, with special emphasis paid to any concurrent valve dysfunction.

Step 2: The delivery mechanism is being prepared. The device that is appropriate for the defect is selected and the delivery system, which adds a device cable, delivery sheath, sheath for loading, and guidewire, is also assembled (Figure 1A).

Step 3: Starting with a transthoracic incision, the size of the wound is from 2 to 4 cm and then lower median sternotomy is recommended. Also, there is another incision - anterior parasternal incision for sub arterial VSDs (Figure 1B).

Step 4: After sternotomy uncovers the pericardium and then selects the anterior free wall of the right ventricle for puncture under control transesophageal echocardiography (Figure 2A).

Step 5: Then, the delivery mechanism is introduced. To do this, a purse-string suture is used on the free wall of the right ventricle facing the location of the defect chosen (Figure 2B), a 6F gauge needle is imported through the purse-string suture, and the guiding wire is inserted into the right ventricle (RV) and then through the defect to the left ventricle (LV) (Figure 2C). A delivery sheath is led into the LV over the guidewire (Figure 2D).

Step 6: Under transesophageal echocardiography on the beating heart the device is deployed. At first, the left ventricular disc is expanded and deployed to the septum with a guidewire (Figure 2E), and then the right ventricular disc is subsequently deployed to begin closing the ventricular septal defect (Figure 2F and G).

Step 7: Prompt postoperative appraisal. After the accomplishment of device placement, transesophageal echocardiography is done for detecting any valve dysfunctions or residual shunts [49,50].

Figure 1 - The delivery mechanism for hybrid method (1A) and surgical incision options (1B).

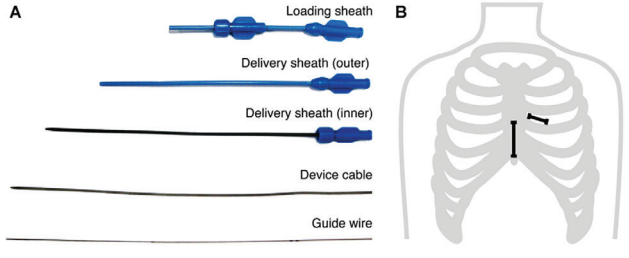
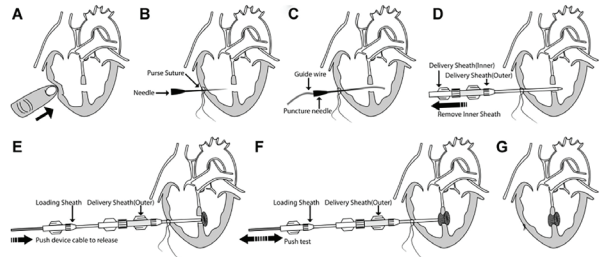


Figure 2 - General steps of the hybrid method.



Conclusion

The hybrid operation for ventricular septal defect without a heart-lung machine is plain, and effective which accompanies minimal surgical trauma, and relatively safeguard options for selected patients with isolated VSD, in contrast to the classical method.

The hybrid operation not only reduces the risk of significant complications and blood product transfusion, but also shortens the duration of hospitalization, and rehabilitation compared with the traditional method with a heart-lung machine but also produces no inferior results compared with the interventional method in selected isolated VSD patients. Moreover, this method is technically not a complex operation compared to the traditional method, in order to know the full potential of this method as the new gold standard of surgical treatment, controlled studies with long-term follow-up are needed.

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Cadaver embalming and fixing solutions from past to present

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Abstract

Cadaver and organ embalming-fixing solutions have a long history. The aim of this study is to follow this historical adventure step by step and to consider the point of embalming and fixation solutions. This study was carried out on the literature published to Google Scholar, PubMed, and Science Direct between 2000 and 2021. During the search, "cadaver, cadaver dissection, cadaver detection, cadaver use, cadaver embalming, cadaver preservation and organ preservation" were chosen as keywords. The discovery of formaldehyde in 1869 was clearly a turning point for cadaver and organ embalming-fixing solutions, and formaldehyde-based solutions are widely used even today. However, in addition to formaldehyde-based solutions, there are methods such as plastinization, paraffinization, resin embedding methods. It is clearly seen in the literature that formaldehyde-based solutions have serious side effects in terms of human health. Therefore, scientists have developed different methods. However, these methods have both application difficulties and accessibility problems compared to formaldehyde-based methods. Solutions that can prevent these problems should be produced in a short time.

Key words: cadaveric fixation, cadaver embalming, cadaver protection

Introduction

The cadaver is an indispensable element of education in order to maintain anatomy education and to process it in a healthy way. In order for the cadaver to be used for training purposes, a preliminary process called embalming and fixation is required [1-3]. Embalming and fixation reduce the risk of infection and ensure that the cadaver is used and stored for many years. There are some differences between these two methods, such as the solution used and the method of application. Thiel is the most commonly used solution for embalming, while formaldehyde is the most commonly used solution for fixation. This chemical difference creates some differences about the flexibility, internal structure and integrity of the cadaver [4-7]. While the solutions used in embalming are generally applied on the cadaver, the solutions used in the fixation process are injected into the veins. This injection is usually performed using the common carotid artery, femoral artery, and femoral vein. However, if the integrity of the cadaver is impaired or there is any problem in the veins, it is performed in regional applications. The amount of solution given during injections and the rate of administration directly affect the quality of cadaver detection [7, 8].

Preservation of cadavers and organs dates back to the 6000s. Social and religious beliefs are among the most important reasons why it dates back to ancient times. Because for most societies, death is seen as a sacred event and man is seen as God's representative on earth. Also, in most ancient cultures such as Egypt, the preservation of the body meant eternal life. It was believed that if the integrity of the body was broken or it started to rot, this person was expelled from the hereafter. For this reason, it is of great importance for individuals to store the cadaver properly for many years. In ancient times, salt, alcohol and herbal mixtures were used to preserve cadavers and organs [8-11]. In the Middle Ages, it was common for mummification to remove organs, immerse the whole body in solutions, and plant plants in different parts of the body. In the following years, the idea of giving embalming solutions to the circulatory system became widespread. In 1326, Alessandro Giliani made attempts to introduce solutions into the vascular system. Leonardo Da Vinci, one of the important anatomists of the century, injected the liquids (lavender oil, sodium nitrate, turpentine) prepared for fixation into the ventricular and arterial system of the cadaver. In the 18th-19th centuries, American Thomas Holmes became the father of modern mummification with his work with alcohol and various chemicals on 4000 soldier cadavers. The discovery of formaldehyde by August Wilhelm von Hofmann in 1869 was a turning point for cadaveric detection. A very short time later, Laskowski developed the Geneva fixation solution using glycerin to prevent the cadaver from hardening

and drying out. Since these dates, many cadaver detection solutions based on formaldehyde have been developed [1, 8, 10, 11]. It is available in different methods as well as formaldehyde-based solutions. For example, plastinization, paraffinization, epoxy resin embedding, alkyd resin [12-14] methods are also available [15]. Plastinization was established in 1978 by Prof. Dr. It was found by Gunther von Hagens at the institute of anatomy and pathology at the university of Heidelberg [16]. The parafinization method was developed by Deegener and Brendt in 1914 [17].

The aim of this study is to reveal the adventure of cadaveric and organ Deciphering solutions from the past to the present, the differences between each other, advantages, disadvantages and the point at which it has come.

Material and methods

The study was conducted using the Pubmed, Google Decadal and Science Direct search engines. The keywords "cadaver, cadaver dissection, cadaver detection, cadaver Decontamination, cadaver embalming, cadaver preservation and organ preservation" were entered into the search engines for scanning and a detailed scan was performed. During the search, articles that were not suitable for our purpose were decommissioned. The screening years were deciphered between 2000-2021. About 97,900 articles were found that matched the keywords. Later, 21 of these articles were selected.

Results

As a result of the literature search, it was clearly seen that cadaver and organ preservation procedures date back to very ancient times and have gained a serious path with the discovery of formaldehyde (Table 1). It was observed that formaldehyde-based solutions continue to be widely used today (Table 2). However, it is clearly reported that formaldehyde-based solutions have serious side effects on the health of expert anatomists working in this field, and are even a carcinogenic substance. In order to cope with these side effects and to better preserve the integrity of the cadaver, various methods are being applied today. The main ones are plastination and resin embedding methods. The spread of these methods has a serious importance for the health of anatomists and health students.

Table 1 Significant developments in cadaver embalming and detection

Year/Century	Important Developments
15-16. century	The first injection for detection was made into the cadaver by Leonardo Da Vinci.
18-19. century	Thomas Holmes (the father of modern embalming) performed embalming on 4000 cadavers of soldiers using alcohol, arsenic, mercury.
1869	August Wilhelm von Hofmann discovered formaldehyde.
1886	Laskowski used glycerin to prevent the cadaver from drying out and developed the Geneva solution.
1914	The paraffinization method was developed by Deegener and Brendt.
1978	Prof. Dr. Gunther von Hagens discovered plastinization.

Table 2 Formaldehyde-based solutions

Name of The Solution	Contents of the Solution
Erskine	Formaldehyde, Ethyl Alcohol, Phenol, Glycerin, Sodium Arsenate, Salicylic Acid, Chlorthymol
Spence	Formaldehyde, Methyl Alcohol, Water Glycerin, Phenol
Larssen	Formalin, Distilled Water, Sodium Chloride, Sodium Bicarbonate, Chloral Hydrate, Sodium Sulphate
Norville	Formaldehyde, Sodium Nitrate, Glycerin, Citronel oil, Borax, Boric Acid, Eosin
Cambridge	Formaldehyde, Water, Ethanol, Polyethyleneglycol, Citricidal
Theil	Formalin, Alcohol, Boric Acid, Ammonium Nitrate, Sodium Sulphate, Potassium Nitrate, Propylene Glycol, Stock II, Morpholine
Modifiye Larssen	Formalin, Sodium Sulphate, Sodium Bicarbonate, Water, Glycerol, Chloral Hydrate, Sodium Chloride
Logan	Formaldehyde, Phenol, Alcohol, Glycerin
Saturated Salt Solution	Formaldehyde, Phenol, Salt, Isopropyl Alcohol, Water, Glycerin

Conclusion

The discovery of formaldehyde was a turning point in the embalming and fixation of cadavers and organs. One of the most important pillars of this turning point is that formaldehyde is easy and accessible [1, 3, 8]. However, in addition to these advantages of formaldehyde, it also has many disadvantages. Experimental studies have shown that formaldehyde both causes various diseases in the respiratory, nervous, reproductive and digestive systems and has a carcinogenic effect. In the respiratory system, inflammation in the nose and throat, pulmonary edema, cough, pneumonia, lung cancer, embryo deaths in the reproductive system, fertility, cryptoorchidism, perforation in the digestive system, ulcer, diarrhea, stomach inflammation, abdominal pain, mutation in the nervous system, tumor, behavioral disorder, It has been clearly stated in the literature that it causes headache, epilepsy and anamol [17-20]. These harmful effects of formaldehyde have led scientists to find methods that will threaten human health less. As a result, plastination and resin embedding methods, which are less harmful to human health, have been developed. Although the cadaver and organ to be preserved during the plastination process are exposed to many chemicals, this rate is reduced to a minimum during use and becomes less threatening to health [16, 21].

Cadaver and organ solutions have made a serious progress over time, and this way has made it less threatening to the health of individuals working and trained on cadavers and has made the cadaver to be used more effectively for many years.

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The relationship between citation-based metrics and Twitter in the area of age related macular degeneration research: Altmetric and bibliometric study

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Abstract

Purpose: The aim of this research is to analyze the bibliometric and altmetric scores of highly cited articles in the area of age related macular degeneration (AMD) research and to assess the correlations between them.

Material and methods: The data of publications in last decade were retrieved from the Web of Science Core Collection database using "age related macular degeneration" as a search term. The top 100 cited articles (T100) list was analyzed by author name, publication year, main topic, study type, journal name, journal impact factor (IF), H-index, total citation number (TCN), average citation per year (ACpY), Altmetric attention score (AAS), and number of tweets (NTs). VOSviewer software was utilized for visualization of bibliometric data.

Results: We discovered 16.984 articles in the last decade. The median values for TCN and AAS were 221 (IQR 178–380.75) and 13 (IQR 4-37.75), respectively in T100 list. The majority of the highly cited articles in AMD research have mainly focused on AMD treatment (n=34), especially anti-vascular endothelial growth factor therapy. However, social attention was primarily on the stem cell therapy. While AAS and NTs did not have significant correlation with TCN, they did show a significant positive correlation with ACpY. AAS and NTs showed significant positive correlation with journal IF and H-index.

Conclusion: Treatment for AMD is the most interested issue in the area. Stem cell therapies are popular on social media. The interest of social media is on articles that continue to be cited over the years rather than articles with high total citations.

Key words: altmetric attention score, altmetric, bibliometric, age related macular degeneration, Twitter

Introduction

Age related macular degeneration (AMD) is the main cause of blindness in persons over the age of 60 in developed countries [1]. The prevalence of AMD is 2% in people over the age of 50 and 25% in people over the age of 80 [2]. Early detection and follow-up of AMD, treatment planning, boosting public awareness, and enhancing communication between healthcare providers and patients are crucial.

Bibliometric analysis is a statistical tool for determining the worth and efficiency of a scientific article by counting the number of citations received since its publication [3]. Bibliometric analysis gives data on the most scientifically effective journals, authors, countries, important topics and keywords, as well as number of citations [4]. Map knowledge domain is a technique for graphing and visualizing bibliometric information in addition to doing co-occurrence assessment and identifying hotspots. It provides researchers information about research topics, new trends, and developing new study aspects [5]. While citation-based analyses are beneficial for determining the quality of articles, they have considerable limitations. A certain period of time must have passed since its publication that limits the rapid evaluation of an article's quality.

Altmetric, which has been using the effect of

social media, has created a new score system for determining the impact of publications. Altmetric attention score (AAS) quantifies the impact value of articles shared, discussed, and viewed on Wikipedia, Mendeley, news, blogs, and social media platforms such as Twitter, Facebook, Pinterest [6-9].

By the beginning of 2021, the global number of daily active Twitter users reached 187 million, with an average of 500 million tweets every day [10]. Medical journals are also intending to boost the accessibility of their publications by posting them on their own Twitter accounts.

There have been no published research that investigate the relationships between altmetric analysis and bibliometric analysis including citation count, journal impact factor (IF), and H-index in the area of AMD research. The purpose of this study is to give bibliometric and altmetric summaries and visualizations of the AMD research. Additionally, we aimed to analyze the effect of Twitter on both metrics in terms of scientific information dissemination.

Material and methods

Study design

This retrospective clinical research has a level of evidence of three or group B under Scottish Intercollegiate Guidelines Network (SIGN) [11].

Compliance with ethical standards

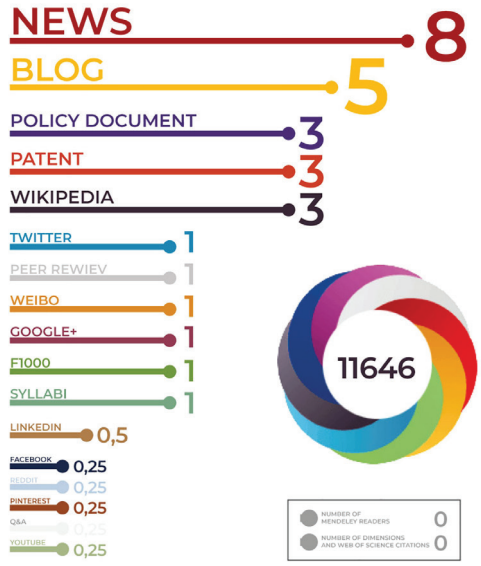
Each author confirms that the study was conducted in accordance with the Helsinki Declaration's Ethical Principles. There is no need for ethical approval for this investigation because it consists of existing publications related to AMD in the literature.

Data collection

The information was obtained from the Web of Science (WoS) Core Collection database (Philadelphia, Pennsylvania, United States) using "age related macular degeneration" as a search term (Date of access: April 3, 2021). The articles published between 2011 and 2021 years were selected. Full text articles were gathered and sorted according to the number of citations for each article [12]. All articles were thoroughly reviewed by each author and PubMed was used to obtain additional information about publications. The articles that were not relevant to AMD in the human health category were excluded. In the human health category, articles on the epidemiology, etiology, pathophysiology, histology, diagnosis, therapy, and prognosis of AMD were included. The articles were rated from top to lowest depending on the amount of citations, and the top-100 cited articles list (T100 list) was created with the agreement of all authors. The data was recorded into Microsoft Excel files and analyzed. The journals IF were registered based on the 2019 Clarivate Journal Citation Reports. The H-index and quartile (Q) scores of journals were determined using the 2020 Scimago Journal and Country Rank (SJCR). Study types and level of evidence were determined using SIGN [11]. All articles of T100 list were extensively evaluated and categorized by journal name, publication year, first author name, total citation number (TCN), average citation number per year (ACpY), study topic, study type, and level of evidence.

VOSviewer software version 1.6.16 was used to visualize the bibliometric statistics of T100 list (https://www.vosviewer.com). The data of top-100 cited articles was acquired from WoS in the “Full record and cited references” formats. A bibliometric coupling analysis was performed on all countries in the T100 list. Threshold value determined as 2 for co-occurrence keyword analysis. The findings of country coupling and keyword co-occurrence analyses were visualized on maps.

Figure 1-Altmetric donuts: Each color on the altmetric donut symbolizes a distinct source of attention. The weight score for posts of each social media platform is displayed.



The Altmetric.com website's "Altmetric it" tool was used to measure AAS of the T100 list. (https://www.altmetric.com/products/free-tools/bookmarklet/) (Date of access: April 3, 2021). AAS was computed by the process with a methodology defined as weighted average of all the attention that each paper received. Each color on the altmetric donut symbolizes a distinct area of attention (Figure 1). Additionally, the number of tweets (NTs) associated with each article was recorded.

Statistical analysis

IBM SPSS for windows version 23.0 (Statistical Package for Social Sciences, Chicago, Illinois, USA) was performed for the statistical analysis. Median and interquartile range (IQRs) were used to describe continuous variables, while percentages were used to define categorical variables. For intragroup and intergroup comparisons, the Mann-Whitney U and Kruskal Wallis tests were utilized. Sperman or Pearson correlation coefficients were used to analyze linear relationship between numerical variables. The correlation coefficients were assessed as follows: less than 0.4, weak; 0.4-0.6, moderate; 0.6-0.8, strong; and 0.81-1.00, very strong association [13]. A univariate linear regression analysis was performed to measure beta coefficients. When P was less than 0.05, statistical significance was assumed.

Results

We discovered 16.984 articles between 2011 and 2021 years using the phrase "age related macular degeneration" in our WoS search. The first author, publication year, TCN, and ACpY, AAS, and NTs for each article are displayed in T100 list, which was generated by sorting the top-100 articles based on TCN (Table 1). Although we did not specify the language option, all articles in the T100 list were written in English.

TCN and AAS analysis

The median values for TCN and AAS were 221 (IQR 178–380.75) and 13 (IQR 4-37.75), respectively in T100 list. The article with the highest TCN was Martin DF et al’s article entitled as "Ranibizumab and bevacizumab for neovascular age-related macular degeneration the CATT research group" and it

Table 1 Top-100 articles by metrics (T100 list)

Citation rank	Title	First author	Year	TCN	ACpY	AAS	NTs
1	Ranibizumab and bevacizumab for neovascular age-related macular degeneration the CATT research group	Martin D.F.	2011	1667	151.6	97	17
2	Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis	Wong W.L.	2014	1302	162.8	204	15
3	Intravitreal aflibercept (vegf trap-eye) in wet age-related macular degeneration	Heier J.S.	2012	1171	117.1	38	3
4	Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration	Martin D. F.	2012	1090	109	49	15
5	Age-related macular degeneration	Lim L.S.	2012	899	89.9	56	9
6	Embryonic stem cell trials for macular degeneration: a preliminary report	Schwartz S.D.	2012	890	89	318	119
7	Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis	Flaxman S.R.	2017	659	131.8	614	81
8	Identifying medical diagnoses and treatable diseases by image-based deep learning	Kermany D.S.	2018	622	155.5	371	175
9	Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies	Schwartz S.D.	2015	613	87.57	423	92
10	Clinical classification of age-related macular degeneration	Ferris F.L.	2013	570	63.33	74	0
11	Lutein plus zeaxanthin and omega-3 fatty acids for age-related macular degeneration the age-related eye disease study 2 (AREDS2) randomized clinical trial	Chew E.Y.	2013	533	59.22	247	77
12	Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration	Chakravarthy U.	2012	522	52.2	21	8
13	Seven new loci associated with age-related macular degeneration	Fritsche L.G.	2013	514	57.11	89	28
14	Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON	Rofagha S.	2013	512	56.89	8	2
15	Autologous ınduced stem-cell-derived retinal cells for macular degeneration	Mandai M.	2017	507	101.4	793	247
16	A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants	Fritsche L.G.	2016	495	82.5	195	57
17	The pivotal role of the complement system in aging and age-related macular degeneration: hypothesis re-visited	Anderson D.H.	2010	472	39.33	15	0
18	Development and validation of a deep learning system for diabetic retinopathy and related eye diseases using retinal images from multiethnic populations with diabetes	Ting D.S.W.	2017	469	93.8	289	328
19	Understanding age-related macular degeneration (AMD): relationships between the photoreceptor/retinal pigment epithelium/bruch's membrane/choriocapillaris complex	Bhutto I.	2012	463	46.3	4	1
20	Quantitative optical coherence tomography angiography of choroidal neovascularization in age-related macular degeneration	Jia Y.	2014	456	57	16	1
21	Alternative treatments to inhibit vegf in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial	Chakravarthy U.	2013	440	48.89	115	34
22	Mechanisms of age-related macular degeneration	Ambati J.	2012	429	42.9	28	7
23	Intravitreal aflibercept injection for neovascular age-related macular degeneration ninety-six-week results of the VIEW studies	Schmidt-Erfurth U.	2014	425	53.13	14	0
24	Choroidal thickness in polypoidal choroidal vasculopathy and exudative age-related macular degeneration	Chung S.E.	2011	381	34.64	3	0
25	DICER1 deficit induces ALU RNA toxicity in age-related macular degeneration	Kaneko H.	2011	381	34.64	43	0
26	Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis	Chakravarthy U.	2010	380	31.67	3	0
27	Genetic variants near TIMP3 and high-density lipoprotein-associated loci influence susceptibility to age-related macular degeneration	Chen W.	2010	373	31.08	33	1
28	DICER1 loss and ALU RNA ınduce age-related macular degeneration via the NLRP3 inflammasome and MYD88	Tarallo V.	2012	348	34.8	23	15
29	Prevalence of age-related macular degeneration in the US population	Klein R.	2011	321	29.18	22	0
30	Risk of geographic atrophy in the comparison of age-related macular degeneration treatments trials	Grunwald J.E.	2014	311	38.88	4	0
31	Immunology of age-related macular degeneration	Ambati J.	2013	307	34.11	15	8
32	Genome-wide association study of advanced age-related macular degeneration identifies a role of the hepatic lipase gene (LIPC)	Neale B.M.	2010	307	25.58	18	0
33	Consequences of oxidative stress in age-related macular degeneration	Jarrett S.G.	2012	275	27.5	11	2

34	Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration the comparison of age-related macular degeneration treatments trials	Maguire M.G.	2016	268	44.67	952	28
35	The prevalence of age-related macular degeneration in Asians a systematic review and meta-analysis	Kawasaki R.	2010	265	22.08	1	1
36	Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration	Busbee B.G.	2013	263	29.22	7	0
37	Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study	Holz F.G.	2011	263	23.91	9	0
38	Reticular pseudodrusen are subretinal drusenoid deposits	Zweifel S.A.	2010	259	21.58	3	0
39	Regulation of angiogenesis and choroidal neovascularization by members of microrna-23 similar to 27 similar to 24 clusters	Zhou Q.	2011	254	23.09	13	1
40	Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study	Schmidt-Erfurth U.	2011	254	23.09	14	1
41	Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration	Holz F.G.	2015	246	35.14	12	7
42	NLRP3 has a protective role in age-related macular degeneration through the induction of IL-18 by drusen components	Doyle S.L.	2012	243	24.3	12	7
43	Polypoidal choroidal vasculopathy and neovascular age-related macular degeneration: same or different disease?	Laude A.	2010	238	19.83	0	0
44	Spectral-domain optical coherence tomography angiography of choroidal neovascularization	de Carlo T.E.	2015	232	33.14	13	5
45	Do we need a new classification for choroidal neovascularization in age-related macular degeneration?	Freund K.B.	2010	230	19.17	1	0
46	Age-related macular degeneration: genetics and biology coming together	Fritsche L.G.	2014	226	28.25	31	2
47	HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration	Singer M.A.	2012	226	22.6	16	2
48	Ranibizumab (lucentis) in neovascular age-related macular degeneration: evidence from clinical trials	Mitchell P.	2010	224	18.67	7	1
49	Inflammation and its role in age-related macular degeneration	Kauppinen A.	2016	223	37.17	7	4
50	Subfoveal choroidal thickness in typical age-related macular degeneration and polypoidal choroidal vasculopathy	Koizumi H.	2011	223	20.27	0	0
51	Guidelines for the management of neovascular age-related macular degeneration by the european society of retina specialists (EURETINA)	Schmidt-Erfurth U.	2014	219	27.38	124	21
52	Subretınal drusenoıd deposıts in non-neovascular age-related macular degeneratıon morphology, prevalence, topography, and biogenesis model	Curcio C.A.	2013	218	24.22	13	0
53	A rare penetrant mutation in CFH confers high risk of age-related macular degeneration	Raychaudhuri S.	2011	212	19.27	30	8
54	Automatic segmentation of nine retinal layer boundaries in OCT images of non-exudative AMD patients using deep learning and graph search	Fang L.	2017	211	42.2	4	1
55	Choriocapillaris vascular dropout related to density of drusen in human eyes with early age-related macular degeneration	Mullins R.E.	2011	203	18.45	0	0
56	Comparıson of choroıdal thıckness among patıents wıth healthy eyes, early age-related maculopathy, neovascular age-related macular degeneratıon, central serous chorıoretınopathy, and polypoıdal choroıdal vasculopathy	Kim S.W.	2011	199	18.09	3	0
57	Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to lucas treat-and-extend protocol	Berg K.	2015	198	28.29	4	2
58	A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact	Gupta O.P.	2010	197	16.42	1	0
59	Dysregulated autophagy in the RPE is associated with increased susceptibility to oxidative stress and AMD	Mitter S.K.	2014	194	24.25	0	0
60	Prevalence and significance of subretinal drusenoid deposits (reticular pseudodrusen) in age-related macular degeneration	Zweifel S.A.	2010	193	16.08	3	0
61	Optical coherence tomography angiography of type 1 neovascularization in age-related macular degeneration	Kuehlewein L.	2015	189	27	1	1
62	Rare variants in CFI. C3 and C9 are associated with high risk of advanced age-related macular degeneration	Seddon J.M.	2013	189	21	23	8
63	Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression AREDS2 report no. 3	Chew E.Y.	2014	188	23.5	37	17
64	Anti-vascular endothelial growth factor for neovascular age-related macular degeneration	Solomon S.D.	2014	188	23.5	14	5
65	The oil spill in ageing bruch membrane	Curcio C.A.	2011	187	17	8	2

66	Autophagy and heterophagy dysregulation leads to retinal pigment epithelium dysfunction and development of age-related macular degeneration	Kaarniranta K.	2013	186	20.67	1	2
67	Molecular pathogenesis of retinal and choroidal vascular diseases	Campochiaro P. A.	2015	182	26	7	1
68	Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD	Avery R.L.	2014	182	22.75	14	5
69	The prevalence of age-related macular degeneration and associated risk factors	Klein R.	2010	182	15.17	0	0
70	Geographic atrophy clinical features and potential therapeutic approaches	Holz F.G.	2014	181	22.63	13	1
71	Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 2	Abraham P.	2010	181	15.08	3	0
72	The estimated prevalence and incidence of late stage age related macular degeneration in the UK	Owen C.G.	2012	180	18	24	2
73	Ciliary neurotrophic factor delivered by encapsulated cell intraocular implants for treatment of geographic atrophy in age-related macular degeneration	Zhang K.	2011	180	16.36	0	0
74	Treatment of macular degeneration using embryonic stem cell-derived retinal pigment epithelium: preliminary results in Asian patients	Song W.K.	2015	179	25.57	111	69
75	The impact of oxidative stress and inflammation on RPE degeneration in non-neovascular AMD	Datta S.	2017	178	35.6	3	0
76	Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration	Ying G.	2013	178	19.78	10	1
77	Animal models of age related macular degeneration	Pennesi M.E.	2012	178	17.8	6	0
78	Age-related macular degeneration	Mitchell P.	2018	177	44.25	50	84
79	Common variants near FRK/COL10A1 and vegfa are associated with advanced age-related macular degeneration	Yu Y.	2011	177	16.09	8	2
80	Dietary sources of lutein and zeaxanthin carotenoids and their role in eye health	Abdel A.	2013	176	19.56	189	14
81	Incidence of legal blindness from age-related macular degeneration in Denmark: year 2000 to 2010	Bloch S.B.	2012	176	17.6	30	23
82	Lutein, zeaxanthin, and meso-zeaxanthin: the basic and clinical science underlying carotenoid-based nutritional interventions against ocular disease	Bernstein P.	2016	175	29.17	158	10
83	Abundant lipid and protein components of drusen	Wang L.	2010	175	14.58	0	0
84	Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab	Bakall B.	2013	174	19.33	24	0
85	Lutein: more than just a filter for blue light	Kijlstra A.	2012	174	17.4	12	9
86	Analysis of choroidal thickness in age-related macular degeneration using spectral-domain optical coherence tomography	Manjunath V.	2011	174	15.82	1	1
87	Characteristics of patients losing vision after 2 years of monthly dosing in the phase III ranibizumab clinical trials	Rosenfeld P.J.	2011	174	15.82	0	0
88	Mechanisms of age-related macular degeneration and therapeutic opportunities	Campagne M.L.	2014	171	21.38	611	2
89	Blood-retinal barrier	Cunha-Vaz J.	2011	169	15.36	9	0
90	The prevalence of age-related eye diseases and visual İmpairment in aging: current estimates	Klein R.	2013	168	18.67	4	1
91	The neovascular age-related macular degeneration database: multicenter study of 92 976 ranibizumab injections	Tufail A.	2014	167	20.88	7	2
92	Phase 1 clinical study of an embryonic stem cell-derived retinal pigment epithelium patch in age-related macular degeneration	da Cruz L.	2018	166	41.5	1420	523
93	Age-related retinopathy in NRF2-deficient mice	Zhao Z.	2011	166	15.09	4	1
94	Parallel findings in age-related macular degeneration and Alzheimer's disease	Ohno-Matsui K.	2011	164	14.91	6	0
95	Stem cells in retinal regeneration: past. present and future	Ramsden C.M.	2013	162	18	30	16
96	Ranibizumab versus bevacizumab for neovascular age-related macular degeneration: results from the gefal noninferiority randomized trial	Kodjikian L.	2013	158	17.56	26	3
97	Laser-induced choroidal neovascularization model to study age-related macular degeneration in mice	Lambert V.	2013	158	17.56	6	0
98	Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis	Rudnicka A.R.	2012	157	15.7	1	1
99	Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration	Ho A.C.	2014	156	19.5	20	2
100	Ultrahigh-speed swept-source OCT angiography in exudative AMD	Moult E.	2014	156	19.5	4	2

TCN: total citation number; ACpY: average citation per year; AAS: altmetric attention score; NTs: number of tweets.

Table 2 Journals of the Top-100 cited articles according to the number of articles

Journal name	Number of articles	IF*	Q category**	H Index**
Ophthalmology	27	8	1	229
Progress In Retinal And Eye Research	7	15	1	141
British Journal Of Ophthalmology	6	4	1	146
American Journal Of Ophthalmology	5	4	1	179
Lancet	5	60	1	747
Nature Genetics	4	28	1	550
Proceedings Of The National Academy Of Sciences Of The United States Of America	4	9	1	737
Molecular Aspects Of Medicine	3	10	1	128
Retina-The Journal Of Retinal And Vitreous Diseases	3	3	1	105
Jama Ophthalmology (Formerly Known As Archives Of Ophthalmology)	3	6	1	190
Autophagy	2	10	1	135
Cell	2	39	1	747
Investigative Ophthalmology & Visual Science	2	1	1	209
Jama-Journal Of The American Medical Association	2	46	1	654
Lancet Global Health	2	22	1	72
New England Journal Of Medicine	2	75	1	987
Plos One	2	3	1	300
Annual Review Of Genomics And Human Genetics	1	7	1	112
Biomedical Optics Express	1	4	1	76
Bmc Ophthalmology	1	1	2	39
Cellular And Molecular Life Sciences	1	6	1	210
Cochrane Database Of Systematic Reviews	1	8	1	261
Development	1	6	1	315
European Journal Of Ophthalmology	1	2	2	51
Graefes Archive For Clinical And Experimental Ophthalmology	1	2	1	96
Human Molecular Genetics	1	5	1	269
Journal Of Pathology	1	6	1	176
Nature	1	43	1	1159
Nature Biotechnology	1	37	1	426
Nature Medicine	1	36	1	524
Nature Protocols	1	10	1	230
Nature Reviews Immunology	1	40	1	371
Neuron	1	14	1	453
Nutrients	1	1	1	93
Ophthalmic Surgery Lasers & Imaging Retina	1	1	2	55
Stem Cell Reports	1	6	1	65

IF: Impact Factor
*: 2019 Clarivate Journal Citation Reports
**: 2020 Scimago Journal and Country Rank

Table 3 Comparison of AAS and TCN of the Top-100 cited articles according to the study types

Study Type-Subtype		Article Number	Level of Evidence**	AAS, median (IQR)	p*	TCN, median (IQR)	p*
Original Scientific Paper		**72**					
	Prospective Randomized Clinical Trial	20	1	20 (8-49)		254 (180-522)	
	Meta-analysis	9					
	Systematic Review	1					
	Experimental Animal and/or Post-mortem Study	9	2	13 (4-89)		212 (174-469)	
	Prospective Cohort Study	3					
	Prospective Comparative Study	10			0.278		0.549
	Retrospective Comparative Study	5					
	Prospective Descriptive Study	3	3	8 (2-19)		220,5 (191-290)	
	Retrospective Descriptive Study	3					
	Cross-Sectional Study	2					
	Case Series	7					
Guideline and Advisory Documents		**1**	4	12 (6-30,5)		206,5 (176,5-291)	
Review		**25**					
Review-Seminar		**2**					

AAS: altmetric attention score; TCN: total citation number
*Kruskal-Wallis Test; p<0.05 significant
**Scottish Intercollegiate Guidelines Network (SIGN)

Table 4 Comparison of TCN and AAS of the Top-100 cited articles based on main topic categories

Main topic	Number of articles	TCN, median (IQR)	AAS, median (IQR)
The whole article	**100**	**221 (178-380,75)**	**13 (4-37,75)**
Treatment	**34**	**225 (179-577)**	**18 (8-97)**
Anti-VEGF injection	25		
Treatment outcome; efficacy and safety	4		
Treatment regimens and outcome; efficacy, safety	15		
Treatment outcome and prognostic features	3		
Switch protocol and treatment outcome	2		
Pharmacokinetics and systemic exposure	1		
Drug implant	*1*		
Retinal stem cell transplantation	*6*		
Dietary Supplements	*2*		
Diagnosis and image analyses	**13**	211 (189-381)	4 (3-13)
Medical image analyses	10		
OCT	4		
OCT-angiography	3		
OCT, FFA, FAF, fundus photo	3		
Artificial intelligence analyses	3		
OCT	2		
Fundus photo	1		
Pathophysiology	**12**	233 (186,5-368)	7,5 (3,5-13,5)
Immunological process	1		
Immunological and inflammatory process	4		
Oxidative stress	2		
Oxidative stress and inflammatory process	2		
Oxidative stress and immunological process	1		
Oxidative stress, inflammatory and immunological process	2		
Pathophysiology and genetics	**12**	**280,5 (205,5-377)**	**26,5 (15,5-38)**
Epidemiology	**10**	**210 (176-321)**	**13 (1-30)**
Histopathology	**6**	**189 (164-218)**	**4,5 (0-6)**
Molecular mechanisms of antioxidant molecules	**3**	**175 (174-176)**	**158 (12-189)**
Pathophysiology and treatment	**3**	**177 (171-899)**	**56 (50-611)**
Classification and staging	**2**	**400 (230-570)**	**37,5 (1-74)**
Prognostic features	**2**	**345,5 (311-380)**	**3,5 (3-4)**
Pathophysiology, diagnosis and image analyses	**1**	**169 (169-169)**	**9 (9-9)**
Histopathology and molecular mechanisms	**1**	**178 (178-178)**	**6 (6-6)**
Diagnosis and therapeutic management	**1**	**219 (219-219)**	**124 (124-124)**

TCN: total citation number, AAS: altmetric attention score, VEGF: vascular endothelial growth factor, OCT: optic coherence tomography, FFA: fundus fluorescein angiography, FAF: fundus autofloresans.

Table 5 Correlation analysis

		TCN	ACpY	NTs	IF	H-index	Q category
AAS	r	0.162	0.382**	0.779**	0.394**	0.238*	-0.066
	p	0.107	0.001	0.001	0.001	0.017	0.512
TCN	r	1	0.889**	0.131	0.516**	0.403**	-0.060
	p		0.001	0.195	0.001	0.001	0.552
ACpY	r		1	0.373**	0.602**	0.389**	-0.086
	p			0.001	0.001	0.001	0.394
NTs	r			1	0.497**	0.351**	-0.055
	p				0.001	0.001	0.585
IF	r				1	0.801**	-0.141
	p					0.001	0.162
H-index	r					1	-0.185
	p						0.065

AAS: altmetric attention score; TCN: total citation number; ACpY: average citation per year; NTs: number of tweets; IF: journal impact factor.
Impact factor: 2019 Clarivate Journal Citation Reports; H index: 2020 Scimago Journal and Country Rank.
**Correlation is significant at the 0.01 level
*Correlation is significant at the 0.05 level
r was obtained from Spearman rank or Pearson correlation coefficient.

was published in 2011 with a TCN of 1667 [14]. There were only eight articles in the T100 list that did not have AAS yet. The article with the highest AAS with 1420 in the T100 list was Cruz L et al's article, which was entitled as "Phase 1 clinical study of an embryonic stem cell-derived retinal pigment epithelium patch in age-related macular degeneration", and it was published in 2018 [15]. Also this article had the highest NTs in accordance with the highest AAS.

Twitter analysis

It was discovered that 68 articles of the T100 list were shared on Twitter. Five of the top-10 articles with the highest NTs dealt with stem cell treatment in AMD; two of them dealt with diagnostic image analyses using artificial intelligence techniques.

Journal perspective

The journal of Ophthalmology published most articles, with 27, among the T100 list's 36 journals (Table 2). The most cited article was from New England Journal of Medicine, which had the greatest IF among T100 journals. The second most cited article was from the journal of Lancet Global Health. The article with the highest AAS was published in the journal of Nature Biotechnology. According to SJCR, all journals received Q1 scores, with the exception of three journals which received Q2 scores.

Article types

According to SIGN, 72 articles of the T100 list represented original scientific research (Table 3). When all publications were categorized by their degree of evidence, there was no statistically significant difference in the median AAS of the four groups. (p=0.278). Similarly, there was no significant difference in the median TCN across the four groups (p=0.549). The level of evidence had no significant effect on the AAS and TCN of the articles, according to these results.

Research subjects

The bulk of publications on the T100 list were about treatment (n=34), followed by diagnosis and image analysis (n=13), pathophysiology (n=12), and pathophysiology and genetics (n=12) (Table 4). But the main subject with the greatest median AAS was molecular mechanisms of antioxidant molecules, with a value of 158 (12-189). The main subject with the greatest median TCN was classification and staging, with a value of 400 (230-570).

Correlation analysis

The correlation analysis findings are shown in Table 5 and Figure 2. While AAS and NTs did not have a significant correlation with TCN (r values were 0.162 and 0.131, p values were 0.107 and 0.195, respectively), they did show a weak positive correlation with ACpY (r values were 0.382 and 0.373, p values were 0.001 and 0.001, respectively). Notably, AAS had a weak positive correlation with journal IF, but NTs had a moderate positive correlation with journal IF (r values were 0.394 and 0.497, p values were 0.001 and 0.001, respectively). Additionally, both AAS and NTs showed weak positive correlation with H-index (r values were 0.238 and 0.351, p values were 0.017 and 0.001, respectively). It is worth noting that, although NTs did not correlate with TCN, they did have a moderate positive linkage with journal IF.

Visualization analysis

The total strength of bibliographic coupling relationships with other nations was estimated and presented for each of the 37 countries in the T100 list (Figure 3A). Countries with large nodes are more efficient and productive. The thickness and distance of links between nodes represent the level of communication and cooperation among countries. The United States was the most productive and impressive country regarding the total amount of documents (76 documents), TCN received (26758 citations), and international cooperation (24677 link strength).

Figure 2-Scatter plot of relationship between Altmetric Attention Score (AAS) and Number of tweets (Figure 2A), relationship between AAS and total citation number (Figure 2B) Figure 2A: There was strong positive correlation between Altmetric Attention Score and Number of Tweet (r=0.779; p=0.001). According to univariate linear regression analysis ~61% of variation in Altmetric Attention Score was explained by Number of Tweet. 1 unit increase in Tweet resulted in 2.36 increase in Altmetric Attention Score model to estimate Altmetric Attention Score was YAltmetric Attention Score = 31.40+2.36*X Number of Tweet Figure 2B: There was weak positive correlation between Altmetric Attention Score and Average citation pear year cite (r=0.382; p=0.001). According to univariate linear regression analysis ~15% of variation in Altmetric Attention Score was explained by Average citation pear year cite. 1 unit increase in Average citation pear year cite resulted in 2.51 increase in Altmetric Attention Score model to estimate Altmetric Attention Score was YAltmetric Attention Score = -10.54+2.51*X Average per Year Citation

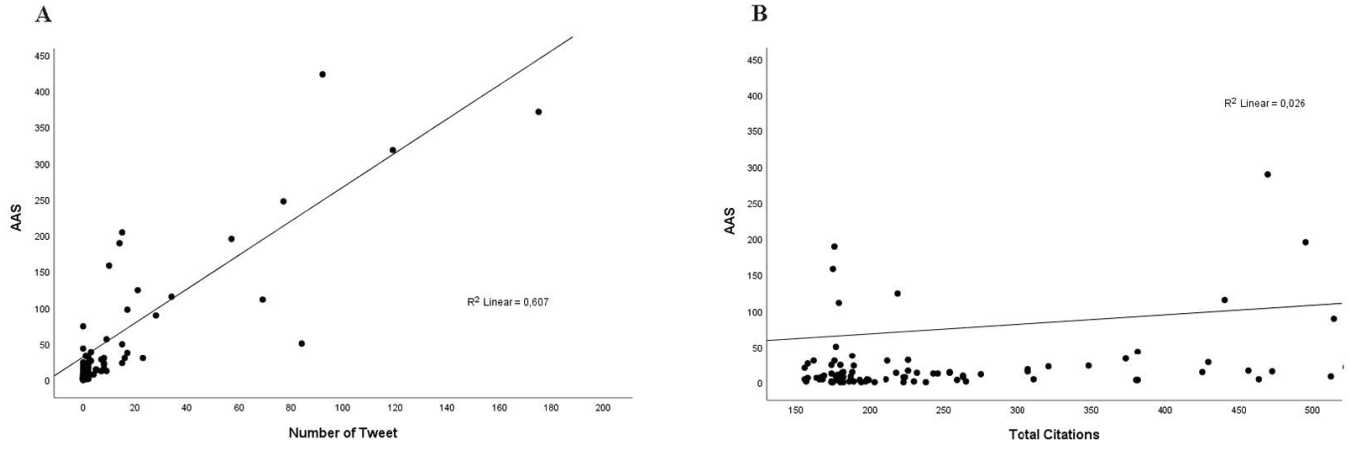
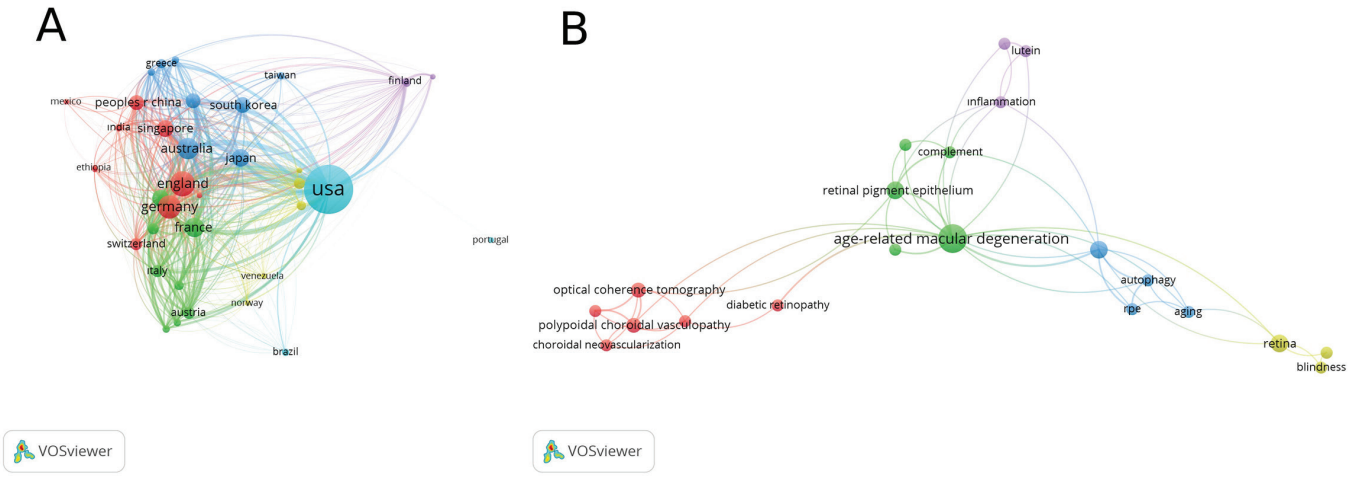


Figure 3-Network visualization maps of age related macular degeneration research The strength of bibliographic country coupling linkages is displayed in Figure 3A. The co-occurrence analysis of high-frequency keywords is displayed in Figure 3B.



The United States was followed by England, Germany, Australia, France, Japan, Singapore, Netherlands, South Korea, and North Ireland, respectively TCN of top-10 countries were 26758, 7882, 7549, 5360, 4379, 4214, 4903, 3001, 2762, and 3098, respectively.

The hotspots of AMD research were discovered with a co-occurrence analysis of frequently used keywords. The minimal number of keyword co-occurrences criteria was chosen to be 2.The criteria was met by 21 of the 129 retrieved keywords related to AMD. The system was used to cluster relevant keywords, and the five major clusters were represented by the colors red, green, blue, yellow, and purple, respectively (Figure 3B). The most prevalent keywords were "age-related macular degeneration" and "oxidative stress".

Discussion

We compared bibliometric analyses to altmetric analyses of the highly cited articles in the field of AMD research in the current study. While there was no relationship between AAS and TCN, a significant correlation between AAS and ACpY was discovered. Additionally, we found a significant correlation between AAS and journal IF and H-index. We noticed that the majority of the highly cited articles in the field of AMD research in the last decade have mainly focused on AMD treatment, especially anti-vascular endothelial growth factor (anti-VEGF) therapy.

While traditional bibliometric analyses are useful for assessing the impact value of scientific articles, they have significant disadvantages. A specific amount of time must pass before the measurement of citation metrics of the published article. Therefore it is not possible to evaluate the impact of a recently published article by bibliometric analysis in its earliest years. It causes difficulty for researchers to find impressive articles, keep track of fresh study subjects, and come up with new research areas. Additionally, the reason of citing the articles is unclear. The possibility of referring highly cited articles is usually raised [6]. Furthermore, citation quantities may be influenced unfairly because of self-citation or citation of relevant authors' articles. Therefore a new technique to quickly evaluate the quality and impact value of articles is needed. This is the first research that we are aware of that evaluated articles with both bibliometric and altmetric analysis in the field of AMD research. While AAS and NTs had no significant correlation with TCN (r values of 0,162 and 0,132, respectively), they did have weak positive correlation with ACpY (r values of 0,382 and 0,373, respectively). This indicates that articles which have been cited regularly over the years and remain actual are more valuable on social media and Twitter. NTs can be used as a valuable indicator for predicting the early period impact values of articles.

While AAS and NTs did not correlate with TCN, AAS did show a weak positive correlation with journal IF, and also TCN showed a moderate positive correlation with journal IF as well. This issue may be explained by the fact that AAS and NTs were positively correlated with ACpY. Journal IF is influenced by citations received in recent years. Articles which continue to be debated receive a greater amount of attention on Twitter. Another explanation could be that journals which have had their own Twitter accounts for a long time have more followers. As the number of social media followers increases, the awareness of the journals and accessing their articles also increase. It was revealed that tweeting about recently published articles increases the number of citations in following years [16-18]. It was found that medical journals with Twitter profiles have greater IF, and that there is a positive association between journal IF and the amount of Twitter account followers [19-21].

Kolahi et al. discovered a statistically significant positive correlation between AAS and TCN in their study [22]. He added that the intensity of this association will rise in the future due to the growth of social media. Gargovich et al. found an increasing positive correlation between AAS and TCN in their altmetric study in the field of pediatric dentistry investigation between 2014 and 2017 [23]. Suzan et al. also revealed a statistically significant positive correlation between AAS and TCN, ACpY, journal IF, and H-index in their altmetric study on malnutrition research [24]. However, Haustein et al. discovered relatively weak correlation between NTs and TCN [25]. Thelwall, a social media analyst with more than a hundred researches on metrics, claimed that there is a negative correlation between NTs and TCN because of long duration which is needed for citation, unlike quick sharing on Twitter [26]. We found both AAS and NTs to have positive correlation with ACpY, journal IF, and H-index. These findings reveal that altmetric and bibliometric parameters are generally compatible and correlated with each other. In accordance with Thelwall, AAS and NTs were not correlated with TCN in our study. We discovered that ACpY is a more important indication than TCN for AAS and NTs. Social media users pay more attention to the articles which continue to be discussed and are current. In addition to this, articles with

older publication years usually have higher TCN because of the accumulation of citations. Due to the fact that social media usage was not widespread in the early years of the last decade, AAS of articles with older publication years may be low. This could also explain why there was no significant association between AAS and TCN in our study.

Seventy two articles of the T100 list articles were original scientific research. Twenty of these articles were randomized clinical trials, and ten of these articles were meta-analyses and systematic reviews with a level of evidence of 1 according to SIGN criteria. Suzan et al. discovered a statistically significant differences between TCN but no statistically significant differences between AAS in terms of study types [24]. We found that the level of evidence did not make a significant difference in TCN and AAS when we classified and compared the articles according to the study types and level of evidence. However, it was notable that both articles with highest TCN and AAS were randomized clinical trials with a level of evidence 1.

It is important to classify the T100 list according to the main subject areas in order to determine which subjects get far more interest from scholars and social media users. The main topics of the articles with the highest TCN median value were classification and staging (400) and prognostic features (345.5). The main topics of the articles with the highest AAS median value were molecular mechanisms of antioxidant molecules (158) and diagnostic and therapeutic management (124). According to the main topic analysis of T100 list, we found out that majority of articles were about treatment, particularly anti-VEGF therapy. In accordance with this, Martin et al.'s article entitled as "Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration The CATT Research Group" received the highest TCN [14]. However, the article entitled as "Phase 1 clinical study of an embryonic stem cell-derived retinal pigment epithelium patch in age-related macular degeneration" by Cruz et al. had both the greatest AAS and NTs in the T100 list [15]. The academic community made the highest citations to the article which is evaluating the treatment protocols, efficacy, and safety of anti-VEGF therapies, which are currently used to treat AMD. On the other hand, anti-VEGF medications are a kind of medication that reduces and suppresses the progression of neovascular AMD but cannot provide a complete cure in advanced AMD. Social media users were most interested in the article about embryonic stem cell therapy, which had the potential to be a more dramatic therapeutic option for AMD than symptomatic anti-VEGF medications. The top ten articles with the highest AAS had the following topics: embryonic stem cell treatment (n=4), anti-VEGF treatment (n=2), diagnostic image analysis using artificial intelligence techniques (n=2), dietary supplement treatment (n=1), and epidemiology (n=1). It was remarkable that social media users showed great interest in newly developed techniques such as embryonic stem cell therapy and artificial intelligence. It was notable that six of the ten articles with the highest AAS were produced in the United States, which was also the most productive country according to the bibliometric visualization analysis.

As a consequence of increasing use of Twitter for professional reasons, scholars and clinicians have begun to frequently utilize Twitter for academic knowledge transfer in recent years. Twitter dismantles academic hierarchy and enables scientists and clinicians from across the globe to interact and debate research topics. According to the report, 71.9 percent of 160 ophthalmologists use social media in 2020 [27]. Additionally, Alfaris et al. reported that 35 percent of medical students use Twitter for vocational training in their study on the effect of social media use on academic achievement in medical students [28]. Numerous medical journals also have their own Twitter accounts. Over 20% of all published articles are announced at least once on Twitter [29]. In our study, 68 articles in the T100 list were shared on Twitter. It is worth noting that the journals of Nature Biotechnology, Jama-Journal Of The American Medical Association, New England Journal Of Medicine, Cell, And Lancet, which published the first five articles with the highest AAS in the T100 list, have their own Twitter accounts. Furthermore, journal of Ophthalmology, which has the most number of articles in the T100 list with 27 articles, also has a Twitter account. On the other hand, it is noteworthy to see that the journals which published the first and second articles with highest TCN (New England Journal of Medicine and Lancet Global Health, respectively) and the journal which published the article with the highest AAS (Nature Biotechnology) were general medicine journals which were not specialized in ophthalmology field.

The limitation of our study is that we used NTs in our altmetric analysis, but we did not define detailed Twitter demographics. The amount of Twitter followers might be used to estimate the amount of individuals contacted and the spread of the content. It might be useful to evaluate the occupations, ages, genders, and geographical regions of Twitter users to determine the hot topics for different target groups. Further altmetric researches are needed to conduct detailed Twitter analyses, involving user classifications, amount of followers, and geography.

Conclusion

This study carried out both detailed altmetric and bibliometric analyses in the field of AMD research. AAS and NTs had significant positive correlation with ACpY, journal IF, and H-index. Therefore, altmetric analysis was found to be a useful option for rapid assessment of the impact of articles whose citation analysis period has not yet completed. Furthermore, AAS and NTs had a significant positive correlation with ACpY, implying that social media users are more interested in articles that continue to be cited over time and remain actual. Additionally, it is worth noting that NTs have a greater impact on journal IF than AAS. The majority of the mostly cited articles in the field of AMD research were about treatment, especially anti-VEGF medication. However social media users paid more attention to embryonic stem cell therapy as a treatment option for AMD. Performing altmetric analyses in the evaluation of articles, in addition to the bibliometric analyses, offers scholars a wealth of information about trending topics in AMD research.

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Evaluation of the effects of kidney function tests on prognosis and mortality in geriatric patients with a pulmonary embolism

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Abstract

Aim: The instant study's aim is to investigate the effect that BUN and creatinine values have on a prognosis in geriatric patients that are diagnosed with pulmonary embolism. Material and methods: Our study was planned as a retrospective data review and included patients over the age of 65 with a diagnosis of pulmonary embolism who were admitted applied to Ümraniye Training and Research Hospital between March 1, 2020, and March 1, 2022. Statistical analysis was performed using SPSS version 26.0.

Results: The study included 148 patients, and 66.89% of them were women. The mortality rate was 28.38%. Considering the blood gas parameters, there was a statistically significant relationship between PH and low saturation and mortality (p=0.029, p=0.001, respectively). Although creatinine values were higher in non-surviving patients than in surviving patients, it was not statistically significant (p=0.252). Blood urea nitrogen was statistically significantly higher in patients who died (p=0.001). Sodium and potassium values were also not associated with mortality (p=0.991, p=0.886, respectively).

Conclusion: The effect of kidney function tests on the prognosis is very important in managing pulmonary embolism. BUN will be more beneficial to the clinician than creatinine and plasma electrolytes in the management of patients with pulmonary embolism.

Key words: pulmonary embolism, BUN, creatinine, sodium, potassium

Introduction

Although the pulmonary embolism is an important disease—the incidence of which increases as age increases—it can be difficult to diagnose in geriatric patients due to reasons such as the vagueness of symptoms and the inability of the patient to clearly express himself. Similar to shortness of breath, chest pain, syncope symptoms may suggest different diagnoses [1]. The high morbidity and mortality rates have caused further investigation of laboratory parameters that affect prognosis, including parameters such as PH, hco3 [2], d-dimer [3], and ionized calcium [4], which were investigated in terms of their relationships with mortality and morbidity. In recent years, the relationship between mortality and troponin, creatinine kinase, BNP [5,6], blood urea nitrogen (BUN) and creatinine has been investigated in patients with a pulmonary embolism [2,5].

Blood urea nitrogen and creatinine are generally used to evaluate kidney function tests. While both are filtered from the glomeruli and can give an idea of the glomerular filtration rate, tubules only reabsorb BUN [7,8]. Instead of the initial evaluation of renal function tests, the relationship between chronic renal failure and prognosis of chronic renal failure was examined. While there was a statistically significant relationship between chronic renal failure and mortality in some pulmonary embolism studies [2,6], other studies showed no relationship between the two [9].

In addition, the number of patients diagnosed with renal failure and diagnosed with pulmonary embolism was low. This suggested the possibility that renal function tests may be more determinative in predicting prognosis. Thus, the effect of kidney function tests on prognosis and mortality to be import in regards to pulmonary embolism in myocardial infarction [10] and ischemic stroke diseases [11].

Aim: The instant study's primary aim is to investigate the effect that BUN and creatinine values have on a prognosis in geriatric patients that are diagnosed with pulmonary embolism. Our secondary aim is to compare the effect of BUN and creatinine values with the effects of sodium and potassium parameters on prognosis.

Material and methods

Study design

Our study was planned as a retrospective data review and included patients over the age of 65 with a diagnosis of pulmonary embolism who were admitted applied to Ümraniye Training and Research Hospital between March 1, 2020, and March 1, 2022. Our hospital is an 836-bed hospital with 2.8 million patient applications per year. There are yellow, green, and red areas in the emergency department and approximately 500,000 patients apply to the emergency department annually.

Study population

We obtained data from the hospital database on patients over 65 years of age who were diagnosed with pulmonary embolism by thorax angio CT (computed tomography). According to their survival status, the patients were divided into two groups—survivors and those who died—according to the National death notification system in Turkey. All patients under 65 years of age, patients over 65 years of age who were not diagnosed with pulmonary embolism, and patients with missing data were excluded from the study.

Data collection

Age, gender, symptoms, and comorbidities of patients over 65 years of age who were diagnosed with pulmonary embolism were recorded. Hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), chronic cardiac failure (CCF), cerebrovascular disease (CVD), chronic renal failure (CRF), and malignancies, blood pressure, pulse, respiratory rate, saturation, PH, PCO2, BUN (blood urea nitrogen), creatinine, sodium, potassium and mortality status (30-day mortality information), length of hospital stay, discharge during the clinical course, service admission, and intensive care admission were recorded. Patients receiving thrombolytic therapy received a bolus of 10 mg t-PA, followed by an intravenous infusion of 90 mg over a 2-hour period. Subcutaneous low molecular weight heparin was used after the thrombolytic therapy. The relationship between mortality and BUN, creatinine, sodium, and potassium values was investigated. This evaluation included consideration of whether these values were superior to each other in affecting mortality.

Ethics committee

The local clinical research ethics committee of our hospital provided approval (date: March 10, 2022; number: B.10.1.TKH.4.34.H.GP.0.01/70).

Statistical analysis

Statistical analysis was performed using SPSS version 26.0. The conformity of the variables to the normal distribution was determined by visual (histogram and probability charts) and analytical (Kolmogorov-Smirnov test) methods. Chi-square and Fishers' exact test were used for categorized data. Quantitative variables were presented as median and interquartile range (IQR, 25th-75th percentile) values, and the Mann-Whitney U test was used to analyze paired groups and kidney function tests. Bonferroni correction was preferred in multiple comparisons. The receiver operating characteristic (ROC) curve analysis was performed in order to evaluate the diagnostic test's performance of the investigated parameters in predicting mortality. This included an analysis of the area under the curve (AUC) values were calculated, and the sensitivity, specificity, and 95% confidence interval (CI) data. Statistical significance was accepted as $p<0.05$ (Jamovi 1.2.27).

Results

The study included 148 patients, and 66.89% of them were women. The mortality rate was 28.38%. A statistically significant correlation was found between high heart rate, low systolic and diastolic blood pressure, and mortality ($p=0.015$, $p<0.001$, $p=0.008$, respectively).

Among the comorbid diseases, only those with congestive heart failure and malignancy had a higher mortality rate than other comorbidities ($p=0.03$, $p=0.05$, respectively). While there was no statistically significant relationship between symptoms and mortality, mortality was significantly higher in patients who were admitted to the intensive care unit compared to those who were discharged from the hospital and those who were admitted to the ward ($p<0.001$). Demographic characteristics, vital signs, and clinical outcomes for the patients are provided in Table 1.

Considering the blood gas parameters, there was a statistically significant relationship between PH and low saturation and mortality ($p=0.029$, $p=0.001$, respectively). Although creatinine values were higher in non-surviving patients than in surviving patients, it was not statistically significant ($p=0.252$). Blood urea nitrogen was statistically significantly higher in patients who died ($p=0.001$). Sodium and potassium values were also not associated with mortality ($p=0.991$, $p=0.886$, respectively).

The most common electrocardiographic (ECG) finding in our patients was sinus rhythm. It was present in 33.3% of the patients who died ($p=0.003$). In 48.64% of the patients, echocardiography (ECO) provided evidence of pulmonary embolism. On the other hand, 57.14% of the patients who died had ECO findings, but did not have a statistically significant correlation between the presence of ECO findings and their mortality ($p=0.20$).

There was a statistically significant relationship between the pulmonary embolism severity index (PESI) and the simplified pulmonary embolism severity index (sPESI) and mortality ($p<0.001$, $p=0.006$, respectively). This was represented in Table 2.

There was a statistically significant difference between high BUN and low saturation and mortality ($p=0.001$, $P=0.001$, respectively). The diagnostic test performance analyses BUN and saturation in predicting mortality revealed that BUN and creatinine were statistically significant in predicting 0.67mortality, with the AUC value being calculated as 0.67(0.591-0.748) for BUN at a cut-off value of 53.5, sensitivity of 69.05, and specificity of 74.53; 0.68(0.597-0.753) for saturation at a cut-off value of 89, sensitivity of 66.67, and specificity of 66.04($p=0.0019$, $P=0.0003$, respectively).

Discussion

Our study determined that high BUN could predict mortality in patients diagnosed with pulmonary embolism. In addition, creatinine, sodium, and potassium could not predict mortality

Table 1 Relationship between demographic data, vital signs, comorbid diseases, and first admission symptoms with mortality

	Total	Survivor	Non-survivor	p
	148(100%)	106(71.62%)	42(28.38%)	
Age (median 25-75)	77(70-82)	77.5(70-82)	76(71.50-83.25)	0.94
Age(mean±std)	77±7.6	76.89±7.46	77.29±8.05	
Gender				0,33
Female	99(66.89%)	68(64.15%)	31(73.8%)	
Male	49(33.11%)	38(35.84%)	11(26.19%)	
GCS (median 25-75)	15(15-15)	15(15-15)	15(11-15)	**<0.001**
GCS(mean±std)	14.38±1.9	14.92±0.52	13±3.14	
Fever(median 25-75)	36.4(36-36.8)	36.4(36-36.7)	36.6(36-37)	0.11
Fever(mean±std)	36.45±0.48	36.42±0.45	36.54±0.54	
Heart rate/min(median 25-75)	101(87-120.75)	100(83-117.25)	109(90-131.50)	**0.015**
Heart rate/min(mean±std)	104.01±23.72	100.38±21.99	113.17±25.67	
Respiratory_rate_min (median 25- 75)	19(18-23)	19(18-22)	21(17-30.25)	0.262
Respiratory_rate_min (mean±std)	21.11±5.8	20.46±4.65	22.74±8.08	
Sistolik_TA(median 25-75)	123(100-142.75)	125.5(110-155.25)	105(91.50-130.25)	**<0.001**
Sistolik_TA (mean±std)	124.68±31.15	130.76±30.75	109.31±26.83	
Diastolik_TA(median 25-75)	74(60.25-87)	76.5(65-90)	69.50(54.75-80)	**0.008**
Diastolik_TA(mean±std)	74.30±18.12	76.79±17.8	68±17.6	
Comorbidities				
Hypertension	60(40.54%)	18(16.98%)	42(100%)	0.71
Diabetes Mellitus	26(17.56%)	18(16,98)	8(19.04%)	0.81
Chronic Obstructive Pulmonary Disease	17(11.48%)	14(13.2%)	3(7.14%)	0.39
Coronary artery disease	24(16.21%)	18(16.98%)	6(14.28%)	0.8
Congestive Heart Failure	12(8.1%)	5(4.71%)	7(16.6%)	**0.03**
cerebrovascular disease	25(16.89%)	14(13.20%)	11(26.19%)	0.08
Chronic Renal Failure	1(0.67%)	0	1(2.38%)	0.28
Malignancy	33(22.29%)	19(17.92%)	14(33.3%)	**0.05**
History of surgery	21(14.18%)	16(15.09%)	5(11.9%)	0.79
History of deep vein thrombosis	12(8.1%)	8(7.54%)	4(9.52%)	0.74
Anticoagulant use	36(24.32%)	21(19.81%)	15(35.71%)	0.05
Symptoms				
Syncope	40(27.02%)	29(27.35%)	11(26.19%)	1
Shortness of breath	84(56.75%)	60(56.6%)	24(57.14%)	1
Chest pain	25(16.89%)	20(18.86%)	5(11.9%)	0.46
Back pain	2(1.35%)	1(0.94%)	1(2.38%)	0.48
Hemoptysis	6(4.05)	4(3.77%)	2(4.76%)	1
Deep vein thrombosis	15(10.13%)	9(8.49%)	6(14.28%)	0.36
Weakness	35(23.64%)	27(25.47%)	8(19,4%)	0.52
Clinical outcome				**<0.001**
Discharge	4(2.7%)	4(3.77%)	0	
Ward admission	96(64.86%)	89(83.96%)	7(16.6%)	
Intensive care hospitalization	48(32.43%)	13(12.26%)	35(83.33%)	

in patients with a pulmonary embolism and were insufficient in determining prognosis. There is no significant superiority between low saturation and high BUN. Many diseases have been the subject of research in terms of the effects of kidney function tests on prognosis and mortality [10,11]. In a study conducted in patients who developed shock due to acute myocardial infarction, there was an increase in BUN and creatinine levels in the non-surviving group; renal blood flow was decreased [10]. In a study examining ischemic stroke patients, there was no statistically significant difference in terms of this and creatinine levels in patients who developed venous thromboembolism and those who did not develop venous thromboembolism. The logistic regression analysis predicted that the BUN/creatinine ratio may be an independent risk factor in ischemic stroke patients who develop venous thromboembolism [11].

Different results were obtained regarding BUN, creatinine, and potassium in pulmonary embolism studies. In a multicentric prospective study, a statistically significant correlation was found between renal dysfunction and mortality in patients diagnosed with acute pulmonary embolism [12]. In a study examining patients with a diagnosis of venous thromboembolism, the urea level was significantly higher in the mortal patient group [13]. In a retrospective study examining 252 patients with pulmonary embolism who received thrombolytic therapy, mortality, need for inotropic therapy, and development of cardiogenic shock were statistically significantly higher in the patient group with high BUN levels upon admission [2]. In our study, the rate of patients given thrombolytic therapy was 6.75%, and there was no statistically significant relationship between thrombolytic therapy and mortality.

Our study found that high creatinine did not affect prognosis. In a study of 206 pulmonary embolism patients high creatinine associated with mortality [14]. In a prospective study in which Kostrubiec et al. examined renal functions in acute pulmonary embolism, they examined 2,845 patients with a mean age of 67±18 years, and a statistically significant

Table 2 Relationship between blood gas, kidney function tests, ECG and ECO findings with mortality

	Total	Survivor	Non-survivor	p value
PH(median 25-75)	7.41(7.36-7.46)	7.41(7.38-7.46)	7.37(7.29-7.44)	**0.029**
PH(mean±std)	7.39±0.1	4.40±0.06	7.35±0.14	
PCO2(median 25-75)	38.4(32.32-43.9)	38.2(31.9-43.65)	39.3(33.3-46.22)	0.272
PCO2(mean±std)	38.84±9.15	38.09±8.47	40.75±10.56	
saturation(median 25-75)	90(85-95)	91(86.75-95)	86.50(82-92)	**0.001**
saturation% (mean±std)	89±7.11	90.32±6.2	85.67±8.19	
Glucose(mmol/l)(median 25-75)	147(116-199.75)	146(117.5-190.25)	152.50(115-230.25)	0.81
Glucose(mmol/l)(mean±std)	167.54±74.93	163.30±62.93	178.26±99.11	
BUN(mg/dl)(median 25-75)	49.2(38.5- 70.45)	47.08(36.38-57.78)	70.31(40.66-94.69)	**0.001**
BUN(mg/dl)(mean±std)	59.41±34.49	52.62±25.21	76.53±47.11	
Creatinine(mg/dl)(median 25-75)	0.99(0.82-1.18)	0.97(0.82-1.17)	1.06(0.81-1.22)	0.252
Creatinine(mg/dl) (mean±std)	1.08±0.44	1.04±0.38	1.17±0.55	
Sodium(mEq/L)(median 25-75)	138(134-140)	138(135-140)	136.50(132.75-143)	0.991
Sodium(mEq/L)(mean±std)	137.63±5.68	137.25±4.09	138.6±8.46	
Potassium(mEq/L)(median 25-75)	4.3(4-4.8)	4.3(4-4.8)	4.25(4-4.9)	0.886
Potassium(mEq/L)(mean±std)	4.36±0.64	4.35±0.63	4.40±0.66	
ECG finding				0.003*
Sinus rhythm	72(48.6%)	58(54.7%)	14(33.3%)	
ST depression	44(29.7%)	31(29.2%)	13(31%)	
Sinus tachycardia	3(2%)	0(0%)	3(7.1%)	
Atrial fibrillation	16(10.8%)	6(5.7%)	10(23.8%)	
T negativity	4(2.7%)	3(2.8%)	1(2.4%)	
Left bundle branch block	1(0.7%)	1(0.9%)	0(%0)	
Right bundle branch block	4(2.7%)	4(3.8%)	0(%0)	
S1Q3T3	4(2.7%)	3(2.8%)	1(2.4%)	
EKO finding	72(48.64%)	48(45.28%)	24(57.14%)	0.20
Thrombolytic therapy	10(6.75%)	6(5.66%)	4(9.52%)	0.47
PESI class	4(3-5)	4(3-4.25)	5(4-5)	**<0.001**
sPESI	2(1-3)	2(1-2.25)	2(1-3)	**0.006**
sPESI risk				0.068
low risk	15(10.1%)	14(13.2%)	1(2.4%)	
high risk	133(89.9%)	92(86.8%)	41(97.6%)	
Length of hospital stay	6.5(4-9)	7(4-10)	5(3-8)	0.095

*BUN, blood urea nitrogen; ECG, electrocardiography; PESI,pulmonary embolism severity index; sPESI, simplified pulmonary embolism severity index

correlation was found between high creatinine and mortality [6]. In a retrospective study conducted in patients diagnosed with normotensive pulmonary embolism, BUN and creatinine values were significantly higher in patients with a poor prognosis [15]. Babaoğlu et al. determined that the serious increase in urea and creatinine levels in patients with a pulmonary embolism increased the risk of mortality. While there was no statistically significant difference in sodium values in low-risk and high-risk pulmonary embolism patients, similar to our study. Unlike in our study, Babaoğlu et al.'s study showed potassium values that were statistically significantly higher in patients with high-risk pulmonary embolism [5].

Our study supported the premise that BUN could predict the prognosis, as previous studies similarly found. However, the relationship between creatinine and prognosis is different than in the literature. We think that BUN should be more prominent in disease management in terms of results that are obtained from geriatric patients. The use of drugs that regulate renal functions due to comorbid diseases may also have caused this result. In our study, hypertension was the most common comorbid disease; there was only a statistically significant correlation between congestive heart failure and malignancy and mortality. In a retrospective study, Fabian et al. determined a statistically significant relationship between comorbidities such as hypertension, diabetes mellitus, peripheral vascular disease, and mortality in patients diagnosed with pulmonary embolism [16]. They found that there was no statistically significant relationship between patients with chronic renal failure and end-stage renal disease and mortality [16]. In a meta-analysis by Xing et al., a significant correlation was found between acute renal failure and mortality in patients diagnosed with pulmonary embolism; they did not find a statistically significant relationship between chronic renal failure and mortality [17]. In our study, PESI and sPESI values were also able to predict mortality in accordance with the literature [9,18,19]. While sinus tachycardia is most common in electrocardiography, sinus tachycardia was the most common in the mortal group. There was no significant correlation with mortality in patients with pulmonary embolism echocardiographic findings. This showed that pulmonary embolism requires more careful management, especially in geriatric patients.

Limitations

In our study, full data of a certain number of patients were available, and the study only included clinical findings at first admission. The patients' 30-day mortality data and hospital stay were reached, and the patient's quality of life at hospital discharge was not recorded.

Conclusion

The effect of kidney function tests on the prognosis is very important in managing pulmonary embolism. BUN will be more beneficial to the clinician than creatinine and plasma electrolytes in the management of patients with pulmonary embolism.

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Factors associated with fibro-cavernous tuberculosis

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Abstract

Objective: To identify socio-demographic, clinical and laboratory risk factors associated with fibro-cavernous tuberculosis.

Material and methods: Clinical and laboratory data of 184 patients with pulmonary tuberculosis who were treated at the National Scientific Center for Phthisiopulmonology of the Ministry of Healthcare of the Republic of Kazakhstan were analyzed. Specific antibodies to the lipoglycan of M.tuberculosis (MBT) were evaluated in an immunochromatographic assay. To assess the significance of differences in groups, the Pearson Chi-Square test was used. To determine factors associated with the fibro-cavernous tuberculosis, a multiple binary logistic regression analysis was carried out.

Results: Multivariate logistic regression analysis showed that low BMI (OR=5,719, 95% CI: 2,049–15,965, p=0,001), TB recurrence (OR=3.374, 95% CI: 1,191–9,561, p=0,022), and a negative specific production of antibodies to lipoglycan of M.tuberculosis (MBT) (OR=0,354, 95% CI: 0,126-0,995, p=0,049) were significantly associated with fibro-cavernous tuberculosis.

Conclusion: Weight deficiency, high antibodies levels and TB relapse are factors associated with fibro-cavernous tuberculosis.

Key words: infiltrative tuberculosis, fibro-cavernous tuberculosis, risk factors, anti-tuberculosis antibodies

Introduction

Tuberculosis (TB) caused approximately 1.2 million deaths in 2019 and is one of the leading causes of morbidity and mortality worldwide [1].

At the same time, the formation of a destructive cavity in the lungs is an unfavorable stage in the course and outcome of the disease. Fibro-cavernous tuberculosis (FCT) and complications arising from it, in 75-80% of cases are the cause of death of TB patients [2].

The formation of a cavitary focus of disintegration of specific inflammation in the lungs can occur with the progression of any form of tuberculosis against the background of predisposing conditions, and is associated with treatment failure, which is manifested, among other factors, by delayed conversion of sputum culture, the relapse development and drug resistance [3]. According to data from various sources, the proportion of tuberculosis patients with cavitary foci in the lungs at the time of diagnosis ranges from 29% to 87% [4].

Studies conducted to date show that low weight, diabetes mellitus, history of alcohol abuse and smoking, and a positive cytology result are associated with fibro-cavernous tuberculosis [5].

However, the number of studies devoted to the analysis of factors associated with fibro-cavernous tuberculosis is limited. In this regard, further search for factors associated with this TB form is necessary, which will contribute to a clearer understanding of the pathogenesis of FCT and to ensure proper control of the relevant factors in the management of patients with tuberculosis.

Objective: To identify socio-demographic and clinical laboratory factors associated with fibro-cavernous form of tuberculosis.

Material and methods

Study population

Clinical and laboratory data of 184 patients with pulmonary tuberculosis who were treated at the National

Scientific Center for Phthisiopulmology of the Ministry of Healthcare of the Republic of Kazakhstan were analyzed. The diagnosis of tuberculosis was confirmed by molecular genetic (GeneXpert/Hain-test) and/or bacteriological (BACTEC) methods. All studies were reviewed and approved by the Local Ethics Committee of the Kazakh National Medical University.

The study population is presented in Table 1.

Table 1 Characteristics of TB patients

Parameters		Pulmonary TB N (%)
Total		184
Gender, n (%)	Male	117 (63,6%)
	Female	67 (36,4%)
Age (M+/-m, лет) 37,80±1,05	Up to 40 years old	113 (61,4%)
	Over 40 years old	71 (38,6%)
BMI, n (%)	Normal	148 (80,4%)
	Deficient	36 (19,6%)
Residence	City	120 (65,2%)
	Suburb	64 (34,8%)
Job	In work	43 (23,4%)
	Unemployed	141 (76,6%)
Income	Above the living wage (LW) *	64 (34,8%)
	Below the living wage (LW)	120 (65,2%)
TB contact	Yes	35 (19%)
	No	149 (81%)
HIV status	Postive	11 (6%)
	Negative	173 (94%)
Comorbidities **	No	124 (67,4%)
	Yes	60 (32,6%)
	1 disease	41 (68,3%)
	2 or 3 diseases	17 (28,3%)
	more than 3 diseases	2 (3,4%)
Microscopy n (%)	+1 +2 +3	63 (34,2%)
	Negative	121 (65,8%)
Molecular genetic technique, n (%)	Hain-test and/or G-Xpert***	169 (91,8%)
	Not conducted	15 (8,2%)
Bacteriological technique, n (%)	BACTEK и/или LJ****	134 (72,8%)
	Not conducted	50 (27,2%)
Drug sensitivity, n (%)	Drug sensitive	46 (25%)
	Drug resistant	
(MDR and/or XDR*****)	138 (75%)	
TB type, n (%)	New case	102 (55,4%)
	Relapse	82 (44,6%)
TB form, n (%)	Infiltrative	113 (61,4%)
	Fibrous-cavernous	36 (19,6%)
	Other forms ******	35 (19%)
Duration of current treatment, n (%)	From 1 to 6 months	141 (76,6%)
	From 6 to 12 months	30 (16,3%)
	>1 year	13 (7,1%)

* living wage for 2018

** Concomitant diseases included the following diseases: allergic dermatitis, hepatitis, anemia, bronchial asthma, diabetes mellitus, chronic alcoholism, chronic cholecystitis, chronic obstructive pulmonary disease, chronic pyelonephritis, Crohn's disease, coronary heart disease, hearing loss, salpingo-oophoritis, scleroderma, rheumatoid arthritis

*** Hain-test/G-Xpert – molecular genetic methods for diagnosing tuberculosis

**** BACTEK/LJ – bacteriological methods for diagnosing tuberculosis

***** MDR/XDR – multidrug resistance/extensive drug resistance

****** Other forms include the following forms of TB: caseous pneumonia, empyema, pleurisy, generalized, disseminated tuberculosis, tuberculoma

In 91.8% of patients the diagnosis was confirmed by Hain-test and/or G-Xpert, in 72.8% the diagnosis was also confirmed bacteriologically. At the same time, only in 34.2% of patients the diagnosis was confirmed by microscopy.

In the study group, there were almost 2 times more males than females (63.6% versus 34.4%, respectively). Moreover, 61.4% were patients under the age of 40 years. Almost one fifth of the patients were underweight. With regard to socio-economic status, 76.6% of TB patients were unemployed, and the number of patients with income below the subsistence level was 65.2%. Almost all patients (94%) were HIV negative. Only 19% of patients were able to indicate the presence of TB contact. With regard to the presence of comorbidities, 67.4% of patients had no history of comorbidities, and 32.6% of patients had various comorbidities. Of these, 68.3% of patients had a history of one disease, 28.3% had 2 or 3 diseases, and 3.4% had more than 3 diseases.

As for the TB characteristics, patients with drug-resistant TB prevailed among patients (75%), almost half of the cases (46.6%) were relapses of the disease, while the infiltrative TB prevailed (61.4%). The period from 1 to 6 months of treatment accounted for 76.6% of cases.

Immunochromatographic analysis

To determine specific antibodies to the lipoglycan of M.tuberculosis (MBT), immunochromatographic analysis was performed on the LioDetect TB-ST platform (Lionex GmbH, Germany).

Statistical methods

The obtained data were analyzed using the Microsoft SPSS 23.0 software package. To assess the significance of differences in groups, the Pearson Chi-Square test was used. To determine the factors associated with FCT, a logistic regression analysis was performed in univariable and multivariable models, where unadjusted and adjusted odds ratios (OR), as well as 95% confidence intervals were calculated. In the multivariable model, we included all variables regardless of the p-values identified in the univariable analysis. At $p<0,05$, the differences were considered statistically significant.

Results

Comparative characteristics of patients with infiltrative (IT) and fibro-cavernous (FCT) TB

In the comparative analysis, we included only the infiltrative and fibro-cavernous TB forms, since other forms of pulmonary TB in our study, along with FCT, were also the result of the process progression, and the identification of factors associated with these forms was not part of the research objectives.

The results of a comparative analysis of patients with infiltrative and fibro-cavernous tuberculosis are presented in Table 2.

When comparing age characteristics, a predominance of persons under 40 years of age was revealed in both groups. At the same time, the differences in the groups “under 40 years old” and “over 40 years old” were more pronounced in the IT group (63.7% and 36.3%, respectively), while in the FCT group this difference was less pronounced (52.8% and 47.2%, respectively).

Males also predominated in both groups, however, in the FCT group, there were 5 times more males than females (83.3% versus 16.7%, respectively); in the IT group, there were 1.5 times more males (60.2% versus 39.8%, respectively).

Table 2 Basic characteristics of patients with infiltrative (IT) and fibrous-cavernous tuberculosis (FCT)

Parameter	Infiltrative TB (n=113)	Fibrous-cavernous TB (n=36)	P
Demographics			
Age (years)			
Up to 40 years old	72 (63,7%)	19 (52,8%)	0,242
Over 40 years old	41 (36,3%)	17 (47,2%)	
Gender, n (%)			
Females	45 (39,8%)	6 (16,7 %)	0,066
Males	68 (60,2%)	30 (83,3 %)	
BMI, n (%)			
Normal	99 (87,6 %)	19 (52,8 %)	0,001
Deficient	14 (12,4 %)	17 (47,2 %)	
Residence, n (%)			
City	72 (63,7 %)	22 (61,1 %)	0,920
Suburb	41 (36,3 %)	14 (38,9 %)	
Socio-economic indicators			
Social status, n (%)			
In work	30 (26,5%)	6 (16,7%)	0,2269
Unemployed	83 (73,5%)	30 (83,3%)	
Income, n (%)			
Above the living wage (LW)	41 (36,3 %)	10 (27,8 %)	0,3482
Below the living wage (LW)	72 (63,7 %)	26 (72,2 %)	
TB contact			
Yes	23 (20,4%)	7 (19,4%)	0,920
No	90 (79,6%)	29 (80,6%)	
HIV status			
Positive	5 (4,4%)	3 (8,3%)	0,298
Negative	108 (95,6%)	33 (91,7%)	
Comorbidities			
Yes	42 (37,2%)	19 (52,8%)	0,2835
No	71 (62,8%)	17 (47,2%)	
TB characteristic			
Microscopy			
Positive	40 (35,4%)	19 (52,8 %)	0,063
Negative	73 (64,6 %)	17 (47,2 %)	
Drug sensitivity, n (%)			
Drug sensitive	19 (16,8%)	5 (13,9%)	0,680
Drug resistant (MDR and/or XDR)	94 (83,2%)	31 (86,1%)	
TB type, n (%)			
New case	67 (59,3 %)	7 (19,4 %)	<0,0001
Relapse	46 (40,7 %)	29 (80,6 %)	
Duration of current treatment, n (%)			
From 1 to 6 months	87 (77%)	22 (61,1%)	
From 6 to 12 months	20 (17,7%)	8 (22,2%)	
>1 year	6 (5,3%)	6 (16,7%)	
Results of specific production of antibodies to lipoglycan of MTB			
Positive	30 (26,5%)	29 (80,6%)	<0,0001
Negative	83 (73,5%)	7 (19,4%)	

The number of underweight individuals was significantly higher in the FCT group of compared to the IT group (47.2% and 12.4%, respectively, p=0,001).

There were no differences in the place of residence of IT patients and FCT patients (urban/rural). The unemployed predominated in both groups, while in the FCT group there were 5 times more unemployed (83.3% of the unemployed versus 16.7% of the employed), while in the IT group there were 2.7 times more unemployed (73% unemployed versus 26.5% employed). In terms of income, similar trends were observed. Individuals with incomes below the subsistence minimum predominated in both groups. The FCT group had 2.6 times more people with income below subsistence compared to people with incomes above the subsistence level (72.2% versus 26.8%), while in the IT group this difference was 1.7 times (63.7% versus 36.3%).

There were no differences in the presence of tuberculosis contact and HIV status in both groups. Concomitant diseases in the IT group were 1.7 times less compared to the absence of such (37.2% vs. 62.8%), while in the FCT group, comorbidities occurred in 52.8% of patients.

A positive microscopy result was found in 35.4% of IT patients, while in FCT patients a positive result was found in 52.8% of patients. There were no differences in the frequency of drug-resistant and drug-resistant forms in both groups. However, the recurrence of the disease occurred 2 times more

Table 3 Regression analysis by factors associated with fibrous-cavernous tuberculosis

№	Factors	Unadjusted OR	p	Adjusted OR	p
1	**Gender**				
	Females	reference	reference		
	Males	3,3088 (1,2745- 8,5902)	**0,010**	2.813 (0.935-8.462)	0.066
2	**Age**				
	Up to 40 years old	reference	reference		
	Over 40 years old	1.5712 (0.736- 3.3545)	0,241	1,454 (0,524-4,035)	0,472
3	**BMI**				
	Normal	reference	reference		
	Deficient	6,3271 (2,6746- 14,9673)	**<0,0001**	5,719(2,049-15,965)	**0,001**
4	**Comorbidities**				
	No	reference	reference		
	Yes	1,5125 (0,7092- 3,226)	0,283	1,358 (0,502-3,673)	0,547
5	**Microscopy**				
	Negative	reference	reference		
	Positive	2,0397 (0,9544- 4,3592)	0,063	1,170 (0,432-3,166)	0,758
6	**TB type**				
	New case	reference	reference		
	Relapse	6,0342 (2,4369- 14,9415)	**<0,0001**	3,374 (1,191-9,561)	**0,022**
7	**Duration of current treatment**				
	From 1 to 6 months	reference	reference		
	From 6 to 12 months	1,5818 (0,6155-4,0655)	0,337	1,789 (0,533-6,005)	0,347
	>1 year	3,9545 (1,1623- 13,4547)	**0,030**	4,413(0,927-21,009)	0,062
8	**Drug sensitivity**				
	Drug sensitive	reference	reference		
	Drug resistant (MDR and/or XDR)	1,2532 (0,4318- 3,6371)	0,680	1,070 (0,279-4,094)	0,922
9	**Results of specific production of antibodies to lipoglycan of MTB**				
	Positive	reference	reference		
	Negative	0,3576 (0,1544- 0,8284)	**0,014**	0,354 (0,126-0,995)	**0,049**

often in FCT patients compared with IT patients (80,6% vs. 40,7%, respectively, p<0,0001).

A positive result of specific production of antibodies to lipoglycan of MTB was found in 26,5% of IT patients, while in FCT patients a positive result was found in 80,6% of patients (p<0,0001).

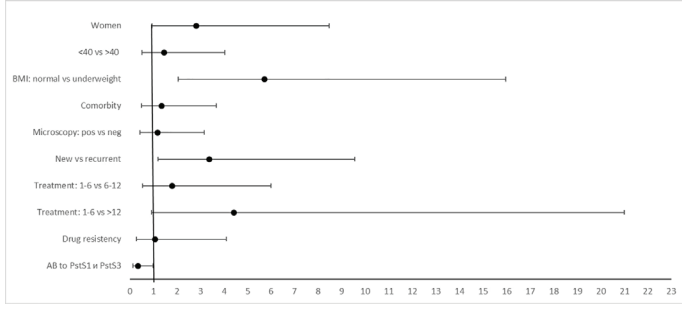
Factors associated with fibro-cavernous form of tuberculosis

The results of the regression analysis are presented in Table 3.

Binaric logistic regression with unadjusted odds ratio showed that male (OR=3.3088, 95% CI: 1.2745 - 8.5902, p=0.010), low BMI (OR=6.3271, 95% CI: 2.6746 - 14.9673, p<0.0001), TB recurrence (OR=6.0342, 95% CI: 2.4369 - 14.9415, p<0.0001), duration of treatment more than 12 months (OR 3.9545, CI: 1.1623-13.4547, p=0.014) were associated with FCT. At the same time, a negative result of specific production of antibodies to lipoglycan of MTB (OR=0.3576 95%, CI: 0.1544 - 0.8284, p=0.014) showed an inverse association with FCT.

We also tested the risk factors identified in the univariable model logistic regression in the multivariate regression model. Multivariate logistic regression analysis confirmed that low BMI (OR=5.719, 95% CI: 2.049–15.965, p=0.001), tuberculosis recurrence (OR=3.374, 95% CI: 1.191–9.561, p=0.022) were significantly associated with FCT. A negative result of specific production of antibodies to lipoglycan of MTB also showed an inverse association with PCT (OR=0.354, 95% CI: 0.126-0.995, p=0,049) (Figure 1).

Figure 1 -Adjusted odds ratio for fibrous-cavernous TB



Discussion

In our study, we found that male sex, low BMI, duration of treatment, recurrence, and increased production of anti-tuberculosis antibodies are factors associated with fibro-cavernous tuberculosis.

With regard to gender, it can be noted that, in general, the incidence of tuberculosis among men is significantly higher than among women, as evidenced by the ratio of men to women in case registration worldwide, equal to 1.7. It is assumed that both gender characteristics of behavior and biological factors associated with sex contribute to this [6].

At the same time, the predominance of men over women is observed in all TB forms.

In our study, multiple logistic regression analysis showed a 2.8-fold predominance of men in the group of FCT compared to women. However, significant differences were not found. The

data obtained by us are consistent with the data of other studies, which show that men are predisposed to such forms as fibro-cavernous, disseminated pulmonary tuberculosis, tuberculous pleurisy, and tuberculosis of the nervous system [7].

In regard to underweight, it can be noted that most studies indicate that low body mass index is a risk factor for active tuberculosis [8]. Moreover, nutritional imbalance can weaken the immune system and affect the outcome of TB treatment [9].

At the same time, the number of studies on the association of reduced weight with the development of fibro-cavernous tuberculosis is limited. Thus, Sun-Hyung Kim et al [5] obtained data similar to our results and showed that low BMI is associated with the risk of developing fibro-cavernous tuberculosis. The authors suggested that this may be due to activation of inflammatory processes. In particular, a reduced BMI has been shown to indicate the presence of nutritional deficiencies and is associated with increased lung inflammation and free neutrophil elastase activity in the lungs [10,11]. It has been suggested that this underlies the association between poor nutritional status and severe lung disease. At the same time, further research is needed to elucidate more precise mechanisms underlying the association between lower BMI and the FCT development. In our study, a low body mass index prevailed 5.7 times in FCT patients with a high level of significance of differences.

We also analyzed the association between the production of antibodies to secretory M. tuberculosis antigens and the FCT development [12].

Analysis of the antibodies production to lipoglycan of MTB antigens indirectly confirmed the hypothesis that in more severe TB forms, including FCT, there is an imbalance between Th1 and Th2 cells [13-16]. In particular, it was found that the cavities formation in TB patients is associated with the predominance of T-helper (Th)2 CD4+ cells in the alveoli [17] and the switching of the immune response to the synthesis of pro-inflammatory cytokines, such as IL-4, IL-5, IL-10 , IL-13. At the same time, switching to Th2 immune response is accompanied by an increase in antibody production [15], and therefore, it has been suggested that there are two types of tuberculosis, reflecting the ability of the immune system to control the antigen. The redirection of the immune response to certain IgG subtypes is accompanied by a decrease in the body's ability to fully eliminate M. tuberculosis. In our study, regression analysis showed that the probability of obtaining a positive result by immunochromatographic analysis of antibody detection in FCT is significantly higher compared to IT (p=0,049). Our data are consistent with the data of other authors, who also revealed an increased production of antibodies in fibro-cavernous tuberculosis [18]. At the same time, the causal relationship between the antibodies level and FCT has not yet been clearly established.

We also found association between the TB recurrence and the FCT. However, despite the fact that our results are consistent with those of Sun-Hyung Kim et al [5], we believe that this association is a reflection of the pathogenesis and course of FCT, which is characterized by a chronic course and a tendency to relapse, and thus, TB recurrence, can rather be considered as a consequence, rather than the cause, of the formation of the FCT.

Thus more studies are needed to clarify the causal association in FCT, both in relation to increased antibody production and the presence of TB recurrence.

We also found a treatment duration of more than 12 months to be almost 4.5 times more common in patients with fibro-cavernous tuberculosis, however, no significant differences were found. These data are also consistent with the data of other authors [5]. For example, it has been shown that refractoriness to treatment leads to the FCT formation [19].

Surprisingly, we did not find an association between the presence of comorbidities and FCT. At the same time, there is sufficient evidence that diabetes mellitus is a risk factor for fibro-cavernous tuberculosis [20,21]. We believe that the lack of association of comorbidities with FCT in our study is due to the fact that the majority of patients in our study group had multiple comorbidities. In this regard, it was not possible to single out a group with the presence of only diabetes mellitus or other concomitant disease. We believe that comorbidity with diseases with multidirectional pathogenesis had a leveling effect on the results of the analysis.

Conclusion

Weight deficiency, increased production of antibodies and disease recurrence are factors associated with fibro-cavernous tuberculosis.

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The association between non-HDL cholesterol and SYNTAX score in premature heart disease

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Abstract

Aim: This study aimed to estimate the association of coronary artery disease complexity with non-HDL-C levels in premature CAD.

Background: Primary prevention has utmost importance in terms of minimizing the number of patients who had premature coronary artery disease (CAD). Non-high density lipoprotein cholesterol (non-HDL-C) contains potentially atherogenic lipoprotein fractions.

Material and methods: Coronary angiographic recordings of two hundred acute coronary syndrome patients were evaluated by two cardiologists. Clinical, demographic and lipid parameters of the patients were compared with SYNTAX score.

Results: Median age of the study group was 41 (18-45) years. One hundred eighty five (90.5%) of them were male, nineteen (9.5%) of them were female. Median SYNTAX score and ejection fraction of the patients were 17 (4.5-39) and 50 (33-68), respectively. SYNTAX score of the male patients was significantly higher compared to females [17 (4.5-39) vs 12 (8-26), p=0.048), similarly, diabetic patients had higher values of syntax score compared to non-diabetic patients [19 (10-39) vs 16 (4.5-37), p=0.005), There were no differences of SYNTAX score with respect to presence of hypertension, smoking status and family history of CAD. There were very strong positive correlation between SYNTAX score and non-HDL-C, TC and LDL-C levels (r=0.958, r=0.946 and r=0.921, respectively, p<0.001 for all). HgA1c levels showed positive correlation, whereas HDL-C showed negative correlation with SYNTAX score (r=0.793 and r=-0.620, respectively, p<0.001 for both).

Conclusion: non-HDL-C was a valuable tool in assessing the complexity of atherosclerotic cardiovascular disease in young patients.

Key words: coronary artery disease, young adult, HDL-C

Introduction

Despite advancements in medical therapy and device industry, cardiovascular diseases have been increasing in young population. In our country, cardiovascular mortality rates of men and women between 45-75 years of age were reported as 0.73% and 0.38%, respectively [1]. Atherosclerosis, which has a complex pathophysiology characterized by dysfunctional immune apparatus, oxidative stress and endothelial dysfunction, is the main cause of coronary artery disease (CAD) [2]. Classical risk factors for CAD plays crucial role in each stage of this process. Several studies have shown that CAD incidence has a positive correlation with total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) and a negative correlation with high density lipoprotein cholesterol (HDL-C). In the past decade, studies about value of lipid fractions for predicting atherosclerosis and coronary events have gained momentum. Lipid measurements such as TC to HDL-C ratio, non-HDL-C, and apolipoprotein-B100 have provided additional prognostic information to measured LDL-C levels [3].

CAD, the incidence of which increases with increasing age, has important genetic and environmental underpinnings [4]. Moreover, the prevalence of premature CAD has steadily risen over the past decades [5]. However, in the literature, there is no consensus about the description of premature CAD. Studies have used the cut-off values of 40 years, 45 years, 50 years and 60 years as the description of premature CAD. Family history of early-onset CAD has been denoted as having a first-degree male relative under the age of 55 years and female relative under the age of 65 years.

SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) score, angiographic grading score based on lesion number, localization, complexity and functional significance, offers guidance to physicians on identification of the most appropriate revascularization strategy [6].

Moreover, it has been shown to have prognostic value in patients who underwent percutaneous coronary intervention [7]. Our aim was to investigate the relation between SYNTAX score and non-HDL-C concentration values and to test whether it has a better predictive value compared to traditional lipid parameters.

Material and methods

For the conduction of this study, data files of patients less than 45 years old who underwent coronary angiography between April 2015 and April 2017 were screened. Patients with prior PCI and/or coronary artery bypass graft surgery, malignancy, creatinine level more than 1.5 mg/dl, thyroid function disorders, statin use, incomplete data were excluded. A total of 200 patients who underwent coronary angiography because of non-ST myocardial infarction (NSTMI), ST-elevation myocardial infarction (STEMI) and unstable angina pectoris (UAP) were enrolled. Demographic and clinical variables including age, gender, hypertension (HT), diabetes mellitus (DM), smoking status, familial history of CAD were recorded. HT was defined as systolic and/or diastolic blood pressure greater than 140/90 mmHg or use of antihypertensive drugs. DM was defined as fasting blood glucose level more than 126 mg/dl or use of antidiabetic medication. All biochemical analysis results were obtained from hospital data system. Biochemical and complete blood count results of the patients during hospital admission were recorded. Venous blood samples were taken for the analysis of fasting LDL-C, HDL-C, triglyceride (TG), TC, HbA1c during first 24 hours of hospitalization. Non-HDL-C were calculated by subtracting HDL-C from TC. If the patients had TG levels more than 400 mg/dl, direct LDL-C measurements were recorded.

All patients underwent echocardiographic examinations with the use of Vivid 9 device which had a sector transducer of 3.2 MHz (Horten, Norway). Echocardiographic assessments were in compliance with current guidelines [8]. Coronary angiographic recordings of the patients were evaluated by two invasive cardiologists. SYNTAX score of each patient was calculated by using Syntax Score version 2.28 from the website www.syntaxscore.com [5]. Since the prognostic value of SYNTAX score in STEMI patients was demonstrated, those patients were not excluded from the study [9]. During evaluation of patients with STEMI, infarct-related artery was considered to be occluded less than 3 months and scored as such.

Statistical analysis

Normality of the data was assessed by Kolmogorov-Smirnov test. Since all the data showed non-normal distribution, they were expressed as median (minimum-maximum). For the comparison of two groups Mann-Whitney U test was used. Comparison of categorical variables was done by Chi-square test. Correlation analysis was done by Spearman correlation analysis. P value of less than 0.05 was considered as significant. All of the analyses were done by SPSS (Statistical Packagefor Social Science for Windows) 22.0 program.

Results

Median age of the study group was 41 (18-45) years. One hundred eighty five (90.5%) of them were male, nineteen (9.5%) of them were female. Clinical characteristics of the study population are given in Table 1. Median SYNTAX score and ejection fraction of the patients were 17 (4.5-39) and 50 (33-68), respectively. SYNTAX score and biochemical variables of the patients are given in Table 2. SYNTAX score of the male patients was significantly higher compared to females [17 (4.5-39) vs 12 (8-26), p=0.048), similarly, diabetic patients had higher values of syntax score compared to non-diabetic patients [19 (10-39) vs 16 (4.5-37), p=0.005), There were no differences of SYNTAX score with respect to presence of hypertension, smoking status and family history of CAD.

Table 1 Clinical characteristics of the study population

Age (years) (median, min-max)		41 (18-45)	
Gender (n, %)	Male	181	90,5%
	Female	19	9,5%
Smoking (n, %)		126	63,0%
Hypertension (n, %)		30	15,0%
Diabetes mellitus (n, %)		51	25,5%
Family history of CAD (n, %)		36	18,0%

CAD: Coronary artery disease.

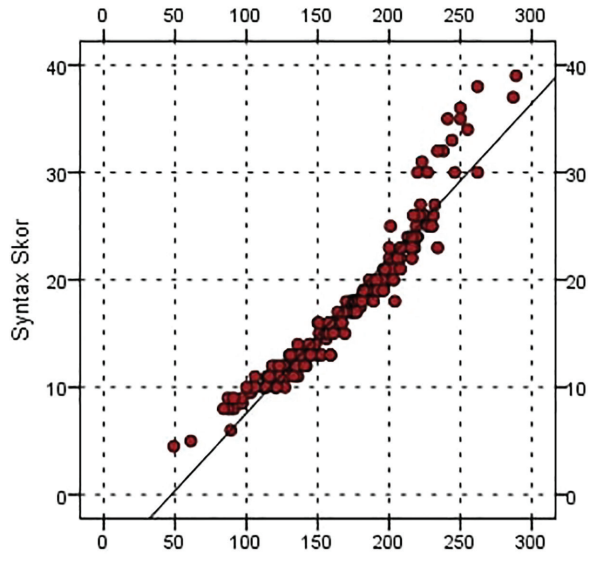
Table 2 SYNTAX score, EF and biochemical variables of the study population

	Min	Max	
Median			
SYNTAX score	4.5	39.0	17.0
Ejection Fraction (%)	33.0	68.0	50.0
HgA1c	4.1	12.6	6.7
Non-HDL-C (mg/dl)	49.0	289.0	169.5
Total Cholesterol (mg/dl)	123.0	326.0	212,0
HDL-C (mg/dl)	23.0	76.0	42.0
LDL-C (mg/dl)	38.0	273.0	152.0
Triglyceride (mg/dl)	35.0	1024.0	138.0

HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol.

There were very strong positive correlation between SYNTAX score and non-HDL-C, TC and LDL-C levels (r=0.958, r=0.946 and r=0.921, respectively, p<0.001 for all). HgA1c levels showed strong positive correlation, whereas HDL-C showed strong negative correlation with SYNTAX score (r=0.793 and r=-0.620, respectively, p<0.001 for both). We found weak positive correlation between TG levels and SYNTAX score (r=0.354, p<0.001). Correlation between SYNTAX score and non-HDL-C is shown in Figure 1.

Figure 1 - Correlation of SYNTAX score with non-HDL-C



Discussion

Premature CAD imposes great burden to patients, families and society. Since the patients are younger, longer sequelae of CAD could hamper quality of life. Hence, primary prevention with risk factor modification has important role in reducing the incidence and prevalence of premature CAD.

Hoit et al. stated that premature CAD is more frequent in males [10]. According to Joshi et al. females had first acute coronary syndrome episode 5.6 years later than their male counterparts [11]. Frequency of premature CAD in males has been reported to be ranged from 79% to 95% [10, 12-14]. One study showed that gender did not have any effect on long term prognosis of acute coronary syndrome [15]. Whereas another study suggested that male patients had more complex CAD in contrast to females. Our study population mainly composed of male patients and they have significantly higher SYNTAX score compared to females.

Prevalence of hypertension in patients with CAD less than 55 years of age has been found as 38.1% [16]. Another study found that 30.8% of acute coronary syndrome patients had hypertension [17]. An Indian study showed that prevalence of hypertension in male CAD patients under the age of 55 years and female CAD patients under the age of 65 years was 49% [18]. The prevalence of HT in our study was less than the aforementioned studies. Moreover, we did not find any difference in SYNTAX scores of patients with or without hypertension. Previous studies reported diabetes mellitus frequency between 14.7% to 44% in premature CAD patients [16-18]. In our study the frequency of DM was 25.1%. Diabetic patients had higher SYNTAX scores indicating more complex atherosclerotic disease.

The incidence of premature CAD has been increasing in developing countries. In INTERHEART study from 52 countries, median age of first myocardial infarction in South Asian countries was significantly lower than the others [19]. In that study, smoking, apolipoproteinB100 to apolipoprotein A-1 ratio, diabetes mellitus, hypertension, abdominal obesity, diet, physical activity and alcohol consumption were the predictive factors of acute coronary syndrome. Smoking was found to be one of the modifiable risk factor for premature CAD. In the literature, prevalence of smoking in premature CAD patients ranges from 51% to 89% [12, 19]. Our results were in concordance with the previous reports with a percentage of 63%. Xiong et al. found that smoking ratio was significantly higher in patients with high SYNTAX score [20]. However, we did not find any difference in SYNTAX score with respect to smoking status.

Family history of CAD is another risk factor for atherosclerotic cardiovascular disease. Several studies reported different values ranging from 41% to 71% for the frequency of family history of CAD [21, 22, 17]. According to Hoit et al.'s study, premature CAD patients had positive family history twice as high as compared to older CAD patients [10]. Our results were lower than the previous reports with a frequency of 18%.

Hyperlipidemia frequency in premature CAD patients differs in the literature. Aggarwal et al. found that frequency of dyslipidemia and low HDL-C concentration levels in premature CAD patients were 91% and 68.9%, respectively [23]. Similarly, Chia et al. revealed that younger CAD patients had higher frequency of hyperlipidemia compared to older ones [17]. On the contrary, Matsis et al. showed that patients with premature CAD had lower risk factors in contrast to older patients. According to their results young patients had at most one risk factor for CAD and they were considered as low risk subjects until the index event [24]. Frequency of dyslipidemia was 73% in our patients. Since we did not include the patients who were under lipid lowering therapy, the frequency of dyslipidemia was expected to be higher than our findings.

Studies about the association of premature CAD with lipid subfractions revealed conflicting results. Goliasch et al. compared the different lipid subfractions using a sample of 302 premature CAD patients [25]. In that study, association between premature CAD and non-HDL-C was found to be stronger compared to very low density lipoprotein cholesterol (VLDL-C), LDL-C, large intermediate density lipoprotein cholesterol (IDL-C), large LDL-C, and intermediate LDL-C. They did not find any correlation between premature myocardial infarction and small-dense LDL-C. 94 Shahid et al. found a positive correlation between low HDL-C concentration levels and premature myocardial infarction [26]. In Quebec Cardiovascular Study, small-dense LDL-C had a predictive value for premature atherosclerotic cardiovascular disease [27]. Rallidis et al. compared 100 premature CAD patients with 100 controls and found that among other lipid subfractions including TC, LDL-C, TG, apoB, lipoprotein(a), apoA; non-HDL-C had the highest predictive value for the premature CAD [28]. In our study, non-HDL-C showed very strong correlation with the extent of CAD in young acute coronary syndrome patients.

In conclusion, in premature CAD patients complexity of the atherosclerotic disease had very strong correlation with non-HDL-C concentration levels. Non-HDL-C might predict atherosclerotic cardiovascular disease better than other lipid parameters. It could be used as a treatment target in young patients.

Limitations of our study are: (1) It was a single center study, (2) sample size was relatively low, (3) Body mass index and waist circumference could not measured because of lack of data, (4) Incidence of familial hyperlipidemia could not determined.

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Operative management of intracerebral hemorrhage: 3 year experience in multidisciplinary city hospital

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Abstract

Hemorrhagic stroke is a hemorrhage in the brain parenchyma or ventricles resulting from a rupture of an intracerebral vessel or increased permeability of its wall. Intracerebral hemorrhage is a serious medical and social problem associated with high mortality and disability worldwide. Our study aimed to analyze the operative treatment results of patients with hemorrhagic stroke to determine the factors influencing mortality.

Key words: hemorrhagic stroke, intracerebral hemorrhage, surgical treatment, stroke mortality.

Introduction

Hemorrhagic strokes account for about 20% of all strokes and are one of the leading causes of death and disability worldwide [1-3]. Even though various drugs are currently being developed to enhance neuroprotection and neuroplasticity, which can be used in combination with rehabilitation to accelerate recovery, surgical and conservative treatment in the acute period remains an important integral component of the treatment of hemorrhagic stroke [4, 5]. The decision to operate is a controversial issue: early surgical treatment to limit brain compression and blood toxicity may limit secondary neuronal damage, but in cases with ongoing bleeding, the risk of surgery may be higher [6].

Aim. Analysis of the surgical treatment of patients with hemorrhagic stroke based on the Multidisciplinary city hospital №1 in Nur-Sultan hospitalized from January 2019 to December 2021 and determine factors influencing the worst outcome.

Material and methods

This is a retrospective analytical study. The study included 63 patients with intracerebral hemorrhage hospitalized at the Multidisciplinary city hospital №1 in Nur-Sultan from January 2019 to December 2021 on an emergency basis. After hospitalization, there was a conjoint decision-making process that included evaluation of neurologic status (Glasgow coma scale), CT data (localization, hematoma volume), and treatment strategy. This process was also influenced by the medical history of the patient, as many of them had concurrent diseases in other systems (cardiovascular, hematologic, gastrointestinal, genitourinary). All data were collected by different authors and double-checked for accuracy. There were strict inclusion criteria: any hospitalized patient with intracerebral hemorrhage in the Multidisciplinary city hospital №1 in Nur-Sultan from January 2019 to December 2021. Exclusion criteria were: patient did not receive surgical treatment and, for some reason, the patient's hematoma volume was not described in any part

of the medical history. All types of operations were divided into three types: Arendt drainage placement, hematoma evacuation by different methods (trephination, endoscopic, aspiration assisted, or simply by syringe), and decompressive craniectomy. For better statistical distribution all localizations were anatomically divided into supratentorial and infratentorial. Supratentorial localization was further investigated by ventricular perforation. The time from admission to the operation was estimated as hours and was divided into intervals: the first three hours, the first 24 hours, and more than 24 hours. After admission, consent to participate in further studies was obtained from patients, or closest relatives if the patient was not able to understand and sign proper papers. Ethical committee approval was not required in this retrospective analysis.

Statistical analysis of patients was made by Jamovi. Student's t-test and Mann-Whitney U test were used to determine significance, and p< .001 was considered significant.

Results

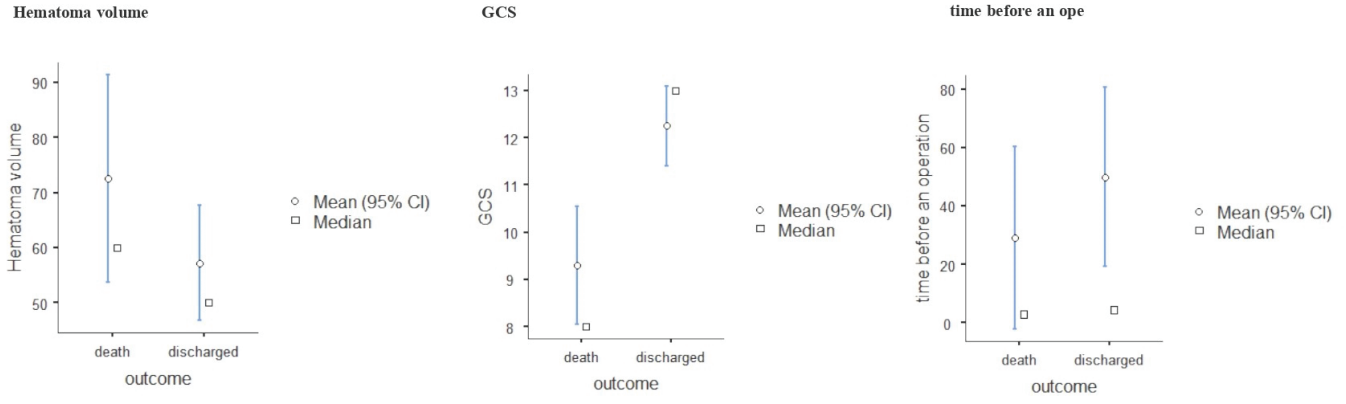
63 patients met all inclusion criteria. 30 (47,6%) male and 33 (52,4%) female patients. The age of the patients ranged from 25 to 80 years; the average age was 54.66±11.9 years. The hematoma volume ranged from 16 to 219 cm3, averaging 63.7±39.56 cm3. In most cases (85,7%), the hemorrhagic focus was located in the cerebral hemispheres, which was considered supratentorial localization, and the remaining 14,7% were in the brainstem, and cerebellum, defined as infratentorial. 38% had a ventricular perforation on the initial presentation.

Figure 1 - Correlation between hematoma volume, CGS, time before operation and an outcome.

Independent Samples T-Test

		statistic	df	p
Hematoma volume	Student's t	1.482 [a]	61.0	0.143
	Mann-Whitney U	423		0.384
GCS	Student's t		61.0	<.001
	Mann-Whitney U			<.001
time before an operation	Student's t	-0.913	61.0	0.365
	Mann-Whitney U	368		0.098

[a] Levene's test is significant (p < .05), suggesting a violation of the assumption of equal variances



Decompressive craniectomy was performed in 32 cases (50,7%), Arendt placement in 8 patients (12,6%), and the rest 23 (36,7%) patients had the hematoma evacuation. In the period of up to 3 hours, operations were performed in 33 (52,4%) patients, 17 patients (26,9%) had an operation in the first 24 hours after admission, and 13 patients (20.6%) had an operation delayed for more than one day. Among all treated patients, lethality in the hospital was 42.8% of cases. 11 patients (17.4%) required tracheostomy. In this study, the initial Glasgow coma scale was the significant predictor of the outcome (Figure 1). It is possible to see the correlation between discharged patients with higher Glasgow coma scores on the initial presentation in Figure 2. Hematoma volume and Glasgow coma scale and operation types are demonstrated in Figure 2. Hematoma volume and Glasgow coma scale and time before an operation and relation for outcomes are demonstrated in Figure 3. Time before an operation and relation to the different localization and operation types are demonstrated in Figure 2. An assessment of the relationship of mortality with the gender and Glasgow coma scale is demonstrated in Figure 3.

Discussion

Despite notable advances in surgical technique and understanding of the mechanisms of secondary brain injury, the prognosis of intracerebral hemorrhage remains unfavorable [7]. The mechanisms responsible for brain damage within a cerebral hematoma are numerous and complex: initially, there is a direct effect of acute bleeding into the brain parenchyma, causing a mass effect, which is subsequently accompanied by hemorrhage arrest in about two-thirds of patients. However, in the remaining third of patients, the hematoma continues to grow during the first 24 hours, which contributes to an additional mass effect, midline shift and leads to further neurological deficit and an increased risk of adverse outcomes [8-10].

Hematoma volume is a known predictor of an outcome [13]. Hematomas larger than 30 ml are statistically associated with poor results. With a hematoma volume of more than 60 ml with a level of consciousness of fewer than 8 points, the predicted mortality within 30 days was 90%. Volumetric hematomas (≥150 ml) usually lead to death in patients due to a sharp increase in intracranial pressure and, as a result, a decrease in cerebral

Figure 2 - Correlation between hematoma volume, CGS, time before operation and anatomical localization and an outcome

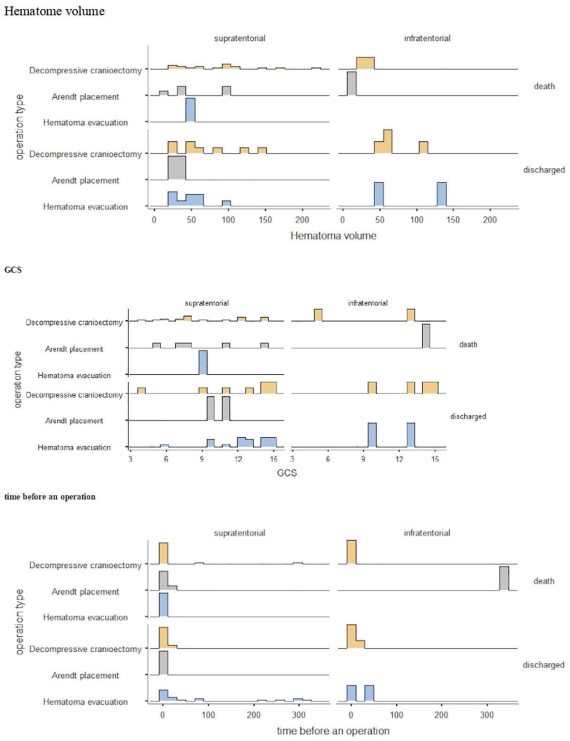
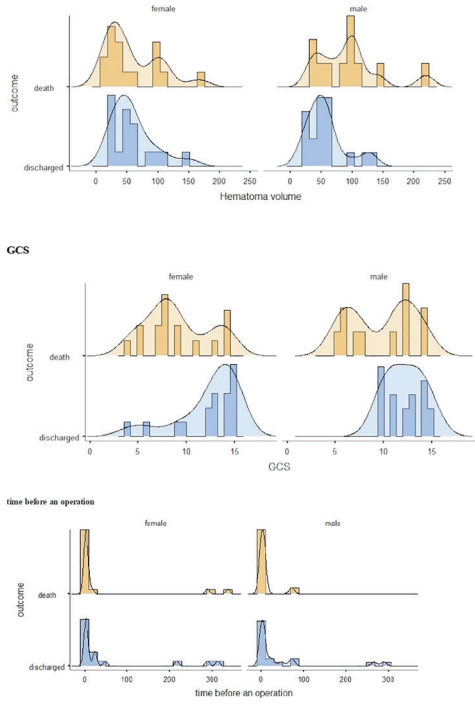


Figure 3 - Correlation between hematoma volume, CGS, time before operation and gender and an outcome



perfusion pressure [8, 15]. Surgical drainage of hematoma has several theoretical advantages, such as prevention of mass effect and dislocation syndrome, reduction of intracranial pressure, reduction of excitotoxicity, and neurotoxicity of blood products. Surgical treatment of intracerebral hematomas includes decompression craniectomy with or without hematoma evacuation, craniotomy with hematoma evacuation, hematoma drainage through a trephine hole, installation of a ventricular drain, and other minimally invasive techniques [8, 17]. Surgical evacuation of the hematoma is considered in patients with large volumes of hemorrhage with breakthrough into the ventricles to prevent compression of the brainstem and subsequent complications. In cases of obstructive hydrocephalus caused by displacement and occlusion of the III-IV ventricles or the Sylvian aqueduct, as well as their tamponade, ventricular drainage is indicated [1, 16]. The Surgical Trial in Intracerebral Hemorrhage (STICH) I and II, a large randomized clinical trial evaluating early surgery versus conservative treatment or delayed surgery, showed a modest benefit in early mortality but no clear benefit in long-term outcome after removal of hematoma in supratentorial intracerebral hemorrhage [18, 19]. Current guidelines [20] state that decompression craniotomy, with or without hematoma evacuation, can reduce mortality in patients with supratentorial hematomas who are comatose and have large hematomas with significant midline displacement or have increased intracranial pressure that is resistant to medical treatment. A case series showed that patients with a Glasgow Coma Score greater than 6 and a hematoma volume of fewer than 50 ml who underwent minimally invasive surgery had better functional outcomes and a shorter length of stay in the intensive care unit compared to traditional craniotomy [16]. Minimally invasive surgery, on the other hand, requires proper time and patient selection to be performed [14]. However, larger randomized controlled double-blinded investigations should be performed to indicate better outcomes.

It is unclear whether ICH is related directly to COVID-19 or reflects expected comorbidity and/or complications observed in severely ill patients [11,12]. Our series of patients included those hospitalized during the strict quarantine, and mortality was not higher than reported in the literature [11]. But it is clear that survival chances significantly decrease in case of acute COVID-19 infection [12].

Although it is suggested that early intervention in acute hemorrhagic stroke is not considered to increase survival rates [14], the sign of acute cerebral edema on initial CT scans prompted sooner operation in our series of patients. Delay in operation in our series of patients was mainly caused by the existence of other medical conditions, and required stabilization first. According to some studies, risk of the lethal outcomes is higher in case of lower Glasgow coma scales on initial presentation in hemorrhagic stroke [21, 22]. Given this fact, our team, if possible, carried out surgical treatment even with a slight decrease in the level of consciousness. A wait-and-see tactic was adopted in cases of unstable hemodynamics, while CT monitoring of the size of the hematoma in dynamics was carried out. Currently, an ongoing prospective study with conservative treatment as a control group is in our consideration.

Conclusion

Despite the multimodal approach, the development of surgical techniques and equipment, and the selection of optimal conservative therapy - the question of determining the tactics for managing and treating hemorrhagic strokes is still controversial. Hematoma volume certainly plays a significant role in the higher mortality rates. Nevertheless, our experience shows patients with a worse initial Glasgow coma scale will have worse outcomes. Multicenter randomized double-blinded studies should be performed to see clearer correlation.

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The effect of inflammatory markers on the CORADS degree and the effects of treatments on RT-PCR test results in COVID-19

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Abstract

Objective: There is still no diagnosis method with high sensitivity and specificity for COVID-19. Patient complaints, real-time reverse transcription-polymerase chain reaction (RT-PCR), inflammatory markers, clinical prognosis, and the degree of involvement in the chest CT, if necessary are evaluated in an effort to make a diagnosis. Delays in diagnosis have led to a rapid spread of the disease. This study aims to evaluate the effectiveness of the inflammatory markers and to determine the follow-up process of the patients by assessing the impact of the treatments administered on RT-PCR test results.

Material and methods: Files of 150 patients monitored in the wards with suspected COVID-19 are analyzed retrospectively. Patients were selected among those who underwent laboratory tests, RT-PCR testing and Thoracic CT within the first 24 hours of admission. Patients were divided into 5 groups based on the severity of involvement in Thoracic CT. Inflammatory markers were compared among the groups. Impact of the administered treatments on follow-up RT-PCR test results was evaluated.

Results: Studied inflammatory markers were in normal ranges and similar across all CORADS groups. Only the C-Reactive Protein (CRP) and Ferritin levels were showing an increase in accordance with CORADS severity. Mean time to testing negative on RT-PCR was 10 days across all treatment groups. Times to testing negative among patients receiving other treatments were similar.

Conclusion: Among the inflammatory markers, CRP and Ferritin values are correlated with CORADS severity. Administered COVID-19 treatments have similar impact on RT-PCR test results.

Key words: COVID-19, RT-PCR, coronavirus, CORADS

Introduction

Declared as a global health problem by World Health Organization (WHO), the novel coronavirus (COVID-19), SARS-CoV-2, emerged in Wuhan, China [1,2]. While COVID-19 may have an asymptomatic prognosis, it may also start with a dry cough, fever, severe headache, fatigue, rapidly progress to acute respiratory distress syndrome (ARDS) and therefore acute respiratory failure.

Leukocytosis, lymphopenia, thrombocytopenia, and high inflammatory markers negatively affect the process (IL-6, ferritin, ESR) [3,4]. The entire world is struggling to develop tests for rapid detection of the SARS-CoV-2 virus, to find the appropriate treatment for the infected people, and to control the spread of COVID-19 by developing a vaccine.

Quantitative reverse transcription-polymerase chain reaction (RT-PCR), thoracic CT scan, and inflammatory markers are used for virus detection, all

of which have unknown precision [5-7]. The sensitivity of RT-PCR testing is approximately 70-75% [8]. A negative test result does not rule out COVID-19 [9]. The latest studies claim that chest CT scanning detected the disease with high sensitivity even in RT-PCR negative patients [10]. A treatment model that could be considered effective is yet to be established. There are some medications currently administered, whose clinical trials are still underway for the prevention of viral replication and the damage caused by the disease [11].

During a pandemic, determining the etiological agent and immunological effects is the highest priority [12]. Changing characteristics of the pathogen since the beginning of the COVID-19 pandemic makes the diagnosis harder. In a pandemic, detecting and isolating the infected people and beginning treatment is the main rule in stopping the spread of the disease. In this paper, we aimed to evaluate the coherence of inflammatory markers and chest CT involvement, aside from RT-PCR and to determine the impact of the types of administered treatments on the RT-PCR test results [13].

Material and methods

This is a single-center, retrospective study involving 150 patients who were followed up and treated in Eskişehir City Hospital with suspected COVID-19 between May and August 2020. Admission criteria were fever, dyspnea, tachypnea, and poor general condition. Patients over 18 years of age, who were scanned with Thoracic Computed Tomography (CT) in the first 24 hours and diagnosed with 2019-nCoV disease according to the WHO's provisional guidelines, were randomly selected according to the order of admission. Those that were admitted to ICU upon worsening medical condition during the following-up and those who died were not included in the study. Peripheral blood samples and reverse transcription-polymerase chain reaction (RT-PCR) swab sample from oropharynx and nasopharynx were obtained from all patients at the time of admission. Patients' laboratory tests obtained at the time of admission, radiological images and medical records were analyzed retrospectively. Epidemiological, demographic, clinical, laboratory, management, and outcome data were obtained from the medical records of the patients. COVID-19 Lung Imaging Reporting and Data System (CORADS) developed by the Dutch Radiological Society was used in the classification of radiological images. CORADS is a scale that evaluates the severity of pulmonary involvement of COVID-19 from very low (CORADS 1) to very high (CORADS 5) [14].

Sociodemographic and categorical variables were expressed as frequency and percentage. Continuous variables were expressed using mean, standard deviation, median, minimum, and maximum values. Obtained results were expressed as means and standard deviations. Shapiro-Wilk test was utilized as the test of normality. An analysis of variances was used in order to evaluate the differences between groups and multiple comparisons were evaluated using the Kruskal-Wallis test. The value of $p<0.05$ was considered as statistically significant. IBM SPSS Statistics 25 software was used for the analysis.

Ethics

The study was approved by the relevant Institutional Review Board with the decision # 35 (Date: 29.09.2020). Written informed consent was obtained from the patient(s) or their legally authorized caregiver(s) for the publication of their anonymized information in this paper.

There was no person or institution financing the study. Relevant authors had full access to all data in the study and had final responsibility to submit for publication.

Results

150 patients admitted with clinically suspected COVID-19 were included in the study. Diagnosis of SARS-CoV-2 infection was verified with a positive real-time reverse transcription test (RT-PCR) result in 91 (60.7%) patients. RT-PCR tests were negative for 59 (39.3%) patients. Patients were divided into five groups according to the CORADS classification. Main characteristics of the study population according to the CORADS classification is shown in Table 1: In almost all CORADS groups, the number of male patients was higher. Only CORADS 5 group included more female patients. Mean age of the patients was 54.63±17 (p=0.064). The rate of testing negative in the first RT-PCR (RT-PCR 1) for the patients with CORADS 1 involvement was 71.4%. As the CORADS severity increased, the rate of testing negative in RT-PCR 1 test decreased. Positive RT-PCR 1 test result had a significant difference across all groups (p=0.020). CORADS 3 involvement in non-chronic disease was found to have the highest involvement and CORADS 5 involvement was the lowest. Presence of diabetes mellitus (DM) (%16), hypertension (%14), chronic obstructive pulmonary disease (COPD) (%5,3) and coronary artery disease (CAD) (%4,6) were found to be the comorbidities most frequently correlated with COVID-19. DM patients were the ones most often using Oral Antidiabetic Drugs, while hypertension patients were the ones most often using Angiotensin converting-enzyme inhibitors (ACEI) containing Calcium Channel Blockers (CCB) or Angiotensin Receptor Blockers (ARB). Inflammatory markers examined were within normal limits in all CORADS groups. In the CORADS 1 group, C-Reactive protein (CRP) and ferritin levels were found to be high even if there was no lung involvement. It showed a progressive increase as the severity of lung involvement increased. No distinctive feature was detected in the laboratory data of the patients, which were examined at the time of admission. This is shown in Table 2. Antiviral and various antibiotic treatments were administered to the patients according to the severity of their clinical condition. A second RT-PCR (RT-PCR 2) was obtained from those with improving clinical status after treatment initiation. 80 (87.9%) patients with a positive first RT-PCR result tested negative. 7 (11.7%) patients with a negative first RT-PCR result tested positive following the treatment. Those who received ceftriaxone and floxacin combination therapy became negative in 8 days, and those who received teicoplanin in 14 days. Those who received oseltamivir treatment became negative in 11 days, those who received Favipiravir treatment became negative in 10 days. Those who did not receive any treatment also became negative in an average of 10 days. The mean time to test negative was 10 days in all treatment groups. Times to test negative were similar among patients receiving other treatments. The types of treatment applied and the change in RT-PCR result according to the treatment are shown in Table 3.

Discussion

COVID-19 pandemic is still continuing all over the world with all its obscurities. Scientists are trying to reach a common consensus regarding diagnosis and treatment. However, the constantly evolving characteristics of the virus are making this harder. There is still no diagnosis method with high sensitivity and specificity for this disease. It is diagnosed based on patient

Table 1 Key Features of the Working groups

PATİENTS		CORADS1 n(%)	CORADS2 n(%)	CORADS3 n(%)	CORADS4 n(%)	CORADS5 n(%)	P Value
Age (year, Mean ±SD)		52±20	55±17	53±17	57±17	55±19	0,064
Sex	Male n(%)	15(%71,4)	22(%57,9)	29(%65,9)	16(%53,3)	7(%41,2)	0,301
	Female n(%)	6(%28,6)	16(%42,1)	15(%34,1)	14(%46,7)	10(%58,8)	
RT-PCR1 n(%)	positive	6(%28,6)	24(%63,2)	31(%70,5)	18(%60,0)	12(%70,6)	0,020
	negative	15(%71,4)	14(%36,8)	13(%29,5)	12(%40,0)	5(%29,4)	
RT-PCR2 n(%)	positive	2(%9,5)	2(%5,3)	4(%9,1)	5(%16,7)	5(%29,4)	0,107
	negative	19(%90,5)	36(%94,7)	40(%90,9)	25(%83,3)	12(%70,6)	
Co-morbidity n(%)	None	10(%47,6)	21(%55,3)	26(%59,1)	14(%46,7)	7(%41,2)	0,078
	Diabetes	2(%9,5)	9(%23,7)	4(%9,1)	8(%26,7)	1(%5,9)	
	Hypertension	5(%23,8)	5(%13,2)	7(%15,9)	1(%3,3)	4(%23,5)	
	Heart Diseas	0(%0,0)	1(%2,6)	4(%9,1)	1(%3,3)	1(%5,9)	
	Renal Failure	0(%0,0)	0(%0,0)	0(%0,0)	2(%6,7)	0(%0,0)	
	COPD*	2(%9,5)	1(%2,6)	1(%2,3)	1(%3,3)	3(%17,6)	
	ASTHMA	0(%0,0)	0(%0,0)	0(%0,0)	2(%6,7)	1(%5,9)	
	Thyroiditis	0(%0,0)	0(%0,0)	1(%2,3)	0(%0,0)	0(%0,0)	
	Epilepsy	0(%0,0)	1(%2,6)	1(%2,3)	1(%3,3)	0(%0,0)	
	Alzheimer's	1(%4,8)	0(%0,0)	0(%0,0)	0(%0,0)	0(%0,0)	
	Lung Cancer	1(%4,8)	0(%0,0)	0(%0,0)	0(%0,0)	0(%0,0)	
Diabetes Medicine n(%)	None Diabetes	19(%90,5)	29(%76,3)	41(%93,2)	22(%73,3)	15(%88,2)	0,120
	Oral Antidiabetic	2(%9,5)	8(%21,1)	3(%6,8)	8(%26,7)	1(%5,9)	
	İnsülin	0(%0,0)	1(%2,6)	0(%0,0)	0(%0,0)	1(%5,9)	
Hyperten-sion (HT) Medicine n(%)	None HT	14(%66,7)	26(%68,4)	34(%77,3)	22(%73,3)	13(%76,5)	0,354
	ACEI/ARB+			6(%13,6)	3(%10,0)	0(%0,0)	
	CCB**	2(%9,5)	8(%21,1)				
	ACEI/ARB	3(%14,3)	2(%5,3)	4(%9,1)	2(%6,7)	1(%5,9)	
	BETA-BLOKÖR	1(%4,8)	0(%0,0)	0(%0,0)	0(%0,0)	1(%5,9)	
	CCB	1(%4,8)	2(%0,0)	0(%0,0)	3(%10)	2(%11,8)	

ANOVA test was used to evaluate the comparison between groups.
* COPD: Chronic Obstructive Pulmonary Disease.
* * ACEI/ARB+CCB: Angiotensin Converting Enzyme İnhibitor/Angiotensin Receptor Blocker+ Calcium Channel Blocker

Table 2 Laboratory Characteristics of study groups

	CORADS				
	CORADS1 Mean ±SD	CORADS2 Mean ±SD	CORADS3 Mean ±SD	CORADS4 Mean ±SD	CORADS5 Mean ±SD
Glucose(mg/dL)	109 ±32	140 ±78	119±45	149 ±92	140 ±71
Serum Ürea Nitrogen(mg/dL)	13 ±4	15 ±7	17 ±8	18 ±11	19 ±11
Alanine Transaminase(u/L))	24 ±23	31 ±31	28 ±19	23 ±15	21 ±12
Aspartate Transaminase(u/L)	27 ±18	33 ±20	32 ±20	24 ±10	26 ±15
Lactate Dehydrogenase(mg/dL	185 ±41	208 ±83	217±93	200±75	213 ±60
White Blood Cell(WBC)(x109/L)	7,9 ±3,3	6,4 ±3,2	6,8±2,9	7,3 ±3,3	6,7 ±2,8
Absolute Neutrophil Count(x109/L)	5,2 ±2,5	4,2 ±2,4	4,7±2,7	5,2 ±3,2	4,9 ±2,4
Absolute Lymphocyte Count(x109/L)	1,6 ±0,6	1,5 ±1	1,4±0,6	1,5 ±0,7	1,3 ±0,5
Platelets (x109/L)	234 ±78	206 ±62	213±67	207 ±99	223 ±77
Neutrophil Lymphocyte Range	4,1 ±3,3	5,5±12,2	4,3±4,3	4,8 ±5,8	4,6 ±3,8
Platelets Lymphocyte Range	172,3±82,6	249,2±376,5	181,8±99,8	190,5±238,1	203,3 ±109,1
Hemoglobin (g/dL)	14,1 ±2	13,8 ±1,7	14,0 ±1,9	13,8 ±1,7	13,1 ±1,3
Hematocrit(g/ dL)	42,4 ±5,6	41,4 ±4,6	41,9 ±5,1	41,3 ±4,5	39,3 ±3,7
C-Reactive Protein(mg/ dL)	24,9 ±49,4	40,8 ±77,5	32,9±41,9	38,9 ±63,8	63,2 ±67,6
Troponin I(pg/ml)	6,2 ±6,7	10,4 ±11,8	10,6±17,2	7,1 ±7,3	4,4 ±7,4
Creatine kinase MB (CK-MB)(ng/ml)	2,1 ±3,5	1,9 ±2,4	1,3 ±1,1	7,1 ±7,3	4,4 ±7,4
D-dimer (mg/ml)	0,7 ±0,7	0,9 ±0,9	0,6 ±0,5	0,8 ±0,7	0,8 ±0,9
Ferritin(ng/ml)	236 ±379	241 ±232	261 ±186	284 ±161	274 ±236

* D-dimer results by coagulometric method.

Table 3 Types of treatment applied and RT-PCR change

		RT-PCR1		RT-PCR2		GÜN
		Positive n(%)	Negative n(%)	Positive n(%)	Negative n(%)	Mean
Chloroqui-ne n(%)	Not use	24(%26,4)	7(%11,9)	8(%44,4)	23(%17,4)	9
	Use	67(%73,6)	52(%88,1)	10(%55,6)	109(%82,6)	10
	P Value	0,032		0,008		
Azithromy-cin n(%)	Not use	47(%51,6)	26(%44,1)	12(%66,7)	61(%46,2)	9
	Use	44(%48,4)	33(%55,9)	6(%33,3)	71(%53,8)	10
	P Value	0,364		0,103		
Anti-viral Treatment n(%)	Not use	40(%44)	27(%45,8)	6(%33,3)	61(%46,2)	10
	Oseltamivir	13(%14,3)	25(%42,9)	4(%22,3)	34(%25,7)	11
	Favipiravir	38(%41,8)	7(%11,9)	8(%44,4)	37(%28)	10
	P Value	0,000	0,297			
Antibiotic Treatment n(%)	Not use	34(%37,4)	21(%35,6)	5(%27,8)	50(%37,9)	10
	Teicoplanin	2(%2,2)	1(%1,7)	0(%0,0)	3(%2,3)	14
	Ceftriaxone+ fourth-generation fluoroquinolone	5(%5,5)	5(%8,5)	0(%0,0)	10(%7,6)	8
	Ceftriaxone	26(%28,6)	24(%40,7)	4(%22,2)	46(%34,8)	10
	fourth-generation fluoroquinolone	24(%26,4)	8(%13,6)	9(%50)	23(%17,4)	10
	P Value	0,300		0,028		

complaints, RT-PCR test result, inflammatory markers, clinical prognosis and the degree of involvement in the chest CT, if necessary. Infection keeps spreading rapidly as diagnosis process is delayed. Lately, it has become very common to have chest CT in patients with negative RT-PCR test results but showing clinical symptoms of the disease. The question whether this should be among COVID-19 diagnosis criteria was brought to agenda in the scientific community. While sensitivity of Thoracic CT for COVID-19 varies between studies, most of these reported sensitivities are higher than those for RT-PCR testing [15, 16]. However, there are also studies stating that these studies involve suspected methodologies and need to be supported by larger studies [17]. Another issue regarding COVID-19 patients is that the process of transfer from pandemic wards to normal ward has not been standardized. This increases the occupancy rate in the hospital and brings a huge burden on the healthcare system. The aim in this study was to determine the relationship between inflammatory markers and severity of pulmonary involvement of the patient and the impact of the treatments administered on the RT-PCR test results.

In our study, we provide evidence for the correlation between CORADS severity and values of inflammatory markers CRP and Ferritin; it can be predicted that the pulmonary damage will exacerbate as CRP and Ferritin increase. The severity of lung involvement also negatively affects the prognosis of the patient. In this case, a more aggressive treatment approach and intensive care process come to the fore. Unfortunately, there is still no effective treatment for COVID-19. Various antibiotics, Favipiravir and Oseltamivir have been among the treatments tried since the onset of the disease. We evaluated these treatments for their effects on RT-PCR test results. Following the treatments administered at the hospital, RT-PCR test results became negative after average 10 days (min:8 days, max:14 days). Antiviral therapy or other treatments used did not affect test negative time. Based on this, we concluded that patients should be admitted to normal wards after a follow-up of at least 10 days in the COVID-19 wards and the insulation time should be for at least 10 days.

It was noted in many studies that high CRP, Ferritin and various inflammatory markers were correlated with severity of disease and poor outcomes [18]. In another research where a total of 21 studies were investigated, when those with severe disease and those without severe disease were compared, white blood cell count (WBC) was found to be significantly increased while lymphocyte and thrombocyte counts were decreased, and serum ferritin value was found to be significant for severe disease [19]. In our study, WBC, Absolute Lymphocyte Cell Count (ALC), Absolute Neutrophil Cell Count (ANC), thrombocytes, Neutrophil Lymphocyte Range (NLR), and Thrombocyte Lymphocyte Range (TLR) values were in normal ranges across all CORADS groups. Only CRP and ferritin values were increased proportionally to CORADS severity. Our patients were those that did not require ICU admission and were discharged from the wards with full recovery. In this case, it should be taken into consideration that in patients with mild disease inflammatory markers other than CRP and Ferritin may not increase even when CORADS severity is increased.

D-Dimer is correlated with clotting increase and thrombotic risk in COVID-19 [20]. D-dimer is a measure of clotting and fibrinolytic system and is used to evaluate the disease severity and plays an important role in risk stratification of patients for improving the clinical management. Increased D-dimer concentrations were associated with poor outcomes in COVID-19 [21]. In our study, D-Dimer was found to be in similar levels across all CORADS groups. Use of anticoagulants such as heparin and low molecular weight heparin (LMWH) in prophylactic treatment is important for limiting the increased clotting in COVID-19 patients [22-25].

In our study, patients admitted due to COVID-19 were given treatments intended for mitigating the viral replication of SARS-CoV-2 and alleviating the body's immune reaction. The treatments administered are shown in Table 3. Since the beginning of the pandemic, the treatments administered for COVID-19 have been questioned by experts, the importance of supportive care was emphasized.

In wards where patients are monitored, follow-up RT-PCR test results are taken into consideration. Based on the test results, patients continued to be isolated or transferred to another

ward. In this way, the spread of infection within the hospital was prevented.

In this respect, it can be thought that our study will contribute to the literature in terms of being a guide for clinicians. It is known that non-evidence-based treatments are used extensively in the treatment of COVID-19. The similarity of the effects of various treatments on RT-PCR test results suggested that treatment strategies should be re-evaluated.

In conclusion we think that our study acts as a guidance especially for the follow-up of patients who are relatively stable, do not have severe diseases, or do not require intensive care. Normal inflammatory biomarkers do not necessarily mean that there is no pulmonary involvement. Increased CRP and Ferritin values can be considered to indicate an increase in pulmonary involvement severity. The treatments administered had no impact on the follow-up RT-PCR test results; patients receiving different treatments became negative approximately 10 days later. This single-center study provides data to clinician on disease severity and patient coordination during the follow-up of ward patients.

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Immune thrombocytopenic purpura healing after removing cardiac thrombosis

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Abstract

Because of the rareness of the reports about immune thrombocytopenic purpura patients undergoing cardiac surgery, there is no sufficient knowledge about perioperative strategies. In this article, we report a 42-year-old female patient with severe mitral regurgitation and large right atrial thrombus, in whom thrombocytopenia had disappeared after mitral valve replacement and thrombectomy from the right atrium. Large thrombi should be kept in mind as the cause of thrombocytopenia.

Key words: open heart surgery, immune thrombocytopenic purpura, thrombocytopenia, cardiac thrombus

Introduction

Publications related to open-heart surgeries in thrombocytopenic patients are rare. Therefore, there is no consensus on perioperative treatments in different situations that create thrombocytopenia. Large thromboses are also clinical problems that can cause thrombocytopenia. In this article, we present a patient whose platelet levels were low despite treatment for immune thrombocytopenia purpura (ITP) but whose platelet levels returned to normal after cardiac thrombosis surgery.

Case presentation

A 42-year-old female patient was taken into coronary intensive care after transesophageal echocardiography (TEE) was performed in a cardiology clinic due to complaints of dyspnea, fatigue and cough, advanced mitral regurgitation, and vegetation extending to the right atrium wall on a permanent catheter in the right atrium. The patient partially recovered with medical treatment and was subsequently admitted to the ward for surgical intervention. The patient had been treated for immune thrombocytopenia purpura (ITP) for 17 years. Splenectomy was performed eight years ago and during the last two years, she had been dialysis twice a week due to decreased renal function. The patient was using 50 mg of eltrombopag daily for ITP and 40 micrograms of darbepoetin alfa once a week for anemia due to chronic renal insufficiency. In TEE, transthoracic echocardiography revealed a vegetative mass of 38x23 mm thrombus in the right atrium extending from the catheter tip to the posterior leaflet of the tricuspid valve in the control of the patient with advanced mitral insufficiency. Blood tests revealed a platelet count of 43,000/μL and hemoglobin of 8.3 mg/dL. In the hematology department, the patient underwent thrombocyte replacement, with a platelet count above 100,000/μL prior to surgery. The patient was taken into dialysis the evening before surgery.

After obtaining written informed consent, the patient was taken to the operating room. After standard median sternotomy and aorto-bicaval cannulation, one unit erythrocyte suspension was added to the reservoir to provide appropriate hematocrit levels. The right atrium was opened. The permanent dialysis catheter has an organizing thrombus approximately 1 cm thick surrounding the catheter on the part of the right atrium. After the catheter was cut from the highest possible level, the remaining part was removed from the entrance point in the neck. There was a mass in the right atrium of about 5x4 cm with irregularly restricted, dark gray-navy colored, right atrium infiltrated into the near wall of the diaphragm and extending to the tricuspid valve. The mass was removed. The infiltrated part of the right atrium wall was thoroughly scraped and cleaned. The mass was sent to the microbiology laboratory for culture purposes. Then the interatrial septum was opened. The mitral valve was rheumatoid. The subvalvular structures under the posterior annulus were attached to the leaflets and the annulus. The chordae tendineae (tendinous chords) were sharply shortened and fused. The anterior leaflet was excised, and

the posterior leaflet was preserved. With 16 pledget stitches, a 27-size mechanical prosthetic valve (St. Jude Medical, St. Paul, Minn., USA) was placed. After the closure of the septum and the right atrium and de-airing of heart chambers, the x-clamp was removed. The surgical procedure was terminated by continuing routinely.

Drainage during the first 24 hours was 400 cc. No platelet replacement was needed. The patient's pre-op and post-op thrombocyte and hemoglobin values are given in Table 1. 6,000 units of enoxaparin twice a day was started at the 12th hour postoperatively. The next morning, warfarin was added. The drainage of the patient on the third postoperative day was lowered to less than 100 cc/24h, and the chest tubes were removed. The patient was transferred to the cardiac surgery (or cardiology) ward. The patient was dialyzed on routine dialysis days during the hospitalization period. The patient was discharged eventless on the 10th postoperative day. Microbiological examination of the intraoperative material revealed a pseudomonas aeruginosa infection, and pathological examination revealed fibrinous tissue showing myxomatous changes.

The patient was seen on the seventh day, third week, and sixth week after discharge. The results of the tests performed here are given in Table 2. The patient was not given any medication to stimulate thrombocyte suspension or platelet production in her follow-up visits. The patient is still followed up routinely by monthly controls, and six months after the operation, her platelet levels are normal. The patient does not use any medication for thrombocytes.

Discussion

ITP is an autoimmune disease caused by autoantibodies to thrombocytes. These autoantibodies generally occur against the glycoproteins IIb/IIa or Ib/IX present in the platelet membrane. The autoantibody-bound thrombocyte is removed from the circulation by phagocytosis through the macrophages, but not through the life cycle, thus resulting in thrombocytopenia [1]. However, platelet production is also suppressed. The incidence in adults is approximately 1.6 to 2.68/100,000 and is more common in women [2].

Reports about open-heart surgeries on ITP patients are very rare. Only 0.2% of open-heart surgery candidates consist of ITP patients [3]. Therefore, there is no consensus on the treatment of ITP patients during open-heart surgeries. The first choice in ITP treatment are glucocorticoids and intravenous immunoglobulin (IVIG), which usually results in an effective and transient increase in platelet counts. However, if effective results cannot be obtained as a result of these treatments, rituximab, splenectomy, thrombopoietin receptor agonists (TPO-A), and immunosuppressants can be used [4]. The platelet increase provided by these treatments is usually longer. One of the most important problems of IVIG treatment is that it can cause renal failure. In our case, IVIG could not be used due to the affected renal functions. Splenectomy was already done eight years ago, and steroid was already in use. For this reason, a direct platelet replacement was performed to increase the platelet count before the operation, and the platelet count was increased to 100,000/μL. Platelet values during the hematology follow-up and diagnosis of intracardiac thrombus are shown in Table 1.

Table 1 Early Postoperative Results

Date	Haemoglobin (g/dL)	Thrombocyte (10^3/μL)
Preoperative	8,3	43
Postoperative	9,1	79
Postoperative first day	8,9	96
Postoperative second day	9,0	103
Postoperative third day	9,2	82
Postoperative fourth day	9,1	87
Postoperative fifth day	9,3	82
Postoperative sixth day	9,6	102
Postoperative seventh day	9,4	116
Postoperative eighth day	9,4	181
Postoperative ninth day	8,8	237
Postoperative tenth day	9,1	254

Table 2 Outcome of Outpatient Clinic

	Haemoglobin (g/dL)	Thrombocyte (10^3/μL)
First Check	9,4	275
Second Check	10,4	212
Third Check	8,5	295

It is interesting that the patient's thrombocyte levels steadily dropped before surgery and her platelet counts were steady at normal levels even one year after the operation. The patient has not received any medication for ITP for the past year despite excessive menstrual bleeding. Although the excess in menstrual bleeding is due to ITP, it has been attributed to the use of warfarin by physicians. We think that the reason for the patient's low platelet level in the preoperative period is the large thrombus in the right atrium despite the treatment. We believe that watching platelets at normal levels without treatment after removal of the thrombus during the operation also supports this view. Studies on ITP patients have shown an increased risk of thrombosis in these patients. Aledort and colleagues detected 18 thromboembolic events in 186 chronic ITP adult patients [5]. These events were thought to be associated with antiphospholipid antibodies (APLAs), although the cause of thrombus development was not fully elucidated [6]. In APLA-positive patients, thrombosis is more common. It has been previously shown that large thromboses in the body may cause thrombocytopenia by agglutinating platelets. Kitchens published three case reports of thrombocytopenia in deep vein thrombosis, indicating that thrombocytopenia may interfere with heparin-induced thrombocytopenia [7].

Conclusion

If thrombocytopenia exists in an open-heart surgery candidate, its cause should be diagnosed correctly, and preparations should be made accordingly. However, it should be kept in mind that large thrombi formations may be the cause of thrombocytopenia even though the patient has already been diagnosed. While publications on open-heart surgeries in ITP patients are very rare, open-heart surgeries can be safely performed in these patients after necessary precautions have been taken.

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Calcified pancreatoduodenal artery aneurysm with filiform celiac stenosis: Follow up for ~6 years (70 months) with no intervention

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Abstract

A 72-year-old male patient was investigated with abdominal ultrasound (US) imaging before the coronary artery bypass graft surgery (CABG). The incidental finding on ultrasound was an aneurysm of the superior mesenteric artery branch. Consequent CT angiography confirmed aneurysm of the inferior pancreaticoduodenal artery (PDAA, size = 25,5x31,0x28,5mm) with filiform celiac artery stenosis. According to the European Guideline asymptomatic >25mm sized PDAA are treated with an urgent repair. However, the discrepancy between PDAA size and risk of rupture and individual parameters of the patient led the multifunctional team to assign regular follow-ups with US imaging. This case report describes rare pathology, which has been followed up for the last ~6 years (70 months) annually with no intervention, and discusses complexities in making decisions in the management of PDAA with celiac artery stenosis.

Key words: pancreatoduodenal artery aneurysm, celiac artery stenosis, visceral artery aneurysm, rare cases

Introduction

Pancreaticoduodenal artery aneurysms (PDAA) with celiac artery (CA) stenosis are rare cases with approximately 120 cases described in the literature between 1970 and 2022. Because of the risk of PDAA rupture and the associated high mortality rate with it (50%), the common interventions in the management include endovascular repair with either coil embolization and/or stent graft placement, and open surgery, which in most cases reserved for hemodynamically unstable patients in case of rupture [1,2]. As the PDAA rupture is not related to the size of the aneurysm, it makes challenging when to plan embolization/surgery and when to follow up without intervention in asymptomatic patients. The first guideline about PDAA management, Clinical Practice Guidelines of the European Society of Vascular Surgery (ESVS, published in 2017 - a year after the current case), suggests urgent repair of the symptomatic aneurysms irrespective of the size and location, while asymptomatic aneurysms with the size of >25mm are suggested to be repaired [3]. ESVS also suggests asymptomatic patients with <25mm aneurysms be followed up every 2-3 years with CT or US. In this case report, we demonstrate an asymptomatic >25mm aneurysm (which according to ESVS should have been repaired) where intervention was considered to be unnecessary by the multidisciplinary team, with annual follow-up imaging for the last ~6 years (70 months). This case is the largest PDAA and the longest PDAA follow-up reported in the literature with no intervention so far [3].

Case presentation

The 72-year-old male was admitted to the ER department with chest pain. Based on the clinical symptoms and ECG results the patient was diagnosed

with ST-elevation myocardial infarction (STEMI) and received full anti-MI treatment with fibrinolytic in the hospital because of the unavailability of coronary angiography. In the next eight hours, the patient was taken to angiography and diagnosed with multivessel coronary artery disease with up to 80% occlusion of the circumflex artery and up to 60% occlusion of other main coronary arteries. The patient has been suggested CABG, and explained the risks and benefits of the procedure, following which informed consent was obtained. During the abdominal US examination, as part of the pre-operative assessment, an aneurysm of the superior mesenteric artery branch was revealed (Figure 1). Consequent CT with contrast revealed inferior pancreatoduodenal artery aneurysm (fusiform shaped, size: 25,5 x 31,0 x 28,5 mm) and filiform stenosis of the celiac artery (D=2-3mm). The walls of the aneurysm were calcified (Figure 2). Considering the asymptomatic flow of the current pathology, potential ischemic injury to corresponding organs (liver, spleen, and stomach) in case of intervention in addition to celiac artery stenosis, technical difficulties associated with the fusiform shape of the aneurysm and its anatomic localization multidisciplinary team decided to follow up the aneurysm and proceed to CABG. After successful cardiac surgery (April 2016), the patient was discharged home on the 17th day of hospitalization. Following CABG the patient's follow-up has been planned every 6 months for the first year and annually thereafter.

Sixth months after CABG (January 2017), on regular follow-up CT angiography with a 3D reconstruction of PDAA was made (Figure 2b). The size of the aneurysm was consistent with prior CT measurements with no change in diameter. As the patient was asymptomatic, he has been taken to further regular follow-up. During the last 70 months we are observing the absence of clinical symptoms, the lack of PDAA increase in size, and the presence of a calcified wall of the aneurysm with up to 2.43mm in thickness (January 2022) (Figure 3). Listed clinical and investigational findings show us no hemodynamic changes and absence of an increase in the size of the aneurysm. Currently, the patient is on continual US follow-up.

Figure 1 - US findings of the superior mesenteric artery branch aneurysm in B- (a) and Color Doppler (b) mode with up to 30mm in diameter.

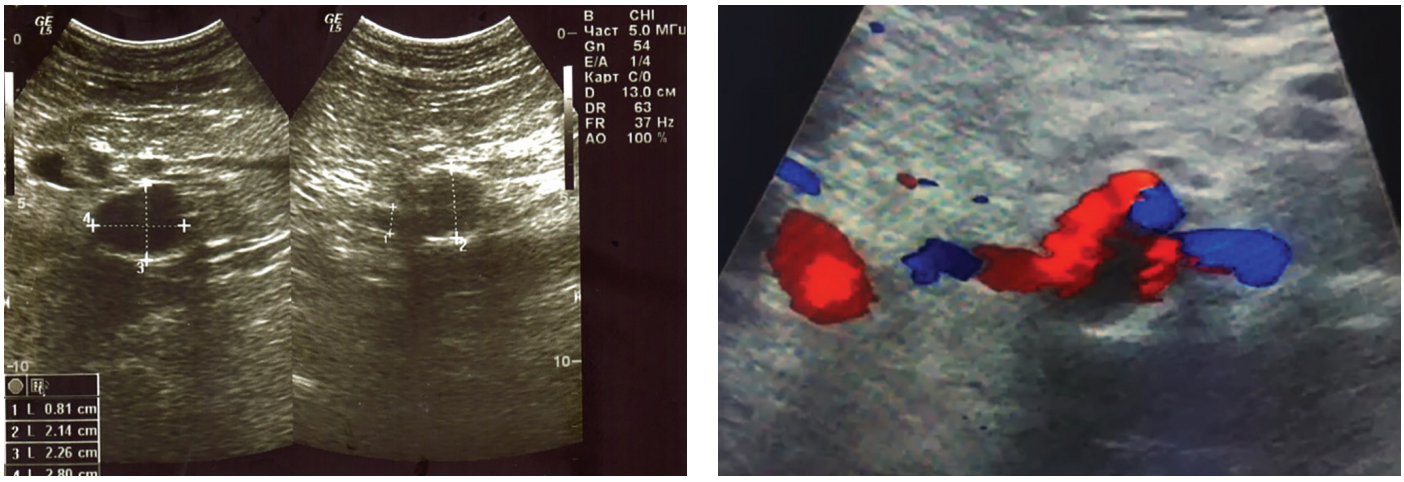


Figure 2 - Coronary angiography has shown the filiform stenosis of the celiac artery up to 1.5mm in diameter (a, b – vertical yellow arrow) and pancreaticoduodenal artery aneurysm with the size of 25,5 x 31,0 x 28,5 mm (horizontal blue arrow) with calcifications of its wall (blue arrowhead).

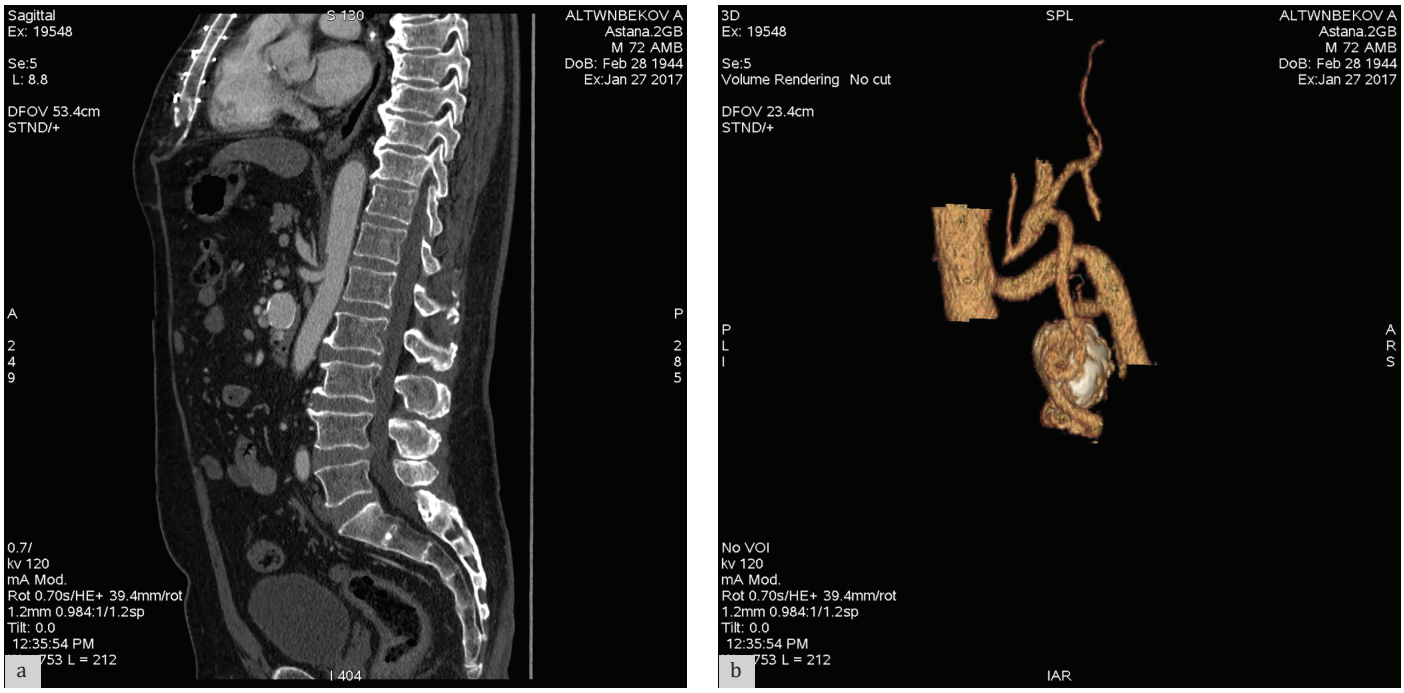
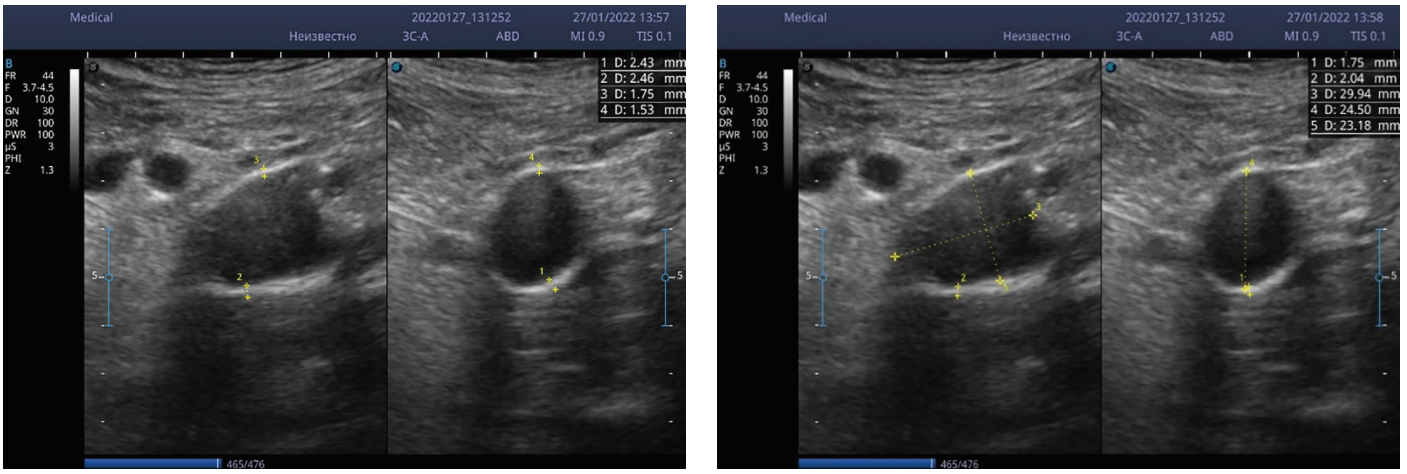


Figure 3 - Last US imaging of PDAA (January 2022): shows the calcified wall with up to ~2.46mm thickness and unchanged diameter of the aneurysm (D~29.94mm) compared to the size ~6 years ago (Figure 2). Note: Slight deviation in the size measurements on US and CT is acceptable, because of difficulty to get the same cut on the US as of CT.



Discussion

Pancreaticoduodenal artery aneurysms (PDAA) are amongst the rarest pathology of all visceral artery aneurysms (2%) along with the gastroduodenal artery (1.5%) and inferior mesenteric artery (rarest) [4]. Most PDAAs are associated with celiac artery stenosis (68-74%) [5]. The development of PDAA is explained by the first development of celiac artery stenosis or occlusion (atherosclerotic lesions, etc.) which leads to an increased pressure in PDA, and in gastroduodenal arteries (GDA), leading to an increased artery wall tension, with subsequent arterial wall weakening and aneurysm development [5]. However, Hye Jeong Yoon et al. have shown that a reverse causal relationship may also be possible, theoretically, demonstrating it based on the simulation using an electric circuit, where the development of aneurysm may result in proximal artery stenosis or occlusion, may it be a superior mesenteric artery or celiac trunk [6].

In the majority of cases, patients with PDAA present with abdominal pain (54%) and in 26% of cases, the pathology is discovered incidentally [7]. A review of PDAA cases has shown that the size of the PDAA with rupture ranged between 0.6cm and 2.0cm, while the unruptured PDAA ranged between 0.7cm and 6.0cm [8]. As the mortality associated with the rupture of the PDAA is high (50%) and the rupture is not related to its size, it brings a dilemma in the management plan, leaving us a new question of whether to include the size of the aneurysm into the criteria in the management plan or not, if yes then what should be the threshold for non-surgical/surgical intervention. Takao et al. reviewed the largest series of unruptured PDAA with no intervention applied to 8 aneurysms in 5 patients. They have proposed that the "risk of rupture of true PDAA might be lower than expected from the data on ruptured aneurysms; however, careful follow-up of untreated aneurysms is necessary". Most notably, the decision to follow up the PDAA with celiac stenosis without intervention was made based on the potential risk of ischemic injury to celiac artery/SMA-supplied organs (liver, spleen, and stomach) and based on the unclear risk of complications after PDAA embolization, despite the absence of reported complications on literature directly associated with the procedure itself. However, in several cases, patients developed other complications like aneurysmal rupture or infection after the intervention. The message of the case series was to draw attention to "balance the risk of aneurysm rupture against the risk of complications from preventive treatment" [9].

In 2017 (a year after the current case), the ESVS was made the first guideline to clarify when to proceed to intervention and when to observe [10]. ESVS divided people with PDAA into two categorical groups, based on symptoms (symptomatic or not) and size (>25mm or <25mm). Symptomatic patients and/or >25 mm-sized aneurysms were absolute indications for urgent surgical repair. While the only criteria for follow-up were asymptomatic patients with D<25mm [3].

To sum up, the current case demonstrates the independence of PDAA aneurysm size with its rupture for the follow-up period between April 2016 and January 2022 (70 months). The decision not to intervene with the patient but to follow up was made based on the patient's parameters (age 73y/o, arterial hypertension, DM type2, MI), absence of symptoms, characteristics of the aneurysm (wall calcification, fusiform shape) and the presence of celiac stenosis, which might have increased complications in case of intervention.

However, current pathology needs further investigations and statistical analysis to find out the risks, which might be directly or indirectly associated with PDAA development and with its outcome in case of intervention or follow-up. We suggest including in the PDAA management criteria blood flow dynamics including Intra aneurysmal velocity (1), which has a direct effect on the wall shear stress, also the aneurysmal wall characteristics (2), such as the presence of calcifications and aneurysmal wall thickness.

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