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Rediscovering clinical utility of QT dispersion: A long-forgotten parameter

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Abstract

Clinical and experimental electrophysiological studies have shown the importance of inhomogeneous myocardial repolarization in ventricular arrhythmias' genesis. Increased dispersion of repolarisation provides a substrate for ventricular arrhythmias by generating functional unidirectional block areas, thereby predisposing to reentry. QT dispersion, defined as the difference between the longest and the shortest QT interval on the surface ECG, is a validated measure of repolarisation dispersion. QT dispersion predicts sudden death and ventricular arrhythmias in patients with chronic heart failure from coronary heart disease and various cardiac diseases.

Key words: QT dispersion, inhomogeneous, arrhythmia

Introduction

The concept of QT dispersion was first introduced by Day et al. in 1990. It was proposed as the dispersion of various ventricular recovery times. Single ECG lead represents the regional myocardial position. Consequently, QT dispersion portrays myocardial repolarization. Clinically, homogenous repolarization on the myocardium is protective toward arrhythmia initiation. Since it was first proposed three decades ago, QT dispersion has been widely studied to assess its clinical applicability.

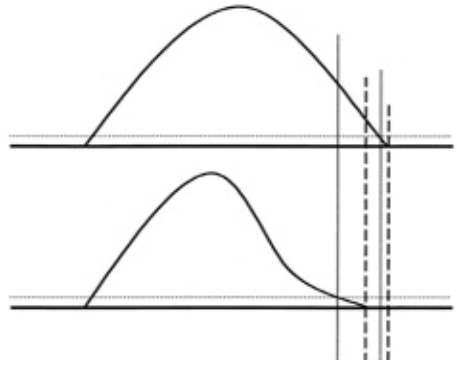
QT dispersion represents an indirect measurement of ventricular repolarization heterogeneity, with T wave interval is the primary determinant of QT interval duration. Ventricular repolarization abnormality may disrupt the dynamicity of T wave loop formation and projections toward ECG, forming variable QT intervals in different leads [1].

Pathophysiology of QT dispersion

T wave offset determines the end of the QT interval and, thus, QT dispersion. Therefore, the T wave loop shape and axis are the major factors leading to true variations in the T loop projections' length. Derangement from normal T loop and axis may significantly affect a single shape of QT interval. Figure 1 showed various T wave morphology and amplitude resulting from different axis projections. T wave variation results in different offset and formation of QT interval and dispersion.

As a consequence of both different actual lengths and different measurable duration of QT intervals, QT dispersion, if the heart vector becomes perpendicular to one of the leads' axis, two imaginary T waves of the same magnitude have different offsets (dashed lines). "This results in the dispersion of the QT intervals "true (vertical dashed lines). In comparison, the two T waves' final component is below the threshold level, with different proportions (e.g., with an automatic threshold method). This refers to the measured dispersion (vertical solid line) of the QT intervals, which is separate from the actual dispersion (Figure 1) [2].

Figure 1 - QT Dispersion resulting from both measurable and real duration of QT intervals (5)

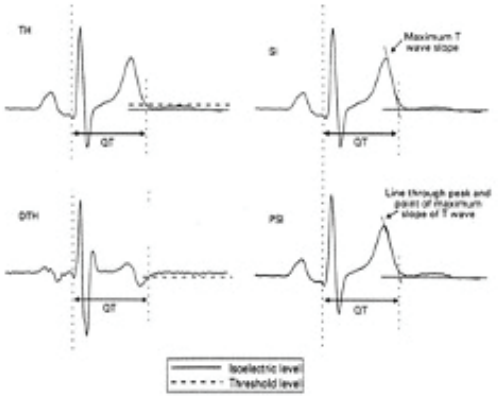


QT dispersion measurement

Based on standard definition, electrocardiographic QT interval measurement start from the QRS onset to the end of the T wave, identified as the T wave returning to the isoelectric line. QT dispersion can be measured from the subtraction of the highest QT interval and lowest QT interval obtained from 12 leads of the ECG simultaneous recording to avoid heart rate-induced QT dynamicity. Determination of T wave offset using the manual method may result in high intra- and interobserver variability. Clinical utilities of automatic repolarization analysis are also not well defined. The intricacy of QT dispersion measurement lies on the T wave endpoint, especially when the T wave is abnormal such as biphasic T wave, T-U wave fusion, and U wave presence [3,4].

Several methods are commonly used for T wave end determination (Figure 2). Threshold methods point to T wave offset as an intercept of the T wave with an imaginary line drawn above the isoelectric line. Slope methods determine the T offset as an interception between an imaginary line drawn following the slope of the descending part of the T wave and the isoelectric line. An imaginary line on the T wave slope can be a straight line from the T wave peak or the steepest tangent line on that slope (Figure 2) [3].

Figure 2 - Methods in Determining T wave Offset (8)



Influence of heart rate on QT dispersion and measurement reliability

Numerous studies have analyzed the effect of heart rate influence on QT dispersion, known as corrected QT dispersion. Corrected QT dispersion can be calculated using Hodges and Framingham formula used for corrected QT calculation. Several variables, such as heart rate, rhythm, and origin of impulse, can affect QT dispersion. Clinical and experimental data concluded a non-significant correlation between monophasic action potential (MAP) and QT dispersion. It proves QT dispersion as a complex form of electrical impulse influenced by a wide array of factors correction solely toward heart rate may cause a bias [5].

Manual QT dispersion measurements are correlated with 25–40% of intra and interobserver variability. Even using gold-standard devices such as digitizing boards, the measurement can produce intraobserver variations in 20% and 10% of observers. The major source of error in QT dispersion measurement is the determination of the isoelectric line and threshold level [6].

Clinical utilities of QT dispersion

QT dispersion on a normal individual from literature reviews varies mostly between 40-65 ms [7]. Rotterdam study with 5,812 healthy adults [age ≥55 years], followed up for 3 to 6.5 years, found its correlation between QT dispersion with cardiac mortality. Strong Heart Study, assessed 1,839 American Indians followed up for 3.7±0.9 years, showed the corrected QTc dispersion as a predictor of 34% of cardiovascular mortality for each 17ms increase in QTc dispersion [8].

Several studies have shown a tendency toward increased QT dispersion in various cardiac diseases. Pooled data from 18 studies with a total of 2,525 post-MI patients have shown a tendency toward increased QT dispersion in various cardiac diseases compared to normal subjects [9]. Repolarization abnormalities expressed as QT dispersion might also be founded in ventricular hypertrophy of various origins, including the athlete's heart. However, similar studies have found abnormalities in QT dispersion due to physical training and left ventricular hypertrophy not significantly different from the healthy subjects [10].

Aggressive recommendation toward revascularization procedures in acute Myocardial Infarction (MI) modulates spontaneous dynamicity and regresses infarction size. QT dispersion is increased in acute MI, with mean values ranging from 40±18 to 162.3±64.8 ms. QT dispersion has a trend toward regression on chronic forms of coronary artery disease [11]. There is a significant association of increased QT dispersion on acute MI and ventricular tachycardia incidence (sensitivity 68%, specificity 88%, relative risk 15.7 ($p<0.001$). The study supported these findings by evaluating the correlation between QT dispersion and infarction size by analyzing viable myocardium by Fluorodeoxyglucose [FDG] uptake and PET scan. Those subjects with increased QT dispersion have a significantly larger infarction size [12].

An indirect relationship of QT dispersion prolongation and infarction size may explain the increased incidence of arrhythmias in acute MI. Increased QT dispersion can be represented as inhomogenous repolarization in the myocardium area. This inhomogeneous as the area can form a substrate for reentrant arrhythmias initiation. Prolongation of the repolarization phase can also induce arrhythmia through the after depolarization mechanism [13].

Several treatments have been correlated with QT dispersion improvement, e.g., reperfusion therapy with the thrombolytic agent, revascularization with the percutaneous coronary intervention, or coronary artery bypass grafting. Restoration of epicardial coronary flow may improve stunned myocardium, reduce scar tissue formation, and induce homogenous repolarization on the myocardial [13–15]. Beta-blocker treatment in a patient with the long-QT syndrome and candesartan for heart failure and hypertension has also decreased QT dispersion [16].

Prognostic Value of QT Dispersion

Data from 23 studies involving 1831 patients with various cardiac diseases with and without serious ventricular arrhythmias during their illness showed significantly dispersed QT in patients with arrhythmias, most of them with coronary artery disease. Contrary to Zabel et al., in his study involving 280 consecutive MI survivors followed up for 32±10 months, it showed non-associative QT dispersion as a predictor of adverse outcome [15].

Analysis from the ELITE heart failure study comparing losartan and captopril showed a reduction of sudden cardiac death in the losartan arm [17]. The DAMOND-CHF Study's substudies, the UK-HEART study, showed a non-significant association of QT dispersion for outcome predictors in heart failure patients. An analysis of the effect of beta-blockers in

dilated cardiomyopathy by Oflaz et al. reported a better response in patients with higher QT dispersion (137±52 vs. 75±38 ms) [18].

Effect of drugs on QT dispersion and the Risk of Torsades de Pointes [TdP]

Class IA anti-arrhythmias have the effect of inducing prolongation of ventricular repolarization. In a patient who develops TdP, class IA antiarrhythmics may induce inhomogeneous prolongation of the repolarization phase expressed as increased QT dispersion. Propafenone, disopyramide, and almokalant (blocker of the rapid component of the delayed rectifier, I Kr) have been shown to increase QT dispersion, whereas, in one study, intravenous dofetilide did not produce increased QT dispersion [19]. The unique effect of amiodarone [class III antiarrhythmic agent] induced a global QT prolongation by its beta-blockade and potassium channel blocking ability, thereby protecting TdP risk and not being associated with increased QT dispersion [19,20].

Sotalol therapy for six months after acute infarction induces variation in QTc and QTc dispersion. Sotalol is associated with increased maximal QTc and reduced QTc dispersion compared to placebo. This effect is protective toward arrhythmia by inducing homogenous ventricular repolarization. A study by Grimm et al. analyzed QTc dispersion and adjusted QTc dispersion on 52 patients with ventricular arrhythmia receiving amiodarone. It is showed non-significant prolongation of QT dispersion before and after amiodarone administration. ECG and QT dispersion can monitor myocardium response during the drug administration with ventricular repolarization modulation activity. QT dispersion >100 ms during drug usage is an absolute parameter of severe repolarization prolongation and potentially induces arrhythmia by afterdepolarization mechanism [21].

Antiarrhythmic agents are the leading cause of drug-induced TdP. As proposed earlier, the QT interval only represents the mean sum of repolarization activities in the ventricular myocardium. Measuring QT dispersion will give additional information on regional repolarization abnormalities that predispose to early afterdepolarization and TdP. Therefore, measurement of QT dispersion is essential during the administration of antiarrhythmics. Class IA agents (quinidine, procainamide, and disopyramide) block both Na and K channels, and TdP can occur either at therapeutic or subtherapeutic doses. Quinidine prolongs QT interval by an average of 10–15% within a week of therapy initiation and carries a 1.5% risk of inducing TdP. Class III agents are potent IKr blockers and prolong QT interval in a dose-dependent manner [22].

Although no single clinical manifestation can be presented by widely dispersed QT, its presence in the therapy of various antiarrhythmic drugs may signal a predisposition in arising of torsade de Pointes (TdP) or polymorphic ventricular tachycardia. Various studies have shown that therapy using amiodarone with its unique combination of all four antiarrhythmics classes is associated with the rarity of drug-induced TdP and superior choice in various arrhythmias [21].

Long QT Syndrome as Model of Congenital Prolong QT Interval

The long QT syndrome (LQTS) is considered a blueprint for studying repolarization anomalies in humans. Cardiac repolarization abnormalities in long QT syndrome is a pure electrical condition without corresponding structural abnormalities. Prolonged ventricular repolarization's arrhythmogenic ability has been extensively studied in both laboratory models and clinical LQTS patients. It is demonstrated that LQTS mutations can establish a fragile substrate with prolonged action potential duration, where early afterdepolarization and triggered activity can occur in the presence of beta-adrenergic stimulation [23].

These results were then verified in two additional studies, demonstrating that transmural variations in action potential recovery times are crucial in determining the heterogeneity of repolarization in a pharmacologically induced LQTS mode. Torsades-de-Pointes arise when this dispersion is exacerbated by the existence of an altered IKs current (as occurs in the LQT1 subtype) and -adrenergic stimulation. It's worth noting that these latter observations, suggesting the pathogenetic significance of the adrenergic nervous system in LQTS, are consistent with our group's clinical evidence. The baseline inhomogenous repolarization of congenital long QT syndrome is a classic manifestation of QT dispersion.

Conclusion

The overlapping of values QT dispersion values in normal and pathological cardiac states render any attempt at establishing reference values. Although theoretically, QT dispersion is a parameter in evaluating ventricular repolarization, conflicting study results hinder QT dispersion applicability as a clinical tool. Twelve lead ECGs may provide regional electrical data. However, simple measurement using QT dispersion has a poor ability to extract that information. Further study is needed to explore the difference between the duration of local, global, and interventricular dispersion. It provides information about a dispersed of the distance electrical impulse that is important for arrhythmogenesis.

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References

1. Tokatli A, Yiginer O, Haholu A, Uzun M. Efficiency of quantification of cardiac electrical heterogeneity: Via QT dispersion, transmural dispersion, or both. *Biology of Sport.* 2015; 32(2):175-6. doi: 10.5604/20831862.1145079.
2. Malik M, Batchvarov VN. Measurement, interpretation, and clinical potential of QT dispersion. *Journal of the American College of Cardiology*. 2000; 36(6):1749-66. doi: 10.1016/s0735-1097(00)00962-1.
3. Vázquez-Seisdedos CR, Neto JE, Marañón Reyes EJ, Klautau A, Limão de Oliveira RC. New approach for T-wave end detection on electrocardiogram: Performance in noisy conditions. *Biomed Eng Online.* 2011; 77. doi: 10.1186/1475-925X-10-77.
4. Erikssen G, Liestøl K, Gullestad L, Haugaa KH, Bendz B, Amlie JP. The Terminal Part of the QT Interval (T peak to T end): A Predictor of Mortality after Acute Myocardial Infarction. *Ann Noninvasive Electrocardiol.* 2012; 17(2):85–94. doi: 10.1111/j.1542-474X.2012.00493.x.

5. Helmy H, Abdel-Galeel A, Taha Kishk Y, Mohammed Sleem K. Correlation of corrected QT dispersion with the severity of coronary artery disease detected by SYNTAX score in non-diabetic patients with STEMI. *Egypt Hear J.* 2017; 69(2):111-117. doi: 10.1016/j.ehj.2016.12.001.
6. Alabd MA, El-Hammady W, Shawky A, Nammas W, El-Tayeb M. QT Interval and QT Dispersion in Patients Undergoing Hemodialysis: Revisiting the Old Theory. *Nephron Extra.* 2011; 1.
7. Wu VC, Lin LY, Wu KD. QT interval dispersion in dialysis patients. *Nephrology*. 2005; 10(2):109-112. doi: 10.1111/j.1440-1797.2005.00391.x.
8. Okin PM, Devereux RB, Howard B V., Fabsitz RR, Lee ET, Welty TK. Assessment of QT interval and QT dispersion for prediction of all-cause and cardiovascular mortality in American Indians: The strong heart study. *Circulation*. 2000; 101(1):61-66. doi: 10.1161/01.cir.101.1.61.
9. Rodríguez-Jiménez AE, Cruz-Inerarity H, Negrín-Valdés T, Fardales-Rodríguez R, Chávez-González E. Corrected QT-interval dispersion: An electrocardiographic tool to predict recurrence of myocardial infarction. *MEDICC Rev*. 2019; 21(2-3):22-25.
10. Ale OK, Ajuluchukwu JNA, Oke DA, Mbakwem AC. QT dispersion in hypertensive Nigerians with and without left ventricular hypertrophy. West Afr J Med. 2013; 32(1):57-61.
11. Demirtaş AO, Urgun OD. Can QT interval prolongation or dispersion detected in a positive exercise ECG test predict critical coronary artery disease? *Arch Med Sci - Atheroscler Dis*. 2019; 4:e7-e12. doi: 10.5114/amsad.2019.83299.
12. Eslami V, Safi M, Taherkhani M, Adibi A, Movahed MR. Evaluation of QT, QT dispersion, and T-wave peak to end time changes after primary percutaneous coronary intervention in patients presenting with acute ST-elevation myocardial infarction. *J Invasive Cardiol*. 2013; 25(5):232-234.
13. Dotta G, Fonseca FAH, de Oliveira Izar MC, de Souza MT, Moreira FT, Pinheiro LFM, et al. Regional QT interval dispersion as an early predictor of reperfusion in patients with acute myocardial infarction after fibrinolytic therapy. *Arq Bras Cardiol.* 2019; 112(1):20-29. doi: 10.5935/abc.20180239.
14. Alici G, Sahin M, Ozkan B, Acar G, Acar RD, Yazicioglu MV, et al. The comparison in reduction of QT dispersion after primary percutaneous coronary intervention according to existence of thrombectomy in ST-segment elevation myocardial infarction. *Clin Cardiol.* 2013; 36(5):276-9. doi: 10.1002/clc.22109.
15. Alasti M, Adel MH, Torfi E, Noorizadeh M, Bahadoram S, Moghaddam MA, et al. QT dispersion: Does it change after percutaneous coronary intervention? *J Tehran Univ Hear Cent.* 2011; 6(1):19-23.
16. Matsuno Y, Minatoguchi S, Fujiwara H. Effects of candesartan versus amlodipine on home-measured blood pressure, QT dispersion and left ventricular hypertrophy in high-risk hypertensive patients. *Blood Press*. 2011; 1:12-9. doi: 10.3109/08037051.2010.532339.
17. Ersoy A, Ersoy C, Guler M, Yildiz A. Losartan and QT Dispersion in Hypertensive Patients on Maintenance Hemodialysis. *Med Sci | Int Med J*. 2014; 3(4):1627-38.
18. Oflaz MB, Balli S, Kibar AE, Ece I, Akdeniz C, Tuzcu V. Effects of carvedilol therapy on cardiac autonomic control, QT dispersion, and ventricular arrhythmias in children with dilated cardiomyopathy. *Med Sci Monit.* 2013; 19:366-72. doi: 10.12659/MSM.883911.
19. Roden DM. Drug-Induced Prolongation of the QT Interval. *N Engl J Med.* 2004; 350(10):1013-22. doi: 10.1056/NEJMra032426.
20. Ogiso M, Suzuki A, Shiga T, Nakai K, Shoda M, Hagiwara N. Effect of intravenous amiodarone on QT and T peak-T end dispersions in patients with nonischemic heart failure treated with cardiac resynchronization-defibrillator therapy and electrical storm. *J Arrhythmia.* 2015; 31(1):1-5. doi: 10.1016/j.joa.2014.01.006.
21. Friedman A, Miles J, Liebelt J, Christia P, Engstrom K, Thachil R, et al. QT Dispersion and Drug-Induced Torsade de Pointes. *Cureus*. 2021; 13(1):1–10. doi: 10.7759/cureus.12895.
22. Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: Mechanisms and clinical management. *Therapeutic Advances in Drug Safety.* 2012. 3(5):241-253. doi: 10.1177/2042098612454283.
23. Prenner SB, Shah SJ, Goldberger JJ, Sauer AJ. Repolarization Heterogeneity: Beyond the QT Interval. *Journal of the American Heart Association.* 2016; 5:e003607. doi: 10.1161/JAHA.116.003607

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Bacterial translocation in colorectal cancer patients

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Abstract

Bacterial translocation is the penetration of intestinal bacteria through the intestinal mucosa into usually sterile tissues and internal organs. Commensal bacteria, despite their presence in the intestine in extremely large numbers, rarely cause local or systemic inflammation, because the unicellular epithelial layer of the intestinal mucosa prevents the migration of these bacteria from the intestine. For years, researchers have wondered how a single layer of intestinal epithelial cells can prevent microorganisms from entering the systemic circulation. Today, the phenomenon of bacterial translocation is considered as one of the main mechanisms of endotoxemia and systemic inflammatory response syndrome in various pathologies, including colorectal cancer and acute bowel obstruction. This narrative review is devoted to the search for factors promoting to bacterial translocation from the intestine in colorectal cancer and acute malignant bowel obstruction.

Key words: bacterial translocation, gut microbiota, intestinal barrier, colorectal cancer, bowel obstruction

Introduction

As per the statement of A. Alexopoulou, bacterial translocation (BT) is the invasion of intestinal bacteria, bacterial endotoxins (ex., bacterial lipopolysaccharide, peptidoglycan, lipopeptide) from the intestinal lumen into the mesenteric lymph nodes and extraintestinal areas [1]. These days, the phenomenon of bacterial translocation is considered one of the main mechanisms of endotoxemia and systemic inflammatory response syndrome (SIRS) in various pathologies, including colorectal cancer (CRC) and acute bowel obstruction (ABO).

Colorectal cancer takes the 3rd place among all diagnosed malignancies. CRC holds the third position among lung and prostate cancer in men (10% of the total) and the 2nd position after breast cancer in women (9.2% of the total) [2, 3]. CRC is the 4th leading cause of cancer deaths in the world [2, 4].

In Kazakhstan, colon and rectal cancers occupy the 5th and 6th places respectively in the oncological diseases' hierarchy. If compared with the data from 2018, there has been an increase in the detection of new cases in 2019 by 1.4% for colon cancer and 2.9% for rectal cancer. In the mortality rate from malignant neoplasms in 2019, colorectal and rectal cancers are on the 5th and 8th places, respectively [5].

More than 66% of patients with CRC are admitted to the hospital with complications, and in most cases these complications are the first symptoms of the disease [6]. Despite the improvement in diagnostic and screening programs, some complicated forms of CRC are diagnosed in 88.9% of newly diagnosed patients, where about 40% of them already have metastases [7]. The most common complication in CRC is acute bowel obstruction, which accounts for about 80-85% of the emergencies related to this pathology [8-10].

Despite the improvement in diagnostic and treatment, there are currently high rates of postoperative complications (46-50% of cases) and mortality (up to 25-52% of cases) in patients with malignant ABO. According to numerous researchers, in case of malignant ABO, both mortality and postoperative complications are 2 to 3 times higher than in operated patients with uncomplicated colon cancer. Additionally, a 5-year survival rate after planned surgeries is 20% higher than after urgent surgeries [11-13]. Today, a number of researchers believe that bacterial translocation is a trigger mechanism for development and enhancement of the SIRS, which can lead to the infectious-inflammatory complications, sepsis and multiple organ dysfunction [14-16]. Thus, a closer look shall be taken to the factors contributing to bacterial translocation in CRC patients and malignant ABO.

Gut bacterial translocation factors

Presently, several factors have been identified as those contributing to bacterial translocation from the intestine.

Imbalance of normal intestinal microbiota and bacterial overgrowth

The intestinal microflora is involved in maintaining homeostasis, playing a crucial role in nutrition and energy metabolism [17], as well as immune modulation [18, 19]. Trillions of commensal microorganisms living in the gastrointestinal tract can compete for adhesion sites with pathogenic bacteria. These microorganisms are the first line of defense against bacterial translocation [20]. According to the latest data, in patients with various diseases (acute pancreatitis, severe trauma, burns, surgical interventions), the composition of the intestinal microbiota is changing. It is characterized by a decrease in the number of commensals and an excessive growth of opportunistic proteobacteria, including Escherichia coli, Pseudomonas spp., Klebsiella spp., Clostridium difficile and Vancomycin-resistant Enterococcus [21-28]. Dysbiosis has been associated with severe complications in critical conditions, including sepsis, multiple organ failures, and even deaths [29, 30].

Normal intestinal microflora plays a critical role in resisting bacterial pathogen colonization, overgrowth and invasion. This phenomenon has been termed as "colonization resistance" [31]. In addition to competing for nutrition and adhesion to the epithelium, normal gut microbiota can indirectly fight the entry of pathogens by enhancing immunity (immune-mediated resistance to colonization) [32, 33].

The composition of normal intestinal microbiota is affected by various factors: diet, gastric and intestinal secretions, bile salts, lysozyme, secretory IgA, antibacterial drugs, endotoxic shock, parenteral nutrition, bowel obstruction, and much more [34]. All these factors can lead to microbiota imbalance and bacterial overgrowth, which in its turn, contributes to BT, as it is been proven in animal models [35] and in humans [36].

The intestinal microbiota takes part in the metabolism of lipids, carbohydrates, proteins. The metabolites of these reactions can be useful or toxic to the body [37]. Lactic acid, fatty acids, bacteriocins are antimicrobial factors for pathogenic flora [38]. However, for example, phenolic and sulfur-containing compounds formed as a result of protein metabolism are toxic to intestinal epithelial cells [39]. They cause an increase in paracellular permeability by destroying intercellular dense junctions [40]. If the normal composition of the microbiota is disturbed, an increase in the production of toxic metabolites is possible, which leads to a disruption of the intestinal epithelial barrier and subsequent BT [41].

Immunity disorders

The gut is an important organ of the immune system that contains all types of white blood cells involved in both innate and adaptive immune responses. As a rule, the innate immune system does not respond to most commensal microorganisms [42]. At the same time, it can also respond quickly to invasion of pathogens and prevent their migration from the intestinal lumen into the systemic circulation. In immunocompetent people, after passing through mucous and epithelial barriers, pathogenic bacteria in mesenteric lymph nodes are recognized and neutralized by macrophages and dendritic cells [43]. Thus, these cells don't produce proinflammatory cytokines, and no inflammatory response occurs. If, at this stage, macrophages fail to neutralize all pathogens, bacteria or their toxins enter the liver through the portal vein system, where they are neutralized by the Kupffer cells. Since critically ill patients are usually accompanied by systemic immunodeficiency or immunosuppression, innate and adaptive immune mechanisms are unable to destroy pathogenic microorganisms. Therefore, surviving bacteria or their components (lipopolysaccharides and peptidoglycans), as well as cytokines and chemokines, pass through the mesenteric lymph nodes, and ultimately enter the systemic circulation through the thoracic duct. Consequently, immunity disorders can lead to increased bacterial translocation [44, 45].

Circulatory hypoxia of the intestinal wall and impaired antioxidant defense

Hypoperfusion, ischemia, and subsequent reperfusion of damaged areas of the intestine enhances the inflammatory response and leads to oxidative stress, which contributes to the death of enterocytes and disruption of tight junctions, thereby increases the intestinal wall permeability and disrupt the intestinal barrier function [46].

Violation of the barrier function of the intestinal mucosa

The first line of defense against bacterial invasion is the intestinal mucosa, which contains mucin and antimicrobial peptides. The mucus produced by the intestinal goblet epithelial cells forms a thick, continuous layer, which prevents bacteria from penetrating through the intestinal wall. Mucous secretions are rich in secretory IgA, which neutralizes toxins and microorganisms and prevents their adhesion and colonization [47]. Any disturbances in microcirculation of the intestinal mucosa lead to hypoperfusion, edema of the mucous membrane, its ischemia, an increase in free oxygen radicals that destroy the cytoskeleton of the mucous membrane, which contributes to the disruption of the integrity of the intestinal barrier and subsequent bacterial translocation [48-52].

As known, colorectal cancer leads to disorders of the immune system. The normal intestinal microflora gets out of balance with the intestinal barrier violated, which occurs at the site of the tumor growth as the tumor causes dysplasia of the epithelium. In the case of ABO, microcirculation disorders occur in the area of obstruction, and subsequent ischemia and hypoxia of the intestinal wall. Therefore, the ongoing changes in CRC and ABO can lead to BT.

Changes in the intestine in malignant ABO

Colon tumors at the site of their growth cause epithelial dysplasia, changing the structure of the intestinal wall, and causing the violation of the intestinal barrier. With ABO, this situation is aggravated by the presence of an obstruction and the disorders caused by it. The intestinal microcirculation disturbances occur both at the site of tumor growth and above the obstruction. There are edema, ischemia and hypoxia of the intestinal wall in place, which results in even greater violations of intestinal permeability.

In case of bowel obstruction, all functions of the large intestine are impaired, including disorders of intestinal motility. Due to the slow evacuation of intestinal contents, there is an increase in pressure in intestine, as a result of which blood circulation in its wall is disrupted with absorption of water, minerals and other substances impaired, and fluid accumulated in intestine. The accumulation of feces above the

tumor localization enhances the processes of putrefaction and fermentation. In addition to fluid in intestine, gas begins to accumulate, the intestinal loops expand, and the disturbance of the regional blood circulation of the intestinal wall is increased. These microcirculation disorders lead to ischemia of the intestinal wall, hypoxia, activation of lipid peroxidation, which ultimately reduces the barrier function of the intestinal wall. As the bowel obstruction progresses, desquamation of the intestinal epithelium and destruction of enterocytes occur, which contributes to the translocation of microorganisms through the intestinal wall and the development of the SIRS and subsequent multiple organ failure. Back in 1971 Dederer Yu.M. described changes in the intestinal wall above the obstruction, which acquired a destructive character: at the first hours of bowel obstruction, the epithelium is exfoliated, after 24-72 hours diffuse leukocyte infiltration is developed, and in later stages, suppuration of the intestinal wall is observed [53].

In the histological examination of resected areas of the colon in patients with ABO Achkasov E.E revealed inflammatory reactions in all layers of the intestinal wall and a significant expansion of lymphatic capillaries [54]. With compensated ABO, there have been signs of myocyte dystrophy with severe neutrophilic infiltration and ulceration of the intestinal wall in areas of tumor obstruction. In the areas above the obstruction there have been microcirculation disorders and interstitial edema. The decompensated ABO has been manifested by the areas of intestinal wall destruction not only in areas of tumor obstruction, but also in the areas remote from the tumor. The microcirculation disorders with interstitial edema have also been present in the small intestine. At the same time, it has been found that with decompensated ABO, the edema of the intestinal wall was less pronounced, which indicated a significant violation of the intestinal barrier permeability. All patients with decompensated and some patients with sub-compensated ABO demonstrated some bacterial translocation into the abdominal cavity, which was confirmed by bacterial cultures of abdominal effusion.

These studies have confirmed that ABO exacerbates changes in the intestinal wall in CRC patients, thereby increasing BT, which may lead to SIRS and infectious and inflammatory complications.

Postoperative complications after surgery for CRC and malignant ABO

The antibiotic prophylaxis in 24 hours after surgery is recommended for patients with CRC and malignant ABO, even without signs of infection. Antimicrobial drugs mainly target gram-negative and anaerobic bacteria due to potential bacterial translocation [3].

Postoperative complications include the following: wound suppuration, anastomotic leak, paracolostomy and abdominal abscesses, peritonitis, eventration, intestinal paresis, gastrointestinal bleeding, pneumonia, pulmonary embolism, etc. Numerous studies have noted that infectious and inflammatory complications are one of the main causes of death in patients with cancer [55, 56].

After any surgical intervention in any patient, a cascade of immune responses is triggered with the release of endogenous pro-inflammatory mediators. However, in immunocompromised patients (including cancer patients), these reactions can spill over into the SIRS, which can subsequently cause multiple organ failure and sepsis [57].

One of the reasons for the occurrence of infectious and inflammatory complications is the gut microflora. The gut microbiota is involved in maintaining homeostasis and plays an important role in nutrition, energy metabolism, immune modulation, and defense, preventing colonization of the intestine by pathogens [58, 59]. Van Praagh by sequencing 16S rRNA in patients after surgery for colorectal cancer confirmed that anastomotic leak and inflammatory reactions were associated with low microbial diversity: a decrease in the number of normal microbiota and an overgrowth of pathogenic bacteria [37]. Thus, dysbiosis of the intestinal microflora can lead to a loss of "colonization resistance", metabolic disorders and impaired barrier function of the intestinal wall. As a result, translocation of pathogenic flora is increased with the endotoxins in the mesenteric lymph nodes and systemic blood flow, causing systemic inflammatory response syndrome (SIRS) [60]. Also, the main cause of postoperative infectious and inflammatory complications in malignant ABO is the violation of the intestinal wall barrier, the mechanism of which was described above.

In patients with CRC the imbalance of the intestinal microflora, immunosuppression, microcirculation disorders, hypoxia and ischemia of the intestinal wall results in the production of a large number of pro-inflammatory mediators. The inflammatory response increases and oxidative stress occurs. These changes contribute to the death of enterocytes, disruption of intercellular tight junctions, which increases the intestinal wall permeability. Bacteria or their endotoxins penetrate the damaged mucous barrier and further enhance the immune response, which becomes systemic, and ultimately, leads to systemic inflammatory response syndrome (SIRS), multiple organ dysfunction and sepsis [56].

In patients with colorectal cancer after resection of colon, M. Schietroma et al. confirmed an increased permeability of the intestinal wall and a significant increase in endotoxemia on the very 1st postoperative day, which subsequently correlated with the development of sepsis [60]. Destruction of the intestinal barrier promotes the translocation of bacteria and endotoxins into the mesenteric lymph nodes and further into the systemic circulation [58, 60]. In a number of studies, researchers have found that bacterial translocation into mesenteric lymph nodes occurs in 65% of patients with colorectal cancer, with predominance in patients with III and IV stages [60].

High rates of postoperative infectious and inflammatory complications in patients with CRC (46-50% of cases), despite the ongoing treatment, are potentially associated with the BT phenomenon, which increases in this group of patients, especially those with ABO.

Bacterial translocation detection methods

As of today, BT takes one of the main roles in the development of infectious and inflammatory complications. Various methods are used and studied for the early diagnosis of such complications, as well as the detection of BT, which are as follows:

1. Direct methods, which determine bacteria in the mesenteric lymph nodes (MLN), through which bacteria then enter the systemic circulation and other organs and tissues. These methods include using cultures of MLN and determining the microbial 16S rRNA in MLN by utilizing a polymerase chain reaction in “real time” (RT-PCR). In experimental studies on modeling bowel obstruction, radioactively labeled bacteria are also used, but this technique is not applicable for humans.

2. Indirect methods are aimed at determining bacteria or BT markers in blood and other biological fluids. These methods include blood culture, detection of bacterial genes by RT-PCR in blood and ascitic fluid, determination of markers of impaired intestinal barrier in blood (zonulin, citrulline, intestinal fatty acid-binding protein), determination of endotoxin (lipopolysaccharide) and markers of inflammation and BT in the blood (C-reactive protein, procalcitonin, interleukins, tumor necrosis factor, presepsin and lipopolysaccharide-binding protein).

The growing interest in the BT phenomenon is gaining its momentum among scientists all over the world. BT is being studied for various pathologies: liver cirrhosis, HIV infection, pancreatitis, burns, parenteral nutrition, renal diseases and other. However, there are few works on the study of BT in CRC and ABO.

In Kazakhstan, insufficient attention is paid to the study of the BT phenomenon. In the Scopus database we found only six articles written by the Kazakhstani scientists, which are devoted to BT from the intestine. In one of the experimental studies, the researchers modeled obstructive and strangulated intestinal obstruction using their own method. Various biomarkers in the rats' blood by immunological and molecular genetic methods (procalcitonin, lipopolysaccharide-binding proteins and interleukin-6) have been detected at different stages of the development of intestinal obstruction. The maximum BT frequency was revealed on the first day of the development of obstruction. There have been no statistically significant differences in the groups with strangulated and obstructive intestinal obstruction, which may indicate the similarity of the pathological mechanisms of intestinal obstruction, leading to BT. Also, some authors found that procalcitonin and lipopolysaccharide-binding proteins are the most valuable markers of BT at intestinal obstruction [61]. In a clinical study of patients with acute surgical pathology, including acute intestinal obstruction, some correlation has been found between an increase in intraabdominal pressure and an increase in the level of presepsin. Moreover, some researchers found that presepsin can be used to stratify the risk of abdominal sepsis [62].

To date, most of the work on BT is experimental, and a large part of clinical studies have been carried out on HIV-infection and liver cirrhosis. BT in CRC and ABO has insufficiently been studied, as its role in the development of SIRS and infectious and inflammatory complications. The questions of the diagnostic value of the proposed biomarkers, their study in dynamics, as well as the relationship between direct and indirect BT markers remain open. These unsolved problems require further in-depth study.

Conclusion

Recently, the studies of bacterial translocation phenomenon have been attracting more and more interest among scientists around the world. Disturbance of the intestinal barrier and subsequent BT is the first step, which ultimately leads to the fact that the intestine becomes the main pro-inflammatory organ that controls the systemic inflammatory response. As of today, many questions remain unresolved, including those on the study of this phenomenon in CRC patients and on the diagnostic value of BT biomarkers. Therefore, further studies are required to be conducted.

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References

1. Alexopoulou A, Agiasotelli D, Vasilieva LE, Dourakis SP. Bacterial translocation markers in liver cirrhosis. *Ann Gastroenterol.* 2017; 30(5):486–497. https://doi.org/10.20524/aog.2017.0178
2. Arnold MS, Laversanne SM, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017; 66(4):683-691. https://doi.org/10.1136/gutjnl-2015-310912
3. Pisano M, Zorcolo L, Merli C, Cimbanassi S, Poiasina E, Ceresoli M, et al. 2017 WSES guidelines on colon and rectal cancer emergencies: obstruction and perforation. *World J Emerg Surg*. 2018; 13(1):36. https://doi.org/10.1186/s13017-018-0192-3
4. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends — an update. *Cancer Epidemiol Biomarkers Prev.* 2016; 25(1):16-27. https://doi.org/10.1158/1055-9965.EPI-15-0578
5. Kaydarova DR, Baltabekov NT, Dushimova ZD, Shatkovskaya OV, Seisenbaeyva GT, Azhmagambetova AE, et al. Indicators of the Oncological Service of the Republic of Kazakhstan for 2019 (statistical and analytical materials) [in Russian and Kazakh]. JSC "Kazakh Institute of Oncology and Radiology" of the Ministry of Health of the Republic of Kazakhstan. Almaty; 2020. 230 p.
6. Kam MH, Tang CL, Chan E, Lim JF, Eu KW. Systematic review of intraoperative colonic irrigation vs manual decompression in obstructed left-sided colorectal emergencies. *Int J Colorectal Dis*. 2009; 24(9):1031-1037. https://doi.org/10.1007/s00384-009-0723-1
7. Harris GJ, Church JM, Senagore AJ, Lavery IC, Hull TL, Strong SA, Fazio VW. Factors affecting local recurrence of colonic adenocarcinoma. Dis. Colon. Rectum. 2002; 45:1029-1034. https://doi.org/10.1007/s10350-004-6355-1
8. Barnett A, Cedar A, Siddiqui F, Herzig D, Fowlkes E, Thomas Jr. CR. Colorectal cancer emergencies. *J Gastrointest Cancer.* 2013; 44(2):132–142. https://doi.org/10.1007/s12029-012-9468-0
9. Gore RM, Silvers RI, Thakrar KH, Wenzke DR, Mehta UK, Newmark GM, Berlin JW. Bowel obstruction. *Radiol Clin N Am*. 2015; 53(6):1225–1240. https://doi.org/10.1016/j.rcl.2015.06.008
10. Catena F., De Simone B., Coccolini F, Di Saverio S, Sartelli M, Ansaloni L. Bowel obstruction: a narrative review for all physicians. World J Emerg Surg. 2019; 14:20. https://doi.org/10.1186/s13017-019-0240-7
11. Webster PJ, Aldoori J, Burke DA. Optimal management of malignant left-sided large bowel obstruction: do international guidelines agree? World J Emerg Surg. 2019; 14(1):23. https://doi.org/10.1186/s13017-019-0242-5
12. Morris EJA, Taylor EF, Thomas JD, Quirke P, Finan PJ, Coleman MP, et al. Thirtyday postoperative mortality after colorectal cancer surgery in England. Gut. 2011; 60(6):806–813. https://doi.org/10.1136/gut.2010.232181
13. Sperry J, Cohen MJ. Acute Obstruction. *Surg Clin North Am*. 2014; 94(1):77-96. https://doi.org/10.1016/j.suc.2013.10.001
14. Stubljar D, Skvarc M. Effective strategies for diagnosis of systemic inflammatory response syndrome (SIRS) due to bacterial infection in surgical patients. *Infect Disord Drug Targets*. 2015; 15(1):53-56. https://doi.org/10.2174/1871526515666150320161804

15. Assimakopoulos SF, Triantos C, Thomopoulos K, Fligou F, Maroulis I, Marangos M, Gogos CA. Gut-origin sepsis in the critically ill patient: pathophysiology and treatment. Infection 2018; 46(6):751-760. https://doi.org/10.1007/s15010-018-1178-5
16. Clark JA, Coopersmith CM. Intestinal crosstalk: a new paradigm for understanding the gut as the 'motor' of critical illness. *Shock*. 2007; 28:384–393. https://doi.org/10.1097/shk.0b013e31805569df
17. Tremaroli V, Backhed F. Functional interactions between the gut microbiota and host metabolism. *Nature*. 2012; 489:242–9. https://doi.org/10.1038/nature11552
18. Kaiko GE, Stappenbeck TS. Host–microbe interactions shaping the gastrointestinal environment. *Trends Immunol*. 2014; 35:538–48. https://doi.org/10.1016/j.it.2014.08.002
19. Kamada N, Chen GY, Inohara N. Control of pathogens and pathobionts by the gut microbiota. *Nat Immunol*. 2013; 14:685–690. https://doi.org/10.1038/ni.2608
20. Natividad JM, Verdu EF. Modulation of intestinal barrier by intestinal microbiota: pathological and therapeutic implications. *Pharmacol Res*. 2013; 69:42–51. https://doi.org/10.1016/j.phrs.2012.10.007
21. Zaborin A, Smith D, Garfield K, Quensen J, Shakhsheer B, Kade M, et al. Membership and behavior of ultra low-diversity pathogen communities present in the gut of humans during prolonged critical illness. *MBio*. 2014; 5:e01361–14. https://doi.org/10.1128/mBio.01361-14
22. McDonald D, Ackermann G, Khailova L, Baird C, Heyland D, Kozar R, et al. Extreme dysbiosis Provisional 40 / 54 of the microbiome in critical illness. mSphere. 2016; 1:e00199–16. https://doi.org/10.1128/mSphere.00199-16
23. Ojima M, Motooka D, Shimizu K, Gotoh K, Shintani A, Yoshiya K, et al. Metagenomic analysis reveals dynamic changes of whole gut microbiota in the acute phase of intensive care unit patients. Dig Dis Sci. 2016; 61:1628–34. https://doi.org/10.1007/s10620-015-4011-3
24. Lankelma JM, van Vught LA, Belzer C, Schultz MJ, van der Poll T, de Vos WM, et al. Critically ill patients demonstrate large interpersonal variation in intestinal microbiota dysregulation: a pilot study. *Intensive Care Med*. 2017; 43:59–68. https://doi.org/10.1007/s00134-016-4613-z
25. Freedberg DE, Zhou MJ, Cohen ME, Annavajhala MK, Khan S, Moscoso DI, et al. Pathogen colonization of the gastrointestinal microbiome at intensive care unit admission and risk for subsequent death or infection. *Intensive Care Med*. 2018; 44:1203–11. https://doi.org/10.1007/s00134-018-5268-8
26. Tan C, Ling Z, Huang Y, Cao Y, Liu Q, Cai T, et al. Dysbiosis of intestinal microbiota associated with inflammation involved in the progression of acute pancreatitis. *Pancreas*. 2015; 44:868–75. https://doi.org/10.1097/MPA.0000000000000355
27. Howard BM, Kornblith LZ, Christie SA, Conroy AS, Nelson MF, Campion EM, et al. Characterizing the gut microbiome in trauma: significant changes in microbial diversity occur early after severe injury. *Trauma Surg Acute Care Open*. 2017; 2:e000108. https://doi.org/10.1136/tsaco-2017-000108
28. Wang X, Yang J, Tian F, Zhang L, Lei Q, Jiang T, et al. Gut microbiota trajectory in patients with severe burn: A time series study. *J Crit Care*. 2017; 42:310–6. https://doi.org/10.1016/j.jcrc.2017.08.020
29. Klingensmith NJ, Coopersmith CM. The gut as the motor of multiple organ dysfunction in critical illness. *Crit Care Clin*. 2016; 32:203–212. https://doi.org/10.1016/j.ccc.2015.11.004
30. Haak BW, Wiersinga WJ. The role of the gut microbiota in sepsis. *Lancet Gastroenterol Hepatol*. 2017; 2:135–43. https://doi.org/10.1016/S2468-1253(16)30119-4
31. Buffie CG, Pamer EG. Microbiota–mediated colonization resistance against intestinal pathogens. *Nat Rev Immunol*. 2013; 13:790–801. https://doi.org/10.1038/nri3535
32. Diehl GE, Longman RS, Zhang JX, Breart B, Galan C, Cuesta A, et al. Microbiota restricts trafficking of bacteria to mesenteric lymph nodes by CX3CR1hi cells. *Nature*. 2013; 494(7435):116–120. https://doi.org/10.1038/nature11809
33. Farache J, Koren I, Milo I, Gurevich I, Kim KW, Zigmond E, et al. Luminal bacteria recruit CD103+ dendritic cells into the intestinal epithelium to sample bacterial antigens for presentation. Immunity. 2013; 38(3):581–595. https://doi.org/10.1016/j.immuni.2013.01.009
34. Meng M, Klingensmith NJ, Coopersmith CM. New insights into the gut as the driver of critical illness and organ failure. *Curr Opin Crit Care*. 2017; 23(2):143-148. https://doi.org/10.1097/MCC.0000000000000386
35. Kabaroudis A, Papaziogas B, Koutelidakis I, Kyparissi-Kanellaki M, Kouzi-Koliakou K, Papaziogas T. Disruption of the small-intestine mucosal barrier after intestinal occlusion: a study with light and electron microscopy. *J Invest Surg*. 2003; 16(1):23–28 https://doi.org/10.1080/08941930390153069
36. Sagar PM, MacFie J, Sedman P, May J, Mancey-Jones B, Johnstone D. Intestinal obstruction promotes gut translocation of bacteria. *Dis Colon Rectum*. 1995; 38(6):640–644 https://doi.org/10.1007/BF02054126
37. 37. Kamada N, Kim YG, Sham HP, Vallance BA, Puente JL, Martens EC, et al. Regulated virulence controls the ability of a pathogen to compete with the gut microbiota. *Science* 2012; 336:1325–9. https://doi.org/10.1126/science.1222195
38. de Sablet T, Chassard C, Bernalier-Donadille A, Vareille M, Gobert AP, Martin C. Human microbiota-secreted factors inhibit Shiga toxin synthesis by enterohemorrhagic Escherichia coli O157:H7. *Infect Immun*. 2009; 77:783–90. https://doi.org/10.1128/IAI.01048-08
39. Hamer HM, De Preter V, Windey K, Verbeke K. Functional analysis of colonic bacterial metabolism: relevant to health? *Am J Physiol Gastrointest Liver Physiol*. 2012; 302:G1–9. https://doi.org/10.1152/ajpgi.00048.2011
40. McCall IC, Betanzos A, Weber DA, Nava P, Miller GW, Parkos CA. Effects of phenol on barrier function of a human intestinal epithelial cell line correlate with altered tight junction protein localization. *Toxicol Appl Pharmacol*. 2009; 241:61–70. https://doi.org/10.1016/j.taap.2009.08.002
41. Cox LM, Yamanishi S, Sohn J, Alekseyenko AV, Leung JM, Cho I, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. Cell. 2014; 158:705–21. https://doi.org/10.1016/j.cell.2014.05.052
42. Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. *Nature*. 2016; 535(7610):65–74. https://doi.org/10.1038/nature18847
43. Levy M, Kolodziejczyk AA, Thaiss CA, Elinav E. Dysbiosis and the immune system. *Nat Rev Immunol*. 2017; 17:219-232. https://doi.org/10.1038/nri.2017.7
44. van der Poll T, van de Veerdonk FL, Scicluna BP, Netea MG. The immunopathology of sepsis and potential therapeutic targets. Nat Rev Immunol. 2017; 17:407–420. https://doi.org/10.1038/nri.2017.36
45. Delano MJ, Ward PA. Sepsis–induced immune dysfunction: can immune therapies reduce mortality? *J Clin Invest*. 2016; 126:23–31. https://doi.org/10.1172/JCI82224
46. Deitch EA. Bacterial translocation or lymphatic drainage of toxic products from the gut: what is important in human beings? Surgery. 2002; 131(3):241–244 https://doi.org/10.1067/msy.2002.116408

47. Zapater P, Francés R, González-Navajas JM. Serum and ascitic fluid bacterial DNA: a new independent prognostic factor in noninfected patients with cirrhosis. Hepatology. 2008; 48:1924-1931. https://doi.org/10.1002/hep.22564
48. Brennan CA, Garrett WS. Gut microbiota, inflammation, and colorectal cancer. *Annu Rev Microbiol.* 70:395–411. https://doi.org/10.1146/annurev-micro-102215-095513
49. Baumgart DC, Dignass AU (2002) Intestinal barrier function. *Curr Opin Clin Nutr Metab Care.* 2016; 5:685-694. https://doi.org/10.1097/00075197-200211000-00012
50. Schietroma M., Pessia B., Colozzi S. Septic complications after resection for middle or low rectal cancer: role of gut barrier function and inflammatory serum markers. *Dig Surg.* 2017; 34(6):507–517. https://doi.org/10.1159/000475847
51. Wiest R, Rath HC. Bacterial translocation in the gut. Best Pract Res Clin Gastroenterol; 2003; 17:397-425. https://doi.org/10.1016/s1521-6918(03)00024-6
52. Steinberg SM. Bacterial translocation. What it is and what it is not. *Am J Surg*. 2003; 186:301-305. https://doi.org/10.1016/s0002-9610(03)00220-4
53. Dederer YuM. Pathogenesis and treatment of acute bowel obstruction. *Moskva: Medicine;* 1971.
54. Achkasov EE, Alekperov SF, Melnikov PV. Histopathological changes in the intestine with colon tumor obstruction [in Russian]. Biomedicine. 2012; 4:117-127.
55. Zembower TR. Epidemiology of infections in cancer patients. *Cancer Treat Res*. 2014; 161:43–89. https://doi.org/10.1007/978-3-319-04220-6_2
56. Galloway-Peña J, Brumlow C, Shelburne S. Impact of the Microbiota on Bacterial Infections during Cancer Treatment. *Trends Microbiol.* 2017; 25(12):992-1004. https://doi.org/10.1016/j.tim.2017.06.006
57. Sears CL, Garrett WS. Microbes, microbiota, and colon cancer. *Cell Host Microbe.* 2014; 15(3):317–328. https://doi.org/10.1016/j.chom.2014.02.007
58. Irrazabal T, Belcheva A, Girardin SE, Martin A, Philpott DJ. The multifaceted role of the intestinal microbiota in colon cancer. *Mol Cell.* 2014; 54(2):309– 320. https://doi.org/10.1016/j.molcel.2014.03.039
59. van Praagh JB, de Goffau MC, Bakker IS. van Goor H, Harmsen HJM, Olinga P, Havenga K. Mucus microbiome of anastomotic tissue during surgery has predictive value for colorectal anastomotic leakage. *Ann Surg.* 2019; 269: 911–916. https://doi.org/10.1097/SLA.0000000000002651
60. Takesue Y, Kakehashi M, Ohge H, Uemura K, Imamura Y, Murakami Y, et al. Bacterial translocation: not a clinically relevant phenomenon in colorectal cancer. *World J Surg.* 2005; 29(2):198-202. https://doi.org/10.1007/s00268-004-7576-0
61. Ivachyov P, Amanova D, Akhmaltdinova L, Koishibayev Z, Turgunov E. Comparison of dynamics of level of procalcitonin, lipopolysaccharide binding protein and interleukin-6 in blood serum of experimental animals at strangulated and obturative intestinal obstruction. Georgian Med. *News.* 2020; 303:173-177.
62. Mugazov M, Turgunov Y, Kaliyeva D, Matyushko D, Koishibayev Z, Omertayeva D, et al. The role of presepsin in patients with acute surgical diseases. Open Access Maced. *J. Med. Sci*. 2019; 7(8):1282-1286. https://doi.org/10.3889/oamjms.2019.292

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The effect of intensive care specialist on mortality in a Teaching Hospital in Turkey

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Abstract

Aim: Specialization in critical care, which has a long history in various countries, is still developing in our country, and the practical outcomes of this relatively new discipline are yet to be not fully understood in our country. In the present study, we investigate the effect on mortality of the introduction of intensivists to a Level III closed intensive care unit.

Material and methods: The study was launched after being granted approval by the ethics committee. In this retrospective study we included the patients who were treated in the same period in two consecutive years. We excluded who were under the age of 18 years, who stayed in the intensive care unit for less than 24 hours and postoperative patients. For the purpose of the study, the patients were divided into intensivist and pre-intensivist groups.

Results: Aside from the shorter stay at the intensive care unit in intensivist group, mortality rate was lower in the pre-intensivist group, there was no statistically significant difference between the intensivist and pre-intensivist groups.

Conclusion: Intensivists have positive effects on patients' clinical outcomes, although a change in even a single factor during the treatment of ICU patients does not be sufficient for a statistical difference.

Key words: intensive care specialist, mortality, length of stay, intensive care

Introduction

An intensivist is a medical professional who has undergone training in critical patient care in a standardized program [1]. Such specialists are responsible for making clinical decisions and patient's admission to and discharge from Intensive Care Unit (ICU) [2]. Their interventions have been found to improve patient outcomes in the intensive care where a multidisciplinary approach is required [3, 4].

In Turkey ICUs are classified in three categories as 1st, 2nd and 3rd levels: Level 3 units are the services where a specialist doctor is available for 24 hours, laboratory and radiology services are provided and advanced invasive monitoring can applied. Level 3 ICUs are usually closed type ICUs which the responsible of the patient is an intensive care physician [5,6]. In our country usually anesthesiology and reanimation department's physicians are responsible for patients. Subspecialty training in intensive care medicine started in 2012, and first multidisciplinary intensivists started to take up positions in 2016. There is still a lack of data on the effect of intensivists on patients' outcomes in multidisciplinary ICUs in Turkey.

In this study we aim to investigate the effect of intensivists who started working in multidisciplinary ICUs on ICU patients' outcomes.

Material and methods

This study was launched after approval was granted by the Ethics Committee of the Republic of Turkey …….. ethical committee (dated …… and No: ……). The study data was garnered from the records of patients admitted to a multidisciplinary adult ICU between January 1, 2017 and June 30, 2017, and between January 1, 2018 and June 30, 2018. The ICU in question provides services under the Anesthesiology and Reanimation Department of the TC SBÜ Bursa Yüksek İhtisas Training and Research Hospital, which is equipped with 17 Level III intensive care beds and four postoperative care beds.

Patients who stayed in the ICU for fewer than 24 hours, those who died within the first 24 hours of admission, and those who were admitted for postoperative

care were excluded from the study. To ensure similar patient density and working patterns, and to reduce seasonal effects, the study included patients who stayed in the unit in the same period in two consecutive years.

The number of nurses was same in both periods for which the records were examined. The working pattern called for one nurse for every two patients, while dayshift physicians prior to 2018 worked in monthly rotations with two anesthesiology and reanimation specialists and one research assistant from the Anesthesiology and Reanimation Department. In August 2017, a physician with a subspecialty in intensive care started work in the general ICU of the hospital. Subsequently, in September 2017 the working pattern of intensive care physicians was given a permanent structure, with the intensivist as the team leader, supported by one anesthesiology and reanimation specialist and one research assistant from the Anesthesiology and Reanimation Department, working in monthly rotations. The night shift and holiday working schedule were same throughout the study, involving one research assistant with at least two years of experience, who was permanent member of staff in the ICU, and one on-call anesthesiologist who was responsible for ICUs and the operating room. The intensivist, when not in attendance available, was on-call via telephone in holidays and nights.

The patients were divided into an intensivist group, who were monitored and treated by the intensivist; and a pre-intensivist group, who were monitored by the anesthesiology and reanimation specialists. The hospital information management system and patient medical records were then accessed for data on causes of admission, referring departments, length of ICU stay, APACHE 2 score, age, gender and mortality rates.

All data were entered into and analyzed with the SPSS (Statistical Package for Social Sciences) for Windows 22 software package. For the data analysis, first, the assumptions that were to be met were tested for the determination of the required tests (parametric/non-parametric tests). The normality of distribution was analyzed with a Kolmogorov-Smirnov test, a Shapiro-Wilk test, kurtosis and skewness values, as the other assumptions of normal distribution, and histograms. An independent two-sample comparison was made with a t-test (Independent Samples t-test) for normally distributed data, while a Mann-Whitney U-test was applied to non-normally distributed data. The differences between two independent categorical variables were tested using Fisher's Exact Chi-square test when the assumptions were not met. The significance of the study results were interpreted based on a significance level of 0.05.

Results

The number of patients who stayed in the ICU in the first six months of 2017 was 452, compared to 559 in the first 6 months of 2018. Of the total, 323 patients were excluded from the study for 2017 and 362 patients for 2018 due to admission for postoperative care and a stay of less than 24 hours. Consequently, the pre-intensivist group included 127 patients and the intensivist group included 197 patients. The characteristics of the study participants are presented in Table 1; both groups of patients had similar characteristics and APACHE 2 score.

The length of ICU stay was shorter in the intensivist group, although the difference was not statistically significant, and the length of stay at the ward after discharge from the ICU was shorter in the pre-intensivist group, with a statistically significant difference (Table 1).

Table 1 Patient characteristics, diagnoses and department of referral to ICU

		Pre-Intensivist	Intensivist	P
		(n=129)	(n=197)	
Gender	Female (n/%)	52/40.31	79/40.10	
	Male (n/%)	77/59.69	118/59.90	
Age (mean ± SD)		61.53±21.42	1.55±20.06	0.993
APACHE 2 (mean ± SD)		26.84±9.00	25.80±7.28	0.302
Length of ICU stay (days) (mean rank)		173.87	155.94	0.09
Mortality (n/%)		47/33.07%	84/42.63%	0.26
Hospitalization after ICU (days) (mean rank)		101.28	204.25	0.01
Diagnostic Categories of Patients (n/%)	Endocrinological	1/0.78	3/1.52	
	Gastroenterological	4/3.1	10/5.08	
	Intoxication	3/2.33	2/1.02	
	Cardiac	15/11.63	14/7.11	
	Malignancy	2/1.55	6/3.05	
	Neurological	35/27.13	60/30.46	
	Renal	6/4.65	3/1.52	
	Sepsis	6/4.65	9/4.57	
	Respiratory	33/25.58	58/29.44	
	Trauma	24/18.6	31/15.74	
	Hematological	0/0	1/0.51	
Department of referral (n/%)	Emergency Department	77/59.99	116/58.88	
	External center	12/9.3	14/7.11	
	Other ICU	6/4.65	13/6.6	
	Wards	34/26.36	54/27.41	

Table 2 Mortality rates

	Pre-intensivist n=129	Intensivist n=197	P
Survived	82/63,56%	113/56,71%	0.26
Died	47/36.43%	84/43,29%	

The pre-intensivist group of patients recorded lower ICU mortality than the intensivist group, but not to a statistically significant degree (Table 2).

Discussion

It is known that a full-time intensivist working in an intensive care unit (ICU) will have a positive effect on mortality [7,8]. In a study comparing 200 randomized surgical patients, one group of patients were under the care of a surgeon, while the other group was under the care of an on-site intensive care team. Although the patients under the intensive care team had higher disease severity (APACHE II) scores, their ICU stays were shorter, they were mechanically ventilated for a shorter time, there was less need for blood and blood products, and had around one-third of the complications as compared to the other group [9]. Morbidity and mortality have been show to decrease in several disease groups when hospital admission, follow-up, treatment and discharge decisions were made by an intensivist [10], although these studies were based on the open vs closed type of ICU working systems. In open unit model ICUs; patients are admitted under the care of an internist, family physician, surgeon, or any other primary attending physician, with the intensivists being available to provide their expertise via elective consultation [6]. These studies have generally demonstrated the positive effects of intensivists on mortality. In our country, ICUs have a relatively different working system, with critical patients cared for in closed intensive care units that are usually managed by the anesthesiology and reanimation departments. Anesthesiology is a medical discipline that takes an integrated approach to patients and diseases and has a wider perspective, unlike disciplines focused on specific organ systems. Accordingly, ICUs tend to be established under the anesthesiology and reanimation departments in our country, similar vein to the organizational structures seen in Europe [11]. Our study has compared the full-time intensivist period and the pre-intensivist period in the closed type ICU connected to the anesthesiology department, no statistically significant difference was identified in either mortality or length of ICU stay.

The intensivist started to work in the ICU in which the study was conducted in August 2017. The study periods were chosen specifically to avoid bias, and the same periods in two consecutive years were chosen to minimize the effects of other variables. No statistically significant difference in mortality was identified between the intensivist and the pre-intensivist groups for the two comparison periods, although a lower mortality rate was noted in the pre-intensivist group. Anesthesiologists were working in monthly rotations in ICU, and we believed that the reduced ICU adaptation of the physicians due to the working pattern of the pre-intensivist group may have had an impact on patient outcomes through the sense of provisionality towards the ICU. This orientation period of the new monthly working pre-intensivist may prolong the discharge and other therapeutic decision periods and end up with the long length of ICU stay in pre-intensivist group. Additionally, futile treatment may be avoided in the presence of a full-time intensivist in the ICU.

A previous study conducted in a cardiovascular surgical intensive care unit of a university hospital in our country compared the outcomes of postoperative patients managed by intensivists and by cardiovascular surgeons. It was found that outcomes such as mortality and length of ICU and hospital stay were similar in the postoperative period following cardiac surgery after intensivists started to manage cardiovascular ICU. While there was a shorter duration of mechanical ventilation, a lower requirement for blood and blood products, and decreased incidences of ICU readmission, all of which are significant indicators of morbidity [12].

Although not to a statistically significant degree, the length of ICU stay was clinically significantly shorter in the intensivist group in our study. The 1.5 times increase in the number of patients admitted in the same period suggests a quicker patient admission and discharge cycle, which may explain the increased patient admission. A protocol-based current approach, a sense of ownership of the ICU, patient–patient relative communication, and especially, continuity in communication with other intensive care staff may result as short length of ICU stay in intensivist group [13-15]. Additionally, the length of hospital stay in ward which evaluated among the patients discharged from the ICU to the ward, was longer and statistically significant in the intensivist group. Because of the approach of pre-intensivists although the patients were no longer indicated for ICU stay, they were expected to have complete or near-complete recovery in the ICU because these clinicians who could not adapt to the intensive care medicine [16]. The approach of intensivists, in contrast, is to discharge patients to the wards at a recovery level that is as yet unfamiliar to clinicians, which might have led to the longer wards stays.

Our study cannot be generalized to the whole country, because of different stuffing and working patterns in different kinds of hospitals. Majority of teaching hospitals ICU's managed by anesthesiology department but their stuffing patterns may be different. Also private hospitals, state hospitals and university hospitals have different working systems.

Conclusion

Our study is the first to investigate the effects of intensivists on patient outcomes in closed ICU in Turkey, but failed to demonstrate statistically the extent to which intensivist involvement improved mortality. No short-term effects on patient outcomes should be expected to result from a change in a single component of intensive care practice, which is carried out as a team. As such, long-term outcomes should be investigated in future studies.

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References

1. Amin P, Robichaud AF, Divatia JV, Pelosi P, Altintas D, Eryüksel E, et al. The intensive care unit specialist: report from the Task Force of World Federation of Societies of Intensive and Critical Care Medicine. *J Crit Care.* 2016; 35:223-8. DOI: 10.1016/j.jcrc.2016.06.001
2. Valentin A, Ferdinande P, ESICM Working Group on Quality Improvement. Recommendations on basic requirements for intensive care units: structural and organizational aspects. *Intensive Care Med.* 2011; 37(10):1575-87. DOI: 10.1007/s00134-011-2300-7
3. Yang Q, Du JL, Shao F. Mortality rate and other clinical features observed in Open vs closed format intensive care units: A systematic review and meta-analysis. *Medicine*. 2019; 98(27):e16261. DOI: 10.1097/MD.0000000000016261
4. Klouwenberg PMK, Ong DYS, Bos LDJ, de Beer FM, van Hooijdonk RTM, Huson MA, et al. Interobserver agreement of Centers for Disease Control and Prevention criteria for classifying infections in critically ill patients. *Crit Care Med*. 2013; 41(10):2373-8. DOI: 10.1097/CCM.0b013e3182923712
5. TC Sağlık Bakanlığı Sağlık Hizmetleri Genel Müdürlüğü. 2008/53 Numaralı Yoğun Bakım Ünitelerinin Standartları Genelgesi. URL: https://www.saglik.gov.tr/TR,10979/yogun-bakim-unitelerinin-standartlari-genelgesi-200853.html. *Last Access time* 12 Jan 2021
6. Chowdhury D, Duggal AK. Intensive care unit models: Do you want them to be open or closed? A critical review. *Neurology India.* 2017; 65(1):39-45. DOI: 10.4103/0028-3886.198205
7. Nagendran M, Dimick JB, Gonzalez AA, Birkmeyer JD, Ghaferi AA. Mortality Among Older Adults Before Versus After Hospital Transition to Intensivist Staffing. *Med Care.* 2016; 54(1):67-73. DOI: 10.1097/MLR.0000000000000446
8. Costa DK, Wallace DJ, Kahn JM. The association between daytime intensivist physician staffing and mortality in the context of other ICU organizational practices: a multicenter cohort study. *Crit Care Med.* 2015; 43(11):2275. DOI: 10.1097/CCM.0000000000001259
9. Hanson CW, Deutschman CS, Anderson HL, Reilly PM, Behringer EC, Schwab CW, Price J. Effects of an organized critical care service on outcomes and resource utilization: a cohort study. Crit Care Med. 1999; 27(2):270-274. DOI: 10.1097/CCM.0000000000001259
10. Çelikel T. Dünyada ve Türkiye'de Yoğun Bakım Uzmanlığı. *Yoğun Bakım Dergisi.* 2001; 1(1):5-9.
11. Telci L. Gökten Üç Elma Düştü. *J Turk Soc Intens Care* 2020; 18(1):0-0
12. Topal ZB. Açık kalp ameliyatı geçiren hastalarda yoğun bakım uzmanı yöntemli hasta takibinin morbidite ve moralite üzerine etkisi. Ankara: Başkent Üniversitesi Tıp Fakültesi Anesteziyoloji ve Reanimasyon Anabilim Dalı Tıpta Uzmanlık Tezi. 2018.
13. Quenot JP, Ecarnot F, Meunier-Beillard N, Dargent A, Eraldi JP, Bougerol F, et al. What are the ethical dimensions in the profession of intensive care specialist? *Annals of Translational Medicine.* 2017; 5(4):47. DOI: 10.21037/atm.2017.09.34
14. Baykara N, Utku T, Alparslan V, Arslantaş MK, Ersoy N. Factors affecting the attitudes and opinions of ICU physicians regarding end-of-life decisions for their patients and themselves: A survey study from Turkey. *PLOSONE.* 2020; 15(5):e0232743. DOİ:10.1371/journal.pone.0232743
15. Akpir K. Yoğun Bakım Etiği. *J Turk Soc Intens Care.* 2010; 8(2):77-84. DOI: 10.4274/tybdd.08.06
16. Gershengorn HB. Is My Intensivist Better Than Your Intensivist? *Ann AM Thorac Soc*. 2018; 15(3):312-314.

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The role of ROX and mROX indices in predicting intubation in COVİD 19 patients treated with high flow nasal oxygen in Intensive Care Unit

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Abstract

Aim: In Coronavirus disease 2019 (COVID-19) - related respiratory failure, high-flow nasal oxygen (HFNO) therapy may delay invasive ventilation. The respiratory rate oxygenation (ROX) and modified ROX (mROX) indices, which can predict the need for invasive ventilation, can also be used in patients with COVID-19 with respiratory failure. The aim of the study was to verify the effectiveness of ROX and mROX to predict entubation need in HFNO therapy patients in intensive care unit.

Material and methods: This retrospective study included 41 patients in the final evaluation.

Results: The overall mortality of patients with similar demographic and laboratory data was 60,97%. Invasive ventilation was required in 27 patients. The cutoff values for prediction of intubation for ROX and mROX at 6 h were determined as 4,95 and 6,01. Conclusion: These indices can predict the need for invasive ventilation during the follow-up of COVID 19 patients who undergo HFNO and can help prevent adverse outcomes.

Key words: ROX, mROX, HFNO, COVİD19, ICU

Introduction

High-flow nasal oxygen (HFNO), a humidified and heated oxygen-rich gas, is administered in patients by special nasal high-flow cannulas. Generally, high flow rates of 30–60 L/min are used. The high flow provides a more stable inspiratory oxygen concentration and positive end-expiratory pressure in the airways compared with conventional oxygen therapy [1]. HFNO has been found to reduce the work of breathing and need for invasive ventilation by reducing physiological dead space in studies involving patients with respiratory failure due to other viral pneumonias [1].

The initial message from the Chinese medical teams was to intubate Coronavirus disease 2019 (COVID-19) patients early, somewhere around a 5-6 liter by nasal prong O2 requirement. However, this also has come at a cost. Mechanical ventilation is inherently associated with a number of well described and accepted complications [2]. Also the use of HFNO was limited in the early stages of the COVID-19 pandemic due to fear of the increased risk of viral transmission through aerosol in patients who developed respiratory failure [3]. The use of HFNO has increased in this patient group, with increasing data indicating that aerosol transmission is not as efficient a transmission route as it was speculated initially [4]. However to the best of our knowledge there is no evidence at an advanced level regarding the use of HFNO in acute respiratory failure due to COVID-19 pneumonia. Despite HFNO large swings in intra-pleural pressure may result in self-inflicted lung injury and worsen the disease process. For this reason it has been stated that delayed intubation and mechanical ventilation support in patients with COVID-19 undergoing HFNO may increase the mortality rate [5].

Respiratory rate oxygenation (ROX) index was developed by Roca et al. to predict the need for intubation and mechanical ventilation in patients who underwent HFNO due to acute respiratory failure secondary to bacterial pneumonia [6]. ROX index, which is defined as ratio of SpO2/FiO2 to the respiratory rate, is easily measured at the bedside, and an ROX score of <3.47 at 6 h has been considered a predictor of HFNO failure. In addition, Goh et al. created a modified ROX (mROX) index incorporating heart rate to improve its diagnostic value [7]. However, data are limited with the use of these two indices in acute respiratory failure due to COVID-19 in intensive care [8].

Our purpose was to evaluate the ROX [6] and

mROX [7] index defined as an early marker of HFNO response and a potential predictor of its failure in the COVİD19 ICU patients with intended to contribute to literature.

Material and methods

The study was planned as a single-center retrospective study. The study was initiated after obtaining an approval from the The study was initiated after obtainig an approval from the ethical commitee. (2011-KAEK-25 2020/06-05 TC SBÜ Bursa Yüksek İhtisas EAH KAEK) ethics committee of YYYY university/institute. Nasopharyngeal swab polymerase chain reaction (PCR) positive patients with COVID-19 with respiratory failure with respiratory rate >30/min and SpO2 <90% despite receiving oxygen with a reservoir mask at 15 L/min and treated with HFNO as first-line ventilator support/who received only HFNO during intensive care follow-up in May and June in the 21-bed adult general intensive care unit of our hospital were included in the study. Patients who underwent noninvasive mechanical ventilation at baseline and did not receive HFNO therapy were excluded from the study. HFNO-related data was collected from admission until HFNO weaning or intubation which defined HFNO failure.

Medical therapy

COVID-19 treatments were arranged according to the current treatment guidelines based on national treatment protocols [9]. 6 mg dexamethasone or 1 mg/kg methylprednisolone treatment, defined as additional treatment in these protocols, was administered to all patients.

HFNO therapy

HFNO therapy was administered via Draeger (Lübeck, Germany) Evita V300 mechanical ventilator. HFNO therapy starts with 50 L/min flow, FiO2 1 and 37°C air temperature. The target SpO2 was set at 90%. When SpO2 was ≥ 90%, the oxygen ratio was first reduced to 0.6, and if no regression was detected in the follow-up values, the flow rate was reduced. HFNO therapy was discontinued in patients with oxygen rate of 0.5 and flow rate of 20 L/min. During HFNO therapy, a surgical mask was placed on the patient's face to reduce aerosol emission, and intermittent prone positioning was applied as per the protocol. Patients with worsening of oxygen saturation levels or clinical deterioration despite HFNO therapy were detected to require intubation and switched to invasive/noninvasive mechanical ventilation.

Outcome measures

ROX and mROX indices at 2, 6, 12, and 24 h following HFNO were determined as the primary outcome measures. ROX index was calculated by dividing the SpO2/Fio2 value by the number of respiration and mROX by dividing the ROX value by the heart rate and multiplying with 100. The duration of HFNO, time until intubation or HFNO withdrawal (days) and hospitalization laboratory parameters were recorded as secondary outcomes. The demographic data of the patients were taken from the electronic database of our hospital.

Statistical analysis

Statistical analyses were performed using SPSS 22 (IBM, USA) package program with significance of $p<0.05$. Categorical variables are described as number (%) and numerical variables as median and interquartile range (IQR). Categorical variables were evaluated using the appropriate chi-square and Fisher's exact test. Mann–Whitney U test was used to determine the statistical difference between the numerical values of the ROX and mROX at 2, 6, 12, 18, and 24-h and the successful and failed HFNO groups. The effect of statistically significant parameters on survival was examined using COX regression analysis. Receiver operating characteristic (ROC) curve analysis of the values determined to have an effect on survival was performed, and the cutoff values and area under the curve values for ROX and mROX were calculated.

Results

During the study period, 127 patients were admitted to the intensive care unit. In total, 41 patients, 23 males and 18 females, meeting the study criteria were included in the evaluation (Table 1). Of the patients, 33 were found to have at least one additional disease. There was no statistically significant difference between the groups in terms of comorbidities. The most common additional disease was diabetes mellitus (48,78%). No statistically significant difference was found between the d-dimer, ferritin, fibrinogen, c reactive protein, values of the patients. Among them, 27 required intubation and 16 were discharged from the intensive care unit (Table 2). In total, 25 (60.97%) of patients died in the intensive care unit.

ROX and mROX indices diagnostic efficacy

COX analysis was performed to predict the need for intubation and evaluate its effect on survival in our study patients. In the survival analysis performed for statistically significant scores of mROX at 6, 18, and 24 h and ROX at 6 h (Table 2), it was determined that the 6-h mROX and ROX values had a statistically significant negative effect on survival (mROX: p = 0.02, hazard ratio [HR] = 0.77 [0.62–0.96]; ROX: p = 0.04, HR = 0.72 [0.53–0.98]).

Table 1 Demographic Data

	HFNO succeed (n:14)	HFNO failed (n:27)	z	p
Age	72.00 (59.50-78.75)	70.00 (65.00-79.00)	-0.51	0.61
APACHE1 2	19.50 (15.00-22.50)	21.00 (16.00-25.00)	-1.07	0.29
ICU LOS2 (day)	10.50 (8.75-14.25)	9.00 (6.00-13.00)	-1.09	0.28
HFNO3 Therapy (day)	6.00 (4.75-9.25)	3.00 (2.00-4.00)	-3.34	0.01
Gender n, (%)				
Male	8 (34.8)	15 (65.2)	X2:0.03	0.92
Female	6 (33.3)	12 (66.7)		

1:Acute Physiologic and Chronic Health Evaluation Score 2, 2:Intensive Care Length of Stay, 3: High Flow Nasal Oxygen
z: Mann Whitney-U test; X2: Chi-square test

Table 2 ROX and mROX indicies

		Median (IQR 1-3)	z	p
ROX 2	HFNO succeeded	4.38 (3.33-6.57)	-0.811	0.417
	HFNO failed	4.80 (4.31-6.14)		
ROX 6	HFNO succeeded	4.61 (3.95-5.83)	-2.145	0.032
	HFNO failed	5.65 (4.69-6.94)		
ROX 12	HFNO succeeded	4.94 (3.83-6.28)	-0.564	0.573
	HFNO failed	5.21 (4.63-6.19)		
ROX 18	HFNO succeeded	4.62 (4.10-6.23)	-1.457	0.145
	HFNO failed	5.97 (4.74-7.35)		
ROX 24	HFNO succeeded	4.08 (3.73-5.11)	-1.54	0.124
	HFNO failed	4.92 (4.14-6.33)		
mROX2	HFNO succeeded	6.31 (4.76-7.91)	-1.70	0.09
	HFNO failed	5.19 (3.58-6.87)		
mROX6	HFNO succeeded	7.50 (6.14-10.17)	-3.24	0.01
	HFNO failed	5.00 (4.24-6.50)		
mROX12	HFNO succeeded	7.42 (5.49-8.74)	-1.80	0.07
	HFNO failed	5.60 (3.93-7.49)		
mROX18	HFNO succeeded	7.75 (5.86-8.80)	-3.12	0.01
	HFNO failed	5.36 (4.14-6.35)		
mROX 24	HFNO succeeded	7.11 (5.41-7.87)	-2.83	0.01
	HFNO failed	4.65 (3.84-6.00)		

z: Mann Whitney-U test

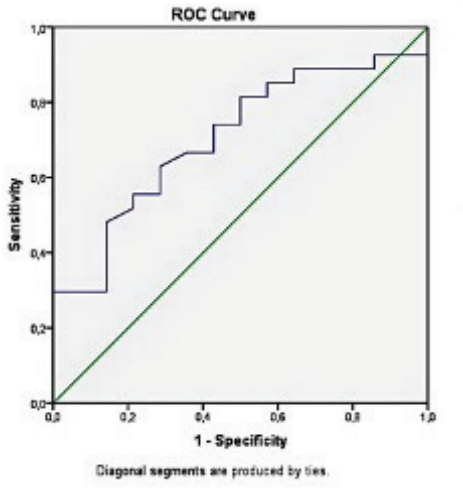

Figure 2 - ROX index ROC curve

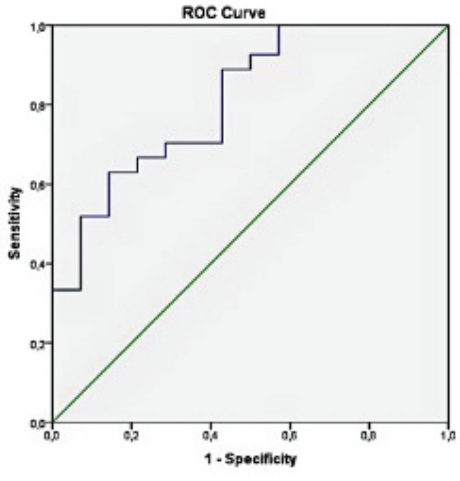

Figure 2 - mROX index ROC curve

ROC analysis was performed to determine the cutoff values of the 6-h ROX and mROX values, which were statistically significant. From this analysis, the cutoff point for HFNO success was 6.01 for mROX (sensitivity 62.96%, specificity 85.71%, area under the curve 0.812 with p<0.05) and 4.95 for ROX (sensitivity 60.61%, specificity 71.43%, area under the curve 0.706 with p<0.05; Figures 1 and 2; area under ROC curves).

Discussion

In our intensive care unit, 14 (34.14%) of our 41 patients who underwent HFNO due to respiratory failure related to PCR-positive COVID-19 pneumonia did not require invasive mechanical ventilation. Of the patients, 27 were switched to invasive mechanical ventilation and 2 were able to wean off the invasive ventilation. In our patients who underwent HFNO, the 6-h ROX and mROX values were found to be significant in predicting the need for invasive mechanical ventilation, and patients with cutoff values <4.95 and <6.01 needed intubation.

Although there are limited data regarding the use of HFNO in respiratory failure due to COVID-19 pneumonia, there are studies indicating its potential reducing the need for invasive ventilation in patients with COVID-19 [3,10]. HFNO may help avoid the potential risks of endotracheal intubation and mechanical ventilation and compensate for the lack of mechanical ventilators in pandemic conditions. However, it is hard to determine when to switch to invasive ventilation in patients with COVID-19. Some authors have emphasized that in patients breathing spontaneously, deep sighing respiration will cause large fluctuations in transpulmonary pressure, resulting in self-induced lung injury [11]. Therefore, they recommended early intubation. However, the studies conducted were not sufficient to show difference in survival between early and late intubations in patients with COVID-19 [12,13]. As the intubation criteria and times differ in such studies, it is difficult to make a comparison. In our patients, intubation need was decided by the ICU physician and the patient's clinical parameters were prioritized. In the group unresponsive to HFNO among our patients, the mean time until intubation and invasive ventilation was 3 days, and it was relatively late. Likewise, the mortality rate (60.97%) of our patients who were unresponsive to HFNO and switched to invasive mechanical ventilation was found to be high. We believe that this high rate might be due to the pathophysiological differences of classic acute respiratory distress syndrome and respiratory failure due to COVID19 rather than the timing of intubation [14].

ROX index recommended by Roca et al. to predict the need for invasive ventilation in patients who developed respiratory failure due to pneumonia and underwent HFNO can also be used in patients with COVID-19 [15–17]. In our study, ROX and mROX indices were evaluated intermittently at the first 2, 6, 12, 18, and 24 h of HFNO application. We determined that the 6-h values of these indices could predict intubation in our patients. In addition, the cutoff values for 6-h ROX and mROX values to predict intubation in our study were 4.95 and 6.01, respectively. Roca et al. stated that patients with a 6-h ROX value >4.88 had lower need for intubation. Although this value has been evaluated in patients with non-COVID-19 respiratory failure, our results are also remarkably close to these values. Belz et al. used the original cutoff value of 4.88 to predict the need for intubation in intensive care patients who underwent HFNO due to COVID-19 and found 81% sensitivity and 38% specificity [18]. In our study, we determined that the cutoff value was 4.95 with 60.61% sensitivity and 71.43% specificity. According to our findings,

6-h ROX values can help predict patients who will benefit from HFNO. In addition, Suliman et al. monitored the ROX index for 3 consecutive days and evaluated their patients' intubation needs in the first week [15]. They stated that the ROX index (adjusted odds ratio [95% CI]: 16.9 [2.4–117], 0.77 [0.69–0.86]) measured only on day 1 was an independent factor in predicting intubation. Although we determined the need for intubation at any time as the endpoint for our study, intubation need emerged, on average, on day 3 in our patient group. This outcome, led us to think that the evaluated index could be used to predict the intubation need in a relatively short term. It seems reasonable to avoid unnecessary intubation and administer HFNO for a longer time by evaluating the ROX index in the patients.

Goh et al. in their studies on patients with non-COVID-19 respiratory failure stated that mROX was more effective in predicting the need for intubation for the same hours evaluated in patients who received HFNO compared with the original index of Roca et al [7]. In our study on patients with COVID-19, we found that 6-h mROX score <6.01 was effective in predicting the need for intubation. In addition, we found that 6-h mROX score was slightly more effective than the 6-h ROX index (sensitivity 62.96% and specificity 85.71%). We suggest that the index, which has not been validated yet but can be easily calculated at the bedside, can be used in addition to the original index to predict the need for invasive ventilation in patients with respiratory failure due to COVID-19 pneumonia who undergo HFNO. There is no study in the literature using mROX values in patients with COVID-19. The major limitation of this index, which is used in different disease groups, is that it is affected by drugs that affect heart rate.

The mROX index can be overestimated in the use of drugs such as beta blockers and opiates that may cause bradycardia. In patients using these drug groups, it may be necessary to evaluate the intermittent measurements and consider the trend of the mROX index instead of making a decision with a single measurement. Among our study patients, no one used drugs of these classes.

The 6-h mROX index evaluated within the scope of this study may be successful in predicting the success of HFNO therapy. We believe that following the standard medical (e.g., favipiravir and hydroxychloroquine) and additional (intermittent prone positioning) treatment protocols according to the national treatment protocol increases the accuracy of the results of the mROX index.

Limitation

The main limitation of this study is the retrospective design and small number of patients. Other limitations included the fact that although intubation criteria were specified, these criteria were flexed in some patients due to intubations performed under emergency conditions and busy schedule. Also we could not be able to add the percentage of lungs involvement with Murray score or any other equivalent which can help to better understand the HFNO failed patients. However, the standard treatment of COVID-19 pneumonia in our patients and the similar characteristics of the patient group might have weakened potential confounders.

Conclusion

HFNO might be effective as a first-line therapy in patients with COVID-19 in whom low-flow oxygen therapy is insufficient. Early administration may be effective to protect patients from the potential negative effects of intubation and mechanical ventilation. In addition uur study findings suggest that using indices such as ROX and mROX at the bedside may be important in monitoring the course of the disease and predicting the need for invasive ventilation.

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References

1. Helviz Y, Einav S. A Systematic Review of the High-flow Nasal Cannula for Adult Patients. *Crit Care.* 2018 20; 22(1):7. DOI:10.1186/s13054-018-1990-4
2. Rola P, Farkas J, Spiegel R, Kyle-Sidell C, Weingart S, Duggan L, et al. Rethinking the early intubation paradigm of COVID-19: Time to change gears? *Clin Exp Emerg Med.* 2020; 7(2):78-80 DOI: 10.15441/ceem.20.043
3. Lyons C, Callaghan M. The use of high- fl ow nasal oxygen in COVID-19. *Anaesthesia.* 2020; 2:843–7. DOI: 10.1111/anae.15073
4. Li J, Fink JB, Ehrmann S. High-flow nasal cannula for COVID-19 patients: Risk of bio-aerosol dispersion. *European Respiratory Journal.* 2020; 55:2000892. DOI: 10.1183/13993003.00892-2020
5. Kaur Matta S. Dilemmas in Covid-19 Respiratory Distress: Early vs Late Intubation; High Tidal Volume and Low PEEP vs Traditional Approach? *J Intensive Crit Care*. 2020; 6(2):1–4. DOI:10.36648/2471-8505.6.2.7
6. Roca O, Caralt B, Messika J, Samper M, Sztrymf B, Hernández G, et al. An index combining respiratory rate and oxygenation to predict outcome of nasal high-flow therapy. *Am J Respir Crit Care Med.* 2019; 199(11):1368–76. DOI: 10.1164/rccm.201803-0589OC
7. Goh KJ, Chai HZ, Ong TH, Sewa DW, Phua GC, Tan QL. Early prediction of high flow nasal cannula therapy outcomes using a modified ROX index incorporating heart rate. *J Intensive Care.* 2020; 8(1):1–14. DOI: 10.1186/s40560-020-00458-z
8. Zucman N, Mullaert J, Roux D, Roca O, Ricard JD, Longrois D, et al. Prediction of outcome of nasal high flow use during COVID-19-related acute hypoxemic respiratory failure. *Intensive Care Med*. 2020; 46(10):1924–6. DOI: 10.1007/s00134-020-06177-1
9. TC Saglik Bakanligi COVİD-19 Rehberi, 2 Nisan 2020. TC Saglik Bakanligi Halk Sagligi Genel Müdürlügü.
10. Panadero C, Abad-Fernández A, Rio-Ramírez MT, Acosta Gutiérrez CM, Calderón-Alcalá M, López-Riolobos C, et al. High-flow nasal cannula for Acute Respiratory Distress Syndrome (ARDS) due to COVID-19. *Multidiscip Respir Med.* 2020; 15. DOI:10.4081/mrm.2020.693
11. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med*. 2020; 46:1099–102. DOI:10.1007/s00134-020-06033-2
12. Siempos II, Xourgia E, Ntaidou TK, Zervakis D, Magira EE, Kotanidou A, et al. Effect of Early vs. Delayed or No Intubation on Clinical Outcomes of Patients With COVID-19: *An Observational Study*. Front Med. 2020; 7:1–6. DOI:10.3390/jcm9092847
13. Lee YH, Choi K-J, Choi SH, Lee SY, Kim KC, Kim EJ, et al. Clinical Significance of Timing of Intubation in Critically Ill Patients with COVID-19: A Multi-Center Retrospective Study. *J Clin Med.* 2020; 9(9):2847. DOI:10.3390/jcm9092847

14. Li X, Ma X. Acute respiratory failure in COVID-19: Is it "typical" ARDS? *Crit Care.* 2020; 24(1):1–5. DOI: 10.1186/s13054-020-02911-9
15. Chandel A, Patolia S, Brown AW, Collins AC, Sahjwani D, Khangoora V, et al. High-flow nasal cannula in COVID-19: Outcomes of application and examination of the ROX index to predict success. *Respir Care*. 2020; 66(5):1. DOI: 10.4187/respcare.08631
16. Suliman LA, Abdelgawad TT, Farrag NS, Abdelwahab HW. Validity of ROX index in prediction of risk of intubation in patients with COVID-19 pneumonia. *Adv Respir Med*. 2020; 1–7. DOI: 10.5603/arm.a2020.0176
17. Calligaro GL, Lalla U, Audley G, Gina P, Miller MG, Mendelson M, et al. The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: A multi-centre prospective observational study. *EClinicalMedicine*. 2020; 28:100570. DOI:10.1016/j.eclinm.2020.100570
18. Blez D, Soulier A, Bonnet F, Gayat E, Garnier M. Monitoring of high-flow nasal cannula for SARS-CoV-2 severe pneumonia: less is more, better look at respiratory rate. *Intensive Care Med*. 2020; 46:2094–5. DOI:10.1007/s00134-020-06199-9

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Analysis of Pulmonary Function Test Results By Using Gaussian Mixture Regression Model

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Abstract

Background: FEV1/FVC value is used in the diagnosis of obstructive and restrictive diseases of the lung. It is a parameter reported in the literature that it varies according to lung disease as well as weight, age and gender characteristics.

Objective: The aim of this study is to investigate the relationship between age, weight, gender and height characteristics and FEV1/FVC value using a heterogeneous population using Gaussian mixture regression method.

Material and methods: GMR was used to separate the data into components and to make a parameter estimation for each component. The analysis performed on this model revealed that the patients were divided into 5 optimal groups and that these groups showed a regular transition from obstructive pattern to restrictive pattern.

Results: The mean values of the components for FEV1/FVC were found as 50.071 (3.238), 67.034 (1.725), 82.156 (1.329), 93.592 (1.041), 98.466 (0.303), respectively. The effect of the weight on the components in terms of parameter estimation and standard errors of the components was determined as 0.445 (0.129)**, 0.226 (0.053)**, 0.173 (0.053)**, -0.036 (0.026), -0.040 (0.018)*, respectively.

Conclusion: Direct proportional relationship between the patient's weight and the severity of the obstructive pattern, and between the severity of the disease and the age of the patient in both the obstructive and restrictive pattern are explicitly proved. Furthermore, it has been revealed that data sets containing heterogeneity can be analysed by dividing them into sub-components using the GMR model.

Key words: Gaussian mixture regression, pulmonary function test, FEV1/FVC, obstructive pattern, restrictive pattern

Introduction

Pulmonary function test (PFT) is diagnostic for obstructive pulmonary diseases (such as asthma, Chronic Obstructive Pulmonary Disease (COPD), restrictive lung diseases (parenchymal diseases, respiratory muscles, chest wall diseases, pulmonary edema, congestive heart failure) and extra-thoracic airway stenosis (trachea obstruction, vocal cord paralysis) [1]. PFT is a test used to diagnose respiratory system diseases and to monitor the progression of patients with known respiratory diseases [2]. Forced expiratory volume in 1 second (FEV1) and the forced vital capacity (FVC) ratio (FEV1/FVC), is a parameter measured in the PFT, used for the diagnosis of respiratory system diseases. FEV1/FVC, especially in the separation of obstructive and restrictive diseases of the lung is the most important parameter used PFT [3]. FEV1 (Forced expiratory volume in 1 second) and FVC (Forced vital capacity) are two of the values measured during PFT. FVC is the maximum air volume that can be blown after full inspiration. It can also be considered as the maximum breath volume of the lung(forced inspiratory vital capacity). FEV1 is the volume of air that can be blown in the first 1 second after a full inspiration [4].

When evaluating PFT results, the FEV1/FVC ratio is taken into account first. First, the obstructive-restrictive distinction is performed [5]. The FEV1/FVC ratio, also

called the Tiffeneau-Pinelli index, is a ratio used to differentiate obstructive from restrictive lung diseases. The ratio of FEV1/FVC (FEV1%) in healthy adults should be about 70-80% [4]. It is recommended by the GOLD criteria that patients with FEV1/FVC below 70% should be evaluated as an obstructive disease [6].

In obstructive diseases, airflow from the lungs becomes difficult due to airway obstruction, the expiratory time is extended and the maximum volume of air (FEV1) blown in the first 1 second decreases [7]. FEV1 decreases in obstructive diseases (asthma, COPD, chronic bronchitis, emphysema) due to increased airway resistance in expiration. The main problem in restrictive diseases is fibrosis in the alveolar lung tissue. The compliance of the lung decreases due to this fibrosis. In restrictive diseases, both FEV1 and FVC are reduced. Since the decrease in FVC is greater than the decrease in FEV1, the ratio of FEV1 / FVC increases [8].

In the guidelines of the American Thoracic Society (ATS) published in 1987, it reported that the FEV1/FVC value should be below 75% for the diagnosis of obstructive pulmonary disease [7]. Later, in the guideline published by the British Thoracic Society (BTS) in 1997, it was proposed to use 70% as the upper limit of the FEV1/FVC value for the diagnosis of obstructive pulmonary disease [9]. In a study investigating ways to develop reference ranges on the relationship between spirometric lung function and height and age, the results were modeled in terms of gender, age and height [10]. In a study where two separate expected value formulas for men and women were tried to be developed in order to create equality for two different genders on spirometric test results, age and height variables were also used [11]. In relation to these variables, Swanney et al. stated that it was not appropriate to determine the FEV1/FVC value as a standard cut-off value [12].

Studies on determining the ranges of FEV1/FVC values that should be accepted as normal in adults are available in the literature [12-15].

The aim of this study is to investigate the relationship between age, weight, gender, and height variables with FEV1/FVC values in a heterogeneous population using gaussian mixture regression method and summarize all data with a multivariate statistical method.

Materials and methods

PFT equipment

SFT measurements were made with Spirobank II (MIR-Medical International Research USA, Inc., 5462 S. Westridge Drive New Berlin, WI 53151-USA) device. During the time that the data used in the study were obtained, all PFTs were made by the same technician. The calibration of the device was done once a day, following automatic procedures.

Study Sample

Those who were admitted to a secondary hospital between May 1, 2018 and May 31, 2018 and had a pulmonary function test were included in the study. A dataset was created by scanning PFT records retrospectively. Age, gender, weight and height information on the records, including PFT results, were recorded. Those missing at least one of these information were excluded from the study. After the information of the people with incomplete data was removed from the dataset, the analysis started with the data of the remaining 171 people. FEV1/FVC variable is determined as dependent variable and height, age, weight and gender are determined as independent variables.

Statistical analysis

While performing statistical analysis, the excess number of variables to be examined makes it difficult to solve by using classical statistical techniques such as clustering and factor analysis. In medical studies, the observed events depend on many factors. At the same time, these factors are interrelated. In order to obtain valid and reliable results, it is recommended that all variables related to the research be participated in the analysis. At this point, the mixture model is a powerful multivariate statistical tool that can be used effectively.

Finite mixture models

In multivariate statistical analysis techniques such as factor and clustering analysis, multiple variables should be clustered in terms of their effect on dependent variables. As a result of this grouping, it is ideal that both heterogeneity between groups and homogeneity within groups are high [16]. In recent years, mixture model approach has been used extensively in multivariate statistics. Mixture models have two important advantages over clustering and factor analysis. The first advantage is the calculation of which component is likely to include each observation. The second important advantage is that it is possible to calculate parameter estimates for each component with the mixture model. This is because mixture modelling also performs multiple regression analysis specifically for each component after dividing the data into components. Gaussian mixture regression analysis is used if the dependent variable fits normal distribution [17].

Another purpose of using mixture models is minimize the probability of misclassification and determine the populations from which they were sampled. In mixture models, parameters estimate by expectation and maximization (EM) algorithm and Maximum Likelihood (ML) method. Entropy is used for calculating true classification probability in mixture modelling [16]. Akaike and Bayesian information Criteria metrics are used for optimum component number [18].

Theoretical background

Component densities $f_i(y_j)$ stated to apply to some parametric distributions. The component densities $f_i(y_j)$ are described as $f_i(y_i;\theta_i)$, where θ_i is the vector of unknown parameters. This vector θ_i, is hypothesized form for the ith component density in the mixture. Mixture density can be formulated as

$$f(y_i;\psi)=\sum_{i=1}^{g}\pi_i f_i(y_i;\theta_i) \quad (1)$$

where vector ψ, involving all unknown parameters in the mixture model can be define as

$$\psi=\left(\pi_1,\pi_2,\cdots,\pi_{g-1},\xi^T\right)^T \quad (2)$$

In Eq.2 vector ξ, contain all the parameters in $\theta_1,\theta_2,\cdots,\theta_g$.

Parametric form of mixture model written as

$$f(y_j;\Psi)=\sum_{i=1}^{g}\pi_i f_i(y_j,\theta_i) \quad (4)$$

where observed random sample $y=\left(y_1^T,\ldots,y_n^T\right)^T$. The loglikelihood for Ψ that can be form the observed data is given by

$$\log L(\Psi) = \sum_{j=1}^{n} \log f(y_j;\Psi) = \sum_{j=1}^{n} \log\left\{\sum_{i=1}^{g} \pi_i f_i(y_j,\theta_i)\right\} \quad (5)$$

Likelihood equation written as;

$$\partial \log L(\Psi)/\partial\Psi = 0 \quad (6)$$

EM algorithm trying to solve Eq.6 using iterative methods and Eq.5.

Model selection

In the mixture model approach, AIC and BIC model fit statistics are widely used to determine how many sub-grouped models are homogeneous within each other [19-21]. The model with the smallest AIC and BIC values is considered to be the best representation of the data set [22]. However, in determining the model that best fits the data set, entropy, which has the possibility of correct classification, is also widely used. The entropy criterion can be considered as the best model in which component model is higher [23].

AIC and BIC were used to determine the optimum number of components. AIC, selects model that can minimize Eq.7.

$$AIC = -2\log L(\hat{\Psi}) + 2d \quad (7)$$

After Akaike, new approaches to the use of AIC to select the number of components in a mixture [23-25].

$$\log p(y) = \log L(\hat{\Psi}) + \log p(\hat{\Psi}) - \frac{1}{2}\log\left|I(\hat{\Psi};y)\right| + \frac{1}{2}d\log(2\pi) \quad (8)$$

Schwarz [26] suggested that Equation 8 omits the term O (1);

$$\left|I(\hat{\Psi};y)\right| = O(n^d) \quad (9)$$

And Bayesian information criterion (BIC) for the number of components g in the mixture model, to be obtained as the smallest in the model selection, with a negative log penalty multiplied by two and written as;

$$-2\log L(\Psi) + d\log n \quad (10)$$

Results

Surface plots of independent variables height – weight, age – height and age – weight versus FEV1/FVC, are shown in Figure 1, Figure 2 and Figure 3 respectively. These plots created by biharmonic enterpolation method. These figures show that the response variable FEV1/FVC have heterogeneous structure versus the independent variables.

These heterogeneous structures were analyzed by homogenous fractionation with using gaussian mixture regression model. Akaike and Bayesian Information Criteria which used to determine how many components and entropy correct classification rates are given in Table 1 and Figure 4.

As a result of the 5 component model obtained using the normal mixture regression model, the number and mixing probability of the individuals entering each component were shown as Table 1. The highest number of individuals was in component 5 and the lowest number of individuals was in component 1(Figure 5, Figure 7).

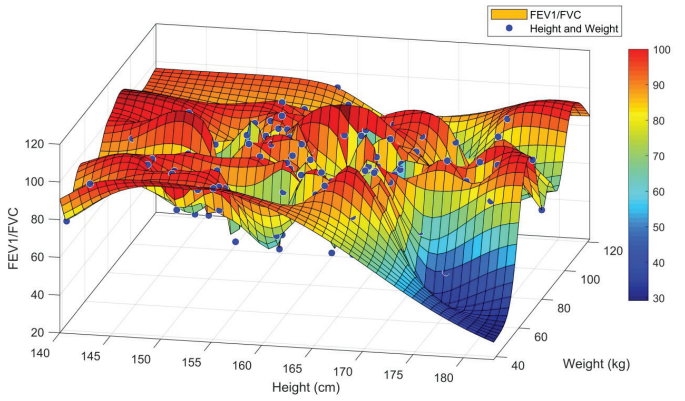

Figure 1. Surface plots of FEV_1/FVCversus height and weight variables

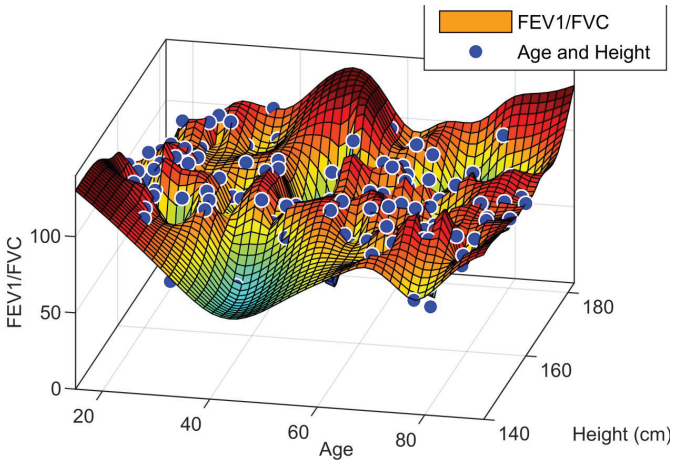

Figure 2. Surface plots of FEV_1/FVCversus age and height variables

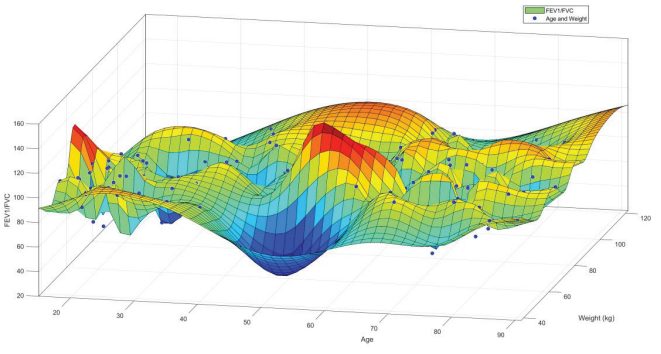

Figure 3. Surface plots of FEV_1/FVCversus age and weight variables

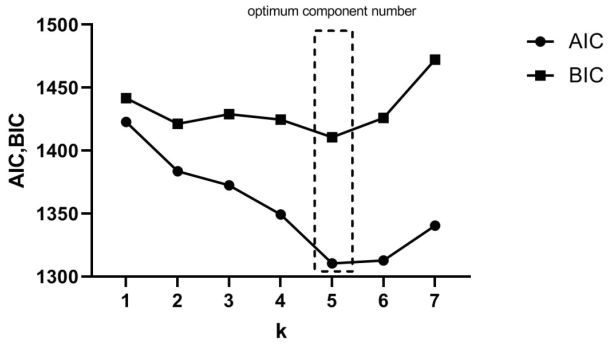

Figure 4. AIC and BIC values versus component number (k)

Table 1 Model selection criteria for components

Components	Model Information Criteria		
	AIC	BIC	Entropy (%)
Model with one component	1422.759	1441.609	87.0
Model with two component	1383.531	1421.231	84.5
Model with three component	1372.400	1428.950	89.3
Model with four component	1349.211	1424.611	90.8
Model with five component	1310.366	1410.616	92.5
Model with six component	1312.757	1425.857	91.9
Model with seven component	1340.366	1472.316	86.2

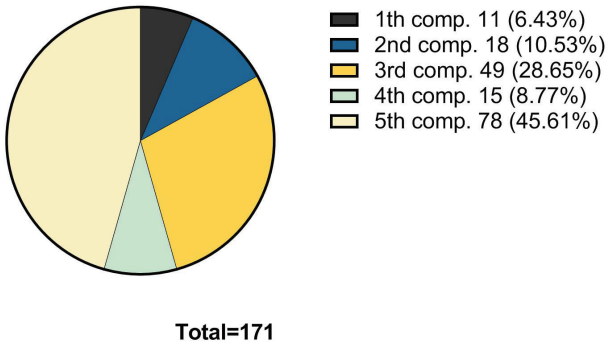

Figure 5. Obtained class sizes and mixing probabilities for components with closest class membership probabilities

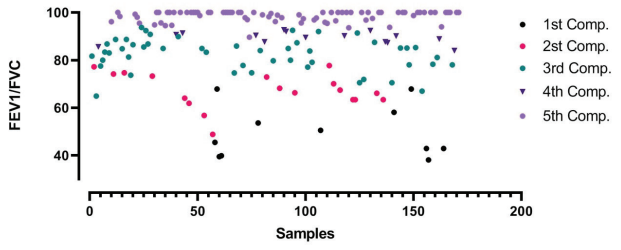

Figure 6. Distribution of dependent variable according to five components

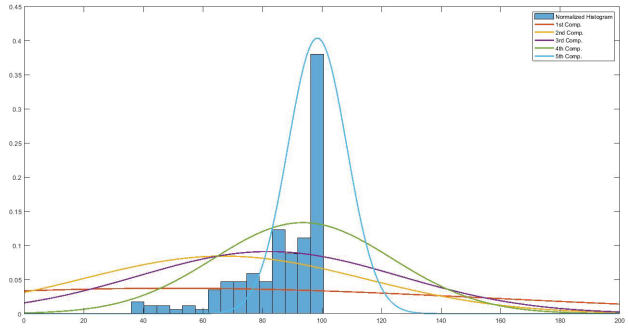

Figure 7. Prior conditional probability density functions of gaussian components

In the model with 5 components, which are the best model in which the data set is distributed (Figure 6), the parameter estimates are given in Table 2.

In the first component, the effect of weight independent variable on FEV1/FVC dependent variable was statistically significant ($p<0.01$); height, age and gender variables were statistically insignificant ($p>0.05$). In the second component, the effects of weight and age independent variables on FEV1/FVC dependent variable were statistically significant ($p<0.01$), the effect of height and gender independent variables was found to be statistically insignificant ($p>0.05$). In the third component, the coefficient of height independent variable on FEV1/FVC dependent variable was found to be statistically insignificant ($p>0.05$); however, the effects of age, gender ($p<0.05$) and weight ($p<0.01$) independent variables were statistically significant. In the fourth component, gender independent variable on FEV1/FVC dependent variable were statistically significant ($p<0.05$) and the effects of weight, height and age independent variables on FEV1/FVC dependent variable were found to be statistically insignificant ($p>0.05$). Finally, in the fifth component, the effect of weight independent variable on FEV1/FVC dependent variable was statistically significant ($p<0.01$); height, gender and age independent variables were statistically insignificant ($p>0.05$) (Table 2).

Mean values of FEV1/FVC dependent variable and estimated means and standart errors of gender, height, weight and age variables are shown in Table 3.

The normal distribution density functions of the five different components formed according to the obtained regression parameters are given in Figure 7. Considering the class sizes obtained for the components with the closest class membership (probability) grades, it was found that the mixing ratio of the fifth component had the highest mixing ratio as 45.61%.

Discussion

FEV1/FVC value is expected to decrease below 70% in obstructive pulmonary diseases, while it is expected to be normal or increase above 75% in restrictive lung diseases [12, 27-29]. FEV1/FVC value for the diagnosis of COPD is expected to be below 70% [28]. In obstructive disorders, there is a disproportionate decrease in the maximum volume of air exhaled from the lung. This represents airway contraction during exhalation and is defined by the FEV1/FVC ratio being less than 70% of the source values [29].

In this study, it was found that AIC and BIC values decreased to 5 component model and then increased. Thus, AIC and BIC with the smallest statistics and entropy value with high accurate classification ratio were obtained in 5 component model (Figure 4). The entropy criterion was obtained as 92.5% in the 5 component model selected as the most fitted model. It is observed that variable FEV1/FVC grows with component index. When components are examined, a regular and significant transition from low to high values for FEV1/FVC variable is observed.

The first component stands out as the component in which the obstructive pattern is most prominent. Considering that the average of the weight variable in component 1 is higher than the average in other components, it can be said that the FEV1/FVC is inversely proportional to weight in patients with low FEV1/FVC. The relationship between obesity and COPD has not been clearly determined yet. In 2014 García-Rio et al. reported that obesity was more prevalent in patients diagnosed with COPD compared to the general population [28]. There are studies reporting improvement in PFT results after weight loss in patients undergoing bariatric surgery [29]. In a study comparing the FEV1/FVC value of obese children compared to normal-weight children, it was reported that the FEV1/FVC value decreased in direct proportion to the increase in BMI (Body Mass Index) [30]. A study published in 2015 reported that when a fixed FEV1/FVC ratio of 0.70 used, it resulted in under-diagnosis of COPD among overweight patients [31]. A review by Dixon et al. has been reported that obesity may cause some

Table 2 Parameter estimation and standard errors of components

			Independent variables Estimated Coefficient (Standart Error)			
Component	Intercept β0	Mean of FEV_1/FVC	Gender (1:Male, 2:Female)	Height (cm)	Weight (kg)	Age (years)
1	-101.05	50.071	8.153 (7.746)	0.626 (0.552)	0.445 (0.129)**	-0.006 (0.179)
2	101.93	67.034	3.984 (3.300)	-0.295 (0.166)	0.226 (0.053)**	-0.226 (0.035)**
3	42.73	82.156	9.144 (4.571)*	0.137 (0.230)	0.173 (0.053)**	-0.188 (0.074)*
4	95.60	93.592	7.740 (2.207)*	-0.074 (0.107)	-0.036 (0.026)	0.019 (0.025)
5	95.06	98.466	-0.467 (0.558)	-0.037 (0.028)	-0.040 (0.018)*	0.019 (0.010)

* coefficient is statistically significant at the alpha=0.05 levels
** coefficient is statistically significant at the alpha=0.01 levels

Table 3 Means of variables according to components

		Independent variables Estimated Mean (Standart Error)				
Component	Mean of FEV1/FVC	Gender (Count, %)		Height (cm)	Wight (kg)	Age (years)
		Male	Female			
1	50.071(3.238)	4 (36.4%)	7 (63.6%)	164.18 (2.717)	78.862 (4.540)	47.643 (6.859)
2	67.034(1.725)	7 (38.9%)	11 (61.1%)	164.80 (1.806)	74.775 (3.713)	42.548 (5.036)
3	82.156(1.329)	17 (34.7%)	32 (65.3%)	163.816 (1.322)	70.099 (2.167)	54.843 (3.009)
4	93.592(1.041)	15 (100%)	0 (0%)	162.667 (1.610)	75.295 (3.181)	55.521 (4.084)
5	98.466(0.303)	30 (38.5%)	48 (61.5%)	162.798 (1.229)	71.341 (1.970)	53.221 (3.014)

changes in the mechanical functions of the lungs and chest wall. In addition, it was concluded that obesity affects lung function through an inflammatory pathway by increasing inflammatory cytokines [32]. It should be noted that the relationship between obesity and FEV1/FVC is not only related to weighted increase, but also the disease-causing effects.

When the components are ranked from small to large in terms of FEV1/FVC scores, the second component with a value of 67.034 FEV1/FVC is in the second place. In this component, the effects of weight and age variables on FEV1/FVC were found statistically significant ($p<0.01$). It was determined that FEV1/FVC value decreased -0.226 times when age increased by one unit and FEV1/FVC value increased by 0.226 times when weight increased. The second component population is a component composed of individuals with an FEV1/FVC value close to 70%. The minimum and maximum FEV1/FVC values of this component are values that converge to 70%.

When the effect of age independent variable on FEV1/FVC is analyzed, it is determined that the coefficient of the age variable is negative in the components where the average value of FEV1/FVC is low. However, it was found that the coefficient for the age variable turned positive in components where FEV1/FVC was close to the 70% threshold value (Table 2). As age increases in patients at this component, FEV1/FVC decreases more clearly than other components. It is concluded that FEV1/FVC value significantly increases with increasing age in this component. In a study conducted by collecting data between 1998 and 2009 in the United States, it was concluded that the prevalence of COPD increases with age for both men and women [33].

Changes such as a significant decrease in lung elasticity, chest wall stiffness and loss of respiratory muscle strength are the physiological effects that occur in the respiratory system with aging [34-36]. These physiological changes were seen as the cause of low FEV1/FVC in the elderly population [12].

The effect of the height independent variable on the FEV1/FVC was found insignificant in all components.

Considering the gender independent variable, the effect on the FEV1/FVC dependent variable was found statistically significant only in the third and fourth components. It was concluded that in cases where FEV1/FVC values were slightly higher or slightly lower, the male sex was predisposed to form groups with moderately low FEV1/FVC, while the female sex was predisposed to form groups with moderately high FEV1/FVC. The third component stands out as the component in which the gender variable is statistically most significant. The relationship between COPD and gender has been investigated since 1987 [37]. McHugh et al. also reported that FEV1/FVC values differ significantly between men and women [38].

Limitations

Retrospective studies have some limitations due to their nature as the data are scanned retrospectively. Our study was conducted with data obtained from 171 patients, and the sample size is relatively small. Prospective studies with larger samples are needed to verify the results of this study. Since we did not investigate the effect of smoking on FEV1/FVC, we did not use smoking history in our study. We think that it would be useful to compare the results of this study with the results of studies with large populations that are homogenized and free from other effects.

Conclusion

In this study, the heterogeneity in the dataset is tried to be understood with the mixture regression model. Using the

mixture regression model gives useful results in the analysis of dependent variables that interact with multiple independent variables, both in determining the existence and power of the relationships. We can say that the relationship between FEV1/FVC value and weight is greater than with other variables, in terms of the characteristics we examine the relationships in our study population. The age variable showed a statistically significant correlation between the FEV1/FVC value. FEV1/FVC results varied according to gender differences, these differences were lower than the difference due to weight and age differences. On the other hand, no significant relationship was found between the height variable and the FEV1/FVC value in the analysis we performed on our population. Stronger results can be obtained if the relationships between FEV1/FVC with age, weight, and sex variables are investigated using a mix regression model in larger populations. We believe it would be more meaningful to consider these relationships when interpreting the FEV1/FVC value.

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References

1. Miller, M.R., et al., Standardisation of spirometry. *Eur Respir J.* 2005; 26(2):319-38. https://doi.org/10.1183/09031936.05.00034805
2. Ferguson, G.T., et al., Office spirometry for lung health assessment in adults: a consensus statement from the National Lung Health Education Program. *Chest*. 2000; 117(4):1146-1161. https://doi.org/10.1378/chest.117.4.1146
3. Minelli, R., Appunti dalle lezioni di fisiologia umana. *La Goliardica Pavese,* 1992: p. Neuroimage.
4. Emmett, M., *Current Clinical Medicine* 2009: Expert Consult Premium Edition by the Cleveland Clinic. Proceedings (Baylor University. Medical Center). 2009; 22(3):291. https://doi.org/10.1080/08998280.2009.11928536
5. Johnson, J.D. and W.M. Theurer, A stepwise approach to the interpretation of pulmonary function tests. *Am Fam Physician.* 2014; 89(5):359-66.
6. Vestbo, J., et al., Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2013; 187(4):347-65. https://doi.org/10.1164/rccm.201204-0596PP
7. Society, A.T. and M.S.o.t.A.L. Association, Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis.* 1991; 144(1202):e18. https://doi.org/10.1164/ajrccm/144.5.1202
8. Quanjer, P., et al., Standardized lung function testing. *Bull Eur Physiopathol Respir.* 1983; 19(5):1-95.
9. Pearson, M., et al., BTS guidelines for the management of chronic obstructive pulmonary disease-Foreword. *Thorax*. 1997; 52:1-28. https://doi.org/10.1136/thx.52.suppl_5.1
10. Stanojevic, S., et al., Reference ranges for spirometry across all ages: a new approach. American journal of respiratory and critical care medicine. 2008; 177(3):253-260. https://doi.org/10.1164/rccm.200708-1248OC
11. Nunn, A. J., & Gregg, I. New regression equations for predicting peak expiratory flow in adults. *BMJ (Clinical research ed.)*. 1989; 298(6680):1068–1070. https://doi.org/10.1136/bmj.298.6680.1068
12. Swanney, M.P., et al., Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax.* 2008; 63(12):1046-1051. http://dx.doi.org/10.1136/thx.2008.098483
13. Falaschetti, E., et al., Prediction equations for normal and low lung function from the Health Survey for England. *Eur Respir J*. 2004; 23(3):456-63. https://doi.org/10.1183/09031936.04.00055204
14. Culver, B.H., Interpretation of spirometry: we can do better than the GOLD standard. *Respiratory Care.* 2006;
15. Hardie, J.A., et al., Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. *Eur Respir J.* 2002; 20(5):1117-22. https://doi.org/10.1183/09031936.02.00023202
16. Wang, P. and M.L. Puterman, Mixed logistic regression models. *Journal of Agricultural, Biological, and Environmental Statistics*. 1998; 175-200. https://doi.org/10.2307/1400650
17. Yesilova, A., et al., Locational classification of walnut (Juglans Regia L.) genotypes collected from Lake Van basin by using mixture modeling. *African Journal of Agricultural Research*. 2010; 5(12):1509-1514. https://doi.org/10.5897/AJAR.9000471
18. Deng, Y. and A. Li, Structural Health Monitoring for Suspension Bridges. Springer. 2019; https://doi.org/10.1007/978-981-13-3347-7
19. Wang, Y. and Q. Liu, Comparison of Akaike information criterion (AIC) and Bayesian information criterion (BIC) in selection of stock–recruitment relationships. *Fisheries Research.* 2006; 77(2):220-225. https://doi.org/10.1016/j.fishres.2005.08.011
20. Penny, W.D., Comparing dynamic causal models using AIC, BIC and free energy. *Neuroimage*. 2012; 59(1):319-330. https://doi.org/10.1016/j.neuroimage.2011.07.039
21. Xie, W., et al., Improving marginal likelihood estimation for Bayesian phylogenetic model selection. *Syst Biol*. 2011; 60(2):150-60. https://doi.org/10.1093/sysbio/syq085
22. McDonald, R.P., An index of goodness-of-fit based on noncentrality. *Journal of classification.* 1989; 6(1): 97-103. https://doi.org/10.1007/BF01908590
23. Liddle, A.R., Information criteria for astrophysical model selection. Monthly Notices of the Royal Astronomical Society: Letters. 2007; 377(1):L74-L78. https://doi.org/10.1111/j.1745-3933.2007.00306.x
24. Bozdogan, H. and S.L. Sclove, Multi-sample cluster analysis using Akaike's information criterion. Annals of the Institute of Statistical Mathematics. 1984; 36(1):163-180. https://doi.org/10.1007/BF02481961
25. Sclove, S.L., Application of model-selection criteria to some problems in multivariate analysis. *Psychometrika.* 1987; 52(3):333-343. https://doi.org/10.1007/BF02294360
26. Schwarz, G., Estimating the dimension of a model. *The annals of statistics.* 1978; 6(2):461-464. https://doi.org/10.1214/aos/1176344136
27. Sahebjami, H. and P.S. Gartside, Pulmonary function in obese subjects with a normal FEV1/FVC ratio. *Chest.* 1996; 110(6):1425-9. https://doi.org/10.1378/chest.110.6.1425

28. García-Rio, F., Soriano, J. B., Miravitlles, M., Muñoz, L., Duran-Tauleria, E., Sánchez, G., Sobradillo, V., & Ancochea, J. Impact of obesity on the clinical profile of a population-based sample with chronic obstructive pulmonary disease. *PloS one.* 2014; 9(8):e105220. https://doi.org/10.1371/journal.pone.0105220
29. Mihmanlı, A., & Bozkurt, E. Effects of Laparoscopic Sleeve Gastrectomy on Respiratory Functions. *Bariatric Surgical Practice and Patient Care*. 2020. https://doi.org/10.1089/bari.2020.0059
30. Köchli, S., et al., Lung function, obesity and physical fitness in young children: The EXAMIN YOUTH study. Respiratory medicine. 2019; 159:105813. https://doi.org/10.1016/j.rmed.2019.105813
31. Çolak, Y., et al., Overweight and Obesity May Lead to Under-diagnosis of Airflow Limitation: Findings from the Copenhagen City Heart Study. COPD: *Journal of Chronic Obstructive Pulmonary Disease.* 2015; 12(1):5-13. https://doi.org/10.3109/15412555.2014.933955
32. Dixon, A.E. and U. Peters, The effect of obesity on lung function. *Expert Rev Respir Med*. 2018; 12(9):755-767. https://doi.org/10.1080/17476348.2018.1506331
33. Akinbami, O.J. and X. Liu, Chronic Obstuctive Pulmonary Disease Among Adults Aged 18 and Over in the United States. 1998-2009. 2011: Citeseer.
34. Runarsdottir, S.B., et al., Prevalence of airflow obstruction in nonsmoking older individuals using different spirometric criteria: the AGES Reykjavik Study. COPD: *Journal of Chronic Obstructive Pulmonary Disease.* 2013; 10(4):493-499. https://doi.org/10.3109/15412555.2013.773303
35. Turner, J.M., J. Mead, and M.E. Wohl, Elasticity of human lungs in relation to age. *J Appl Physiol*. 1968; 25(6):664-71. https://doi.org/10.1152/jappl.1968.25.6.664
36. Knudson, R.J., et al., Effect of aging alone on mechanical properties of the normal adult human lung. *J Appl Physiol Respir Environ Exerc Physio.* 1977; 43(6):1054-62. https://doi.org/10.1152/jappl.1977.43.6.1054
37. Burrows, B., et al., The course and prognosis of different forms of chronic airways obstruction in a sample from the general population. *N Engl J Med.* 1987; 317(21):1309-14. https://doi.org/10.1056/nejm198711193172103
38. McHugh, J., Duong, M., Ma, J., Dales, R. E., Bassim, C. W., & Verschoor, C. P. A comprehensive analysis of factors related to lung function in older adults: Cross-sectional findings from the Canadian Longitudinal Study on Aging. Respiratory medicine. 2020; 173:106157. https://doi.org/10.1016/j.rmed.2020.106157

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Analysis of the effects of anatomy committee exam stress on visual and auditory reaction time and cortisol level: A neuroperformance study

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Abstract

Objective: The present study aims to find out the effects of exam stress, which exists in every moment of education life, on visual and auditory reaction time (VRT, ART), cortisol level and stress perception.

Material and methods: A total of 66 students (36 males, 30 females) were included in the study. VRT and ART measurements were carried out with reaction timer by asking the participants to use their dominant hands. Reaction times were recorded on two occasions, namely 30 days before the committee exam (relaxed period) and, again, on the day of exam (stressed period). Additionally, students provided salivary samples and filled in State Trait Anxiety Inventory-I on both occasions.

Results: Median values of cortisol, STAI-I, VRT and ART scores of male and female students were higher during stress period than that of the relaxed period ($p<0.05$). Correlation analysis showed a positive weak correlation between cortisol level and STAI-I scores of students in exam period (male: $r=0.317$, $p<0.05$; female: $r=0.253$, $p<0.05$). Moreover, cortisol levels were positively correlated with VRT (male: $r=0.155$, $p<0.05$; female: $r=0.227$, $p<0.05$) and ART (male: $r=0.159$, $p<0.05$; female: $r=0.163$, $p<0.05$) scores both male and female students.

Conclusion: The results show that stress increase was found to increase cortisol level and STAI-I scores. Increased cortisol level was associated with longer reaction times as measured by VRT and ART.

Keywords: stress, reaction time, saliva, cortisol, neuroperformance

Introduction

In our daily lives, stress is everywhere. Stress can balance behavioural and hormonal reactions [1,2] and radically change neural responses given to information received [3,4]. Acute stress has a considerable influence on various cognitive processes including attention, cognitive control, memory and social cognition [5,6].

Stressful encounters and also individuals' psychological reactions to these encounters activate the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic nervous system, causing excessive levels of stress hormones, especially cortisol and catecholamines, to be secreted. When stress hormones are secreted, bodily functions, especially immune, cardiovascular and metabolic functions may undergo dysregulation [7]. One of the naturalistic stressor examples is academic exams. These exams are time-limited and generally considered to be aversive and they are seen as psychological and physiological

reactions to stressful encounters. Based on cognitive theories of stress, the present study analyses the effects of cognitive appraisals of stress in exam situation and test anxiety. According to cognitive approach, the individual who has coping sources to cope with a stressful situation evaluates the threat or challenge in the stressful situation through cognitive processing in stressful encounters like academic exams [8]. The coping strategies individuals use in the face of stressful situations affect their evaluations and determine the psychological (e.g., experienced stress, test anxiety) and physiological results of the encounter. In addition to cognitive aspects (i.e., worry) and the elements of emotional and physiological arousal (i.e., emotionality), test anxiety includes particular cognitive, emotional and physiological reactions caused by the stimuli of testing [9-11]. In every stage of our lives, we are faced with decisions that we have to make. The speed, quality and hit rates of the decision made are the most important parameters of success. The stressful environment an individual is in has negative influences on the individual's biological and psychological state. This stress experienced causes carelessness and low concentration, low performance and inefficiency [12-14].

Reaction time (RT) is the time between the presentation of a sensory stimulus and the following behavioural reaction [15,16]. RT is closely associated with the speed of making a decision [17]. For a move fit for the purpose, sensory and motor systems should be working in coordination. In humans, reaction speed is a direct indicator of nerve transmission speed. RT is different from reflex time, which is the automatical response given to an external stimulus. It is a completely voluntary situation in which central nervous system is enabled [18]. Characteristics such as the transmission speed of the nerves which have a role in the stimulus reaching the central nervous system and the response being carried to the effector organ and the effector muscle being a fast or slow muscle creates differences of milliseconds from person to person [18].

A great number of studies report RT being influenced by stress and anxiety [19,20]. Stress is present in every moment of our education life. The idea that stress can affect the reaction is the hypothesis of our study. This study aims to examine the effects of exam stress, which exists in every moment of students' educational life and influences students negatively most of the time, on visual and auditory RT (VRT-ART) and cortisol level.

Material and methods

Participants

The study includes 66 students (36 males, 30 females; mean age 19.4±1.8 years; range, 18 to 20 years) who were studying at Inönü University, Faculty of Medicine between May 2018 and June 2018 and who signed informed consent form.

Inclusion criteria consisted of the following: being physically healthy, not having any medical obstacles to prevent participation in the study, not having any disease, no previous history of orthopaedic surgery, not having performed resistance exercise at least six months before the start of the study, not using food supplement, such as keratin during the study. Antidepressant drug and herbal relaxant use before the stressed and relaxed periods were exclusion criteria.

Students using hearing aids and contact lenses and glasses were not included in the study. Female students in menstrual cycle or those to enter this cycle in three days were also excluded [21]. Malatya Clinical Researches Ethical Board (2018/110) approved the study protocol and the principles of the Declaration of Helsinki were followed. Participants were informed about the study and an informed consent form was signed.

The relaxed period was accepted as the period 30 days before the committee exam and the first RT measurements and saliva samples were taken then. The stressed period was the day of the committee exam and the second RT measurements and saliva samples were taken. Since we thought that students would have high levels of stress before the test, this period was considered stressed. State Trait Anxiety Inventory-I (STAI-I) and cortisol measurements were used to support this hypothesis. There was a period of 30 days between the relaxed period and the stressed period. All students were given STAI-I, a commonly used scale in the assessment of anxiety, during the relaxed and stressed periods. Öner and Le Compte conducted the validity and reliability of STAI-I's Turkish version [22]. Classification of the points was as follows in STAI-I scale: ≤36 as "no anxiety", 37-42 as "mild anxiety", ≥42 as "high anxiety".

RT measurements

Hubbard Scientific Reaction Timer (Model: 6027, USA) was used to make VRT and ART measurements. Two different warnings as visual (light) and auditory (sound) are obtained from Reaction Timer device. RT measurements were performed in a noise free environment with sufficient light between 09:30 and 11:00. Each subject was asked to put their dominant hands on a table in front of them which had a button and a Reaction Timer 10 cm away from the button. With "ready" command, either sound or light stimulant was given and the subjects were asked to press the buttons in shortest time in accordance with the stimulants. Each subject made 10 trials for sound and light stimuli, the first of which was taken as practice. The average of the last trials was determined as RT [23].

Analysis of cortisol in saliva

In order to minimize the impact of extra test components on cortisol levels, the subjects were told to avoid smoking, caffeine, and physical exertion for 3 hours before coming to their appointment, in the preliminary information provided, that all samples should be given at 10:00 (am). They were asked to eat a low fat and protein meal and not eat or drink for 1 hour before coming to their appointment. Passive droll method was used to collect saliva samples, as shown by Granger et al. [24]. Samples were kept in a laboratory freezer at -20 °C. After thawing, the samples were centrifuged at 4000 g for 10 min and supernatant was used for ELISA analyses. Samples were diluted 1:5 and assayed in triplicate with assay buffer. ELISA procedure; Cortisol-BSA stock solution (1 mg/mL) was diluted with carbonate buffer, pH 9.6 before adding to a 96-well microtiter plate at 200 µL/well. For one night, the microtiter plate was incubated at +4 °C and washed five times with wash buffer and eight-channel pipette. With blocking buffer (200 µL/well), binding places that had no coating antigen were blocked at 37 °C for 2 h. After washing, standard solutions or samples (40 µL/well) and diluted 1st Ab (antiserum) (40 µL/well) were put in duplicate and incubated for 45 min at 37 °C. Later, after the washing process, following the addition of biotinylated anti-Rabbit antibody (100 µL/ well), the plate was incubated for 30 min at 37 °C. After washing for 5 times, the plate was incubated at +4 °C for 15 min following the addition of streptavidin peroxidase solution (100 µL/well). Next, after the plate was washed for another 5 times, substrate solution (150 µL/well) was added and incubated in dark for 10 min. Stop solution (50 µL/well) was added after incubation and microplate reader was used to measure absorbance at 450 nm. While intra-assay variation (CV) was found as 5.6%, inter-assay variation was found as 7.8%. Elisa test was made by the same expert in the same laboratory [21].

Statistical analysis

Normality assumption of the data was tested with Kolmogorov Smirnov test. The data without normal distribution were analysed with Wilcoxon paired samples test. Spearman Rho coefficient was used to calculated the correlations. Significance was considered at $p<0.05$ level and IBM SPSS Statistics 22.0 for Windows program was used. In calculating the sample size, the 95% confidence interval in the G-Power 3.1.7 package program was calculated for the paired samples t test. For determining at least 1ms of change in RT, minimum sample size for $\alpha= 0.05$ and 1-beta= 0.80 was calculated to be 52 with the effect size estimated as 0.40.

Results

According to the results of the analysis we conducted, cortisol level and STAI-I score median values were found to increase in the stressed period when compared with the relaxed period. Wilcoxon paired-samples test was given to the data to determine whether there were changes in cortisol and STAI-I scores during transition from relaxed period to the stressed period. Analysis results showed that the increase in cortisol level and STAI-I scores of both men and women during transition from relaxed period to the stressed period was statistically significant ($p<0.05$). According to Spearman rho correlation analysis of cortisol and STAI-I scores in exam period, a positive weak correlation was found in both male (r:0.317, $p<0.05$) and female (r:0.253, $p<0.05$) students (Table 1).

Table 1 Median (Min-Max) values of cortisol and STAI-I, Wilcoxon paired-samples test results between relaxed and stressed, Spearman rho correlation analysis results between cortisol level and STAI-I in exam period

Sex	Variables	Relaxed		Stressed		p	Exam Period	
		Median	Min-Max	Median	Min-Max		Correlation	Cortisol
Male	Cortisol	14.7	2.9-58.3	24.5	8.8-196	.013	STAI-I*	r: .317 p: .025
	STAI-I*	46	32-70	55	31-76	.041		
Female	Cortisol	14.9	3.4-61.5	27.5	7.91-779.7	.019		r: .253 p: .018
	STAI-I	43	27-67	50	28-77	.042		

*STAI-I: State Trait Anxiety Inventory-I

According to the Wilcoxon paired-samples test results, both VRT and ART were found to increase statistically significantly during transition from relaxed period to the stressed period ($p<0.05$), (Table 2). With these data, it can be concluded that VRT and ART increase as stress increases.

Table 2 Median (Min-Max) values of VRT and ART measurements and Wilcoxon paired-samples test results between relaxed and stressed

Sex	Variables	Relaxed		Stressed		p
		Median	Min-Max	Median	Min-Max	
Male	VRT*	31.6	24.6-44.3	35.6	28.3-54.6	.008
	ART**	37.6	27.6-51	41.3	27.3-60.6	.007
Female	VRT*	32.6	23.6-44	41.3	27.6-51.6	.003
	ART**	36.3	24.6-51	40.3	26.3-51.3	.011

*VRT: Visual reaction time
**ART: Auditory reaction time

Spearman's rho correlation analysis was performed to determine how VRT and ART values differed with Cortisol and STAI-I scores (Table 3). According to the results of the analysis conducted, a positive and weak correlation was found between VRT and ART and cortisol level and STAI-I scores in both male and female students (Table 3).

Table 3 Spearman rho correlation analysis results conducted on the VRT and ART scores

Variables	Test statistics	Male		Female	
		Cortisol	STAI-I	Cortisol	STAI-I
VRT*	r	.155	.314	.227	.348
	p	.048	.039	.046	.011
ART**	r	.159	.172	.163	.276
	p	.049	.042	.047	.035

*VRT: Visual reaction time
**ART: Auditory reaction time

Table 4 Change of individual numbers according to STAI-I score

Sex	Period	<36 (no anxiety)		37- 42 (mild anxiety)		>42 (high anxiety)	
Male	Relaxed	19	52.8%	7	19.4%	10	27.8%
	Stressed	3	8.3%	6	16.6%	27	75.1%
Female	Relaxed	16	53.3%	5	16.6%	9	30.1%
	Stressed	3	10%	4	13.3%	23	76.7%

The number and percentage of the individuals in groups called no anxiety, mild anxiety and high anxiety during relaxed and stressed periods according to STAI-I scores were given in Table 4. According to these data, the number of individuals in high anxiety group were found to increase significantly in stressed period when compared with relaxed period in terms of both males and females (Table 4).

Discussion

In the current study, cortisol and STAI-I anxiety scores were higher in stressed period when compared with the relaxed period. In addition, there was a positive and weak correlation between cortisol levels and STAI-I scale scores of male and female during the stressed period. This result shows the accuracy of cortisol measurements and that participants are stressed during exams period. It was found that VRT and ART values of males and females who participated in the study increased in stressed period when compared with the relaxed period. It was found that stress had an adverse effect on the sense of VRT and ART. To the best of our knowledge, this is the first study in the literature. When previous studies are examined, the present study seems to be quite unique, which makes it difficult to discuss the results we found.

Stress affects our performance, how we feel and many physical functions (neuro-physiological) [25]. Individuals faced with stress respond with a physiological or psychological response [26]. When compared with relaxed individuals, it has been reported that it is easy for stressed individuals to make mistakes, they are more anxious and uneasy [27]. RT is a significant detail for duties requiring attention. In their studies, Welford [28] and Brebner and Welford [29] stated that individuals moved slower when they were under stress. In the study they conducted, Saha et al., [19] stated that noisy stress decreased VRT and ART.

A great number of researchers state that auditory reaction is faster than visual reaction and average auditory RT's are between 140 and 160 ms, while visual RT's are between 180 and 200 ms [30, 31]. It was stated that maybe the reason for this

was the fact that it took about 8-10 ms for an auditory stimulant to reach the brain [30, 32] , while it took 20-40 ms for a visual stimulant [33]. Bellis (34) found VRT as 220 ms in men and as 260 ms in women, while ART was found as 190 ms in men and 200 ms in women.

In their study, Engel et al. [35], found ART in men as 227 ms and as 242 ms in women. Silverman [36] stated that since women drove more carefully recently and that they participated in fast-action sports more, it was possible for them to have a better VRT when compared with men. In their study with lacrosse players, Spierer et al. [37] found that VRT and ART had faster scores in men when compared with women. In a study conducted in Germany, it was stated that in general, women were better than men in handcrafts and ability [38]. In another study conducted, while no significant difference was found between men and women in RT's for visual stimulants, men were found to have faster movement time [39]. In their study, Binboğa et al. [40] found that although men had shorter auditory simple RT than women, the difference was not found to be statistically significant. Gürsoy et al. [41] compared sedentary men and women and found that while right hand visual simple RT of men were found to be significantly shorter, ($p<0.05$), left hand visual simple RT of men were also found to be shorter, but not significantly ($p>0.05$).

Gender is a significant factor in RT. Women have slower RT when compared with men. This time is 30% shorter in adolescence and maturity. In a study they conducted on 56 females and 57 males between 11 and 14 years of age, Taimela and Kujala concluded that women were slower than men in simple and optional RT's [42].

In every part of life, primarily in educational and business life, individuals who can cope with stress, those who have a high professional efficiency and a high percentage of making right decisions are preferred. Success shown in such situations will put both individuals and institutions a step ahead. The present study has some limitations. First of all, sample size can be larger. However, since we made measurements during students' exam periods and since the measurements took long, we had some problems. Despite all difficulties, a suitable number of participants were included in the power analysis. Secondly, some of the participants in exam stress stated that they got sedatives before measurements in stressed periods and these students were excluded from the study.

Conclusion

As a conclusion, our study results showed that stress had a negative influence on VRT and ART. This study should be taken into consideration by educators, by individuals who experience exam stress, and by families who think that their children have too much stress in exams. The fact that no similar study was found in our literature research reveals the originality of this study. Exams exist in every moment of our lives and we are faced with important decisions that we have to make at every stage of our lives. The speed, quality and accuracy of the decisions we make are the most important parameters of our success. Considering the results of this study, we should change our perspective on life and remember that excessive stress will negatively affect us. We believe that the present study, which did not have much of a place in literature in detail previously, can be a source for future studies.

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References

1. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: atheoretical integration and synthesis of laboratory research. *Psychol Bull.* 2004; 30:355-391. https://doi.org/10.1037/0033-2909.130.3.355.
2. Foley P, Kirschbaum C. Human hypothalamus-pituitary-adrenal axisresponses to acute psychosocial stress in laboratory settings. *Neurosci Biobehav Rev*. 2010; 35(1):91-96. https://doi.org/10.1016/j.neubiorev.2010.01.010.
3. Shackman AJ, Maxwell JS, McMenamin BW, Greischar LL, Davidson RJ. Stress potentiates early and attenuates late stages of visual processing. *J Neurosci.* 2011; 31:1156-1161. https://doi.org/10.1523/JNEUROSCI.3384-10.2011.
4. Qi M, Gao H, Guan L, Liu G, Yang J. Subjective Stress, Salivary Cortisol, and Electrophysiological Responses to Psychological Stress. *Front Psychol.* 2016; 18(7):229. https://doi.org/10.3389/fpsyg.2016.00229.
5. Qin S, Hermans EJ, van Marle HJ, Luo J, Fernández G. Acute psychological stress reduces working memory-related activity in the dorsolateral prefrontal cortex. *Biol Psychiatry*. 2009; 66(1):25-32. https://doi.org/10.1016/j.biopsych.2009.03.006.
6. Sandi C, Haller J. Stress and the social brain: behavioural effects and neurobiological mechanisms. *Nat Rev Neurosci.* 2015; 16(5):290-304. https://doi.org/10.1038/nrn3918.
7. Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. Psychoneuroimmunology and psychosomatic medicine: back to the future. *Psychosom Med.* 2002; 64(1):15-28. https://doi.org/10.1097/00006842-200201000-00004.
8. Lazarus R, Folkman S. Stress, appraisal and coping. New York: Springer. 1984. https://doi.org/10.1007/978-1-4419-1005-1009
9. Liebert RM, Morris LW. Cognitive and emotional components of test anxiety: a distinction and some initial data. *Psychol Rep*. 1967; 20(3):975-978. https://doi.org/10.2466/pr0.1967.20.3.975.
10. Spielberger CD, Vagg PR. Test anxiety: a transactional process model. In: Spielberger CD, Vagg PR, editors. Test anxiety: theory, assessment, and treatment. Washington: *Taylor and Francis.* 1995; 3-14.
11. Lindahl M, Theorell T, Lindblad F. Test performance and self-esteem in relation to experienced stress in Swedish sixth and ninth graders-saliva cortisol levels and psychological reactions to demands. *Acta Paediatr.* 2005; 94(4):489-495. https://doi.org/10.1111/j.1651-2227.2005.tb01922.x
12. Yenice E. Performans Ölçümünde Karşılaşılan Sorunlar ve Kurumsal Karne (Balanced Scorecard) Yaklaşımı. *Bütçe Dünyası.* 2007; 2(25):95-100.
13. Barlı Ö. Davranış Bilimleri ve Örgütlerde Davranış, 4. Baskı, Aktif Yayınevi, Erzurum. 2010.
14. Soysal A. Farklı Sektörlerde Çalışan İşgörenlerde Örgütsel Stres Kaynakları: Kahramanmaraş ve Gaziantep'te Bir Araştırma. *The Journal of Faculty of Economics and Administrative Sciences.* 2009; 14(2):333-359.

15. Hick WE. On the rate of gain of information. *Q J Exp Psychol.* 1952; 4:11-26. https://doi.org/10.1080/17470215208416600
16. Bunce D, MacDonald SW, Hultsch DF. Inconsistency in serial choice decision and motor reaction times dissociate in younger and older adults. *Brain Cogn.* 2004; 56(3):320-327. https://doi.org/10.1016/j.bandc.2004.08.006
17. Duvan A, Toros T, Şenel Ö. Effects of maximum exercise intensity on visual reaction time of elite fencers. *Niğde Üniversitesi Beden Eğitimi ve Spor Bilimleri Dergisi.* 2010; 4(3):146-511.
18. Ganong WF. Review of Medical Physiology. San Francisco. McGraw-Hill. 2001; 49-51.
19. Saha S, Gandhi A, Das S, Kaur P, Singh SH. Effect of noise stress on some cardiovascular parameters and audiovisual reaction time. *Indian J Physiol Pharmacol.* 1996; 40(1):35-40. PMID: 8864769.
20. Panayiotou G, Vrana SR. The role of self-focus, task difficulty, task self-relevance, and evaluation anxiety in reaction time performance. *Motivation and Emotion.* 2004; 28(2):171-196. https://doi.org/10.1023/B:MOEM.0000032313.69675.0d.
21. Ozgocer T, Ucar C, Yildiz S. Cortisol awakening response is blunted and pain perception is increased during menses in cyclic women. *Psychoneuroendocrinology*. 2017; 77:158-164. https://doi.org/10.1016/j.psyneuen.2016.12.011.
22. Öner N, Le Compte A. Durumluk-Sürekli Kaygı Envanteri El Kitabı. İstanbul: *Boğaziçi Üniversitesi Yayını.* 1983.
23. Tamer K. Sporda Fiziksel-Fizyolojik Performans Ölçülmesi ve Değerlendirilmesi Ankara: *Türker Kitabevi.* 1995.
24. Granger DA, Kivlighan KT, el-Sheikh M, Gordis EB, Stroud LR. Salivary alpha-amylase in biobehavioral research: recent developments and applications. *Ann N Y Acad Sci.* 2007; 1098:122-144. https://doi.org/10.1196/annals.1384.008.
25. Mathews A, MacLeod C. Induced processing biases have causal effects on anxiety. *Cognition & Emotion.* 2002; 16: 331-354. https://doi.org/10.1080/02699930143000518
26. Apoorvagiri D, Nagananda MS. Mental Stress and its Implications on Reaction time. IJCTT. 2013; 4(5):1426-1430.
27. Preuss D, Schoofs D, Schlotz W, Wolf OT. The stressed student: influence of written examinations and oral presentations on salivary cortisol concentrations in university students. *Stress*. 2010; 13(3):221-229. https://doi.org/10.3109/10253890903277579
28. Welford AT. Choice reaction time: Basic concepts. In A. T. Welford (Ed.), Reaction Times. Academic Press, *New Yor*k. 1980; 73-128.
29. Brebner JT, Welford AT. Introduction: an historical background sketch. In A. T. Welford (Ed.), Reaction Times, Academic Press, *New York.* 1980; 1-23.
30. Teichner WH, Krebs MJ. Laws of visual choice reaction time. Psychol Rev. 1974; 81(1):75-98. https://doi.org/10.1037/h0035867.
31. Luce RD. Response Times: Their Role in Inferring Elementary Mental Organization. Oxford University Press, *New York.* 1986.
32. Kemp BJ. Reaction time of young and elderly subjects in relation to perceptual deprivation and signal-on versus signal-off condition. Dev Psychol. 1973; 8(2): 268-272.
33. Marshall WH, Talbot SA, Ades HW. Cortical response of the anaesthetized cat to gross photic and electrical afferent stimulation. *J Neurophysiol.* 1943; 6:1-15. https://doi.org/10.1152/jn.1943.6.1.1.
34. Bellis CJ. Reaction time and chronological age. *Proceedings of the Society for Experimental Biology & Medicine*. 1933; 30:801-803. https://doi.org/10.3181/00379727-30-6682.
35. Engel BT, Thorne PR, Quilter RE. On the relationships among sex, age, response mode, cardiac cycle phase, breathing cycle phase, and simple reaction time. J Gerontol. 1972; 27(4):456-460. https://doi.org/10.1093/geronj/27.4.456
36. Silverman IW. Sex Differences in Simple Visual Reaction Time: A *Historical Meta-Analysis. Sex Roles*. 2006; 54(1-2):57-69. https://doi.org/10.1007/s11199-006-8869-6
37. Spierer DK, Petersen RA, Duffy K, Corcoran BM, Rawls-Martin T. Gender influence on response time to sensory stimuli. *J Strength Cond Res.* 2010; 24(4):957-963. https://doi.org/10.1519/JSC.0b013e3181c7c536.
38. Dündar U. Antrenman Teorisi. Ankara, Bağırgan Yayınevi. 1997.
39. Gündüz N. Antrenman bilgisi. İzmir: Saray Tıp Kitabevleri. 1997.
40. Binboğa E, Pehlivan M, Çelebi G. The effects of auditory stimuli with varying frequency and intensitiy on human simple reaction time. Ege Journal of Medicine. 2007; 46(2):67-72.
41. Gürsoy R, Akarsu S, Hazar K. Examination of correlation among reaction time, strength, and flexibility of sedentary and athletes in different branches. *Journal of Human Sciences*. 2017; 14(4):3282-3291. https://doi.org/10.14687/jhs.v14i4.4786.
42. Taimela S, Kujala UM. Reaction times with reference to musculoskeletal complaints in adolescence. *Percept Mot Skills*. 1992; 75(3 Pt 2):1075-1082. https://doi.org/10.2466/pms.1992.75.3f.1075.

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Evaluation of the relationship between subacromial space volume and rotator cuff injury by Magnetic Resonance Imaging with SPACE technique

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Abstract

Aim: To investigate the relationship between the degree of tearing in the rotator cuff tendons and the subacromial region volume using the proton-density weighted Sampling Perfection with Application optimized Contrasts using different flip angle Evolution technique and the contribution of this technique to shoulder magnetic resonance imaging.

Material and methods: A total of 125 patients who underwent shoulder magnetic resonance imaging for shoulder pain between January 2016 and December 2016 were included in this single-center, retrospective study. Rotator cuff tendon injury grading was performed using coronal plane 2D short tau inversion recovery T2-weighted sequences (grades 1–4). Subacromial region volume was calculated from PD-weighted 3D SPACE sequence images in sagittal oblique plane. The relationship between rotator cuff tears and subacromial region volumes was evaluated using Pearson's correlation analysis. The measurements were made at different times by two independent radiologists.

Results: There was a strong negative correlation between the grade of RC tendon tear and subacromial volume ($p<0.05$; r: -0.83).

Discussion and conclusion: Shoulder magnetic resonance imaging with high-contrast resolution can be obtained by the Sampling Perfection with Application optimized Contrasts using different flip angle Evolution technique. The degree of rotator cuff tendon tear, which is a cause of shoulder pain, is associated with the subacromial region volume. Using the Sampling Perfection with Application optimized Contrasts using different flip angle Evolution technique can also easily reveal the cause of the damage.

Key words: rotator cuff, shoulder, magnetic resonance imaging, SPACE technique

Introduction

Rotator cuff (RC) tendon pathologies occur widely [1-3], and there are many reasons for their etiology. The development and progression of RC injury remain uncertain, particularly when associated with external shoulder compression [1-3]. Traditionally, certain acromial morphologies have been thought to physically reduce the subacromial area and contribute to RC injury [1-3]; however, the relationship between subacromial space volume (SAV) and RC tearing has never been experimentally confirmed [1-3].

In 1972, Neer coined the term subacromial impingement and proposed a pathomechanical process in which mechanical compression of the soft tissues in the subacromial space occurred due to a narrowing of the subacromial space [4]. He asserted that the soft tissues most commonly involved was the bursal side of the supraspinatus and long head of biceps tendons which compress against the anterior and lateral edge of the acromion and coracoacromial ligament [4]. Neer proposed that any reduction of the subacromial space would lead to impingemnt syndrome [4].

The factors contribute to the shoulder impingement syndrome can be divided into extrinsic factors and intrinsic factors. Extrinsic factors that compress the structures with in the subacromial space (extra-tendinous), and intrinsic factors are those associated with degeneration of the rotator cuff tendons (intratendinous) [5].

In the literature, it is mentioned that the volume reduction of the subacromial region causes tendon degeneration by causing repetitive shear and compression forces [4]. It is also argued that histological changes in tendons, mechanical properties, morphology and vascularity of the tendon play a role in RC tendinopathy [6].

In this retrospective study, we measured the subacromial region volume of patients with RC tears by magnetic resonance imaging (MRI) and investigated whether it affects the degree of RC tearing.

Material and methods

Patients

A total of 125 patients who had MRI performed in the radiology department due to shoulder pain between January 2016 and December 2016 were included in the study.

Ethics committee approval was obtained for this single-center retrospective study.

Patients with a history of shoulder trauma or surgery, inflammatory pathology, or infection were excluded from the study. Pediatric patients and patients with any contraindicated conditions (stenting, pregnant patients, claustrophobic patients, etc.) were also excluded from the study.

MRI technique

MRI of the shoulder was performed by a 1.5 Tesla device (Avanto; Siemens) while the patients were lying in the supine position with the shoulder joint in slight external rotation. The shoulder MRI sequence parameters are summarized in Table 1.

All were scanned using our routine 2D sequence protocol and the 3D Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (SPACE) sequence.

Table 1 Shoulder magnetic resonance imaging sequence parameters

Sequence	2D FS-PD	2D FSTIR	T2 TSE	2D T1-TSE	3D PD SPACE
Plane	Axial	Coronal oblique	Sagittal oblique	Coronal oblique	Coronal oblique
TR (ms)	2000–4000	>1500	>2000	400–800	1100
TE (ms)	30–50	20–40	90–110	minimum	30–50
TI (ms)	-	150	-	-	-
ETL	8	8	8	-	-
BW	16	16	16	16	
Slice thickness (mm)	4	3.5	3.5	3	0.7
Interslice gap (mm)	1.2	1	1	0.5	0
Matrix	256 x 256	256 x 166	256 x 256	256 x 256	256 x 256
FOV (mm)	160	160	160	160	160
Time (min) average	1:40	1:35	1:14	1:08	7:20

TSE: turbo spin echo image, SPACE: Sampling Perfection with Application optimized Contrasts using different flip angle Evolution, FS-PD: fat-suppressed proton density-weighted image, TE: echo time, TR: repetition time, FA: flip angle, FOV: field of view, ETL: echo train length, BW: bandwidth, ms: millisecond, mm: millimeter, min: minute

Image analysis

SAV measurements of the patients were made automatically in picture archiving and communication systems.

The initial diagnostic reading of the images was based on our routine 2D proton-density (PD) fat-suppressed (fs) protocol (Table 1). RC tendon tears were graded by the 2D short tau inversion recovery (STIR) technique, with fs T2-weighted Fast Spin Echo (FSE) sequences. In the visual evaluation, a tendon showing a T2 signal similar to the water signal was considered to be ruptured. A smaller T2 signal increase compared to the water signal was evaluated in favor of tendinosis and/or tendinopathy. This group of patients was excluded from the study.

The tendon tears were divided into three groups according to their location: tears extending to the joint surface of the tendon, tears extending to the bursal surface of the tendon, and tears within the tendon.

When classified according to the degree of tendon tear, the tendon thickness in the craniocaudal direction was graded as follows: If the tear was less than one-third of the tendon, it was accepted as a minimal partial tear (grade 1). If the tear was more than two-thirds of the tendon, an advanced partial tear was accepted (grade 3). Classifications between these two grades were accepted as a moderate partial tear (grade 2). If there was a loss of integrity in the tendon, it was accepted as a full-thickness tear (grade 4) (Figure 1a, b). Scoring increased with the degree of tendon tear.

Figure 1a. - 46-year-old female patient. The shoulder MRI performed for shoulder pain shows a moderate partial tear in the supraspinatus tendon on the bursal surface (thin blue arrow). It was observed in more than half the thickness of the torn tendon (small blue star) (grade 3).

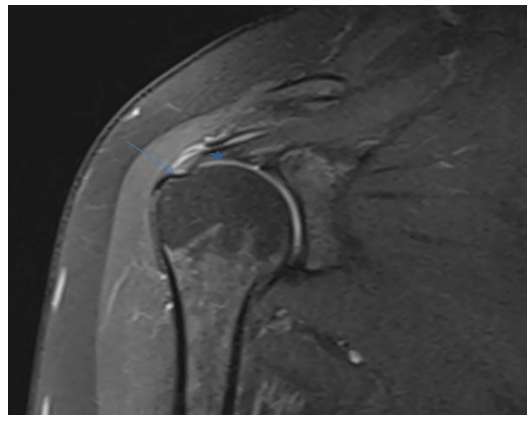
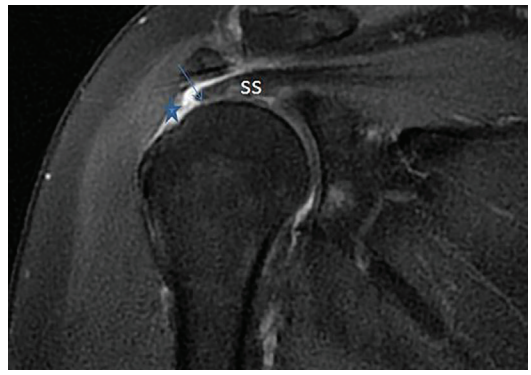


Figure 1b. - 48-year-old male patient. The supraspinatus tendon (small blue star) is not observed in the subacromial area in the shoulder MRI taken for shoulder pain. The supraspinatus (SS) tendon is seen as total ruptured. Proximal retraction of the ruptured fibers is observed (thin blue arrow).



Subacromial region volume calculation

SAV measurements were made from the sagittal oblique plane PD-weighted 3D-SPACE sequence images. The area between the lower surface of the acromion and the chondral surface of the humeral head was calculated in serial sagittal oblique images from the acromial end to the acromioclavicular joint. The region of interest (ROI) areas marked on each section were automatically collected and multiplied by the number and thickness of the section, which automatically calculated the volume (cm3) of the subacromial region (Figure 2).

Two fully trained radiologists with 10 and 8 years' experience, respectively, in musculoskeletal imaging independently assessed all the exams. Diagnosis, gender, age, and clinical history were blinded for the reviewers.

Figure 2 - 38-year-old male patient. The volume measurement of the subacromial region is observed in the proton-density (PD) image made with the SPACE technique. A manually drawn ROI drawing with reference to the acromion lower cortex and the corresponding humeral joint face is shown. This process was repeated in every section where the acromion was visible. The drawn ROIs gave the result as an area; therefore, the result obtained was multiplied by the number and thickness of the sections, and the result was calculated as cm3.

Statistical analysis

The distribution of outcome categories was assessed using the Shapiro–Wilk test. Data are presented as means ± standard deviation based on the normality of the data. The categorical variables are reported as counts and percentages.

The relationship and degree of relationship between SAVs and RC tendon damage were tested by Pearson's correlation analysis. The correlation values (r) were very poor > 0.25; poor 0.25–0.50; medium 0.50–0.70; high 0.70–0.90; or very high 0.90–1.00.

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software (Version 22.0; SPSS Inc., Chicago, IL, USA).

A p-value <0.05 was considered statistically significant.

Results

The average age of the 125 patients included in the study was 52 years (48 years for women and 57 years for men).

The distribution percentages of the tendon tear classifications and the average SAVs in our patient population are summarized in Table 2.

There was statistically high agreement between the two observers in terms of RC tear classification (r: 0.82).

There was a strong negative correlation between the grade of RC tendon damage and SAV ($p < 0.05$; r: -0.83) (Table 2).

The mean volumes for the subacromial region for mild partial tears were 3.48 cm3 for males and 3.16 cm3 for females and 2.52 cm3 and 2.47 cm3 for moderate partial RC tears, respectively. The mean volumes for full-thickness RC tears were 2.18 cm3 in men and 2.05 cm3 in women. The SAV measurements of the two observers were very consistent (r: 0.96).

Discussion

The RC consists of four muscles that come out of the scapula and attach to the humerus head. These muscles join as they pass the glenohumeral joint, adding strength and dynamic stability to the joint. The RC is important for shoulder motion [4,5]. The initiation of shoulder abduction relies on the function and integrity of the supraspinatus muscle and its tendon and other RC tendons [4-7].

During arm lift, the anterior acromion and the upper border of the subacromial space should move upward so that the head of the humerus is raised. If this does not happen, the rotator cuff tendon is compressed on the bursal side by the anterior acromion [4-7].

RC tendon tears occur in more than half of the population over the age of 60. Shoulder pain is one of the most common musculoskeletal complaints, and shoulder impingement syndrome is the most commonly diagnosed shoulder disease [7-11]. The etiology of RC tears is multifactorial [7-11].

Morphology of the acromion has been considered to contribute to narrowing of the subacromial space, hence reducing the out let for the rotator cuff tendons. Bigliani and Levine evaluated acromion types and their frequencies in their study on 140 cadavers. They stated that Type 3 hooked acromion is the type most associated with RC tendon ruptures [7].

Narrowing in the subacromial area can be determined by direct or indirect measurement methods [12]. Indirect methods include acromion anterior slope, lateral acromial angle (LAA), acromion index (AI), acromio-glenoid angle (AGA), and critical shoulder angle. High slope angle, low LAA values, and increased AI are also associated with RC tears [12–14]. Tetreault et al. noted that low AGA values indicated a narrowing of the supraspinatus output [12-14]. According to theory, these measurement parameters show a decreased subacromial zone volume, and compression of the tendon in the subacromial region is an important finding [12-14].

Superficial migration of the humeral head in the chronic tears of RC tendons reduces the subacromial distance and thus the volume of the subacromial space [13,14]. Significant subacromial volume reduction in the early stage of RC tears indicates that humeral head migration has begun with the development of the RC tear [13,14].

In the study of Lee et al., 40 fresh cadavers with and without RC tears were examined. According to the results of the study, no significant difference was found between the two cadaver groups in terms of acromion shape. As a result, it was

Table 2 Distribution of rotator cuff (RC) injury and subacromial region volumes according to gender and degree of damage with correlation matrix

RC tear degrees	Number (n) and percentage (%) of patients		Subacromial region volume (cm3)		Correlations between variant	
	n	%	Male	Female	Significant (2-tailed)	Pearson correlation
Grade 1	26	21	3.48 ± 1.9	3.16 ± 0.6	0,002	-0,93
Grade 2	35	28	2.52 ± 1.3	2.47 ± 1.4	0,034	-0,83
Grade 3	39	31	2.24 ± 0.6	2.21 ± 1.2	0,04	-0,87
Grade 4	25	20	2.18 ± 0.5	2.05 ± 0.8	0,00	-0,96

concluded that "factors other than the acromion shape may play a role in the pathogenesis of rotator cuff tears" [15].

Other studies on subacromial decompression surgery, where the subacromial burs were excised, showed that the results were not different, whether performed with or without acromioplasty [13,14]. As a result, the idea that acromion morphology has nothing to do with subacromial impingement syndrome and this view is supported by many authors has been supported. Based on the available evidence from studies in the literature, the hypothesis that a reduction in subacromial area is a cause in impingement has not been firmly established [16,17].

Independent of all these results, detailed imaging of the RC and subacromial region is extremely important in terms of elucidating the etiology [18,19].

Computed tomography (CT) examination allows for high temporal resolution [3,14]; however, when evaluated in terms of contrast resolution, MRI is superior. In addition, contrast resolution is very important in a joint with complex anatomy, such as the shoulder joint. MRI is the gold standard imaging examination for the presence of intra-articular fluid, evaluation of bicipital labral pathologies, and detailed evaluation of muscle tissue and ligament pathologies [18,19]. The absence of radiation exposure and any invasive procedure in the evaluation of most intra-articular pathologies are other advantages [18,19].

Surgical treatment may be considered in symptomatic RC tears and subacromial impingement that do not respond to conservative therapy [2,3]. Therefore, SAV measurement maybe a guide at this point.

The images we obtained with the SPACE sequence had high-contrast resolution, and we easily obtained reformatted images in 3D planes with the thin sections we obtained. We were also able to create oblique plane formats of these. In this way, we were able to follow each tendon throughout its entire course [18,19].

Besides visual information about the shoulder junction muscle and bone tissue, measurements can also be made using shoulder MRI with appropriate position and technique. High-resolution images with very thin slice thicknesses can be obtained with CT. Images can be obtained in the axial plane, with a slice thickness of 1–3 mm that partially overlapped each other, and reconstructed to obtain thin sections [18,19]. Thus, 3D images can be obtained. Using the SPACE MR technique, a section thickness of 0.7 mm was obtained. The advantage of this examination is that the patient does not experience radiation exposure [18,19].

Our study has some limitations. First, we did not classify patients according to age. In the advanced age group, fat atrophy in the RC and deltoid muscle is a finding that may contribute to impingement findings [1–3]. Consequently, the subacromial volume of older patients may be further decreased compared to younger patients. This issue may be explored in a future study. Second, this study had a small population and lacked clinical diversity. The third limitation is that patients with a diagnosis of subacromial impingement and subacromial volume measurement did not have arthroscopic findings. Clinical follow-up data for these patients were not available.

Conclusion

In conclusion, we were able to show the shoulder and subacromial region in MRIs with very thin slice thicknesses in three planes. We found that the degree of RC tendon damage, one of the causes of shoulder pain, correlated with the volume of the subacromial area. Images with high-contrast resolution can be obtained with shoulder MRI obtained using the SPACE technique. In this way, the etiology of shoulder pain can be easily illuminated.

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References

1. Kanatli U, Ayanog, T, Aktas E, Özer, M, Çetinkaya, M. Grade of coracoacromial ligament degeneration as a predictive factor for impingement syndrome and type of partial rotator cuff tear. *J Shoulder Elbow Surg.* 2016; 25(11):1824-1828. https://doi.org/10.1016/j.jse.2016.02.026
2. Daghir AA, Sookur PA, Shah S, Watson M. Dynamic ultrasound of the subacromial-subdeltoid bursa in patients with shoulder impingement: a comparison with normal volunteers. *Skeletal Radiol.* 2012; 41(9):1047-53. https://doi.org/10.1007/s00256-011-1295-z
3. Moosikasuwan JB, Miller TT, Burke BJ. Rotator Cuff Tears: Clinical, Radiographic, and US Findings. *RadioGraphics.* 2005; 25:1591-1607. https://doi.org/10.1148/rg.256045203
4. Neer, C.S.I., 1983. Impingement Lesions. *Clinical Orthopaedics & Related Research.* 1983; 70-77. https://doi.org/10.1097/00003086-198303000-00010
5. Seitz, A.L., McClure, P.W., Finucane, S., Boardman III, N.D., Michener, L.A., 2011. Mechanisms of rotator cuff tendinopathy: Intrinsic, extrinsic, or both? Clinical Biomechanics. 26:1-12. https://doi.org/10.1016/j.clinbiomech.2010.08.001
6. Girish G, Lobo LG, Jacobson JA, Morag Y, Miller B, Jamadar DA. Ultrasound of the Shoulder: *Asymptomatic Findings in Men. AJR.* 2011; 197:W713-W719. https://doi.org/10.2214/AJR.11.6971

7. Bigliani, L.U., Codd, T.P., Connor, P.M., Levine, W.N., Littlefield, M.A., Hershon, S.J., 1997. Shoulder Motion and Laxity in the Professional Baseball Player. *Am J Sports Med*. 25:609-613 https://doi.org/10.1177/036354659702500504
8. Craik JD, Mallina R, Ramasamy V, Little, NJ. Human evolution and tears of the rotator cuff. *Int Orthop*. 2014; 38(3):547-552. https://doi.org/10.1007/s00264-013-2204-y
9. Durmaz MS, Karahan Y. Omuz Ultrasonografi İncelemesi Manyetik Rezonans Görüntüleme' nin Yerini Alabilir Mi? [in Turkish]. *Dicle Med J*. 2020; 47:929-939. https://doi.org/10.5798/dicletip.850507
10. Teefey SA, Middleton WD, Payne WT, Yamaguchi K. Detection and Measurement of Rotator Cuff Tears with Sonography: Analysis of Diagnostic Errors. *AJR*. 2005; 184:1768-1773. https://doi.org/10.2214/ajr.184.6.01841768
11. M. J. Tuite MJ, Small KM. Imaging Evaluation of Nonacute Shoulder Pain. *AJR*. 2017; 209:525-533. https://doi.org/10.2214/AJR.17.18085
12. Pepe M, Kocadal O, Gunes Z, Calisal E. Subacromial space volume in patients with rotator cuff tear: The effect of surgical repair. Acta Orthop. Traumatol. *Turc*. 2018; 52(6):419-422. https://doi.org/10.1016/j.aott.2018.08.003
13. Nyffeler RW, Meyer DC. Acromion and glenoid shape: Why are they important predictive factors for the future of our shoulders? EFORT Open Rev. 2017; 2(5):141-150. https://doi.org/10.1302/2058-5241.2.160076
14. Titreault P, Krueger A, Zurakowski D, Gerber C. Glenoid version and rotator cuff tears. *J Orthop Res*. 2004; 22(1):202-207. https://doi.org/10.1016/S0736-0266(03)00116-5
15. Lee SB, Itoi, E., O'Driscoll, S.W., An, K.-N., 2001. Contact geometry at the undersurface of the acromion with and without a rotator cuff tear. Arthroscopy: *The Journal of Arthroscopic &Related Surgery.* 17:365-372. https://doi.org/10.1053/jars.2001.19974
16. Budoff, J.E., Rodin, D., Ochiai, D., Nirschl, R.P., 2005. Arthroscopic Rotator Cuff Debridement Without Decompression for the Treatment of Tendinosis. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 21:1081-1089. https://doi.org/10.1016/j.arthro.2005.05.019
17. Henkus, H.E., Witte, P.B. de, Nelissen, R.G.H.H., Brand, R., Arkel, E.R.A. van, 2009. Bursectomy compared with acromioplasty in the management of subacromial impingement syndrome a prospectıve randomısed study. *J Bone Joint Surg Br*. 91-B:504-510. https://doi.org/10.1302/0301-620X.91B4.21442
18. Karsten J, et al. Comparison of 3D turbo spin-echo SPACE sequences with conventional 2D MRI sequences to assess the shoulder joint. Eur. *J. Radiol.* 2014; 83(1):1843-1849. https://doi.org/10.1016/j.ejrad.2014.06.011
19. Henninger B, Raithel E, Kranewitter C, Steurer M, Jaschke W, Kremser C. Evaluation of an accelerated 3D SPACE sequence with compressed sensing and free-stop scan mode for imaging of the knee. *Eur. J. Radiol.* 2018; 102:74-82. https://doi.org/10.1016/j.ejrad.2018.03.001

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First steps in forecasting the health workforce in Kazakhstan: A baseline scenario

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Abstract

Background: The purpose of this study was to consider the basic scenario for predicting the need for general practitioners in Kazakhstan until 2030.

Material and methods: A basic health care human resource planning model consists of supply and demand components, analysis of the outcomes of the prediction, and planning future actions. Stock-flow consistent model was built by using current situation and projected Kazakhstan population, retirement rate, attrition rate and adding the estimated number of new graduates.

Results: According to the proposed scenario, in some years of the forecast period, both an excess and a lack of a general practitioners offer are possible. The largest surplus, 226 doctors, is predicted in 2024. However, starting in 2027 their shortage is possible, with a peak of 339 general practitioners in 2030.

Conclusion: Considered scenario leads to the fact that inflow does not cover the increasing needs of primary health care associated with population growth. In this case, our forecast is the basis for medical schools to adjust the number of general practitioners students in internship, seeking a balance of supply and demand.

Key words: human resources forecasting, health care workforce, workforce planning, public health

Introduction

At present, the World Health Organization and many countries of the world pay great attention to the problems of health care workforce planning [1]. Health workforce planning involves assessing demands and supplies, correctly resources distribution, and making plans to address potential imbalances [2].

The involvement of a wide range of stakeholders in the human resources planning process, especially in the discussion of the modeling itself, has an overall impact on human resources for health policy, as it increases the engagement of various stakeholders and encourages them to engage in dialogue. This leads to the fact that health policy is not developed by a narrow circle of people, but takes into account the views of various interested sectors of society. This interaction opens up new trends in this area and develops new ideological approaches to healthcare [3].

Approaches commonly used to predict future human resources for health care (HRH) include: population ratio method [4], health need method [5], health demand method [6], service target-based approaches [5]. According to Dresh N. and his colleagues each of these approaches has its advantages and disadvantages [7].

Basically, health care human resource planning model consists of supply and requirement components, analysis of the outcomes of the prediction, and planning future actions, or in simpler terms, analysis of supply, demand, gap and solution [8, 9].

In the process of planning and modeling of medical personnel, it is necessary to take into account the following aspects: components that make up demand and supply, methods of their assessment, an algorithm for combining them, initial conditions and assumptions, changes in parameters over time, possible development scenarios (one or more) [10].

Typically, most planning systems consider more than one scenario - a baseline scenario and one or more alternative scenarios. The health workforce projection model can create different scenarios, taking into account possible changes in the socio-economic, epidemiological and demographic situation in the country, as well as

changes in health policy. The developed scenarios differ depending on the profession and the purpose of forecasting.

The Republic of Kazakhstan occupies a vast territory of 2724902 sq. km., while the population density is extremely low (6.51 people per sq. km). Different regional administrative subdivisions (central, northern, eastern, southern and western) differ in the level of socio-economic development, population density, climatic conditions and the degree of urbanization. Like other countries of the world, Kazakhstan suffers from a geographically uneven distribution of human resources for health. In all regions, except megacities, there is a shortage of medical workforce. The approaches to HRH forecasting and planning used until recently were ineffective. Human resource planning has historically not been a priority for health policy implemented by local health authorities. There is guideline "Methods of planning and forecasting human resources for health care" on the website of the Republican Center for Health Development [11]. In addition to simple models based on population size and service targets, the authors propose a regression model that includes demographic, sociocultural, and epidemiological factors. However, this planning tool can best be classified as a demand-based model – there is no supply side and it do not measure expected balance between the required and available number of health professionals for the next years. The disadvantages of linear models include the fact that the relationship between HRH and independent factors may be non-linear and the linear regression model in this case may be insignificant. In available scientific literature we did not find examples of practical application of any health workforce projection models in Kazakhstan.

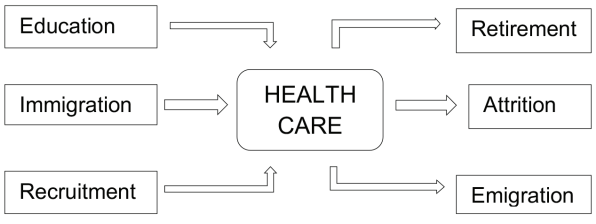
The purpose of this study was to consider the basic scenario for predicting the need for General Practitioners (GP) in Kazakhstan until 2030.

Material and methods

The basic workforce forecasting model is based on the stock-flow methodology and consists of supply and demand submodels. An integral part of modeling is the analysis of forecasting results and the development of actions that can prevent a possible imbalance in human resources. Stock-flow models were proposed by Godley and Cripps [12] and extended by Godley and Lavoie [13] and Kinsella et al. [14] for financial systems in macroeconomics. The methodology is based on the idea that everything should come from somewhere and go somewhere [15].

The model is designed to predict the supply and demand of GP in Kazakhstan for the period from 2019 to 2030. The base year is 2018. The model uses variables that are the most accessible and most accurate at the present time and most significantly affect the state of the labor force in primary health care. Figure 1 shows the relationships between stocks and inflows and outflows over time.

Figure 1 - Stock-flow consistent model



Data collection

The main challenge for implementing our workforce planning model was the availability and reality of data. Among the weaknesses of the human resources management system of the Republic, one can single out disparate HRH databases and inconsistency of HRH credentials with international standards [16]. Workforce information can be found in the reporting forms of Ministry of Health: "Medical organization Report", "Report on medical resource", as well as in the database "Personnel", on the portal of the Republican e-health center, in the department of science and human resources of Ministry of Health, in employment departments of medical universities. None of these sources is comprehensive. The parameters of the model were determined according the information provided to us by various government agencies regulating the health care of Kazakhstan. This information included data on health care professionals, on the need for medical care and on the training of doctors in the republic's universities. Table 1 details these sources and their content.

Table 1 Data sources

Model parameter	Source
Number of doctors in primary health care in 2014-2018	Republican Center for Health Development
Amount of FTE per doctor in 2014-2018 years	Republican Center for Health Development
Demographic developments in 2018-2030	Ministry of Economy and Budget Planning
New graduates (all medical universities in Kazakhstan)	Department of Science and Human Resources of the Ministry of Health
Recruitment	Department of Science and Human Resources of the Ministry of Health
Exits from the health workforce due to retirement	Department of Science and Human Resources of the Ministry of Health
Exits from the health workforce due to another reasons	Department of Science and Human Resources of the Ministry of Health

Results

Current situation

In Kazakhstan, the functioning model of primary health care inherited from the USSR the local principle of serving the population with the definition for each primary health care specialist of a clearly limited service area with a certain number of adults for the therapist and children for the pediatrician. According to standards, one local therapist is for 2200 adults and one pediatrician is for 900 children. In this well-built model, a new post of GP, taken from the experience of developed countries, has been introduced. In the future, the GP should become the main link in the primary health care system. He has the knowledge and skills to help with the most common diseases for all age groups. His team includes skilled secondary medical, social workers and other professionals required to deliver health services to a designated population. The GP is charged with serving the population in 2000 without dividing into age categories [17]. However, these standards are not binding and every health care facility has the right to adjust it annually.

A GP performing this standard and working 40 hours a week is assigned 1 Full Time Equivalent (FTE). Due to low wages and staff shortages, many GP take on additional workload (without increasing the number of hours) and receive additional payment due to vacant rates, so the amount of FTE per GP is more than 1.

In recent years, the number of doctors in the primary health care system of Kazakhstan has increased with an average growth rate of 6% (Table 2). Firstly, this was due to an increase in the population of the Republic (an average growth rate of 1.3% per year) and, secondly, to a decrease in the number of assigned population per doctor. If in 2014 the workload was 2054 population per 1FTE, then in 2018 it was already 1728. Over the years one FTE doctor accounted for 1858 people on average. Currently, the density of primary health care doctors in the republic is 57 per 100000 population.

Table 2 Primary healthcare workforce in Kazakhstan

	Population size	Number of doctors	Density per 100,000	Population per doctor	FTE per doctor	Population per 1FTE	Head counts of FTE
2014	17267141	8240	48	2096	1,02	2054	8405
2015	17503080	8805	50	1988	1,02	1949	8981
2016	17735340	9492	54	1868	1,02	1832	9682
2017	17962170	10 279	57	1763	1,02	1728	10394
2018	18182015	10 314	57	1763	1,02	1728	10520

Demand

In the baseline we project the demand for healthcare workers assuming that the same level of service (defined as attached population per GP) is provided for an increasing population. We used the projection for the population of Kazakhstan until 2030, compiled by the Ministry of Economy and Budget Planning of the Republic of Kazakhstan. Based on these data, the number of FTE was calculated as compared to 2018 (Table 3). According to these data, it is predicted that in Kazakhstan until 2030, the need for GP will increase at an average rate of 0.9%.

Table 3 Healthcare demand in 2019-2030

Year	Population	Growth rate (comparing with 2018)	Health care demand (FTE)
2019	18393708	1,004	10879
2020	18596568	1,015	10999
2021	18790610	1,025	11107
2022	18976379	1,036	11226
2023	19154791	1,045	11324
2024	19327060	1,055	11432
2025	19494551	1,064	11530
2026	19658707	1,073	11627
2027	19821112	1,082	11725
2028	19983452	1,091	11822
2029	20147304	1,099	11909
2030	20313981	1,109	12017

Outflow variables

A part of the specialists is lost annually due to leaving associated with full or early retirement, emigration, death in service and other reasons (leaving work or the labor market). There are several challenges in outflow assessing. One of these problems is associated with finding information about the number of people who have left the profession.

To assess the various flows, we used data for the last four years, provided to us by the Department of Science and Human Resources of the Ministry of Health (Table 4).

Retirement. According to the Department of Human Resources and Science of the Ministry of Health of the Republic of Kazakhstan in recent years, from 2014 to 2017, approximately 1% of primary health care workers every year leave their occupation due to retirement. We assumed that this share would remain permanent in future years.

Emigration. Emigration, in our opinion, does not have a significant effect on attrition. According to the data from the Table 4, it is approximately 0.1% of the total number of primary health care GP.

Attrition for other reasons. Major reason to leave primary health care is decision to apply to different highly specializations and continue their studies in residency. The reasons can also be migration within the country, transfer from one medical facility to another, military service, transfer to another field of activity, maternity leave, illness and death. We did not single out any groups for reasons that lead to the fact that people leave their profession at different stages of life, and just used the available data on outflow rates. As can be seen from Table 4 for four years attrition in the whole of Kazakhstan averaged 15% and this value was used in our model.

Deficits. The Ministry of Health estimates that the shortage of GP in primary health care is 3%. We have calculated how many GP will be needed in the future to compensate for the output flows, as well as the deficit.

Table 4 Healthcare resource flows in 2014-2017

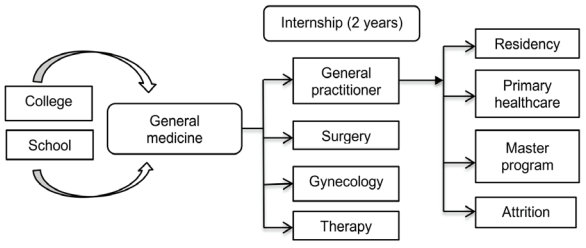
	Headcount at the beginning of the year	Recruitment (without new graduates)	%	Emigration	%	Retirement	%	Attrition	%
2014	8240	1057	13	13	0,2	106	1	1190	14
2015	8805	996	11	13	0,1	101	1	1344	15
2016	9492	831	9	9	0,1	127	1	1187	13
2017	10279	871	8	15	0,1	149	1	1632	16
Mean			10		0,1		1		15

Inflow variables

Recruitment (without new graduates). These are newly recruited GP. Among them may be those who have moved to another place of residence or, for some reason, moved from one hospital to another. It can also be those who have completed military service, came from maternity leave, moved from related fields of medicine, or decided to return to medical practice after a break. According to our data they are 10%.

Education. The main source of new health care workforce is the national medical education system. In Kazakhstan 80% of students study for free under state educational grants. The period of training of GP is 7 years: future doctors of 5 years are studying undergraduate degrees in General medicine and then 2 years of internship. The internship is preparing for several clinical specialties, including the specialty "general practitioner". The number of places allocated to each specialty, the university determines on its own, based on the needs of health care. Later part of the graduates of the specialty GP go to the residency or magistracy, the other part goes to work in primary health care (Figure 2).

Figure 2 - Medical education system in Kazakhstan



If in 2009-2014 the number of medical students was increased, then, as the shortage of medical workers was eliminating, from 2015 to 2018, the government reduced the number of grants allocated to medical specialties, including the specialty General Medicine (Table 5). In subsequent years, from 2019 to 2021, according to a government decree, the number of grants will remain unchanged at 2,700.

According to the Departments of Employment of Medical Universities, about 30% of those entering the specialty "General Medicine" after completing the internship work in primary healthcare. In accordance with this, we accepted that in 2019-2021 each year 900 new GP graduates will enter the labor market, then, in 2022-2024, this number will decrease to 800 and further, in 2025-2030, to 700 GPs.

Baseline projections

Table 6 presents the algorithm for calculating elements of inflow and outflow. 2018 was adopted as the base year.

Similarly, supply and demand for the following years were calculated (Table 7). The table also presents the input and output flows, as well as the projected deficit or surplus of GP for each year until 2030.

In the baseline scenario we project the demand for GP assuming that the level of service provided to a growing population will remain unchanged. Such an indicator as the density of GP per population will not change. So, the total need for GP is determined based on the demand due to population growth and the demand for replacement (losses due to retirement, emigration, etc.). The population is projected to reach 20.3 million in 2030.

Discussion

Baseline results should only be interpreted as a need for replenishment based solely on anticipated population growth, while maintaining a workload per GP. According to the proposed scenario, in some years of the forecast period, both an excess and a lack of a GP offer are possible. The largest surplus, 226 GP, is predicted in 2024. However, starting in 2027 their shortage is possible, with a peak of 339 GP in 2030 (Figure 3).

As noted above, after five years of study, students are assigned to a 2-year internship in four specialties, including the "General practitioner". The number of places is determined by the university itself in accordance with requests from regional health departments. Today, graduates do not have problems with employment, since many regions are experiencing a deficit of primary health care workforce and offer various incentives for young professionals, so that up to 98% of new GP graduates find a job. However, the deficit of GP is gradually eliminated and, in accordance with this, the government reduces the number of grants for medical education. And we can expect decreasing number of GP in the labour market. But at the beginning of the 20s, it will still have an effect on the admission of students in 2013-2017, which may lead to a workforce oversupply.

Figure 3 - General Practitioner forecasting

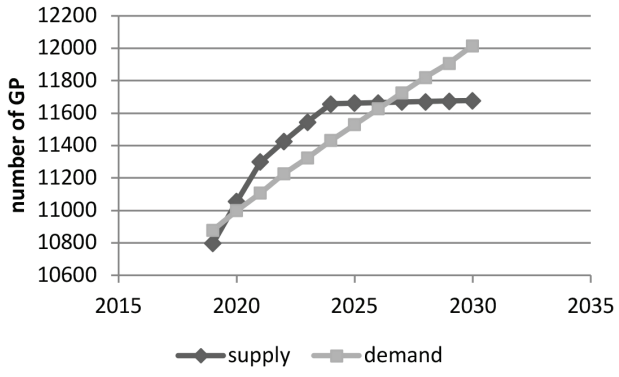


Table 5 Number of students in medical education

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Government grants for medical education (total)	3500	3600	3600	3700	3700	3700	3000	3000	3150	2700
Government grants for "General medicine" (undergraduate program)	3263	3356	3356	3433	3434	3438	2528	2433	2700	2152
Internship «General practitioner» output	No data	No data	No data	No data	No data	938	1047	1547	2060	2103
From them entered the labour market (primary healthcare)	No data	No data	No data	No data	No data	476	664	980	1128	

Table 6 Model elements calculation

Current available supplay	For 2018, the total number of available GP was 10314. On average GP worked 1,02 FTE. With these numbers, the total available supply in FTE for 2018 can be calculated as 10520 FTE.
Current required supply	According to the Ministry of Health in 2018 the deficits between health-care demand and available supply was 3%. Based on the total available supply in 2018 of 10520 FTE and the gap of 3%, the required health-care is estimated at 10836 FTE
Outflow	Outflow due to retirement is calculated as 1% of 10314 and equal 103 GP Emigration is estimated as 0,1% (10 GP) Attrition is 15% of 10314 (1547 GP) Total recruitment requirement 1661 GP
Inflow	New graduates – 900 GP Recruitment (10% of 10314) – 1031 GP Total: 1931 GP
Future available supply	The number of GP available in 2019 is calculated using the number of GP in the baseline year (2018) and the outflow and inflow of GP in the alternate years (10314-1661+1931=10585) FTE in 2019 is defined by multiplying the projected number of GP available (element 9) with the projected percentage of FTE per doctor (10585*1,02 =10797)
Future required supply	For 2019, it has been projected that the total required supply is 10879, based on the required supply in 2018 (10836 FTE, including unmet demand) and demographic developments until 2019 (which will increase demand by 0,4%)
Gap	If the baseline model is applied, there will be an excess demand in 2019 of 10879-10797=83 FTE.

Table 7 Forecasting results

	Retirement	Immigration	Attrition	Recruitment	New graduates	GPs supply	FTE supply	Demand supply	Gap*
2019	103	10	1547	1031	900	10585	10797	10879	82
2020	106	11	1588	1059	900	10839	11056	10999	-57
2021	108	11	1626	1084	900	11078	11300	11107	-193
2022	111	11	1662	1108	800	11202	11426	11226	-200
2023	112	11	1680	1120	800	11319	11545	11324	-221
2024	113	11	1698	1132	800	11429	11658	11432	-226
2025	114	11	1714	1143	700	11433	11662	11530	-132
2026	114	11	1715	1143	700	11436	11665	11627	-38
2027	114	11	1715	1144	700	11440	11669	11725	56
2028	114	11	1716	1144	700	11443	11672	11822	150
2029	114	11	1716	1144	700	11446	11675	11909	234
2030	114	11	1717	1145	700	11449	11678	12017	339

* A positive gap indicates excess demand (shortage of healthcare workers); a negative gap, excess supply.

We do not know anything about the government's plans in medical education after 2021. Therefore, we stopped on 800 and 700 new graduates of GP in subsequent years. This scenario leads to the fact that inflow does not cover the increasing needs of primary health care associated with population growth. In this case, our forecast is the basis for medical schools to adjust the number of GP students in internship, seeking a balance of supply and demand.

Another element that has a significant impact on human resource planning is staff turnover. It is associated with the flow of specialists from rural to urban areas and with low wages in primary health care in comparison with other sectors of health care, as well as with the transition from the public to the private sector. It is expected that greater stimulation in the primary health care sector will contribute to solving the problem of workforce.

In this study, we developed a quantitative supply and demand model for GP in Kazakhstan. The model was used to predict the additional recruitment of GP due to the expected population growth, without changing other influencing factors such as socio-economic, epidemiological and others. The model allowed us to assess the ability of the medical education system to meet this basic requirement.

We understand that the base model is only the first step in forecasting human resources in health care. It has a number of drawbacks, since we generally assume the "status quo" on the supply side and demand side for all other non-demographic variables. We also made a cautious assumption that the number of new GP will be reduced in accordance with the plans of the Ministry of Health. In addition, the model assumes that some components of demand remain unchanged: for example, the use of health care, the provision of health services, or an increase in health care costs. Now it is necessary to go further and try to assess future changes in healthcare: an increase in demand for medical services from every member of society, an increase in medical services from medical institutions, changes related to the age and gender structure of the population. Also, it is necessary to reflect possible future changes in the health status of the population using epidemiological data, trends in socio-cultural development.

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References

1. World Health Organization. Global strategy on human resources for health: workforce 2030. Geneva: *WHO*; 2015. 25 p.
2. Minimum Planning data requirements for health Workforce Planning. Joint Action Health Workforce Planning and Forecasting D.051 – Release 1 available at http://euhwforce.weebly.com/results.html
3. Roberfroid D, Leonard C, Stordeur S. Physician supply forecast: better than peering in a crystal ball. *Human Resources for Health*. 2009; 7(10):1-13. https://doi.org/10.1186/1478-4491-7-10
4. Hall TL. Demand and supply. In: Hall TL, Mejia A., editors. Health manpower planning: principles, methods, issues. Geneva: *WHO*. 1978; 57–116.
5. Models and tools for health planning and projections. Geneva: WHO; 2010. 19 p.
6. McQuide P, Stevens J, Settle D. An overview of human resources for health (HRH) projection models: Technical brief 12. Chapel Hill: *The Capacity Project;* 2008; 4.
7. Dreesch N. et al. An approach to estimating human resource requirements to achieve the Millennium Development Goals. *Health Policy and Planning.* 2005; 20(5):267–276. https://doi.org/10.1093/heapol/czi036
8. Malgieri A, Michelutti P, Van Hoegaerden M. Handbook on Health Workforce Planning Methodologies across EU countries. Slovakia: Joint Action Health Workforce Programming & Forecasting, Funded by the Health Programme of the European Union; 2015
9. Al-Sawai A, Al-Shishtawy MM. Health Workforce Planning: An overview and suggested approach in Oman. *Sultan Qaboos University medical journal*. 2015; 15(1):27-33.
10. Roberfroid D, Leonard C, Stordeur S. Physician supply forecast: better than peering in a crystal ball? *Human Resources for Health*. 2009; 7:10. https://doi.org/10.1186/1478-4491-7-10
11. Koikov VV, Turumbetova TB, Zhashkenova NS. et al. Methods of planning and forecasting human resources health care in terms of compulsory social health insurance. *Astana: Republican Center for Healthcare Development;* 2016 http://www.rcrz.kz/docs/nauka/mr4.pdf
12. Godley W, Cripps F. Macroeconomics. London: *Fontana*. 1983; 200.
13. Godley W, Lavoie M. Monetary Economics: an integrated approach to credit, money, income, production and wealth. London: *Palgrave-Mac Millan.* 2007; 530.
14. Kinsella S, Greiff M, Nell EJ. Income distribution in a stock-flow consistent model with education and technological change. *Eastern Economic Journal.* 2011; 37(1):134-149. https://doi.org/10.1057/eej.2010.31
15. Copeland MA. Social accounting for money flows. *The Accounting Review* 1949; 24(3):254-264.
16. Ministerstvo zdravoohranenija Respubliki Kazahstan. Nacionalnaja politika upravlenija kadrovymi resursami zdravoohranenija, Astana, 2017, 21 p. http://www.rcrz.kz/files/nauka/Национальная%20политика%20управления%20КРЗ.pdf
17. The demographic forecast of the Republic of Kazakhstan: main trends, challenges, practical recommendations. Order of the Minister of Health of the Republic of Kazakhstan; 2010. https://www.akorda.kz/upload/nac_komissiya_po_delam_zhenshin/Демографическая%20политика/4.2%20рус.pdf

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Impact of target coronary artery stenosis severity measured by instantaneous wave-free ratio on to bypassed graft patency

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Abstract

Background: This study aimed to assess the impact of the measurement of the degree of target coronary artery stenosis using the instantaneous wave-free ratio (iFR) on patency of attached grafts.

Materials and methods: A total of 86 grafts were assessed by computed tomography angiography after coronary artery bypass grafting in 24 patients with multivessel coronary artery disease. The iFR was evaluated for all target coronary arteries. The coronary artery stenoses were divided into three groups based on the iFR value: iFR < 0.86 (group 1); iFR 0.86–0.90 (group 2); and iFR > 0.90 (group 3).

Results: Computed tomography angiography was performed at 192±44 days (range: 80–318 days). The correlation coefficient (r) between iFR and failed grafts was 0.332 (p=0.035). Graft failure was detected in three grafts (8.1%) for group 1, in two grafts (8.3 %) for group 2, and in four grafts (16%, all arterial grafts) for group 3. Statistically significant differences were found between groups 1 and 3 (p=0.041) and between groups 2 and 3 (p=0.044). No significant differences were found between groups 1 and 2 (p=0.228).

Conclusion: The degree of coronary artery stenosis measured by iFR is a risk factor for attached graft failure. In a coronary artery where the iFR was haemodynamically non-significant, a higher rate of graft failure was detected.

Key words: coronary artery bypass grafting, instantaneous wave-free ratio, graft failure, computed tomography angiography

Introduction

Invasive coronary angiography (ICA) used to be the gold standard for decision making in guiding myocardial revascularisation, and was used as a benchmark to compare new methods to. However, limited correlations between angiographic findings and functional stenosis severity [1] enabled the development of functional assessment of coronary stenoses using intracoronary guidewires.

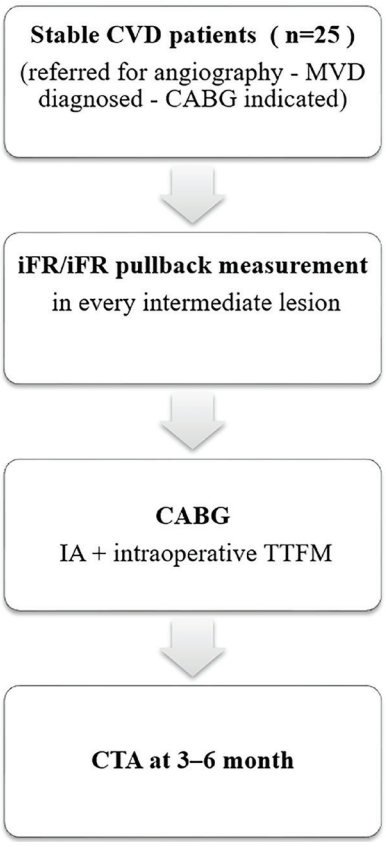
In the last decade, there has been renewed interest in the field of coronary physiology, driven by the introduction of a new, non-hyperaemic, pressure-based index of stenosis severity: the instantaneous wave-free ratio (iFR) [2]. In 2018, European cardiologists recommended iFR for the assessment of intermediate-grade stenosis [3]. There are currently no powerful data to assess the clinical benefits of iFR in guiding coronary artery bypass grafting and no data showing that iFR can be a direct strong predictor of graft patency. Given the close association between iFR and flow in the coronary artery, and considering effect of the competitive flow on the graft patency, iFR may be suitable for guiding bypass grafting [4]. The aim of our study is to evaluate the impact of the iFR-determined coronary lesion severity as a factor for predicting graft failure.

Material and methods

Study population

Our prospective study included 25 patients with stable multivessel coronary artery disease who underwent coronary artery bypass grafting (CABG) surgery (Figure 1). This study is a follow-up to an article we previously published, where we investigated the correlation between

Figure 1 - Flow chart of study design. CVD—coronary vessel disease; MVD—multivessel disease; iFR—instantaneous wave-free ratio; CABG—coronary artery bypass grafting; IA—intraoperative angiography; TTFM—transit time flow measurement; CTA—computed tomography angiography.



preoperative coronary artery stenosis severity measured by iFR and intraoperative transit time flow measurement (TTFM) of attached grafts [5].

iFR was measured in all angiographically intermediate (40–75% by diameter) stenoses of coronary arteries. The attached grafts were divided into three groups according to the preoperative iFR degree: group 1 (iFR < 0.86), group 2 (iFR 0.86–0.90), and group 3 (iFR > 0.90). Consensus about target arteries based on angiography findings was reached before iFR measurements were taken, and grafts in this study were attached despite negative iFR results. The standard medical treatment according to the European Society of Cardiology (ESC) guidelines on chronic coronary syndrome was provided for all patients [6]. The enrollment of the patients was consecutive. Computed tomography angiographies (CTA) were performed in 24 patients.

Permission for the study was confirmed by the Kaunas Regional Biomedical Research Ethics Committee on 9 September 2019 (Nr. BE-2-70).

iFR measurement

iFR was performed using a standard technique, at the catheterisation laboratory. Physiological measurements were taken using a coronary pressure guidewire (Verrata, Philips Volcano, San Diego, CA, USA). To avoid vasomotor reactions, intracoronary nitrates were administered before every measurement. The iFR cut-off point was 0.90, where stenosis with iFR > 0.9 was considered haemodynamically non-significant [2,7], while stenosis with an iFR of 0.86–0.90 was considered to be the "gray zone" and iFR < 0.86 was considered severe coronary stenosis [8]. All iFR measurements were done by the same operator, and iFR was measured distally and with pullback to localise the most severe lesion in each targeted vessel.

Revascularisation

All CABG procedures were performed in a hybrid operating room, via median sternotomy on cardiopulmonary bypass (CPB), with heparinisation and ensuring activated clotting time (ACT) > 480 s. In all cases, we used antegrade cardioplegia (cold St. Thomas solution). Harvesting of internal mammary artery (IMA) grafts was performed with diathermy cautery coagulation on pedicle clips. For the second and third graft, a saphenous vein graft (SVG) was used. Harvesting for SVG was performed using the complete continuous open technique and interrupted bridging skin incision with skeletonisation. IMA distal anastomosis was performed using 8-0 Prolene (Ethicon, monofilament) sutures using the "parachute" technique. For SVG distal anastomoses, 7-0 Prolene (Ethicon, monofilament) sutures were used, using the "parachute" technique, and for proximal anastomoses on the ascending aorta, 6-0 Prolene (Ethicon, monofilament) was used. All attached grafts were assessed by intraoperative completion angiography and TTFM.

Computed tomography angiography

The CTA was performed within 3–6 months of CABG on a 320 slice multidetector computed tomography (MDCT). All patients were given sublingual 0.3–0.4 mg nitroglycerin and/or beta-blockers (oral metoprolol 30–70 mg) 2 minutes prior to CTA, with Electrocardiography (ECG) heart rate control. The contrast agent was administered intravenously using an injector. Scans were undertaken with collimation of 0.6–0.625, a gantry rotation time of 275–350 ms, and a voltage of 120 kV. All patient data were rendered on a workstation using multiplanar reconstructions and three-dimensional volume rendering. Any stenosis of more than 70% within the grafts was considered as a loss of graft patency.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 23 (Armonk, NY, USA: IBM Corp. Software). We calculated statistical characteristics such as the total observation number, mean, median, and standard deviation using descriptive statistics. Continuous variables are presented as the mean and standard deviation (SD), or median and interquartile range (IQR), while categorical data are expressed as numbers (percentages). After testing for normality, group differences were tested using Student's t-test and Kruskal–Wallis analysis of variance (ANOVA) to compare samples. The correlation between graft patency and iFR was evaluated by one-way ANOVA analysis. The qualitative analysis of the groups was performed using the chi-square test. Variables with a two-sided p value < 0.05 were considered statistically significant.

Results

Study population

The participant characteristics (Table 1) and graft characteristics (Table 2) of this study were discussed in our previous article [5]. The left internal mammary artery (LIMA) was used in situ for bypassing the left coronary territory. The right internal mammary artery (RIMA) and bilateral internal mammary artery (BIMA) were not used in this study. SVG were mainly used for the right coronary artery or circumflex artery.

Table 1 Patient characteristics

Variable	Value
Age	63.8 ± 8.9 (48–78)
Body mass index (kg/m2)	27.2 ± 4.79
Sex	
Male	23 (92%)
Hypertension	23 (92%)
Diabetes mellitus	2 (8%)
Dyslipidemia	22 (88%)
Arrhythmia	4 (16%)
Previous PCI	9 (36%)
Previous MI	15 (60%)
History of smoking	15 (60%)
LV EF %	47.12 ± 6.4
NYHA	
II	19 (76%)
III	6 (24%)
Euro score II	1.38 ± 0.75
Syntax score	31.38 ± 4.33
Distal anastomoses per pt.	3.56 ± 0.82 (2–5)

Abbreviations: PCI—percutaneous coronary intervention; MI—myocardial infarction; LV EF—left ventricular ejection fraction; NYHA —New York Heart Association; and pt—patient.

Table 2 Graft characteristics

Variable	Group 1 (iFR < 0.86)	Group 2 (iFR 0.86–0.90)	Group 3 (iFR > 0.90)
Distal anastomosis	40	24	25
Grafts	36	22	23
SVG to RCA	7 (17.5%)	4 (16.6%)	3 (12%)
SVG to PDA	8 (20%)	5 (20.8%)	2 (8%)
SVG to OM	11 (27.5%)	6 (25%)	9 (36%)
SVG to diagonal	3 (7.5%)	2 (8%)	4 (16%)
LIMA to LAD	11 (27.5%)	7 (29%)	7 (28%)
Sequential grafts	4	2	2

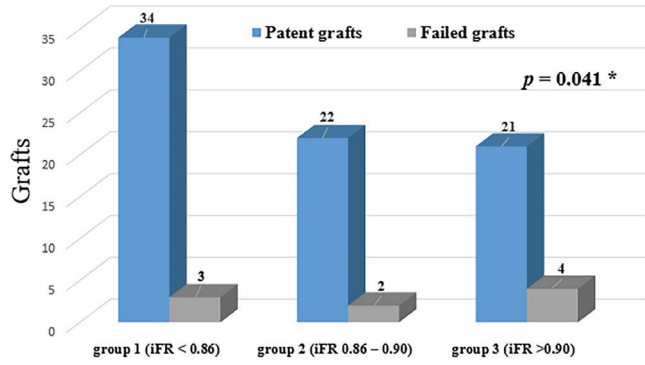
Abbreviations: SVG—saphenous vein grafts; RCA—right coronary artery; PDA—posterior descending artery; OM—obtuse marginal artery; LIMA—left internal mammary artery; LAD—left anterior descending artery; results reported as total number and percentage of all grafts.

CTA results

Perioperative mortality was documented for one patient. CTA was performed at 192±44 days (range 80–318 days) after CABG for 86 attached grafts in 24 patients. There were 37 grafts (27 SVG and 10 LIMA) in group 1 (iFR < 0.86), 24 grafts (17 SVG and 7 LIMA) in group 2 (iFR 0.86–0.90), and 25 grafts (18 SVG and 7 LIMA) in group 3 (iFR > 0.90).

The correlation coefficient (r) between iFR and graft failure was 0.332 (p=0.035). Graft failure was detected in 3 grafts (8.1%, 2 SVG and 1 LIMA) for group 1, in 2 grafts (8.3 %, 1 SVG and 1 LIMA) for group 2, and in 4 grafts (16%, all LIMA) for group 3 (Figure 2). Statistically significant differences were found between groups 1 and 3 (p=0.041) and between groups 2 and 3 (p=0.044). No significant differences were found between groups 1 and 2 (p=0.228).

Figure 2 - This graph shows the proportion of failed grafts in each group. * Significant difference between group 1 and group 3.



Discussion

This was a small prospective pilot study of 25 patients (aged 63.8±8.9 (48–78)) who underwent preoperative iFR measurement of the target arteries and postoperative follow-up by CTA (in 24 patients) of the attached grafts. Globally, coronary artery disease (CAD) has become the most common cause of death in countries from all income groups [9]. Even though CABG remains the mainstay in the treatment of symptomatic CAD patients [3,10], graft failure after CABG is a determining factor for morbidity and mortality [11,12]. CTA has recently become the standard clinical tool in graft assessment after CABG procedures. A meta-analysis of more than 2000 combined grafts showed 97.6% sensitivity and 96.7% specificity of the results of graft obstruction in CTAs with both 16 and 64 sections [13]. In another prospective study, graft patency was assessed using a 64-slice CTA followed by an invasive coronary angiography. This showed a sensitivity of 97%, specificity of 97%, and positive and negative prognostic values of 93% and 99% [14].

Despite the fact that ICA has long been the gold standard in assessing graft patency after CABG, it carries a 0.08% risk of myocardial infarction and a 0.7% risk of minor complications in clinically stable patients [15]. A significantly higher radiation exposure was observed for CTA (18–45 mSv) than ICA (7–9 mSv), but the volume of contrast agent was lower for 64-slice CTA (130–148 mL) than for ICA (110–223 mL) [14,16]. CTA with 128 slices showed low radiation exposure (2.3 ± 0.3 mSv), comparable to ICA [17]. There are limitations to CTA, with difficulties in accurate visualisation of distal anastomoses and clip associated artifacts [18]. The development of technology and integration of CTA with the fractional reserve flow (FFR) improved the visual assessment of graft patency and perfusion with a functional indicator [19,20]. At the moment, there is little FFR CT data to assess graft patency in patients after CABG. However, this is undoubtedly a promising direction, and perhaps with the development of scanning technology, it will replace ICA in the near future.

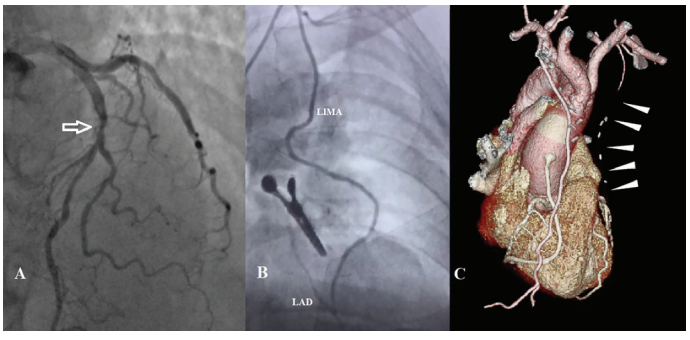
Our results show that non-significant coronary artery stenosis (iFR > 0.90) is associated with an increased risk of graft failure. In addition, all of the lost grafts were arterial grafts (LIMA) in group 1 (iFR > 0.90), which is possibly related to the sensitivity of arterial grafts to competitive flow from the native coronary artery [21,22]. However, the LIMA graft demonstrated superior patency compared with other grafts and the strategy of grafting to the left anterior descending artery is considered the "benchmark" for coronary revascularisation [23,24]. The internal mammary artery endothelium possesses a number of properties

that make it resistant to the development of atherosclerosis [25]. Current data recommend skeletonised internal mammary artery harvesting for revascularisation, with low thermal damage providing an improved endothelial layer and better integrity of the vessel wall [26]. IMA graft failure most commonly results from damage during mobilisation or harvesting, spasm, inflammation or suboptimal target vessel anastomosis [22]. In our study, we excluded technical errors due to errors of the surgeon by means of intraoperative angiography and TTFM. Interestingly, the degree of target vessel stenosis does not impact on SVG patency rate, as perfusion was directly from the aorta with higher pressures compared to arterial grafts [27]. Nevertheless, the process of SVG atherogenesis begins with early circumferential intimal thickening within the first year, followed by multilayered foam-cell accumulation. Between two and five years after bypassing, a necrotic core develops in the SVG intima and after 5–10 years the plaque will usually rupture; this corresponds to the period of SVG patency [22]. Acute thrombosis is usually the cause of an early SVG failure that occurs within days or months [28]. After harvesting of the vein with skeletonisation, there is disruption and damage to the adventitia and nutritional disturbance of the vessel occurs, which in turn leads to the development of acute thrombosis with intimal hyperplasia [29–31]. After bypass, the vein is exposed to wall stress, increasing the vein diameter and reducing blood velocity [32,33]. The data show that over-distension of the vein to check for leakage also contributes to the removal and/or dysfunction of the endothelium and medial damage [34]. Venous valves with turbulent flow can also cause intimal hyperplasia and thrombosis [35].

In a previous study, Wada et al. assessed the impact of iFR on graft failure after CABG, showing that target vessels with iFR 0.90–0.94 or 0.95–1.0 had a 28% and 50% (p = 0.002) failure rate of attached arterial grafts at one year post-treatment [36]. In group 3 (iFR > 0.90) of our study, the loss rate of arterial grafts was 40% (Figure 3).

Figure 3 - 65-year old female with three-vessel disease. Coronary angiography before coronary artery bypass grafting. Proximal LAD had 75% stenoses angiographically and the iFR was 0.92 (A, white arrow). Selective intraoperative angiography demonstrated attached LIMA graft patency (B). CTA showed that the LIMA to LAD graft had failed (C, white arrowheads).

iFR—instantaneous wave-free ratio; LAD—left anterior descending coronary artery; LIMA—left internal mammary artery; CTA—computed tomography angiography.



The iFR is a promising method for evaluation of coronary physiology. Based on comparisons to FFR, the cut-off point for iFR is 0.90 [2,7]. Define-Flair and iFR Swedeheart are prospective, randomised trials, which have compared FFR and iFR for the guided revascularisation strategy, and iFR showed similar results [37,38]. The Define-Flair trail demonstrated deferral from revascularisation in the iFR group, affecting 54% (677) of patients and 50% (625) of patients in the FFR group [38]. The significant advantages of iFR compared to the existing methods for the evaluation of coronary physiology have been shown [4]. These advantages include: being adenosine-free, the time of the study is quicker than for FFR, the low level of discomfort for patients, ability to assess serial lesions, and superior signal-to-noise ratio compared to Pd/Pa. However, Rey et al. noted the importance of collateral blood flow to the target vessel and correct assessment of coronary physiology (iFR) to guide decision-making for CABG, which can reduce the risk of early graft failure [39].

Coronary revascularisation is crucial in the treatment of patients with coronary artery disease [3] and well-coordinated heart teamwork is required to avoid subjecting patients to inappropriate revascularisation of functionally insignificant stenoses.

Limitations

Our study has several limitations. The cohort consisted of a small number of participants in a single-center study. This study combines the cardiologists' and surgeons' efforts, and recruiting a large sample of patients within a set period of time was a limitation of our study. For the calculations, we used data from both arterial and venous grafts and no separation of the revascularisation area. Graft patency on CTA was assessed over an average of 192±44 days (range, 80–318 days), with no data collected on long-term outcomes.

Conclusion

The degree of coronary artery stenosis measured by iFR is a predictor of attached graft failure. In coronary arteries where the iFR was haemodynamically non-significant, a higher rate of graft failure was detected.

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References

1. C. W. White et al. Does Visual Interpretation of the Coronary Arteriogram Predict the Physiologic Importance of a Coronary Stenosis? *N. Engl. J. Med.* 1984; 310(13):819–824.doi: 10.1056/NEJM198403293101304.
2. S. Sen et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary waveintensity analysis: Results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J. Am. Coll. Cardiol.* 2012; 59(15):1392–1402. doi: 10.1016/j.jacc.2011.11.003.
3. M. Sousa-Uva et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur. J. Cardio-thoracic Surg.* 2019; 55(1):4–90. doi: 10.1093/ejcts/ezy289.
4. M. Götberg, C. M. Cook, S. Sen, S. Nijjer, J. Escaned, and J. E. Davies. The Evolving Future of Instantaneous Wave-Free Ratio and Fractional Flow Reserve. *J. Am. Coll. Cardiol.* 2017; 70(11):1379–1402. doi: 10.1016/j.jacc.2017.07.770.
5. A. Tolegenuly, R. Ordiene, A. Mamedov, R. Unikas, and R. Benetis. Correlation between preoperative coronary artery stenosis severity measured by instantaneous wave-free ratio and intraoperative transit time flow measurement of attached grafts. *Med*. 2020; 56(12). doi: 10.3390/medicina56120714.
6. J. Knuuti. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Russ. J. Cardiol.* 2020; 25(2). doi: 10.15829/1560-4071-2020-2-3757.
7. A. Jeremias et al. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pawith fractional flow reserve: The RESOLVE study. J. Am. Coll. Cardiol. 2014; 63(13):1253–1261. doi: 10.1016/j.jacc.2013.09.060.
8. B. Modi et al. Revisiting the Optimal FFR and iFR Thresholds for Predicting the Physiological Significance of Coronary Artery Disease. Circ. Cardiovasc. Interv. 2018; 11(12):e007041. doi: 10.1161/CIRCINTERVENTIONS.118.007041.Revisiting.
9. World Health Organization, "DALY estimates, 2000-2016," no. June, 2018.
10. 10. F. J. Neumann et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur. Heart J.,* 2019; 40(2):87–165. doi: 10.1093/eurheartj/ehy394.
11. L. Rupprecht, C. Schmid, K. Debl, D. Lunz, B. Flörchinger, and A. Keyser. Impact of coronary angiography early after CABG for suspected postoperative myocardial ischemia. J. Cardiothorac. Surg. 2019; 14(1):1–7. doi: 10.1186/s13019-019-0876-0.
12. P. K. Hol et al. The importance of intraoperative angiographic findings for predicting long-term patency in coronary artery bypass operations. Ann. Thorac. Surg. 2002; 73(3):813–818. doi: 10.1016/S0003-4975(01)03459-2.
13. M. Hamon et al. Diagnostic performance of 16- and 64-section spiral CT for coronary artery bypass graft assessment: Meta-analysis. Radiology. 2008;. 247(3):679–686. doi: 10.1148/radiol.2473071132.
14. T. S. Meyer et al. Improved Noninvasive Assessment of Coronary Artery Bypass Grafts With 64-Slice Computed Tomographic Angiography in an Unselected Patient Population. *J. Am. Coll. Cardiol.* 2007; 49(9):946–950. doi: 10.1016/j.jacc.2006.10.066.
15. F. L. Gobel et al. Safety of coronary arteriography in clinically stable patients following coronary bypass surgery. Post CABG Clinical Trial Investigators. Cathet. Cardiovasc. Diagn. 1998; 45(4):376–81.
16. R. Jabara et al. Comparison of Multidetector 64-Slice Computed Tomographic Angiography to Coronary Angiography to Assess the Patency of Coronary Artery Bypass Grafts. Am. J. Cardiol. 2007; 99(11):1529–1534. doi: 10.1016/j.amjcard.2007.01.026.
17. R. Goetti et al. Low dose high-pitch spiral acquisition 128-slice dual-source computed tomography for the evaluation of coronary artery bypass graft patency. *Invest. Radiol.* 2010; 45(6):324–330. doi: 10.1097/RLI.0b013e3181dfa47e.
18. J. Gabriel, S. Klimach, P. Lang, and D. Hildick-Smith. Should computed tomography angiography supersede invasive coronary angiography for the evaluation of graft patency following coronary artery bypass graft surgery? Interact. Cardiovasc. Thorac. Surg. 2015; 21(2):231–239. doi: 10.1093/icvts/ivv078.
19. K. M. Chinnaiyan et al. Rationale, design and goals of the HeartFlow assessing diagnostic value of non-invasive FFRCT in Coronary Care (ADVANCE) registry. *J. Cardiovasc. Comput. Tomogr.* 2017; 11(1):62–67. doi: 10.1016/j.jcct.2016.12.002.
20. R. Nakazato et al. Noninvasive fractional flow reserve derived from computed tomography angiography for coronary lesions of intermediate stenosis severity results from the DeFACTO study. Circ. Cardiovasc. *Imaging*. 2013; 6(6):881–889. doi: 10.1161/CIRCIMAGING.113.000297.
21. M. Gaudino et al. Radial-artery or saphenous-vein grafts in coronary-artery bypass surgery. *N. Engl. J. Med.* 2018; 378(22):2069–2077. doi: 10.1056/NEJMoa1716026.
22. D. Collins and S. Goldberg. Care of the Post-CABG Patient. Cardiol. Rev. 2020; 28(1):26–35. doi: 10.1097/CRD.0000000000000261.
23. J. Tatoulis, B. F. Buxton, and J. A. Fuller. Patencies of 2,127 arterial to coronary conduits over 15 years. *Ann. Thorac. Surg*. 2004; 77(1):93–101. doi: 10.1016/S0003-4975(03)01331-6.
24. S. Goldman et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: Results from a Department of Veterans Affairs Cooperative Study. *J. Am. Coll. Cardiol.* 2004; 44(11):2149–2156. doi: 10.1016/j.jacc.2004.08.064.
25. F. Otsuka, K. Yahagi, K. Sakakura, and R. Virmani. Why is the mammary artery so special and what protects it from atherosclerosis? Ann. Cardiothorac. *Surg.* 2013; 2(4):519–51926. doi: 10.3978/j.issn.2225-319X.2013.07.06.
26. A. Zientara et al. Skeletonized internal thoracic artery harvesting: A low thermal damage electrosurgical device provides improved endothelial layer and tendency to better integrity of the vessel wall compared to conventional electrosurgery. *J. Cardiothorac. Surg.* 2018; 13(1):1–8. doi: 10.1186/s13019-018-0797-3.
27. G. Tinica, R. Chistol, D. Bulgaru Iliescu, and C. Furnica. Long-term graft patency after coronary artery bypass grafting: *Effects of surgical technique. Exp. Ther. Med*. 2018; 359–367. doi: 10.3892/etm.2018.6929.
28. G. M. Lawrie, J. T. Lie, G. C. Morris, and H. L. Beazley. Vein graft patency and intimal proliferation after aortocoronary bypass: Early and long-term angiopathologic correlations. *Am. J. Cardiol.* 1976; 38(7):856–862. doi: 10.1016/0002-9149(76)90798-0.
29. E. Chignier and R. Eloy. Adventitial resection of small artery provokes endothelial oss and intimal hyperplasia. *Surg. Gynecol. Obstet*. 1986; 163(4):327–334.

30. W. R. Brody, J. C. Kosek, and W. W. Angell. Changes in vein grafts following aorto-coronary bypass induced by pressure and ischemia. *J. Thorac. Cardiovasc. Surg*. 1972; 64(6):847–854. doi: 10.1016/s0022-5223(19)39813-7.
31. J. K. Mcgeachie, S. Meagher, and F. J. Prendergast. Vein-to-artery grafts: the long-term development of neo-intimal hyperplasia and its relationship to vasa vasorum and sympathetic innervation. *Aust. N. Z. J. Sur*g. 1989; 59(1):59–65. doi: 10.1111/j.1445-2197.1989.tb01466.x.
32. M. S. Lemson, J. H. M. Tordoir, M. J. A. P. Daemen, and P. J. E. H. M. Kitslaar. Intimal hyperplasia in vascular grafts. *Eur. J. Vasc. Endovasc. Surg.* 2000; 19
33. (4):336–350. doi: 10.1053/ejvs.1999.1040.
34. E. Allaire and A. W. Clowes. Endothelial cell injury in cardiovascular surgery: The intimal hyperplastic response. *Annals of Thoracic Surgery.* 1997; 63(2):582–591. doi: 10.1016/S0003-4975(96)01045-4.
35. N. Roubos, F. L. Rosenfeldt, S. M. Richards, R. A. J. Conyers, and B. B. Davis. Improved preservation of saphenous vein grafts by the use of glyceryl trinitrate-verapamil solution during harvesting. *Circulation*. 1995; 92(9). doi: 10.1161/01.cir.92.9.31.
36. T. Z. Lajos, F. Robicsek, M. Thubrikar, and H. Urschel. Improving patency of coronary conduits 'valveless' veins and/or arterial grafts. J. Card. Surg. 2007; 22(2):170–177. doi: 10.1111/j.1540-8191.2007.00380.x.
37. T. Wada. Impact of instantaneous wave-free ratio on graft failure after coronary artery bypass graft surgery. *Int. J. Cardiol.* 2021; 324(2013):23–29. doi: 10.1016/j.ijcard.2020.09.046.
38. M. Götberg et al. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N. Engl. J. Med.* 2017; 376(19):1813–1823. doi: 10.1056/NEJMoa1616540.
39. J. E. Davies et al.Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N. Engl. J. Med.* 2017; 376(19):1824–1834. doi: 10.1056/NEJMoa1700445.
40. F. Rey, S. Degrauwe, S. Noble, and J. F. Iglesias. The dynamic effect of coronary artery bypass grafting on the instantaneous wave-free ratio in the collateral donor artery of a patient with chronic total occlusion. *Eur. J. Cardio-Thoracic Surg*. 2020; 00:1–3. doi: 10.1093/ejcts/ezaa463.

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Utilization trend of magnetic resonance imaging examinations in an academic emergency department and the weekend effect

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Abstract

Aim: The utilization of magnetic resonance imaging in the emergency department is gradually increasing. An update is needed on how the use of magnetic resonance imaging exams in the emergency department has evolved. To reveal the magnetic resonance imaging utilization trends of the emergency department in the last five years (2015-2019) and whether the weekend effect affects the magnetic resonance imaging test requests of the emergency physician.

Material and methods: Emergency department-ordered magnetic resonance imaging examinations were obtained from the hospital's electronic database retrospectively. Magnetic resonance imaging were grouped as abdominopelvic, neuroimaging, musculoskeletal, and others.

Results: A total of 9870 magnetic resonance imaging examinations were performed in the 5 years. The rate of emergency department-ordered magnetic resonance imaging tests was 2.65%. Magnetic resonance imaging for neuroimaging, including brain and spinal examinations, was the most ordered examination, with a rate of 98.8%. The average time between imaging order and acquisition was 46 minutes. No significant difference between the magnetic resonance imaging examinations and the weekend effect (p=.121). 25.85% of those who had magnetic resonance imaging examinations were hospitalized.

Conclusion: Magnetic resonance imaging examination for neuroimaging purposes has become an emergency department routine. Other magnetic resonance imaging are ordered at a nominal rate. The acquisition of an image took an average of 46 minutes. The weekend effect does not affect the decision of the emergency physician to request a magnetic resonance imaging examination.

Key words: emergency department, examination, magnetic resonance imaging, utilization, weekend

Introduction

Radiological imaging methods are one of the vital parts of diagnostic evaluation, along with physical examination, anamnesis, and laboratory studies. With technological developments in the past thirty years, computed tomography (CT) and magnetic resonance imaging (MRI) have become widespread worldwide and have gained crucial importance in the evaluation of patients [1-5]. Currently, there is a rapid trend towards advanced imaging methods in patients' diagnostic processes, especially in areas such as the emergency department (ED), where patient density is high and patient evaluation time is very limited [1, 6].

MRI, a powerful medical diagnostic tool, is frequently used as a part of neuroimaging in the ED and has also become a preferred modality in musculoskeletal system pathologies, cardiac rheumatological diseases, and pregnant and pediatric patients [7]. While the use of MRI in ED is gradually increasing [2,7,8], studies on this area's problems are limited. There is a need for an update on how the utilization of MRI examinations in EDs has evolved.

With the first demonstration that weekend hospitalizations increase mortality in Canadian hospitals, the weekend effect has become a research subject [9]. The "weekend effect" refers to more negative outcomes for those who are hospitalized over the weekend than for those who are hospitalized on weekdays. It has been demonstrated that weekend effects have adverse effects, especially in emergency patient groups such as acute stroke, myocardial infarcts, pulmonary embolism, and the need for emergency surgery [10-13]. Patients in need of emergency care constitute the significant burden of ED admissions on the weekend [14]. Additionally, reasons such as the low number of supporting health personnel and clinicians working actively on the weekend, limited access to resources, and difficulty accessing interventional radiologists or specialists for diagnostic endoscopy can cause the weekend effect to have bad results [14-16]. There has been no study evaluating the influence of the weekend effect on MRI orders to determine whether these reasons affect the emergency physician's utilization of imaging methods to reach the correct diagnosis. This study aimed to determine both the MRI utilization trend in the ED and whether the weekend effect affects MRI orders.

Materials and methods

Study setting and design

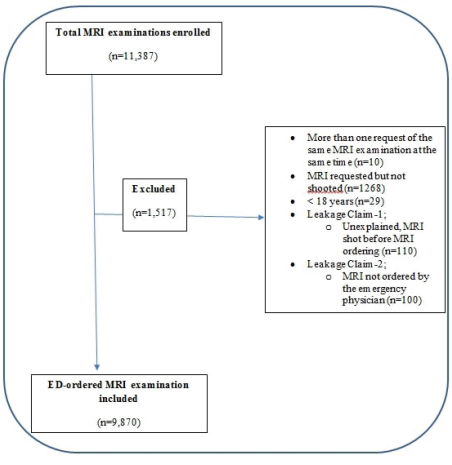
Within the scope of this study, MRI examinations ordered by the emergency physician for patients admitted to the academic emergency department of a tertiary care hospital in Turkey between 01.01.2015 and 31.12.2019 were retrospectively examined for five years. The research was initiated after obtaining approval from the XXXXX University Non-Invasive Health Research Ethics Committee (approval ID 2020/33; dated March 2, 2020).

The study's center is the adult ED of a tertiary care university hospital with 310 beds and a 24-hour MRI service. It is also an ED where traumatic pediatric patients can be admitted. On average, 75,000 emergency patient admissions occur annually. In the center where the study was conducted, the ED requests always have high priority for MRI.

Selection of participants and measurements

Patients aged 18 years and over who were admitted to the ED in 5 years (2015-2019), requested MRI, and underwent imaging were included. Those whose data could not be accessed through the electronic database and archive records of the hospital or who had incomplete data were excluded. Exclusion criteria were given in the form of a flow chart (Figure 1).

Figure 1.



ED= emergency department; MRI= magnetic resonance imaging

In this context, a total of 9870 MRI examinations ordered by the emergency physician in the ED were included in the study. In addition to the total number of MRI examinations, the total number of ED admissions was also recorded.

Ordered MRI examinations were classified into four groups as follows:

(1) Abdomen + MRI cholangiography + perianal MRI: Abdominopelvic MRI;

(2) Brain + Neck + Diffusion + Perfusion + MRI, Angiography + MRI, Venography + Vertebra MRI: Neuroimaging;

(3) Joint + extremity + arthrography MRI: Musculoskeletal MRI;

(4) Ear, orbital, pituitary gland, temporomandibular joint and breast MRI: Other MRI

The patients included in the study were analyzed in terms of the following: age, gender, application year, application day, working and out of hours (08:00-16:00, 16:00-24:00, 24:00-08:00), type of MRI examination, MRI order-shooting time difference (in hours), weekend effect, and hospitalization.

Statistical analysis

The research data were uploaded and evaluated using IBM SPSS Statistics 19.0 software (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.). Descriptive statistics of categorical variables are presented as numbers and percentages. Descriptive statistics of numerical variables are presented as the mean (±) standard deviation for normally distributed variables and the median (25th-75th percentile) for nonnormally distributed variables. In the comparison of categorical variables, using cross tables, the "Pearson chi-square test" was applied. RStudio for Windows version 1.0.143 (R Studio, Inc., Boston, MA 02210, USA) was used to visualize data. The statistical significance level was accepted as $p < .05$.

Results

In the five years (2015-2019), a total of 372,900 patients were 18 years old and older and applied to the ED. During this period, a total of 9870 MRI examinations were performed on 9438 patients (an average of 1.04 MRI requests per patient). In this process, the rate of requesting MRI per application for ED is 2.65% (total number of MRI/total number of applications x 100), while the rate of patients who have undergone MRI is 2.53% (9438/total number of patient applications x 100). In the same period, 29 of the pediatric patients requested MRI in our ED. The low number may be due to the admission of only pediatric patients with traumatic injuries to the adult ED.

The number of MRI examinations per year increased from 1872 MRIs in 2015 to 2219 MRIs in 2019 (i.e., an increase of 19%). The year with the highest number of MRI shots was also determined to be 2018, the year with the highest number of patient applications (Table 1).

Table 1 The total MRI examinations ordered from the emergency department and the total number of admissions to the emergency department by the years

Years	2015	2016	2017	2018	2019
Total number of enrolled patients	63364	70076	73876	88049	77535
Total number of MRI exams	1872	1638	1686	2455	2219
MRI examination/ admission rate (%)	2.95	2.33	2.28	2,78	2,86

MRI=Magnetic resonance imaging

Table 2 Distribution of emergency department-ordered MRI tests by examination types

	MRI examination subtypes	Frequency	Percent
Abdominopelvic	MRI, abdomen, lower	11	0,11
	MRI, abdomen, upper	5	0,05
	MRI, perianal	1	0,01
	MR, cholangiography	10	0,10
Neuroimaging	MRI, angiography	30	0,30
	MRI, venography	19	0,19
	MRI, brain	176	1,78
	MRI, diffusion-weighted	9264	93,86
	MRI, perfusion	12	0,12
	MRI, vertebra, lumbar	143	1,45
	MRI, vertebra, cervical	78	0,79
	MRI, vertebra, thoracic	33	0,33
Musculoskeletal	MRI, arthrography	1	0,01
	MRI, joint, single	53	0,54
	MRI, limb, unilateral	24	0,24
Other	MRI, pituitary gland	3	0,03
	MRI, ear	2	0,02
	MRI, breast	2	0,02
	MRI, Orbita	2	0,02
	MRI, Temporomandibular joint (unilateral)	1	0,01
	Total	9870	100,0

MRI=Magnetic resonance imaging

According to the body region, the distribution of 9870 MRI requests, which the emergency physician ordered during the five years, is presented in Table 2. The most ordered MRI type is neuroimaging (98.8%). Diffusion-weighted (DWI) MRI has been the most specific imaging request from the ED, with a rate of approximately 94%.

The distribution of MRI examinations ordered by the emergency department by year is shown in Figure 2.

Figure 2.

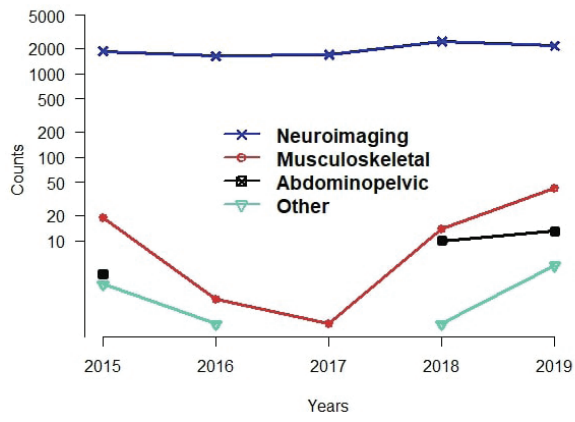


Table 3 Evaluation of ED-ordered MRI examinations in terms of age, gender, working and out of hours, the weekend effect, order and shooting time difference, and hospitalization

Variables		Abdominopelvic	Neuroimaging	Musculoskeletal	Other	Total
Age, years		54±18.9 (21-90)	63.14±18.6 (18-105)	38.01±14.03 (18-83)	40.9±21.9 (18-87)	62.9±18.8 (18-105)
Gender	Female	16 (0.3)	5056 (99)	28 (0.5)	6 (0.1)	5106 (51.7)
	Male	11 (0.2)	4699 (98.6)	50 (1)	4 (0.1)	4764 (48.3)
Working and out of hours	08:00-16:00	18 (0.4)	4200 (98.7)	34 (0.8)	5 (0.1)	4257 (43.1)
	16:00-24:00	7 (0.2)	4115 (98.8)	37 (0.9)	5 (0.1)	4164 (42.2)
	24:00-08:00	2 (0.1)	1440 (99.4)	7 (0.5)	0	1449 (14.7)
The Weekend effect	Weekdays	19 (0.3)	6909 (98.9)	50 (0.7)	10 (0.1)	6988 (70.8)
	Weekend	8 (0.1)	2846 (98.8)	28 (1)	0	2882 (29.2)
Order and shooting time difference, hours		1.89±3.7 (0.10-19.10)	0.76±1.8 (0.10-34.5)	1.85±5.3 (0.10-34.10)	6.58±13.3 (0.10-36.6)	0.78±1 (0.10-36.60)
Hospitalization	Internal wards	1 (0)	2207 (99.8)	3 (0.1)	1 (0)	2212 (86.7)
	Surgical wards	8 (3)	255 (94.1)	5 (1.8)	3 (1.1)	271 (10.6)
	Intensive care unit	0 (0)	69 (100)	0 (0)	0 (0)	69 (2.7)

ED= emergency department; MRI= magnetic resonance imaging; The results are expressed as mean±standard deviation (SD) (min-max), or number and percent (%).

It was observed that more than 97% of the MRI examinations in all years were neuroimaging. In total, neuroimaging was 98.8%, while abdominopelvic MR, musculoskeletal MR, and other MR requests remained below 1%.

MRI examinations ordered from the ED were analyzed in terms of the following variables: age, gender, working and out of hours, weekend effect, MRI order-shot time difference, and hospitalization (Table 3). While the age at which MRI requests for neuroimaging purposes were made stood out as the highest average age, with an average age of 63.14±18.6 years, musculoskeletal MRI requests constituted the youngest group, with 38.01±14.03 years.

A significant difference was found in gender in MRI examinations ordered from the emergency service (p=0.033). It was observed that MRI examinations were ordered more often for females.

According to working and out of hours, over 85% of MRI requests were between 08:00-24:00 hours. Simultaneously, organ-specific (such as breast, pituitary gland, ear MRI) "other MRI" requests were not performed in the ED after 24:00 and on the weekend.

The time between MRI ordering and shooting was, on average, 0.78 (46 min) hours (min 0.1-36.6 hours max). This interval is from least to most; the times were 0.76 hours (46 min) in neuroimaging, 1.85 hours (111 min) in musculoskeletal MRI, 1.89 hours (113 min) in abdominopelvic MRI, and 6.58 hours (395 min) in "other" MRI requests.

When all MRI examinations ordered from the ED were

examined according to the days of the week, it was observed that the rates remained stable between 13-15%. While the day with the least MRI requests was Wednesday, with 13%, the day with the highest number of calls was Monday, with 15.2%. There was no significant difference between the MRI requests made from the ED and the weekend effect (p = .121).

Among the patients who had MRI imaging in the ED, 2552 (25.85%) were hospitalized. A total of 86.7% of these patients were admitted to internal services. A total of 2.7% of hospitalized patients were admitted to intensive care. Interestingly, it was observed that none of the patients who received an MRI request other than neuroimaging were admitted to the intensive care unit.

Discussion

The use of CT in the emergency department is almost indisputable. Nevertheless, information on the place of MRI utilization in the ED is limited [2,7,8]. A study conducted by Rankey et al. on the use of MRI in a tertiary academic center between 2001 and 2005 found the rate of requesting MRI from the ED to be 0.45% [7]. In the study by Quaday et al. investigating the MRI examinations requested from an academic ED between 2007 and 2011, they found that MRI was ordered at a rate of 2.36%, and there was also a decrease in CT requests [2]. We evaluated the MRI examinations ordered in the ED of a tertiary care academic university hospital between 2015 and 2019 and found the MRI order rate to be 2.65%. Considering the studies reported on the utilization of MRI from different parts of the world, it becomes evident that the usage of MRI in emergency services has increased over the years. MRI test requests may have increased due to the widespread use of MRI, as the test is more accessible, does not contain radiation, and provides diagnostic accuracy, as mentioned below. Simultaneously, the low number of physicians in the face of the high number of patients in Turkey and the competition against time in the ED may have increased the imaging requests.

Acute stroke is a medical emergency, and proper prompt treatment of patients and limitation of brain damage are essential to ensure the best possible outcomes [17]. DWI is a necessary imaging method for diagnosing stroke, with a sensitivity exceeding 90% to detect acute ischemia [18]. In addition to the diagnosis of stroke, MRI is more sensitive and specific than CT in the following four items to evaluate spinal trauma: spinal cord injury, extra-axial lesions, ligament injury, and spinal fractures [19]. However, longer exposure time is a disadvantage. In the study of Rankey et al., neuroradiological examinations took first place, with a rate of approximately 87% in MRI examinations requested from the ED [7]. Quaday et al. reported that approximately 94% of the MRI tests ordered from the ED consisted of neuroimaging MR requests [2]. In our study, the number of MRI examinations increased by 19% in the fifth year compared to 2015. At the same time, the number of ED admissions showed an increasing trend. We found that among all MRI requests ordered from the ED, MRI requests for neuroimaging purposes (head and spinal imaging) ranked first, with almost 99%. The brain-DWI request came to the fore in ED-ordered MRI tests at a rate of 94%. For emergency physicians, concern with the medical-legal consequences of skipping a diagnosis, such as an acute stroke diagnosed with high accuracy by MRI, can also be a driving force in MRI orientation [20]. However, due to our study's nature, the medical necessity of the tests requested was not questioned.

The MRI tests requested from the ED are mostly composed of neuroimaging. MRI has become an increasingly used and well-established imaging modality for diagnosing acute neurological disease processes, particularly those considered neurosurgical emergencies [21]. In addition to brain imaging, spinal imaging is also a part of neuroradiological evaluations. Traumatic cord injury is rare, but early detection of conditions that may cause neural compression, such as an epidural hematoma, compressed disc, or bony material in the spinal canal, is essential to maximize potential neurological recovery in decompressive surgery [22]. Therefore, health services should provide uninterrupted service regardless of the day and time of stroke [23]. For this reason, there should not be any time restrictions for ED-ordered MRI examinations.

It was reported that higher mortality was detected in patients hospitalized for various medical conditions on weekends, which was called the “weekend effect” [9,10,12-14,24,25]. While the influence of the weekend effect on diseases has been studied, to our knowledge, there has been no study investigating the impact of the weekend effect on MRI examinations ordered from the ED. One study reported little delay in neuroimaging (CT/MRI) requests on weekends compared to weekdays in patients with acute stroke [26].

In our study, no significant difference was found between the ED-ordered MRI tests and the weekend effect (p =.121). The weekend effect does not affect the MRI request of the emergency physician. In our study, it was observed that MRI was requested in the 13-15% band on all days of the week. The day with the most requests came to the fore as Monday. This may be because Saturdays and Sundays are counted as weekend breaks in Turkey and accumulate on Monday, the first day of work. Emergency physicians order MRI examinations to reach a diagnosis regardless of the notion of working hours.

In addition, it was revealed that "other MRI" test requests, such as breast and pituitary gland, ear MRI were not performed after 24:00 and on weekends in the ED. This may be because imaging tests with low urgency can be requested in polyclinics or because the branches that require expertise do not work out-of-hours.

Acute ischemic stroke occurs in women more than in men [27]. In our study, a significant difference was found between MRI examinations ordered from the ED and gender (p=.033). It was observed that more MRI requests were required in female patients in all examination types, except for musculoskeletal MRI requests. In addition to the higher number of female patients for whom MRI was requested, considering the neuroimaging request at the rate of 99% in our study, it is revealed that women mostly presented with neurological complaints.

Additionally, while the time between MRI requests and shootings was performed in a reasonable period of 46 minutes in neuroimaging, it reached almost 7 hours for "other" MRI requests. MRI, a useful imaging method for obtaining a diagnosis in some life-threatening situations, can unfortunately cause a crowd in the ED in terms of the examination duration. Kocher et al. stated that advanced imaging methods such as CT/MRI prolonged the stay in the ED by at least 50 minutes and reported that blood tests and imaging methods are the two most effective ED crowd causes [28]. Redd et al. also noted that the use of MRI in the ED increased significantly after the installation of a fully accessible MRI in the ED and noted that the duration of stay in the ED was prolonged in patients who underwent MRI in the ED. Nevertheless, they reported reduced hospitalization rates or lengths of stay in hospitals in patients presenting to the ED with a suspected stroke [29]. Perhaps because of not abusing MRI in the ED and preventing requests for "other" MRI examinations without urgency from the ED, awareness training can be

provided to clinicians. Informative training can be organized to not engage the clinician with the request for MRI from the ED despite the absence of active complaints.

In the utilization of emergency MRI, we can argue that MRI examinations for neuroimaging have firmly stabilized by almost 99% and have practically become an ED routine in neurological suspicions. Apart from this, it was observed that abdominopelvic MRI, musculoskeletal MRI, and "other" MRI examinations were ordered from the ED at a rate of less than 1%. Since MRI is relatively expensive and requires time, its use in unstable patients remains in the background. However, it may be preferred in special groups such as pregnant or pediatric patients because it does not contain radiation [30]. Although acute abdominal pain is one of the frequent complaints, it was seen that the request for abdominopelvic MRI from the ED remained at approximately 0.3%. Inflammatory bowel diseases such as acute pancreatitis, acute cholecystitis with cholelithiasis, acute appendicitis, Crohn's, and ulcerative colitis cause abdominal pain requiring hospitalization or surgery in some cases [31]. Familiarity with MRI may increase over time in the ED evaluation of other abdominal pathologies, such as the fact that MRI-cholangiopancreatography has largely replaced the diagnostic endoscopic cholangiopancreatography evaluation of acute abdomen [32]. Nevertheless, the increasing use of abdominopelvic MRI, especially in busy EDs, seems to be a remote possibility for now.

One of the common reasons for emergency services is undoubtedly complaints about the musculoskeletal system. Although not always used as a primary imaging modality in the emergency setting, MRI can be a valuable aid in diagnosing and treating musculoskeletal emergencies. The benefit of MRI in detecting small infection foci, necrosis, and pathological fluid accumulations is superior to other imaging techniques such as CT and ultrasonography. A few musculoskeletal emergencies that are thought to be useful in diagnosis and treatment management can be listed as rhabdomyolysis, diabetic myonecrosis, septic arthritis, cellulitis, necrotizing fasciitis, compartment syndrome, and ligament and tendon injuries [33]. However, the usefulness of these in the ED does not seem possible due to the time requirement and high cost. In our study, it was observed that musculoskeletal MRI requests from the ED were realized at a rate of 0.8%, and at the end of five years, a total of 10 "other" MRI tests were requested. Emergency physicians do not adopt "other" MRI examinations, such as breast, pituitary gland, and ear examinations, from the ED.

Finally, we witnessed that 1 out of every four patients for whom MRI was requested from the ED were hospitalized as a result. A total of 86.7% of these patients were admitted to internal services. A total of 2.7% of hospitalized patients went to the intensive care unit. Interestingly, it was observed that no patients were admitted to the intensive care unit except those who underwent MRI for neuroimaging purposes. It has been reported that there is a strong relationship between in-hospital mortality and acutely ill patients hospitalized after MRI performed in the ED. Additionally, it has been stated that the delay in the time of MRI acquisition is related to the duration of hospitalization [34]. Although we did not reach the mortality outcomes of the patients, we believe that the high rate of hospitalization of the patients who underwent MRI and its association with in-hospital mortality as stated in the previous study and the patients who had MRI examinations requested from the ED are a riskier group than those who did not have MRI examinations ordered. We believe that the clinician should keep these factors in mind.

Limitations

The study aimed to reveal which MRI examinations have been requested from an academic ED in the last five years and the utilization of MRI in the ED. It was also investigated whether the weekend effect affected the emergency physician's decision to request an MRI test. Thus, although the following issues were excluded from the study's subject, they were accepted as limitations. The study's first limitation was that it was retrospective. Second, the reasons for the MRI request were not questioned. Third, the effect of MRI on the diagnosis was not examined. Fourth, it was not checked whether additional or other imaging methods were performed before or after MRI. Fifth, medical necessity was not questioned in the MRI requests. Sixth, the effect of a patient's presence on the need for sedation for MRI or awaiting stabilization due to unstable conditions on the duration of exposure could not be examined. Seventh, a cost analysis was not performed. These issues also need to be investigated.

Conclusion

There has been an increase in MRI requests in the ED. Although almost all MRI examinations are requested from the ED, MRI requests for neuroimaging purposes have become an emergency department routine. It was observed that MRI requests added an average of 46 minutes to the length of ED stay. The weekend effect has no impact on the decision of the emergency physician to request an MRI examination.

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References

1. Dick EA, Varma D, Kashef E, Curtis J. Use of advanced imaging techniques during visits to emergency departments—implications, costs, patient benefits/risks. *Br J Radiol.* 2016; 89(1061):20150819. doi: 10.1259/bjr.20150819.
2. Quaday KA, Salzman JG, Gordon BD. Magnetic resonance imaging and computed tomography utilization trends in an academic ED. *Am J Emerg Med*. 2014; 32(6):524-528. doi: 10.1016/j.ajem.2014.01.054.
3. Tung M, Sharma R, Hinson JS, Nothelle S, Pannikottu J, Segal JB. Factors associated with imaging overuse in the emergency department: a systematic review. *Am J Emerg Med.* 2018; 36(2):301-309. doi: 10.1016/j.ajem.2017.10.049.
4. Oguz KK, Yousem DM, Deluca T, Herskovits EH, Beauchamp NJ. Effect of emergency department CT on neuroimaging case volume and positive scan rates. *Acad Radiol*. 2002; 9(9):1018-1024. doi: 10.1016/s1076-6332(03)80477-4.

5. Demir MC, Akkas M. Awareness of Risks Associated with the Use of Plain X-Ray, Computed Tomography, and Magnetic Resonance Imaging Among Emergency Physicians and Comparison with that of Other Physicians: A Survey from Turkey. *Med Sci Monit.* 2019; 25:6587-6597. doi: 10.12659/MSM.918381.
6. Korley FK, Pham JC, Kirsch TD. Use of advanced radiology during visits to US emergency departments for injury-related conditions, 1998-2007. JAMA. 2010; 304(13):1465-1471. doi: 10.1001/jama.2010.1408.
7. Rankey D, Leach JL, Leach SD. Emergency MRI utilization trends at a tertiary care academic medical center: baseline data. *Acad Radiol.* 2008; 15(4):438-443. doi: 10.1016/j.acra.2008.01.003.
8. Ohana O, Soffer S, Zimlichman E, Klang E. Overuse of CT and MRI in paediatric emergency departments. *Br J Radiol*. 2018; 91(1085):20170434. doi: 10.1259/bjr.20170434.
9. Bell CM, Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. *N Engl J Med.* 2001; 345(9):663-668. doi: 10.1056/NEJMsa003376.
10. Roberts SE, Thorne K, Akbari A, Samuel DG, Williams JG. Mortality following Stroke, the Weekend Effect and Related Factors: Record Linkage Study. *PLoS One.* 2015; 10(6):e0131836. doi: 10.1371/journal.pone.0131836.
11. Kumar G, Deshmukh A, Sakhuja A, Taneja A, Kumar N, Jacobs E et al. Acute myocardial infarction: a national analysis of the weekend effect over time. *J Am Coll Cardiol*. 2015; 65(2):217-218. doi: 10.1016/j.jacc.2014.09.083.
12. Coleman CI, Brunault RD, Saulsberry WJ. Association between weekend admission and in-hospital mortality for pulmonary embolism: An observational study and meta-analysis. *Int J Cardiol*. 2015; 194:72-74. doi: 10.1016/j.ijcard.2015.05.098.
13. Zapf MA, Kothari AN, Markossian T, Gupta GN, Blackwell RH, Wai PY et al. The "weekend effect" in urgent general operative procedures. Surgery. 2015; 158(2):508-514. doi: 10.1016/j.surg.2015.02.024.
14. Somasundram K, Neville JJ, Sinha Y, Agarwal T, Raje D, Sinha A et al. The weekend effect - How can it be mitigated? Introduction of a consultant-delivered emergency general surgical service. *Ann Med Surg (Lond)*. 2020; 57:315-320. doi: 10.1016/j.amsu.2020.08.013.
15. Scott JW, Tsai TC, Neiman PU, Jurkovich GJ, Utter GH, Haider AH et al. Lower emergency general surgery (EGS) mortality among hospitals with higher-quality trauma care. *J Trauma Acute Care Surg.* 2018; 84(3):433-440. doi: 10.1097/TA.0000000000001768.
16. Ozdemir BA, Sinha S, Karthikesalingam A, Poloniecki JD, Pearse RM, Grocott MP et al. Mortality of emergency general surgical patients and associations with hospital structures and processes. *Br J Anaesth*. 2016; 116(1):54-62. doi: 10.1093/bja/aev372.
17. Gomez CR. Time is brain: the stroke theory of relativity. *J Stroke Cerebrovasc Dis*. 2018; 27(8):2214-2227. doi: 10.1016/j.jstrokecerebrovasdis.2018.04.001.
18. Gonzalez RG, Schaefer PW, Buonanno FS, Schwamm LH, Budzik RF, Rordorf G et al. Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset. *Radiology.* 1999; 210(1):155-162. doi: 10.1148/radiology.210.1.r99ja02155.
19. Provenzale J. MR imaging of spinal trauma. *Emerg Radiol.* 2007; 13(6):289-297. doi: 10.1007/s10140-006-0568-7.
20. Birbeck GL, Gifford DR, Song J, Belin TR, Mittman BS, Vickrey BG. Do malpractice concerns, payment mechanisms, and attitudes influence test-ordering decisions? Neurology. 2004; 62(1):119-121. doi: 10.1212/01.wnl.0000101709.87316.0c.
21. Rozell JM, Li S. Recognition and appropriate use of magnetic resonance imaging for emergent neuroradiology. *Semin Ultrasound CT MR.* 2017; 38(4):424-438. doi: 10.1053/j.sult.2017.02.007.
22. Fehlings MG, Vaccaro A, Wilson JR, Singh A, W Cadotte D, Harrop JS et al. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). *PloS one.* 2012; 7(2):e32037. doi: 10.1371/journal.pone.0032037.
23. Angerer S, Buttinger K, Stummer H. The weekend effect revisited: evidence from the Upper Austrian stroke registry. *Eur J Health Econ.* 2019; 20(5):729-737. doi: 10.1007/s10198-019-01035-4.
24. Aylin P, Yunus A, Bottle A, Majeed A, Bell D. Weekend mortality for emergency admissions. A large, multicentre study. *Qual Saf Health Care.* 2010; 19(3):213-217. doi: 10.1136/qshc.2008.028639.
25. Pauls LA, Johnson-Paben R, McGready J, Murphy JD, Pronovost PJ, Wu CL. The weekend effect in hospitalized patients: a meta-analysis. *J Hosp Med.* 2017; 12(9):760-766. doi: 10.12788/jhm.2815.
26. Jungehulsing G, Rossnagel K, Nolte CH, Muller-Nordhorn J, Roll S et al. Emergency department delays in acute stroke–analysis of time between ED arrival and imaging. *Eur J Neurol.* 2006; 13(3):225-232. doi: 10.1111/j.1468-1331.2006.01170.x.
27. Persky RW, Turtzo LC, McCullough LD. Stroke in women: disparities and outcomes. Curr Cardiol Rep. 2010; 12(1):6-13. doi: 10.1007/s11886-009-0080-2.
28. Kocher KE, Meurer WJ, Desmond JS, Nallamothu BK. Effect of testing and treatment on emergency department length of stay using a national database. *Acad Emerg Med.* 2012; 19(5):525-534. doi: 10.1111/j.1553-2712.2012.01353.x.
29. Redd V, Levin S, Toerper M, Creel A, Peterson S. Effects of fully accessible magnetic resonance imaging in the emergency department. *Acad Emerg Med.* 2015; 22(6):741-749. doi: 10.1111/acem.12686.
30. Ditkofsky NG, Singh A, Avery L, Novelline RA. The role of emergency MRI in the setting of acute abdominal pain. *Emerg Radiol.* 2014; 21(6):615-624. doi: 10.1007/s10140-014-1232-2.
31. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology.* 2012; 143(5):1179-1187.e3. doi: 10.1053/j.gastro.2012.08.002.
32. Stoker J. Magnetic resonance imaging and the acute abdomen. *Br J Surg*. 2008; 95(10):1193-1194. doi: 10.1002/bjs.6378.
33. Mehta P, Morrow M, Russell J, Madhuripan N, Habeeb M. Magnetic resonance imaging of musculoskeletal emergencies. *Semin Ultrasound CT MR.* 2017; 38(4):439-452. doi: 10.1053/j.sult.2017.04.001.
34. Cournane S, Creagh D, O'Hare N, Sheehy N, Silke B. MRI in acutely ill medical patients in an Irish hospital: influence on outcomes and length of hospital stay. J Am Coll Radiol. 2014; 11(7):698-702. doi: 10.1016/j.jacr.2014.01.014.

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A rare case report: Concurrent COVID-19 and acute cerebrovascular ischemic stroke in a patient with Sheehan's syndrome

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Abstract

Introduction: SARS-Corona Virus-2 (SARS-CoV-2/COVID-19) is a novel member of coronaviridae family. This new disease first appeared in China in December 2019, and can cause severe respiratory failure in advanced cases. COVID-19 was announced as a pandemic in March 2020 by the WHO. It has infected 76 million people and has caused the death of more than 1.5 million people until December 2020. Common symptoms of this disease are fever, cough, shortness of breath, anosmia, and fatigue. But atypical presentations have also being reported. Here, we present a COVID-19 patient with an unusual neurological symptom.

Case: 82-years-old female patient with a history of hypertension and Sheehan's syndrome came to the emergency room with the complaint of fever, shortness of breath and left hemiplegia. Although nasopharyngeal swab PCR test was negative (twice), acute phase reactants were elevated and chest CT revealed typical findings of COVID-19 pneumonia, so the patient was diagnosed as COVID-19. Since the patient had left hemiplegia, a cranial CT and diffusion-weighted MRI were performed to see whether a central neurological pathology was present. Both imaging revealed the findings of acute ischemic stroke (AIS). Afterwards, the patient was hospitalized and was started on Hydroxychloroquine, acetylsalicylic acid (ASA), favipiravir and methylprednisolone. At the 7th day of follow up, the nasopharyngeal swab PCR test was performed and found as positive. On the 10th day of treatment, the symptoms and acute phase reactants regressed. Left hemiplegia of the patient also regressed and she was discharged from the hospital at the 12th day of admission without a sequelae.

Discussion and conclusion: Since there has been a recent evidence of strong relationship between COVID-19 and acute ischemic pathologies due to pathophysiology of COVID-19, we should be suspicious of acute ischemic stroke in a COVID-19 patient with neurological symptoms, especially when the patient had a history like Sheehan's syndrome disease may aggravate or hide the symptoms.

Key words: Sheehan's syndrome, COVID-19, cerebrovascular disease

Introduction

SARS-Corona Virus-2 (SARS-CoV-2/COVID-19) is a novel member of coronaviridae family that first appeared in China in December 2019, causing severe acute respiratory failure [1-3]. The severe infectious disease caused by COVID-19 was announced as a pandemic in March 2020 by the WHO. It has infected 76 million people and caused the death of more than 1.5 million people until December 2020 [4]. Although there may be atypical presentations, common symptoms are mostly fever, cough, shortness of breath, anosmia, and fatigue. The disease can cause severe conditions such as ARDS, multiple organ failure, coma, and death, especially in elderly patients [5, 6]. Fortunately, most patients with

COVID-19 can be cured and far fewer infected people result in death. In a study including more than 40,000 COVID-19 patients, 81% of patients had mild manifestations, 14% had severe manifestations, and 5% had critical manifestations [7]. Two well observed complications of COVID-19 so far, are thromboembolic and neurological complications. Thromboembolic complications include pulmonary embolism and acute stroke (even in patients younger than 50 years of age without risk factors), while neurological complications include encephalopathy, stroke, movement disorders, motor and sensory deficits, ataxia, and seizures [8].

Infarction of the pituitary gland after postpartum hemorrhage is called Sheehan's syndrome and it is one of the causes of hypopituitarism [9]. In developed countries, postpartum hemorrhage now less often results in Sheehan's syndrome than previously, largely due to improvements in obstetrical care [10, 11]. At the time of diagnosis, 55 percent had panhypopituitarism and 45 percent had partial hypopituitarism [12]. Evaluation of postpartum hypopituitarism should be performed whenever it is suspected after a delivery associated with unusually heavy blood loss. If the blood loss is severe and especially if it is associated with hypotension, the patient should be evaluated and treated for adrenal insufficiency immediately [9]. In this case report, we tried to present a patient with a history of Sheehan's syndrome, who was diagnosed with COVID-19 and acute stroke concurrently.

Case-presentation

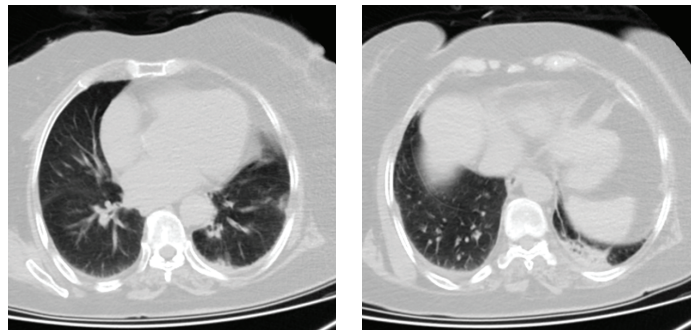
A 82-years-old female patient with a history of hypertension and Sheehan's syndrome came to the emergency room with the complaint of fever, shortness of breath and left hemiplegia. On physical examination, her blood pressure was 90/60 mmHg, heartbeat: 95/min spo2: 94 %, and fever: 39.3oC. Her Glasgow Coma Scale score was 15, she had crepitant rales especially in the left hemithorax on thoracic auscultation, she had tachypnea and dyspnea, her heart sounds were ryhtmic but tachycardic, she had weakness in the left extremities, and other system examinations were normal. Important lab test results of the patient included Na: 146 mmol/L, CRP: 33.86 mg/mL, Ferritin: 318 ml/ng, D-dimer: 987 ugFEU/L (Table 1).

Table 1 Laboratory Findings

PARAMETERS	At admission day (18 April 20)	At 7th day (25April 20)	Normal range
Glukose (mg/dl)	110	187	70-126
Urea (mg/dl)	40	40	17-43
Creatinine (mg/dl)	0.7	0.45	0.67-1.17
ALT (U/L)	41	17	0-50
AST (U/L)	35	35	0-50
Na (mmol/L)	146	134	136-146
K (mmol/L)	3,8	4.5	3.5-5.1
CRP (mg/L)	33.86	16.3	0-5
PH	7.3	7.45	7.35-7.45
HCO3 (mmol/L)	29	23.9	22-26
PCO2 (mmHg)	47	42	35-48
WBC (k/uL)	11.93	7.48	4600-10200
NEU (k/uL)	4.78	7.05	2000-6900
LYM(k/uL)	1.81	0.410	
HB (g/dl)	12.3	11.8	12,2-18
PLT (k/uL)	183000	164000	142000-424000
DDİMER (ugFEU/L)	987	13400	
LDH (U/L)	288	538	
FERRİTİN(ml/ng)	318	228	

Although nasopharyngeal swab PCR test was negative (twice), acute phase reactants were elevated and chest CT revealed typical findings of COVID-19 pneumonia such as ground glass opacities in the left inferior lobe, and crazy-paving pattern in the inferior part of this opacity (Figure 1A-B). As a conclusion, the patient was diagnosed as COVID-19. Since the patient had left hemiplegia, doctors of emergency department consulted neurologist, and neurologist ordered a cranial CT and diffusion-weighted MRI to see whether a central neurological pathology was present. Cranial CT showed at the lateral ventricle level that there is a large density reduction in gray and white matter in the parietal and occipital lobes, and there is no evidence of bleeding. These findings were compatible with acute ischemic stroke (Figure 2).

Figure 1. In the left inferior thorax lobe, there were two areas showing the ground glass opacities (A), in the lower area of ground glass opacities , these is crazy-paving pattern (B)



(A) (B)

Figure 2. IAt the lateral ventricle level, there is a large density reduction in gray and white matter in the parietal and occipital lobes, and there is no evidence of bleeding.

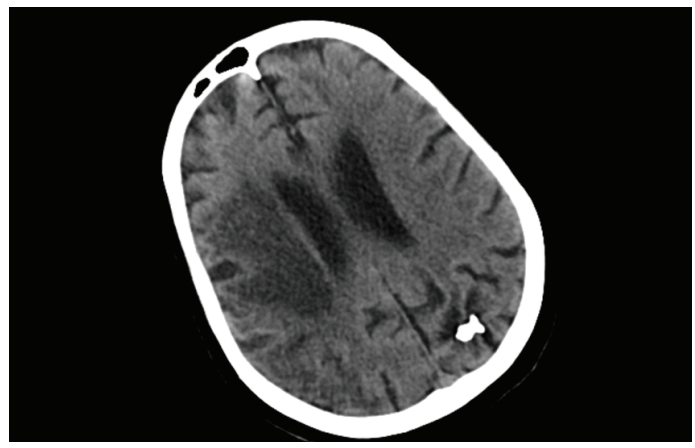
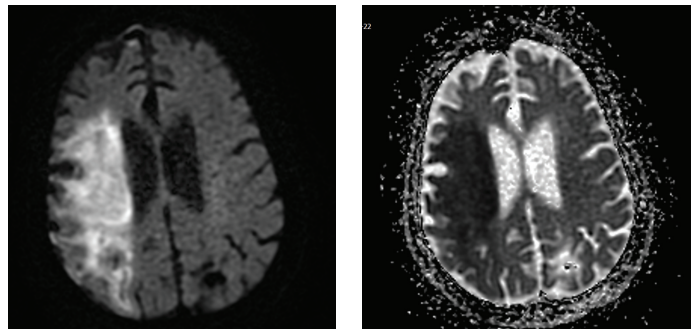


Figure 3. Diffusion image in the same CT section (A) and in the ADC sequences (B). Diffusion reduction was spotted and compatible with acute ischemia in the area fed by the right middle cerebral artery.



(A) (B)

After cranial CT showed acute ischemic stroke, cranial MRI and diffusion-weighted MRI was performed. MRI showed diffusion image in the same CT section (Figure 3A) and in the Apparent Diffusion Coefficient (ADC) sequences (Figure 3B) diffusion reduction was spotted and was compatible with acute ischemia in the area perfused by the right middle cerebral artery (Figure 3).

The patients was hospitalized and was started on hydroxychloroquine sulfate, acetylsalicylic acid (ASA), enoxaparin sodium (Low Molecular Weight Heparin), azithromycin, favipiravir and methylprednisolone. Her first two COVID-19 PCR test results were negative. Since the severity of symptoms and acute phase reactants progressed on the 6th day of follow up, we wanted to rule out other etiological factors and confirm our diagnosis. Thus, on the 7th day of follow up, the nasopharyngeal swab PCR test for COVID was reperformed and found as positive. Since the patient was suffering from resistant fever and hypoxia (spo2: 85%), favipiravir 2x200 mg was added to the treatment following the loading dose. In addition, 20 mg methylprednisolone was given to the patient who had been using 4 mg of methylprednisolone due to Sheehan's syndrome. Since TSH level of the patients was in normal range, levothyroxine which was had been used by the patient regularly, was continued as 25 mcg/day. On the 4th day of favipiravir treatment, the patient no longer had fever and/ or hypoxia (spo2> %92 in the room air), so favipiravir treatment was discontinued at the 6th day. At the 10th day of treatment, the symptoms and acute phase reactants regressed. As the acute phase levels decrease, with the help of physical rehabilitation, her neurological symptoms also regressed. She was discharged from the hospital on the 12th day of admission without sequelae.

Discussion

The most common symptoms in COVID-19 infection are fever, cough, sputum, and myalgia. But in some cases headache, shortness of breath, abdominal pain / diarrhea, sore throat and chest pain have also been reported [1-3]. Ground glass opacities, consolidation areas, interlobular septal thickening and crazy-paving pattern has been commonly reported in thorax CT [13]. İncreased white blood count, neutrophil, CRP, D-dimer and lactate, and decreased albumin, lymphocyte, platelet and hemoglobin levels are well known laboratory findings with COVID-19 and these findings are compatible with mortality [14]. Although standard reference test is seen as PCR in the diagnosis of COVID-19, it is stated that Thorax CT can be used in COVID-19 diagnosis by some sources because of the concerns about sensitivity and the fact that PCR test may be false negative / positive [15,16].

In the chest tomography of our case, there were findings compatible with COVID-19 such as ground glass opacities, although the patient's PCR test was negative, the patient was accepted as COVID-19, and treatment was started. Lab results of the patient were also compatible with COVID-19 with increased Ferritin, D dimer, CRP and raised WBC levels.. In our country, on that date in which this case occurred, the standard treatment of hydroxychloroquine, enoxaparin, azithromycin was given to the patient. However on the 3th day of admission, the exacerbations of symptoms directed us to start advanced treatments such as favipiravir and methylprednisolone. With the help of these additions, COVID-19 symptoms of the patient started to decrease by the 7th day of admission.

Acute ischemic stroke (AIS) is the most commonly reported cerebrovascular event complicating COVID-19. It may presents with nonfocal deficits, including encephalopathy, and involve multiple vascular territories. This heterogeneity suggests that the mechanisms of stroke in COVID-19 are multiple and may include both specific pathophysiological features of the SARS-CoV-2 virus, including endothelial activation and thrombosis, as well as nonspecific effects of inflammation and coagulation dysfunction, superimposed on preexisting risk factors like hypertension, diabetes, malignencies [17]. In a meta-analysis of 4466 COVID-19 patients, the pooled incidence of AIS was 1.2% with mean age of 63.4±13.1 years. Mean duration of AIS from COVID-19 symptoms onset was 10 ± 8 days in this study (18). The stroke incidence reported in retrospective studies of European and Chinese hospitalized COVID-19 patients varies between 2.5% to 6% [19-21). In a study of 219 patients hospitalized with COVID-19 in Wuhan, China, those with acute stroke (N = 11; 5.0%) were more likely to be older, to present with severe symptoms, to have cardiovascular risk factors, such as hypertension and diabetes, and a history of cerebrovascular disease [22]. In our case, the patient had a history of hypertension and Sheehan's syndrome (a type of cerebrovascular disorder) which is compatible with these analyses.

The pathophysiological mechanism causing Sheehan's syndrome is simply the interruption of blood flow to the pituitary gland. Considered potential mechanisms causing this interruption are arterial thrombosis similar to that seen in stroke, development of arterial spasm as a result of severe hypotension that is due to massive uterine bleeding, or compression of pituitary vessels due to relatively small sella turcica volume associated with enlargement of the pituitary during pregnancy [23]. In this respect, although there is no clear evidence in the literature, we might suggest that patients with Sheehan's syndrome might be more prone to acute ischemic stroke since there are similar pathophysiological mechanisms related to these two diseases.

Conclusion

Since there has been a recent evidence of strong relationship between COVID-19 and acute ischemic pathologies due to pathophysiology of COVID-19, we should be suspicious of acute ischemic stroke in a COVID-19 patient with neurological symptoms, especially when the patient has a history of cerebrovascular disease such as Sheehan's Syndrome. The hypercoagulability secondary to COVID-19 might further contribute to the thrombotic states such as acute ischemic stroke. More studies and case reports are needed to clarify the relationships between these complex disorders.

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References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020; 395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5. Epub 2020 Jan 24. Erratum in: Lancet. 2020 Jan 30;: PMID: 31986264; PMCID: PMC7159299.
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med.* 2020; 382(8):727-733. doi: 10.1056/NEJMoa2001017. Epub 2020 Jan 24. PMID: 31978945; PMCID: PMC7092803.
3. Gorbalenya AE, Baker SC, Baric RS, et al. Severe acute respiratory syndrome-related coronavirus: the species and its viruses - a statement of the coronavirus study group. *bioRxiv* 2020.02.07.937862; doi: https://doi.org/10.1101/2020.02.07.937862.
4. Coronavirus disease weekly epidemiological update (22 December 2020) https://www.who.int/publications/m/item/weekly-epidemiological-update---22-december-2020
5. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10223):507-513. doi: 10.1016/S0140-6736(20)30211-7. PMID: 32007143; PMCID: PMC7135076.
6. Chung M, Bernheim A, Mei X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). Radiology. 2020; 295(1):202-207. doi: 10.1148/radiol.2020200230. Epub 2020 Feb 4. PMID: 32017661; PMCID: PMC7194022.
7. Weekly CC, The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. *China CDC Weekly.* 2020; 2:113–22. https://doi.org/10.46234/ccdcw2020.032.
8. McIntosh K., (2020). Coronavirus disease 2019 (COVID-19): Clinical features. UpToDate. Available from https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-clinical-features?search=complications+of+covid&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H749004236
9. Snyder PJ. . Cooper DS., Martin KA et all. Causes of hypopituitarism., (Eds.), UpToDate. Available from https://www.uptodate.com/contents/causes-of-hypopituitarism?search=sheehan+syndrome&source=search_result&selectedTitle=1~23&usage_type=default&display_rank=1#references
10. Feinberg EC, Molitch ME, Endres LK, Peaceman AM. The incidence of Sheehan's syndrome after obstetric hemorrhage. Fertil Steril. 2005; 84(4):975-9. doi: 10.1016/j.fertnstert.2005.04.034. PMID: 16213852..
11. Zargar AH, Singh B, Laway BA, Masoodi SR, Wani AI, Bashir MI. Epidemiologic aspects of postpartum pituitary hypofunction (Sheehan's syndrome). *Fertil Steril.* 2005; 84(2):523-8. doi: 10.1016/j.fertnstert.2005.02.022. *PMID*: 16084902.
12. Diri H, Tanriverdi F, Karaca Z, Senol S, Unluhizarci K, Durak AC, Atmaca H, Kelestimur F. Extensive investigation of 114 patients with Sheehan's syndrome: a continuing disorder. *Eur J Endocrinol.* 2014; 171(3):311-8. doi: 10.1530/EJE-14-0244. Epub 2014 Jun 10. PMID: 24917653.
13. Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, Li C. The Clinical and Chest CT Features Associated With Severe and Critical COVID-19 Pneumonia. Invest Radiol. 2020; 55(6):327-331. doi: 10.1097/RLI.0000000000000672. PMID: 32118615; PMCID: PMC7147273.
14. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med*. 2020; 58(7):1021-1028. doi: 10.1515/cclm-2020-0369. PMID: 32286245.
15. Gündüz Y, Öztürk MH, Tomak Y. The usual course of Thorax CT findings of Covid-19 infection and When should control Thorax CT scan? *Turk J Med Sci.* 2020; 50(4):684–6. doi: 10.3906/sag-2004-293. Epub ahead of print. PMID: 32351103; PMCID: PMC7379429.
16. 16. Wong HYF, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, Lui MM, Lee JCY, Chiu KW, Chung TW, Lee EYP, Wan EYF, Hung IFN, Lam TPW, Kuo MD, Ng MY. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. Radiology. 2020; 296(2):E72-E78. doi: 10.1148/radiol.2020201160. Epub 2020 Mar 27. PMID: 32216717; PMCID: PMC7233401.
17. 17. Elkind MSV., Cucchiara BL., Koralnik IJ. Biller J, Rabinstein AA, Kasner SE, Goddeau RP. Coronavirus disease 2019 (COVID-19): Neurologic complications and management of neurologic conditions. UpToDate. Available from https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-neurologic-complications-and-management-of-neurologic-conditions?search=covid+and+neurological+symptoms&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H2388981520
18. Tan YK, Goh C, Leow AST, Tambyah PA, Ang A, Yap ES, Tu TM, Sharma VK, Yeo LLL, Chan BPL, Tan BYQ. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. *J Thromb Thrombolysis*. 2020; 50(3):587-595. doi: 10.1007/s11239-020-02228-y. PMID: 32661757; PMCID: PMC7358286..
19. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* 2020; 77(6):683-690. doi: 10.1001/jamaneurol.2020.1127. PMID: 32275288; PMCID: PMC7149362.
20. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, Studt JD, Sacco C, Bertuzzi A, Sandri MT, Barco S; Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. 2020; 191:9-14. doi: 10.1016/j.thromres.2020.04.024. Epub 2020 Apr 23. PMID: 32353746; PMCID: PMC7177070.
21. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020; 191:145-147. doi: 10.1016/j.thromres.2020.04.013. Epub 2020 Apr 10. PMID: 32291094; PMCID: PMC7146714.
22. Li Y, Li M, Wang M, Zhou Y, Chang J, Xian Y, Wang D, Mao L, Jin H, Hu B. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol.* 2020; 5(3):279-284. doi: 10.1136/svn-2020-000431. Epub 2020 Jul 2. PMID: 32616524; PMCID: PMC7371480.
23. Diri H, Sener EF, Bayram F, Tascioglu N, Simsek Y, Dundar M. Etiopathogenesis of Sheehan's Syndrome: Roles of Coagulation Factors and TNF-Alpha. *Int J Endocrinol.* 2014; 2014:514891. doi: 10.1155/2014/514891. Epub 2014 Apr 10. PMID: 24891849; PMCID: PMC4003783.

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Radiofrequency ablation of renal allograft cancer: Case report

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Abstract

Renal cell carcinoma of an allograft kidney is an extremely rare type of neoplasm and accounts for about 0.22-0.5% of all kidney recipients. Kidney recipients undergo routine check-up, including ultrasound examination of the graft. Renal cell carcinoma is often asymptomatic and can be an incidental finding on routine examination. In this case study, we describe a patient who developed clear cell carcinoma 9 months after the kidney transplantation from a living related donor. Radiofrequency ablation was chosen as the treatment option, considering small size solitary lesions in a renal allograft. The complete ablative response was achieved after one treatment. In a 4-year follow-up period patient did not show any new or recurrent tumor. Radiofrequency ablation is a good therapeutic option for kidney allograft carcinoma.

Key words: kidney transplantation, kidney ablation, immunosuppression, kidney transplant cancer

Abbreviations
RCC- Renal cell carcinoma
ESRD- End-stage renal disease
CNI- Calcineurin inhibitors
MMF-mycophenolate mofetil
KTx- Kidney transplantation
PET-CT- Positron-emission tomography-computed tomography
CT – computed tomography
RFA- Radiofrequency ablation
MRI - Magnetic Resonance Imaging

Introduction

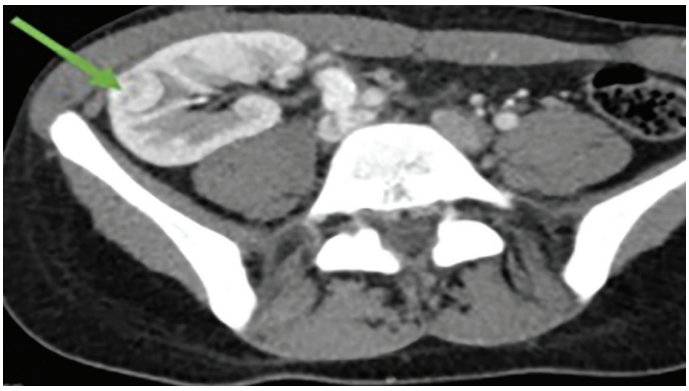
Kidney recipients are at high risk of tumor development due to obligatory immunosuppressive therapy [1]. The incidence of de-novo cancer among kidney recipients was reported in 0.2-0.5 % cases, which is 15-30 times higher than in the general population [2]. Currently, there are no clinical guidelines on the treatment of kidney allograft neoplasm [3]. Ablative therapy was proposed as the treatment option for a patient with neoplasm in a transplanted kidney [4-6]. In this clinical case, we describe the successful treatment of clear cell carcinoma in a transplanted kidney.

Case presentation

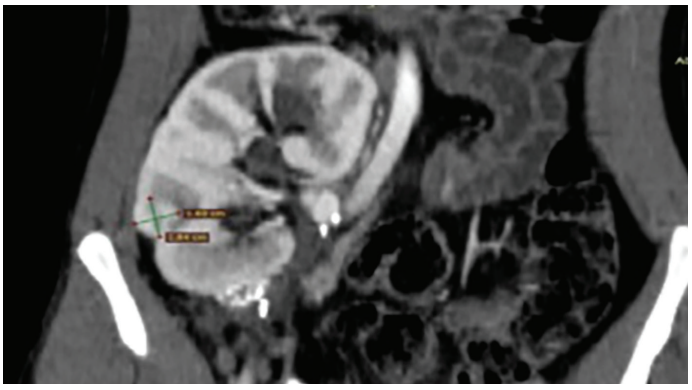
A 25-year-old woman with end-stage renal disease (ESRD) secondary to glomerulonephritis underwent pre-emptive kidney transplantation from a living related donor in November 2015. In April 2016, 9 months after KTx, during a regular check-up, the patient underwent ultrasonography, which showed the lesion in the renal graft. The computed tomography (CT) was performed as a further evaluation, the size of the lesion- 1.7 cm (Figure 1). The lesion was biopsied, the pathological investigation showed clear cell carcinoma.

Positron-emission tomography-computed tomography (PET-CT) detected active growth of a renal transplant and no signs of regional and distant metastasis. The patient was diagnosed with clear cell carcinoma of the kidney graft. Considering the small size of the tumor and absence of regional and distant metastases, Radiofrequency ablation (RFA) therapy was chosen as a therapeutic option. Implantation of coordination markers into renal lesion prior to RFA was done. RFA was performed while the patient was sedated, in the outpatient department.1 month after RFA the patient underwent Magnetic Resonance Imaging (MRI). Two experienced radiologists and a transplant surgeon interpreted MRI scans as complete necrosis (Figure 2). There were no new or metastatic lesions. The kidney function was good.

Figure 1 -CT image before radiofrequency ablation



a) The size of the lesion (measured and marked with arrows)



b) Lesion in renal allograft (marked with arrow)

Figure 2 - Renal allograft after RFA, tumor with distinct borders (capsulated) with debris inside (necrosis)- marked with arrows

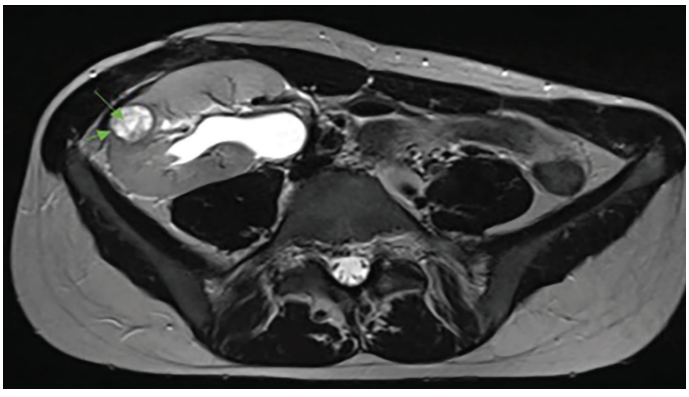
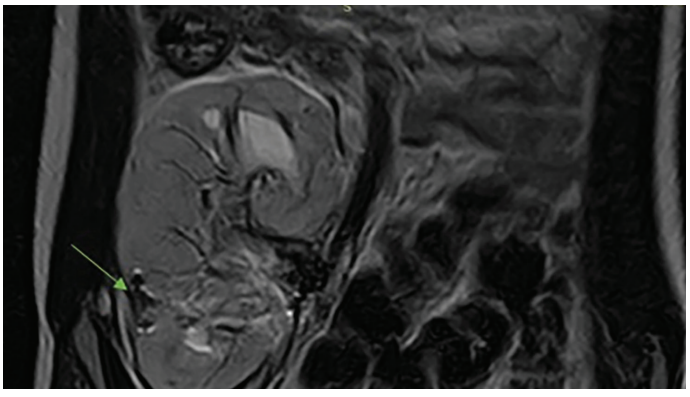


Figure 3 - MRI image 4 years after radiofrequency ablation. Post-ablative tissue changes absence of cystic component



The oncologist and transplant surgeon monitored the patient's condition. The patient did not show any new or metastatic tumors during the follow-up period. 4 years after RFA MRI scans showed post-ablative renal tissue changes and no cystic component (Figure 3).

Discussion

The success of modern immunosuppressive therapy led to better outcomes of kidney transplantation [7]. However, it also led to the incidence of various complications. Renal allograft tumor is one of the complications of immunosuppressive therapy [8]. Kidney recipients with de-novo cancer in renal allograft comprise a complex group of patients. The treatment option should be chosen in consideration of the preservation of the kidney allograft as much as possible. Radical removal of the allograft with the tumor increases the risk of death due to renal failure and return to dialysis [9]. For many years, nephrectomy was considered the only radical surgical treatment for patients with renal tumors. The desire to preserve the graft and its function stimulated the development of organ-preserving surgeries. It was reported, that patients after nephron-sparing surgery have similar outcomes as those after total nephrectomy [10]. However, partial nephrectomy is a challenging surgical procedure and has various complications [11]. The use of alternative options, such as cryoablation (CA); radiofrequency ablation (RFA); high-intensity focused ultrasound (HIFU) and microwave ablation (MWA) is increasing steadily [12].

RFA is a widely accepted technique for treating small renal tumors. It uses a high-frequency, alternating current within the targeted tissue to cause ionic agitation generating frictional heat, which results in cancer cell destruction when the temperatures exceed 60°C. Numerous studies showed its clinical effectiveness. The technical success rate ranges from 90 to 100 %. Small tumor size (less than 3 cm) and exophytic location were independent predictors of complete necrosis of the lesion after the first ablation [13].

In our clinical observation, the patient had a small (1.7 cm) solitary renal tumor without regional or distant metastases. The pathologist could differentiate the type of tumor- clear cell carcinoma. Considering the above factors, as well as a normal graft function we decided to choose RFA for this patient. The complete ablation of the tumor was achieved after one procedure that is similar to previous reports.

In conclusion, we suppose that RFA is a good therapeutic option for recipients with RCC of the renal allograft. RFA is a minimally invasive procedure, preserving renal function and good clinical outcomes.

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References

1. Penn I. Cancer in transplant recipients. *Adv Ren Replace Ther* 2000; 7(2):147-56.PMID:10782732
2. A.C.W. Chapman Jr and G. Wong, Cancer in the transplant recipient, *Cold Spring Harb Perspect Med*, vol. 3, no. 7, Article ID a015677, Jul 2013.
3. Favi E., Raison N., Ambrogi F., Delbue S. et al. Systematic review of ablative therapy for treatment of renal allograft neoplasms. *World J Clin Cases* 2019 September 6; 7(17): 2487-2504 doi: 10.12998/wjcc.v.ii7.2487
4. Olweny EO, Park SK, Tan YK, Best SL, Trimmer C, Caddedu JA. Radiofrequency ablation versus partial nephrectomy in patients with solitary clinical T1a renal cell carcinoma : comparable oncologic outcomes at a minimum of 5 years of follow-up. Eur Urol 2012 ; 61 :1156-1161[PMID : 22257424 doi : 10.1016/j.eurro.2012.01.001]
5. Thompson RH, Atwell T, Schmitt G, Lohse CM, Kurup AN, Weisbrod A. et al. Comparison of partial nephrectomy and percutaneous ablation for cT1 renal masses. *Eur Urol.* 2015; 67:252-259. doi: 10.1016/j.euroro.2014.07.2011]
6. Campbell S, Uzzo RG, Allaf ME, Bass EB, Caddedu JA, et al. Renal Mass and Localized Renal Cancer. AUA Guideline. *J Urol*. 2017; 198:520-529. doi: 10.1016/j.juro.2017.04.100
7. Vial T., Descotes J., *Immunosuppressive drugs and cancer Toxicology.* 2003; 185(3):229-40. doi: 10.1016/s0300-483x(02)00612-1.
8. Martin P. Gallagher, Patrick J. Kelly, Meg Jardine, Vlado Perkovic, Alan Cass, Jonathan C. Craig, Josette Eris, Angela C. Webster. Long-Term Cancer Risk of Immunosuppressive Regimens after Kidney Transplantation. *J Am Soc Nephrol*. 2010; 21(5):852–858. doi: 10.1681/ASN.2009101043
9. Rao PS, Schaubel DE, Jia X, Li S, Port FK, Saran R. Survival on dialysis post-kidney transplant failure: results from the Scientific registry of Transplant Recipients. *Am J Kidney Dis.* 2007; 49:294-300. doi:10.1053/j.ajkd.2006.11.022
10. Chambade D, Meria P, Tariel E, Verine J, De Kerviler E, Peraldi MN, Glotz D, Desgrandchamps F, Mogniat-Artus P. Nephron-sparing surgery is a feasible and efficient treatment of T1a renal cell carcinoma in kidney transplant: a prospective series from a single center. *J Urol.* 2008; 180:2106-2109. doi: 10.1016/j.juro.2008.07.055
11. Lowrance WT, Yee DS, Savage C, Cronin AM, Obrien MF, Donate SM,Vickers A, Russo P Complications after Radical and Partial Nephrectomy as a Function of Age *J Urol.* 2010; 183(5):1725-1730 doi: 10.1016/j.juro.2009.12.101
12. Barama A, St-Louis G, Nicolet V,Hadjeres R, Daloze P Renal cell carcinoma in kidney allografts: a case series from a single center. *Am J Transplant.* 2005; 5:3015-3018. doi: 10.1111/j.1600-6143.2005.01099.x]
13. Gervais D, McGovern FJ, Arellano RS, McDougl WS, Mueller PR Radiofrequency ablation of renal cell carcinoma: Part 1, Indications, Results, and Role in patient management over a 6-year period and ablation of 100 tumors *AJR Am J Roentgenol.* 2005; 185(1):64-71. doi: 10.2214/ajr.185.1.01850064

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Acute lymphoid leukemia developing in the course of Crohn's Disease: Are there any guilty agents?

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Abstract

Anti-tumor necrosis factor-alpha drugs (anti-TNF-α), which are monoclonal antibodies, have revolutionized the treatment of severe and refractory inflammatory bowel disease in the last two decades. However, these drugs pose a risk for the formation of hematological malignancies such as lymphoma and acute leukemia. To our knowledge, acute lymphoblastic leukemia has been reported in the literature in only two Crohn's patients with a history of anti-TNF-α therapy.

In this article, we reported a case of Philadelphia chromosome positive acute lymphoid leukemia occurring during the course of disease with a history of azathioprine and anti-TNF-α treatment with the diagnosis of Crohn's disease. In addition, we wanted to emphasize that the patient was followed up in remission for five years after allogeneic bone marrow transplantation although he did not receive treatment for Crohn's disease.

Key words: acute lymphoid leukemia, inflammatory bowel disease, anti-tumor necrosis factor-alpha drugs

Introduction

Crohn's disease is a chronic inflammatory gastrointestinal system disease of unknown etiology that causes deterioration in the patient's quality of life [1]. A chimeric immunoglobulin monoclonal antibody [anti-tumor necrosis factor alpha (anti-TNF-α)] drugs that neutralize the biological activity of TNF-α have revolutionized the treatment approach of inflammatory bowel disease (IBD) patients with severe or refractory disease in the last two decades [2-4]. However, these drugs pose a risk as a cause of triggering and/or emergence of various malignancies. In recent years, after various anti-TNF-α treatments, hematological malignancies such as lymphoma, acute myeloid leukemia and fewer hematological malignancies such as acute lymphoid leukemia have been reported [5].

We aimed to report a Philadelphia chromosome positive acute lymphoid leukemia [Ph (+) ALL] patient after the use of infliximab and azathioprine for the treatment of severe Crohn's disease.

Case presentation

A 22-year-old male patient without a known disease was diagnosed with Crohn's disease with complaints of abdominal pain and weight loss, ileocolonoscopy images and histopathological findings of colonoscopic biopsy. Azathioprine treatment was started in the patient who was A2-L3-P (A2, between 17 and 40 years; L3, ileocolonic; P, perianal disease) according to the Montreal classification [6]. Infliximab 5 mg/kg was started as fistulas did not regress in 10 months of follow-up and Crohn's Disease Activity Index was above 150. Clinical response was obtained and perianal fistulas closed, after 3 months of this treatment.

In blood tests, erythrocyte sedimentation rate and C-reactive protein, leukocyte and platelet counts were also found to be normal. However, it was seen that ileocolonic ulcers continued in endoscopic control (Figure 1). Azathioprine was discontinued after 10 months alone and 9 months in combination with infliximab. Skin lesions compatible with leukocytoclastic vasculitis appeared in the feet after using infliximab treatment for 23 months. Since this situation was thought to be related to infliximab, the patient was in clinical and biochemical remission, and infliximab treatment was discontinued. Aphthous ulcers in the colon were observed to persist in the colonoscopy performed while infliximab was discontinued (Figure 2). While C-reactive protein increased progressively during the

Figure 1 - Colonoscopy findings in a patient under infliximab and azathioprine treatment: (A, B) arrows show aphthous ulcers on the colon mucosa, (C) shows exudative ulcers at the level of the ileocecal valve (arrow).

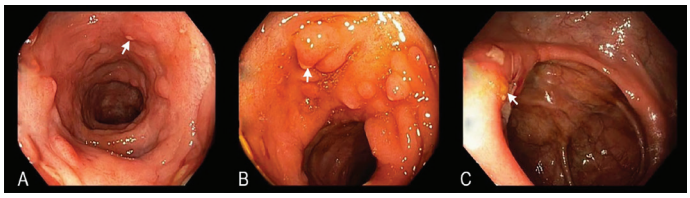

Figure 2 - Endoscopic findings in colonoscopy after infliximab discontinuation. (A) Normal mucosal areas in the terminal ileum, (B, C, D) showing aphthous ulcers in the colon.

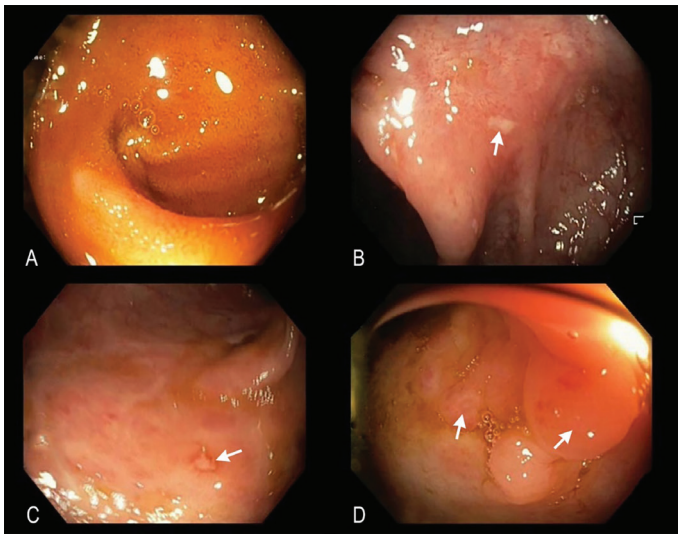

Figure 3 - Lymph nodes in the neck, mediastinum (arrows) and Lymphadenopathies in the axillary region (arrow heads).

14-month follow-up without treatment, complaints of weight loss and abdominal pain occurred.

Adalimumab treatment was planned for the patient who did not accept colonoscopic examination. Three weeks after adalimumab treatment leukocytosis [32400/mm3 (80.5% lymphocytes)], thrombocytopenia (41000/mm3) and anemia (9 gr/dL) were observed in hemogram analysis. On physical examination, lymphadenopathies in the neck and bilateral inguinal region were detected. Pathological lymphadenomegalies were observed in the neck, thorax and abdominal CT scans (Figure 3). The hematologist detected blastic cells in the peripheral smear. Cytogenetic procedure was performed with bone marrow aspiration and biopsy upon these findings. Cytogenetic examination revealed Philadelphia chromosome, and a diagnosis of Ph (+) ALL was made by bone marrow biopsy. After a total of 2 cycles of Hyper-CVAD chemotherapy (including cyclophosphamide, vincristine sulfate, Adriamycin and dexamethasone), remission was achieved and the patient was transplanted with haploidentic stem cell transplantation from his father, since he was not a fully compatible human leukocyte antigen (HLA) sibling donor. The patient, who has not received treatment for Crohn's disease for 5 years, is in remission and is followed up by hematology and gastroenterology outpatient clinics.

Discussion

To our best knowledge, three cases of acute lymphoblastic leukemia have been reported so far with Infliximab [7-9]. A 40-year-old patient followed by Özdemirkiran et al. has a 10-year history of ankylosing spondylitis. This patient was diagnosed with Ph (+) ALL after using indomethacin and sulfasalazine for 9 years, followed by infliximab and adalimumab for 10 months each. A 62-year-old patient reported by Cessani et al. has a 23 years' history of Crohn's disease. This patient was diagnosed with Ph (+) ALL after 14 years of frequent use of steroids with azathioprine and only 4 months of adalimumab use. The 40-year-old patient reported by Alcain et al. has only a 4-year history of Crohn's disease. This patient could not use azathioprine treatment due to gastrointestinal intolerance, and infliximab treatment was initiated when she was unresponsive to the treatment after short-term methotrexate use. She was diagnosed with Ph (+) ALL after only 1.5 months of infliximab use. It is noteworthy that both Ph (+) ALL cases reported had a long duration of chronic disease, one had a long anti-inflammatory (salazopyrine) treatment period, and the other received a long-term immunomodulatory (azathioprine) treatment [7, 8]. In the other case, there was a fairly short history of anti-TNF-α and immunomodulatory therapy [9]. The common point of these three cases is the severe course of chronic inflammatory disease and poor response to standard therapy. In long-term safety studies conducted with infliximab and adalimumab, the relationship between anti-TNF-α and hematological malignancies alone could not be demonstrated [10]. In the European Crohn's and Colitis Organization guideline, it is reported that anti-TNF-α alone are not associated with malignancy and the use of azathioprine in IBD increases the risk of lymphoma, especially in Crohn's disease [11]. It has been reported that the risk of T-cell hepatosplenic lymphoma increases especially with the use of azathioprine and anti-TNF-α combination for more than two years [10]. It is stated that the risk of myeloid leukemia increases in the long term with thiopurines [10]. In our case, a total of 23 months of infliximab and 19 months of azathioprine (9 months in combination) was used, and Ph (+) ALL developed. This patient, like the other three reported patients, shares the common point of severe chronic inflammatory disease and poor response to treatment. Considering these patients, we think that besides the effect of long-term immunomodulators, anti-TNF-α and anti-inflammatory drugs, duration of the chronic inflammatory disease and duration of the active disease, poor response to standard treatments, and the severe course of the disease may have an effect on the development of ALL. In addition, it is known that it poses a risk in terms of various malignancies, especially lymphoproliferative disease, even after the treatment is discontinued due to DNA damage that occurs during the period when immunomodulators are used, and this risk is multiplied when anti-TNF is added to the treatment [11]. The fact that he has been in remission for 5 years without treatment after allogeneic bone marrow transplant demonstrates the effectiveness of allogeneic bone marrow transplantation in Crohn's disease [12].

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References

1. Feuerstein JD, Cheifetz AS. Crohn Disease: Epidemiology, Diagnosis, and Management. *Mayo Clin Proc*. 2017; 92(7):1088-1103. doi: 10.1016/j.mayocp.2017.04.010.
2. Côté-Daigneault J, Bouin M, Lahaie R, Colombel JF, Poitras P. Biologics in inflammatory bowel disease: what are the data? *United European Gastroenterol J*. 2015; 3(5):419-28. doi: 10.1177/2050640615590302.
3. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther*. 2008; 117(2):244-79. doi: 10.1016/j.pharmthera.2007.10.001.
4. Plevy SE, Landers CJ, Prehn J, Carramanzana NM, Deem RL, Shealy D, et al. A role for TNF-alpha and mucosal T helper-1 cytokines in the pathogenesis of Crohn's disease. *J Immunol*. 1997; 159(12):6276-82.
5. Askling J, Fored CM, Baecklund E, Brandt L, Backlin C, Ekbom A, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. *Ann Rheum Dis*. 2005; 64(10):1414-20. doi: 10.1136/ard.2004.033241.
6. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*. 2006; 55(6):749-53. doi: 10.1136/gut.2005.082909.
7. Cesarini M, Vernia P, Angelucci E. Acute lymphoid leukemia in a Crohn's disease patient during treatment with adalimumab after a prolonged treatment with azathioprine and steroids. *Inflamm Bowel Dis*. 2010; 16(3):371-2. doi: 10.1002/ibd.21005.
8. Özdemirkiran FG, Payzin BK, Çoban E, Bayram KB, Küçükzeybek B. Acute lymphoid leukemia after anti-TNF-alpha treatment: a case report and review of the literature. *Turk J Rheumatol*. 2015; 30:349-52. DOI: 10.5606/ArchRheumatol.2015.5669.
9. Alcaín G, Andrade RJ, Queipo de Llano MP, Moreno MJ, García-Cortés M, Franquelo E. Acute leukemia after infliximab therapy. Am *J Gastroenterol*. 2003; 98(11):2577. doi: 10.1111/j.1572-0241.2003.08682.x.
10. Annese V, Beaugerie L, Egan L, Biancone L, Bolling C, Brandts C, et al. ECCO. European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies. *J Crohns Colitis*. 2015; 9(11):945-65. doi: 10.1093/ecco-jcc/jjv141.
11. Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *J Crohns Colitis*. 2020; 14(1):4-22. doi: 10.1093/ecco-jcc/jjz180.
12. Oliveira MC, Elias JB, Moraes DA, Simões BP, Rodrigues M, Ribeiro AAF, et al. A review of hematopoietic stem cell transplantation for autoimmune diseases: multiple sclerosis, systemic sclerosis and Crohn's disease. Position paper of the Brazilian Society of Bone Marrow Transplantation. *Hematol Transfus Cell Ther*. 2021; 43(1):65-86. doi: 10.1016/j.htct.2020.03.002.

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A giant bulla case that developed in the late period after Covid 19: a case report

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Abstract

Covid 19 patients' lung imaging, parenchymal pneumonic opacity areas with ground glass density, mostly located in the subpleural regions, are observed. With the increase in the number of cases, different lung complications have begun to be seen in cases other than pneumonic consolidations. Here, we wanted to emphasize the necessity of follow-up of Covid 19 patients after discharge by presenting our case who developed giant bulla in the late period, but not in the early follow-up after Covid 19.

Key words: giant Bulla, Covid 19, thoracoscopy

Introduction

The new type of Coronavirus 19 (Covid-19) disease was first seen in Wuhan, China, in December 2019. By showing human-to-human transmission, it quickly took hold of the whole world. In these patients' lung imaging, parenchymal pneumonic opacity areas with ground glass density, mostly located in the subpleural regions, are observed. [1]. With the increase in the number of cases, different lung complications have begun to be seen in cases other than pneumonic consolidations. Here, we wanted to emphasize the necessity of follow-up of Covid 19 patients after discharge by presenting our case who developed giant bulla in the late period, but not in the early follow-up after Covid 19.

Case presentation

Our 51-year-old male patient was admitted to the hospital on 01.09.2020 with complaints of cough, shortness of breath, joint pain, fever, and Oronasal Covid-19 Polymerase chain reaction (PCR) test came out positive. On physical examination, breathing sounds could not be detected in the left basales. Oxygen saturation at room air was 90%. He has never smoked. There was no known history of asthma or COPD.

The patient's blood test results are as follows: leukocyte 5.79 x10^3/uL, neutrophils 83.5%, lymphocytes: 13%, hemoglobin 14.6 g/dl, platelets: 165000 10^3/uL LDH: 730 IU/L CRP: 146.9 mg/dl, Ferritin 1420 mg/l. In Thoracic Tomography Peripherally located infiltrations with ground glass density were observed in the upper, middle, and lower lobes of both lungs and the appearance was primarily evaluated in favor of viral pneumonia due to Covid 19 (Figure 1).

Figure 1 - Covid 19 pneumonic infiltrations

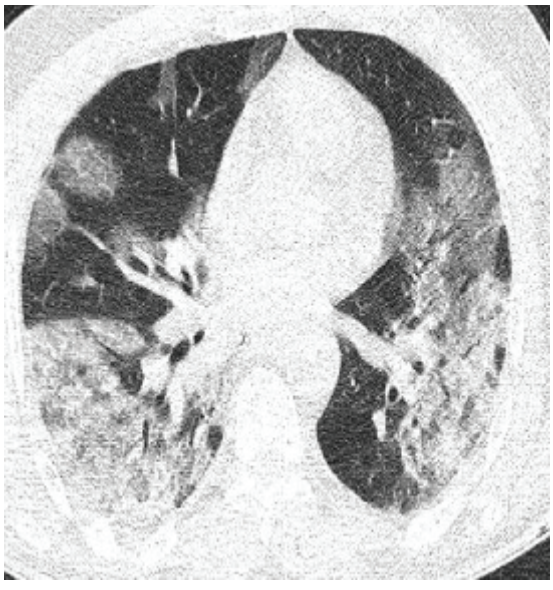


Figure 2 - Chest radiography of After ten day than Covid 19

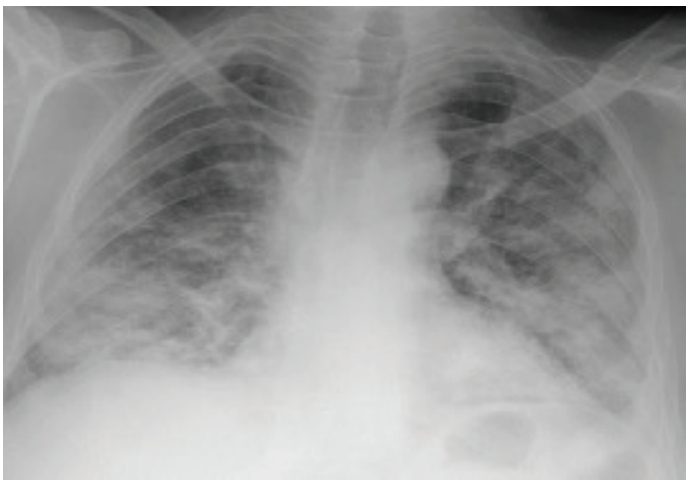


Figure 3 - Thorax bt and paac graphs taken in the 5th month

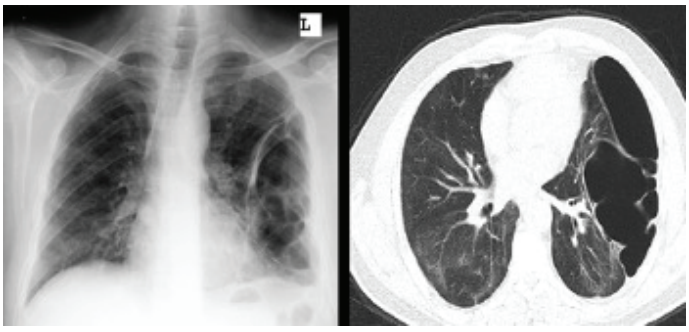
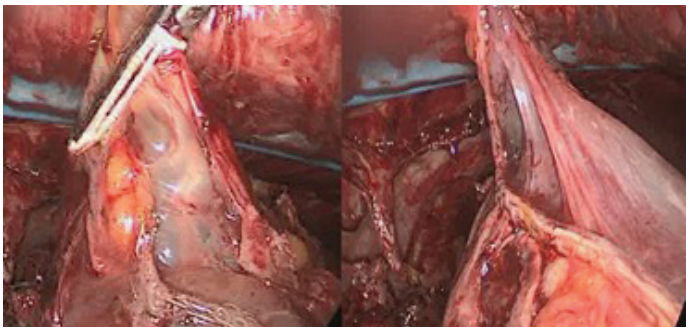


Figure 4 - Operation images



He was hospitalized for about one week and received medical support in nasal oxygen support, Plaquenil, Favipavir, Methylprednisolone, Enoxaparin, and antibiotherapy. When the result of the Covid PCR test, which was taken twice during the patient's follow-up, was negative, and when the blood values improved, he was discharged and completed the quarantine period at home. A partial decrease in ground glass densities was detected in the control chest X-ray ten days after discharged, and his follow-up was continued (Figure 2).

At the 5th month of the patient, bullous formations with a diameter of about 16x8x17 cm continuing along the upper lobe of the left lung, lingula, and lower lobe superior segments were noted in the Thorax CT performed due to chest pain (Figure 3).

Thereupon, surgery was recommended to the patient, stating a risk of bullae growth and explosion. With the uniportal video thoracoscopic approach, the giant bullous structure originating from the lower lobe superior segment of the left lung was removed by wedge resection (Figure 4).

In the pathological examination of the extracted specimen, typical features for Covid-19 histopathology, vascular thrombi, and vasculitis findings were not discovered. However, extensive perivascular lymphocytic infiltrations were observed in small diameter vessels.

The patient, who stayed in the hospital for two days after surgery, was discharged without any problems after the drain was removed.

Discussion

As the new type of coronavirus became widespread worldwide, cases such as pneumatocele, giant bulla development, mediastinal emphysema, and pneumothorax development have started to be reported in some published cases [1]. Although the exact mechanism of bulla formation is not fully understood, it is thought that it may be due to the patients' underlying emphysema, previous air space, or cystic changes in the parenchyma [2]. Besides, since high flow oxygen therapy, positive pressure mechanical ventilation with CBAP or intubation is applied to patients desaturated during the Covid process, there is a possibility of alveolar damage and bulla formation pneumothorax. It has been reported that Covid 19 pneumonia itself causes cystic changes in the parenchyma by causing alveolar damage [3-4]. Bilateral diffuse alveolar damage desquamates in pneumocyte cells, and hyaline membrane formation has been reported in autopsy studies in patients with Covid 19 who died. Thrombosis, microangiopathy, leukocyte infiltration consisting mostly of lymphocytes have been frequently reported. It has been stated that diffuse alveolar damage may develop due to endothelial and vascular damage caused by microthrombi [3]. It is predicted that air cysts resulting from alveolar damage may coalesce to form pneumotoceles, and these pneumotoceles may rupture, merge and grow, and thus giant bullae may form. As a result of the explosion of these giant bullae, complications such as pneumothorax and pneumomediastinum have been reported to be possible to develop [2-4]. In the pathological specimen examination of our patient, vascular thrombi and vasculitis findings were not discovered. However, extensive perivascular lymphocytic infiltrations were observed in small diameter vessels.

In one of the published cases, they stated that CBAP and high-flow oxygen were applied to the patient during the Covid-19 process and that they could not fully evaluate whether the pneumothorax developed in this process was related to this [5]. Yaskawa et al. stated that in their patient hospitalized for Covid pneumonia for ten days with nasal oxygen therapy, tension pneumothorax developed in the right hemithorax on the 14th day after discharge. They stated that they observed bilateral infiltrations and giant bulla formation at the right middle lobe level in the thorax CT imaging performed after the drain was inserted [4].

While there was no bulla formation in the initial period of Covid disease in a case published by Berhane et al., it was stated that giant bullae developed in the right hemithorax during the follow-up of the patient who received CBAP treatment for eight days due to severe pneumonia and desaturation due to Covid 19 [5].

In most of the published cases, it is seen that the development of complications in the form of bulla and pneumothorax is encountered during the hospitalization period due to Covid 19 or during the early recovery period [1-5]. However, in publications, it has begun to be stated that Covid 19 patients with severe lung involvement and positive pressure respiratory support with mechanical ventilation or non-invasive mechanical ventilation should be followed up with tomography to develop bulla pneumothorax after treatment [6].

In this article, we wanted to present our case whose giant bulla was detected in the 5th month after the recovery of Covid-19 disease. While the development of giant bulla or pneumothorax in the majority of the cases that have been included in the literature so far occurred either during the active disease period in which Covid 19 patients were hospitalized or during the early discharge after recovery, a case with a giant bulla in the 5th month, like ours, has not been reported in the literature yet. Based on this case, we would like to emphasize that cases with severe pneumonic involvement during the Covid 19 disease period should be evaluated with a control tomography image at least six months after discharge.

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References

1. Sun R, Liu H, Wang X. Mediastinal Emphysema, Giant Bulla, and Pneumothorax Developed during the Course of COVID-19 Pneumonia. *Korean J Radiol*. 2020; 21(5):541-544. https://doi.org/10.3348/kjr.2020.0180
2. O.M.P. Jolobe, Air leaks, pneumatoceles, and air spaces in Covid-19 pneumonia. *American Journal of Emergency Medicine.* https://doi.org/10.1016/j.ajem.2020.08.098
3. Janssen ML, Van Manen MJG, Cretier SE, Braunstahl G-J. Pneumothorax in patients with prior or current COVID-19 pneumonia. *Respiratory Medicine Case Reports*. 2020; 31. https://doi.org/10.1016/j.rmcr.2020.101187
4. KYasukawa K, Vamadevan A, and Rollins R. Bulla Formation and Tension Pneumothorax in a Patient with COVID-19. *Am. J. Trop. Med. Hyg.* 2020; 103(3):943–944 https://doi.org/10.4269/ajtmh.20-0736
5. Berhane S, Tabor A, Sahu A, Singh A.Development of bullous lung disease in a patient with severe COVID-19 pneumonitis. *BMJ Case Rep.* 2020; 13:e237455. doi:10.1136/bcr-2020-237455
6. Xu W, Luo X, Wang H, Shen C, Song Y, Sun T, Chen M, Pulmonary emphysema, bullae, and pneumothorax in COVID-19 pneumonia. *Radiology Case Reports.* 2021; 16:995 – 998

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Barriers and strategies in cancers services development in the Republic of Kazakhstan

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Abstract

Introduction: To fight cancer, in 2018, Kazakhstan adopted a comprehensive plan for the development of cancer care for the country's population.

Aim: to present the state of collection of statistics, and perspectives for the oncology service development of the Republic of Kazakhstan through the implementation of the project to create the National Research Oncology Center in Nur-Sultan.

Methods: Official statistical data of international and domestic healthcare organizations, as well as the capabilities of the National Research Oncology Center for further development of the oncology service and training of highly professional personnel.

Results: The official statistics on cancer morbidity and mortality of the Health Ministry of the Republic of Kazakhstan and KazIOR differs from the WHO (International Agency for Research on Cancer) data.

The analysis showed that the current issues of the oncological service of Kazakhstan are low detection rates, insufficient screening coverage of the population, limited access of the population to high-tech methods of diagnosis and treatment, and a shortage of oncologists.

To provide the population by oncological service in accordance with international standards, it is planning to: equip the National Research Oncology Center with high-technological medical and diagnostic equipment; functioning of a research center with six scientific laboratories; training of clinical and non-clinical specialists in the world's leading medical and scientific centers.

Conclusion: Our study found that in Kazakhstan statistical data on cancer morbidity and mortality are not the same by different officials, and has lower rates of early diagnosis. To become the National Research Oncology Center, as center for cancer control in Kazakhstan and in the countries of Central Asia, the National Research Oncology Center needs to improve the cancer statistics, innovate a high-quality of cancer care, and provide an accessibility of the population of the Republic of Kazakhstan to high-tech cancer care.

Key words: cancer care, statistics, high-tech methods, staff training, scientific laboratories

Introduction

The age-standardized incidence rate (World) (per 10,000 people) in Kazakhstan (166.9) is lower in compare than in the USA (362.2), Germany (313.2), and Russia (234.3), whereas the age-standardized mortality rate (World) (per 100,000 people) in Kazakhstan (98.5) is higher or approximately equal in compare with the USA (86.3), Germany (102.3), and Russia (113.7) [1]. This may indicate to some problem in cancer service of Kazakhstan, for instance to cancer screening and cancer prevention. Cancer care is the most high-cost effectiveness in Kazakhstan's healthcare budget [2].

To fight cancer, in 2018, Kazakhstan adopted a comprehensive plan until 2022 for the development

of cancer care [3, 4]. As part of the comprehensive plan, a construction of a new building of the National Research Oncology Center (hereinafter - NROC) is underway. Tasks of NROC are: ensuring accessibility of the Kazakhstan population as well as the countries of Central Asia to high-tech cancer care; reducing cancer mortality by increasing the accessibility in high-tech methods of prevention, early diagnosis and treatment of cancer in accordance with international standards. The vision of the NROC is to become a leading scientific center in oncology field in the Central Asian region countries with a contemporary infrastructure and trinity integration of clinic, science and education.

The aim of this publication was to present the state of collection of official statistical data, and to detect perspectives for the oncology service development of the Republic of Kazakhstan through the implementation of the project to create NROC in Nur-Sultan.

Material and methods

Analysis of the current situation and development prospects for the fight against oncological diseases according to the data of official international and domestic health organizations, as well as studying the possibility of the NROC in the further development of the country's oncological service and training highly professional personnel.

Results

Cancer is one of the leading causes of death worldwide. According to the World Health Organization (hereinafter - WHO), in 2018, 18.1 million new cases and 9.6 million deaths from cancer were registered worldwide. Kazakhstan is one of the countries with the largest number of cancer [5]. Below, Table 1 presents the comparative data on morbidity and mortality from cancer in the Republic of Kazakhstan with the economic-leading countries of the world in 2018 [2, 6, 7].

Table 1 Comparative data on morbidity and mortality from cancer in the Republic of Kazakhstan with economic developed countries of the world in 2018 (per 100,000 people)

No.	Data	The RK data according to	USA	Germany	Russia		
		WHO	MH RK	KazNIIOiR			
1	Morbidity	170.1[6]	195.7[4]	175.2[3]	352.2	313.1	222.1
2	Mortality	109.5[6]	80.81[4]	78.1[3]	91	104.2	119.2

Abbreviations: MH RK, the Ministry of Health of the Republic of Kazakhstan; KazIOR, Kazakh Institute of oncology and Radiology.

Table 1 shows significantly difference on morbidity and mortality from cancer in Kazakhstan between the official statistics of the Ministry of Health of the Republic of Kazakhstan, Kazakh Institute of oncology and Radiology, and WHO with the International Agency for Research on Cancer. According to internal statistics (MH RK and KazIOR) in comparison with external statistics (WHO data), morbidity has an increased data, and mortality a reduced data. Data of morbidity and mortality according to the Ministry of Health of the Republic of Kazakhstan and KazIOR are somewhat different from each other. Such a significant difference in these statistical data of morbidity and mortality may be signs of different collecting methods and material analyzing, which should be standardized.

The table results in the USA and Germany morbidity data are more three times than mortality data, and in Russia are more two times, while in Kazakhstan are only 1.7 times. The mortality data in the USA and Germany are lower than in Kazakhstan. These data may testify that Kazakh has low rates of detection of cancer.

Thus, the current problem of Kazakhstan's cancer service are:

- unreliable statistics of data on morbidity and mortality on cancer;
- low rates of detection and early diagnosis;
- insufficient coverage of the population with cancer screenings;
- limited access of the population to high-tech methods of diagnosis and treatment;
- shortage of oncologists (125.6 free vacancies) [7].

To implement the comprehensive plan for the development of cancer care in the Republic of Kazakhstan, the NROC is working in three main areas:

1) the delivery of cancer care to population of the Republic of Kazakhstan in accordance with leading international standards;

2) the implementation of personified methods of diagnosis, treatment and prevention in oncology field; the conduct of multicenter scientific research;

3) development and training of high professional staff for cancer service of the Republic of Kazakhstan.

To provide cancer care in accordance with leading international standards there is planned to equip NROC with high-advanced equipment for diagnosis and treatment of cancer diseases, such as:

- proton therapy;
- radionuclide therapy;
- radiation therapy;
- laser therapy;
- chemo-targeted therapy and immunotherapy.

In all developed countries of the world the above-mentioned high-tech methods of treatment are used as to treat cancer. Many of Kazakhstan people are forced to travel abroad to receive these treatment methods. In this regard, realization and functioning of the above diagnostic and treatment methods will allow patients to receive the full range of cancer care from early diagnosis to high-tech treatment and rehabilitation in Kazakhstan, without needs to go abroad.

NROC plans to open a research center with six research laboratories for:

- carrying out molecular genetic research;
- carrying out proteomic and metabolomic studies;
- creation of tumor immunotherapy;
- creation of a bank of cells and tissues;
- carrying out tissue engineering;
- carrying out bioinformatic analysis.

NROC has created the necessary conditions for holding scientific studies in oncology field. In 2019, NROC was accredited as a subject of scientific and scientific-technical activities, and there are functioning the local ethical commission, temporary research teams, a research department, and a scientific electronic

library. Currently, the following research projects are conducted in NROC:

- allogeneic skin transplantation for large oncological interventions;
- the use of the extracellular matrix as a xeno peritoneum in neurosurgical operations;
- multi-oms markers for risk determining of malignant transformation in the lungs;
- retrograde renal graft reperfusion at kidney transplantation;
- evaluation of the complex therapy effectiveness in patients with hemoblastosis and hematopoietic depression with COVID-19;
- desensitizing protocols for patient-recipients with high immunological risk for organ transplantation;
- acellular xenogeneic matrix for breast oncoplasty;
- aging and prolongation of healthy life expectancy with School of Medicine at Nazarbayev University;
- investigation of atmospheric pressure changes in observational study, and its effect on basal/active metabolism.

As the result of scientific research studies in NROC the following high-tech medical services are conducting:

- replacement of joints and/or bones in case of tumor diseases;
- skin allotransplantation for tumor diseases;
- transplantation of autologous, allogeneic hematopoietic stem cells;
- liver and kidney transplantation from cadaver;
- procurement of stem hematopoietic blood cells for autotransplantation.

NROC over the past few years is providing the entire population of the republic with several unique technologies in order to reduce mortality from cancer. The technologies are in great demand by patients, but it are not reimbursed by government (the free guaranteed volume of medical care, or high-tech medical care service, or the compulsory social health insurance). To take the reimbursement the Ministry of Health of the Republic of Kazakhstan requests to collect of the number of diagnosed and treated patients, which is extremely economically and financially costly for the NROC budget.

To increase the accessibility of the country's population to high-tech methods of diagnostics and treatment in accordance with leading international standards, the Ministry of Health of the Republic of Kazakhstan should introduce a system of reimbursement of high-tech unique technologies for diagnosis and treatment through creation of a technology transfer program.

To develop and train of a high-professional staff for oncological care service NROC cooperates with the World Bank, internships and fellowship trainings in foreign high educational universities within the framework of the Bolashak program, organizes private clinical residency.

Along with the training of clinical specialists, medical physicists, chemists, dosimetric technicians, radiation safety engineers and other specialists for nuclear medicine, proton and radiation therapy are being trained.

NROC has strategic partners for training that are the world's leading medical and research centers, with which it has agreements and memorandums for cooperation:

- West German Cancer Center (Essen, Germany);
- Charite hospital of Oncohematology (Berlin, Germany);
- University of Manchester (Manchester, UK);
- Danish Proton Center (Aarhus, Denmark);
- National Cancer Center (Tokyo, Japan);
- International Atomic Energy Agency (IAEA),
- National Cancer Center (Goyang, South Korea);
- Seoul National University (Seoul, South Korea);
- Medical Institute of S. Berezina (St. Petersburg, Russia);
- Federal center of nuclear medicine projects design and development (Moscow, Russia);
- Minsk Scientific and Practical Center for Surgery, Transplantology and Hematology (Minsk, Belarus).

Conclusion

Our study found that statistical data in Kazakhstan on cancer morbidity and mortality are not the same by different officials. Kazakhstan has comparatively lower rates of early diagnosis. To become NROC as a center for coordination and control over the development of cancer in the Republic of Kazakhstan as well as in Central Asia countries, first of all, NROC has to improve the cancer statistics, and to innovate all worlds' unique technologies for the diagnosis, treatment and prevention of cancer.

New medical technologies, scientific researches and qualified specialists are the main strategy for the development of a contemporary cancer care service to improve the quality of cancer care, as well to ensure an accessibility of the population of the Republic of Kazakhstan to high-quality cancer care.

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References

1. https://gco.iarc.fr/today/fact-sheets-populations The Fact sheets provide a snapshot of the burden of cancer in a selected country or region, or a global overview for a given cancer type (2020).
2. Data of the cancer care service of the Republic of Kazakhstan for 2018, statistical and analytical data. Almaty: 2019. p. 214.
3. The Republic of Kazakhstan Government Decree "On approval of the Comprehensive plan to cancer care in the Republic of Kazakhstan for 2018 - 2022". June 29, 2018, No. 395.
4. The Republic of Kazakhstan Government Decree "On the establishment of the National Research Oncological Center". May 11, 2018, No. 255.
5. https://almaty.tv/news/meditsina/1150-nur-sultanda-onkologiyalyk-aurulardyn-aldyn-aluga-arnalgan-dgahandyk-sammiti-bastaldy Global Summit of Leaders in Cancer Prevention and Treatment.
6. Health of the Republic of Kazakhstan population and the activities of healthcare organizations in 2019, Stat. collection. *Nur-Sultan:* 2020. p. 324.
7. www.parlam.kz › mazhilis › download Measures to improve the quality of medical care for cancer within the framework of the State Program for the Development of Healthcare of the Republic of Kazakhstan "Densaulyk" for 2016-2019.

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