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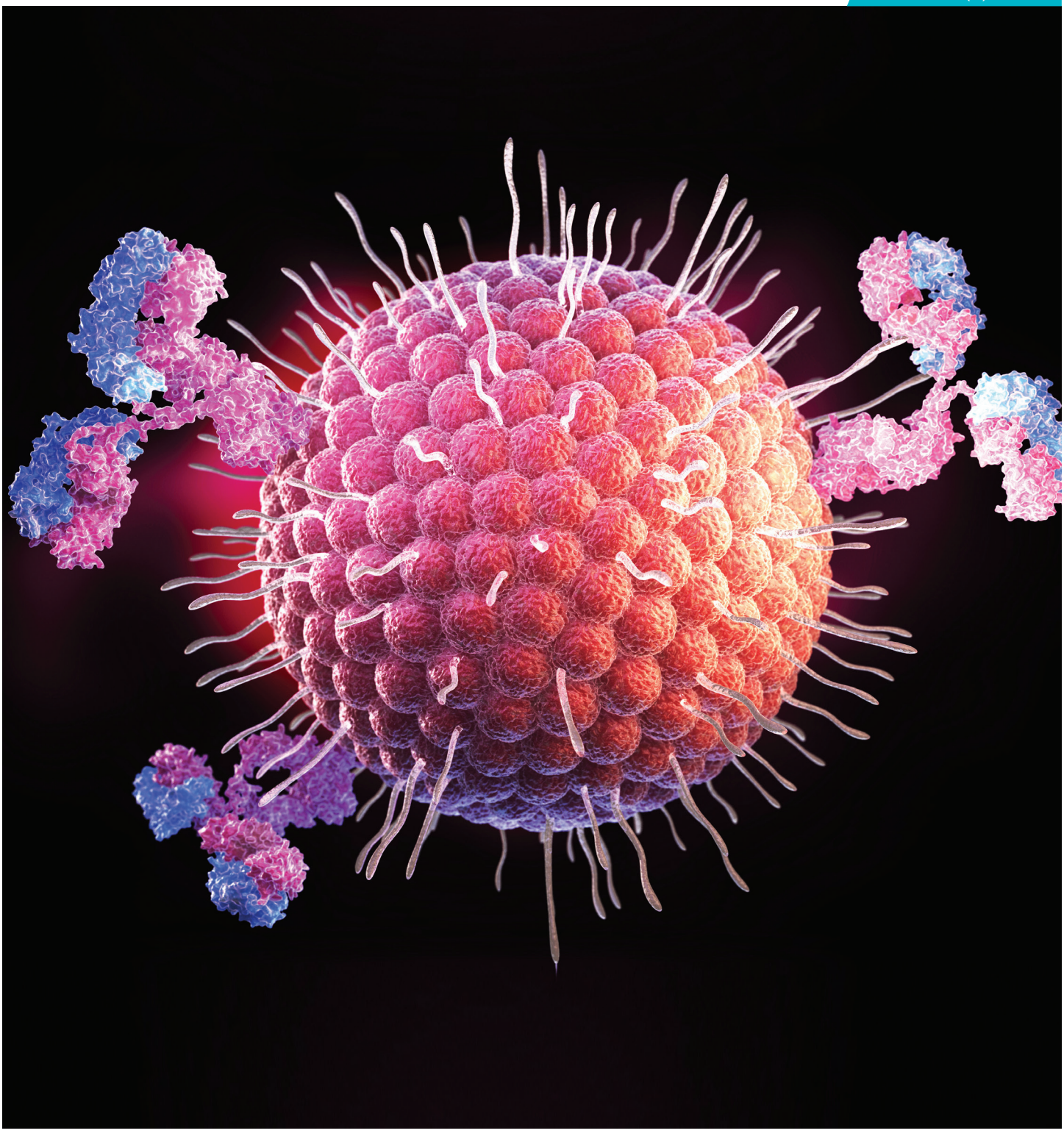
Online ISSN 2313-1519
Print ISSN 1812-2892
www.clinmedkaz.org

№20 (1) 2023



COVID-19 and diabetes mellitus: Clinical and laboratory features in hospitalized patients

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Online ISSN 2313-1519
Print ISSN 1812-2892
№20 (1) 2023г.
Published since 2004.

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EDITORIAL

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Journal "Clinical Medicine of Kazakhstan" (ISSN 1812-2892) is a multi-field dedicated peer-reviewed medical journal. The main thematic scope – publication of materials on medical science and practice, education and healthcare organization. Joint Stock Company "National Scientific Medical Center" publishes the journal bimonthly in a year (in February, April, June, August, October, and December).

All articles sent to editors undergo double-blind review. Manuscripts are judged by two experts exclusively on the basis of their contribution to initial data, ideas and their presentations. Editors accept articles for consideration and publication at no cost. Detailed information is available in the section Information for authors at the end of this material.

The Journal of "Clinical Medicine of Kazakhstan" to the full extent is wedded to initiative of open access and ready to provide free access to full texts of articles, as soon as they will be published and available in the Internet (www.clinmedkaz.org).

Journal was registered in the Ministry of Information of the RK on 05.04.2004 and currently included to the list of Publications, approved by the Committee for Control of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan for publication of the main outcomes of scientific activity.

The journal is indexed in such international scientific-information bases as Russian Science Citation Index, "Cyberleninka" scientific electronic library, Index Copernicus International, Google Scholar, CrossRef. DOAJ.

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN

Scientific and practical journal

JCMK
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NATIONAL SCIENTIFIC MEDICAL CENTER JSC, NUR-SULTAN CITY, REPUBLIC OF KAZAKHSTAN

INTERNAL MEDICINE

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JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Letter to Editor DOI: https://doi.org/10.23950/jcmk/12676

Acknowledgment to JCMK Editorial Board and Peer-Reviewers for contribution in 2022

Laura Dybyssova

Executive Secretary, on behalf of editorial team of the Journal of Clinical Medicine of Kazakhstan

On behalf of the Journal of Clinical Medicine of Kazakhstan, we would like to express our appreciation to all editorial and advisory board members, reviewers and authors who contributed to this journal in year 2022.

J Clin Med Kaz 2023; 20(1):4-6

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Journal of Clinical Medicine of Kazakhstan published 6 regular issues in 2022
- Volume 19, Number 1 (2022) with 15 articles
- Volume 19, Number 2 (2022) with 13 articles
- Volume 19, Number 3 (2022) with 13 articles
- Volume 19, Number 4 (2022) with 11 articles
- Volume 19, Number 5 (2022) with 10 articles
- Volume 19, Number 6 (2022) with 21 articles

Acceptance/Rejection rate:
2022 - 47% (71 accepted, 81 rejected)
2021 - 52% (96 accepted, 88 rejected)

AUTHORS 2022

Authors and coauthors who contributed to this journal in 2022 were from the following countries: Kazakhstan, Turkey, Ukraine, Russia, Uzbekistan, India, USA, China, Pakistan, Ecuador.

The editorial team of the Journal of Clinical Medicine of Kazakhstan would like to express gratitude for your valuable support and being part of our excellent team. We appreciate your continuous efforts and hope to continue receiving your great feedback, valuable ideas, and interesting scientific papers to further improve the quality and impact of the Journal of Clinical Medicine of Kazakhstan.

Sincerely yours,

JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/12828

CT-criteria for left atrium appendage thrombus detection

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Received: 2022-02-28.
Accepted: 2022-12-16

J Clin Med Kaz 2023; 20(1):7-13

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Abstract

Objective: Atrial fibrillation is strongly associated with stroke and accounts for 60% of cardioembolic stroke. Assessing thromboembolic risk is important for patients with atrial fibrillation. Approximately 90% of all thrombus are localized in the left atrium appendage (LAA). This study aimed to determine the efficacy of cardiac computed tomography (CT) for LAA thrombus detection.

Material and methods: This retrospective study included 292 patients. LAA thrombus was confirmed or excluded by cardiac CT with the reference to transesophageal echocardiography (TEE). We excluded patients with allergic reactions to iodide, increased creatinine levels, thyroid disease (hyperthyroidism), pregnancy, and age <18 years.

Results: According to the cardiac CT, 103 of 292 people had LAA thrombus, while according to TEE, only 48 of patients had LAA thrombus. The sensitivity and specificity of CT were 97.7% and 77%, respectively. The sensitivity and specificity of the CT was higher in 2016–2020, when the delayed phase was added to the standard protocol, compared to 2012–2015 years. Older age, higher BMI, higher CHA_2DS_2-VASc and HAS-BLED scores, and larger LA and LVESV were significantly associated with LAA thrombus detection on cardiac CT. Higher LVESV and LVEDV indexes (LVESVI and LVEDVI) and lower LV ejection fraction measured by TEE were also predictors of LAA thrombus detection by cardiac CT.

Conclusion: Our findings show that cardiac CT has high sensitivity and specificity for excluding or confirming LAA thrombus, and can also be exclusively used to determine the presence or absence of a thrombus.

Key words: left atrium appendage thrombus, cardiac computed tomography, atrial fibrillation, cardioembolic stroke, transesophageal echocardiography

Introduction

Cardioembolism is one of the major causes of ischemic strokes and comprises 14–30% of all cerebral infarctions [1-2]. Atrial fibrillation (AF) accounts for up to 60% of cardioembolic strokes [3]. The mechanism of stroke development in patients with AF is well known. Once, a patient develops AF, the dysrhythmia causes contractile dysfunction and stasis, which further lead to thrombus formation and an increased risk of thromboembolism [4]. Approximately 90% of all thrombi are localized in the left atrium appendage (LAA) [5-8]. Current therapeutic strategies for AF are pharmacological and non-pharmacological [9]. The majority of patients with AF are treated with antiarrhythmic drugs and anticoagulation drugs, and only a minority with a persistent form of AF require different types of cardioversion [10]. Electrical cardioversion with radiofrequency pulmonary vein antral isolation is an effective approach in the treatment of persistent AF [11-12]. However, the presence of blood clots in the LAA is a contraindication to electric cardioversion [13-14]. After normalization of sinus rhythm, restoration of contractility and blood flow

can lead to the detachment of a blood clot from the LAA and subsequent cardioembolic stroke. Assessing the risk of stroke in patients with AF is crucial. The gold standard for identifying an LAA thrombus is transesophageal echocardiography (TEE) [15-16]. However, TEE is a semi-invasive procedure with various complications [17]. Computed tomography (CT) is widely used in clinical practice, and recent technological improvements in cardiac CT have made the method more attractive because of its non-invasiveness, and it is a viable alternative to TEE. The development of CT-derived criteria for an increased risk of LAA thrombus can be an effective method for diagnosing thromboembolism. Studies in this area have been done before has shown that LAA thrombus detection with additional data collection tends to increase [18]. Despite this, the data obtained are mixed, and the reliability of the study differs sharply from each other in the results provided [19-20]. In this study, we analyzed the efficacy of cardiac CT for diagnosing LAA thrombus with reference to TEE data.

Material and methods

We retrospectively analyzed the data of 292 patients diagnosed with AF, who were admitted to our institution from February 2012 to September 2020. All patients underwent both TEE and cardiac CT. The exclusion criteria for CT were allergic reactions to iodide, increased creatinine levels, thyroid disease (hyperthyroidism), pregnancy, and age <18 years. The institutional ethics committee approved the study following the Declaration of Helsinki. In addition, the patients signed consent to the study.

Transesophageal echocardiography

TEE was performed using a Phillips IE33 device. The study included the assessment of left ventricular (LV) function (LV ejection fraction), valve apparatus, and left ventricular end-systolic and end-diastolic volumes (LVESV and LVEDV).

Computed tomography

CT scanning was performed with a Siemens Somatom Definition 64 device with retrospective cardiosynchronization and reconstruction with a slice thickness of 0.6 mm and pitch of 0.2 mm. We used the standard patient position (supine), with intravenous contrast bolus injection using an automatic bolus-free CT injector (Ohio Tandem; speed 5 mL/s), followed by the introduction of saline solution (50 mL). The scan was performed with "bolus tracking" at the ascending aorta at 170 units. At the starting level of the scan at the tracheal bifurcation, the delay after the introduction of contrast was 10 seconds. Patients were scanned employing electrocardiographic synchronization. The dose of the contrast agent was calculated based on the patient's weight.

The study was carried out within the limits of the LAA in order to reduce the exposure of the patient to the minimum possible. When a hypodense area was detected with contrast filling of the LAA, a 60-second scan was brought into the arterial phase. Two experienced cardiologists, who were blinded to the CT results, analyzed the TEE.

The analysis of the CT angiography data was performed by two experienced radiologists. Uniform filling of the LAA was regarded as normal. A defect in the filling of the LAA was regarded as a blood clot. The volume of the left atrium (LA) was measured on a Syngo Via workstation using the volume application along the inner contour of the LA, including the LA ear manually on each slice. Figure 1 shows an image of the LA volume calculation. Figure 2 illustrates the detection of the LAA thrombus by CT and TEE.

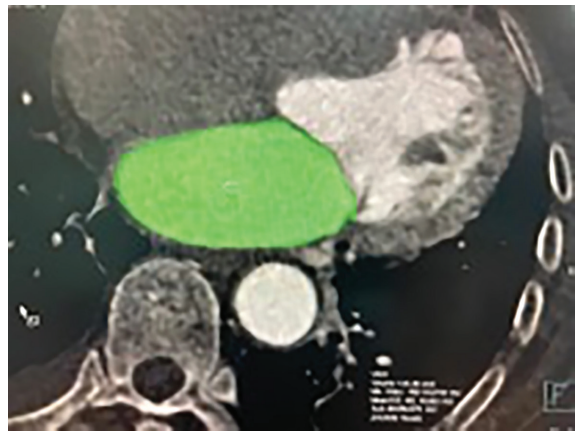

Figure 1 - A calculation of the volume of the left atrium.

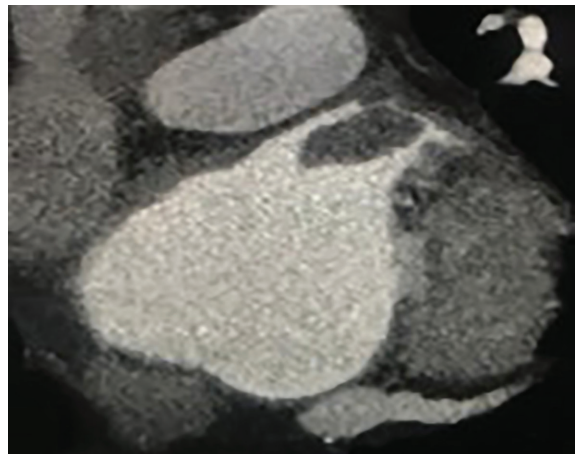

Figure 2A - LAA thrombus detected by CT

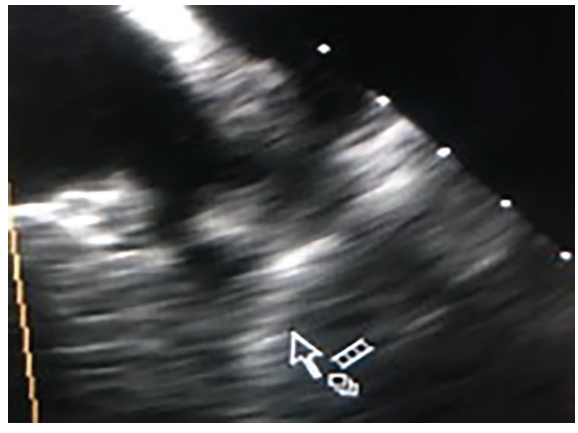

Figure 2B - LAA thrombus confirmed by TEE in the same patient

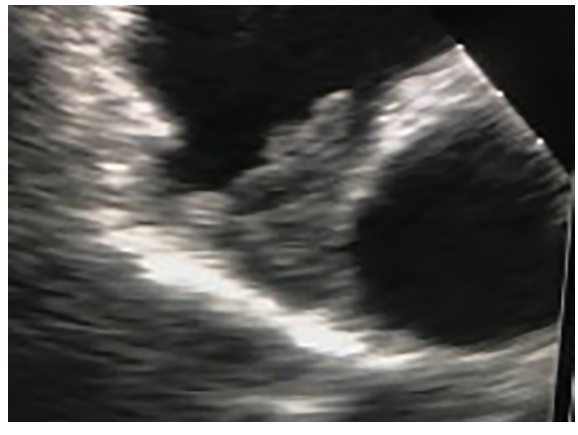

Figure 2C - LAA thrombus confirmed by TEE in the same patient

Statistical analysis

As TEE is considered a gold standard for determining the presence or absence of thrombi, CT was evaluated for sensitivity and specificity with respect to TEE. Quantitative variables are reported as means and standard deviations. Categorical variables are presented as numbers and percentages in each respective class. Each variable underwent bivariate analysis with respect to the primary outcome to determine their statistical significance. For continuous data, the Student t-test was used to determine the differences between means of variables in the groups. For qualitative data, Pearson's chi-square and Fisher's exact tests were used to determine a significant association with the outcome in two groups. The significance level was set at $\alpha = 0.05$. All statistical analyses were performed using STATA 14.0 software.

Results

The mean age of the 292 patients was 57.1 years (range 19–86), 62.3% were men, and the mean body mass index (BMI) was 29.2 kg/m^2. The mean CHA_2DS_2-VASc score was 1.99 (range 0–6), the mean HAS-BLED score was 1.45 (range 0–5); 67.5% of patients had a history hypertension, and the average LA volume measured by cardiac CT was 127.4 cm^3. The Table 1 shows the identified clinical and demographic features. According to cardiac CT and TEE, 103 (Table 2) and 48 (Table 3) patients, respectively, of the 292 patients had LAA thrombus.

Older age, higher BMI, higher CHA_2DS_2-VASc and HAS-BLED scores, and larger LA and LVESV were significantly associated with LAA thrombus detection on cardiac CT (p=0.012, <0.001, 0.001, <0.001, <0.001, and 0.004, respectively) (Table 2).

Higher LVESV and LVEDV indexes (LVESVI and

Table 1 Demographic and medical characteristics of the patients (N=292)

	Mean or n	SD or %
Age, years	57.1	±11.4
Sex		
Female	110	37.7%
Male	182	62.3%
Body mass index, kg/m2	29.2	±5.1
CHA2DS2-VASc score	1.99	±1.45
HAS-BLED score	1.45	±1.2
Weight, kg	83.8	±17.1
Hypertension		
Yes	197	67.5%
No	95	32.5%
PT, sec	15.9	±6.2
INR, sec	1.34	±0.6
Fibrinogen, g/L	3.41	±3.3
APTT, sec	40.7	±13.2
TEE		
ESD, cm	3.5	±0.7
EDD, cm	4.8	±0.7
ESV, mL	48.4	±27.7
EDV, mL	105.7	±34.7
IVS, cm	1.06	±0.24
Cardiac CT		
LA volume, cm3	127.4	±46.7

Values are presented as mean ± SD or as n (%).
Abbreviations: APTT, activated partial thromboplastin time; CT, computed tomography; EDD, end-diastolic dimension; EDV, end-diastolic volume; ESD, end-systolic dimension; ESV, end-systolic volume; INR, international normalized ratio; IVS, interventricular septum; LA, left atrium; PT, prothrombin time; TEE, transesophageal echocardiography

Table 2 Demographic and medical characteristics of patients with and without LAA thrombus according to CT (N=292)

	No LAA thrombus		
(n=189)	LAA thrombus		
(n=103)	p-value		
Age	55.9 ± 11.6	59.4 ± 10.8	0.012
Sex			
Female	69 (62.7)	41 (37.3)	0.578
Male	120 (65.9)	62 (34.1)	
Body mass index, kg/m2	28.2 ± 4.6	31.1 ± 5.4	<0.001
CHA2DS2-VASc score	1.75 ± 1.4	2.43 ± 1.5	<0.001
HAS-BLED score	1.16 ± 1.03	1.96 ± 1.3	<0.001
Weight, kg	83.4 ± 18.3	84.7 ± 14.6	0.517
Hypertension			
Yes	123 (62.4)	74 (37.6)	0.238
No	66 (69.5)	29 (30.5)	
PT, sec	15.6 ± 6.3	16.6 ± 5.9	0.203
INR, sec	1.32 ± 0.61	1.4 ± 0.7	0.283
Fibrinogen, g/L	3.32 ± 3.3	3.56 ± 3.3	0.549
APTT, sec	40.9 ± 14.1	40.3 ± 11.5	0.684
TEE			
ESD, cm	3.5 ± 0.7	3.6 ± 0.8	0.044
EDD, cm	4.75 ± 0.7	4.95 ± 0.7	0.017
ESV, mL	45 ± 18.6	54.7 ± 38.6	0.004
EDV, mL	102.8 ± 32.4	111 ± 38.1	0.051
IVS, cm	1.04 ± 0.2	1.09 ± 0.3	0.066
Cardiac CT			
LA volume, cm3	116.7 ± 42.2	147.3 ± 48.3	<0.001

Values are presented as mean ± SD or as n (%).
Abbreviations: APTT, activated partial thromboplastin time; CT, computed tomography; EDD, end-diastolic dimension; EDV, end-diastolic volume; ESD, end-systolic dimension; ESV, end-systolic volume; INR, international normalized ratio; IVS, interventricular septum; LA, left atrium; LAA, left atrial appendage; PT, prothrombin time; TEE, transesophageal echocardiography

Table 3 Demographic and medical characteristics of patients with and without LAA thrombus according to TEE (N=292)

	No LAA thrombus (244)	LAA thrombus (48)	p-value
Age	56.9 ± 11.2	58.2 ± 12.5	0.505
Sex			
Female	89 (80.9%)	21 (19.1%)	0.342
Male	155 (85.2%)	27 (14.8%)	
Body mass index, kg/m2	29.1 ± 5.1	30.2 ± 4.9	0.158
CHA2DS2-VASc score	1.96 ± 1.4	2.17 ± 1.6	0.365
HAS-BLED score	1.37 ± 1.2	1.8 ± 1.2	0.017
Weight, kg	84.3 ± 17.6	81.7 ± 13.9	0.353
Hypertension			
Yes	165 (83.8%)	32 (16.2%)	0.897
No	79 (83.2%)	16 (16.4%)	
PT, sec	15.7 ± 5.9	17.4 ± 7.1	0.076
INR, sec	1.32 ± 0.6	1.5 ± 0.8	0.112
Fibrinogen, g/L	3.3 ± 2.95	4.1 ± 4.8	0.118
APTT, sec	40.7 ± 13.6	40.6 ± 11.4	0.956
TEE			
ESD, cm	3.5 ± 0.7	3.7 ± 0.9	0.086
EDD, cm	4.8 ± 0.7	3.9 ± 0.8	0.616
ESV, mL	47.3 ± 26.6	54.2 ± 32.2	0.113
EDV, mL	104.3 ± 31.9	112.7 ± 46.1	0.125
IVS, cm	1.04 ± 0.22	1.14 ± 0.32	0.008
Cardiac CT			
LA volume, cm3	123.04 ± 44.5	127.5 ± 51.3	<0.001

Values are presented as mean ± SD or as n (%).
Abbreviations: APTT, activated partial thromboplastin time; CT, computed tomography; EDD, end-diastolic dimension; EDV, end-diastolic volume; ESD, end-systolic dimension; ESV, end-systolic volume; INR, international normalized ratio; IVS, interventricular septum; LA, left atrium; LAA, left atrial appendage; PT, prothrombin time; TEE, transesophageal echocardiography

Table 4 Comparison of volume measurements between patients with and without LAA thrombus according to CT (N=292)

	Overall	No LAA thrombus		
(n=189)	LAA thrombus			
(n=103)	p-value			
LVESVI, mL/m2	24.8 ± 13.9	23.1 ± 8.9	28.04 ± 19.9	0.004
LVEDVI, mL/m2	54.2 ± 16.9	52.7 ± 15.1	56.9 ± 19.7	0.045
LVEF, %	55.9 ± 8.9	56.8 ± 7.3	54.1 ± 11.2	0.015

Values are presented as mean ± SD
Abbreviations: LAA, left atrial appendage; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index

Table 5 Multivariate analysis of predictors of left atrial appendage thrombus according to CT (N=292)

	OR	95% CI	p-value
Age	1.01	0.98 – 1.04	0.579
BMI, kg/m2	1.14	1.07 – 1.23	0.000
CHA2DS2-VASc score	1.11	0.89 – 1.38	0.359
HAS-BLED SCORE	1.88	1.42 – 2.48	<0.001
ESD, cm	0.99	0.62 – 1.56	0.951
EDD, cm	0.93	0.87 – 0.99	0.023
LA volume, cm3	1.014	1.01 – 1.02	<0.001
LVESVI, mL/m2	1.19	1.04 – 1.35	0.010

Abbreviations: BMI, body mass index; CT, computed tomography; EDD, end-diastolic dimension; ESD, end-systolic dimension; LA, left atrium; LVESVI, left ventricular end-systolic volume index

Table 6 Sensitivity, specificity, positive and negative predictive values of cardiac CT: 2012–2020

		cardiac CT	
		negative	positive
†GS	negative	188	56
	positive	1	47

†Echocardiography results are taken as the gold standard (GS)

Sensitivity = TP/(TP+FN) = 47/(47+1) = 97.9%
Specificity = TN/(TN+FP) = 188/(188+56) = 77%

CT, computed tomography; FN, false negative; FP, false positive; TEE, transesophageal echocardiography; TP, true positive

Table 7 Sensitivity, specificity, positive and negative predictive values of cardiac CT: 2012–2015

		cardiac CT	
		negative	positive
†GS	negative	48	17
	positive	1	34

Sensitivity = TP/(TP+FN) = 34/(34+1) = 97.1%
Specificity = TN/(TN+FP) = 48/(48+17) = 73.85%

Positive predictive value = TP/(TP+FP) = 34/(34+17)=66.7%
Negative predictive value = TN/(TN+FN) = 48/(48+1)=98%
Accuracy = (TP+TN)/ (TP+TN+FP+FN)=(34+48)/(34+48+17+1)=82%

CT, computed tomography; FN, false negative; FP, false positive; TEE, transesophageal echocardiography; TP, true positive

Table 8 Sensitivity, specificity, positive and negative predictive values of cardiac CT: 2016–2020

		cardiac CT	
		negative	positive
†GS	negative	140	39
	positive	0	13

Sensitivity = TP/(TP+FN) = 13/(13+0) = 100%
Specificity = TN/(TN+FP) = 140/(140+39) = 78.2%

Positive predictive value = TP/(TP+FP) = 13/(13+39)=25%
Negative predictive value = TN/(TN+FN) = 140/(140+0)=100%
Accuracy = (TP+TN)/ (TP+TN+FP+FN)=(13+140)/(13+140+39+0)=79,6%
CT, computed tomography; FN, false negative; FP, false positive; TEE, transesophageal echocardiography; TP, true positive

Table 9 Comparison of volume measurements between patients with and without LAA thrombus according to transesophageal echocardiography (N=292)

	Overall	No LAA thrombus		
(244)	LAA thrombus			
(48)	p-value			
LVESVI, mL/m2	24.8 ± 13.9	24.2 ± 13.04	28.1 ± 17.6	0.089
LVEDVI, mL/m2	54.2 ± 16.9	53.3 ± 14.9	58.9 ± 24.9	0.041
LVEF, %	55.9 ± 8.9	56.2 ± 8.4	54.2 ± 11.4	0.166

Values are presented as mean ± SD
Abbreviations: LAA, left atrial appendage; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index

Table 10 Multivariate analysis of predictors of left atrial appendage thrombus according to transesophageal echocardiography (N=292)

	Odds ratio	95% CI	p-value
HAS-BLED score	1.31	1 – 1.71	0.046
Interventricular septum, cm	3.2	0.95 – 10.6	0.060
Left atrial volume, cm3	1.01	1 – 1.01	0.003

LVEDVI) and lower LV ejection fraction measured by TEE were also predictors of LAA thrombus detection by cardiac CT (Table 4). After adjustment for age, CHA_2DS_2-VASc score, and LV end-systolic dimension, multivariate logistic regression showed that an increase in BMI by 1 kg/m^2 increased the risk of LAA thrombus by 14% ($p<0.001$). Higher HAS-BLED score and LVESVI were significantly associated with LAA thrombus detection on cardiac CT. An increase in LVESVI by 1 mL/m2 increased the possibility of blood clot formation by 19% (Table 5). Although LA volume was significantly related to the disease, the increase in risk was not notable (odds ratio [OR]=1.014, $p<0.001$).

The sensitivity and specificity of CT were 97.7% and 77%, respectively (Table 6).

The sensitivity and specificity of the CT was higher in 2016–2020, when the delayed phase was added to the standard protocol, compared to 2012–2015 years. The positive predictive and negative predictive values of CT detection of true thrombus were 66.7% and 98% respectively for first-pass scans, and 25% and 100% for the delayed scans, respectively (Tables 7 and 8).

A higher HAS-BLED score, larger interventricular septum, larger LA volume, and higher LVEDVI were significantly associated with LAA thrombus detection on TEE ($p = 0.017$, 0.008, <0.001, and 0.041, respectively) (Tables 3 and 9). Multivariate logistic regression model showed that only a higher HAS-BLED score was significantly associated with LAA thrombus detection on TEE (OR=1.31, $p=0.046$) (Table 10).

Discussion

Cardiac CT can provide important clinical data necessary for the assessment and treatment of arrhythmias by ablation, such as the anatomy and size of vessels carrying blood to the left atrium, atherosclerotic changes and features of the anatomy of the coronary arteries, the presence of a LAA thrombus with high accuracy. In a recent publication by Lazoura et al. [21], a CT scan of the heart performed on 122 patients undergoing surgery for arrhythmias showed a 100% predictive value using a delayed scan and confirmed by TEE, which was approved when we found an arterial phase sensitivity and specificity of 97.1 % and 73.8%, and with the addition of a delayed scan, the data corresponding to 100% and 78.2%. Filling the LAA with contrast takes additional time due to anatomical and physiological features; that is why delayed scanning improves the diagnostic value of the study and reduces the number of false-positive results. In this clinical experience, we found that 1-min delayed phase is appropriate to differentiate thrombus of LAA.

CT sensitivity and negative predictive value are enhanced by a two-phase technique that includes delayed imaging. Cardiac computed tomography, especially when delayed imaging is used, is a viable alternative to TEE for the diagnosis of LA/LAA thrombi/clot, avoiding the inconvenience and hazards of TEE. A non-invasive approach equivalent to TEE for diagnosing intracardiac thrombus with high reliability and precision would have great clinical use. CT is a well-established yet underutilized imaging method for cardiac thrombus. CT is capable of detecting intracardiac thrombus with good diagnostic sensitivity [22, 23 24]. A recent meta-analysis indicated that the high overall accuracy of cardiac CT, relative to TEE, may be utilized to identify LA or LAA thrombus in patients with AF. The researchers included 19 trials with a total of 2955 patients and determined that the weighted mean sensitivity and specificity were 96% (95% CI: 92–100%) and 92% (95% CI: 91–93%), respectively, while the positive and negative predictive values were 41% (95% CI: 37–44%) and 99% (95% CI: 99–100%) [25]. The results of studies presented by Romero et al. showed that biphasic delayed-scan greatly improved the specificity and diagnostic accuracy of imaging to 91% than conventional angiography, which is equal to 41% [25]. This is due to the fact that a pseudo-filling defect, such as flow standstill, may also generate an apparent filling defect on CT scans, simulating a thrombus. Due to the fact that CT detects a cardiac thrombus based on its anatomical appearance, it might be difficult to distinguish between thrombus and flow stagnation.

It is revealed that TEE data as high left atrial volume, LVESV, and LVEDV were independently associated with evidence of thrombus in the LAA in patients with confirmed AF and treating with anticoagulant therapy. Furthermore, the same result was received even BMI and CHA_2DS_2-VASc score correction. LV ejection fraction and patient gender were not significantly associated with the presence of a LAA thrombus, which is associated with a low number of patients with heart failure. Increased LVEDVI remained a significant predictor of LAA thrombus detection on TEE. A previous report showed that increased LA systolic and diastolic volume indexes were independently associated with LAA thrombosis in patients with AF [26]. An increase in the volume of the left atrium is associated with coronary atherosclerosis, which can be the cause of coronary artery disease and ischemic stroke, making it an independent risk factor. [27-28]. An increase in LA volume is often associated with a relapse of AF after radiofrequency ablation [29]. We found that the CHA_2DS_2-VASc score showed a statistically significant association with the detection of LAA thrombosis detected by cardiac CT unlike for TEE.

The association between AF and obesity has been studied in patients with cardiac pathology. Several epidemiological studies have found a strong association between obesity and AF [30]. In our study, an increased BMI was associated with the risk of LAA thrombus.

An increase in LA volume measured by CT and an increase in LVESV and LVEDV were independently associated with the presence of an LAA thrombus. These data suggest that patients who have an increased LA volume, BMI, and end-systolic volume have a high risk for thromboembolism and should therefore be carefully monitored.

Conclusion

Our findings show that cardiac CT has high sensitivity and specificity and cannot only be used to exclude or confirm the presence of LAA thrombus, it can also be exclusively used to determine the presence or absence of thrombus. These results are consistent with previous studies. We propose the use of cardiac CT, which is non-invasive, as an initial step in diagnosis, with TEE only being employed for the confirmation of an LAA thrombus. This can reduce the various complications that occur after TEE, which is a semi-invasive procedure. Moreover, this approach seems economically beneficial for the government and patients.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

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JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/12854

COVID-19 and diabetes mellitus: Clinical and laboratory features in hospitalized patients

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Received: 2022-11-14.
Accepted: 2022-12-21

J Clin Med Kaz 2023; 20(1):14-17

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Abstract

Introduction: In December 2019, China first encountered an unknown SARS-CoV-2 virus, after which a global lockdown began, first in European countries, and after a while the virus spread around the world. The course of COVID-19 aggravates the presence of concomitant diseases in the patient, among which diabetes mellitus occupies one of the first places. It should also be noted that the two-way interaction between COVID-19 and diabetes mellitus creates a vicious circle in which COVID-19 leads to worsening of dysglycemia, and diabetes mellitus, in turn, exacerbates the severity of COVID-19.

In this article, we evaluated the relationship between diabetes mellitus and the prognosis of COVID-19 in patients of the Shymkent Infectious Diseases Hospital.

Aim: Assessment of the relationship of type 2 diabetes mellitus (DM2) with the course and outcomes of COVID-19, depending on clinical and laboratory parameters and concomitant diseases in an infectious hospital in Shymkent.

Material and methods: Electronic medical records of groups of COVID-19 patients with diabetes mellitus (DM) (n=49) and without diabetes mellitus (n=151) were analyzed: demographic, clinical, laboratory and instrumental research methods; treatment regimens, complications and outcomes.

Results: Compared with patients without diabetes mellitus, patients with diabetes mellitus had a significantly higher incidence of bilateral pneumonia (95.92%). According to complications and clinical outcomes, the incidence of respiratory failure (42% vs. 24%, P=0.022), acute heart failure (51% vs. 18%, P<01) and death (24% vs. 8.0%, P=0.01) in the diabetes group was significantly higher than in the group without diabetes mellitus. In addition, patients with diabetes mellitus had higher levels of neutrophils (P=012), C-reactive protein (P=008), procalcitonin (P<01) and D-dimer (P=032) and lower levels of lymphocytes (P=0.032) and albumin (P=034).

Conclusion: Diabetes is a significant risk factor for an unfavorable prognosis of COVID-19. In order to avoid adverse outcomes, more attention should be paid to timely prevention and treatment of patients with diabetes, especially those who need insulin therapy.

Key words: COVID-19, diabetes mellitus, prognosis, retrospective, comorbidity

Introduction

Coronavirus infection 2019 (COVID-19) is a disease that causes an RNA-containing coronavirus, which is a recombinant between an unknown coronavirus and a bat coronavirus [1]. COVID-19 is a highly contagious disease, and the outcomes directly depend on the presence or absence of concomitant diseases [2]. According to the results of the data of most published studies, one of the most common SDS is type 2 diabetes mellitus (DM2), which aggravates the course and worsens the prognosis of COVID-19 [3]. According to epidemiological studies, diabetes increases the risk of hospitalization in hospital, hospitalization in intensive care and mortality due to COVID-19 [4]. Of all deaths in hospitals, 7.8% - 33% were patients with diabetes mellitus [5]. In one multicenter study, it was reported that in patients with diabetes, the risk of death was 1.49 times higher [6]. According to the results of other studies, it was noted that in patients with diabetes mellitus, the risk of hospitalization in the intensive care unit and the need for a ventilator doubled

[7]. Another meta-analysis reports a two- to three-fold increase in the risk of severe forms of COVID-19 [8]. Therefore, attempts should be made to assess the potential role of diabetes mellitus at the systemic level.

Material and methods

In this retrospective study, we analyzed the data of 200 patients hospitalized in the infectious diseases hospital of the city of Shymkent, in the period from January 2021 to October 2021 with a diagnosis of COVID-19, including 49 cases with diabetes mellitus, and 151 without diabetes mellitus.

Data collection

Patient data, including demographic, clinical, laboratory, instrumental methods, treatment methods, complications and outcomes were taken from electronic medical records of patients.

Criteria for inclusion in the study: the SARS-CoV-2 virus has been verified, diabetes and age over 18 years.

Exclusion criteria: absence of coronavirus infection in the patient, age under 18, pregnancy.

Statistical analyses

All statistical analyses were carried out using the SPSS program (version 21.0, SPSS, Chicago, Illinois, USA). Quantitative continuous variables with asymmetric distribution were summed as median and interquartile range, continuous variables with normal distribution were summed as mean and standard deviation, and percentages were used to express qualitative characteristics (%).

Results

In total, 200 patients with COVID-19 were included in this retrospective study. The average age was 61 years, of which 108 patients (54%) were women. The most common symptoms of the disease were fever (87%), followed by cough (66%), anorexia (37%), fatigue (38%) and shortness of breath (42.5%). Almost half of the patients had one or more comorbid pathologies, such as arterial hypertension (63%), sugar diabetes (24.5%), cardiovascular diseases (57%), chronic respiratory diseases (8.4%), chronic liver diseases (6%), and chronic kidney diseases (1,4%). 69 (34,5%) the patients were in critical condition.

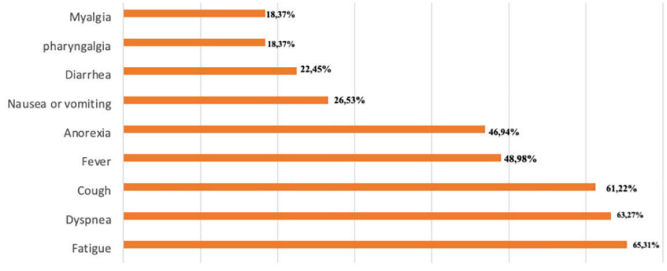

Figure 1 - Symptoms in patients with diabetes mellitus

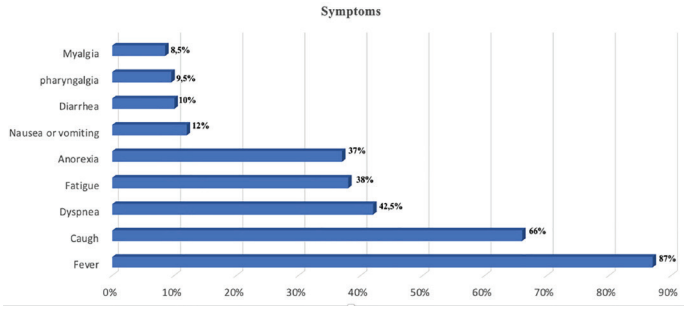

Figure 2 - Symptoms in patients without diabetes mellitus

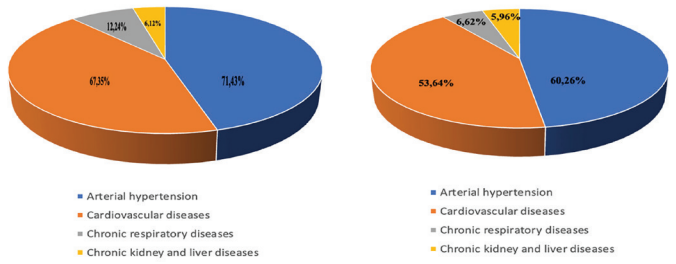

Figure 3 - Concomitant diseases in patients

Most of the available evidence suggests a significant increase in severity and mortality from COVID-19 in people with type 2 diabetes mellitus, especially when combined with poor glycemic control [9]. In recent years, both in Kazakhstan and abroad, there has been a sharp increase in the incidence of diabetes mellitus, especially in industrialized countries, where its prevalence is 5-6% and tends to increase further, primarily in age groups older than 40 years [10]. Many studies have shown that aging is one of the important risk factors affecting the prognosis of COVID-19 [11]. Thus, a large number of elderly patients in the group of diabetes mellitus may indicate a poor clinical outcome. In this study, arterial hypertension was more often detected in patients with diabetes mellitus (71%) (Figure 3). And also, according to the severity of the condition, patients with diabetes mellitus had a severe infection (73%).

Recent data have shown that COVID-19 patients with diabetes had lower lymphocyte counts and higher neutrophil counts compared with COVID-19 patients without diabetes [12]. Upon admission, many patients had a tendency to lymphopenia (1.04) (Table 1), elevated levels of infection-related biomarkers (C-reactive protein (34.5) and procalcitonin (0.8)) and relatively high levels of neutrophils (7.92), alanine aminotransferase (46), total bilirubin (9.7), albumin (36.0), blood urea nitrogen (6), serum creatinine (70), cardiac troponin (0.012) and D-dimer (0.41) (Table 2). Patients with COVID-19 are more likely to have lymphopenia, but thrombocytopenia and leukopenia are relatively rare. In patients with diabetes mellitus, especially with severe conditions, the levels of serum biomarkers of inflammation, such as interleukin-6, C-reactive protein and procalcitonin, are significantly increased, and these indicators are predictors of an unfavorable prognosis of COVID-19 (Table 1) The D-dimer is a product of fibrin degradation and is one of the main markers coagulation activity [13]. High concentration of serum D-dimer is closely associated with various thrombotic diseases, including myocardial infarction, cerebral infarction, pulmonary embolism and venous thrombosis [13]. In our study, we found that the concentration of serum D-dimer in patients with diabetes was significantly higher than in patients without diabetes mellitus, indicating that patients with COVID-19 with diabetes are more likely to develop a hypercoagulated prothrombotic condition.

It is safe to say that there is still no evidence that antiviral treatment can significantly improve the condition of patients with COVID-19 [14]. Most patients received only such types of treatment as oxygen therapy, infusion therapy and respiratory support. Some patients received antibiotics, corticosteroids. Critically the patients needed observation and artificial lung ventilation in the intensive care unit. In our study, diabetic patients were more likely to receive hormone therapy and artificial lung ventilation than patients without diabetes, which indicates that diabetic patients have more severe complications and require more complex therapy.

Table 1 The main demographic indicators of patients

Gender / Age	Overall (n=200)	Patients with diabetes mellitus (n=49)	Patients without diabetes mellitus (n=151)
Female	108/200 (54%)	29/49 (59,18%)	79/108 (73,15%)
Male	92/200 (46%)	20/49 (40,82%)	72/92 (78,26%)

Table 2 Blood test

Blood cells	Normal range	Overall(n=200)	Patients with diabetes mellitus (n=49)	Patients without diabetes mellitus (n=151)
Leukocytes, x 109/l	3,5-9,5	5	6,85	5,35
Neutrophils, x 109/l	1,8-6,3	3	7.92	2
Lymphocytes x 109/l	1,1-3,2	1,5	1,04	4,8
Platelets x 109/l	125-350	196	190	193
Hemoglobin x 109/l	130-175	127	126	127 (116, 137)
Alanine aminotransferase, IU/l	9-50	26 (13, 35)	46 (16, 50.5)	22 (13, 35)
Aspartate Aminotransferase, IU/l	15-40	27 (18, 38)	26 (21, 38,5)	25 (18, 38)
Total bilirubin, mmol/l	2-23	8 (5.7, 11)	9.7 (7.4, 13.05)	7.5(5.5, 10.7)
Albumin, g/l	40-55	37 (33.3, 41.5)	36,0 (30.9, 41.5)	37.)(33.7, 41.5)
Blood urea nitrogen, mmol/l	3,6-9,5	4.38 (3.43, 5.79)	6 (3.68, 6.59)	4.3 (3.41, 5.61)
Serum creatinine, mmol/l	57-111	64(53. 74)	70 (55, 79.5)	63 (52.7, 73)
Cardiac troponin, ng/ml	0-0,014	0,008 (0.006, 0.014)	0.012 (0.008, 0.028)	0.008 (0.005. 0.013)

Biomarkers associated with infection. Blood clotting function	Normal range	Overall(n=200).	Patients with diabetes mellitus (n=49)	Patients without diabetes mellitus (n=49)
C-reactive protein, mg/l	0-3	18 (2.3, 57.4)	34,5 (6.1, 84.3)	16 (2.0, 51.7)
Procalcitonin, ng/ml	0-0,1	0.05 (0.03, 0.013)	0.8 (0.04, 00.23)	0.05 (0.03, 0.11)
prothrombin time, s	9,3-12,9	12.3 (85, 13.62)	12,98 (11.6, 13.62)	12.3(11.5, 13.2)
D-dimer, µg/l	0,-0,243	0.21 (0.10, 0.61)	0.41 (0.13, 1,06)	0.19 (0.09, 0.52)

According to the results of this study, the main cause of death of patients with COVID-19 was the development of complications — the simultaneous development of ARDS (48.98%) and the development of sepsis (4.08%), acute renal failure with a combination (6.12%) with thrombotic complications (38.78%). The results obtained by us are generally consistent with the results of data from foreign studies, which the main causes of death of patients with COVID-19 were sepsis, ARDS, acute renal failure and cardiovascular complications [15].

Conclusion

The retrospective analysis made it possible to evaluate the factors associated with deaths in patients with COVID-19 both without DM2 and with concomitant DM2. These factors include age >60 years, hyperglycemia and hypoglycemia, the presence of concomitant disease, the development of complications. The results of this retrospective analysis are consistent with previously published data, but further studies are needed to assess outcomes depending on clinical and laboratory parameters, the presence of a comorbid background and complications of COVID-19. It should also be noted that the two-way interaction between COVID-19 and diabetes mellitus creates a vicious circle in which COVID-19 leads to worsening of dysglycemia, and diabetes mellitus, in turn, exacerbates the severity of COVID-19. Thus, it is very important that patients with diabetes mellitus take all necessary preventive measures and ensure good glycemic control in a pandemic.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

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JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/12897

Informed consent research at a tertiary hospital: How impactful is competency in simpler versus standard consent forms for intravitreal injection therapy?

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Received: 2022-12-05.
Accepted: 2022-12-24

J Clin Med Kaz 2023; 20(1):18-23

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Abstract

Aim: To compare the impact of competency in intravitreal injection therapy (IVIT)-related simpler versus standard consent forms (CFs).

Material and methods: Four hundred patients scheduled for IVIT in a tertiary hospital were enrolled between April 1, 2022 and June 30, 2022. These patients were eligible for the study if they had their first IVIT in one eye; those scheduled for IVIT in the other eye were not. Data, including age, gender, educational level, whether the patient was admitted alone or with a companion, and prior IVIT status were collected. A trained clinic secretary first gave the patients the commonly used standard CFs, followed by simpler CFs.

Results: The mean age was 66.10±9.90 years. 93.80% had previously received IVIT. 53.80% of the patients consented on their own. While 98.00% consented without reading standard CFs, 56.00% consented after reading simpler CFs ($p<0.001$). The need for IVIT-related extra information and the desire against having IVIT were significantly higher in simpler than standard CFs ($p<0.001$). 5.00% of those who approved IVIT without reading both forms were illiterate, and 29.20% had vision issues. The probability of simpler CF reading increased by 4.653 and 7.510 times in high school and university graduates, respectively, relative to primary school graduates.

Conclusion: Simpler CFs had a much higher reading rate, which was linked to a higher rate of patients opting against IVIT. In medical fields like ophthalmology, where many procedures and research are performed, ethically approved informed consent requires consideration of patients' education and prior treatment experience.

Key words: consent forms, educational level, ethics, intravitreal injection therapy, readability

Introduction

Informed consent is not only a legal requirement. It also entails a moral and ethical obligation to safeguard a patient's right to shared decision making. This procedure refers to a discussion between patients, physicians, and/or researchers that ultimately results in the patient's approval to undergo a specific therapeutic procedure or participate in a clinical research [1]. In clinics, consent forms (CFs) are frequently not clearly prepared. This is primarily due to the fact that researchers, physicians, and consenting patients frequently regard these documents as an unnecessary procedural component. These forms are typically prepared by physicians performing a specific procedure to fulfill their legal responsibilities, and hence signing the CFs by patients may absolve the physician from legal liability. Nonetheless, preparing an insufficiently appropriate CF indicates a failure to meet ethical responsibilities. What is legal is not always

what is ethical, and physicians must abide by both the law and professional ethics principles [2-4].

In clinical studies and before any therapeutic interventional procedure, obtaining informed consent is critical. Nevertheless, it has always been questioned whether or not the procedures is totally understood by patients. The patients' competence, the amount of information and understanding they require, and, most importantly, whether they truly and voluntarily consent to the procedure have long been contested [5]. The possibility that patients were not adequately informed about the procedure before participating in a study or having a therapeutic procedure could have serious ethical ramifications. Given the lower educational level (EL), particularly in developing countries, CFs should be prepared in much clearer and more readable language, and the informed consent process should be handled much more delicately [6,7]. The term *"readability"* is used to describe the EL for which a particular text is written. Consent forms should be written in a way that low-education patients can easily read and understand [8].

Intravitreal injection therapy (IVIT) is a common interventional procedure performed in ophthalmology clinics for different indications, including age-related macular degeneration (AMD) [9], retinal vein occlusion (RVO) [10], diabetic retinopathy (DR) [11], etc. Around 170 million people worldwide suffer from AMD-related vision loss, with that figure expected to rise to 288 million by 2050 [12,13]. It is estimated that 28 million people worldwide suffer from RVO [10]. Besides, a global prevalence of DR is expected to reach 191 million by 2030 [11]. Intravitreal injection therapy is also used to treat cystoid macular edema secondary to uveitis, Irvine-Gass syndrome, and retinitis pigmentosa [14-16].

The current study sought to determine the impact of competency in IVIT-related simpler versus standard CFs. In this context, the rate of reading simpler CFs prepared according to lower EL, the relationship of EL with CF reading behaviors, and the impact of simpler CFs on the decision-making behavior of the patients were compared to standard CFs.

Material and methods

This single-centered comparative study enrolled 400 patients who were recommended for IVIT after being examined in a tertiary hospital at the Afyonkarahisar Health Sciences University Faculty of Medicine Department of ophthalmology between April 1, 2022 and June 30, 2022. The study protocol adhered to the Declaration of Helsinki's ethical principles and received full approval from the institutional review boards of Afyonkarahisar Health Sciences University Ethics Committee with approval ID: 2022/278. All patients who agreed to take part in the study were informed about it and consented.

The patients were eligible for the study if they received IVIT for the first time in one eye. Those who were scheduled for IVIT in the contralateral eye were not included in the study again. Demographic details such as age, gender, and EL were collected, as well as whether the patient was admitted to the hospital alone or with a companion. In cases where there were companions, their closeness to the patient was determined. After determining whether the companion was the participant's child, spouse, distant relative, or caregiver, the data was divided into subgroups for descriptive statistics. Participants were also asked if they had received IVIT at another medical facility.

Intravitreal injection therapy-related standard CFs, which are routinely used in our ophthalmology clinic, were analyzed using the Bezirci-Yilmaz [17] and Ateşman [18] readability formulas, which have been proved to be reliable for Turkish, the local language in which the form was prepared. As a result, the Bezirci-Yilmaz readability formula yielded a readability with the EL of approximately 13 years, while the Ateşman readability formula yielded a readability with the EL of approximately associate degree level (13-14-15 years). On the other hand, the Bezirci-Yilmaz and Ateşman readability formulas determined that the new, simpler CFs in an easier-to-read format for the patients were readable with 7 years and 9-10 years of ELs, respectively.

At first, a trained clinic secretary distributed the commonly used standard CFs to the patients under the direction of an experienced ophthalmologist (HHG). This was followed by determining whether the patients had completely read CFs and confirming once more by asking whether they had read CFs immediately after signing the forms. Simpler CFs were then distributed to patients and/or companions. In the event that the companions read CFs, they were also asked about their EL, and the data was recorded. Testing was performed to determine whether simpler CFs were completely read, and again, confirmation of the reading was performed after signing the forms. After reading simpler CFs, patients were divided into three groups: a) those who approved the IVIT, b) those who needed IVIT-related extra information before approving, and c) those who decided against IVIT. Analysis was then performed in conjunction with the demographic characteristics of the patients.

Statistical analysis

Statistical analysis was carried out using Predictive Analytics SoftWare (PAWS) Statistics version 18 (SPSS Inc., version 18.0, Chicago, IL, USA). Categorical variables were represented as percentages and frequencies in the descriptive statistics results, while continuous variables were represented as mean and standard deviation. To compare categorical variables in independent groups, the Chi-Square and Fisher Exact tests were used; in dependent groups, the McNemar test was used. Univariate and Multivariate Logistic Regression tests were used to evaluate variables that had statistically significant differences. The results of logistic regression were presented as odds ratios (OR) and 95% confidence intervals (95% CI). A $p<0.05$ was accepted as the statistical significance level.

Results

The study included 400 patients, with females accounting for 51.00%. The mean age was 66.10±9.90 years with 53.80% of the patients being over 65.70% had primary school education. Over 93% had previously received IVIT. The majority of patients (53.80%) were found to be alone while consenting. 56.5% of those who signed CFs had primary school education. Table 1 summarizes the patients' demographic characteristics.

In terms of standard CF reading rates, 98.00% consented without even reading CFs, and only 2.00 % read them completely. Simpler CFs, on the other hand, were read completely by 56.00%, and partially by 4.50% of the participants who were evaluated alongside those who did not read CFs at all. A comparison of standard CF reading rates with those of simpler CFs revealed that the latter were associated with statistically significantly higher reading rates ($p<0.001$) (Table 2).

Standard CFs were read significantly more frequently by the first IVIT recipients (16%) than by prior IVIT recipients (1.10%) ($p=0.001$). Simpler CFs had higher reading rates in both groups, with first IVIT recipients having the highest reading rates (68.00%) compared to prior IVIT recipients (52.20%),

Table 1 Demographic characteristics of the patients receiving IVIT

Parameters	*n (%)*
Educational level	
Illiterate	42 (10.50)
Literate	11 (2.70)
Primary school	280 (70.00)
High school	35 (8.80)
University	32 (8.00)
Signers	
Him/herself	215 (53.80)
Children (Son, Daughter)	92 (23.00)
Spouse	48 (12.00)
Others	45 (11.20)
Educational level of the signers	
Illiterate	20 (5.00)
Literate	2 (0.50)
Primary school	226 (56.50)
High school	74 (18.50)
University	78 (19.50)
First time IVIT	
Yes	25 (6.20)
No	375 (93.80)

n: Number of participants, %: Percent, IVIT: Intravitreal injection therapy

though this difference was not statistically significant (p=0.212). 83.00% of those who read simpler CFs changed their prior consent decisions for the procedure and eventually approved it. However, before approving, 15.60% asked IVIT-related extra questions. 1.30% decided against having IVIT. Compared to standard CF readers, the need for IVIT-related extra information and the desire against having IVIT were found to be statistically significant based on simpler CFs (p<0.001) (Table 3).

5.00% of the patients who consented to IVIT without reading both forms were illiterate, and 29.20% had vision problems that made it difficult to see clearly. Thus, both of these variables were identified as absolute risk factors for failing to read CFs. After excluding 137 patients, logistic regression analysis was performed, taking into account their ELs and prior IVITs. In comparison to primary school graduates, the likelihood of simpler CF reading increased by 4.653 times in high school graduates and 7.510 times in university graduates. Receiving IVIT for the first time was found to be a non-significant factor. The likelihood of reading simpler CFs increased 4.652 times in high school graduates and 7.536 times in university graduates, according to multivariate logistic regression analysis, and receiving the IVIT for the first time was revealed to be a non-significant factor once more (Table 4).

Table 2 Comparative analysis of the respective CF reading rates among patients receiving IVIT

		Simpler CFs		Total n, (%)	P value
		Didn't read, n (%)	Read, n (%)		
Standard CFs	Didn't read, n (%)	176 (44.00)	216 (54.00)	392 (98.00)	<0.001
	Read, n (%)	0 (0)	8 (2.00)	8 (2.00)	
Total n, (%)		176 (44.00)	224 (56.00)	400 (100.00)	

n: Number of participants, %: Percent, IVIT: Intravitreal injection therapy, CF: Consent form

Table 3 Comparative analysis the patients' pre-IVIT preferences based on simpler CFs

	Simpler CFs		Total n, (%)	P value
	Didn't read, n (%)	Read, n (%)		
Decided against IVIT	0 (0.0)	3 (1.3)	3 (0.8)	<0.001
Asked extra questions, approved	0 (0.0)	35 (15.6)	35 (8.8)	
Approved without asking	176 (100.0)	186 (83.0)	362 (90.5)	
Total n, (%)	176 (100.0)	224 (100.0)	400 (100.0)	

n: Number of participants, %: Percent, IVIT: Intravitreal injection therapy, CF: Consent form

Table 4 Analysis of simpler CFs based on ELs in first-time and multiple IVIT recipients using logistic regression

	B	SE	Wald	P value	OR	95% CI for OR	
						Lower	Upper
Univariate							
Primary school*							
High school	1538	0.556	7.65	0.006	4.653	1.565	13.833
University	2.016	0.624	10.443	0.001	7.510	2.211	25.512
First-time IVIT**	0.545	0.441	1.526	0.217	1.725	0.726	4.094
Multivariate							
Primary school*			16.206	<0001			
High school	1.537	0.556	7.647	0.006	4.652	1.565	13.829
University	2.020	0.624	10.464	0.001	7.536	2.216	25.620
First-time IVIT*	-0.110	0.682	0.026	0.872	0.896	0.235	3.409

**Taken as a reference, ** Multiple IVITs were taken as reference, IVIT: Intravitreal injection therapy, CF: Consent form, EL: Educational level, SE: Standard error, OR: Odds ratio, CI: Confidence of interval*

Discussion

Informed consent has a long history in different fields, including medicine, moral philosophy, and the law. It is inextricably linked to philosophical ideas such as personhood and individual self-determination [19-21]. In daily clinical practice, having obtained patient informed consent is highly essential. Informed consent in human research, on the other hand, presents a unique set of challenges, almost always as a result of the study design regarding specific interventional procedure. Patients should completely understand the procedure during informed consent process, which is an ethically acceptable principle that applies to both clinical interventional procedures and research. This is because, in order to participate in any research or therapy, patients must make conscious decisions based on rational information. Consent forms should be composed in such a way that participants can easily read and comprehend the entire procedure, including all potential risks [2-4]. As CFs have profound and beneficial practical and moral implications for clinical practice, the risk-management elements of CFs should not be underestimated. In terms of ethics, a physician's responsibility to disclose is more of a necessity for individual autonomy than the primary goal of CFs [21].

In the ophthalmology field, as in all other medical fields, an appropriate informed consent process is required before any particular research or therapy. It is widely accepted that when an individual signs CF, he or she is indicating acceptance. Signing CF without being extensively informed about a particular research or therapy, on the other hand, does not imply that an individual voluntarily and truly consents, nor does it mean that ethical responsibilities have been fulfilled [22]. This condition was essentially evidenced in the current study, which found that, when compared to standard CFs commonly used in clinical practice, the simpler and more understandable the CFs, the higher the rate of reading and, as a result, the higher the rate of decision against IVIT among patients who were recommended for this therapy. Moreover, patients who are receiving multiple doses of the same therapy are more likely to voluntarily consent without even reading CFs repeatedly. This was also the case in the current study, which found that patients who received multiple IVITs were less likely to read simpler CFs. Despite this, the logistic regression analysis determined that the condition was not significant and that the patients' EL and CF readings were closely related.

Five components of valid informed consent are voluntarism, capacity, disclosure, comprehension, and decision [23]. Patients must be free of "coercion, unfair persuasions, and inducements" in order to be voluntary participants [24]. The ability of a patient to make health-care decisions is described as *capacity*. A related concept is *competence*, which refers to the patient's legal standing to make health-care decisions. *Disclosure* entails providing a patient with comprehensive information about a specific therapeutic procedure, including its goal and basic features, in addition to its risks, potential benefits, and available options. Despite the fact that there is barely any agreement in law or ethics concerning what constitutes adequate *understanding*, this condition necessitates that the patient comprehend the information provided and recognize its applicability to his or her specific situation. The term *decision* refers to the patient's permission for the specific therapy to be performed by a physician [19,23]. Although CFs aid in the facilitation and documentation of this permission, they should be perceived as supplementary to the process by which the patient and researcher or physician talk and negotiate the particular research or therapy.

As far as EL was concerned, the current study revealed that the majority of EL among patients was primary school education, which was also found in more than 56.00% of CF signers. High school education increased the likelihood of simpler CF reading by 4.653 times relative to primary school education, while university education increased it by 7.510 times. Furthermore, 5.00% of the patients who consented to IVIT without reading both CFs were illiterate, and more than 29.00% had vision issues that made it impossible for them to read CFs. All of these patients stated that they had previously undergone IVIT; however, it is unclear whether they had companions to assist them with CF reading and comprehension during prior IVITs. As explained previously [23], whether or not these patients have previously undergone the same procedure, there may be ethical implications to performing an interventional procedure based on informed consent without the opportunity to extensively read and understand CFs.

It is reasonable to anticipate that the patients' visual acuity will be inadequate, particularly before undergoing ophthalmological interventional procedures. If necessary, larger-font CFs could be ethically useful for these patients. Fundamentally, patients have the right to be informed about all IVIT-related risks [9,23], so alternative measures that leverage current technological advancements should be considered for patients with vision issues. For conditions where hearing is not an issue, the written consent text could be presented as an audio recording. Likewise, obtaining an informed CF before cataract surgery using video has been shown to increase patient satisfaction while also shortening the consent process [25]. In the event that these resources aren't available, the importance of preparing CFs in a more readable and understandable manner increases dramatically.

The fact that CFs are usually not read carefully enough, or that patients who do read the form completely are unaware of the IVIT-related risks, appears to be a point of contention in the medical community. One study found that 69.00% of patients who received IVIT were unaware that endophthalmitis could develop secondary to the procedure [26]. Endophthalmitis, one of the most serious IVIT-associated complications, may be unknown to the patients on whom the procedure will be performed, which could be an ethically unacceptable situation. Another study found that converting CFs that could be read with an average of ten-year education into CFs that could be read with a seven-year education increased reading by about 6.5 times [27]. Likewise, in the current study, simpler CFs that could be read with an eight-year education were prepared to replace standard CFs commonly used in clinical practice that could be read with a 16-year education, and the former were eventually found to be associated with a 28-fold higher reading rate. It should be noted that the patients' attention might have been drawn in this direction while simpler CFs were being distributed, which could explain the significantly increased CF reading rate. This is possible despite the fact that no instructions were provided during the consent process, which could have influenced their reading behaviors and, as a result, the IVIT-related final decisions. Attempts should be made during the informed consent process to reduce patients' therapeutic misunderstanding.

The current study does have some limitations. The time required for the entire IVIT-related consent process was not considered because all participants were not given a time limit to make their final decision with respect to this therapy. Giving patients more time to consider participating has been linked to a significantly increased patient comprehension [28].

The experienced ophthalmologist oversaw the distribution of CFs by a trained clinic secretary. Regardless, discrepancies in CF distribution between the earlier and later learning periods of the study could have contributed to data bias. Essentially, informed consent is inextricably linked to the deontological concept of personhood; however, it also serves a critical and positive contribution to medicine. This can lead to improved patient-physician interactions, the physician having a better understanding of the patient's disease, and the patient complying to therapy. Nonetheless, the informed consent framework has some flaws that should be addressed. Even though informed consent improves physician-patient interaction and decision-making, it cannot foster autonomy when such options are unavailable. Additionally, since informed consent evolved in a particular societal perspective, it may not be universally applicable to all societies or cultures [29].

In comparison to past studies on informed consent process, the current study has a great advantage in that it included a significantly larger number of patients. Consequently, it provides clinically useful evidence-based findings from an ethical perspective that extends beyond the field of ophthalmology. It also paves the way for large-scale multi-racial and multi-lingual studies to investigate this extremely sensitive subject when it comes to fully reading and comprehending CF before participating in any research or therapy.

Conclusively, simpler CFs had a much higher reading rate, which was associated with a higher rate of decision against IVIT among patients recommended for this therapy. Patients who had previously received IVIT had a lower probability of reading simpler CFs. Despite having previously undergone the same procedure, there may be ethical implications in performing an interventional procedure based on informed consent without the opportunity to thoroughly read and understand CFs. In medical fields such as ophthalmology, where many interventional procedures and clinical research are performed, obtaining CFs in accordance with ethical principles is critical, especially when patients' ELs and prior treatment experience are considered.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

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JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/12904

Comparison of direct low density lipoprotein cholesterol measurement with the Friedewald formula and alternative formulas

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Received: 2022-10-21.
Accepted: 2022-12-24

J Clin Med Kaz 2023; 20(1):24-30

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Abstract

Aim: Our aim was to compare the direct enzymatic measurement with four formulas which are used in determining the value of low density lipoprotein cholesterol (LDL-C) levels.

Material and methods: A total of 33842 patients' files were retrospectively reviewed and data was collected. Triglyceride (TG) group 1, 2, 3, 4 and 5 were consisted of TG levels ≤99 mg/dl, 100-199 mg/dl, 200-299 mg/dl, 300-399 mg/dl and ≥ 400 mg/dl, respectively. LDL-Group 1, 2, 3, 4 and 5 were composed of LDL-C≤100 mg/dl, 101-130 mg/dl, 131-160 mg/dl, 160-190 mg/dl and >190 mg/dl, respectively.

Results: All formulas tended to undervalue LDL-C concentrations compared to direct method (p<0.001 for all). The Chen formula had higher degree of correlation compared to other formulas. Acceptable result of Friedewald formula was 53.77%, Chen formula was 62.72%, Hattori formula was 24.72, and Anandaraja formula was 45.98%. Bland-Altman plot results showed disagreement of four formulas with significant proportional and systematic bias compared to direct method. There was no agreement of calculated LDL-C with direct LDL-C when the data was subgrouped according to TG levels. No agreement between direct LDL-C and calculated LDL-C was found. Correlation analysis showed moderate to high level of correlation for Friedewald, Chen, and Hattori calculations, whereas Anandaraja formula showed low to moderate correlation. The Friedewald and Anandaraja formulas mostly misclassified LDL-Group 3 subjects, whereas the Chen and Hattori formulas mostly misclassified LDL-Group 4 subjects.

Conclusion: The Chen formula might be an acceptable alternative of the Friedewald formula and other formulas.

Key words: lipids, laboratory methods, cardiology

Introduction

Low density lipoprotein cholesterol (LDL-C) is complicit in the pathophysiology of atherosclerotic coronary artery disease (CAD). LDL-C lowering therapy has been a major target both in the treatment and follow-up of patients with hyperlipidemia and CAD. Current cardiac guidelines highlight the importance of achieving and maintaining recommended LDL concentrations based on cardiovascular risk exposure. National Cholesterol Education Programme (NCEP) Working Group advocates that the total analytical error of LDL-C measurement should be within ±12% [1]. Hence accurate estimation of LDL-C levels is crucial.

Ultracentrifugation followed by beta-quantification

is the best method for measuring LDL-C levels. However, it is expensive, laborious and requires skilled staff which makes it difficult for them to use in most clinical laboratories [2]. In addition homogenous direct methods are used to measure cholesterol from LDL fraction [3]. But these methods are also expensive and not readily available in most laboratories. Therefore indirect calculation of LDL-C levels from other lipid parameters is more practical approach in daily practice. The Friedewald formula continues to be the most frequently used method in clinical settings. This formula assumes a fixed factor of 5 for triglyceride (TG) to very low density lipoprotein cholesterol (VLDL-C) ratio and its use is limited in patients who had TG > 400 mg/dl, diabetes mellitus, nephrotic syndrome, and alcoholism [4,5]. This formula does not take in account inter-individual variability in TG to VLDL-C ratio. Lipid Research Clinics Prevalence study demonstrated that TG to VLDL-C ratio range from 5.2 to 8.9 [6]. It has been shown that Friedwald formula underestimates LDL-C levels by 8% in diabetic patients. Another drawback of Friedwald formula is that it needs fasting in order to calculate LDL-C levels since nonfasting status leads to underestimation of LDL-C levels. If TG levels are greater than 150 mg/dL, the formula commonly calculates LDL-C levels less than 70 mg/dL, despite directly measured levels of greater than 70 mg/dL [2]. In the era when the Friedewald equation was proposed, an LDL-C ≤70 mg/dL was not yet established as an ideal secondary prevention target for the treatment of high-risk patients. As such, Friedewald formula could lead to misclassification of the patients [7]. In order to circumvent the limitations of the Friedewald formula, several other formulas have been proposed with different results in different populations. In this study direct enzymatic measurement of LDL-C levels was compared with measurements using four different formulas that are used in determining the value of LDL-C levels.

Material and methods

This was a retrospective comparative study which compares direct method of LDL-C measurement with 4 different formulas. It was conducted in a tertiary hospital and the data regarding patient's biochemical variables was obtained from hospital database system which was screened between January 2016 and January 2018. Ethical approval was obtained from Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Education Hospital ethical committee and it was carried out in conformity with the Declaration of Helsinki. A total of 33842 patients were included in the study. Mean age of the study population was 53.23±14.35 years, 18816 (55.6%) of them were female, 15026 (44.4%) of them were male. Patients with hepatic/renal failure, ischemic heart disease, stroke, heart failure, diabetes mellitus, malignancy, thyroid function abnormalities, high density lipoprotein cholesterol (HDL-C) < 20 mg/dl were excluded. After overnight fast venous blood samples were drawn from the patients. All measurements were done by using Roche/Hitachi Cobas c 501 auto analyzer system (Roche Diagnostics catalog number: 07005717 system ID 07 7565 7.). A homogeneous enzymatic colorimetric assay was used to measure direct LDL-C. This automated direct estimation of LDL-C based on micellar solubility of LDL-C with nonionic detergent and interaction of a sugar compound and lipoproteins. For the assessment of cholesterol in lipoprotein subgroups, cholesterol esterase/cholesterol oxidase linking reaction was conducted. This analysis met the NCEP criteria in terms of precision, accuracy. And total analytical error was less than 12 %. TG level evaluated by lipoprotein lipase.

LDL-C levels were measured by four different calculations including Friedewald, Chen, Hattori, and Anandaraja formulas. Calculation of LDL-C for each formula were as follows:

Friedewald formula: LDL-C (mg/dL) = Total cholesterol (TC) -HDL-C -TG/5

Chen formula: LDL-C (mg/dL) = (TC-HDL) x 90 TG×%10

Hattori formula: LDL-C(mg/dL) = 0.94x TC-0.94 ×HDL -0.91 × TG

Anandaraja formula: LDL-C (mg/dl) = 0.9 x TC - 0.9xTG/5 – 28

Since Friedewald formula has acceptable accuracy when LDL-C is average and TG levels are not elevated, we divided patients according to their TG and LDL-C levels [8]. Data were splitted into 5 groups according to TG levels. TG group 1, 2,3,4 and 5 were consisted of TG levels ≤99 mg/dl, 100-199 mg/dl, 200-299 mg/dl, 300-399 mg/dl and ≥ 400 mg/dl, respectively. Subjects were also split into five groups according to their LDL-C levels: LDL-Group 1, 2, 3, 4 and 5 were composed of LDL-C≤100 mg/dl, 101-130 mg/dl, 131-160 mg/dl, 160-190 mg/dl and >190 mg/dl, respectively. For each group, calculated LDL-C was compared with direct method. In addition, misclassification percentages of LDL-C levels were also calculated. Each LDL-Group was further analysed according to TG concentrations: TG concentrations less than 200 mg/dl (n=25357), TG concentrations between 200-400 (n=7715), and TG concentrations higher than 400 mg/dl (n=770). If the difference between calculated and direct LDL-C concentration fell into range of ±10 mg/dl, that was described as an acceptable result. Acceptable result of each formula was also calculated. Flowchart of the study is shown in Figure 1.

Statistics

Normality of the data was assessed by Kolmogorow-Smirnow test. Normally and non-normally distributed data were expressed as mean±SD and median-IQR, respectively. For the comparison of two groups Mann-Whitney U test was used. Correlation analysis was done by Spearman Correlation analysis. In order to assess agreement of two methods, Bland Altman plot analysis was done. Analyses were done by using MedCalc Statistical Software version 12.7.7 programme.

Results

Average age of the study population was 54.27+13.09 years, 15183 (44.9%) of them were male and 18659 (55.1%) were female. The mean LDL-C concentration value via direct measurement was 128.43±31.46 mg/dl, TC levels were 199.86±37.68 mg/dl, TG levels were 170.82±83 mg/dl. Most of the subjects had LDL-C values between 100-130 mg/dl (32.8%). Males had significantly higher levels of LDL-C levels in contrast to females (129.92±31.01 mg/dl vs 126.59±31.90 mg/, p<0.001). A comparison analysis showed that all formulas tended to undervalue LDL-C concentration compared to direct method (p<0.001 for all). Mean differences between direct method and the Friedewald, Chen, Hattori, and Anandaraja formulas were 9.22±16.19 mg/dl, 7.47±13.42 mg/dl, 16.71±15.65 mg/dl and 7.31±18.15 mg/dl, respectively. Mean percentage change of LDL-C levels between calculated and direct methods were -7.22±14.17%, -5.37±11.73%, -13.06±13.38%, -5.12±15.69% for the Friedewald, Chen, Hattori, and Anandaraja formulas, respectively. Correlation analysis showed that the Chen formula had higher degree of correlation compared to other formulas. Biochemical results and correlation analysis of the calculated and direct LDL-C are shown in Table 1. Bland-Altman plot results showed disagreement of four formulas with significant proportional and systematic bias compared to direct method (Table 2, Figure 2). There were no agreement of calculated LDL-C with direct LDL-C when the data was subgrouped

Table 1 Biochemical parameters of the patients.

		TG Group 1 TG≤99 mg/dl (n=3888)	TG Group 2 100-199 mg/dl (n=21469)	TG Group 3 200-299 mg/dl (n=6146)	TG Group 4 300-399 mg/dl (n=1565)	TG Group 5 ≥400 mg/dl (n=774)
Age (years)	55 (18-97)	54 (18-93)	55 (18-97)	54 (18-92	53 (19-92)	53(19-86)
TC (mg/dl)	199 (81-379.6)	181(81-289)	196(84-304)	211(101-319)	223(120-305)	240(151-379.6)
TG (mg/dl)	148 (87-985)	93(87-99.9)	138(100-99,9)	233(200-299.8)	335(300-399)	474(400.1-985)
HDL-C (mg/dl)	45 (30-108)	43(30-105)	44.4(30-108)	46(30-104)	46(30-92.30)	47(30-93)
LDL-C (mg/dl)	128 (35-200)	84(35-100.3)	122.5(71-160.3)	162(130.9-200)	174(118.11-200)	175(160.6-200)
F-LDL-C (mg/dl)	(16.6-216.12)	75.6(16.6-211.8)	113.6(17-215)	150.6(17.6-216.1)	162.4(21.4-214)	165.3(36.8-214.6)
Direct-Friedewald						
difference	9.22±16.19	6.17±15.77	8.82±15.48	10.33±15.85	16.91±23.15	11.24±17.56
r**	0.886	0.767	0.817	0.815	0.553	0.593
C-LDL-C (mg/dl)	(24.4-210.06)	80.2(24.4-199.9)	115.4(25.7-207.9)	150.8(26.7-210.0)	161(38.7-200.6)	163(61.9-208)
Direct- Chen						
difference	7.47±13.42	1.8±13.25	6.79±12.49	10.40±12.54	17.19±19.49	12.15±13.94
r**	0.913	0.819	0.861	0.868	0.657	0.688
H-LDL-C (mg/dl)	111.34 (14.9-202.9)	70.75(15.17-198.86)	106.42(14.89-201.85)	141.13(15.89-202.89)	152.34(19.42-200.96)	154.93(33.81-201.39)
Direct-Hattori						
difference	16.71±15.65	10.95±14.98	15.97±14.77	19.76±15.03	26.85±21.87	21.49±16.64
r**	0.885	0.765	0.815	0.813	0.550	0.590
A-HDL-C (mg/dl)	120.68(22.94-215.36)	79.64(23.66-213.56)	116(22.94-215)	150.15(25.64-215)	161(36.8-214.28)	164(36.6-215.36)
Direct-Anandaraja						
Difference	7.31±18.15	1.09±17.42	6.45±17.43	10.90±17.50	17.90±23.20	12.24±19.16
r**	0.842	0.658	0.736	0.739	0.472	0.509

** All correlations are significant at the 0.01 level (2-tailed). TC: Total Cholesterol, TG: Triglyceride, HDL-C: High density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, F-LDL-C: Friedewald low density lipoprotein cholesterol, C-LDL-C: Chen low density lipoprotein cholesterol, H-LDL-C: Hattori low density lipoprotein cholesterol, A-LDL-C: Anandaraja low density lipoprotein cholesterol

Table 2 Bland-Altman plot results of the four formulas.

	Mean	Upper limit	Lower limit	p
Friedewald	9.22	40.97	-22.52	<0.0001
Chen	7.47	33.79	-18.83	<0.0001
Hattori	16.71	47.39	-13.95	<0.0001
Anandaraja	7.31	42.89	-28.28	<0.0001

Table 4 Misclassification of subjects according to calculated LDL-C values.

	Friedewald	Chen	Hattori	Anandaraja
LDL Group 1 (%)	6.3	6.73	3.89	15.90
LDL Group 2 (%)	33.67	24.05	49.28	38.65
Underclassified	28.61	19.97	47.01	26.66
Overclassified	5.06	4.08	2.27	11.99
LDL Group 3 (%)	39.60	34.74	60.98	45.20
Underclassified	35.64	32.41	59.84	37.54
Overclassified	3.96	2.33	1.14	7.66
LDL Group 4 (%)	46.1	45.4	69.6	53.3
Underclassified	42.5	44.3	69.1	47.7
Overclassified	3.6	1.1	0.5	5.6
LDL Group 5 (%)	64.6	77.4	91.0	69.8

LDL-C: low density lipoprotein cholesterol.

according to TG levels (Bland-Altman p value <0.0001, for all). All formulas underestimated LDL-C concentration in all TG groups. Acceptable result of the Friedewald formula was 53.77%, the Chen formula was 62.72%, the Hattori formula was 24.72, and the Anandaraja formula was 45.98%.

We analyzed data according to LDL-C levels in order to evaluate whether there were an agreement between calculated and directly measured LDL-C levels. There were no agreement between direct LDL-C and calculated LDL-C by four formulas.

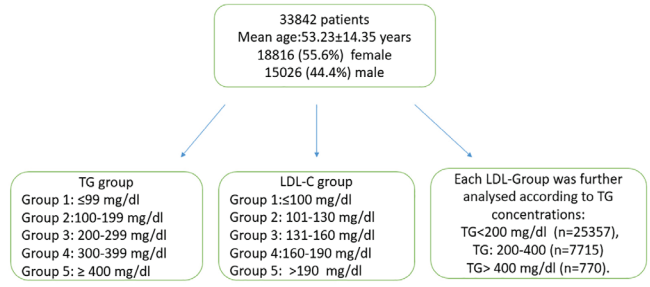

Figure 1 - Flowchart of the study.

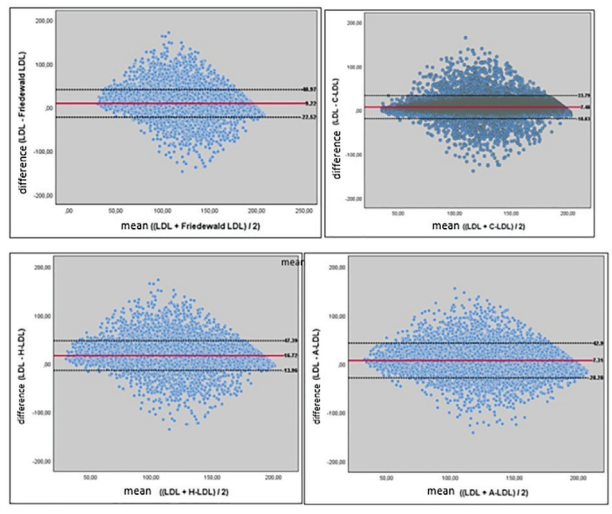

Figure 2 - Bland-Altman plots showing proportional and systemic bias between two sets of measurements. The solid line shows the mean difference between the values while the dotted lines are the upper and the lower limits of agreement (95% observed differences).

Table 3 Correlation analysis and Bland-Altman plot results of LDL-C groups.

LDL GROUP 1 (<100 mg/dl, n=6701)	**Bland-Altman plot results**				**Correlation analysis**		**Correlation analysis (TG <200)**		**Correlation analysis (TG 200-400)**		**Correlation analysis (TG >400)**	
	Mean	Upper limit	Lower limit	p	r	p	r	p	r	p	r	p
Friedewald LDL-C	6.31	39.01	-26.38	**<0.0001**	0.706	**<0.001**	0.766	**<0.001**	0.666	**<0.001**	0.643	**<0.001**
Chen LDL-C	2.09	29.58	-25.39	**<0.0001**	0.770	**<0.001**	0.784	**<0.001**	0.707	**<0.001**	0.595	**<0.001**
Hattori LDL-C	11.27	42.27	-19.28	**<0.0001**	0.703	**<0.001**	0.765	**<0.001**	0.664	**<0.001**	0.645	**<0.001**
Anandaraja LDL-C	1.25	36.57	-34.04	**<0.0001**	0.589	**<0.001**	0.652	**<0.001**	0.628	**<0.001**	0.638	**<0.001**
LDL GROUP 2 (100-130 mg/dl, n=11115)	**Bland-Altman plot results**				**Correlation analysis**		**Correlation analysis (TG <200)**		**Correlation analysis (TG 200-400)**		**Correlation analysis (TG >400)**	
	Mean	Upper limit	Lower limit	p	r	p	r	p	r	p	r	p
Friedewald LDL-C	8.65	36.72	-19.41	**<0.0001**	0.616	**<0.001**	0.699	**<0.001**	0.648	**<0.001**	0.484	**<0.001**
Chen LDL-C	6.06	28.04	-15.51	**<0.0001**	0.713	**<0.001**	0.732	**<0.001**	0.680	**<0.001**	0.420	**<0.001**
Hattori LDL-C	15.18	42.04	-11.16	**<0.0001**	0.612	**<0.001**	0.697	**<0.001**	0.647	**<0.001**	0.483	**<0.001**
Anandaraja LDL-C	-6.14	26.71	-38.38	**<0.0001**	0.459	**<0.001**	0.532	**<0.001**	0.581	**<0.001**	0.492	**<0.001**
LDL GROUP 3 (130-160 mg/dl n=10360)	**Bland-Altman plot results**				**Correlation analysis**		**Correlation analysis (TG <200)**		**Correlation analysis (TG 200-400)**		**Correlation analysis (TG >400)**	
	Mean	Upper limit	Lower limit	p	r	p	r	p	r	p	r	p
Friedewald LDL-C	10.08	40.33	-20.15	**<0.0001**	0.571	**<0.001**	0.660	**<0.001**	0.625	**<0.001**	0.510	**<0.001**
Chen LDL-C	9.32	33.37	-14.72	**<0.0001**	0.671	**<0.001**	0.684	**<0.001**	0.661	**<0.001**	0.452	**<0.001**
Hattori LDL-C	18.49	47.14	-10.62	**<0.0001**	0.568	**<0.001**	0.658	**<0.001**	0.624	**<0.001**	0.510	**<0.001**
Anandaraja LDL-C	9.37	43.06	-24.32	**<0.0001**	0.447	**<0.001**	0.530	**<0.001**	0.578	**<0.001**	0.476	**<0.001**
LDL GROUP 4 (160-190 mg/dl, n=954)	**Bland-Altman plot results**				**Correlation analysis**		**Correlation analysis (TG <200)**		**Correlation analysis (200-400)**		**Correlation analysis (TG >400)**	
	Mean	Upper limit	Lower limit	p	r	p	r	p	r	p	r	p
Friedewald LDL-C	11.95	49.05	-25.14	**<0.0001**	0.389	**<0.001**	0.609	**<0.001**	0.584	**<0.001**	0.514	**<0.001**
Chen LDL-C	12.53	42.66	-17.59	**<0.0001**	0.442	**<0.001**	0.637	**<0.001**	0.630	**<0.001**	0.547	**<0.001**
Hattori LDL-C	22.01	57.07	-13.90	**<0.0001**	0.387	**<0.001**	0.608	**<0.001**	0.582	**<0.001**	0.511	**<0.001**
Anandaraja LDL-C	13.15	52.27	-12,59	**<0.0001**	0.383	**<0.001**	0.522	**<0.001**	0.534	**<0.001**	0.561	**<0.001**
LDL GROUP 5 (>190 mg/dl, n=712)	**Bland-Altman plot results**				**Correlation analysis**		**Correlation analysis (TG <200)**		**Correlation analysis (TG 200-400)**		**Correlation analysis (TG >400)**	
	Mean	Upper limit	Lower limit	p	r	p	r	p	r	p	r	p
Friedewald LDL-C	13.75	58.67	-31.15	**<0.0001**	0.176	**<0.001**	0.226	**<0.001**	0.265	**<0.001**	0.353	0.044
Chen LDL-C	15.01	52.84	-22.81	**<0.0001**	0.260	**<0.001**	0.270	**<0.001**	0.316	**<0.001**	0.434	0.012
Hattori LDL-C	23.46	67.41	-17.30	**<0.0001**	0.174	**<0.001**	0.226	**<0.001**	0.264	**<0.001**	0.346	0.049
Anandaraja LDL-C	16.47	59.47	-26.51	**<0.0001**	0.121	**<0.001**	0.159	**0.001**	0.241	**0.001**	0.352	0.044

LDL-C: low density lipoprotein cholesterol.

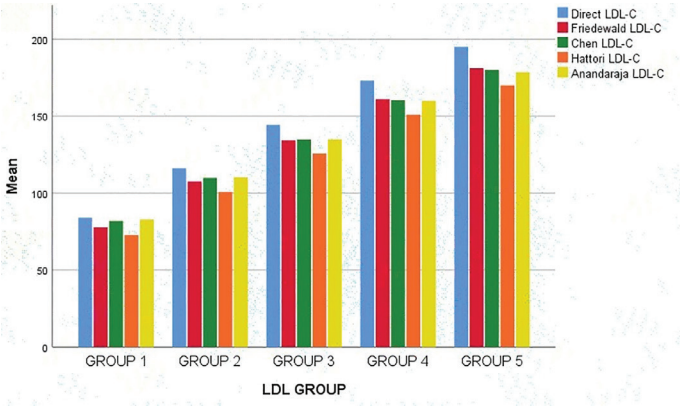

Figure 3 - Comparison of direct LDL-C measurement with Friedewald, Chen, Hattori and Anandaraja formulas in LDL-C groups.

In addition, all of the four formulas were in disagreement with respect to TG level analysis (TG<200 mg/dl, TG 200-400 mg/dl, and TG>400 mg/dl. Bland-Altman plot analysis showed p values less than 0.0001 for all calculations. Figure 3 shows the mean level of LDL-C of LDL-C groups. Correlation analysis showed moderate to high level of correlation for the Friedewald, Chen, and Hattori calculations, whereas the Anandaraja formula showed low to moderate correlation. Bland-Altman plot results and correlation analysis of the four groups are shown in Table 3. The Friedewald and the Anandaraja formulas mostly misclassified LDL-Group 3 subjects, whereas the Chen and the Hattori formulas mostly misclassified LDL-Group 4 subjects. The percentages of misclassification of the subjects with respect to calculated formulas are shown in Table 4.

Discussion

Our analysis indicates that all of the formulas tested underestimated the LDL-C concentration levels compared to direct enzymatic method and were in disagreement with it. The Bland-Altman plot results reveal a systematic and proportional bias in the four formulas. Further analysis of the data as a function of TG fractions indicates that there is no agreement between the calculated LDL-C values and the direct measurement values. Although Anandaraja formula had a slightly lower mean value than that obtained using the formula, the Chen formula had the narrowest range of limits of agreement (between 33.79 and to 18.83 mg/dl). Furthermore, the acceptable result of the Chen formula was 62.72%, higher than the results yielded by the other formulas. Of all the formulas, only the Chen formula had very high correlation with the direct LDL-C measurement.

Despite its limitations, the Friedewald formula remains the most widely used LDL-C calculation method in laboratories. Several studies have shown that the Friedewald formula yields erroneous estimations of LDL-C levels in clinical situations where the TC, TG, and LDL-C concentration levels are low. In addition, the Friedewald formula loses its accuracy when the values for HDL-C levesl are considerably low [9]. This accuracy is dependent on the accurate measurement of TG, TC, and HDL-C levels and a mathematical formula that estimates VLDL-C level. Our findings on the Friedewald formula are consistent with most of the other studies, which found that the Friedewald formual yields lower LDL-C concentration values than the direct enzymatic method [10-13]. According to a Korean study, the Friedewald formula tends to underestimate LDL-C concentration values when TG >150 mg/dl, and then overestimates these values when <150 mg/dl [14]. We found a mean difference of 9.22±16.19 mg/dl between the direct method and the Friedewald calculation. The Friedewald formula underestimated LDL-C concentration values for all TG subgroups in our study, and its correlation with the direct measurement was highest at TG levels between 100 mg/dl-299 mg/dl, with only a moderate correlation at TG levels higher than 300 mg/dl. When the data was analyzed as a function of LDL-C concentrations levels, the correlation between the Friedewald formula and the direct enzymatic method decreased with increasing LDL-C concentration values, with a significantly weak correlation at LDL-C levels greater than 190 mg/dl.

It has been proposed that the Anandaraja formula, which requires two parameters for LDL-C estimation, has a lower analytical error than other formulas [15]. Anandaraja et al. found a strong correlation between their formula and direct measurements, with a correlation coefficient of 0.97. Other studies have reported correlation coefficient values of between 0.658 to 0.930 [16-19]. In most previous reports, the Anandaraja formula underestimated LDL-C levels compared to the direct enzymatic method. Gupta et al. showed that the Friedewald and Anandaraja formulas underestimated LDL-C concentration values, with reported values of 10.8 and 14 mg/dl, respectively [18]. Yet another study also reported that these two formulas underestimated LDL-C concentration leves, with reported values of 17 and 22 mg/dl, respectively [19]. In a study by Gasko et al., the mean difference between the direct method and the Anandaraja formula was only -1 mg/dl [20]. Krishnavemi et al. discovered that the Friedewald calculation had a stronger correlation with the direct enzymatic method than the Anandaraja calculation [21]. In our study, the Anandaraja formula showed a moderate correlation with the direct method ($r=0.842$, $p<0.001$), with an average underestimation of 7.31±18.15 mg/dl. The correlation decreased with increasing LDL-C concentration levels and approximately half of the subjects in LDL-Group 3 and LDL-Group 4 and two thirds of LDL-Group 5 subjects were underclassified.

Martin et al. compared the Friedewald, Chen, Cordova, and Hattori formulas using a sample of hospitalized South African patients and found that the Chen formula overestimated LDL-C concentration values, while the Hattori formula had outperformed other formulas, with an underestimation value of only 1.55 mg/dl [22]. In an Iranian study, eight different formulas were evaluated using a sample of healthy subjects, and values from the Hattori and Cordova formulas were the least different from the estimation values. The Hattori formula over- and underestimated LDL-C levels at TG levels below 150 mg/dl and above 150 mg/dl, respectively. Although the Chen formula overvalue LDL-C levels at all TG concentrations, the Anandaraja formula overestimated and underestimated LDL-C levels at TG levels below 60 mg/dl and above 60 mg/dl, respectively [23]. In the present study, the Hattori formula had the highest mean of difference, which increased with increasing LDL-C concentration values. Ninety one percent of the patients in LDL-group 5 were underclassified. LDL-C is the paramount target for cardiovascular risk stratification, preventive strategies and medical treatment of patients. In this context, difference between the direct and calculated methods of deriving LDL-C values is critical for the classification of patients. Our results favored the Chen formula because of all the formulas, it had the highest correlation with the direct enzymatic method, had a mean difference with a narrowest limits of agreement, and lower misclassification rate than the Friedewald, Hattori, and Anandaraja formulas.

Because beta quantification via ultracentrifugation is costly and time-consuming, direct homogenous measurement of LDL-C is the preferred alternative method in most biochemistry laboratories [24]. Research showed that most of the homogenous methods meet the requirements prescribed by the NCEP [25,26]. This present study used the Roche direct LDL-C method, which is a precise and justifiable alternative of beta quantification. Miller et al. compared direct method, which was performed according to Roche/Hitachi analyzer manufacturer instructions, with reference measurement procedures. Their results showed that direct method met the NCEP goals for measuring HDL-C and LDL-C concentration levels in healthy individuals [27]. Our total analytical error was less than 12 %, which is within the total error goal stipulated by the NCEP. Major factor behind the incorrect of LDL-C concentration calculations of various formulas is that they typically need three terms. Hence, any measurement error in the TC, TG, and HDL-C values affect LDL-C estimation. It has been shown that direct measurements of TC and TG levels are in agreement with our reference method; however, it is not the case for HDL-C measurement. Oliveira et al. compared eight different direct HDL-C methods. They found that the accuracy of calculated formula was depend on the specific HDL-C measurement [28]. Measurement errors of HDL-C might be one of the reasons for underestimation of LDL-C.

Limitations

Our study was not generalizable to patients with various comorbidities since we enrolled only healthy subjects in this study. In addition, we did not evaluate outcomes of the subjects. Beta-quantification procedure is international standard method for determining the values obtained from LDL-C direct method by homogeneous assay. In our study, calculated LDL-C levels were not compared with reference method. Lastly, we did not measure lipoprotein(a) concentrations which would have impact on LDL-C measurement.

Conclusion

Our study aimed to find an important research question for countries where homogenous direct measurement methods are not in general distribution. According to our results, the Chen formula might be an acceptable alternative of the Friedewald formula. All the formulas analyzed in the present study had the best correlation at TG levels between 100 mg/dl-299 mg/dl and LDL-C concentrations less than 130 mg/dl. Neverthless, it should be remembered that direct enzymatic LDL-C measurement does not need for fasting and allows us to get results from single analysis.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

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JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/12911

The use of Remdesivir in pregnant women with COVID-19

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Received: 2022-11-04.
Accepted: 2022-12-25

J Clin Med Kaz 2023; 20(1):31-34

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Abstract

Objectives: This study was conducted to investigate the use of Remdesivir among pregnant women with probable and confirmed Covid-19 coronavirus infection.

Material and methods: To implement the study, a comprehensive examination of 120 pregnant women with severe and extremely severe forms of coronavirus infection was conducted.

Results: Statistically significant differences were obtained (p=0.019) at the time of comparison between the main and control groups, depending on the age of the subjects. The studied differences are due to the higher frequency of the age group 33-42 years among patients taking Remdesivir compared to those who were in the control group (p = 0.036). Women of the main group (Me = 9.00; Q1-Q3 = 8.00-11.0) stayed longer in the hospital compared to women in the control group (Me = 8.00; Q1-Q3 = 7.00-10.0). The more severe condition of patients in this group is cause of that. There are statistically significant differences in changes in amniotic fluid according to ultrasound data in the control and main groups (p=0.013). According to the results of our study, it was found that the decrease in temperature to a normal level occurred earlier in the control group (68%) than in the main group.

Conclusion: The older age group and the third trimester of pregnancy are risk factors for the transition to a severe form of the disease. Reliable efficacy of the etiotropic drug Remdesivir could not be traced.

Key words: COVID-19, pregnancy, Remdesivir

Introduction

The Covid-19 coronavirus infection is a disease characterized by relentless progression and an increase in infections and deaths since when it is discovered in China in December 2019. Currently, SARS-CoV-2 is continuously transforming into new mutations as it replicates: B .1.1.7 (alpha), B.1.351 (beta), P.1 (gamma), B.1.617. 2 (Delta), and the latest version B.1.1.529 (Omicron) released at the end of 2021. The most modified version of Omicron has about fifty mutations, 32 of which are in the spike protein [1]. As of October 17, 2022, the total number of cases in the world was 629,959,595, of which 6,571,489 deaths. In our republic, the total number of cases was 139,287, of which 13,692 were deaths. At the same time, 959 people continue to receive treatment, of which 107 patients are in hospitals, and 852 patients are on an outpatient basis. 3 patients are in serious condition, 3 patients are in a state of extreme severity, 1 patient is on mechanical ventilation [2, 3]. It should be noted that, 38 thousand 149 cases were registered in our city, of which 1646 were pregnant for the period 2020-2022: 537 - in 2020, 892 - in 2021, 217 - women in 2022 [3]. The most vulnerable group of people to COVID-19 includes not only the elderly, but also pregnant women. At the beginning of the COVID-19 pandemic, studies conducted by American and Chinese scientists revealed that the risk of transition to a severe course of the disease in pregnant women was higher than in non-pregnant ones [1, 4-6]. The progression of the disease caused by the SARS-CoV-2 virus is directly dependent on the entry of the virus into host cells after binding to angiotensin-converting enzyme 2 (ACE2). ACE2 replicates on cell membranes and tropen in the placenta throughout pregnancy. This phenomenon is a possible etiology of

predisposition of pregnant women to COVID-19 [1]. Reduced immune reactivity and other physiological changes during gestation cause an increased susceptibility to respiratory diseases and severe pneumonia in pregnant women, which can lead to hospitalization in intensive care units and mechanical ventilation [7]. A lightning-fast development of a critical condition is possible against the background of a fairly stable course of the disease in pregnant women with coronavirus infection COVID-19 [8]. A systematic review including 18 studies found that the most common symptoms in pregnant women were fever (87.5%) and cough (53.8%). In addition, fatigue (22.5%), diarrhea (8.8%), shortness of breath (11.3%), sore throat (7.5%) and myalgia (16.3%) are common [9]. The treatment of COVID-19 is significantly complicated by the lack of a single generally accepted protocol for the treatment of various clinical forms of this disease. This issue is especially relevant in relation to pregnant women, as drugs have a possible effect on the fetus. The coronavirus pandemic has led to the need to prescribe drugs to pregnant women with no evidence of effectiveness and no guarantee of serious consequences for the fetus. The main dilemma for scientists was the creation of a drug that suppresses SARS-CoV-2. The antiviral drug Remdesivir, due to a positive past, was urgently used for pregnant women with COVID-19. [10]. In Kazakhstan, from August 5, 2021, women during the gestation period are prescribed Remdesivir intravenously as an etiotropic drug according to the scheme intravenously of 200 mg on the 1st day, then 100 mg daily, course of 5 days [10]. This drug is included in the prescription list for patients based on foreign and domestic experience [10-12]. Our aim was to study the effectiveness of the use of Remdesivir in pregnant women with coronavirus infection Covid-19.

Material and methods

This study is a retrospective, cohort, analytical, non-interventional study. We analyzed 120 cases of pregnant women admitted to the city infectious diseases center from December 2021 to May 2022 with severe and extremely severe forms of COVID-19 coronavirus infection. The subject of the study were pregnant women with severe and extremely severe forms of coronavirus infection COVID-19. Inclusion criteria: confirmed and probable cases of coronavirus infection in pregnant women, use of Remdesivir, severe and extremely severe Covid-19. Criteria for exclusion from the study: pregnancy without Covid-19, mild and moderate severity of the disease in pregnant women.

Statistical analysis

The normality of the distribution was checked according to Kolmogorov-Smirnov with the Lilliefors correction. Since all data showed a non-normal distribution, the median and interquartile range were subsequently used. Categorical variables are presented as absolute numbers, percentages, and frequencies. A $p<0.05$ value was considered statistically significant. Statistical processing of the obtained data was carried out using the IBM SPSS Statistics 26.0 program. Nominal variables were analyzed using Pearson's chi-square test, Fisher's exact test, odds ratio, and relative risk.

Ethics

The study was approved by the Local Bioethical Committee of JSC "SKMA" (date: 03/16/2021). Written informed consent for publication in the article was obtained from patients or their legal representatives.

Results

Patients were divided into two groups, depending on the use of the antiviral drug remdesivir, 60 pregnant women each. The highest incidence rate by trimester was obtained in both groups in the period from 28 to 40 weeks (63.3% and 65%, respectively) (Figure 1).

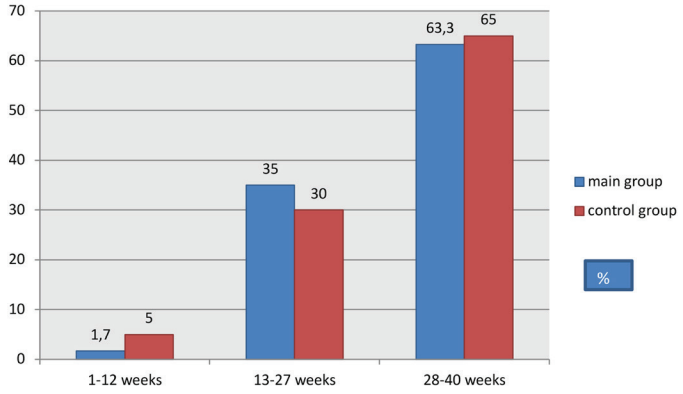

Figure 1 - Distribution of women depending on the duration of pregnancy

During the study, it was found that women in the age group from 33 to 42 years in the main group met more often than in the comparison group ($p = 0.019$). According to Cramer's V, a correlation of medium closeness was observed ($V = 0.250$). The antiviral drug Remdesivir was prescribed to women who had 5 or more pregnancies (25.0%), and in the presence of 4 or more pregnancies - 18.3%. In the analysis of pregnant women, depending on the diagnosis, according to the PCR result, statistically significant differences were obtained ($p = 0.02$).

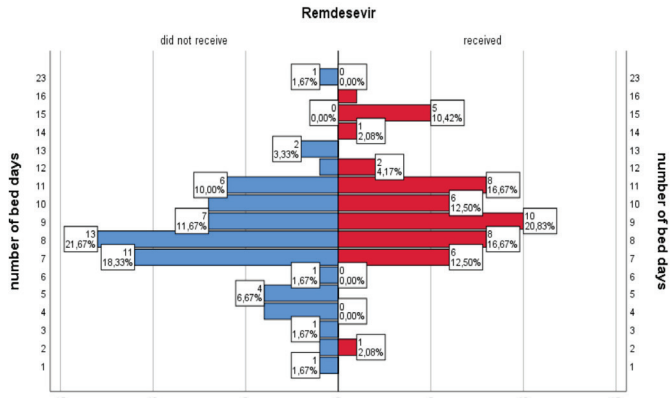

Figure 2 - Number of hospital bed days for pregnant women with coronavirus infection COVID - 19

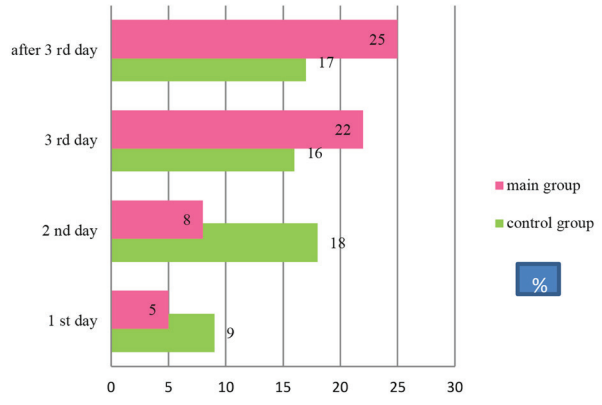

Figure 3 - Dynamics of improvement in the RR indicator

Table 1 Comparative table of age, gestation parity among pregnant women with COVID-19, confirmed and probable cases

Index		Therapy with Remdesivir (n=60)		Therapy without Remdesivir (n=60)		p
		Abs.	%	Abs.	%	
Age, full years	18-25	17	28,3	22	36,7	0,019*
	26-32	18	30,0	27	45,0	
	33-42	25	41,7	11	18,3	
Pregnancy parity	1	6	10,0	17	28,3	0,111
	2	14	23,3	8	13,3	
	3	14	23,3	12	20,0	
	4	11	18,3	8	13,3	
	5 и more	15	25,0	15	25,0	
Diagnosis based on the PCR result	U07.1	48	80	54	90	0,02*
	U07.2	12	20	6	10	

* - differences in indicators are statistically significant (p<0,05)

One of the indicators by which women in the gestation period were studied was the number of bed-days spent in the hospital, shown in Figure 2.

When comparing the main and control groups in terms of the number of bed-days, statistically significant differences were established (p=0.001). Women in the main group (Me = 9.00; Q1-Q3 = 8.00-11.0) stayed longer in the hospital compared to those who were in the control group (Me = 8.00; Q1-Q3 = 7.00-10, 0). This is caused by the more severe condition of patients in this group.

We took the following criteria for the effectiveness of Remdesivir therapy among pregnant women with COVID-19: the timing of temperature normalization, an improvement in respiratory rate, and a subjective decrease in dyspnea. In the Remdesivir group, the subjective sensation of shortness of breath ended on day 2 in 4 pregnant women (6.6%), on day 3 in 11 pregnant women (18.3%), after day 3 in 40 patients (66.6%) (Figure 3).

A decrease in body temperature to normal values in the group without Remdesivir therapy on days 1-2 was observed in 68% (41) of pregnant women, which is associated with a less severe course of COVID-19 in this group of patients, while in the main group - in 28% (17) research. An increase in SpO_2 by more than 95% and the abolition of oxygen therapy on the 1st-2nd day in the main group in 71% (43), up to 4 days from the start of antiviral therapy in 10% (6) of cases, but only in 68% (41) cases on the 7-8th day after the start of etiotropic treatment. In another group, more than 95% withdrawal of oxygen therapy was observed in 26 pregnant women (43%) on the 1st day, in 38% (23) on the 3rd-4th day, in 15% 9) - on the 5th-6th day; 4% (2) - after 7-8 days from the start of therapy.

Discussion

Coronavirus infection COVID-19 is an ongoing dilemma around the world. Scientists are constantly striving to come to a consensus regarding the treatment of patients. However, the constant transformation of the virus does not solve this issue. The status of treatment of pregnant women with COVID-19 is higher, which is associated with the risk of possible teratogenic effects of drugs [13,14]. The COVID-19 pandemic has led to the prescription of a huge number of drugs without an evidence base and no guarantee of long-term effects on the fetus [13]. The development of drugs for etiotropic treatment takes a long process, so the effectiveness of existing antiviral drugs was studied. One of these was Remdesivir, which previously showed good results, and was eventually urgently prescribed to pregnant women with COVID-19 [13-16]. To evaluate the efficacy and safety of the antiviral drug Remdesivir in pregnant women with COVID-19, further studies are needed to be included in international recommendations for the treatment of coronavirus infection COVID-19 [13-16].

During the study, it was found that in the main group, the age group from 33 to 42 years old made up the majority (41.7%). The course of coronavirus infection is aggravated in multiparous women and in the third trimester of pregnancy. Women who received antiviral therapy stayed in the hospital for 2 bed-days longer than pregnant women in the control group. The criteria for the effectiveness of Remdesivir in women in the gestational period with COVID-19 were the dynamics of temperature normalization, improvement in respiratory rate, and subjective reduction in dyspnea. According to the results of our study, it was found that the decrease in temperature to a normal level occurred earlier in the control group (68%) than in the main group. Subsequently, an increase in SpO_2 by more than 95% in more patients was observed on days 3-4 in the main group (71%) and on days 1-2 in the control group (43%). After 3 days in the main group, respiratory rate improved (41.6%) and a decrease in subjective dyspnea (66.6%).

A randomized controlled trial (RCT) showed that Remdesivir therapy in pregnant women with Ebola was safe and without significant side effects [17]. The use of this antiviral drug for moderate to severe COVID-19 requiring oxygenation has shown modest benefit [18]. This was also confirmed in our study. According to various authors, among pregnant women with SARS-CoV-2 coronavirus infection, the use of Remdesivir for 5 days leads to a clinical improvement in the course of moderate COVID-19 [19], which is consistent with data in the general population [20]. Berwick et al. reported that Remdesivir given intravenously for 10 days clinically improves severe COVID-19 in pregnant and postpartum patients [21]. But in our study, the use of a 5-day course of Remdesivir showed no clinical improvement in patients.

Recruitment of pregnant women with COVID-19 during the pandemic has been rapid, which is one of the strengths of the study. However, the limitation was the creation of a comparison group. The prescription list for patients with severe and extremely severe COVID-19 included the antiviral drug Remdesivir. Therefore, the comparison group included those pregnant women who did not give informed consent to additional treatment. Another limitation was that this study is single center, which does not provide extended results. It should be noted that the sample size was relatively small.

Conclusion

The use of Remdesivir in the appointment of pregnant women for the treatment of COVID-19 has not shown positive results. However, the application must be carefully monitored to detect adverse reactions. Also, as a result of the study, it was found that multiparous women are prone to a more severe course of coronavirus infection. The older age group and the third trimester of pregnancy are risk factors for the transition to a severe form of the disease. Further studies are needed to evaluate the efficacy and safety of the antiviral drug Remdesivir in pregnant women with COVID-19 for inclusion in international recommendations for the treatment of coronavirus infection COVID-19

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

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JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/12917

Effects of sevoflurane and propofol on hemodynamics during cardiac surgery: A randomized controlled clinical trial

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Received: 2022-08-26.
Accepted: 2022-12-26

J Clin Med Kaz 2023; 20(1):35-39

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Abstract

The anaesthetic support for various types of cardiac surgery such as coronary artery bypass grafting, heart valve repair or replacement is essential for success of a surgery. The planning of anaesthesia depends on the intended surgical procedure. The traditional approach is total intravenous anesthesia with propofol and inhalation with sevoflurane.

Objectives: To identify the advantages and disadvantages of propofol and sevoflurane when cardiac surgery in adults.

Material and methods: A total of 40 patients were assigned randomly into two groups to receive: in Group 1 - propofol and in Group 2 - sevoflurane. The induction to general anesthesia started with intravenous fractional administration of 1-1.5 mg/kg propofol, 5-7 μg/kg fentanyl and 1.5-2 mg/kg ketamine. Pipecuronium bromide 0.07-0.1 mg/kg was used as a myorelaxant in all patients in both groups. The anaesthesia in group P was supported with propofol 4-6 mg/kg/min intravenously by means of a perfusor as anaesthetic. In group 2, sevoflurane at a dose of 1.7-1.9 MAC was used as an anaesthetic. To maintain anaesthesia in both groups, there was a fractional administration of fentanyl at a dose of 100 μg intravenously when the heart rate and blood pressure increase, piperonium bromide in a dose of 2 mg intravenously was used for muscle relaxation.

Results: The mean arterial pressure, oxygen demand, energy expenditure, cardiac index, total peripheral resistance showed statistically significant differences between propofol and sevoflurane groups. Through the correlation analysis, the relationship between cardiac index and oxygen consumption was moderately relevant, as R was 0.4 and P>0.05.

Conclusion: When the use of sevoflurane for anesthesia, the hemodynamic parameters were stable. The oxygen consumption, energy expenditure in patients were significantly lower compared to propofol using the sevoflurane anesthesia.

Key words: hemodynamic, oxygen consumption, energy expenditure, sevoflurane, propofol, cardiac output

Introduction

Despite significant advances in anesthetic support when open heart surgeries and technological achievements in the cardiopulmonary bypass methods, the problem of intraoperative myocardial protection continues to be relevant. The anesthesia management for coronary artery bypass grafting, cardiac valve repair or replacement and ascending aorta surgery has many common principles. The planning of anaesthesia depends on the intended surgical approach to revascularisation. The surgery is usually performed via a midline sternotomy incision using cardiopulmonary bypass. The coronary artery bypass grafting without cardiopulmonary bypass can be performed either via a complete sternotomy or via a small anterior thoracotomic incision only in separate patients, and it's called minimally invasive direct coronary artery bypass grafting.

The patients who have undergone cardiac surgery are usually subject to risk of developing myocardial injury [1,2].

The incidence of perioperative myocardial infarction, the leading cause of death and complications in these

patients, can be as high as 30% of all interventions [3]. The myocardial injury is a frequent complication in patients undergoing the cardiac surgery, which could lead to delayed recovery and increase of length of hospital stay [4,5]. Several approaches are available to protect the myocardium against the injury associated with cardiac surgery [6]. A meta-analysis has shown that inhalation anaesthetics, including sevoflurane, have cardioprotective effects in patients when cardiac surgery [7]. The intravenous anaesthetics such as propofol have also been reported to have cardioprotective effects. These include a noticeable reduction in myocardial infarction size, reduced troponin release and reduction in mortality after cardiac surgery [8-10]. The increase in oxygen extraction, the oxygen consumption to oxygen delivery ratio have been shown to be associated with poor post-operative outcomes. The oxygen consumption can vary differently in the perioperative period, but it is rarely monitored directly as part of routine care [11]. TIVA has various characteristics that make it a reasonable alternative to the use of volatile substances. In Europe and elsewhere in the world, TIVA has made a cost-effective method, allowing precise titration for clinical effect. The TIVA benefits include organ protection; patient well-being; and accelerated recovery after cardiac surgery, especially when propofol is combined with remifentanil, which also contributes to cardioprotection [12]. The halogenated anaesthetics, including sevoflurane, desflurane, isoflurane, enflurane and halothane, lower the mean arterial pressure by increasing the anaesthetic gas concentration in a dose-dependent manner. The mechanism of arterial pressure reduction is related to a decrease in systemic vascular resistance, except for halothane, which decreases the systolic arterial pressure through a direct depressant effect on the myocardium and thus unchanged decreases the cardiac output [13]. Sevoflurane has less effect on haemodynamics than desflurane and isoflurane [14]. A multicentre RCT demonstrated no difference between sevoflurane anaesthesia and propofol TIVA in terms of stay in the ICU, mortality, or both in patients undergoing cardiac surgery [15]. The inhalation anaesthetics can significantly improve the haemodynamics and the inflammatory response to surgery in elderly patients [16]. The intraoperative anaesthesia and postoperative sedation with sevoflurane reduces myocardial damage and improves renal function in patients undergoing the off-pump myocardial revasculization surgery [17].

Purpose and objectives: to study the effects of sevoflurane and propofol on haemodynamics, blood oxygen transport function, metabolic cost of the body, and pharmaco-efficiency of anaesthetics when cardiac surgery in adult patients.

Material and methods

The examination and treatment data of 40 patients operated in the Cardiosurgical Department of the Medical Center Hospital of the Presidential Administration of the Republic of Kazakhstan were included in the study. All patients underwent the coronary artery bypass grafting (CABG) under cardiopulmonary bypass (CPB).

Study design: Single-centre prospective randomised controlled clinical trial.

The patients in the study subgroups were comparable at baseline, and the table shows demographic, anthropometric data, surgical volume, cardiac index, oxygen consumption, total peripheral vascular resistance (TPR), oxygen delivery and oxygen utilization (Table 1).

All patients had multivessel coronary disease. All patients had arterial hypertension of grade 3 risk 4, according to anamnesis, and the smoking history (COPD) of almost all patients numbered 30-40 years.

Table 1

Demographic, anthropometric data, surgical volume, cardiac index, oxygen consumption, oxygen delivery and oxygen utilization.

Indicator	Propofol (n=20)	Sevoflurane (n=20)
Sex		
M	13 (75%)	16 (85%)
F	7 (25%)	4 (15%)
Age, years	59,8 ± 3,1	60,5 ± 4,2
Weight, kilograms	80,5 ± 11,2	82,2 ± 13,6
Height, centimetre	167,1 ± 9,3	169,6 ± 8
Surgery duration, hour	3,9 ± 0,6	3,7 ± 0,5
AC time, minutes	70,8 ± 23,6	80,2 ± 38,2
Cardiac index, l/min/m2	2,4 ± 1,2	2,5 ± 0,7
Oxygen consumption, ml/min/m2	124,9 ± 62,8	128,9 ± 57,1
TPR, din-s-cm−5	3325,3 ± 533,5	3162,8 ± 655,0
Oxygen delivery, ml/min/m2	438,6±85,	463,1±103,2
Oxygen recovery, %	30,1±9,1	28,3±5,2
Note: P> 0.05.		

The echocardiography (echocardiography) showed the ejection fraction equal to 55-61% in all patients. 27% of all patients had also type 2 diabetes mellitus. Objectively there was no edema in extremities. Exertional dyspnea.

All patients were divided up into 2 groups: Group 1 (n=20) consisted of patients whom were administrated propofol (P) during anaesthesia. In Group 2 (n=20) inhalational anaesthesia was carried out with sevoflurane (S) as main anaesthetic.

The study was conducted in 5 stages:

1) patient's baseline values determination before anaesthesia;

2) after tracheal intubation;

3) Before the CPB;

4) after the CPB;

5) post-operative period until the patient is extubated.

At admission to the operating unit before induction into anaesthesia, haemodynamic monitoring with Nihon Kohden monitors (Japan) started. The right radial artery was catheterised for invasive systemic pressure monitoring and arterial blood sampling, after that the catheter was introduced into the central jugular vein (assisted by ultrasonic apparatus) and guided into the right atrium for mixed venous blood sampling. There was no indication for Swan-Ganz catheter insertion.

The cardiac stroke (CS) volume was determined by transthoracic echocardiography (RR=end diastolic volume-end systolic volume).There were also determined the cardiac output (CO=CS x heart rate), cardiac index (CI=CO/body surface area). Blood oxygen content was derived from formula CaO2 (arterial ABS) and CvO2 (central mixed venous ABS) = [(1.34 × Hb × SO2) + (PO2 × 0.031)] / 100, arterio-venous difference (AVD) = CaO2-CvO2. The oxygen delivery was found by formula (DO2 = CI* CaO2), oxygen consumption (VO2 = Cardiac index *AVD or VO2 = CO × (CaO2 - CvO2) ~ CB × Hb × 1,34 × (SaO2 - SvO2) / 100), oxygen utilization factor (KYO2) = VO2 / DO2 × 100 = [(CaO2 - CvO2) / CaO2] × 100.

In the second stage after tracheal intubation performed to determine VO2, energy expenditure during anaesthesia, the indirect calorimetry was used by means of a spirometer "Spirometry" (UK Oxford) which was connected to the endotracheal tube and continuously reported the oxygen demand and energy expenditure. Additionally, cardiac output and cardiac index were investigated using Fick's formula. In the third and

fourth stages of anaesthesia the same tests (cardiac index, cardiac output, oxygen intake, oxygen delivery, oxygen utilization and energy expenditure) were determined. At the last stage, to assess the pharmaco-efficiency of anaesthetics, the consumption of muscle relaxants and opioid analgesics was calculated, and the recovery and extubation time was recorded.

All patients continued their usual antihypertensive medication both before and on the day of surgery to prevent the development of withdrawal syndrome and to reduce the risk of perioperative myocardial ischaemia.

All patients in both groups were given fentanyl in a dose of 5-7 µg/kg, ketamine 1.5-2 mg/kg, and propofol 1-1.5 mg/kg intravenously fractionally. Pipecuronium bromide 0.04-0.07 mg/kg was used as muscle relaxant in all patients. To maintain anaesthesia in Group 1 P, propofol 4-6 mg/kg/hr intravenously on a perfusor (BBRAUN) was used as an anaesthetic, fentanyl 100 µg intravenously was administered fractionally to increase heart rate and blood pressure, and pipecuronium bromide 2 mg intravenously for myorelaxation. In group 2, sevoflurane was used as an anaesthetic, at a dose of 1.7-1.9 MAC. Fentanyl 100 µg intravenously was also fractionally administered to increase heart rate and blood pressure, piperonium bromide was used in a dose of 2 mg intravenously for myorelaxation. During CPB in all patients in both groups, propofol was administrated in a dose of 5-7 mg/kg/h intravenously via perfusion, analgesic regimen: fentanyl 100 µg intravenously every 30 min; myorelaxant piperonium bromide 2 mg every 40-60 min. Norepinephrine solution was administered at a dose of 0.07 µg/kg/min intravenously on a perfusor after CPB to all patients at similar dosages in both groups.

The purpose of the norepinephrine application:

1. In order to maintain mean arterial perfusion pressure (cytokine storm and vasodilation are caused by CPB).

2. For inotropic support (for reperfusion syndrome, resulting in a lower ejection fraction).

The statistical analysis was performed using SPSS package with Student's t-test for independent samples and nonparametric Mann-Whitney test. Mann-Whitney test was used only for myorelaxant consumption, as this parameter produced an abnormal distribution. Pearson correlation analysis was also performed to determine the significance of the association between cardiac index and transport, oxygen consumption and energy expenditure.

Results

The data of 40 patients operated in the Cardiosurgical Department of the Medical Center Hospital of the Presidential Administration of the Republic of Kazakhstan were included in the study. All patients underwent coronary artery bypass grafting (CABG) under cardiopulmonary bypass (CPB).

Both groups of patients were comparable in terms of baseline heart rate and mean arterial pressure (MAP). The heart rate (HR) increased from 75.8±9.4 to 89.1±8.5 bpm after tracheal intubation in the propofol group. A decrease in HR was seen after CPB and until the end of surgery of 78.1±8.4 bpm in patients treated with propofol (P=0.01). At the same time, in the sevoflurane group a significant HR decrease was noted before CPB, 64,1±10,9 bpm, and after CPB, 63,5±7,6 bpm, a slight increase to 66±4,9 bpm at the end of anesthesia was noted (P=0.01). (Figure 1). During anaesthesia, there was a significant decrease in mean arterial pressure from 93.9±9.2 to 69.4±5.8 mmHg in the propofol group (P=0.01) and to 79±8.5 mmHg in the sevoflurane group (P=0.01) (Figure 2).

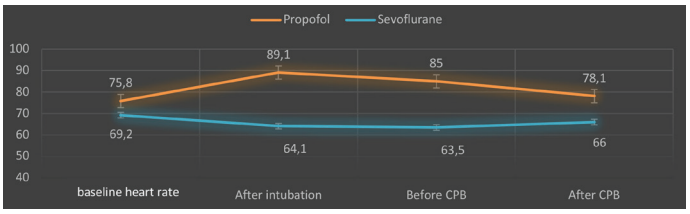

Figure 1 - Heart rate in both groups before and during anaesthesia.

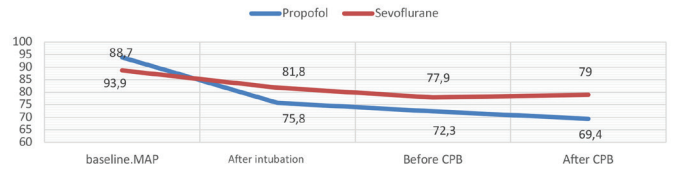

Figure 2 - Changes in mean arterial pressure before and during surgery.

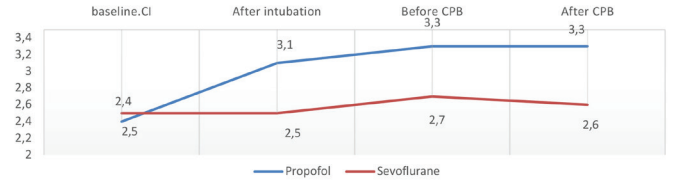

Figure 3 - Cardiac index before anaesthesia and during surgery.

Before induction into anaesthesia, mean cardiac index (CI) values were similar in both groups of patients. Propofol markedly increased CI from 2.4±1.2 l/min/m2 to 3.3±0.7 l/min/m2 during surgery (P=0.02). At the same time, there was a slight decrease in SI to 2.5±0.6 L/min/m2 in the sevoflurane group during the second phase of the study, but it increased to baseline 2.6±0.5 l/min/m2 (P=0.02) after CBP (Figure 3). Baseline total peripheral vascular resistance (TPR) values were similar. Anaesthetics reduced TPR regardless the type of anaesthesia. However, propofol significantly reduced TPR throughout the surgery from 3225.3±533.5 dyne-s-cm–5 to 1315.2±328.1 dyne-s-cm–5 after CBP (P=0.01). In the group where sevoflurane was used, the decrease in TPR was noted only after induction in anaesthesia to 2209.7±510.7 dyne-s-cm–5 (P=0.02). And then after tracheal intubation and until the end of surgery, the TPR remained practically at the same level of 2132.5±582.5 dyne-s-cm–5 (p=0.01) (Figure 4).

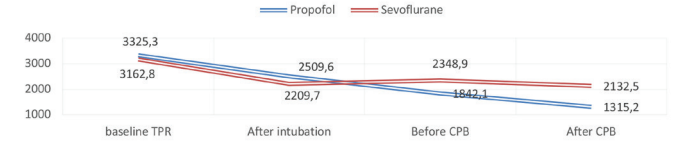

Figure 4 - Total peripheral vascular resistance before and during anaesthesia.

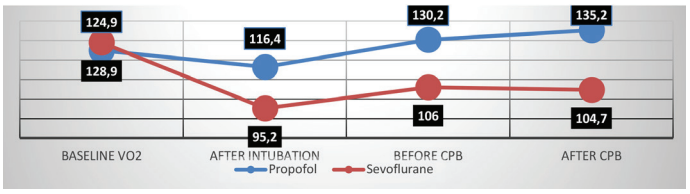

Figure 5 - Change in oxygen consumption before anaesthesia and during surgery.

Propofol anaesthesia after tracheal intubation markedly increased the oxygen delivery from 438.6±85.3 ml/min/m2 to 510.9±83 ml/min/m2 (p=0.0001). However, its decrease was noted at the pre CPB stage of 450.3±86.8 ml/min/m2 and after CPB 467.1±73.1 mL/min/m2 (p<0.01). At the same time, sevoflurane decreased DO2 throughout anaesthesia from 463.1±103.2 ml/min/m2 to 357±52.1 ml/min/m2 (p=0.01). Baseline oxygen consumption was similar in both groups. After induction into anaesthesia, both drugs dramatically reduced VO2 to 116.4±27.7 ml/min/m2 in group S and to 95.2±31.2 ml/min/m2 during propofol anaesthesia (P=0.03). However, an increase in VO2 was noted after tracheal intubation before the end of anaesthesia for propofol anaesthesia, which was 135.2±26.4 ml/min/m2 (P=0.001). In the group where sevoflurane was used, there was a non-significant increase in oxygen requirement in the third and fourth stages of the study to 106±22.3 ml/min/m2 and 104.7±13.1 ml/min/m2 after tracheal intubation (p=0.05) (Figure 5). Both groups of anaesthetics decreased the oxygen utilization during induction into anaesthesia, but after tracheal intubation there was an increase in oxygen utilization from 28.9±6.7% in group P and 21.8±2.9% in group S to 30.5±4.3% and 24±2.8% respectively (p=0.001) throughout the anaesthetic period. After tracheal intubation and after connecting the spirometry device to the intubation tube, the energy expenditure (EE) was 1444.8±174.9 kcal/d in the propofol group (P=0.003) and 1491.8±222.5 kcal/d in the sevoflurane group (P=0.004). But propofol anaesthesia after tracheal intubation prior to CPB markedly increased EE to 1842.7 ± 442.3 kcal/day, but then there was a slight decrease of energy expenditure after CPB 1592.6 ± 306.5 kcal. In S group, there was a slight increase in EE before CPB by 1524.7±285.9 kcal. At the same time, sevoflurane insignificantly decreased EE after CPB by 1430.4±199.2 kcal/day (p < 0.05) (Figure 6).

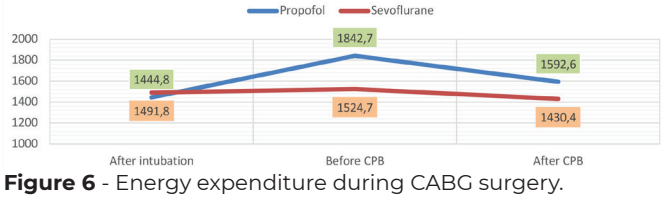

Figure 6 - Energy expenditure during CABG surgery.

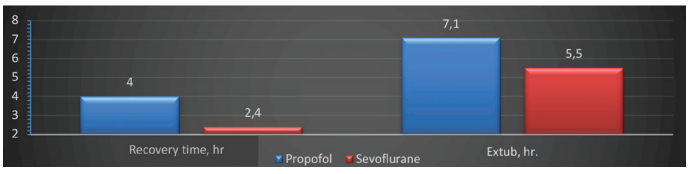

Figure 7 - Recovery and extubation times in both patient groups.

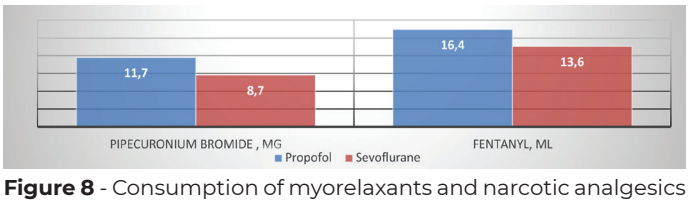

Figure 8 - Consumption of myorelaxants and narcotic analgesics in both patient groups.

The recovery time and extubation time were significantly different between the groups (Figure 7). Recovery time was equal to 4.0±1.3 hours in TIVA group and to 2.4±0.8 hours in the sevoflurane group (P=0.01). The weaning time was 7.1±1.3 h in the propofol group and 5.5±2.2 h in the sevoflurane group (P=0.01). Pipecuronium bromide 11.7±3.0 milligrams and fentanyl 8.7±1.7 ml were more required by myorelaxant and narcotic analgesics in propofol anaesthesia compared to inhaled anaesthetic 16.4±3.8 milligrams and 13.6±3.3 ml respectively (P=0.01) (Figure 8).

The correlation analysis shows that the relation between cardiac index and oxygen consumption is moderately significant, as R equals 0.4 and P>0.05. Also the correlation between cardiac index and energy expenditure is not significant, as R equals to 0.12 and P>0.05.

Discussion

The choice of optimal anaesthesia techniques for cardiac surgery is an important task. However, the TIVA and VA use during cardiac surgery is often impaired by the strength of instinct, personal experience, tradition in a given department, etc. Therefore, various authors have conducted studies on blood flow, blood oxygen transport function, energy expenditure during TIVA and inhalational anaesthesia. On the basis of the data published in Scopus, Web of Science, PubMed, Cyberleninka, Cochrane, the meta-analysis of these literature sources we found that the effect of total intravenous anesthesia with propofol and VA on haemodynamics, blood oxygen-transport function, energy expenditure during cardiac surgery is not uniform. The works of researchers have been studied [Symons J, Myles P. 2006] claiming that inhalation anesthetics, including sevoflurane, have cardioprotective action on patients during cardiac surgery. However, the authors [8-10] report that intravenous anaesthetics, such as propofol, have cardioprotective action. This includes a marked reduction in the size of myocardial infarction, a decrease in troponin release and a reduction in mortality after cardiac surgery. However, researchers [G. Landoni F. Guarracino, 2014] in a multicentre randomized trial found no difference between sevoflurane anaesthesia and propofol TIVA in terms of stay in ICU, mortality or both in patients undergoing cardiac surgery. The authors [Xinyu Chen, et al. 2020], note that intraoperative anaesthesia and postoperative sevoflurane sedation reduces myocardial damage in patients undergoing myocardial revascularisation surgery without cardiopulmonary bypass. Also, according to the author [StefanSchraag, 2015] TIVA has various characteristics that make it a reasonable alternative to the use of inhalational anaesthetics. In Europe and elsewhere in the world, TIVA has made it a cost-effective method to allow precise titration for clinical effect. Benefits of TIVA include organ protection; patient well-being; and accelerated recovery after cardiac surgery, especially when propofol is combined with remifentanil, which also contributes to cardio protection.

The present study determined changes in hemodynamics, blood oxygen transport function and body energy expenditure during sevoflurane inhalation anesthesia and propofol intravenous anesthesia in patients undergoing CABG. Our results show that rapid recovery can be achieved with both techniques, maintaining the same degree of anaesthesia during surgery in both groups. However, Sevoflurane provided better intraoperative haemodynamic stability than propofol during the CABG surgery. The mean arterial pressure was better maintained with sevoflurane compared to propofol. The heart rate differed significantly between the groups. During sternotomy when propofol was used, tachycardia occurred. The mean arterial pressure did not differ significantly between the groups. Significant increase in CI was noted in the group where propofol was used for anaesthesia only after CPB. Sevoflurane decreased the cardiac index to baseline after CPB. Both anaesthetics reduced TPR, but propofol reduced it more significantly compared to sevoflurane. The drugs decreased the oxygen uptake after tracheal intubation. However, propofol significantly increased VO2 after tracheal intubation. Sevoflurane was superior to propofol in effectiveness in reducing energy expenditure. During anaesthesia with propofol a sharp increase in energy expenditure

was noted. The patient's recovery and extubation time was longer in the propofol group compared to sevoflurane. Also, the pharmaco-economic consumption is greater in the propofol group than in the sevoflurane group.

In summary, stability of hemodynamics is very important during cardiac surgery because it allows patients to wake up quickly, regain consciousness and reduce the lung ventilator time for patients and length of their stay in the intensive care unit. In addition, the low consumption of energy during the operation has a great influence on rapid recovery of patients and rapid wound healing in the postoperative period.

Limitations of the study

This study has several limitations. The first limitation of our study lies in the fact that it was a single-center study. Multicenter studies reduce influence of the special characteristics of one single institution. The second limit of our study is the sample size, because it affects the statistical significance of the study. But we believe that randomized controlled clinical trials with a large number of patients are required.

Conclusion

Sevoflurane had the advantage over propofol with regard to better intraoperative hemodynamic stability. There was a significant difference between sevoflurane and propofol. Sevoflurane excelled in reducing oxygen demand and energy expenditure during cardiac surgery. Sevoflurane is probably a reliable alternative to propofol for cardiac surgery patients.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

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JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/12919

Seasonal and epidemiological profile of chickenpox cases in Kazakhstan

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Received: 2022-10-26.
Accepted: 2022-12-31

J Clin Med Kaz 2023; 20(1):40-43

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Abstract

Background: According to the National infectious disease monitoring report, there is a fluctuating pattern of incidence of chickenpox in the country, but there are no studies reporting the epidemiological situation in Kazakhstan. There is a discernable association of varicella epidemiology with climate, particularly temperature dependency. We aimed to analyze the incidence and seasonality of chickenpox in the absence of universal varicella vaccination in Kazakhstan.

Material and methods: A retrospective analysis of the long-term dynamics of chickenpox was carried out, and data of registered patients between 2010 and 2020 were retrieved from the National infectious disease monitoring report and the Unified Payment System (UPS) database from 2014 to 2020, which is part of the Unified National Electronic Health System (UNEHS).

Results: The highest incidence rate for the studied period was registered in 2014 – 363.96 and the lowest was in 2020 – 95.8 per 100,000 population. Overall, 17,520 cases of chickenpox were recorded with an incidence rate of 95.8 per 100,000 population in the country in 2020 (against 41,841 cases, with an indicator of 228.9 in 2019). The highest proportion of cases is observed among children from 4 to 6 years old (29%), children from 1 to 3 years old (24%) and from 7 to 9 years old (15%). Similar to previous years, there was an autumn-winter spreadingof morbidity, with the highest registration of morbidity in January.

Conclusion: Based on our study, the highest incidence rate of chickenpox in Kazakhstan was registered in 2014 (363.96 per 100,000 population) and morbidity was distributed in the autumn-winter season. These findings might aid in forecasting future outbreaks of infection based on the influence of climate change on chickenpox, and help in making a decision about the implementation of varicella preventive and control initiatives in the country.

Key words: infectious diseases, epidemiology, chickenpox, Kazakhstan

Introduction

Varicella, also known as chickenpox, is a highly contagious disease [1] caused by the *varicella-zoster virus* (VZV). It is considered as a self-limited disease of childhood, but can result in hospitalization and death [2,3]. It is primarily transmitted from person to person through direct contact or inhalation of aerosolized droplets from vesicular rash or respiratory tract secretions of patients with varicella [4]. In the absence of a varicella vaccination (VV), almost everyone is expected to be infected by mid-adulthood [5]. The incidence of varicella is difficult to ascertain as it is a non-reportable disease, and may vary depending on the immunization coverage in different countries.The global impact of the VV program reported the implementation of VV in 36 countries in 2019 [6], mostly comprised of developed countries. None of the Central Asian countries, including Kazakhstan, embraced the VV in

the immunization calendar yet [7]. WHO recommends close surveillance of epidemiological situations to assess the health burden of VZV to evaluate the potential need for VV [8].

There is a discernable association of varicella epidemiology with climate, particularly temperature dependency[9]. This could be attributed to biological characteristics of the VZV virus which is inactivated by high temperatures or a humid environment [10]. This can be observed in studies demonstrating different ages-specific incidences of VZV in various climate zones. For example, in temperate climates the reported average age of affected individuals was early childhood (less than 9 years of age) [10,11] with the majority of people infected by the adolescent years. In tropical countries, age-specific incidence was higher, most commonly affecting adolescents and adulthood [12]. The incidence of chickenpox was associated with temperature, latitude, and seasons, and climatic variables should be considered as one of the important prognostic predictors of varicella incidence in Asia [13-15].

Based on the WHO report, seasonality influences the VZV outbreak process: the highest incidence rates correspond to winter and spring seasons [16]. The occurrence of chickenpox is normally increased every 2-4 years, although VZV immunization is not widespread [5]. The age range of 3-6 years has the highest incidence overall, indicating that chickenpox remains primarily a childhood virus. The epidemic phase of acute morbidity outbreaks can be seen, whereas outbreaks are reported not only in organized preschool and school groups but also among military conscripts and in health care institutions (nosocomial outbreaks); a substantial part of chickenpox detection and severe cases are documented in people over the age of 14.

Kazakhstan is a vast and sparsely populated country with a temperate climate. There are no studies reporting the incidence of *Varicella zoster virus* in the country, and the current epidemiological situation of chickenpox or shingles is unknown. Hence, this population-based study aims to assess data from the National infectious disease monitoring report and the UPS to show the country-wide epidemiologic and seasonal profile of chickenpox in the absence of universal varicella immunization. We expect our research to increase understanding of chickenpox distribution dynamics throughout the country, resulting in better evidence-based decisions in prevention, diagnosis, and treatment.

Material and methods

Study population and data sources

This is a retrospective study of the Kazakhstani population diagnosed with VZV according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) from 2010 to 2020. The diagnosis of patients included in the present analysis was identified by the following ICD-10 code for chickenpox: B01-B01.9.

The official data of registered patients between 2010 and 2020 were retrieved from the National infectious disease monitoring report and the UPS database from 2014 to 2020, which is part of the Unified National Electronic Health System (UNEHS).

Exposures and covariates

The registry included data on dates of admission, regions, RPN ID, ICD-10 codes, and incidence rates. Regions were divided into big cities of republican significance (Nur-Sultan, Almaty, and Shymkent cities), North Kazakhstan (Kostanay, Akmola, Pavlodar, and North Kazakhstan regions), South Kazakhstan (Kyzylorda, Turkestan, Zhambyl and Almaty regions), Central Kazakhstan (Karaganda region), East Kazakhstan (East Kazakhstan region) and West Kazakhstan (Atyrau, Aktobe, Mangystau, and West Kazakhstan regions).

Outcome assessment

The incidence rates and patterns of seasonality were assessed. The incidence rate was calculated by dividing the new disease cases during the same period by the population size during the same time x 100,000. Seasonality was tracked using the number of new cases each month from 2014 to 2020, as well as an epidemiological week graph for the last years due to a larger number of recorded patients.

Data were represented as descriptive, with absolute values and percentages generated for categorical variables. Incidence rates within the population are given per 100,000 population.

The study was approved by the Institutional Review and Ethics Committee (NU-IREC 315/21092020 on 23/09/2020) with an exemption from informed consent.

Results

Chickenpox

The frequency of decline and increase in the incidence of chickenpox is highlighted in the long-term dynamics of the incidence from 2010 to 2020. The highest incidence rate for the study period was registered in 2014 and the lowest in 2020 with 363.96 and 95.8 per 100,000 population, respectively (Figure 2). In 2020, 17,520 cases of chickenpox were registered in the country, with an incidence rate of 95.8 per 100,000 population (against 41,841 cases with an indicator of 228.9 in 2019) (Figure 1 A).

Figure 1 - The incidence rate of chickenpox in Kazakhstan in 2019 (A) and 2020 (B).

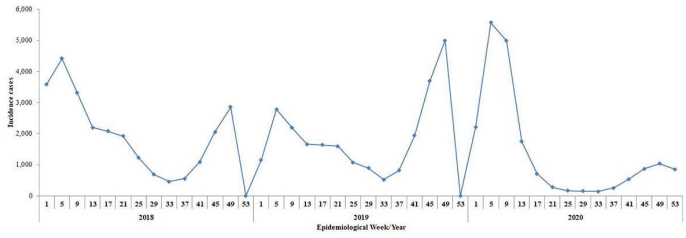

Figure 2 - Incidence of chickenpox (№ of cases) by epidemiological week and year.

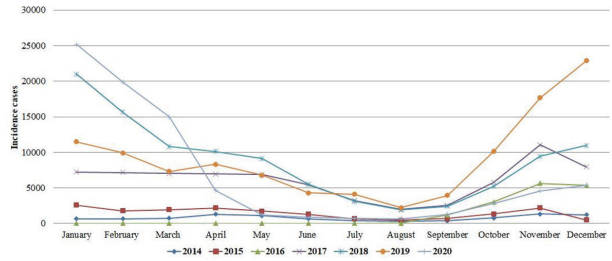

Figure 3 - Incidence cases of chickenpox by year.

Exceeding numbers (or higher than expected numbers) were noted in Akmola (133.8), Aktobe (191.0), Atyrau (132.3), East Kazakhstan (106.2), West Kazakhstan (130.4), Karaganda (177.9), Kostanay (127.9), Mangystau (168.2), North Kazakhstan (176.07) regions and Nur-Sultan (103.4) in 2020 (Figure 1 B). Morbidity was primarily observed during the autumn-winter season showing a similar pattern to previous years with the highest morbidity registration in the winter periods (Figure 3).

According to the National infectious disease monitoring report the age structure of incidence, the highest proportion of cases is observed among children from 4 to 6 years old (29%), children from 1 to 3 years old (24%) and from 7 to 9 years old (15%). As the contingents of patients infected with chickenpox, children attending preschool organizations are more often affected - 37.6%, schoolchildren - 29.9% and unorganized children - 18.8% [17].

Discussion

Our research determined the basic epidemiological characteristics of the primary varicella virus in the country, with mapping of the spreadingand correlation with climate. The seasonality of varicella and the correlation of temperature with varicella had been a topic of many investigations. A number of studies showed a strong seasonality of varicella in temperate climates and in most tropical environments with a peak incidence around winter and spring [16, 18], which is comparable to other respiratory infectious disorders. Our study confirmed the incidence spreadingin cold months. We also observed two incidence peaks: one during the winter months and another from March to May. This could be due to prolonged winters lasting from November to April in northern parts of the country, which is supported by the higher spreading of cases in central and northern Kazakhstan. And more importantly, this may be due to the fact that the youngsters congregate in schools and kindergartens, as well as epidemiological aspects of varicella. The congregation of children in schools and kindergartens undoubtedly increases the spread of VZV in these groups, making them the main susceptible population for varicella. The seasonal trend for cases among non-student adults, preschool children, and infants was not so apparent in previous studies [19]. The reasons for the seasonal incidence differences may relate to properties of VZV, climate models, geographical locations, population density, risk of exposure [20], and other potential factors [21].

We report an incidence range of 95,8 to 363.96 per 100,000 population over a six-year period. The reported incidence of primary varicella in Kazakhstan is substantially lower in comparison to the reported annual incidence in European countries prior to the implementation of universal varicella vaccination [22]. Such low numbers could be due to low-level reportability deu to self-limiting course of illness, low level of detection due to serologic limitations, or may actually represent the true incidence of primary chickenpox cases in the country. Unfortunately, without information on the clinical severity and mortality associated with the reported cases, our understanding of the varicella burden in the country is limited. Therefore, the need for universal vaccination in Kazakhstan is still unclear.

It should be mentioned that the incidence of all respiratory illnesses was lowest in 2020, due to broad preventative measures implemented to battle the novel coronavirus infection COVID-19, which had a significant influence on lowering the incidence of airborne-transmitted respiratory infections in general. At the same time, we must not forget that understanding the potential influencing factors is the foundation for developing preventive and control strategies.

There are a few limitations that should be highlighted. Firstly, due to the use of official statistics alone, our data lack information on the demographic information, and clinical course of the disease, including complications and mortality. Secondly, there is a probable underestimation of cases due to underreporting in young children with mild and self-limited clinical cases. Thirdly, we did not correlate with humidity, air pressure, wind speed, or precipitation, because these measurements were not available.

Conclusion

In summary, the current study assessed the incidence and patterns of the seasonality of chickenpox infection in Kazakhstan in the absence of universal varicella immunization for the period of 2014-2020. The highest incidence rate was registered in 2014 (363.96 per 100,000 population) and morbidity was distributed in the autumn-winter season. These findings might aid in forecasting future outbreaks of infection based on the influence of climate change on chickenpox, and may help in making a decision about the implementation of varicella preventive and control initiatives in the country.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: This work was supported by the Ministry of Education and Science of the Republic of Kazakhstan grant funding [Funder Project Reference: #AP09259016, title: Epidemiology and Forecasting of Infectious Diseases in Kazakhstan Using Big Healthcare Data, Mathematical Modeling, and Machine Learning].

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JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/12928

Validation of the Kazakh version of the Brief Index of Affective Job Satisfaction in medical universities faculty staff sample

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Received: 2022-09-24.
Accepted: 2023-01-09

J Clin Med Kaz 2023; 20(1):44-49

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Abstract

Aim: The present study aimed to perform validation and assessment of psychometric properties of the Kazakh version of the Brief Index of Affective Job Satisfaction on the academic faculty staff.

Material and methods: The translation of the Brief Index of Affective Job Satisfaction was performed following the World Health Organization Guidelines on the translation and adaptation of research instruments. 715 medical educators of Kazakhstani medical universities represented the study population. Preliminary statistical analysis included Cronbach's alpha calculation. The psychometric properties of the instrument were examined using exploratory and confirmatory factor analysis.

Results: Cronbach's alpha obtained 0.88, outlining good internal consistency of the scale. The Kaiser-Meyer-Olkin index reached 0.830, which indicated meritorious sample adequacy. CFA identified good factorial validity of the scale: all model fit indices exceeded the threshold values. The inter-item correlation index varied between r=0.616 and r=0.716, designating an acceptable correlation between variables. The total job satisfaction level was moderate (3.15±0.78).

Conclusion: Our findings provide support to the psychometric properties of the Kazakh version of the BIAJS as an instrument for the assessment of job satisfaction. The major advantages of the BIAJS are that it is optimally brief, highly affective, and has good internal validity.

Key words: job satisfaction, medical faculty, psychometrics, validation study

Introduction

Enhancing the healthcare system is one of the priority directions of the state policy of Kazakhstan. Modernization of human resources policy in healthcare entails advancing the competitiveness of graduates, which implies expansive updating educational programs at all levels of education, aimed at mastering core competencies and the ability to apply them in real life [1]. As international experience shows, medical education reform intensifies the competition between universities, which predetermines a higher responsibility of faculty members towards the educational process and research activities [2]. However, numerous studies enlighten that high workload and bureaucratic paperwork may lead to faculty discontent and job stress with the further intention to leave academia [3–8]. The American Association of Medical Colleges (AAMC) [9] reported that 53% of all faculty remained in their medical schools, 10% switched to another institution, and 38% left academic medicine within 10 years. Moreover, clinical faculty with Ph.D. were more likely to leave or switch medical schools.

At the moment, comprehensive work on the transition to a six-year medical education is being implemented in Kazakhstan. The new program is developed to succeed the current 5+2 (baccalaureate+internship) program and requires six years of continuing education. Given the increased

burden on teachers who, along with their daily pedagogical, educative, or clinical activities, are obliged to develop new curricula and revise learning outcomes, the organizational commitment is rapidly diminishing.

Many authors express concerns that low job satisfaction may jeopardize the qualified training of future healthcare providers. However, the adverse effects of faculty discontent do not end with this. Medical schools struggle with serious financial losses as a result of faculty turnover [4,10], aside from the deterioration of the institutional image both inside and outside academia [11,12]. In this regard, investigating faculty job satisfaction is of paramount importance, since medical educators are the cornerstone of the academic success of institutions on the national and global stage [13,14].

One of the earliest references for job satisfaction dates back to Hoppok (1938) [15], who defined it as a combination of psychological, physiological, and environmental circumstances that makes a person satisfied with his or her job. Locke (1969) [16] classically conceptualized JS as "a pleasurable or positive emotional state resulting from the appraisal of one's job or job experiences". These early interpretations emphasize the affective side of JS, based on feelings related to their experience at the job.

Research on academic faculty job satisfaction is quite rich, as well as the variety of instruments aimed to measure it. The instruments are constructed in a diverse manner and may be applied subject to different aims of the study. Some scales are dedicated to measuring overall satisfaction, such as the Job in General Scale (JIG), which comprised 18 items [17], or Andrew and Withey Job Satisfaction Questionnaire with 5 items [18]. But the vast majority of instruments evaluate specific job facets, impacting satisfaction, such as Job Descriptive Index (JDI), which contains 72 items and covers 5 dimensions: general job satisfaction, supervision, salary, relations with colleagues, and promotion opportunities [19], or the Minnesota Satisfaction Questionnaire (MSQ) short form [20], which has 20 statements and is aimed to assess intrinsic and extrinsic aspects, recognition, and authority/social utility. The Measure of Job Satisfaction (MJS) consists of 38 questions and evaluates personal satisfaction, workload, support, education, salary, and prospects [21]. Other multidimensional instrument is the 36-item Job Satisfaction Survey (JSS), which is developed for the social service sector and consists of 9 subscales: salary, promotion, supervision, fringe benefits, rewards, operating policies and required rules, coworkers, nature of work, and communication [22].

There are several problematic areas in measuring job satisfaction. First, a huge variety of tools allows researchers to prefer the one that best suits the purpose of the study. However, some tools are designed for specific samples (JSS, MJS) and may not be applied to other sectors. There are also some scales developed on general samples, that may not be applicable to specific professions [23].

Another focus that demands scrutiny is the structure of job satisfaction. Some authors argue that it comprises several cognitive facets. In this regard, difficulties arise in determining which facets should be included in the evaluation of JS and what specific weight they would have in overall satisfaction [24]. Many authors criticize that JS is more than the aggregated outcome of several aspects of a job, but appears to be an emotional construct, and therefore must be evaluated in an affective aspect. A growing number of studies contemplate the affective facets of JS, rather than cognitive, related to the rational perception of job conditions (such as pay, career promotion, rewards, etc.) [25–28]. In that context, affective instruments, such as the Brief Index of Affective Job Satisfaction (BIAJS), have gained wide adoption in the last decade. The unidimensional scale proved its temporal stability in test-retest study (r = 0.57), and had good internal consistency (Cronbach's alpha obtained 0.83 in the initial study). To date, the BIAJS is considered a unique measure that is both specifically affective and applicable for testing an exhaustive range of psychometric properties vital to ensuring research integrity. Moreover, the tool demonstrated its cross-national and cross-population equivalence in different ethnic and social groups (corrected item-total correlations ranged from 0.51 to 0.74) [29]. The scale has already been translated into other languages and validated in Spain [24], Argentina [30], Russia [31], and China [26]. Therefore, our study aimed to perform validation and assessment of psychometric indicators of the Kazakh version of the BIAJS on the academic faculty staff.

Material and methods

Study sample

The present study was conducted between October and December 2021 and involved the academic faculty of Kazakhstani medical universities. The selection process was performed using the non-probability convenience method. The EpiInfo version 7.0 software was used for sample size calculation, with a risk of loss of 20% and a confidence interval of 95%. Six institutions were purposively selected to represent institutions of republican (Astana Medical University, Asfendiyarov Kazakh National Medical University, the Kazakhstan School of Public Health) and regional status (Semey Medical University, Karaganda Medical University, West Kazakhstan Marat Ospanov Medical University) (Figure 1). 715 faculty members from different departments were recruited for the survey. Eligibility criteria included educators who willed to participate in the survey, worked in selected universities, and were social media users. Faculty members who refused to participate or were on leave at the moment of the study were withdrawn from the study. An online self-administered survey was distributed among faculty via WhatsApp messenger.

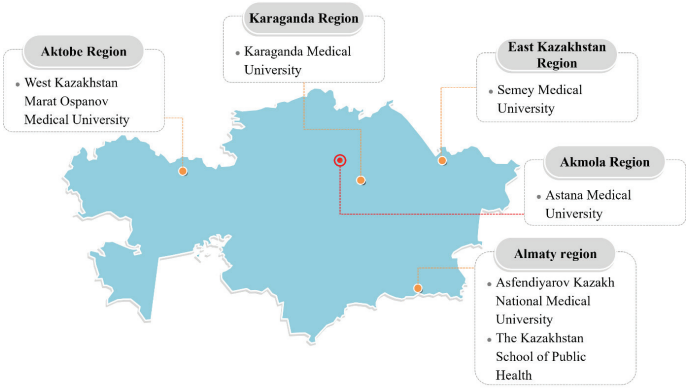

Figure 1 - The geographical spread of medical universities recruited for the study

Ethical statement

The study was approved by Semey Medical University Ethics Committee (No 2, 28-10-2020). All participants were sent a statement informing about (1) the goals and rationale of the study, (2) the rights of the participants, (3) the ability to withdraw at any moment of the study (4) the contact number of the principal researcher in case of the difficulties in completing the form. An informed consent form was sent to responders before data collection. No incentives or compensations were offered to encourage teachers to participate in the study.

Study instrument

The BIAJS is a unidimensional scale for measuring affective job satisfaction. The BIAJS was developed and initially validated in Australia and Hong Kong [29]. The tool is composed of four items: "I find real enjoyment in my job", "I like my job better than the average person", "Most days I am enthusiastic about my job", and "I feel fairly well satisfied with my job". Furthermore, the scale includes three distracter items: "My job is unusual", "My job needs me to be fit", and "My job is time consuming", which help reduce method variance.

The responses were rated on a 5-point Likert scale (1 – Strongly disagree, 2 – Disagree, 3 – Neutral, 4 – Agree, 5 – Strongly agree).

Procedures

Primarily, we contacted the principal author of the BIAJS scale Edmund R. Thompson via e-mail. Permission was obtained aiming to develop the Kazakh version of the scale.

The BIAJS translation procedure was carried out following the World Health Organization (WHO) Guidelines on the translation and adaptation of research instruments [32].

In the first stage, two translators familiar with the terminology independently translated the original English version of the BIAJS into Kazakh. The specialists provided translations with a detailed report on the difficulties and uncertainties that arose in the process. Afterward, the provided documents were compared and discussed by translators for the appropriateness of translation, which made it possible to agree on a single version of the questionnaire (V1). Questions with controversial wording were revised and corrected.

For the second stage, the expert panel including a healthcare specialist, a Kazakh language philologist, and translators reviewed the V1. The purpose of the discussion was to minimize translation errors and misinterpretations.

In the third stage, another bilingual translator who was not aware of the content of the original BIAJS was invited for the back translation. The back translation of the unified version of the questionnaire into English was the necessary measure to ensure the content was not impacted during the translation. The final version of the questionnaire (V2) was grammatically and semantically comparable to the original English-language questionnaire.

Pilot study

30 volunteer teachers from Semey Medical University were recruited for the pilot study to (1) verify the cultural appropriateness of the Kazakh version of the BIAJS and (2) to check the initial psychometric properties of the scale. Eligibility criteria included being the faculty staff, fluency in Kazakh, and absence of mental disorders. The participants were asked about the clarity and certainty of the questions and options, as well as any difficulties in understanding the expressions or selecting the option.

Data analysis

The statistical analysis was performed with SPSS 23.0 (IBM Corp.) and AMOS 26.0 (IBM Corp.).

A preliminary analysis was performed to examine the internal reliability of the BIAJS scale. Exploratory factor analysis EFA was performed using principal component analysis. In exploratory factor analysis (EFA), we considered the Kaiser-Meyer-Olkin (KMO) index and the Bartlett test of sphericity. The following cutoff values were used: KMO > 0.60, the Bartlett test of sphericity $p < 0.05$. Determination of the number of factors considered eigenvalues higher than 1.0. Inter-item correlation test was run to explore the internal consistency of the scale items.

In confirmatory factor analysis (CFA) with maximum likelihood estimation (MLE), the indices of overall fit were tested. The chi-square test (χ^2) was used for assessing the difference between observed and expected covariance matrices. The goodness of fit (GFI) and adjusted goodness of fit (AGFI) were applied to evaluate the fit between the model and the observer covariance matrix with the cutoff value >0.95 and >0.90, respectively. The normed fit index (NFI) and the Tucker-Lewis index (TLI) analyzed the difference between the proposed model chi-square value and the null model chi-square value with the cutoff value >0.90 and >0.95, respectively. The relative fit index (RFI) and the incremental fit index (IFI) were used to compare the chi-square for the proposed and null models with the cutoff value >0.90. The comparative fit index (CFI) was performed to compare the hypothesized model fit to the null model fit with the cutoff value >0.90. The root mean square error of approximation (RMSEA) was applied to determine model efficiency to fit population covariance matrix with optimal chosen parameters with the cutoff value <0.08. The root mean square residual (RMR) was used as a measure of the discrepancy between the sample covariance matrix and the model covariance matrix with the cutoff value <0.08.

The means and standard deviations (SD) were calculated for continuous variables. Categorical variables were presented in frequencies and percentages. Pearson's correlation coefficient was used to reveal the connection between continuous variables. An independent t-test and one-way ANOVA were applied to examine the distribution of job satisfaction scores among demographic variables.

Results

Pilot study

30 faculty teachers agreed to participate in the pilot testing of the Kazakh version of the BIAJS. 73.33% of all participants (n=22) were females. The mean age±SD was 38.17±9.0. In the pilot study, the internal consistency of the BIAJS, as measured by Cronbach's alpha, was 0.83 (crude Cronbach's alpha before the exclusion of distracter items was 0.77). KMO was 0.727, which indicated average sample adequacy, the Bartlett test of sphericity obtained $\chi^2=57.196$, df=6, $p<0.001$. The scree plot analysis revealed 1 factor with an eigenvalue of 2.77 explaining 69.21% of all variance.

All responders (100%) agreed with the content clarity and cultural appropriateness.

Sample

Overall, 715 faculty members provided complete data for job satisfaction survey. The mean age±SD was 40.75±11.39 for females and 41.30±11.08 for males. Slightly over half of the participants (54.3%) were theoretical and basic faculty staff, whilst 45.7% worked in clinical departments. The vast majority of participants comprised full-time faculty (77.9%). Three-quarters of the sample hold different academic degrees (Master – 36.4%, Ph.D. – 13.0%, Professor or Candidate – 26.3%). The mean job satisfaction±SD was 3.15±0.78 (3.13±0.81 for females, 3.20±0.72 for males). Complete socio-demographic data of the participants are displayed in Table 1.

Table 1 Socio-demographic characteristics of the sample (N = 715)

Variable	N (%)	
	Satisfied	Dissatisfied
Gender		
Male	99 (42.3)	135 (57.7)
Female	195 (40.5)	286 (59.5)
Work experience		
Less than 1 year	7 (29.2)	17 (70.8)
1-5 years	31 (19.1)	131 (80.9)
5-10 years	39 (22.8)	132 (77.2)
Over 10 years	217 (60.6)	141 (39.4)
Department focus		
Theoretical/basic	161 (41.5)	227 (58.5)
Clinical	133 (40.7)	194 (59.3)
Employment status		
Full-time	260 (46.7)	297 (53.3)
Part-time	34 (21.5)	124 (78.5)
Academic qualification		
No	65 (37.4)	109 (62.6)
Master	72 (27.7)	188 (72.3)
Ph.D.	25 (26.9)	68 (73.1)
Professor/Candidate	132 (70.2)	56 (29.8)

Reliability and exploratory factor analysis of the BIAJS

Cronbach's alpha of 0.88 denoted good internal consistency of the scale (crude Cronbach's alpha before the exclusion of distracter items was 0.83). Table 2 demonstrates preliminary descriptive statistics for responses.

Table 2 Preliminary descriptive statistics for the BIAJS scale (N = 715)

Item	M	SD	SEM	α if the item is deleted
BIAJS_1	3.16	0.87	0.032	0.853
BIAJS_2	3.30	0.90	0.034	0.863
BIAJS_3	2.93	0.95	0.035	0.852
BIAJS_4	3.22	0.92	0.032	0.830
M: Mean, SD: Standard deviation, SEM: Standard error of the mean				

KMO was 0.830, which indicated meritorious sample adequacy, the Bartlett test of sphericity obtained χ^2=1530.917, df=6, p<0.001. The scree plot analysis revealed 1 factor with an eigenvalue of 2.96 explaining 74.06% of all variance.

Inter-item correlation test displayed an acceptable correlation between scale variables (Table 3).

Table 3 Inter-item correlation matrix for the BIAJS scale

	BIAJS_1	BIAJS_2	BIAJS_3	BIAJS_4
BIAJS_1	-	0.628*	0.619*	0.699*
BIAJS_2	0.628*	-	0.616*	0.645*
BIAJS_3	0.619*	0.616*	-	0.716*
BIAJS_4	0.699*	0.645*	0.716*	-
*All correlations were significant at p < 0.01				

Confirmatory factor analysis

The theoretical model for assessing affective job satisfaction was examined using maximum likelihood estimation (MLE) and demonstrated a good fit. The fit statistics were as follows: χ^2=9.186 (df=2, p<0.010), GFI/AGFI=0.994/0.969, NFI=0.994, RFI=0.982, IFI=0.995, TLI=0.986, CFI=0.995, RMSEA=0.071, RMR=0.010 (Figure 2).

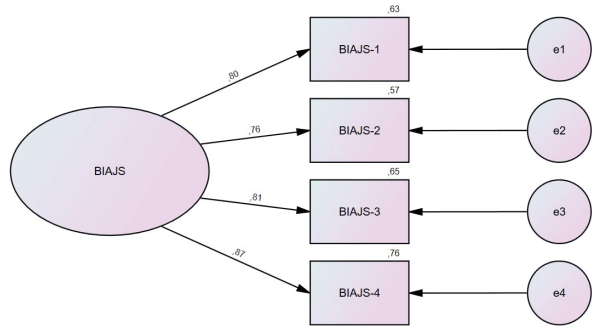

Figure 2 - Graphical representation of the Kazakh version of the BIAJS model

Discussion

The BIAJS is a valid tool used worldwide for measuring affective job satisfaction. The present study aimed to perform translation, validation, and adaptation of the Kazakh version of the BIAJS in the academic faculty staff.

The Kazakh version was developed using the WHO Guidelines on translation. Primary testing of semantic appropriateness was performed on the pilot group of 30 medical educators in Semey city. The Cronbach's alpha was 0.83 and showed good reliability.

We used standard methods to evaluate the psychometric properties of the scale. Cronbach's alpha of 0.88 demonstrated good internal reliability, which is somewhat higher than in the original scale (α between 0.81 and 0.83) [29], the Argentinian (α=0.83) [33], and the Chinese sample (α=0.87) [26]. However, the score was lower than in the American (α=0.89) [34] and Spanish (α=0.92) samples [35]. This displayed that the BIAJS has similar indices of reliability in different populations. According to Taber (2018) [36], the reliability of the scale with an alpha less than 0.70 is found to be questionable or unsatisfactory.

EFA revealed one factor with an eigenvalue above 1.0, which confirmed the one-dimensional structure of the BIAJS. To assess the internal consistency of the scale, an inter-item correlation test was applied. The test revealed an acceptable correlation between variables, which varied between r=0.616 and r=0.716. CFA identified good factorial validity of the scale: all model fit indices exceeded the threshold values. This is consistent with prior studies intended to validate the tool [24,26,30]. Therefore, these findings verified the reliability of the internal and structural consistency of the Kazakh version of the BIAJS.

Our findings have several implications. First, to date, none of the valid instruments that have international recognition were adapted specifically for the Kazakh population. Second, since the major changes in the healthcare and education sectors imply the faculty demands to be considered, the use of the BIAJS may help conceptualize effective retention policies in medical institutions.

Conclusion

Overall, the present study provides support to the psychometric properties of the Kazakh version of the BIAJS as an instrument for the assessment of job satisfaction. The findings of our study demonstrated that the factor structure of the Kazakh scale is very close to that of the original instrument. The scale was approved as a valid one-dimensional tool, which may assist the administration of medical universities to identify faculty satisfaction levels. The major advantages of the BIAJS are that

it is optimally brief, highly affective, and has good internal validity. Furthermore, our study shed light on the need to correct the faculty retention policies in the era of medical education reforms and curricular changes.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

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JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/12929

Diagnostic significance of hematological parameters in brucellosis

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Received: 2022-12-02.
Accepted: 2023-01-13

J Clin Med Kaz 2023; 20(1):50-55

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Abstract

Introduction: Changes in hematological parameters are frequently observed in brucellosis patients. In this study, it was aimed to evaluate the diagnostic significance of some hematological parameters in patients with brucellosis.

Material and methods: In this case-control study, the data of brucellosis patients and healthy volunteers followed up in the Outpatient Clinic of Infectious Diseases between 2018 and 2020 were retrospectively examined. In the hemogram examination of patients with brucellosis and health volunteers; hematological parameters such as the leukocyte, hemoglobin, neutrophil, lymphocyte, monocyte, platelet, ratio of neutrophil/lymphocyte, ratio of platelet/lymphocyte, ratio of monocyte/lymphocyte and mean platelet volume were compared.

Results: 255 people, 169 (66.3%) of whom were diagnosed with brucellosis and 86 (33.7%) from the control group, were included to the study. These participants of 112 (43.9%) were male and 143 (56.1%) were female. The patients diagnosed with brucellosis, of 62 (36.7%) were considered acute, of 62 (36.7%) subacute, and of 45 (26.6%) chronic brucellosis. leukocyte, hemoglobin, neutrophil, and neutrophil/lymphocyte levels were found to be lower in the brucellosis group compared to the control group, while mean platelet volume level was found to be higher. Hemoglobin was found to be lower and mean platelet volume higher in all brucellosis subgroups.

Conclusion: In this study, the following findings were determined to be important: the lowness of leucocyte and hemoglobin and highness of mean platelet volume in brucellosis patients, as well as the highness of lymphocyte levels and lowness of neutrophil/lymphocyte and platelet/lymphocyte levels in the subacute brucellosis subgroup. In addition, it was concluded that the mean platelet volume parameter can be used as a diagnostic test for brucellosis.

Key words: brucellosis, MPV, lymphocyte, NLR, PLR

Introduction

Brucellosis is a common zoonotic disease that is considered endemic worldwide and is caused by gram-negative coccobacilli from the *Brucella* genus [1]. Approximately 500,000 new cases of human brucellosis are reported each year [2]. The disease is a zoonotic infection seen most frequently in Turkiye especially in Eastern, Southeastern, and Central Anatolia [3]. The disease has a wide spectrum of clinical symptoms, such as fever, sweating, fatigue, and osteoarthritis, and sometimes it can lead to more serious damage in different organs [3-5].

Early and accurate diagnosis of brucellosis plays an important role both in controlling and eradicating the disease and in improving public health [6]. Microbiological diagnosis of human brucellosis is based on three different modalities: culture, serology, and nucleic acid amplification tests (NAATs). Bone

marrow and blood culture are the gold standard methods [7]. Hematological complications due to brucellosis are prevalent. *Brucella spp.* shows tropism to structures in the reticuloendothelial system (RES), such as bone marrow and some peripheral organs. Changes in hematological parameters are observed in most patients [8, 9].

Various hematological and inflammatory parameters have been widely used as biomarkers in the preliminary diagnosis of bacterial infections [6, 10, 11]. Hematological markers, including white blood cell count, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), mean platelet volume (MPV), platelet count (PLT), platelet distribution width (PDW), red cell distribution width (RDW), and C-reactive protein (CRP) test, have been used in the preliminary diagnosis of brucellosis with serological tests [6, 12]. Recently, it has been reported that platelets are also associated with inflammation. MPV is associated with platelet activation and function, and it has been reported as an inflammatory marker in some diseases, such as community-acquired pneumonia and brucellosis [13-15]. In this study, it was aimed to evaluate whether some hematological parameters that can be examined in simple hemogram examination have a diagnostic importance in terms of brucellosis.

Material and methods

Study protocol

In this case-control study, the data of brucellosis patients and healthy volunteers followed up in the Outpatient Clinic of Infectious Diseases at Cizre State Hospital between 2018 and 2020 were retrospectively examined. Information about the patients, such as age, sex, and laboratory test results, obtained from the hospital information management system. Brucellosis was categorized into 3 subgroups according to the duration of clinical signs and symptoms: acute brucellosis (0–2 months), subacute brucellosis (2–12 months), and chronic brucellosis (> 12 months) [3]. The criteria used for the diagnosis of brucellosis are growth in the culture of *Brucella spp*. in blood or other body fluids together with clinical symptoms such as fever, sweating, chills, joint-muscle pain, headache, and weakness, being of serum Brucella tube agglutination titer equal to or greater than 1/160, or being of at least a four-fold titer increase in the serum sample taken at two-week intervals. The control group was selected from healthy volunteers without any symptoms or signs.

Blood sample analyses

2 ml of venous blood sample from each patient was taken into an anticoagulant tube containing ethylenediaminetetraacetic in a sterile environment. Immediately after blood collection, it was inverted for 8 seconds. The prepared sample was studied on the SYSMEX- XN-1000 (Japan) hemogram device with laser reading system.

From the hematological examinations at the time of the brucellosis patients and healthy volunteers inclusion in the study, the results of leukocytes, hemoglobin (HGB), neutrophils, lymphocytes, monocytes, platelets, NLR, PLR, MLR, and MPV were evaluated.

Ethical committee

This study was approved by the Clinical Research Ethics Committee of Harran University with the number 91074 on December 24, 2021. All procedures in the study were performed in accordance with the World Medical Association Declaration of Helsinki.

Statistical analysis

All statistical analyses were carried out using the SPSS 22 (SPSS Inc., Chicago, IL) packet program. A one-sample Kolmogorov–Smirnov test was used to check whether continuous variables such as leukocyte, HGB, and neutrophil follow the normal distribution. All continuous variables are presented as mean ± standard deviation. An independent samples t-test was used to compare the means of two continuous variables that followed the normal distribution, and a Mann–Whitney U test was used to compare the means of two continuous variables that did not follow the normal distribution. A one-way ANOVA test was used to compare the means of more than two normally distributed continuous variables, and a Kruskal–Wallis test was used to compare the means of more than two continuous variables that did not follow the normal distribution. To determine which groups the difference originated from, multiple comparison tests were used in cases where the assumption of normal distribution was provided, and the Mann–Whitney U test was used in cases where the assumption of normal distribution was not provided. Receiver Operating Characteristic (ROC) analysis was carried out to evaluate the overall diagnostic performance of the hematological variables. The Youden Index was used to determine the cut-off points of the parameters found to be statistically significant. We considered a *p-value* < 0.05 statistically significant for all statistical analyses.

Results

A total of 255 participants, 169 (66.3%) of whom were patients with a diagnosis of brucellosis and 86 (33.7%) of whom constituted the control group, were included in the study. Of the participants, 112 (43.9%) were male, and 143 (56.1%) were female. Of the patients with brucellosis, 51 (30.2%) were male, and 118 (69.8%) were female. In the control group, 61 (70.9%) participants were male, and 25 (20.1%) were female. The mean age of the participants with brucellosis was 40.08, and the mean age of the participants in the control group was 39.71.

When the brucellosis patients and the control group participants were compared, the differences in, leukocyte HGB, neutrophil, MPV, and NLR were statistically significant. The brucellosis patients were found to have lower leukocyte, HGB, neutrophil, and NLR levels and higher MPV levels than the participants in the control group (Table 1).

Table 1 The results of the statistical analysis between brucellosis patients and the control group

Parameters	Control	Brucellosis	p-value
Age	39.71±15.18	40.80±13.79	0.57
Leukocyte	7105.19±1344.90	6638.99±1696.00	**0.02**
HGB	14.59±1.58	13.13±1.49	**0.00**
Neutrophil	4009.98±1040.79	3585.27±1257.57	**0.00**
Lymphocyte	2282.77±489.44	2344.73±687.79	0.41
Monocyte	571.50±176.04	552.28±189.30	0.17
Platelet	253.57±48.26	246.75±61.70	0.24
MPV	9.58±1.24	9.99±0.90	**0.03**
NLR	1.82±0.55	1.65±0.72	**0.00**
PLR	0.12±0.03	0.11±0.04	0.27
MLR	0.26±0.08	0.25±0.09	0.06

HGB: hemoglobin, MPV: mean platelet volume, NLR: neutrophil–lymphocyte ratio, PLR: platelet–lymphocyte ratio, MLR: monocyte–lymphocyte ratio

Table 2 Evaluation of hematological parameters according to the control group and brucellosis subgroups

Parameters	Control	Acute	Subacute	Chronic	p-value
Age	39.71±15.18	38.32±13.95	42.29±13.41	42.18±13.90	0.35
Leukocyte	7105.19±1344.90	6657.90±1802.18	6782.74±1526.10	6414.89±1780.53	**0.10**
HGB	14.59±1.58	13.11±1.58	13.15±1.35	13.15±1.57	**0.00**
Neutrophil	4009.98±1040.79	3595.81±1374.74	3583.39±1140.94	3573.33±1270.15	0.07
Lymphocyte	2282.77±489.44	2288.87±627.56	2545.00±619.48	2145.78±791.69	0.01
Monocyte	571.50±176.04	562.19±211.90	567.95±163.72	517.02±188.83	0.41
Platelet	253.57±48.26	245.40±67.75	251.15±60.55	242.56±55.13	0.70
MPV	9.58±1.24	10.00±0.91	9.89±0.88	10.12±0.91	**0.02**
NLR	1.82±0.55	1.66±0.73	1.46±0.50	1.88±0.90	**0.00**
PLR	0.12±0.03	0.11±0.04	0.10±0.03	0.13±0.05	**0.02**
MLR	0.26±0.08	0.25±0.10	0.23±0.06	0.26±0.11	0.20

Table 3 P-values of post-hoc and pairwise comparison tests for the significant hematological parameters

Parameters	Group/Subgroup	Control	Acute	Subacute	Chronic
HGB	**Control**	-	**0.00**	**0.00**	**0.00**
	Acute	-	-	0.88	0.88
	Subacute	-	-	-	0.99
Lymphocyte	**Control**	-	0.95	**0.01**	0.22
	Acute	-	-	**0.02**	0.24
	Subacute	-	-	-	**0.00**
MPV	**Control**	-	**0.02**	0.08	**0.01**
	Acute	-	-	0.54	0.57
	Subacute	-	-	-	0.26
NLR	**Control**	-	0.15	**0.00**	0.62
	Acute	-	-	0.1	0.09
	Subacute	-	-	-	**0.00**
PLR	**Control**	-	0.88	0.06	0.12
	Acute	-	-	0.11	0.11
	Subacute	-	-	-	**0.00**

Of the participants diagnosed with brucellosis, 62 (36.7%) had acute brucellosis, 62 (36.7%) had subacute brucellosis, and 45 (26.6%) had chronic brucellosis. The hematological parameters of the brucellosis subgroups were compared with those of the control group. According to the statistical results, it was observed that the HGB, lymphocyte, MPV, NLR, and PLR values included statistically significant differences (Table 2). Each brucellosis subgroup had lower HGB and higher MPV values than the control group. The subacute brucellosis subgroup had higher lymphocyte, lower NLR, and lower PLR values than the other brucellosis subgroups and control group. Multiple comparison and pairwise comparison tests revealed that the following groups had statistical differences between them: acute–control, subacute–control, chronic–control, in terms of HGB; control–subacute, acute–subacute, chronic–subacute, in terms of lymphocytes; acute–control and chronic–control, in terms of MPV; control-subacute and subacute–chronic, in terms of NLR; and subacute–chronic, in terms of PLR (Table 3).

With the aim of evaluating overall diagnosis performance of hematological parameters found as the significant, ROC analysis was performed between the following pairs: acute–control, subacute–control, chronic–control, acute-subacute, acute-chronic, subacute-chronic, and control-brucellosis (Table 4). The Youden Index was used to determine the cut-off points for the hematological parameters that were found to be statistically significant. The following distinctive parameters were found: HGB between the control group and the acute brucellosis subgroup, the control and the subacute brucellosis subgroup, and the control and the chronic brucellosis subgroup, lymphocyte counts between the control group and the subacute brucellosis subgroup, MPV between the control group and the chronic brucellosis subgroup, NLR between the control group and the subacute brucellosis group (Figure 1), lymphocyte counts between the acute and the subacute brucellosis subgroups and the subacute and the chronic brucellosis subgroups, NLR and PLR between the subacute and chronic brucellosis subgroups (Figure 2), and leucocyte, HGB, Neutrophil, MPV and NLR between the control group and the brucellosis group (Figure 3).

The Youden Index was used to determine the cut-off points of the parameters found to be statistically significant. The results of the cut-off values can be summarized as follows.

Results obtained for the brucellosis subgroups and the control:

- The cut-off value was calculated as 14.25 for the HGB parameter between the control and acute brucellosis group, and between the control and subacute brucellosis group. It was concluded that HGB could discriminate control group participants with 69% accuracy, acute patients with 79% accuracy, and subacute patients with 87% accuracy. The cut-off value was calculated as 14.15 for the HGB parameter between the control and chronic brucellosis group. It was concluded that HGB could discriminate control group participants with 70% accuracy and chronic patients with 78%.
- The cut-off value was calculated as 2305 for the lymphocyte parameter between the control group and the subacute brucellosis subgroup. It was concluded that lymphocyte

Table 4 Results of ROC Analysis for Blood Parameters

Groups	Parameters	AUC	Cut off point	Sensitivity(%)	Specificity (%)	+PV	-PV	Accuracy
Control-Acute	**HGB**	0.75	14.25	79	69	0.64	0.82	0.73
	MPV	0.58	8.95	92	27	0.48	0.82	0.55
Control-Subacute	**HGB**	0.76	14.25	87	69	0.67	0.88	0.76
	LYMP	0.62	2305	68	58	0.54	0.71	0.62
	NLR	0.68	1.67	66	62	0.55	0.72	0.64
Control-Chronic	**HGB**	0.74	14.15	78	70	0.57	0.86	0.73
	MPV	0.63	9.65	73	49	0.43	0.78	0.57
Acute-Subacute	**LYMP**	0.62	2305	68	58	0.62	0.64	0.63
Subacute-Chronic	**LYMP**	0.66	2305	62	68	0.42	0.71	0.64
	NLR	0.63	1.96	38	87	0.68	0.66	0.66
	PLR	0.64	0.1093	60	66	0.56	0.69	0.64
Control-Brucellosis	**Leucocyte**	0.59	6065	42	79	0.80	0.41	0.55
	HGB	0.75	14.25	82	69	0.84	0.66	0.77
	NEUT	0.61	3805	60	58	0.74	0.43	0.60
	MPV	0.58	9.05	87	29	0.71	0.53	0.67
	NLR	0.61	1.1912	31	88	0.84	0.40	0.51

Figure 1 - The results of ROC analysis between the brucellosis subgroups and the control group for the significant hematological parameters

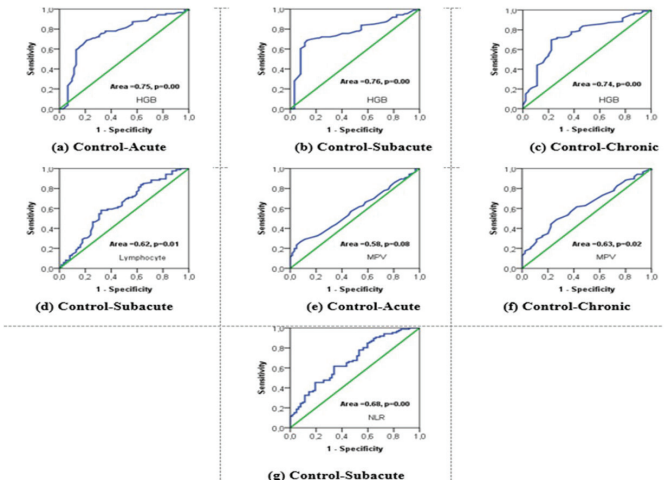
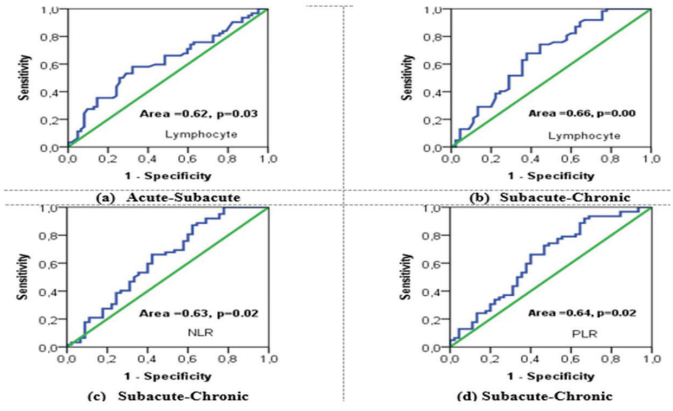


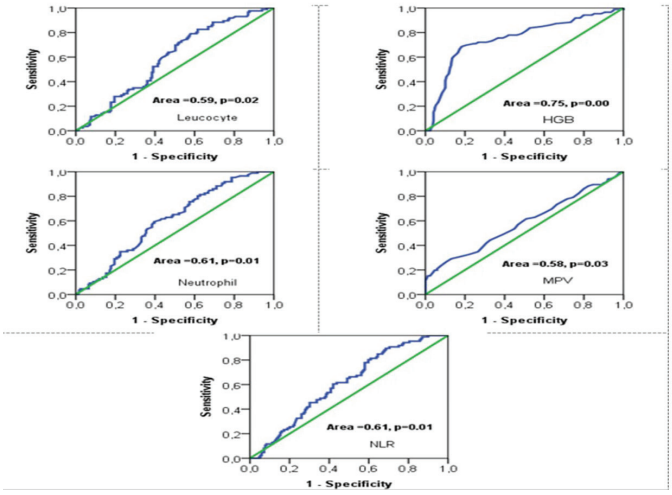
Figure 2 - The results of ROC analysis between the brucellosis subgroups for significant hematological parameters



count could discriminate subacute patients with 68% accuracy and control group participants with 58% accuracy.

• The cut-off value between the control group and the chronic brucellosis subgroup was determined to be 9.65 for MPV. It was concluded that MPV could discriminate chronic brucellosis patients with 73% accuracy and control group participants with 49% accuracy.

Figure 3 - The results of ROC analysis between the brucellosis group and control group for significant hematological parameters



• The cut-off value was calculated as 1.67 for the NLR parameter between the control group and the subacute brucellosis subgroup. It was concluded that NLR could discriminate subacute brucellosis patients with 66% accuracy and control group participants with 62% accuracy.

Results obtained for the brucellosis subgroups:

• The cut-off value was calculated as 2305 for the lymphocyte count parameter between the acute and the subacute brucellosis subgroups, and between subacute and chronic brucellosis subgroups. It was concluded that lymphocyte count could discriminate acute brucellosis patients with 58% accuracy, subacute brucellosis patients with 68% accuracy, chronic brucellosis patients with 62% accuracy.

• The cut-off values between the subacute and chronic brucellosis subgroups were 1.9602 for NLR and 0.1093 for PLR. It was concluded that subacute brucellosis patients could be discriminated with 87% accuracy via NLR and 56% accuracy via PLR, while chronic brucellosis patients could be discriminated with 38% accuracy via NLR and 60% accuracy via PLR.

Results obtained for the brucellosis group and control group:

• The cut-off value was 6065 for leucocyte. The brucellosis patients could be discriminated with 42% accuracy and the control group participants with 79% accuracy via leucocyte.

• The cut-off value was 14.25 for HGB. HGB could discriminate control group participants with 69% accuracy and brucellosis patients with 82% accuracy.

• The cut-off value of neutrophil was equal to 3802. It was concluded that neutrophil could discriminate control group participants with 58% accuracy and brucellosis patients with 60% accuracy.

• The cut-off value of MPV was 9.05. It was concluded that MPV could discriminate control group participants with 29% accuracy and brucellosis patients with 87% accuracy.

• The cut-off value was 1.1912 for NLR. It was concluded that NLR could discriminate control group participants with 88.4% accuracy and brucellosis patients with 31.32% accuracy.

Discussion

Brucella is an intracellular bacterium that can live in phagocytic cells, such as neutrophils and macrophages. Following primary infection, the disease spreads to the lymph nodes and then passes into the bloodstream, causing systemic infection. In addition to an increase in the number of leukocytes and neutrophils, changes in inflammatory indexes occur during infection. The disease also contributes to the pathogenesis of platelets [6]. Brucellosis can cause leukopenia, lymphomonocytes, and mild anemia [8]. Studies conducted in recent years have shown that some hematological biomarkers reflect systemic inflammation and can be used in the diagnosis of some diseases [6, 13, 16, 17]. Olt et al. [18] found a significant relationship between HGB and NLR levels and brucellosis. In a case-control study conducted in Iran, it was shown that leukocyte, CRP, and neutrophil counts can be used as biomarkers in the preliminary diagnosis of brucellosis [6]. Şen et al. [19] showed that the PLR value increased in patients with complicated brucellosis and that the increase in NLR and PLR values and the decrease in MLR were significantly associated with specific organ involvement. Bozdemir et al. [20] found that in the pediatric age group, there were significant differences in HGB, platelet, MPV, and NLR values between the patient and control groups; moreover, they stated that MPV and NLR values were particularly useful as inflammation markers in childhood brucellosis.

The hemogram plays an important role in the diagnosis of infectious diseases. MPV is one of the parameters that can be studied in a hemogram. It gives the mean platelet size and shows platelet activation. It has been shown that MPV levels are affected not only by prothrombotic conditions but also by rheumatic and infectious diseases [12]. In Parlak et al.'s [21] case-control study, the MPV value was found to be significantly higher in brucellosis patients, and it was stated may have prognostic value in brucellosis. Bozkurt et al. [22] and Kader et al. [23] predicted that MPV values before treatment in brucellosis patients were lower than after treatment and that MPV values could be a beneficial parameter in evaluating disease activity and response to treatment. Togan et al. [24] found no significant difference between the MPV values of patients with acute brucellosis and the control group participants.

The idea behind this study is that some hematological sub-parameters in the hemogram maybe distinctive among brucellosis clinical groups. In our literature review, no study was found in which hematological sub-parameters were compared between the brucellosis subgroups and the control group. Therefore, our study is significant in that it is the first study to carry out such comparisons.

The results obtained from the study can be summarized as follows. The differences between the brucellosis group and the control group in terms of leucocyte, HGB, neutrophil, MPV, and NLR were found to be statistically significant. The brucellosis group had higher MPV and lower mean leucocyte, HGB, neutrophil, and NLR levels than the control group. The brucellosis subgroups were compared with the control group, and the differences in HGB, lymphocyte, MPV, NLR, and PLR values were found to be statistically significant. Each brucellosis subgroup had a lower mean HGB and a higher mean MPV than the control group. In addition, it was observed that the following parameters could be used as diagnostic tests according to the results of ROC analysis: lymphocyte value for the subacute brucellosis subgroup and the other brucellosis subgroups and the control group, HGB for the control group and the brucellosis group, and the control group and the brucellosis subgroups, MPV values for the brucellosis group and the control group and the control group and the chronic brucellosis subgroups, NLR for the control group and subacute brucellosis subgroup, subacute and chronic brucellosis groups, and the control group and the brucellosis group, and PLR values for the subacute and the chronic brucellosis subgroups.

Conclusion

Brucellosis continues to impact both individual and public health. Although various tests are used in the diagnosis and follow-up of the disease, some hematological and biochemical parameters may be useful in the early diagnosis of the disease. In this study, the following findings were determined to be important: the lowness of leucocyte and HGB and highness of MPV in brucellosis patients, as well as the highness of lymphocyte levels and lowness of NLR and PLR levels in the subacute brucellosis subgroup. In addition, it was concluded that the MPV parameter can be used as a diagnostic test for brucellosis.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

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JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/12930

HALP score as a new prognostic factor for Covid-19

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Received: 2022-11-18.
Accepted: 2023-01-22

J Clin Med Kaz 2023; 20(1):56-60

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Abstract

Objective: This research aims to analyze the HALP. (hemoglobin, albumin, lymphocyte. platelet) score of.survivor-deceased Covid-19 patients.

Material and methods: 590 patients with. Covid-19 were. included. in. this. study. Patients. were. divided. into two groups as survivor (n:296) and deceased (n:294). Patient information was collected from the hospital online system. The Study was conducted retrospectively, and it aims to.investigate.the association.between HALP score and.mortality.in Covid-19.patients.

Results: In.the deceased group.the.mean.age was 71.32±10.9 (n:294) while in the survivor.group, it.was 59.97±16.2 (n:296) (p:0.000). 65,6% of the deceased group were.male, while 55% of survivor group were male (p<0.001). The median HALP score was 11,45 (1,00-1594,00) in the deceased group, while it was 23,58 (1,73-231,75) (p<0.001) in survivor group. Through our analysis,.we have found.that.the.HALP score.was associated with mortality, thus the.relationship.between 1/HALP.score.and.mortality was examined. While the median 1/HALP was 0.08 (0.01-1.00) in deceased group, it was 0.04 (0.01-0.58) in the survivor group. ROC (receiver. operating.characteristic) analysis was executed for determining the cut off value of 1/HALP. The cut.off.value of 1/HALP for mortality was 0,064 ((AUC: 0,724 (0,682-0,767); 67,3% Sensitivity, 67,0% Specificity; p<0.001)).

Conclusion: There is a meaningful correlation established between low HALP score and.mortality. in.Covid-19.patients. We.have reached the.conclusion that using HALP score.to. predict.mortality.in.Covid-19. patients might be useful.

Key words: HALP, Covid-19, ICU, mortality

Introduction

A.new.virus,.from the coronavirus family,.which. was called as Sars-Cov-2 in December 2019, led to the outbreak of a pandemic in March 2020. The disease due to this virus was defined as Covid-19 [1]. The pandemic, which affected approximately 613,972,905 people, has caused 6,516,982 deaths since its onset [2]. With the increasing significance of determining the Covid-19 prognosis, many new markers and scoring systems, in addition to well-known markers such as serum ferritin level, neutrophil lymphocyte ratio and d-dimer were found to successfully show the Covid-19 progression [3–5]. A relationship between low hemoglobin level and Covid-19 mortality was described, which is thought to be due to the lower oxygen carrying capacity in anemic patients, especially in elderly with comorbidities [6]. Similarly, a relationship.was.found.between.low. albumin.and Covid-19 mortality. A low albumin level increases the risk of mortality for Covid-19, regardless of other mortality-increasing characteristics such as age and comorbid situations [7]. The lymphocyte level can be found higher or lower in viral infections and, a significant relationship was depicted among low lymphocyte level and mortality in Covid-19 [8]. Thrombocytopenia is a well-known poor prognostic component in multi-organ failure, and an important parameter in Acute Physiology Score II, which is a widely used scoring system for detecting mortality [9].

The HALP score, is a mathematical formula produced from albumin, hemoglobin, lymphocyte

and platelet counts, which are frequently used as inflammation markers. This scoring system is used as a new prognostic factor especially for malignancies and was shown to be related with increased inflammation. The HALP score is computed with this equation: lymphocytes(/L).x.albumin(g/L).x.hemoglobin(g/L) / platelets.(/L) [10]. In addition to its use for determining inflammation, HALP.score.can also be.used as predictor. of.mortality in ischemic.stroke [11].

There are no other studies in the current literature depicting the association between the HALP score and Covid-19. The relationship between inflammatory processes and Covid-19 is well known, thus we aim.to investigate.relationship.between. Covid-19.and HALP score which is a novel inflammatory indicator.

Material and methods

Data.from.590.patients.with.Covid-19.from.15/03/2020 to 15/01/2021 in internal.medicine wards.and ICUs included study and analyzed retrospectively. Demographic information and laboratory findings were gathered from the hospital electronic system. Decision for ICU admission was made according to the Covid-19 guide by the.World.Health.Organization. According. to.these.guides, patients.with.confusion, PaO2/FiO2. <300, respiratory.rate ≥ .30/min, SpO2 <90% despite.5 L/min.oxygen. therapy, systolic.blood.pressure.<90 mmHg, mean.arterial. pressure <65 mmHg, acute.organ dysfunction such as.acute. bleeding diathesis,acute.kidney.injury,.impaired.acute.liver. function.tests,.immunosuppression.were.followed.up in the ICU [12]. Patients were described in two groups as deceased or survivor. Standard deviation and mean value were used for quantitative0values, whereas.percentages.and numbers were.used.to represent.qualitative.values. Shapiro-Wilk.was. used.for determining normality.distribution. For comparing the qualitative values, Chi-square test was used. Meanwhile, Mann-Whitney-U and Independent T.tests were executed for. quantitative.values according.to normality.distribution. HALP score was calculated using the laboratory data of patients.at hospital.admission. Due to the correlation between low HALP score and mortality, ROC analysis was performed to anticipate the functionality of 1/HALP level.for identifying. the severity of disease and mortality.separately. For.statistical.significance, p<0.05 was. accepted. IBM SPSS, Version 20.0 package. program.was performed for.execute statistical. analysis.

Results

Mean.age.of deceased group.was 71.32±10.9 (n:294) and.the.mean.age. for.the.survivor group.was.59.97±16.2 (n:296) (p<0.001). 65,6% of the deceased group were.male,. and 55% of the survivor.patients.were male (p<0.001) (Table1). Regarding comorbid diseases, the frequency of coronary.artery. disease,.hypertension,.congestive.heart.failure.and.diabetes was higher in deceased patients, which was statistically.significant (Table 1). While.the.mean .CRP level of deceased.patients.was 140.0±97.4 mg/L, this.level.was 67.3±68.5 mg/L in the survivor patients (p<0.001). Median procalcitonin level was 0.67 (0.02-100) ng/dl in the deceased group, and it was.0.1 (0.01-100). ng/dl (p<0.001) in the survivor.group. When ferritin level was examined, the median ferritin was 855,00 (6,69-40002,00) µg/L in the deceased group, while it was 289,00 (1,90-6321,00) µg/L in the survivor group (p<0.001). The mean.LDH level was 521,00 (126,00-10056,00) U/L in the deceased group, and 4319,00 (118,00-1196,00) U/L (p<0.001) in the survivor.group. The.difference.between.positive acute phase.reactants.between the deceased and.the survivor.group was also statistically. significant (Table 1).

When.the.albumin level.was examined,.the mean albumin level.of the deceased group and survivor.group were 28,70±4,63 g/L and 33,49±5,62 mg/dl (p<0.001) respectively. Median lymphocyte level was 0,57 (0,06-8,74) k/uL in the deceased group, and 0,85 (0,11-4,87) k/uL (p:0.006) in the survivor.group. Mean thrombocyte level.was 201,24±93,89 k/uL in the deceased group, and 208,09±88,99 k/uL (p:0.363) in.the survivor group. The.difference between.thrombocyte level in deceased and survivor group was.not statistically significant (Table 1).

Median HALP score was 11,45 (1,00-1594,00) in the deceased group, while this ratio was 23,58 (1,73-231,75) (p<0.001) in the survivor group. Since a low.HALP.score was correlated with.high mortality,.we investigated the relationship.

Table 1 Demographics and comparison of laboratory findings in deceased and survivor patients.

Age	Deceased	Survivor	P
	71.32 ±10.92 (n:294)	59.97±16.24 (n:296)	<0,001
Gender (n)	M:193 (%65.6) F:101 (%34.4)	M:165 (%55.9) F:130 (%44.1)	<0,001
Comorbidities			
Diabetes Mellitus	108 (%36,6)	81 (%27,5)	0,019
Hypertension	172 (%58,3)	138 (%46,7)	0,005
Chronic Kidney Failure	40 (%13,6)	26(%8,7)	0,067
Coronary artery disease	83(%28,2)	49 (%16,5)	0,001
Congestive Heart Failure	48 (%16,3)	18(%6,0)	<0,001
Laboratory findings			
CRP	140,60±97,48	69,52±68,80	<0,001
Procalcitonin	0,67 (0,02-100,00)	0,1 (0,01-100,00)	<0,001
Ferritin	855,00 (6,69-40002,00)	289,00 (1,90-6321,00)	<0,001
LDH	521,00 (126,00-10056,00)	319,00 (118,00-1196,00)	<0,001
Hemoglobin	12,07±2,09	12,51±1,87	0,006
Albumin	28,70±4,63	33,49±5,62	<0,001
Lymphocyte	0,57 (0,06-8,74)	0,85 (0,11-4,87)	0,006
Thrombocyte	201,24±93,89	208,09±88,99	0,363
HALP	11,45 (1,00-1594,00)	23,58 (1,73-231,75)	<0,001
1/HALP	0,08 (0,01-1,00)	0,04(0,01-0,58)	<0,001

Table 2 ROC curve for estimate mortality in Covid-19.

Parameter	AUC %95 Cl	Cut-off	Sensitivity %	Specificity %	P
1/HALP	0,724 (0,682-0,767)	0,064	67,3	67,0	p<0.001

between.1/HALP.and.mortality. While the median 1/HALP was 0.08 (0.01-1.00) in the deceased group, it was 0.04 (0.01-0.58) in the survivor group (p<0.001) (Table 1). A Roc.analysis was used for.determining the cut.off. value.of 1/HALP, and the sensitivities, specificities, cut.off.values, and area.under.the curve. were.calculated. Cut off.value.of 1/HALP for mortality. was calculated as 0,064 ((AUC: 0,724 (0,682-0,767); 67,3% Sensitivity,. 67,0% Specificity. p<0.001) (Table 2). (Figure1).

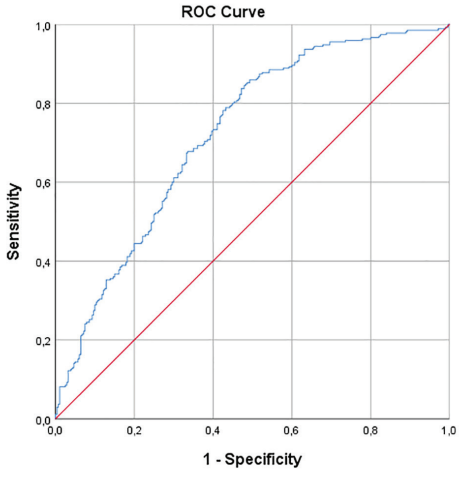

Figure 1 - ROC curve for estimate mortality in Covid-19.

Discussion

It is well-known that increased positive acute phase reactants are related with.increased mortality.and.severity. of Covid-19. Many studies and reviews in current literature has shown that increased CRP, LDH, and procalcitonin levels. were.related with high Covid-19 morbidity and mortality [13,14]. Similarly, in our study, increased CRP, LDH,.and. procalcitonin.levels. were associated with increased mortality in deceased.group (p<0.001, p<0.001, p<0.001). SARS-Cov-2 virus is known to impact red blood cell membrane (RBC) and hemoglobin oxygen affinity. It is also assumed that the adaptation mechanism of RBCs in compliance with the oxygen demand is impaired as well [15]. Additionally, the inflammatory indicators and the rate.of.mortality were higher in Covid-19.patients with low hemoglobin levels [16,17]. In a.retrospective.cohort study conducted on.222.patients diagnosed with Covid-19, the mean. hemoglobin.level was 11.1 g/dl.in patients with severe disease compared to 12.8 g/dl in non-severe patients [18]. In our group of patients, the mean hemoglobin level of deceased patients was 12.07±2.09, and 12.51±1.87 in survivor patients (p:0.006). In some other studies, a positive association was shown between increased ferritin levels due to inflammatory iron mechanism, the length.of.stay in hospital, the need for ICU, and the need for mechanical ventilators [19,20]. Similarly, in.our.study, we also found a positive association between the increased serum ferritin and mortality (p<0.001).

Albumin is a plasma colloid that has a critical function in preserving the intravascular oncotic pressure and the carriage of some substances in the plasma. It is also a well known negative acute phase reactant which decreases in inflammatory processes, nutritional deficiencies, and in conditions such as cirrhosis given that it is synthesized from the liver [21]. It is believed that ARDS condition in Covid-19 worsens due to the extravasation of the intravascular volume caused by low albumin, which also causes deterioration of kidney and gastrointestinal system functions [22]. In line with the current literature, we demonstrated a the strong correlation between low albumin and.mortality. in Covid-19.patients (p<0.001).

Lymphopenia is commonly.seen.in Covid-19.patients, almost up to 85% of the.patients.who. are.severely ill [23]. In a meta-analysis.of 23 studies,.lymphopenia was linked with the development of ARDS and the increased need for ICU [24]. In Covid-19, lymphopenia develops rapidly after infection, which is believed to be due to lymphocyte sequestration [25]. In another meta-analysis conducted with 71 studies, a relationship was found between lymphopenia and increased mortality [26]. Similar to the recent literature findings, we also pointed out a significant correlation between low lymphocyte level and mortality (p:0.006).

The platelets are an important component of the primer coagulation system. Even though they do not play a part in the inflammatory process, approximately 40% of severely ill Covid-19 patients have thrombocytopenia [27]. One meta-analysis.of 17.studies and 3481 patients. showed that a low (<150000) platelet count was associated with poorer outcomes [28]. In our. study,.no statistically.significant result was.found. between thrombocyte level and.mortality.

The HALP.score.is a newly introduced scoring.system that.is.calculated.as hemoglobin x albumin x lymphocyte / platelet. The first study in the literature on the HALP scoring system outlined the relationship between low HALP level and poor prognosis in 820 locally advanced colorectal cancer patients in 2016 [29]. Similarly, some studies showed that there was an inverse relationship between survival in bladder cancer and HALP.score, which is also an.independent risk factor.for predicting nephrectomy in renal cell carcinoma. It was also stated that the HALP score is a powerful tool to determine the inflammatory state in these patients [30,31]. Furthermore, in another study implemented on 1337 patients diagnosed with acute ischemic stroke, a positive correlation between low HALP score, and re-stroke and mortality was discovered [11]. According to a study investigating the relationship between inflammation and HALP score, although no correlation existed between the HALP score and prognosis of ANCA-positive vasculitis patients, a low HALP score could be partially useful for initial diagnosis [32]. In the study that we have established, a significant correlation was evident between low HALP score and mortality (p<0.001).

Conclusion

As a result, a significant correlation was found between a low HALP score and mortality in Covid-19. We strongly believe that HALP.score.could.be.a.useful.parameter to determine mortality in Covid-19 patients.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

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JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Original Article DOI: https://doi.org/10.23950/jcmk/12931

The frequency of allelic variants of the VDR gene and the level vitamin D in children under one year old in the Kazakh population

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Received: 2022-10-27.
Accepted: 2023-01-22

J Clin Med Kaz 2023; 20(1):61-64

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Abstract

Introduction: The study of the genetic aspects of bone metabolism disorders in children is a theoretical and practical interest for pediatrics, especially according to the age and ethnic positions. There is a number of gene polymorphisms (primarily the vitamin D receptor (VDR) gene) that determine the norm and pathology of bone tissue formation. Calcium absorption worsens when there is no functional VDR and active forms of vitamin D. As a result the level of bone mineralization decreases. In children such disorders lead to the development of osteopenia.

Objective: To determine the frequency of allelic variants of the VDR gene (rs1544410, rs2228570) and to evaluate its relationship with the level of vitamin D in children under one year old in the Kazakh population.

Material and methods: 197 children under one year of age were examined for vitamin D by electrochemiluminescent immunoassay and genotyping of the VDR polymorphism (rs1544410, rs2228570) by PCR.

Results: It was found out that children with the C allele of the VDR rs2228570 gene have a reduced level of vitamin D by 1.84 times (95% CI 1.10 - 3.07) and CC - by 2.3 times compared with children with normal vitamin D levels.

Statistical analysis by the Kruskal-Wallis method showed that the serum level of vitamin D in AA carriers for the VDR rs1544410 was significantly reduced comparing to the level in GG and GA carriers (p=0.03).

Conclusion: The study confirms the need for further in-depth study of the genetic aspects of bone metabolism disorders in children for the development of personalized medicine.

Key words: vitamin D, VDR gene polymorphism, children, osteopenia

Introduction

Nowadays much attention is paid to the issues of bone mineral density in children. The results of a number of studies show that about 70-80% of the variability in bone mineral density in a population is determined by genetic factors [1,2].

There is a number of gene polymorphisms that determine the norm and pathology of bone tissue formation, the most relevant of which is the vitamin D receptor (VDR) gene [3,4].

The "VDR gene" (vitamin D receptor) encodes an intracellular vitamin D receptor, which is also a transcription factor. It is expressed in various tissues, mostly in the intestines, kidneys, parathyroid glands and bones - all these tissues and organs are integrated into the system for maintaining calcium homeostasis. In the absence of a functional VDR and an active form of vitamin D, calcium absorption worsens and, as a result, the level of bone mineralization decreases. In children such disorders lead to the development of osteopenia, in adults - to osteoporosis [5,6].

General statements about the role of genetic factors in osteopenic conditions cause no doubts, but there are still enough questions on the contribution of specific genes that regulate the growth and development of the skeletal system, especially from age and ethnic positions. The study of the genetic aspects of bone metabolism disorders in children, especially at an early age, is a theoretical and practical interest in pediatrics.

Purpose: To determine the frequency of allelic variants of the VDR gene (rs1544410, rs2228570) and to evaluate its relationship with the level of vitamin D in children under one year old in the Kazakh population.

Material and methods

197 children of Kazakh population under one year old were examined in the city of Aqtobe. The sample size was calculated according to the "Epi Info" program. The recruitment of children was carried out using the method of probability sampling.

Inclusion criteria: children from 0 to 12 months, of the I and II health groups, according to the order № 145 dated March 16, 2011, in a satisfactory condition at the time of the study, with informed consent signed by parents or legal representatives.

Exclusion criteria: children with hereditary and acquired diseases of the musculoskeletal system, registered in the dispensary account for severe chronic somatic diseases; disability due to other diseases; with genetic syndromes.

After a clinical examination all children underwent the venous blood sampling for molecular genetic analysis. Isolation of genomic DNA from the peripheral blood of the subjects was performed using "DNA-Blood-M-100" reagent kits from TestGen LLC (Russia). The principle of the method is based on the reversible binding of nucleic acids on the surface of magnetic particles.

Genotyping of the VDR polymorphism (rs1544410, rs2228570) was carried out by real-time polymerase chain reaction (PCR) on a DT-prime amplifier (DNA-technology, Russia) using commercial kits of reagents of LLC TestGen (Russia) by the method of fluorescent detection. The method is based on the degradation of oligonucleotide probes using synthetic analogues of oligonucleotides.

The process of DNA amplification consists in repeated cycles of thermal denaturation of DNA, annealing of primers with complementary sequences, and next completion of polynucleotide chains from these primers by Taq polymerase. Signal probes, containing FAM and HEX fluorescent labels, were introduced into the amplification mixture for each variant of the determined genetic polymorphism (mutation).

After the end of PCR, the duplexes, formed by the amplicons and signal probes, go through a round of thermal melting. As the result, the fluorescence level changes. It is fixed and presented in the form of a graph.

Genotyping was carried out at the Scientific and Practical Center of the WKMU named after Marat Ospanov.

The electrochemiluminescent immunoassay method was used to determine the concentration of vitamin D in blood samples (5 ml), It is a quantitative method of measuring an antigen or antibody based on changes in the electrochemiluminescence signal before and after the immunoreaction [7]. Vitamin D sufficiency was evaluated in accordance with the criteria of the National Program "Vitamin D Deficiency in Children and Adolescents of the Russian Federation: Modern Approaches to Correction", 2018. [8].

Nonparametric criteria were used for statistical processing of quantitative data. Using the Kruskal-Wallis test, the distribution of genotypes (GG, AG, AA/TT, CT, CC) for 2 polymorphisms of the VDR gene between groups with different levels of vitamin D was determined.

The Mann-Whitney test was used to perform pair-matched comparisons of groups (GG with AG, GG with AA, AG with AA and TT with CT, TT with CC, CT and CC). At the same time, the Bonferroni correction was held with the significance level of 0.017. The obtained data were processed by the statistical licensed program Statistica 10 and SPSS 25.

Results

A total of 197 children under one year old of the Kazakh population were examined for the content of vitamin D. It was found that the normal level of vitamin D was observed in 36 (18.3%), and hypovitaminosis - in 161 (81.7%) children.

Next, the distribution frequency of genotypes and alleles of the polymorphism of the VDR rs1544410 gene was determined. The results of the survey are presented in Table 1.

Table 1 Frequency distribution of genotypes and alleles of VDR rs1544410 polymorphism

VDR rs 1544410 polymorphism	Genotype frequency			Allele frequency	
	GG	GA	AA	G	A
	0,58	0,4	0,02	0,76	0,14

The results of studying the frequency distribution of genotypes and alleles of the VDR rs2228570 polymorphism are presented in Table 2.

Table 2 Frequency distribution of genotypes and alleles of VDR rs2228570 polymorphism

VDR rs2228570 polymorphism	Genotype frequency			Allele frequency	
	TT	TC	CC	T	C
	0,28	0,25	**0,47**	0,52	0,68

During the process of further research, the analysis of the frequency distribution of genotypes and alleles of the VDR rs1544410 depending on the level of vitamin D in the blood was made (Table 3).

Table 3 Frequency distribution of genotypes and alleles of the VDR rs1544410 depending on the level of vitamin D

rs1544410	**Vitamin D deficiency** (n = 161)	**Norm of vitamin D** (n = 36)	**χ2**	**p**	**OR (95% CI)**
G allele A allele	0.784 0.216	0.764 0.236	0.13	0.72	1.12(0.61 – 2.05) 0.89 (0.49 – 1.64)
G/G genotype G/A genotype A/A genotype	0.591 0.384 0.024	0.528 0.472 0.000	1.66	0.44	1.30 (0.63 – 2.67) 0.70 (0.34 – 1.44) 2.05 (0.11 – 38.86)

Table 4

Frequency distribution of genotypes and alleles of the VDR rs1544410 depending on the level of vitamin D

rs2228570	**Vitamin D deficiency** (n = 161)	**Norm of vitamin D** (n = 36)	**χ2**	**p**	**OR (95% CI)**
T allele *C* allele	0.378 0.622	0.528 0.472	5.49	0.02	0.54 (0.33 – 0.91) 1.84 (1.10 – 3.07)
T/T genotype *T/C* genotype *C/C* genotype	0.262 0.232 0.506	0.361 0.333 0.306	4.78	0.09	0.63 (0.29 – 1.35) 0.60 (0.28 – 1.32) 2.33 (1.08 – 5.04)

The results of the frequency distribution of genotypes and alleles of the VDR rs2228570 depending on the level of vitamin D are presented in Table 4.

At the next step, the distribution of the GG, AG, AA/TT, CT, CC genotypes of the VDR gene polymorphisms (rs1544410, rs2228570) and the level of vitamin D in blood serum in children under one year of age of the Kazakh population were compared using the Kruskal-Wallis nonparametric test. Comparison of VDR rs544410 genotypes and vitamin D levels is presented in Table 5.

Table 5

Relationship between VDR rs544410 genotypes and vitamin D levels

Dependent: Vitamin D 30–80 ng/ml	p (bilateral) for multiple comparisons; Vitamin D 30–80 ng/ml Group (independent) variable: VDR rs1544410 Kruskal-Wallis test p =0,0167		
	GG	GA	AA
	R:95,569	R:110,82	R:37,125
GG		0,209516	0,141243
GA	0,209516		0,038855
AA	0,141243	0,038855	

Discussion

An analysis of the frequency of distribution of genotypes and alleles of the VDR rs1544410 polymorphism, presented in Table 1, indicates that the GG genotype in children of the study group was found in 58% of cases compared with the GA and AA genotypes. According to the written above, the G allele frequency occurs more than the A allele. This fact is of a big interest, because a number of studies have shown that the GG genotype is responsible for reducing the risk of disorders of low bone mineral density, GA - intermediate risk, AA - increased risk [9, 10].

The result of the study of the distribution frequency of genotypes and alleles of the VDR rs2228570 polymorphism (Table 2) shows that the CC genotype (47%) and the C allele (68%) of the VDR rs2228570 were most common in children under one year of age in the Kazakh population.

The VDR rs2228570 polymorphism is currently under study. This polymorphism affects bone mineral density in children. According to literary sources, its results often vary depending on race and nationality [11].

Thus, a study among residents of Pakistan demonstrated the association of VDR polymorphisms with the appearance of bone metabolism disorders [12]. Similar associations of VDR polymorphisms are also observed in other groups: Egyptian (rs7975232, rs2228570 and rs1544410), French (rs10735810), Canadian (rs10735810), and Tunisian (rs10735810) [13]. Such studies provide a basis for studying the role of genetic factors in osteopenic conditions, depending on the ethnicity of the respondents.

Analysis of the frequency distribution of genotypes and alleles of the VDR rs1544410 gene depending on the level of vitamin D from Table 3 shows that the distribution of G and A alleles of the VDR rs1544410 polymorphism does not depend on the level of vitamin D. There were no statistically significant differences in the distribution of GG, GA and AA genotypes revealed.

Analysis of the frequency distribution of genotypes and alleles of the VDR rs2228570 gene depending on the level of vitamin D (Table 4) in groups of children with different levels of vitamin D revealed differences in the frequency of T and C alleles (p=0.02). A decrease in the level of vitamin D is observed in children with the C allele by 1.84 times and the CC genotype by 2.3 times.

When comparing VDR rs1544410 genotypes with vitamin D levels, it was noted that the level of vitamin D in blood serum in carriers of the AA genotype is reduced comparing to the level in carriers of the GG and GA genotypes. The results indicate that there are significant statistical differences between the AA and GA genotypes (p≥0.03) (Table 5).

When studying the relationship between VDR rs2228570 genotypes and vitamin D levels, it was found that the level of vitamin D in the blood serum of carriers of the TC, TT, and CC genotypes did not have statistically significant differences (p≥0.94). This appears to be due to weak link rather than insufficient statistical power.

Conclusion

The results of the molecular genotypic examination of 197 children under one year old in the Kazakh population made it possible to state the obvious predominance of the GG genotype of the VDR rs1544410 gene (58%) over the GA and AA genotypes, which generally corresponds to global data.

As part of the study, it was established that children with the C allele of the rs2228570 have a reduced level of vitamin D by 1.84 times (95% CI 1.10–3.07) and a CC genotype by 2.3 times compared with children with normal vitamin D content.

Statistical analysis by the Kruskal-Wallis method revealed that the level of vitamin D in blood serum in carriers of the AA genotype of the VDR rs1544410 gene was significantly reduced compared to the level in carriers of the GG and GA genotypes (p=0.03).

The study of the genetic aspects of bone metabolism disorders in children under one year of age is one of the premises for the development of personalized medicine, but requires further in-depth analysis.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

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JOURNAL OF CLINICAL MEDICINE OF KAZAKHSTAN (E-ISSN 2313-1519)
Case Report
DOI: https://doi.org/10.23950/jcmk/12829

Parameatal cyst: A presentation of a rare case and literature review

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Received: 2022-03-10.
Accepted: 2022-12-19

J Clin Med Kaz 2023; 20(1):65-67

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Abstract

Parameatal cysts are very rare in clinical practice due to their asymptomatic course. This article presents one such case. A 25-year-old male patient with a formed spherical cystic tumor measuring 0.7 cm in the area of the external opening of the urethra. Total resection of the cystic formation, suturing of the resulting imperfections was carried out. According to the results of histology, the cyst is formed by a flat and cylindrical epithelium. After 3 months of follow-up, good results were established without relapse and cosmetic appearance.

Key words: cystoma, resection, meatus, relapse

Introduction

Cyst formation in the parameatal area is a rare and unusual disease first described by Thompson and Latin in 1956 [1]. Since then, about 50 cases have been published [2,3]. Most reported cases were from the Japanese population, and an extensive literature search found that a few cases were reported from India.

These cysts mainly occur on one side of the urethral meatus. These benign lesions usually occur in boys, although they can be seen in infants and adults. The aetiology and pathogenesis of these cysts have yet to be established. In most cases, they are asymptomatic, but they can cause a change in the urine stream or interfere with intercourse. Simple excision is the preferred treatment option, while aspiration or marsupialization leads to relapses. In this report we want describe our first experience of parameatal cyts in our practice. Based on our case-based review, we try describe the best surgical treatment of parameatal cysts.

Case presentation

A 25-year-old man had a cystic formation that appeared in the area of glans penis and gradually increased over five years. There were no urinary symptoms other than spraying of the urinary stream and poor cosmesis. The formation did not bother the patient except for cosmetic concerns. On examination, a painless cyst 0.7 cm x 0.5 cm in diameter was found anterior to the urethral meatus (Figure 1). The cyst was soft on palpation. Examination of other areas of the penis, scrotum, and perineum was unremarkable. Palpable inguinal lymphadenopathy was not observed. The patient's urinalysis and blood test results were normal. An ultrasound examination revealed an isoechoic cystic lesion anterior to the urethral orifice (Figure 1.1). There was no evidence of a solid component, septation, or vascularization within the cyst.

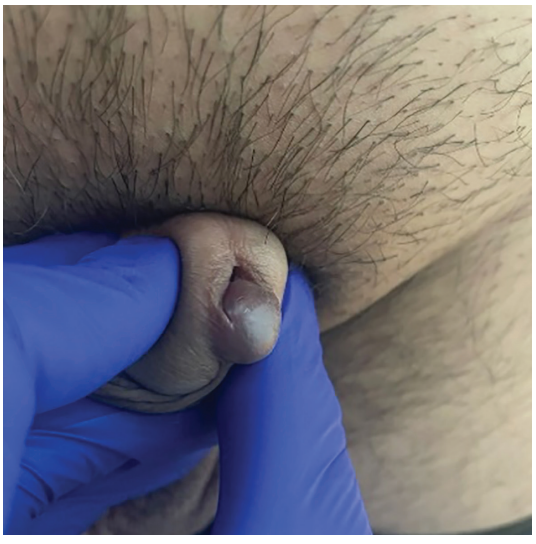

Figure 1 - Parameatal cyst appearance.

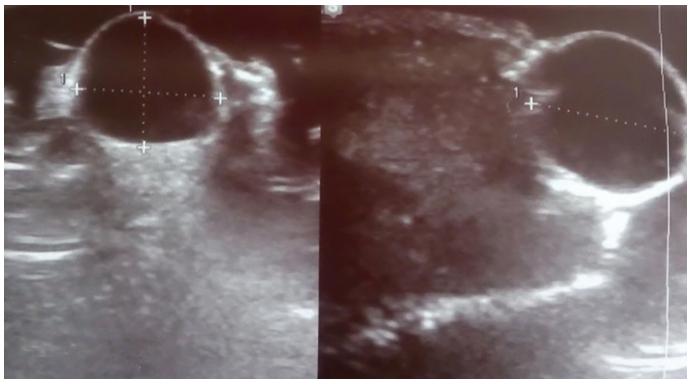

Figure 1.1 - Ultrasound of parameatal cyst. An isoechoic cystic lesion anterior to the urethral orifice

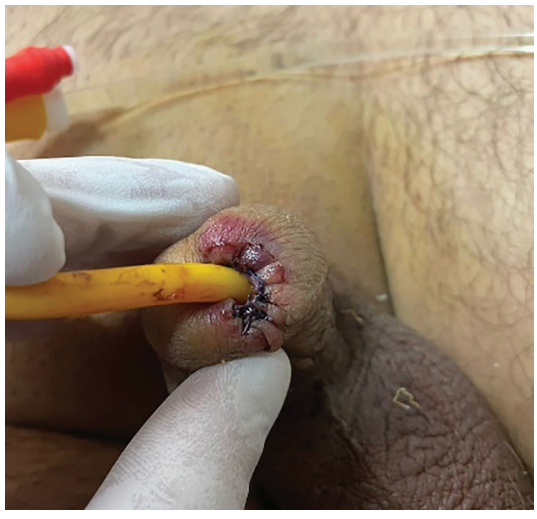

Figure 2 - The post-operative appearance of parameatal cyst. Placement of the urinary catheter.

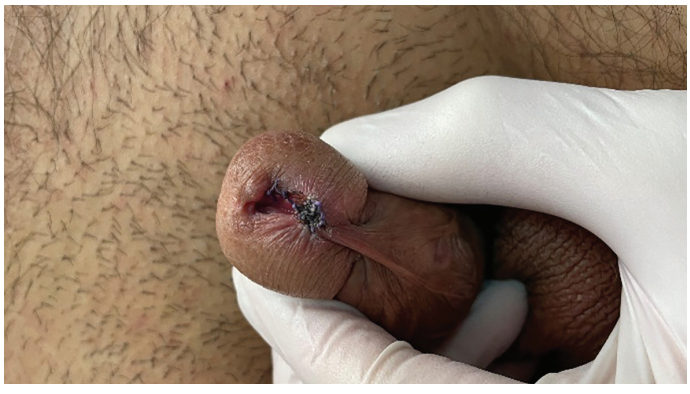

Figure 3 - Parameatal cyst appearance of the cyst in 7 days post-surgery.

Total resection of the cystic formation was performed under local anaesthesia. The edges of the incision were sutured with 3-0 catgut. A urinary catheter has been placed (Figure 2). The patient was discharged 3 hours after the surgery. We prescribed him a daily treatment of the wound with chlorhexidine. Within seven days, the wound healed and with satisfactory cosmetic appearance (Figure 3). In the further visit, the sutures and the urinary catheter were removed. The histology showed that the cyst was formed by squamous and columnar epithelium (Figure 4). After three months of follow-up, the patient did not have a relapse. A follow-up appointment was scheduled six months later.

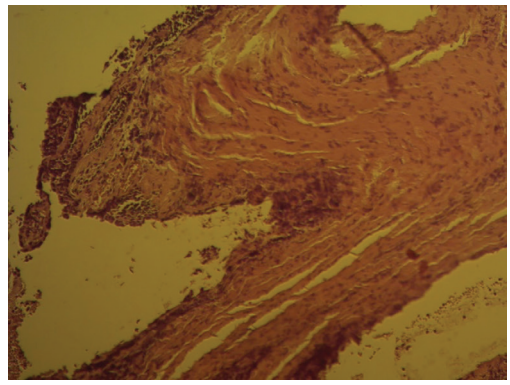

Figure 4 - a) Microscopic image (hematoxylin and eosin, 100X magnification) showing the squamous cell epithelium lining the cyst wall.

Table 1 Clinical characteristics of the median cyst of the penis in three large reviews

	Shao *et al*.[14]	**Matsuyama *et al*.[15]**	**Navalon-Monllor *et al*.[16]**
Number of cases	55a	23	28
Cyst size range	0,2–2,1 cm	from 0,1 to> 1 cm	0,5–3,5 cm
Mean cyst size	0,88 cm	n/a	1.1 cm
Location			
Parameatal	19 (33.9)	b	8 (28)
Glans of penis	4 (7.1)	–	–
Penile shaft	24 (42.9)	11 (47.8)	10 (36)
Scrotum/ perineum	2 (3.6)	2 (8.7)	2 (7)
Prepuce	7 (12.7)	–	3 (11)
Multiple areas		4 (17.4)	2 (7)
Corona / frenulum		6 (26.1)	3 (11)
Symptoms			
Asymptomatic	40 (72.7)	19 (82.6)	22 (79)
Symptomatic	15 (27.3)	4 (17.3)	4 (21)

Discussion

A parameatal cyst is a rare lesion in men, and, as reported in the literature, only about 50 cases have been reported to date [2,4]. Parameatal cysts of the glans penis have been described under various diagnostic terms such as mucoid cyst, urethral cyst, and apocrine cystadenoma. The pathology is more common in boys than in girls. Cysts can be congenital and form at any age [3]. The pathogenesis still needs to be studied. The aetiology of a paraurethral cyst is unknown, but it may occur due to obstruction of the paraurethral ducts secondary to infection in adults [4]. It is believed that their formation occurs due to inflammation, but this does not explain the aetiology of congenital parameatal cysts [5]. Other causes are occlusions of the paraurethral ducts and additional male gonads in the urethra [6]. The development of parameatal cysts was explained by preserving cystic spaces in the line separating the foreskin from the glans [1]. Some scientists have suggested that paraurethral duct obstruction was the cause, while others have suggested that infection may be a possible cause of the obstruction [7-9]. Recently, two neonatal cases have been reported in which paraurethral cysts have been associated with vaginal bleeding and breast enlargement; these factors have shown the possibility of the role of estrogens in their development [10]. The origin of parameatal urethral cysts from accessory male gonads in the urethra has been demonstrated by immunohistochemistry with PSA in the cells of these cysts [11].

It is usually a tiny cystic mass located on the lateral margin of the external urethral meatus, averaging about 1 cm in diameter [12]. They can sometimes be bilateral. Most paraurethral cysts are asymptomatic, but sometimes patients may experience painful intercourse, dysuria, difficulty with urination, or even acute urinary retention [6,13]. A physical examination alone is usually enough to make a diagnosis. The cyst may be traumatized by bleeding or infection, and spontaneous rupture may occur. The lining of the cyst wall varies depending on the origin of the affected urethral segment, and it can be columnar, cuboidal, squamous, or transitional epithelium [9,12]. The lining epithelium plays no role in treatment and relapse. The differential diagnosis includes inflammatory lesions of the urethra [12]. The treatment of choice is total cyst excision. Other options include aspiration or marsupialization, which have unsatisfactory cosmetic results and lead to frequent relapses [3]. We suppose the best surgical treatment choice is total cyst excision compare to aspiration or marsupialization in terms of relapse and cosmetic appearance.

Conclusion

A parameatal cyst is a rare pathology that occurs in men. Although these cysts are primarily asymptomatic, patients may present because of poor cosmetic appearance or urination problems. The treatment of choice is total cyst excision, while other methods, such as aspiration or marsupialization, can lead to recurrence and poor cosmetic appearance.

Summary

Parameatal cysts are very rare in clinical practice due to their asymptomatic course. This article presents one such case, a 25-year-old male patient with a spherical cystic tumour 0.7 cm in size in the area of the external opening of the urethra. According to the histology results, the cyst is formed by a flat and cylindrical epithelium. All histological findings in parameatal cases are benign. Total resection of the cystic formation was performed, and the resulting imperfections were sutured. After three months of follow-up, good results were established without recurrence and a cosmetic appearance.

Disclosures: There is no conflict of interest for all authors.

Acknowledgements: None.

Funding: None.

Patient informed consent: Obtained.

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