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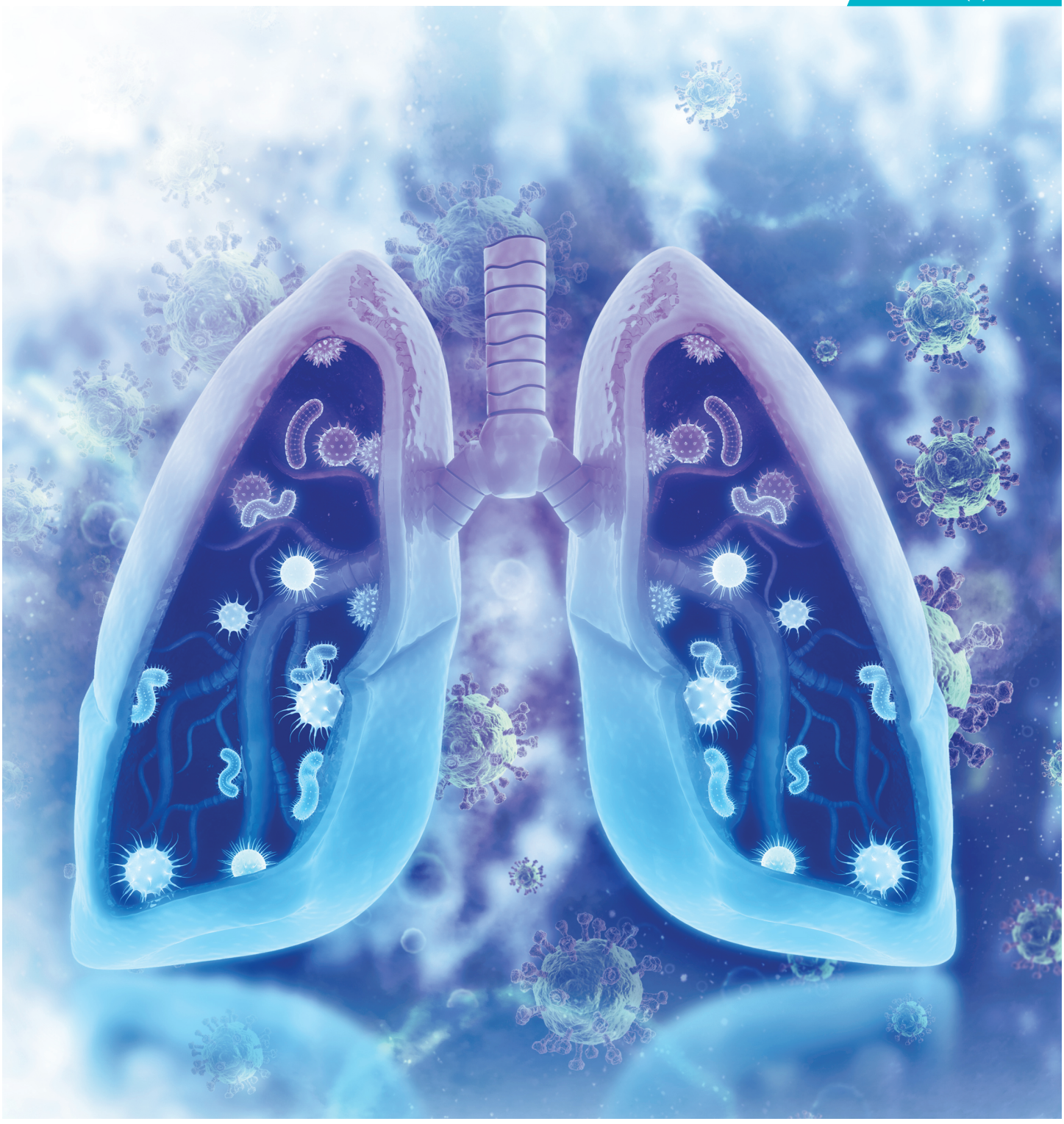

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Prognostic value of depression, anxiety disorders and inflammatory markers in patients with reduced and mildly reduced ejection fraction heart failure

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Abstract

Aim: Patients with heart failure (HF) have greater rates of depression and anxiety than the general public. The researchers wanted to investigate if there was a relationship between depression, anxiety, and inflammatory markers, as well as survival and hospitalization, in HF patients with reduced and mildly reduced ejection fractions (HFrEF and HFmrEF).

Materials and methods: This prospective research comprised 122 consecutive individuals having a left ventricular ejection fraction (LVEF) of less than 50%. The inflammatory system was investigated using the specific markers. Hamilton Depression and Anxiety Rating Scales (HAM-D and HAM-A) were used to diagnose of depression and anxiety.

Results: The median duration of follow-up was 36.4 months. Non-survivors had lower glomerular filtration rate, LVEF, and blood sodium levels than survivors, while they were older. Age, LVEF, and GFR are independent predictors for mortality. No independent relation was found between depression, anxiety, inflammatory parameters and mortality. Anxiety was found as independent predictors for hospitalization.

Conclusion: Anxiety, depression, and inflammatory conditions indicators were not associated with mortality in people with HFrEF and HFmrEF. Neutrophil-to-lymphocyte ratio (NLR) and anxiety were found as independent predictors for hospitalization.

Key words: heart failure, depression, anxiety, inflammatory markers, mortality

Introduction

Heart failure (HF) still reduces the quality of life because of recurrent hospitalizations, and it has high mortality despite improvements in medical and interventional treatment strategies. HF was reported to be related to psychological stress and incidence of clinically significant anxiety disorders (8%–16%), including general anxiety disorder and panic attack [1,2]. The relationship between HF and depression is a new area in daily practice. The frequency of depression in patients with HF is 2–3 times higher than that in the normal population [3]. Sometimes, depression is overlooked in routine daily practice because these two diseases have many similar symptoms, and HF symptoms may lead to over-reporting in patients with depression who are thought to have worsened perception [4].

Like HF, depression is associated with high morbidity and mortality rates [5]. While some investigations have reported that the concurrence of two disorders has increasing adverse outcomes, others reported the opposite. The mechanism of the relationship between depression with HF progression and mortality is unclear. Inflammation is thought to be a possible mechanism in patients with these conditions [6-9]. High levels of inflammatory markers may be related to the progression of HF [10]. Some studies have supposed that in patients with depression without HF, inflammatory markers are also increased [11,12]. However, it is unknown whether inflammation is the cause or consequence.

Our study aimed to explore the relationship among inflammatory markers, anxiety, and depression and determine the prognostic effects on long-term

mortality, hospitalization, and quality of life in patients having HF with reduced and mildly reduced ejection fraction (HFrEF and HFmrEF) by using objective psychiatric evaluation.

Materials and methods

Study population

Consecutive outpatients with HF visiting the cardiology clinic between November 2011 and September 2013 were included. Patients with HF and left ventricular ejection fraction (LVEF) ≤50%, aged <75 years, and were stable for at least one-month. Patients with malignancy, liver failure, chronic inflammatory disease, and cognitive disorders, aged <18 years and >75 years (quality of life may affect test results in the older population), were excluded. All patients have received appropriate treatment for HF with reduced ejection fraction and other comorbidities.

Of the 160 patients, 131 agreed to participate. 9 individuals were excluded because they did not have a depression score at the time of inclusion and blood was not taken at the time of baseline. Therefore, 122 patients who had complete data at inclusion (blood and questionnaires) were included. Routine controls were performed every 6 months. In this study, the follow-up was completed in December 2015. An interview was used to examine demographic and clinical variables. New York Heart Association (NYHA) functional class information, risk factors, comorbidities, and medication was obtained from the patients through interview by a cardiologist.

Blood sample

Venous blood sample was obtained with a jelly tube at admission. Samples were centrifuged at 4000 rpm. Serum samples were stored −80°C for analysis of B-type natriuretic peptide (BNP), IL-6, tumor necrosis factor (TNF)-α, and high-sensitivity CRP (hs-CRP). IL-6 (Catalog No. KHC0061, Invitrogen Corporation, Camarillo, CA, USA) and TNF-α (Catalog No.: KHC3011, Invitrogen Corporation) levels were studied by enzyme-linked immunosorbent assay (ELISA) in ELX 808 IU model ELISA device. The NT-proBNP level was studied by using the electrochemiluminescence method in Cobas e601 analyzer. The hs-CRP level was examined by the immunoturbidimetric method in Cobas c501 analyzer by using Roche kits (Roche Diagnostics GmbH). All routine biochemical tests were carried out with the Cobas 6000 Integra (Roche) auto-analyzer using the chemiluminescence method at admission. Transthoracic echocardiography was performed on each patient in the outpatient clinic. Simpson's method was used to assess the LVEF.

An independent psychiatrist evaluated patients. The Hamilton Depression Rating Scale for depression (HAM-D), HAM scale for anxiety (HAM-A), and Short-Form 36 (SF-36) quality of life scale were used in the face-to-face interview. HAM-D score >7 indicates depression [13]. HAM-A, which is a standard psychiatric interview commonly used in research and clinical trials, score >11 represents anxiety [14]. The SF-36, which is a self-questionnaire survey, was used to determine the patients' quality of life. Physical health composite score (PCS) and mental health composite score were calculated as follows:

SF-36PCS= Σ (z score of each scale x respective physical factor coefficient) x 10 + 50

SF-36 MCS = Σ (z score of each scale x respective mental factor coefficient) x 10 + 50 formulas in the SPSS software [15].

After the initial assessment, all patients were periodically referred to our hospital for control checkup. Patients were interviewed (directly or over the phone) to acquire endpoint information, their families, hospital records, or social insurance if patient information cannot be reached.

Depression and anxiety were only assessed at baseline. Cardiovascular death was described as the primary endpoint, and the secondary endpoint was defined as hospitalization because of cardiovascular disease.

All participants agreed and provided consent to participate in the research, and the approval of the local ethics committee was obtained (Date: 09/03/2012, Decision no: 050.99-55). The study follows the principles guided in the Helsinki Declaration.

Statistical analysis

All statistical analyses were carried out with the SPSS program (version 21.0, SPSS, Chicago, IL, USA). Quantitative/continuous variables with a skewed distribution were summarized as median and interquartile range, continuous variables with a normal distribution were summarized as mean and standard deviation, and Percentages were used to express qualitative characteristics (%). To determine the normality of all measures, the Kolmogorov–Smirnov test was used. The Student T or Mann–Whitney U-test was used to compare continuous variables between the two groups. The Chi-square test was used to compare categorical variables. Correlations between LVEF, BNP, IL-6, hs-CRP, BNP, HAM-A score, HAM-D score, and SF-36 score were evaluated by a Pearson correlation test. A Kaplan–Meier with the log-rank statistics was used to determine survival rates for depression and anxiety. Cox proportional regression analysis including age, LVEF, GFR, serum sodium level, NLR, inflammatory markers, HAM-A, HAM-D scores and SF-36 parameters was as independent predictors of mortality. A p value <0.05 was accepted significantly.

Results

Baseline demographic and clinical parameters of the study population are summarized in Table 1. Most of the patients were male (77.9%) and hypertensive (69.7%), and 27.9% of the population has atrial fibrillation. Patients were receiving appropriate medications, including renin–angiotensin–aldosterone system blockers and beta-blockers. Moreover, 4.9% and 19.7% of the patients have mild and severe depression according to the HAM-D scale, respectively, and 19.7% and 36.9% of the patients have mild and severe anxiety according to the HAM-A scale, respectively. A total of 39 (32%) patients died; 45 (36.9%) patients were hospitalized at a median follow-up period of 36.4 months.

Depression and anxiety

Results of the comparison of depression and anxiety groups are summarized in Table 2. Baseline demographic parameters, endpoints, and inflammatory marker levels were similar in patients with and without depression except for the use of beta-blockers (91.1% vs. 76.6%, p=0.045). HAM-D and HAM-A scale scores were significantly high, and the SF-36 scores were significantly low in patients with both depression and anxiety. Baseline demographic, laboratory, and inflammatory marker findings were similar in patients with and without anxiety and depression. Patients with anxiety had a greater hospitalization rate (44.9% vs. 26.4%, p=0.036).

Table 1 Demographic, laboratory and psychological parameters of study population

Parameter	Value
Age (Years)	63.5 ± 9.8
Male/Female	95/27
Heart Rate (bpm)	76 ± 12
Ejection Fraction (%)	34.3±6.6
BMI (kg/m2)	28.3 ± 5.2
Hypertension % (n)	%69.7 (85)
Diabetes Mellitus % (n)	%41 (50)
CAD history % (n)	64.8 % (79)
Smoking % (n)	19.7 % (24)
Atrial Fibrillation % (n)	27.9 % (34)
Medications % (n)	
ACE inhibitor	61.5 % (75)
Beta Blocker	82 % (100)
ARB	20.5 % (25)
Hydrochlorothiazide	43.4% (53)
Furosemide	48.4 % (59)
MRA	46.7 % (57)
Oral anticoagulation	22.9 % (28)
Laboratory analysis	
Glucose (mg/dl)	136.9 ± 7.7
TG (mg/dl)	141.5 ± 76.2
LDL (mg/dl)	113.7 ± 3.1
HDL (mg/dl)	44.9 ± 12.7
GFR	60.9±20.4
NLR	3.19±1.77
SF physiological function	16.8 ± 10.5
SF physiological role	15.9 ± 8.7
SF pain	28.2 ± 11
SF general health	26.9 ±10.6
SF vital	33.8 ± 13
SF social function	37 ± 13.9
SF mental health	42.1 ± 28.6
HAM-D	6 (1-43)
HAM-D (8-16)	4.9 % (6)
HAM-D (>16)	27 % (33)
HAM-A	14 % (1-40)
HAM-A (11-17)	19.7 % (24)
HAM-A (>17)	36.9 % (45)
Follow-up	
Time (month)	36.4 (1-41)
Death % (n)	32 % (39)
Hospitalisation % (n)	36.9 (45)
Death ± Hospitalisation % (n)	54.1 % (66)

BMI: Body Mass Index, CAD: Coronary Artery Disease, ACE: Angiotensin Converting Enzyme, ARB: Angiotensin Receptor Blocker, MRA: Mineralocorticoid receptor antagonist, TG: Triglyceride, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, GFR: Glomerular Filtration Rate, NLR: Neutrophile to Lymphocyte Ratio, SF: Short Form for quality of life, HAM-D: Hamilton D rating scale, HAM-A: Hamilton A rating scale.

Mortality groups

When compared with survivors, non-survivors patients were older (68.6±9.7 vs. 61 ± 8.8 years, p < 0.001) and have lower LVEF (32.5±6.4% vs. 35.1±6.5%, p=0.037), decreased glomerular filtration rate (GFR) (51.3±19.5 vs. 65.6±19.3 ml/min, p<0.001), and blood sodium level (135±19 vs. 139±2 mEq/ml, p=0.04). NYHA functional capacity was poor in non-survivors (p<0.001) (Table 3).

Survival analysis

Kaplan–Meier survival curves of depression and anxiety are shown in Figure 1 and 2. Univariate Cox regression analysis showed that age, LVEF, GFR, serum sodium level, neutrophil-to-lymphocyte ratio (NLR), SF-36 pain, SF-36 general health, and NYHA functional classifications were predictors of mortality. Age, LVEF, and GFR were independent predictors of mortality (Table 4).

Figure 1 - Kaplan–Meier survival curves of the study population according to depression groups.

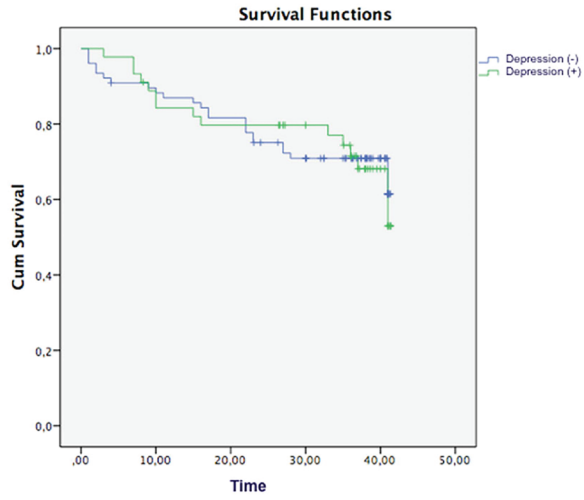

Figure 2 - KaplaMeier survival curves of the study population according to anxiety groups.

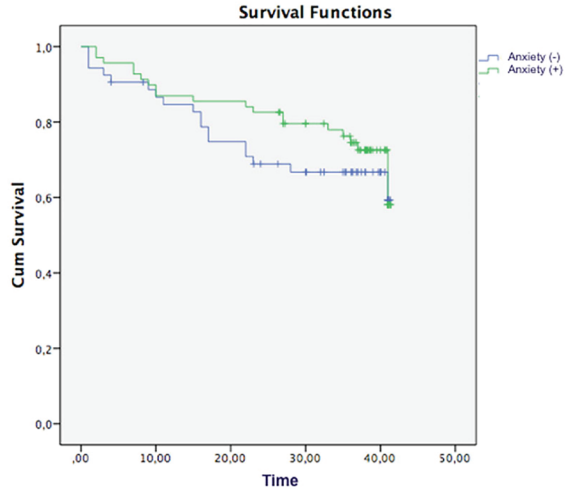

Figure 3 - Kaplan–Meier survival curve according to the effective cut-off value of the neutrophil-to-lymphocyte ratio

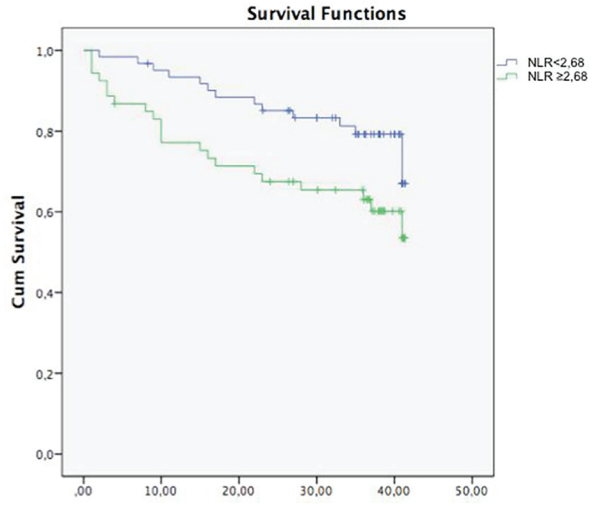

Table 2 Comparisons of demographic, laboratory and psychological parameters of study groups

Parameter	Depression (+) n (45)	Depression (-) n (77)	p	Anxiety (+) n (68)	Anxiety (-) n (54)	p
Age (Years)	64.0 ± 9.5	63.1 ± 9.9	0.685	63.0 ± 9.6	64.0 ± 9.9	0.593
Male, % (n)	82.2 % (37)	75.3 % (58)	0.376	76.8 (53)	79.2 (42)	0.748
Heart Rate (bpm)	76±12	76 ± 12	0.910	75 ± 11	78 ± 14	0.509
Ejection Fraction (%)	33.6 ± 7.3	34.7 ± 6.1	0.369	34.7 ± 6.7	33.7 ± 6.4	0.435
BMI (kg/m2)	28.3 ± 5.5	28.3 ± 5.1	0.990	28.4 ± 5.5	28.2 ± 5	0.851
Hypertension % (n)	68.9 (31)	71.1 (54)	0.801	69.1 (47)	71.7 (38)	0.738
Diabetes Mellitus % (n)	37.8 (17)	43.4 (33)	0.542	39.7 (27)	43.4 (23)	0.683
CAD history % (n)	66.7 (30)	63.6 (49)	0.735	63.8 (44)	66 (35)	0.795
Smoking % (n)	20 (9)	19.7 (15)	0.761	19.1 (13)	20.8 (11)	0.775
Atrial Fibrillation % (n)	38.5 (15)	28.4 (19)	0.213	66.4 (18)	48.4 (16)	0.647
Medications % (n)						
ACE inhibitor	644 (29)	59.7 (46)	0.606	62.3 (43)	60.4 (32)	0.827
Beta Blocker	91.1 (41)	76.6 (59)	**0.045**	87 (60)	75.5 (40)	0.102
ARB	22.2 (10)	19.5 (15)	0.717	18.8 (13)	22.6 (12)	0.606
ASA	88.9 (40)	76.6 (59)	0.095	85.5 (59)	75.5 (40)	0.160
Hydrochlorothiazide	48.9 (22)	40.3 (31)	0.354	478 (33)	37.7 (20)	0.265
Furosemide	51.1 (23)	46.8 (36)	0.642	49.3 (34)	47.2 (25)	0.818
Laboratory analysis						
Glucose (mg/dl)	109 (73-394)	112 (72-315)	0.716	111 (73-394)	112 (72-315)	0.822
TG (mg/dl)	140 ± 74	142 ± 77	0.895	146 ± 80	135 ± 70	0.463
LDL (mg/dl)	112 ± 29	114 ± 38	0.752	113 ± 33	113 ± 37	0.952
HDL (mg/dl)	41 ± 10	47 ± 13	**0.039**	43 ± 11	46 ± 13	0.236
GFR	60.4 ± 18.2	61.2 ± 21.7	0.840	62.9 ± 20	58.4 ± 20.6	0.234
NLR	3.49±1.86	3.02±1.7	0.181	3.31±1.78	3.05±1.75	0.430
Hs-CRP	3.7 (0.3-69)	43 (0.4-38)	0.493	4.1 (0.3-69)	4.4 (0.7-18.1)	0.936
TNFα	17.3 (6.6-243.1)	16.7 (2.9-237.4)	0.937	17.3 (2.9-243.1)	16.2 (5.4-139.8)	0.960
IL-6	5.6 (1.9-209.9)	5.8 (2.2-452.9)	0.375	5.3 (2.5-209.9)	6.9 (1.9-452.9)	0.064
NT-proBNP	923 (43-13179)	1134(105-134)	0.306	923(43-13179)	1257 (105-35000)	0.106
Depression and anxiety						
SF physiological function	11 ± 6	20 ± 11	**0.000**	12 ± 6	23 ± 11	**0.000**
SF physiological role	10 ± 5	19 ± 8	**0.000**	12 ± 6	20 ± 8	**0.000**
SF pain	22 ± 8	31 ± 11	**0.000**	24 ± 9	32 ±11	**0.000**
SF general health	21 ± 7	30 ± 10	**0.000**	23 ± 9	31 ± 10	**0.000**
SF vital	23 ± 6	40 ± 11	**0.000**	28 ± 11	40 ± 11	**0.000**
SF social function	24 ± 8	44 ± 11	**0.000**	31 ± 14	43 ± 10	**0.000**
SF mental health	23 ± 11	53 ± 30	**0.000**	32 ± 17	54 ± 35	**0.000**
HAM-D	21 (7-43)	4 (1-7)	**0.000**	13 (1-43)	4 (1-24)	**0.000**
HAM-A	22 (3-43)	8 (1-43)	**0.000**	22 (11-43)	5 (1-10)	**0.000**
Baseline NYHA Class			0.420			0.427
I	8.9 (4)	5.2 (4)		8.7 (6)	3.8 (2)	
II	71.1 (32)	62.3 (48)		66.7 (46)	64.2 (34)	
III	20 (9)	31.2 (24)		24.6 (17)	30.2 (16)	
Follow-up						
Time (month)	36.5 (3-41)	36.3 (1-41)	0.934	37 (2-41)	35 (1-41)	0.062
Death % (n)	33.3 (15)	31.2 (24)	0.805	30.4 (21)	34 (18)	0.679
Hospitalisation % (n)	44.4 (20)	32.5 (25)	0.186	44.9 (31)	26.4 (14)	**0.036**

BMI: Body Mass Index, CAD: Coronary Artery Disease, ACE: Angiotensin Converting Enzyme, ARB: Angiotensin Receptor Blocker, TG: Triglyceride, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, GFR: Glomerular Filtration Rate, hs-CRP: High sensitive C-reactive protein, TNFα: Tumor necrosis factor alfa, IL-6: Interleukin-6, NT-proBNP: N-terminal pro-brain natriuretic peptide, NYHA: New York Heart Association, SF: Short Form for quality of life, HAM-D: Hamilton D rating scale, HAM-A: Hamilton A rating scale.

A receiver operating characteristics curve analysis was performed for NLR. The area under the curve was 0.62 (CI 0.50–0.73, p=0.042), and 2.68 was selected as an optimal effective cut-off point according to sensitivity of 60% and specificity of 60%). Kaplan–Meier's survival curve of NLR is shown in Figure 3.

Hospitalization

Age, LVEF, serum sodium level, SF-36 pain, MCS, NLR, HAM-D score, HAM-A score, and NYHA functional capacity were found as predictors in the univariate analysis. NLR, HAM-A score, serum sodium level, and NYHA functional capacity were found as independent predictors for hospitalization (Table 5).

Table 3 Comparisons of survivors and non-survivors

Parameter	Non-Survivors n (39)	Survivors n (83)	p
Age (Years)	68.6 ± 9.7	61±8.8	**0.000**
Male	79.5 (31)	77.1 (64)	0.768
Ejection Fraction (%)	32.5 ± 6.4	35.1 ± 6.5	**0.037**
BMI (kg/m2)	27.6 ± 5.4	28.6 ± 5.2	0.398
Hypertension % (n)	76.9 (30)	67.1 (55)	0.268
Diabetes Mellitus % (n)	46.2 (18)	39 (32)	0.457
CAD history % (n)	59 (23)	67.5 (56)	0.360
Smoking % (n)	35.8 (14)	36.1 (30)	0.569
Atrial Fibrillation % (n)	39.4 (13)	28.8 (21)	0.462
Medications % (n)			
ACE inhibitor	56.4 (22)	63.9 (53)	0.431
Beta Blocker	76.9 (30)	84.3 (70)	0.321
ARB	28.2 (11)	16.9 (14)	0.148
ASA	71.8 (28)	85.5 (71)	0.07
Hydrochlorothiazide	46.2 (18)	42.2 (35)	0.679
Furosemide	51.3 (20)	47 (39)	0.658
MRA	43.6 (17)	45.8 (38)	0.820
Laboratory analysis			
Glucose (mg/dl)			0.259
TG (mg/dl)	136 ± 72	143 ± 78	0.692
LDL (mg/dl)	116 ± 37	112 ± 34	0.544
HDL (mg/dl)	41 ± 10	46 ± 13	0.116
GFR	51.3 ± 19.5	65.6 ± 19.3	**0.000**
Sodium	135 ± 19	139 ± 2	**0.04**
Potassium	4.8 ± 1.1	4.6 ± 0.4	0.131
NLR	3.8 ±2.8	2.8 ± 1.3	**0.005**
hsCRP	6.4 (0.3-39.8)	4 (2.9-16.2)	0.120
TNF alfa	17.5 (8.3-17.5)	16.2 (2.9-243.1)	0.190
IL-6	6.8 (3.6-367.8)	5.6 (1.9-452.9)	0.290
NT-proBNP	1257 (223-7392)	961 (43-35000)	0.199
Depression and anxiety			
SF physiological function	15 ± 9	17 ± 11	0.354
SF physiological rol	13 ± 7	16 ± 9	0.081
SF pain	23 ± 9	30 ± 11	**0.003**
SF general health	23 ± 8	28 ± 11	**0.014**
SF vital	33 ± 13	34 ± 13	0.637
SF social function	34 ± 13	38 ± 13	0.123
SF mental health	45 ± 43	40 ± 17	0.435
HAM-D	5 (1-43)	6 (1-38)	0.858
HAM-A	11 (3-43)	13 (1-43)	0.456
NYHA Class			**0.000**
I	7.7 (3)	6 (5)	
II	41 (16)	77.1 (64)	
III	48.7 (19)	16.9 (14)	
Follow-up Time	16 (1-41)	38 (4-41)	**0.000**

BMI: Body Mass Index, CAD: Coronary artery disease, ACE: Angiotensin Converting Enzyme, ARB: Angiotensin Receptor Blocker, TG: Triglyceride, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, GFR: Glomerular Filtration Rate, NLR: Neytrophile to Lymphocyte ratio, hs-CRP: High sensitive C-reactive protein, TNFα: Tumor necrosis factor alfa, IL-6: Interleukin-6, NT-proBNP: N-terminal pro-brain natriuretic peptide, NYHA: New York Heart Association, HAM-D: Hamilton D rating scale, HAM-A: Hamilton A rating scale.

Correlation analysis

A Pearson correlation analysis showed that NLR was negatively correlated with LVEF (r= −0.218, p=0.002) and hs-CRP and IL-6 levels were positively correlated with NT-proBNP (r=0.368, p<0.001 and r=0.650, p<0.001, respectively). Table 6 shows other correlated parameters.

Discussion

In our study including HFrEF and HFmrEF patients we found that 1) Depression and anxiety were not related to mortality 2) NLR, NYHA, and HAM-A scores were independent predictors for hospitalization 3) Age, LVEF, and GFR were independent predictors of mortality 4) Serum NT-proBNP, IL-6, TNF-α, and hs-CRP levels were not related to mortality, also.

The incidence of depression is nearly 2–3 times increased in patients with HF than in the normal population, and the estimated prevalence is 24%–42% [16]. The prevalence of depression in HF differs by health status, demographic factors, and social factors. In our study population, depression and anxiety occurred in 36.9% and 56.6% of the cases, respectively, similar to that in previous studies. Depression has also been associated with developing HF [17]. Because arguments on

Table 4 Cox regression analysis for cardiovascular mortality

	Univariate			Multivariate		
Variable	**HR**	**CI 95%**	**p**	**HR**	**CI 95%**	**p**
Age (years)	1.08	1.04-1.12	**<0.001**	1.08	1.04-1.14	**<0.001**
EF	0.94	0.9- 0.98	**0.015**	0.93	0.89-0.98	**0.014**
GFR	0.96	0.95-0.98	**<0.001**	0.97	0.95-0.99	**0.028**
Sodium	0.98	0.96-0.99	**0.036**			
NLR	1.31	1.12-1.52	**<0.001**			
hsCRP	1.01	0.99-1.04	0.216			
TNFα	1.00	0.99-1.01	0.789			
IL-6	1.00	0.99-1.00	0.870			
NT-proBNP	1.00	1.00-1.00	0.970			
SF pain	0.95	0.92-0.98	**0.006**			
SF general health	0.96	0.93-0.99	**0.037**			
MCS	1.01	0.98-1.05	0.322			
PCS	0.98	0.96-1.01	0.240			
NYHA class	2.77	1.63-4.7	**<0.001**			
HAM-A	1.0	0.97-1.03	0.622			
HAM-D	1.00	0.97-1.03	0.819			

EF: Ejection fraction, GFR: Glomerular Filtration Rate, NLR: Neytrophile to Lymphocyte ratio, hs-CRP: High sensitive C-reactive protein, TNFα: Tumor necrosis factor alfa, IL-6: Interleukin-6, NT-proBNP: N-terminal pro-brain natriuretic peptide, SF: Short Form for quality of life, MCS: mental composite health score, PCS: Physical composite health score NYHA: New York Heart Association, HAM-D: Hamilton D rating scale, HAM-A: Hamilton A rating scale.

Table 5 Cox regression analysis for hospitalization

	Univariate			Multivariate		
Variable	**HR**	**CI 95%**	**p**	**HR**	**CI 95%**	**p**
Age (years)	1.04	1-1.07	**0.02**			
EF	0.95	0.91-0.99	**0.034**			
GFR	0.99	0.97-1	0.231			
Sodium	0.97	0.96-0.99	**0.006**	0.97	0.95-0.99	**0.006**
NLR	1.25	1-1.05	**0.011**	1.32	1.06-1.65	**0.012**
hsCRP	1.01	0.99-1.03	0.157			
TNFalfa	1.00	0.99-1.01	0.166			
IL-6	1.00	0.99-1.01	0.866			
NT-proBNP	1.00	1.00-1.00	0.885			
SF pain	0.96	0.93-0.99	**0.03**			
SF general healh	0.97	0.94-1.00	0.131			
MCS	0.95	0.91-0.99	**0.035**			
PCS	1.01	0.98-1.05	0.322			
NYHA class	2.47	1.47-4.16	**0.001**	2.48	1.37-4.48	**0.003**
HAM-A	1.02	1.00-1.05	**0.036**	1.04	1.01-1.07	**0.010**
HAM-D	1.02	1.00-1.05	**0.049**			

EF: Ejection fraction, GFR: Glomerular Filtration Rate, NLR: Neytrophile to Lymphocyte ratio, hs-CRP: High sensitive C-reactive protein, TNFα: Tumor necrosis factor alfa, IL-6: Interleukin-6, NT-proBNP: N-terminal pro-brain natriuretic peptide, SF: Short Form for quality of life, MCS: mental composite health score, PCS: Physical composite health score NYHA: New York Heart Association, HAM-D: Hamilton D rating scale, HAM-A: Hamilton A rating scale.

Table 6 Correlation analysis between some parameters with EF and BNP

EF			BNP		
Variable	r	p	Variable	r	p
GFR	0.164	0.077	GFR	-0.233	0.021
BNP	-0.006	0.530	Hs-CRP	0.368	<0.001
Hs-CRP	-0.178	0.072	TNF-α	0.009	0.929
TNF-α	-0.050	0.605	IL-6	0.650	<0.001
IL-6	0.035	0.723	NLR	0.561	0.06
NLR	-0.218	0.002	MCS	0.094	0.436
MCS	-0.086	0.349	PCS	0.078	0.436
PCS	0.048	0.603	SF physiological function	0.235	0.017
HAM-D	-0.039	0.671	SF physiological role	0.187	0.059
HAM-A	0.007	0.942	SF pain	0.185	0.061

EF: Ejection fraction, GFR: Glomerular Filtration Rate, NT-proBNP: N-terminal pro-brain natriuretic peptide, hs-CRP: High sensitive C-reactive protein, TNFα: Tumor necrosis factor alfa, IL-6: Interleukin-6, NLR: Neytrophile to Lymphocyte ratio, MCS: mental composite health score, PCS: Physical composite health score HAM-D: Hamilton D rating scale, HAM-A: Hamilton A rating scale.

depression are related to increased mortality, the combination of systolic HF and depression has become a more important issue nowadays. In the HF population, some investigations have showed that patients with depression and anxiety have higher rates of mortality and morbidity [18]. Moomersteeg et al. [19] reported that depression, CRP, and TNF-α receptors are associated with higher mortality rates in a study including 104 patients with HFrEF. However, in that study, diabetes mellitus was more common in the cardiovascular death group. By contrast, some authors have reported that depression is not an independent predictor of cardiovascular mortality in patients with HF [20,21]. Pelle et al. [22] showed that anxiety and depression symptoms were not related to mortality and was an independent risk factor for hospitalization in a study including 662 patients with HFrHF aged 40 years. In that study, patients were already hospitalized for HF at beginning of the study, were younger, and had follow-up for 1 year. Recently, metaanalysis investigating the relation between anxiety, depression and all-cause mortality in HF patients showed that depression is an independent predictor. However, these meta-analyses including a mixed HF population for reduced, mildly-reduced and preserved EF. Last European Heart Failure Guideline emphasized the depression was related to poor outcomes and worse clinical status in HF patients [23]. Depression and anxiety worsen the symptoms of heart failure and diminish the quality of life. Controversial findings about depression and anxiety's influence on mortality in HF patients and ineffectiveness of antidepressant treatment on clinical outcome may related to HF types, comorbidities, drug-drug interactions, follow-up time and used different depression scales. In our study, we included patients with compensated HFrEF-HFmrEF and the follow-up period was longer than other studies. We found that the depression and anxiety scores were related to hospitalization (HR 1.025 and 1.029, respectively) in the univariate analysis. Anxiety was an independent predictor of repeated hospitalization in our study population.

In most of the studies on depression, inflammatory markers, and HF, investigators used self-questioning scales such as the BDI scale, Patient Health Questionnaire depression module, and Center for Epidemiological Studies Depression-Scale for detecting depression or anxiety. Patients with both HF and depression suffer from reduced exertion tolerance, worsening quality of life, and poor NYHA functional capacity, which are symptoms present in both diseases. Some studies have suggested that depression is minimally related to an objective assessment of HF severity such as peak oxygen consumption, LVEF, and BNP levels; however, it significantly affected symptoms of HF such as NYHA capacity or results of the 6-minute walk test [24,25]. Therefore, we preferred HAM-D and HAM-A scales because they are applied through face-to-face interviews by a specialist and provide an objective assessment of symptoms. Different from previous studies, we used HAM-D and HAM-A to evaluate the presence of depression and anxiety scale by an interview with a physiatrist.

The relationship between the inflammation system and cardiovascular disease is widely known. Neutrophils play a role in the HF process because it is reflected in the pro-inflammatory status. NLR is a worse outcome biomarker for patients with high-risk status. Studies suggest that both HF is characterized by low-grade chronic inflammation [26,27]. In our study, NLR was significantly increased in non-survivors. It was related to a 1.3-fold risk increase for mortality in the univariate regression analysis and a 1.21-fold independent risk increase for hospitalization in the multivariate regression analysis. In this study, NLR of ≥2.68 is related to decreasing survival rates in the Kaplan–Meier analysis. In addition, we found a significant correlation between LVEF and NLR. These results emphasized that NLR reflects a low-grade inflammatory status in patients with HFrEF and HFmrEF.

Although increased CRP relates to new, recurring, or long-term depression, the relationship between inflammation and depression is unclear. While some studies suggested that depression and associated autonomic dysfunction might prolong immune activation and resulted in an inflammatory state in patients with HF, others have suggested that increased inflammation might worsen depressive symptoms [28,29].

TNF is a cytokine that promotes inflammation that activates immune cells. Studies have reported that serum IL-6 and TNF-α levels correlated with HF symptoms and poor prognosis [30,31]. Some authors have found that TNF-α receptor but not TNF-α level was related to cardiovascular mortality in their study [32]. Parissis et al. [33] found no relationship between serum IL-6 and TNF-α levels and cardiovascular outcomes; only IL-10 and BNP levels were independent predictors of cardiovascular mortality at 1-year follow-up in patients with HF and hospitalized. In our study serum BNP, TNF-α, hs-CRP, and IL-6 levels are not associated with cardiovascular mortality and hospitalization. Different results of previous studies may be related to the patient's LVEF because of the inflammation appears more prominent in HFpEF patients, functional capacity, compensated or non-compensated status, and immune-compromised status because of aging.

NT-proBNP is an indicator of volume overload as well as a diagnostic biomarker of HF. BNP level is related to the severity of HF and cardiovascular outcomes [34]. In our study, serum BNP levels were not related to cardiovascular mortality and hospitalization. It significantly correlated with IL-6 and hs-CRP levels like in previous studies [35].

This study has limitations. First, limited number of patients and the follow-up period were relatively short. Second, serum inflammatory levels and psychological assessments were evaluated only at baseline. Third, we did not re-evaluate serum biomarkers and LVEF during the study period. Finally, we evaluated functional capacity with an interview and not with the 6-minute walk test.

Conclusion

This study revealed that depression and anxiety are not related to cardiovascular mortality in HFrEF and HFmrEF patients. However, anxiety is an independent predictor for hospitalization. The levels of serum BNP, IL-6, TNF-, and hs-CRP are not associated to cardiovascular outcomes. NLR is related to repeated hospitalization.

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Coronavirus-19 phobia and health literacy in adults: A descriptive-correlational study

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Abstract

Aim: The aim of this study was to determine the levels of health literacy (HL) and COVID-19 Phobia (C19P-S) in adult individuals and was to evaluate the relationship between health literacy and coronavirus-19 phobia among adults.

Materials and methods: The sample of this descriptive and correlational study consisted of 545 people living in Kahramanmaras city center and meeting the study criteria. Study data were collected through google forms using personal information form, Health Literacy Scale and Coronavirus-19 Phobia Scale (C19P-S).

Results: The mean C19P-S score of the participants was 30±16.33. A statistically significant difference was determined between the mean C19P-S scores of women and men ($p<0.05$). It was determined that those with a middle income level, those who reported that they took adequate precautions to protect against coronavirus and those who did not receive health education had higher C19P-S score averages. According to the correlation analysis, there is no relationship between the health literacy total score and C19P-S [$r(545)=-0.054$; $p>0.05$]. There was a weak negative statistically significant correlation between the somatic sub-dimension of C19P-S and health literacy total score, access, understanding, and appraisal sub-dimensions ($p<0.05$).

Conclusion: HL adult population was generally high and the coronavirus phobia was moderate. Addressing HL as a variable may be beneficial in the management of coronavirus phobia.

Key words: adult, covid-19 phobia, health literacy

Introduction

The World Health Organization classified the COVID-19 outbreak as an "international public health emergency" on January 30th. The COVID-19 pandemic was described as a pandemic on March 11 due to the occurrence of COVID-19 cases in 113 countries other than China, where the first outbreak began, and the spread and severity of the virus. Studies on COVID-19 in Turkey started on January 10, 2019 and the first COVID-19 case was seen on the 11th of March. As of February 09, 2022, the total number of cases and deaths in Turkey was 11,343,693 and 86,871, respectively [1].

Appropriate guidance of human behavior in an epidemic environment is the key factor that should be accompanied by medical measures. The fact that health institutions consider the principles of health literacy provide easily understandable and applicable information, and create accessible information resources may be among the factors that determine the course of the epidemic [2]. Health literacy, which is significantly affected by the factors that determine health and plays an important determinant role in shaping health behaviors and health outcomes, is an important condition that should be taken into account in disaster periods and in ordinary periods [3].

Health literacy enables a person to understand what factors affect the health of his family and society and to know how to deal with them [4]. Health literacy is a term that was first defined in 1974 and is gaining in importance in public health and health services [5]. The World Health Organization defines health literacy as "the ability of the individual to access, understand and use health knowledge for the protection and maintenance of health" [6]. Despite different definitions, health literacy has been evaluated as the knowledge, skills, attitudes, and motivation of individuals in accessing, understanding, evaluating, and applying the health information necessary for individuals to take the necessary decisions and evaluate them to improve their quality of life, prevent diseases and improve their health throughout their lives [7]. The COVID-19 pandemic has shown that health literacy is critical not only for preventing non-communicable diseases but also for preventing communicable diseases [8].

In a national study conducted in the United States of America based on the health literacy situation in the world, it was stated that 53% of the adult population had a moderate level of health literacy, 36% were inadequate, and 22% had a basic level [9].According to the health literacy research conducted in Turkey in 2014, it has been reported that the total of those with insufficient health literacy and those with problematic-limited health literacy is 68.9%. When these two categories are evaluated as limited, it is seen that limited health literacy stands out as an important public health problem affecting seven out of every ten people in the country [10].

Coronaphobia refers to the extreme fear and anxiety of being infected by a coronavirus [11]. Moreover, Lee et al. (2020) highlight the need for healthcare professionals to be aware of coprophobia that coprophobia refers to pandemic-related stress, and pandemic-related stress is increasingly valid as a major indicator of psychological distress [12]. In a study by Hermans et al. (2021) in Belgium to evaluate the relationship of health literacy with mental health, compliance with COVID-19 preventive measures, and health expectations, it was reported that anxiety disorders, depression, and sleep disorders are less common in people with adequate health literacy. In the same study, it was emphasized that health literacy is a critical factor in the management of the COVID-19 epidemic [13]. COVID-19 may cause phobia in patients with anxiety disorders who have psychological, psycho-somatic, economic, and social fears [14].

There are many sources of information and misinformation regarding COVID-19. This situation causes fear and panic among the people to spread much faster than the virus itself. The disease has become one of the biggest challenges for healthcare systems and healthcare professionals worldwide. As a public health problem, health literacy should not be ignored in the fight against the epidemic. There is a need to create individual and social awareness to combat the epidemic and disease.

Identifying the impact of health literacy has become crucial to preparing individuals and societies for emergencies such as the COVID-19 outbreak that require immediate action and rapid control. The serious adverse physiological, social, and economic effects of the COVID-19 pandemic have been observed in many countries. These negative effects cause conditions such as stress, depression, psycho-somatic and psycho-social disorders. It is important to detect the early signs of COVID-19 phobia, identify the influencing factors and provide timely psychological support to individuals with higher levels of phobia.

When the literature is examined, no study has been found in the country or abroad examining the relationship between health literacy and coronaphobia. It is considered that this study will contribute to the literature on the measures to be taken in epidemic management.

Materials and methods

Aim

The aim of this study was to determine the levels of health literacy (HL) and COVID-19 Phobia (C19P-S) in adult individuals and was to evaluate the relationship between health literacy and coronavirus-19 phobia among adults.

Research questions

1. What is the health literacy level of the participants?
2. What is the coronavirus phobia level of the participants?
3. Is there a relationship between health literacy level and coronavirus phobia?

Type of research

This research was a descriptive and correlational type.

Sample group

The population of this research consisted of 5594 individuals over the age of 18 who were registered in a family health center in Kahramanmaraş. The purpose of the study was explained to the adult individuals who applied to the family health center at the time of the research using the random sampling method, and individuals with an android phone were invited to the study. 545 individuals who agreed to participate in the study were included in the sample. The research data were sent to the participants online via WhatsApp via a google form. Participants were asked to participate in the research by answering the questions within a week. A reminder message was sent a second time to those who did not fill out the questionnaires. Research data were collected between March 2021 and June 2021.

Inclusion and exclusion criteria

Being 18 years of age or older, being literate, using social media, and not having a mental illness. Not wanting to participate in the research, being illiterate, not using a smartphone.

Data collection tools

Research data were collected using a personal information form, Health Literacy Scale, and the Coronavirus-19 Phobia Scale (C19P-S).

Personal information form

In the personal information form, there were questions about the socio-demographic characteristics of the individuals (age, gender, place of residence, marital status) and health problems (either being positive for Covid-19, dealing with coronavirus news, taking precautions for protection from coronavirus, getting health education).

Health literacy scale

The scale developed by Toçi et al. (2013) was adapted to Turkish by Bayık and Aras (2017). The scale, which consisted of 25 items and four sub-dimensions, was in the 5-point Likert type. The scale was scored as "I have no difficulty: 5," "I have little difficulty: 4," "I have some difficulty: 3," I have several difficulties: 2," I am unable to do/I have no ability/impossible: 1." The sub-dimensions of the scale were as follows: "Access to information subscale: Items 1 to 5," "Comprehension of information subscale: Items 6 to 12," "Appraisal/Evaluation subscale: Items 13 to 20," "Application/Using subscale: Items 21 to 25." The score to be obtained from the whole scale is minimum 25 and maximum 125. Low scores indicate insufficient, problematic, and weak health literacy, while high scores indicate adequate and excellent [15, 16]. The Cronbach's alpha value of the scale was .92, and the alpha values of the sub-dimensions were between .62 and .79.

Coronavirus-19 phobia scale (C19P-S)

The scale developed by Arpacı, Karataş, and Baloğlu (2020) is a 5-point likert-type self-assessment scale. Scale items are evaluated between 1 "Absolutely Disagree" and 5 "I Strongly Agree." The scale consists of four sub-dimensions: Psychological Sub-Dimension; (Items 1, 5, 9, 13,17, and 20.), Somatic Sub-Dimension; It measures (Items 2,6,10,14, and 18), Social Sub-Dimension (Items 3, 7, 11, 15, and 19), and Economic Sub-Dimension (Items 4, 8, 12, and 16). While the sub-dimension scores are obtained from the sum of the answers

given to the items belonging to that sub-dimension, the total C19P-S score is obtained from the sum of the sub-dimension scores. The score obtained from the scale varies between 20 and 100. High scores indicate high coronavirus phobia [17].

Data Collection

The online form, which each participant can fill in approximately 15–20 minutes, consists of 61 questions and was arranged in such a way that the participants could see all the questions at the same time after logging in. To prevent the same participants from filling out surveys again within the scope of the Study, the Google Forms settings limited answers to one answer feature enabled, allowing each participant to answer once. To prevent data loss, form settings were adjusted to prevent any questions from left blank, and all questions must be answered.

Ethical aspect of research

An approval from the Social and Human Sciences of Kahramanmaraş Sütçü İmam University Ethics Committee numbered 27/01/2021/E 6742/05 was obtained for the implementation of the research. Additionally, approval was obtained from the Turkish Ministry of Health. An informed consent form explaining the purpose of the study was sent to the participants before completing the questionnaires. The participants were informed that they could participate in the study voluntarily. Additionally, the question the "Do you agree to participate in the study?" was added to the online form, and their consent was obtained with the answers given by the participants. The study was carried out in accordance with international declaration, guideline, etc.

Data analysis

The data were analysis in the SPSS 24 package program. In the study, the number of units (n), percentage (%), mean (standard deviation) were used as statistics. The normality distribution of the data was evaluated with the Kolmogorov–Smirnov test and the Q-Q graph. Cronbach's alpha was used to determine the reliability of the scales used. Since the data were normally distributed, an Independent t-test was used to compare binary variables in the statistical analysis of the study, and the One-Way ANOVA test was used for comparison with three or more variables. Tukey HSD multiple comparison tests were used to determine the differences between the groups. It was decided whether there was a significant relationship between the scales by using correlation analysis. Pearson correlation test was applied in the correlation relationship since the data had a normal distribution. In the evaluations, $p<0.05$ was accepted as the level of significance.

Results

The mean age of the individuals participating in the study was 39.61± 10.72. The lowest age was 18, and the highest was 68. 62.8% of the participants were women, 38.7% were at undergraduate and higher education levels, 74.1% were living in the city center. 60.0% were married. 72.8% of the participants described their economic situation as moderate. 85.7% of the participants reported that they did not have coronavirus, 64.2% did not take adequate precautions to be protected, and 55.6% did not receive any health education (Table 1).

We observed that the health literacy levels of the participants were high (108.97±13.09) and they scored above the average

Table 1 Demographic characteristics of the participants

Characteristics	N	(%)
Gender		
Female	342	62.8
Male	203	37.2
Educational status		
Primary school	81	14.8
Middle School	143	26.2
High school	110	20.3
Bachelor and above	211	38.7
Longest Living Place		
Centre	404	74.1
District	88	16.1
Rural	53	9.8
Marital status		
Married	327	60.0
Single	218	40.0
Economic condition		
Low	114	20.9
Middle	397	72.8
High	34	6.3
The state of being coronavirus positive or knowing a person who has it		
Yes	78	14.3
No	467	85.7
The state of being interested in news about the coronavirus		
Yes	96	17.6
No	449	82.4
The state of taking measures to protect		
Sufficient	195	35.8
Insufficient	350	64.2
Receiving Health Training		
Yes	242	44.4
No	303	55.6

in all sub-dimensions. Participants received 22.22±3.14 points from the access to information sub-dimension. They scored 30.83±3.98 in the sub-dimension of understanding information. They got 34.72±5.05 points from the appraisal sub-dimension. They got 21.18±3.41 points from the sub-dimension of using the application It was determined that the coronavirus phobia scores of the participants were at a moderate level (50.30±16.33). The somatic sub-dimension and economic sub-dimension were the lowest, with 9.67± 4.09 and 8.20± 3.30 mean scores, respectively. The Cronbach's alpha values of the scales were determined as 0.925 for health literacy and 0.945 for coronavirus phobia (Table 2).

Table 2 Total and Sub-Dimensional Means of Health Literacy and Coronavirus Phobia (N=545)

Scale and Scale Sub-Dimensions	x±ss	Cronbach's Alpha	Min - Max
Health Literacy Overall score	**108.97±13.09**	0.925	25.00- 125.00
Access	22.22±3.14	0.836	5.00- 25.00
Understanding	30.83±3.98	0.792	7.00- 35.00
Appraisal	34.72±5.05	0.885	8.00- 40.00
Application	21.18±3.41	0.778	5.00- 25.00
COVID-19 Phobia Scale (C19P-S) total score	**50.30±16.33**	0.945	20.00–100.00
Psychological	18.77± 6.00	0.836	6.00–30.00
Psyho-somatic	9.67± 4.09	0.863	5.00–25.00
Social	13.64± 5.02	0.861	5.00–25.00
Economic	8.20± 3.30	0.793	4.00–20.00

The table shows the health literacy scores of the participants according to some variables. According to the results obtained, women's health literacy scores (110.05±12.14) were higher than men's (107.16±14.39). According to the statistical analysis, it was determined that there was a significant difference between health literacy and gender (t= 2.509; p<0.012), and this difference favored women.

It was seen that the health literacy scores of the participants with secondary school education were high (114.92±11.71), and the scores of the participants with primary school (108.36±14.01) and undergraduate and graduate education (108.57±13.36) were low. No significant difference was determined between education status and health literacy (p>0.05).

Participants living in the city center for a long time had higher health literacy (109.29±13.13), while those living in rural areas for a long time had the lowest scores (106.88±13.54).

Those with a high-income level (111.82±15.81) had high health literacy scores and it was determined that there was a significant difference between economic status and health literacy (F=13.821; p<0.000).

The health literacy scores of the participants who stated that they were not positive for the coronavirus (109.04±13.37),

Table 3 Analysis of the Socio-demographic Characteristics of the Participants and their Health Literacy Total Scores

Characteristics	Health Literacy		
	Health Literacy Total x±ss	**Test**	**P**
Gender			
Female	110.05±12.14	t= 2.509	p<0.012
Male	107.16±14.39		
Educational status			
Primary school	108.36±14.01	F=1.359	p>0.254
Middle School	114.92±11.71		
High school	110.23±11.44		
Bachelor and above	108.57±13.36		
Longest Living Place			
Centre	109.29±13.13	F=0.802	p>0.449
District	108.79±12.62		
Rural	106.88±13.54		
Economic condition			
Low	103.42±16.08	F=13.821	***p<0.000***
Middle	110.33±11.37		
High	111.82±15.81		
The state of being coronavirus positive or knowing a person who has it			
Yes	108.56±11.27	t=-0.303	p>0.762
No	109.04±13.37		
The state of being interested in news about the coronavirus			
Yes	108.83±11.20	t=-0.121	p>0.904
No	109.01±13.47		
The state of taking measures to protect			
Sufficient	108.42±12.55	t=-0,737	p>0.461
Insufficient	109.28±13.39		
Receiving Health Training			
Yes	110.35±12.52	t=2.200	***p<0.028***
No	107.88±13.44		

Table 4 Analysis of Coronavirus Phobia Total Scores According to Some Characteristics of the Participants

Characteristics	Coronavirus Phobia		
	Coronavirus Phobia total x±ss	Test	P
Gender			
Female	50.85±15.79	t= 1.022	*p>0.307*
Male	49.37±17.20		
Educational status			
Primary school	47.00±13.68	F=2.349	p>0.072
Middle School	59.14±14.45		
High school	47.53±15.30		
Bachelor and above	50.60±16.54		
Longest Living Place			
Centre	50.30±16.46	F=0.510	p>0.601
District	49.20±17.06		
Rural	52.07±14.06		
Economic condition			
Low	47.71±16.95	F=2.360	*p>0.095*
Middle	51.22±15.84		
High	48.17±19.03		
The state of being coronavirus positive or knowing a person who has it			
Yes	47.69±14.51	t=-1.526	p>0.127
No	50.73±16.59		
The state of being interested in news about the coronavirus			
Yes	48.00±14.68	t=-1.524	p>0.128
No	50.79±16.63		
The state of taking measures to protect			
Sufficient			p>0.419
Insufficient	51.06±16.27	t=-0.809	
	49.88±16.37		
Receiving Health Training			
Yes	48.82±16.40	t=-1.895	*p>0.059*
No	51.48±16.21		

those who stated that they were not interested in the news about the coronavirus (109.01±13.47) and received health education (110.35±12.52) were high. It was determined that there was a significant difference between the status of receiving health education and health literacy (t=2.200; p<0.028), and this difference favored the participants who received health education (Table 3).

Table 4 shows the coronavirus phobia scores of the participants according to some variables. According to the results obtained, the coronavirus phobia scores of women (50.85±15.79) were higher than men (49.37±17.20).

According to the education level, participants with primary school education got 47.00±13.68 points, participants with secondary school education got 59.14±14.45 points, those who were at high school level got 47.53±15.30 points, and participants with undergraduate and graduate education got 50.60±16.54 points.

According to the place of residence, the participants who reported living in the countryside had the highest coronavirus phobia scores (52.07±14.06), the scores of the participants living in the city center (50.30±16.46) were moderate, and the scores of the participants living in the district were the lowest (49.20±17.06) (Table 4).

People with a medium-income level (51.22±15.84), those who stated that they were not positive for coronavirus (50.73±16.59), those who reported that they were not interested in news about coronavirus (50.79±16.63), and those who reported that they took adequate precautions to protect themselves from coronavirus (51.06±16.27) had high coronavirus phobia scores. The coronavirus phobia scores of the participants (51.48±16.21) who stated that they did not receive health education were high. No significant difference was found between the independent variables and the statistical analysis of coronavirus phobia (Table 4).

No association was found between total health literacy and total coronavirus phobia [r(545)=-0.054; p>0.05]. It was found that there was a weak negative correlation between the somatic sub-dimension of coronavirus phobia and the total health literacy, access to information, Understanding Information, and Appraisal sub-dimensions (p<0.05). It was determined that there was a statistically significant weak relationship between the economic sub-dimension of coronavirus phobia and the total health literacy and access to information sub-dimension. (p<0.05) (Table 5).

Table 5 Correlation of Health Literacy and Coronavirus Phobia Scale

Variables	**C19P-S total score**	Psychological	Psyho-somatic	Social	Economic
Health Literacy Overall score	-,054	-,006	**-,094***	-,034	-,086*
Access	-,083	-,045	**-,085***	-,078	-,103*
Understanding	-,062	-,006	**-,114****	-,048	-,083
Appraisal	-,019	-,026	**-,063****	,006	-,071
Application	-,028	-,013	-,056	-,012	-,031

**. The correlation was significant at the 0.01 level (2-tailed). *.Correlation is significant at the 0.05 level (2-tailed).

Discussion

It was determined that the participants' health literacy levels were high and they scored above the average in all sub-dimensions of the Health Literacy scale in this study, which was conducted to evaluate the relationship between health literacy level and Coronavirus-19 Phobia.

In the study by Berberoğlu et al. (2018) with individuals in the 18–65 age group, the health literacy level of more than half of the participants was categorized as insufficient. In the same study, it was stated that only 17.2% of the participants have sufficient and excellent health literacy levels [18]. In a population-based study conducted by the Bakan and Yıldız to determine the level of health literacy and related factors between the ages of 21–65 in a province located in the east of Turkey, it was reported that 55.4% of the participants had insufficient health literacy, 22.4% were problematic and limited, and only 22.2% had sufficient or excellent health literacy [19]. İkiışık et al. (2020) conducted a study in a tertiary healthcare institution located in a socioeconomically high-ranking district of Istanbul, 18.9% of the participants had insufficient health literacy, 44.8% of them had problematic and limited health literacy, 36.8% of the participants. was found to be adequate or excellent in health literacy [20]. Similarly, in other studies conducted in Turkey, the health literacy level of a large number of participants was evaluated as insufficient [21-23]. However, in a study by Özdemir in a family health center in Turkey, 51.8% of the participants reported to have a sufficient or excellent level of health literacy [24]. Our research findings are in parallel with the results of previous studies in the region. However, in general, it is seen that the level of health literacy in Turkey varies according to region and is very low in some regions. It is thought that the health literacy levels of individuals should be increased with pieces of training.

In this study, gender, economic level, and health education status was found to affect the health literacy score average of the participants ($p<0.05$). Women's health literacy scores were higher and more significant than men's. Various factors affecting the health literacy levels of individuals have been reported in the literature. In addition to studies that found that the gender variable did not affect health literacy, there are studies showing that gender affects health literacy. [19-21, 23, 24]. Our study findings are compatible with the literature. It can be interpreted that women's ability to read, understand and evaluate basic health information is higher.

In our study, the status of receiving health education was determined as a factor affecting health literacy. Similarly, there are studies in the literature showing that the health education received affects the level of health literacy [19, 22].

In our study, the total mean score of the participants for COVID-19 phobia was determined as 50.30±16.33. It was determined that there was no statistically significant difference between the C19P-S and sub-dimension mean scores of the participants according to gender, education level, economic status, being positive for coronavirus or knowing a person with coronavirus, and being interested in news about coronavirus, taking precautions to protect against the coronavirus and status of receiving health education ($p>0.05$). In the study by Arslan et al. (2021) to determine the COVID-19 phobia levels of healthcare personnel working in the pandemic hospital, it was stated that the variables of age, gender, having a child, presence of chronic disease, marital status, smoking status did not affect the C19P-S scores [25]. In a study conducted in Egypt to investigate the factors associated with coronaphobia in physicians, the level of coronaphobia was reported to be higher in physicians who were female, who were non-smokers, who were with death wish and/or thoughts of self-harm, who were inadequately trained, who were dissatisfied with personal protective equipment, and who were more likely to have co-workers infected with the COVID-19 virus [26]. In a community-based study conducted in South Korea, it was found that the variable of education level affects the mean C19P-S score, and individuals with higher education levels have lower coronaphobia levels. In the same study, it was reported that the mean scores of the psychological, somatic, and social subscales of individuals infected with COVID-19 were statistically significantly higher than individuals uninfected with COVID-19 [24]. In the validity and reliability study of the coronavirus phobia scale in the Arab population by Alnaddaf and Baloğlu (2021), it was stated that the C19P-S scores of women were significantly higher than men in all sub-dimensions. In the same study, it was reported that the psychological and economic sub-dimensions of singles scored significantly higher than those married people [28]. Another validity and reliability study of the C19P-S was conducted in the United States. In this study, there was a statistically significant difference between the coronavirus phobia levels of men and women, but phobia was not associated with factors such as marital status, presence of chronic disease, covid-19-infected friends and relatives. In the same study, it was reported that there is a relationship between anxiety and COVID-19 phobia, and individuals with high anxiety have high levels of coronavirus phobia [29]. Similarly, in the study by Ardestani et al. with patients with anxiety disorders, it was reported that patients with generalized anxiety and panic disorder showed higher phobic reactions related to COVID-19 than those with social anxiety disorder and specific phobia [14]. Our research findings are compatible with the studies in the literature.

According to the correlation analysis performed in this study, it was determined that there was a statistically significant, negative, and weak relationship between SOY total and C19P-S somatic and economic sub-dimensions ($p<0.05$). A weak negative correlation was determined between Access and Information, Understanding Information, and Appraisal Sub-Dimensions and C19P-S somatic sub-dimension. In the literature, there is no study published in Turkish or English that evaluates the relationship between Health Literacy and Coronavirus Phobia. However, a study was conducted to evaluate the relationship between the COVID-19 fear scale and health literacy. In this study, it was found that there was a significant relationship between the level of fear of COVID-19 and health literacy, and a high level of health literacy was associated with a low level of fear of COVID-19 [30]. In a study by Rohwer et al. (2021) with caregivers during the COVID-19 process in Germany, it was reported that the perceived stress during the COVID-19 process and the anxiety associated with COVID-19 was associated with the level of health literacy [31]. This research shows that individuals' access to information, their level of understanding, and evaluation of information are effective on coronavirus phobia.

Conclusion

This research has shown that the health literacy level of adult individuals is generally high, coronavirus phobia is moderate, and gender, education, and income level are effective on health literacy. It has been determined that there is no sociodemographic variable affecting coronavirus phobia in adults. It has been understood that there is a weak negative relationship between health literacy and coprophobia With these research results, it can be predicted that increasing the level

of health literacy in the development of effective individual strategies for protection from coronavirus infection during the pandemic process will also affect coronavirus phobia and reduce it. For this reason, it is recommended to develop targets and policies to increase the health literacy level of society during the epidemic and to conduct studies examining the relationship between health literacy and coronavirus phobia in different societies.

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Analysis of various models of chronic osteomyelitis in experimental animals

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Abstract

Introduction: Chronic osteomyelitis occurs in 3-25% of cases after open fractures and in 1-8% of cases after surgical treatment of closed fractures. It accounts for 3 to 10% in the structure of purulent surgical diseases. Traditional treatment methods many times do not provide a complete cure for osteomyelitis. In modern medicine, many experimental models have been created on different types of laboratory animals in order to reproduce the model of chronic osteomyelitis and subsequently improve its therapy. Of all the experimental animals, we chose rabbits for the application of the developed method for the treatment of chronic osteomyelitis and for the selection of the optimal model of bone tissue suppuration.

The **objective** was to conduct a clinical, radiological and histological analysis of various models of chronic osteomyelitis in experimental animals.

Materials and methods: The experiment was carried out on 90 outbred rabbits. All rabbits were randomly divided into 5 groups. The rabbits were kept in a room with controlled temperature (16-21 °C) and relative humidity (45-65%). The rabbits were placed in special cages – 2-3 rabbits per each. Surgical intervention was performed under general anesthesia. Surgical access was made along the anterior surface of the distal metaepiphyseal area of the left femur. All animals were intraosseus injected with Staphylococcus aureus as an infectious agent. The development of chronic osteomyelitis was assessed by clinical, radiological, microbiological, histological and statistical methods.

Results: The study showed that X-ray and histological methods play an important role in the analysis of experimental models. The signs of osteomyelitis development can be seen on the 14th day after the operation with the help of the X-ray method, while wound healing, weight and temperature cannot be indicators. According to the results of the experiment, the signs of chronic osteomyelitis developed in all 5 groups, but its activity was different. Histological examination showed that osteomyelitis developed differently in different groups, fibrosis developed unevenly.

Key words: bone infection, Staphylococcus aureus, rabbits, osteomyelitis model, experimental model

Introduction

The share of chronic osteomyelitis (CO) in the structure of purulent surgical diseases is 3-10% of cases with the probability of recurrence after surgical treatment [1-3]. In recent decades, the incidence of surgical infection has remained unchanged against the background of the use of modern antiseptics, antibacterial agents and improved surgical techniques [1-5]. The percentage of complications caused by suppuration of the musculoskeletal system in mechanical trauma is observed in 5.3-75.4% of patients. This is due, among other things, to an increase in the occurrence of high-energy injuries, an increase in surgical activity, iatrogenic factors (operation technique violation, non-compliance

with the rules of asepsis and antisepsis by surgeons), a change in the species composition of microorganisms, and impaired activity of the body's immune system [6-8]. Osteomyelitis develops in 3-25% of cases as a result of open fractures and in 1-8% after surgical interventions in closed fractures. At the same time, relapses of osteomyelitis occur in 20-35% of cases, which requires the further use of radical methods of treatment, up to amputation [9-12].

Traditional methods of antibiotic treatment and alternative methods of therapy have not led to impressive results of complete osteomyelitis cure [13]. In research medicine, many experimental models of osteomyelitis have been created in different animal species in order to induce a disease state and subsequently treat it [14-17]. It was necessary to choose the optimal model for the development of osteomyelitis in rabbits. To this end, we analyzed 5 different models of osteomyelitis in experimental animals.

Objective: to conduct a clinical, radiological and histological analysis of various models of chronic osteomyelitis in experimental animals.

Research tasks:

1. To compare the most commonly used animal osteomyelitis models.

2. To conduct clinical, radiological, microbiological and histological analysis of the selected models.

3. To determine the optimal model of experimental osteomyelitis for further research.

Materials and methods

The experiment was carried out on 90 outbred rabbits. The average age of the rabbits at the beginning of the experiment was 2±1 months, and the average individual weight was 2±1 kg. All rabbits were randomly divided into 5 groups. The experiment was realized in the vivarium of Non-commercial joint-stock company «Karaganda Medical University». The conditions of animals keeping in the vivarium ensured the experiment purity. The rabbits were kept in a room with controlled temperature (16-21°C) and relative humidity (45-65%). The rabbits were placed in special cages – 2-3 rabbits per each. The experiment was fulfilled in accordance with international ethical standards, approved by the Ethical Committee of the university (protocol №4 (13) from 25.09.2017).

Surgical operation was performed under general anesthesia (xylazine 7 mg/kg+ ketamine 35 mg/kg intramuscularly). To prepare the surgical field, the hairline in the surgical area was removed with scissors, treated with antiseptic solutions for three times and covered with sterile linen. Access was carried out along the anterior surface of the distal metaepiphyseal region of the left femur, a longitudinal incision with a layered dissection of the skin, subcutaneous tissue, fascia 3.0 cm long. Sharp retractors parted the edges of the wound. The femur was skeletonized with a raptor over an area of 2.0x1.0 cm, defects in the periosteum, cortical layer, and spongy substance were formed by a drill with a diameter of 2.0 mm in all groups.

Staphylococcus aureus (ATCC 43300) was used as an infectious agent in all animals, as it was the most frequently detected representative of the wound flora in patients with chronic osteomyelitis. The animals were infected with a daily culture mixture in sterile saline at a dose of 106 CFU/ml.

In group I, 0.2 ml of Staphylococcus aureus (SA) was injected into the bone defect after perforation. In group II, a cotton swab pre-soaked in a solution with SA was input into the bone defect, followed by closing the defect with Prime-Dent filling material. In group III, Ethoxysclerol (a sclerosing drug) and a cotton swab moistened with SA solution were added to the created bone tissue defect. In group IV, a cotton swab pre-soaked in solution with SA without additional sealing of the hole was added to the perforated hole. In group V, Ethoxysclerol was injected after perforation of the distal femur, and it was also filled with cotton swab soaked in SA solution. However, then the hole was closed with Prime-Dent filling material. Wounds in all groups were sutured in layers.

The development of chronic osteomyelitis was assessed by clinical, radiological, microbiological and histological data. Clinical evaluation was performed based on the activity of the rabbit, measurements of temperature and body weight, as well as the condition of the postoperative wound. A visual assessment of the severity of the inflammatory process was carried out in the area of the postoperative wound and adjacent soft tissues. The assessment was carried out in points: 0 points – no inflammation, 1 point – inflammation of soft tissues in the projection of the postoperative wound, 2 points – suppuration of the postoperative wound.

X-ray examination was performed for all rabbits in 2, 4, 6 and 8 weeks after the defect formation. Radiography was performed in frontal and lateral projections using the device «Arman 1.8L3» in dose 75 kV, 25 mAc, 18 mA on digital cassettes. Features of the shape and structure of the bone tissue were visualized in the area of the focus, their exact location and configuration were determined. Digital X-ray images are archived on the PC of the Department of Surgical Diseases. Radiography was performed 1 time in 2 weeks for 8 weeks. X-ray assessment was carried out according to a scoring system, where the following indicators were evaluated: periosteal reaction: no – 0 points, yes – 1 point; osteolysis, foci of destruction: no – 0 points; yes – 1 point; involvement into the process of the diaphysis: no – 0 points, yes – 1 point; involvement of the bone marrow canal in the process: no – 0 points, yes – 1 point. The highest score of 16 points showed the severity of the osteomyelitic process throughout the entire observation period.

Microbiological studies were carried out at the Department of Clinical Immunology, Allergology and Microbiology of Non-commercial joint stock company « Karaganda Medical University». Biosubstrate sampling for bacteriological analysis was performed at 2 weeks after the bone defect creating. The material for the study was the metaepiphyseal zone of the femur. The sampling of material from the lesion with a total weight of up to 1 gm were placed in a sterile container. The material was taken by the postoperative wound dissection after the re-introduction of the rabbit into anesthesia. Microorganisms were identified by the classical cultural method on an analyzer [18].

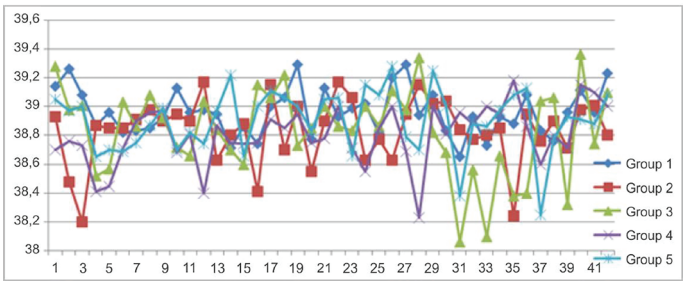
Histological examination was carried out after 2, 4, 6 and 8 weeks. All rabbits were euthanized from the experiment. Animals were euthanized by an overdose of anesthesia, then the test material was taken. The exarticulation of the femur was carried out after dissection of the implantation zone and the adjacent muscle mass, followed by osteotomy within healthy tissues at the level of the middle third of the thigh. The obtained material was sent to the Pathomorphological laboratory of the Department of Pathology of Non-commercial joint stock company «Karaganda Medical University».

Statistical data processing was carried out using a Microsoft Excel 2016 spreadsheet and STATISTICA 8.0 software (StatSoft, USA). The mean (M) and standard deviation (SD) were calculated for quantitative data with a normal distribution, in the case of a non-normal distribution – the median (Me) and quartiles (Q25; Q75). Qualitative values were presented as a percentage (in %) and its 95% confidence interval.

Results

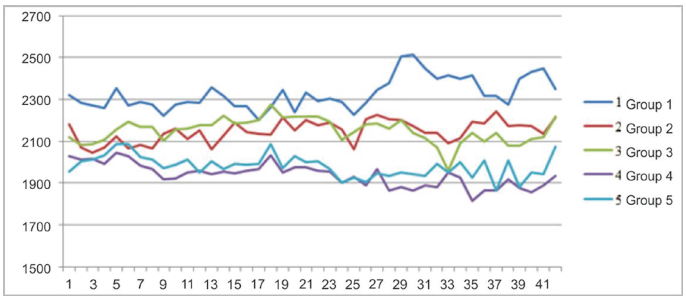
The body temperature of all experimental animals was measured with a non-contact thermometer during the entire observation period – 8 weeks. The body temperature curve in all five groups was similar: it gradually increased from the 1st to the 3rd day with a gradual decrease from the 3rd day to the 14th and was maintained at a stable level from the 14th to the 42nd day. The body temperature of rabbits in groups III, IV was higher than in groups I, II, V on the 3rd day ($p<0.05$) and there were no differences between five groups from the 3rd day to the 42nd ($p>0.05$) (Figure 1).

Figure 1 - Body temperature of rabbits in dynamics



The body weight of the rabbits was measured using standard scales during the entire observation period at the same time every day. The body weight of rabbits was lowest on the 3rd day. Rabbits of groups I, II, V lost less weight than in groups III, IV on the 3rd day ($p<0.05$). Body weight gradually increased from the 3rd day to the 42nd day and there was no difference between the five groups ($p>0.05$). On average, the total weight loss was 200±20 g (Figure 2).

Figure 2 - Body weight of rabbits in dynamics



Clinical evaluation of the data showed that in all groups, except group I, the animals showed exhaustion, decreased appetite, general condition depression, weak motor activity, and hair loss. After anesthesia termination, the operated animals on the first day after the operation did not lean on the operated limb, squeezing it, pulled the paw during examination, which was regarded as a sign of pain. Data on the state of the postoperative wound are shown in Table 1.

Table 1 Visual assessment of the postoperative wound

Group	2 weeks	4 weeks	6 weeks	8 weeks
Group I	0	0	1	0
Group II	0	0	1	0
Group III	0	1	2	2
Group IV	0	1	2	2
Group V	0	1	2	0

As can be seen from the Table 1, hyperemia, local temperature increase, fluctuation were observed from the 4th to the 8th week of observation in groups III and IV. The total score in these groups was 5, which indicates the severity of the clinical course. In group V, there was a moderate release of purulent exudate of a creamy consistency from the wound at the 6th week of observation, which healed on its own. In groups I and II, 1 point was registered – inflammation of soft tissues around the postoperative wound was noted at the 6th week and spontaneously disappeared during the next week.

The support ability of the limb improved from the second day after the operation in all groups, despite changes in the wound. The rabbits were actively moving. The general condition of the animals returned to normal.

Staphylococcus aureus was determined in the wound discharge in all groups in all animals during microbiological study after 2 weeks.

X-ray changes in the experimental groups are presented in Table 2.

As can be seen from Table 1, the most expressed periosteal reaction was observed in group III in all radiographs (15 points for the entire observation period). The least expressed reaction in terms of duration was observed in group I (1 point for the entire observation period). Osteolysis with destruction foci in groups III and IV was manifested in 3 out of 4 presented radiographs. The reaction from the diaphyseal part of the bone was the longest in group III throughout the entire observation period, while in group I it was completely absent. The reaction from the bone marrow canal was also observed throughout the observation period in group III and in group I there were no changes at all. Thus, the X-ray picture was most expressed in group III (15 points for all assessment indicators for the entire observation period), and the least expressed in group I (1 point for the entire observation period for all assessment indicators).

As can be seen from the presented series of X-ray images, X-ray changes in group I were noted only in the form of a periosteal reaction and persisted for 4 weeks. Changes regressed by 6-8 weeks of the study (Figure 3). Signs of osteolysis, destruction foci involving the medullary canal were noted in groups II and V from the 4th week and began to decrease by the 8th week (Figure 4 and 7). In groups III, IV, an extensive defect of the bone tissue in the metaepiphyseal area with alternating foci of clarification and darkening was revealed, while in group III the joint was involved (Figure 5, 6).

Table 2 X-ray control in dynamics

Group/ week / Parameter	Group I				Group II				Group III				Group IV				Group V			
	2	4	6	8	2	4	6	8	2	4	6	8	2	4	6	8	2	4	6	8
Periosteal reaction	0	1	0	0	0	1	1	0	1	1	1	1	0	1	1	1	0	1	1	0
Osteolysis, destruction foci	0	0	0	0	0	1	1	0	0	1	1	1	0	1	1	1	0	1	1	0
Involvement into the diaphysis process	0	0	0	0	0	1	1	0	1	1	1	1	0	1	1	1	0	1	1	0
Marrowy canal	0	0	0	0	0	1	1	0	1	1	1	1	0	1	1	1	0	1	1	0

Figure 3 - Radiography of group I in dynamics (A – 2 weeks, B – 4 weeks, C – 6 weeks, D – 8 weeks)

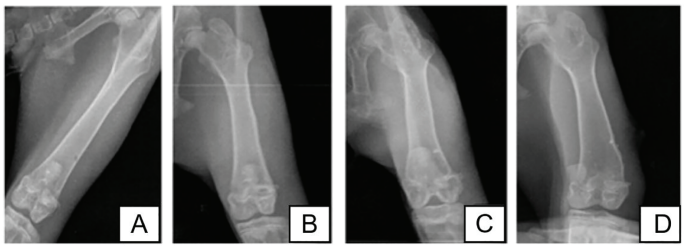


Figure 4 - Radiography of group II in dynamics (A – 2 weeks, B – 4 weeks, C – 6 weeks, D – 8 weeks)

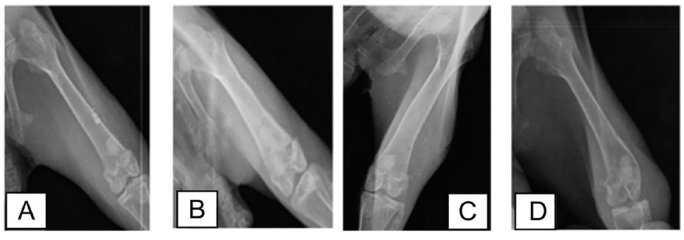


Figure 5 - Radiography of group III in dynamics (A – 2 weeks, B – 4 weeks, C – 6 weeks, D – 8 weeks)

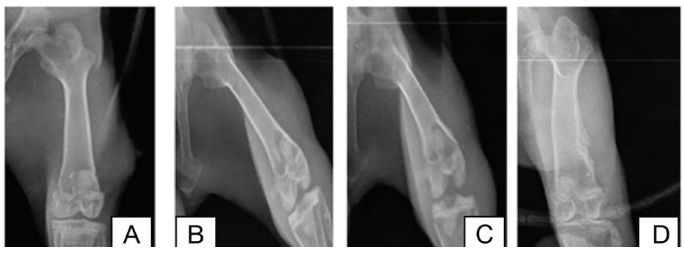


Figure 6 - Radiography of group IV in dynamics (A – 2 weeks, B – 4 weeks, C – 6 weeks, D – 8 weeks)

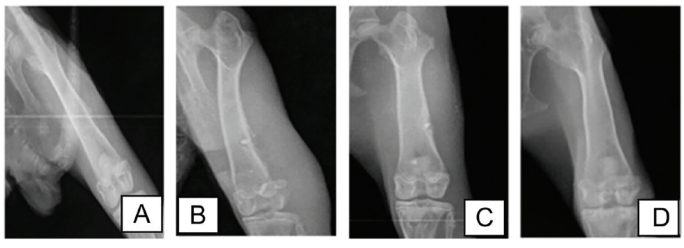
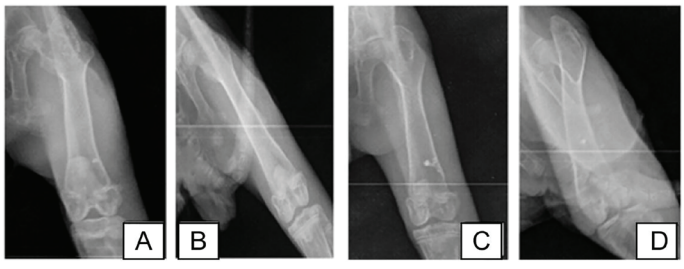


Figure 7 - Radiography of group V in dynamics (A – 2 weeks, B – 4 weeks, C – 6 weeks, D – 8 weeks)



Histological examination was performed once in 2 weeks after surgery. The following indicators were evaluated: the presence of periosteal reactions, changes in the medullary canal, the presence of osteonecrosis, soft tissue necrosis, granulocytic, lymphocytic, plasma, macrophage infiltrate. Osteomyelitis was considered to be actively proceeding in the presence of all these factors.

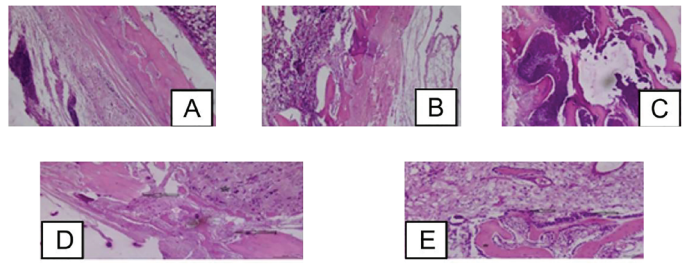
Histological examination revealed the following changes: chronic inactive osteomyelitis was formed in group I. The formed defect of the cortical plate was partially replaced by fibrous tissue with activated osteoblasts. Chronic inflammation was noted in the adjacent soft tissues and periosteum. The intramedullary area was represented by bone marrow with mature adipose tissue (Figure 8A).

Chronic inactive osteomyelitis was also registered in group II. For microscopy, the part of the formed cortical defect was presented, where the bone plate was partially replaced by fibrous tissue. The intramedullary area was with mild fibrosis, predominantly in the subcortical region. The integrity of the cortical plate was preserved. Osteocytes in the bone matrix were located in lacunae. Inactive osteoblasts were determined on the surface of bone trabeculae. The bone marrow area was filled with mature fat (Figure 8B).

Chronic active osteomyelitis of the 3rd stage and severe degree was detected in group III after 2 weeks of the study. Cortical and intramedullary cavities were filled with necrotic detritus and leukocytes merging with each other. The bone beams were of indefinite shape, thinned, in a state of necrosis and necrobiosis. The adjacent intramedullary area was presented by fibrous tissue infiltrated by lymphocytes, plasma cells, and granulocytes (Figure 8C).

Chronic active osteomyelitis developed gradually in group IV. The histological picture showed mild osteomyelitis after 2 weeks of the study, which gradually progressed to stage 3 at the 4th and the 6th weeks of the experiment. For the study, a place for modeling a defect in the bone was selected. The cortical bone defect was replaced by fibrous tissue with newly formed bone trabeculae surrounded by osteoblasts. Lymphoplasmacytic infiltration and fragments of foreign material with single giant multinucleated cells of foreign bodies were noted in the thickness of the fibrous tissue (Figure 8D).

Figure 8 - Histological examination of chronic osteomyelitis (A – group I, B – group II, C – group III, D – group IV, E – group V



Chronic active osteomyelitis of the 1st stage and mild degree was formed in group V. Severe fibrosis with mild lymphoplasmacytic infiltration and fragments of foreign material with single giant multinucleated cells of foreign bodies were noted. Newly formed subperiosteal bone tissue with active osteoblasts was recorded. The bone tissue lacked the plates or lines present in mature bone. Fibrous tissue with mild lymphohistiocytic infiltration was present in the intramedullary space. The intramedullary space was replaced by fibrous tissue with scattered lymphoplasmacytic infiltration. Bone beams were thin, single, with active osteoclasts (Figure 8E). A total of 90 rabbits were used, 5 groups of 18 rabbits per group.

Discussion

5 variants of osteomyelitis models were selected to achieve the objective and tasks of the study. Animals were subjected to clinical observation after the formation of all 5 models of osteomyelitis. Radiography and histological analysis were performed. According to the obtained results, the optimal model was chosen for the creation of chronic osteomyelitis

in order to conduct further research aimed at treating this pathology. Methods for the formation of models of experimental osteomyelitis are described in detail in the materials and methods chapter.

The earliest authors of experimental models of osteomyelitis in rabbits were Sheman in 1941 [19] and Norden in 1970 [20]. Both researchers developed osteomyelitis on the tibia of rabbits.

Norden used a sclerosing agent in the metaphysis of the tibia, injected with a suspension of S. aureus to produce progressive chronic osteomyelitis. The infection rate was 70 or 100%, depending on the bacterial load. In addition, the degree of infection ranged from mild to severe local bone changes in the analyzed studies, especially when the time to develop osteomyelitis varied from 2 to 4 weeks and according to differences in the bacterial strain used. The sclerosing material has mainly been used to evaluate new antibiotic therapies or antimicrobial drug delivery systems [21, 22, 23-31].

The models proposed by Scheman [19] and Norden [20] resembled hematogenous osteomyelitis. It usually occurs in children and becomes chronic if left untreated and diffuses through the tibial metaphysis.

Early publications include studies by Rodeheaver et al. in 1983 [32]. They inoculated S. aureus and E. coli into the intramedullary canal of the femur through an opening in the medial femoral condyle. Bone cement was injected through the same opening into the canal to promote the formation of osteomyelitis. Jacob et al. [33] reported their model of osteomyelitis on the femur in 1985 according to the method of Norden and Kennedy. Osteomyelitis was caused by intramedullary injection of a sclerosing agent (3% sodium tetradecyl sulfate) and S. aureus (5×106 CFU). X-ray showed osteomyelitic changes in 10 of 13 animals that survived over the 10-week time period. The diagnosis was confirmed histopathologically in 8 out of 10 cases. Later, Schulz et al. (2001) [34] reported a similar femoral model: 1.0 ml of bone marrow was taken through a biopsy needle inserted into the interpuncture fossa. Next, 0.1 ml of sodium morruate, S. aureus, and saline were injected. The results showed that the incidence of chronic progressive osteomyelitis was increased up to 100% using this method.

Rutledge et al. (2003) [35] created the same model by percutaneous injection. Models from other publications are similar – sclerosing agents and pathogens are injected through holes made in the proximal femur [36-37].

Despite the presence of studies indicating that the development of osteomyelitis with the addition of just SA or with the use of a filling preparation allows the use of these methods for an experimental model, in our case they did not confirm themselves. In groups where SA is simply added to the perforation hole and when using a filling preparation, the clinical picture of chronic osteomyelitis rarely develops, self-curability does not allow evaluating the possibilities of treatment. The use of a sclerosing drug allows the development of rapidly flowing chronic osteomyelitis with a high prevalence. The use of medical cotton wool (hygroscopic material as a carrier) allows the development of long-term chronic osteomyelitis, which cannot be cured on its own.

Conclusions

1. Clinical assessment showed an expressed severity of the course of the disease in group III, where the score was 15 points according to the scale. In group I, 0.2 ml of Staphylococcus aureus (SA) was injected into the bone defect after perforation. In group II, a cotton swab pre-soaked in a solution with SA was input into the bone defect, followed by closing the defect with Prime-Dent filling material. In group III, Ethoxysclerol (a sclerosing drug) and a cotton swab moistened with SA solution were added to the created bone tissue defect. In group IV, a cotton swab pre-soaked in solution with SA without additional sealing of the hole was added to the perforated hole. In group V, Ethoxysclerol was injected after perforation of the distal femur, and it was also filled with cotton swab soaked in SA solution. However, then the hole was closed with Prime-Dent filling material. Wounds in all groups were sutured in layers.

2. Temperature changes in the groups showed a gradual increase from the 1st day to 3nd with a gradual decrease from the 3nd day to the 14th. The body temperature of rabbits in groups III, IV was higher than in groups I, II, V on the 3rd day ($p<0.05$). There was no difference between 5 groups from the 3rd day to 42nd ($p>0.05$).

3. Changes in the body weight of rabbits showed that on the 3rd day there was a maximum weight loss of up to 220 g ($p<0.05$). The average total weight loss was 200±20 g.

4. X-ray assessment showed that the X-ray picture was most expressed in group III (15 points for all evaluation indicators for the entire observation period), and the least Expressed in group I (1 point for the entire observation period for all evaluation indicators).

Clinical assessment does not give a clear picture of the development of chronic osteomyelitis. The clinical picture of experimental animals is blurred, so X-ray and histological studies are required, which show local changes after 2 weeks from the start of the study. The X-ray and histological picture showed an actively flowing chronic osteomyelitis

It was revealed that the use of a sclerosing agent and a hygroscopic material gives the greatest effect. The introduction of a sclerosing drug leads to a rapid course of chronic osteomyelitis. Thus, the study showed that the modeling of osteomyelitis with hygrocosmic material (medical cotton wool) in 100% of cases leads to the development of classical active chronic osteomyelitis, which develops gradually. But the use of a sclerosing drug (Ethoxysclerol) led to a rapid course of chronic osteomyelitis.

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Morphology of echinococcal liver lesions during treatment with high-intensity focused ultrasound

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Abstract

Aim: The purpose of morphological studies was to study pathogenetic mechanisms of the therapeutic effect of HIFU ablation on hepatic echinococcosis.

Material and methods: Ablation of echinococcal cysts and alveococcal liver lesions no larger than 5 cm in size with high-intensity focused ultrasound was performed on JC Focused Ultrasound Therapeutic System (China). Biopsy material of hepatic echinococcal masses in 37 patients after HIFU-ablation were taken for morphological light-optical and electron microscopic studies.

Results: Protoscolexes lost their superficial syncytial layer, the parenchyma looked vacuolized, the disembodied heads with suckers and hooks were fragmented and separated from the body. Small vacuolization of hyaloplasm, homogenization of membranes and mitochondrial matrix, blurring of organelle contours in parenchymatous protoscolex cells were observed. Laminar shells of brood capsules and larvocysts of echinococcus were homogenized and ruptured, germinative cells were sloughed off. The laminar and germinal sheaths of the alveolar vesicles were irregularly thickened, unfolded, ruptured, and surrounded by necrotized liver cells and structureless masses. Destructively altered stem cells and calcareous calcium corpuscles of the laryngeal membrane were observed electron microscopically.

Conclusion: Morphological data revealed destructive effect of HIFU ablation on mature and germinative forms of hydatid and alveolar echinococcus of the liver, as well as the safety of the selected optimal HIFU power on the surrounding hepatic tissue, which explains the absence of recurrence and confirms high effectiveness of HIFU ablation as a minimally invasive method of treatment of echinococcal growths of certain acceptable sizes.

Key words: hepatic echinococcosis, high-intensity focused ultrasound, light-optical and electron microscopic morphology

Dedicated to the blessed memory of Professor Imankulov Suindyk Bopezhanovich.

Introduction

High-intensity focused ultrasound (HIFU) is a new and successful noninvasive method of treating tumors of various localizations [1, 2]. The theoretical foundations of HIFU ablation, established back in the 1940s at the University of Illinois, were implemented as a result of the creation of high-tech equipment model JC Focused Ultrasound Therapeutic System (Chongqing HAIFU Technology Co., China). Without damaging the skin or healthy organs, the method creates a high- energy concentration of radiation in the focus of the tumor, resulting in a second death of tumor cells. Total safety of the method, efficiency of use in primary and metastatic tumors of many organs, combination with any type of systemic exposure (chemo-, radiation and immunotherapy) led to the use of NIFU for ineffective surgical and palliative treatment of tumors. In 2010, Prof. S.B. Imankulov for the first time proposed the use of NIFU as a mini-invasive method of treatment of hydatidosis and alveolar echinococcosis of the liver in conditions of continuing severe emidemiological situation and unsolved many issues of the course, diagnosis and treatment of hepatic echinococcosis [3-5]. The developed indications and contraindications for HIFU use in hepatic echinococcal lesions, permissible sizes of parasitic masses, selection of optimal HIFU power, analysis of immediate and long-term results, comparative assessment of traditional surgical intervention and HIFU ablation were the basis for positive results and effective treatment of alveolar and hydatid liver echinococcosis by HIFU ablation [6-8].

The purpose of morphological studies was to study pathogenetic mechanisms of the therapeutic effect of HIFU ablation on hepatic echinococcosis. Presented at the international level in the form of reports [9-12], they are presented in full in the present work and dedicated to the blessed memory of Suindyk Bupezhanovich Imankulov.

Material and methods

Ablation of echinococcal cysts no larger than 5 cm in size with high-intensity focused ultrasound was performed on JC Focused Ultrasound Therapeutic System (Chongqing HIFU Technology Company, China) with a 15 cm diameter treatment lens, 0.9 MHz radiation frequency with the focused ultrasound traveling vertically in 5 mm slices. Power of radiation intensity averaged over time was 180 - 250 W. Centrifugate and biopsy material of hepatic echinococcal masses in 37 patients before, during the nearest (3-4 days) and long term (6 months) after HIFU-ablation were taken for morphological light-optical and electron microscopic studies. Transcutaneous puncture was performed under the control of ultrasound imaging. Safe taking of lifetime biopsy material of echinococcal cysts contents after Hi-Fu ablation was ensured by qualified performance and experience, special equipment and careful observance of the technique. The effectiveness of ablation was determined by computerized, magnetic resonance imaging and ultrasound examination. The cytological smears were stained by Papanicolaou. Histological and electron microscopic material was obtained according to conventional methods. Histological sections were stained with hematoxylin and eosin. Semi-thin sections (high-resolution light-optical microscopy) were stained with methylene blue, azure-2, and basic fuchsin [13]. Ultrathin sections were contrasted with uranyl acetate, Reynolds lead citrate, and studied in a Libra-120 electron microscope (Carl Zeiss).

Results

On cytological and light-optical examination of the contents of hydatid echinococcal cysts in the immediate aftermath of thermal and cavitational HIFU ablation the sedimentary material included, in addition to echinococcal structures, destroyed inflammatory cells, small vacuolar, granular material and calcareous crystals (Figure 1 A). Electron microscopically, the contents and superficial layered membranes of even the smallest ultrastructures ranging in size from 200 to 800 nm were necrotic (Figure 1 B). In the light-optical study of protoscolexes on cytomasks and semi-thin sections, there was a sharp decrease in their size due to gelation (Figure 1 C). Protoscolexes lost their superficial syncytial layer, the parenchyma looked vacuolized, the disembodied heads with suckers and hooks were fragmented and separated from the body. At the ultrastructural level, small vacuolization of hyaloplasm, homogenization of membranes and mitochondrial matrix, blurring of organelle contours in parenchymatous protoscolex cells were observed (Figure 1 D).

Laminar shells of brood capsules and larvocysts of echinococcus were homogenized and ruptured at the light-optical level, germinative cells were sloughed off (Figure 2 A). At high magnification, sharp cleavage of chitin sheath plates was clearly visible (Figure 2 B).

Electron microscopically, the surface of the fibrous layers of the chitin sheath plates was necrotic and had an osmiophilic appearance (Figure 2 C). The less dense inner granular layers of the plates contained electron-transparent vacuolized granular aggregates. The hyaloplasm of the glycogen-containing cells of the germinal membrane was ruptured, and the organelles were "fused" (Figure 2 D).

The condition of the echinococcal cyst wall itself was assessed by pathomorphological histological examination of rare surgical material that underwent HIFU ablation. The germinal

Figure 1 - Contents of echinococcal cyst 3 days after HIFU ablation. A - sedimentary material of echinococcal cyst contents. Semi-thin slice x 1000. B - necrosis of fine ultrastructure. Electronogram x 34,000. C - helicization and vacuolization of cytoplasm, detachment of protoscolex heads. Cytological smear preparation. Papanicolaou staining x 1 000. D - vacuolization of hyaloplasm and destruction of organelles in protoscolex cells. Electronogram x 24 000.

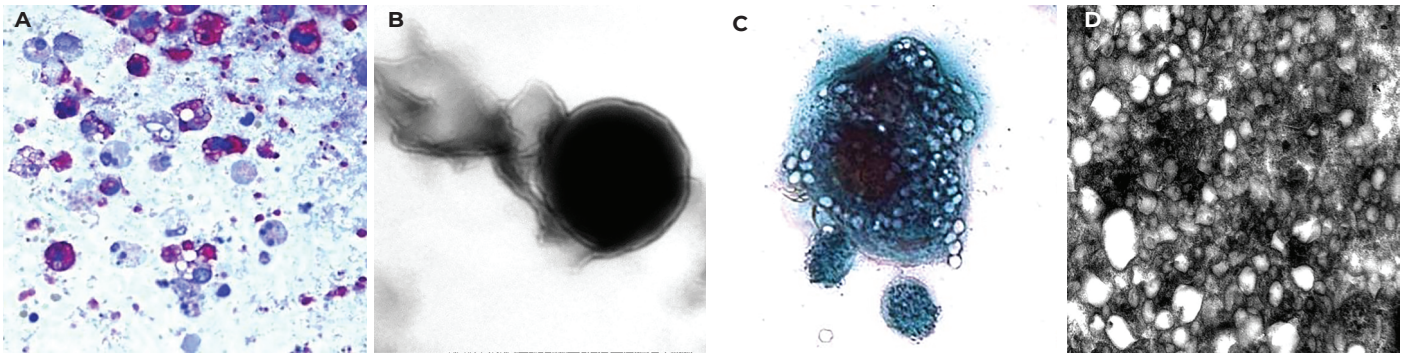
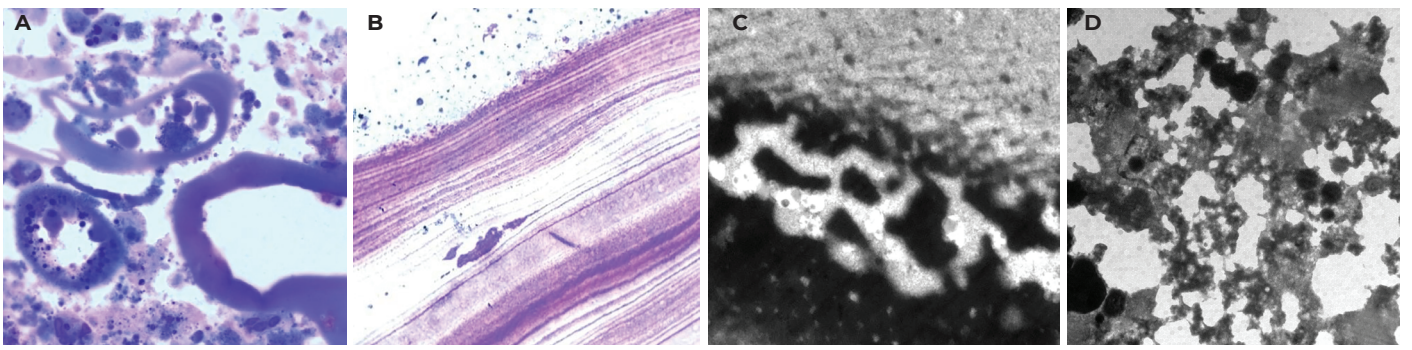


Figure 2 - Contents of echinococcal cyst 3 days after HIFU ablation. A - homogenization, laminar sheath rupture, desquamation of germinal sheath of brood capsules and larvocysts of echinococcus. Semi-thin slice x 500. B - delamination of laminar shell plates. Semi-thin slice x. 1000. C - necrosis of surface of fibrous layers, vacuolization of granular aggregates of internal layer of laminar shell plates. Electronogram x 30,000. D -destruction of glycogen-containing cell of laryngeal lamina membrane. Electronogram x 24 000.



layer of the cyst and the protoskeletons and brood capsules attached to the cambial zone were destroyed (Figure 3A). The chitin sheath layers were delaminated, fragmented, and necrotized (Figure 3 B). The fibrous sheath of hydatid echinococcus, where protoscolexes might normally be located, was characterized by a broad zone of the inner necrotic layer, although in small cysts the necrotic layer might have been absent. The hyaline layer showed granular disintegration of collagen fibrils (Figure 3 C). The outer layer of loose connective tissue with inflammatory cells and vessels was loosened. Adjacent to the fibrous capsule, the liver tissue was characterized by hepatocyte dystrophy, hepatic trabeculae rearrangement and periportal connective tissue overgrowth common in echinococcosis (Figure 3 D).

Figure 3 - Echinococcal cyst wall 3 days after HIFU ablation. A - thinning, destruction of germinal layer of the wall and brood capsule of echinococcal cyst. Histological section x 200. B - delamination and necrosis of chitin sheath plates of echinococcal cyst. Histological section x 400. C - granular disintegration of collagenous fibrils of hyaline layer, loosening of outer layer of loose connective tissue. Histological section x 200. D - dystrophy of hepatocytes, rearrangement of hepatic trabeculae, overgrowth of periportal connective tissue of hepatic tissue. Histological section x 200.

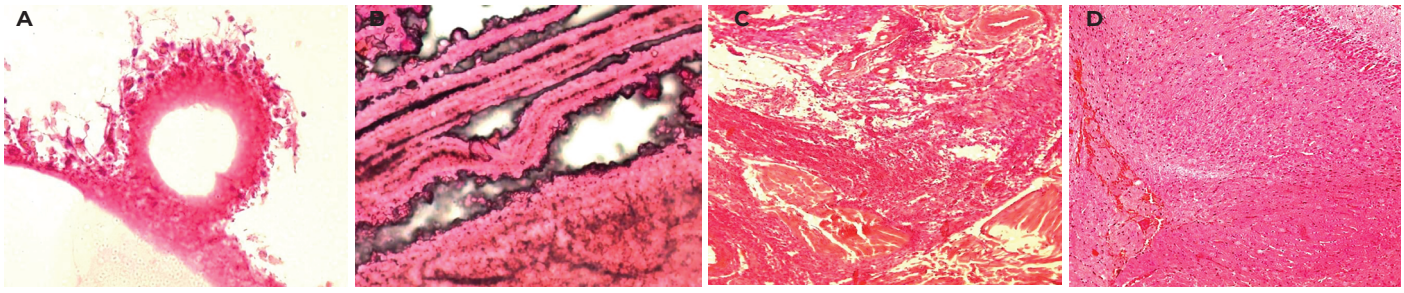
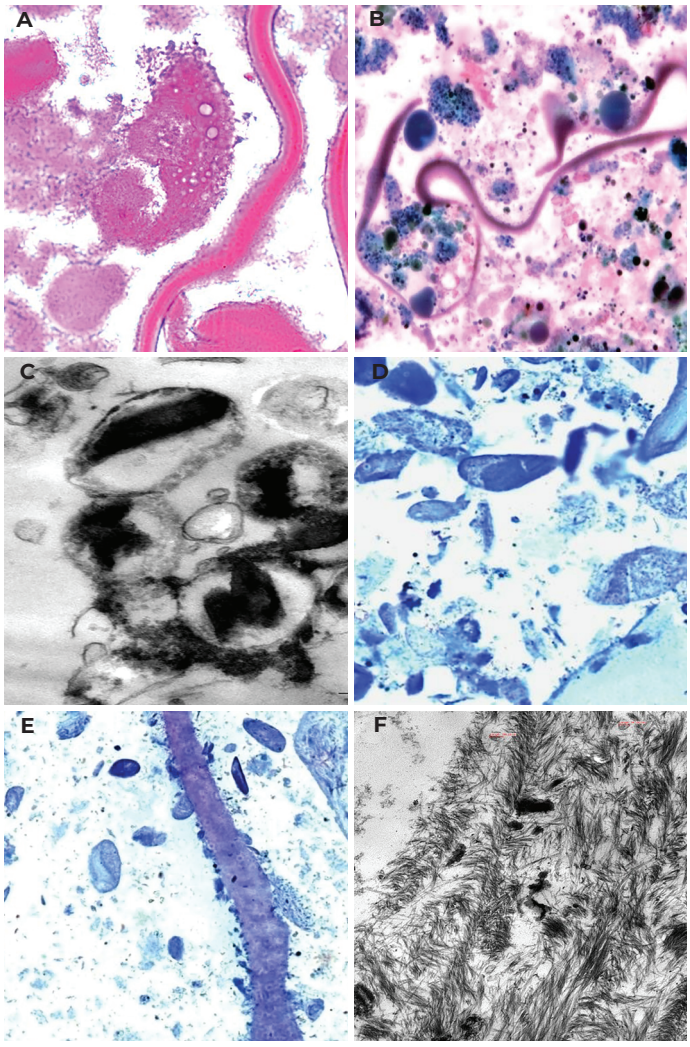


Figure 4 - Alveococcus of the liver 3 days after HIFU ablation. A - Destruction of protoscolex and laminae of alveococcal vesicles. Histological section x 400. B - Destruction of alveococcal larvocysts. Semi-thin slice x 1000. C - fragments of the destroyed calcium-containing cell. Electronogram x 34,000. D - numerous feather-like microcapsules. Semi-thin slice x 1000. E - microcapsules attached to and detached from the chitin sheath of alveococcus. Semi-thin slice x 1000. F - Destruction of the cell membrane of the microcapsule. Electronogram x 40000.



After HIFU-ablation of alveococcal liver lesions, destructively altered blurred contours of alveolar vesicles were seen cytologically. The histological material showed destruction of the body of germinal scolexes and laminae of alveococcus (Figure 4 A). On semi-thin sections, the laminar and germinal sheaths of the vesicles were irregularly thickened, unfolded, ruptured, and surrounded by necrotized liver cells and structureless masses (Figure 4 B). Destructively altered stem cells (amebocytes) and calcareous calcium corpuscles of the laryngeal membrane were observed electron microscopically (Figure 4 C). Of certain interest were peculiar microcapsules of irregular "feather-like" shape of different sizes (Figure 4 D). Close connection of microcapsules with ruptured chitinous shells of larvocysts was noted (Figure 4 E). Electron microscopically, the microcapsules were about 18 thousand nanometers in size and consisted of fibrillar structures similar to the chitin sheath structure of larvocysts. The ultrastructure of the outer membrane of the microcapsules was destroyed (Figure 4 F).

At 6 months after HI-FU exposure, fields of fibrinoid necrosis with altered alveolar larvocysts were determined histologically in the operatively removed material. Chitin sheaths of larvocysts were homogenized, unstructured. Cellular elements of the germinal layer and the contents of larvocysts were necrotic. Necrotically altered areas of the liver and larvocysts of alveococcus were surrounded by fibrous and granulation tissue overgrowth with pronounced plasmacytic and leukocytic infiltration.

Discussion

Thus, high - intensive focused ultrasound ablation caused destruction of both germinal forms of hydatidosis echinococcus protoscolex and all elements of the germinal shell of brood capsules and larvocysts, which are the carriers of all life functions of the parasite [14]. Fine vacuolization of hyaloplasm, homogenization of mitochondrial membranes and matrix, blurring of organelle contours testified to the termination of all redox processes in parenchymatous, including germinative cells of protoscolex stem from which acephalocysts develop, more stable and dangerous in terms of invasion [15]. We did not encounter acephalocysts themselves in the echinococcal cyst contents, although small ultrastructural fragments of destroyed

cells (from 200 to 800 nm) could belong to the destroyed parts of acephalocysts, constituting one to two thousandth of their size (100-200 microns). Our assumption is confirmed by the absence of relapses in this method of echinococcus treatment.

The echinococcal cyst wall was characterized by dissection and necrosis of all chitinous shell layers, where transcutaneous channels with protoscolexes and even small parasitic cysts located in them are formed during active parasite fertilization, contributing to exogenous echinococcal dissemination. It is also extremely important that HIFU ablation did not lead to severe destructive changes in the liver, preserving the functions of the organ.

After HIFU ablation of alveolar echinococcus electron microscopically revealed destruction of stem cells (amebocytes) and numerous calcareous calcium corpuscles of the laryngeal shell, presumably being temporarily inactivated by mineralization stem cells, playing an important role in alveococcal metastasis [16]. An interesting finding was the discovery of peculiar microcapsules closely associated with the ruptured chitin sheaths of larvocysts. The fibrillar structure of the microcapsules was identical to that of the chitin sheath of larvocysts. Assuming the relation of these structures to the poorly studied genesis of alveococcal brood capsules, there is no doubt that HIFU ablation, causing destruction of the outer membrane of microcapsules, destroyed even the most initial forms of this parasite development. In the distant terms after HIFU exposure the pathologically changed alveolar larvocysts were necrotized and littered with fields of fibrous and granulation tissue, which indicated a complete blockade of alveolar echinococcal development.

Conclusion

Morphological data revealed destructive effect of HIFU ablation on mature and germinative forms of hydatid and alveolar echinococcus of the liver, as well as the safety of the selected optimal HIFU power on the surrounding hepatic tissue, which explains the absence of recurrence and confirms high effectiveness of HIFU ablation as a minimally invasive method of treatment of echinococcal growths of certain acceptable sizes.

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Components of obstetric violence: A descriptive study on physical abuse, non-consented care and non-confidential care

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Abstract

Objective: This study aimed at assessing the components of obstetric violence of women in receiving care during labor and postnatal period.

Material and methods: This research was designed as a web-based descriptive study. The study was conducted with 556 women who had a vaginal delivery were within the first 6 weeks after delivery. The data of the research were collected between November-December 2021.

Results: The mean age of women was 27.33±5.75, and the mean gestational week was 38.96±1.42. It was determined that while 95% of the women who underwent the intervention had a vaginal examination for less than 4 hours, 86.9% of them had no freedom of positioning at birth, and information was not provided to 41.2% of them before shaving, 22.2% of them before the amniotomy, 6.3% of them before oxytocin administration, 7.8% of them before episiotomy administration, 23.6% of them before fundal pressure, and 88.9% of them before vacuum support. It was found that 69.8% of the women did not have a companion during the delivery process, 67.1% of them were not involved in the decisions during the delivery process, and 93.9% of them asked for getting permission and providing information in the interventions during the delivery process. Additionally, the difference between the distributions of exposure to obstetric violence according to some sociodemographic and obstetric characteristics of the women was not statistically significant ($p<0.05$).

Conclusion: According to the result of the study, it was determined that women were subjected to some types of obstetric violence during labor and the delivery process.

Key words: obstetric violence, physical abuse, non-consented care, non-confidential care, midwifery

Introduction

Obstetric violence (OV), is a specific type of violation of women's rights in medical practice during health care related to the child birth processes [1]. Women who give birth may be subjected to different forms of OV in the delivery room during labor and in the early postnatal period [2]. Exposure to such maltreatment and abuse creates a psychological distance between expectant mothers and caregivers, and consequently, women who are afraid of being exposed to abuse and violence avoid applying to health systems [3, 4]. Avoidance of going to the hospital and thus getting away from the health system becomes a more significant barrier than geographical or financial barriers among the barriers encountered in providing maternal health care [3, 5].

For expectant mothers who receive obstetric care, respectful care at birth is defined as "a universal human right that includes respect for women's feelings, dignity, choices and preferences and also pays regard to ethical principles" [6, 7]. It is indicated that women are exposed to many disrespectful and abusive treatments by health care workers while receiving care during the

birth process and in the early postnatal period. These treatments include physical abuse (beating, slapping and pinching), failure to provide sufficient information and to obtain consent in the interventions or care to be provided (e.g., for cesarean section or tubal ligation), disregard for privacy in care (e.g., lack of physical privacy or sharing confidential information), insulting while providing care (e.g., shouting, scolding and insulting comments), leaving alone (e.g., leaving alone during delivery), discrimination based on ethnic origin, age or wealth, or detention in institutions for non-payment of care fees [8-11].

In 2015, the world's leading authorities (The World Health Organization-WHO, The International Confederation of Midwives-ICM, The International Federation of Gynecology and Obstetrics-FIGO, The White Ribbon Alliance-WRA and The International Pediatric Association-IPA) reached a consensus on the Mother and Baby Friendly Birth Facility (MBFBF) program and determined seven basic categories of disrespect and abuse in this intervention: 1) Physical abuse: hitting, roughly forcing legs apart, fundal pressure for normal delivery; 2) Non-consented care: no informed consent for procedures, such as when provider elects to perform unnecessary episiotomy; 3) Non-confidential care: no privacy (spatial, visual, or auditory); 4) Non-dignified care: humiliation by shouting, blaming, or degrading; 5) Discrimination based on specific patient attributes: HIV status, ethnicity, age, marital status, language, economic status, educational level, etc.; 6) Abandonment of care: facility closed despite being 24/7, or if open, no staff can or do attend delivery; 7) Detention in facilities: Not releasing mother until bill is paid [12]. By declaring a consensus, these authorities propose a number of criteria and indicators to facilitate classification of health institutions in accordance with maternal and newborn care. Some of these criteria are as follows: "Every woman has the right to a positive birth experience and dignified and caring care during childbirth, even in case of complications. Every woman and every newborn baby should be protected from unnecessary intervention, practices and procedures that are not based on evidence, practices that do not respect their culture, physical integrity and dignity" [13].

The United Nation General Assembly published a report identifying violence against women in reproductive health services, especially the situation of women subjected to obstetric violence during delivery (July-2019) and called for countries to mobilize against such abusive practices [14]. It recommends adopting a human rights-based approach to the various forms of maltreatment to which women are subjected in the obstetric context by insisting that it not only violates women's right to a life free from violence, but also endangers their right to life, health, physical autonomy and autonomy [15].

While some countries in the world legally define obstetric violence and consider the practices as a crime, Turkey has not yet made a legal definition of obstetric violence. Naturally, limited evidence on OV was found in the literature review. Therefore; this study aimed at assessing the components of obstetric violence of women in receiving care during labor and postnatal period, in Turkey 2021.

Materials and methods

Study design and participants

This web-based descriptive study was planned to determine the components of obstetric violence. The survey questions in the study were created by reviewing the national and international literature. As a result of the literature review, there were 15 questions to determine the components of obstetric violence, apart from the personal information form. Computer-assisted, self-interviewing (CASI) was used as it would allow for more efficient collecting of research data. However, the evaluation of the components of obstetric violence form could not be validated due to the technical unavailability of proper focus group related to the web character of the study.

The sample size was calculated by performing power analysis in OpenEpi, version 3, publicly available statistical software (http://www.openepi.com). In this study, assuming 50% of the components of obstetric violence, the sample size was calculated as at least 383 women, with an error level of 5%, a two-sided significance level with a confidence interval of 95% and a power of 80%. 590 women initially participated in the study; however, 556 valid questionnaires were evaluated since the questionnaires of the women who did not meet the inclusion criteria (n=15) and filled out the questions incompletely (n=19) were not taken into consideration.

The inclusion criteria for the study were determined as: women who had a vaginal delivery, who were within the first 6 weeks after delivery (postpartum period), who had no risk in pregnancy, who had a healthy baby, and who were aged 18 and older.

The exclusion criteria of the study were determined as: women who were diagnosed with psychological illness, who had mental disability, who were hospitalized in the intensive care unit after delivery, and whose babies stayed in the intensive care unit.

Measures

The results of the study were collected through questionnaire forms developed by using the Google forms application (https://docs.google.com/forms) between November-December 2021. The prepared questionnaire form was shared on accessible social media platforms (facebook, instagram, twitter, etc.) where women in the postpartum period shared about themselves and their babies. In the first stage of the questionnaire, the criteria for inclusion in the study were included. In order to ensure the participation of those who were in the puerperal period, women who did not meet the inclusion criteria and stated this were not included in the study.

Accordingly, information about the subject and aim of the study was shared on the first page of the questionnaire form, and a consent text, in which it was determined that the information and answers of the participants would be kept confidential, was added. Voluntary postpartum women who approved the consent text were directed to the online survey platform prepared via an electronic link.

Personal information form

The personal information form was developed by the researchers and was structured in three parts. The first part included questions determining some descriptive characteristics of women (age, educational level, employment status, income status, etc.), the second part included questions determining their obstetric characteristics (gestational week, number of pregnancies, number of abortions, number of curettages, etc.), and the third part included questions about preparation for labor, and delivery (participation in prenatal education classes, mode of delivery, etc.) (13-15).

The form prepared to evaluate the components of obstetric violence

This form was prepared with reference to the disrespect and abuse categories in the *Mother and Baby Friendly Birth Facility (MBFBF) jointly published by the world's leading authorities (The World Health Organization-WHO, The International*

Confederation of Midwives-ICM, The International Federation of Gynecology and Obstetrics-FIGO, The White Ribbon Alliance-WRA and The International Pediatric Association-IPA) in 2015 (12). Among these published categories, there are questions aimed at determining the categories of "Physical abuse", "Non-consented care" and "Non-confidential care".

Abuse categories

Physical abuse assessment questions: Questions prepared to determine the situations of continuous application of Non-Stress Test (NST), oral restriction during delivery, frequent vaginal examinations (at intervals of less than 4 hours), and inability to take the desired position during labor and delivery. (The questions were determined as follows: NST Implementation Status, Fluids and oral intake, Vaginal examination status, Did you have freedom of position until birth?, Did you have position freedom at the time of birth?)

Non-consented care assessment questions: Questions prepared to determine the situations of shaving, application of enema, performing amniotomy, Bladder catheter application, oxytocin application, performing episiotomy, fundal application, Vacuum-assisted delivery without obtaining consent. (The questions were determined as follows: Shaving, Enema, Amniotomy, Bladder catheter application status, Induction of labor with oxytocin, Episiotomy, Fundal pressure, Vacum assisted delivery)

Non-confidential care assessment questions: Questions prepared to determine the situations of ensuring privacy, and restrictions on birth partners. (The questions were determined as follows: Was your privacy considered important during the birth process?, Was your privacy considered important at the time of birth?, Were you free to have any companion you want with you during the birth process?)

Data analysis

The data obtained within the scope of the study were first organized in Microsoft Excel and then transferred to the SPSS 25.0 for Windows (SPSS, Chicago, Il, USA) package program and evaluated. The data and descriptive statistics are presented as numbers and percentages. Statistical significance was determined as $p<0.05$.

Ethical considerations

Ethical approval was obtained from XXX University Non-Invasive Clinical Research and Publication Ethics Committee to conduct this study (Decision No: 2021/2329). This study was conducted in accordance with the Principles of the Declaration of Helsinki. On the first page of the questionnaire, informed consent indicating that they accepted the study was obtained from the women.

Results

A total of 556 women who had a vaginal delivery were evaluated in the study. While the mean age of women was 27.33±5.75 (range 18-46), it was determined that 78.8% of them had high school or below education, 79.9% of them had health insurance, 85.3% of them were unemployed, 81.1% of them had middle income, and 86.5% of them had a nuclear family structure. The mean gestational week of the women was 38.96±1.42 (range 30-42) and it was determined that 64.2% of them were multigravida, 85.6% of them had never had a miscarriage, 96.8% of them had no curettage, and 39.4% of them had at least one living child. It was determined that 98.7% of the women did not attend the prenatal education class and that 72.8% of them did not read books and magazines about delivery.

The distribution of women according to their exposure to physical abuse during the birth process is presented in Table 1. It was determined that while 86.7% of women had intermittent NST, 54.1% of them did not have oral restriction, 95% of them had vaginal examination at intervals of less than 4 hours, 91.5% of them had freedom of position until delivery, and 86.9% of them did not have freedom of position during delivery (Table 1).

Table 1 The Distribution of Women According to Their Exposure to Physical Abuse During the Birth Process

Variables	**Interventions**	
	n (556)	**%**
NST Implementation Status		
Continuous NST performed	74	13.3
Intermittent NST performed	482	86.7
Fluids and oral intake		
Yes	255	45.9
No	301	54.1
Vaginal examination status		
At intervals of less than 4 hours	528	95.0
At least 4 hours apart	28	5.0
Did you have freedom of position until birth?		
Yes	509	91.5
No	47	8.5
Did you have position freedom at the time of birth?		
Yes	73	13.1
No	483	86.9

Table 2 The Distribution of Women According to Their Exposure to Non-Consented Care During the Birth Process

Variables	Interventions		Information	
	n	%	n	%
Shaving				
Yes	17	3.1	10	58.8
No	539	96.9	7	41.2
Enema				
Yes	22	4.0	15	68.2
No	534	96.0	7	31.8
Amniotomy				
Yes	180	32.4	140	77.8
No	376	67.6	40	22.2
Bladder catheter application status				
Yes	124	22.3	112	90.3
No	432	77.7	12	9.7
Induction of labor with oxytocin				
Yes	431	77.5	404	93.7
No	125	22.5	27	6.3
Episiotomy				
Yes	358	64.4	330	92.2
No	198	35.6	28	7.8
Fundal pressure				
Yes	258	46.4	197	76.4
No	298	53.6	61	23.6
Vacum assisted delivery				
Yes	9	1.6	1	11.1
No	547	98.4	8	88.9

The distribution of women according to their exposure to non-consented care during the birth process is presented in Table 2. In the care provided to women, it was determined that while 3.1% of them were shaved and 41.2% of them were not informed before the procedure, enema was applied to 4.0% of them and 31.8% of them were not informed before the procedure, 32.4% of them underwent amniotomy and 22.2% of them were not informed before the procedure, bladder catheter was applied to 22.3% of them and 9.3% of them were not informed before the procedure, oxytocin was applied to 77.5% of them and 6.3% of them were not informed before the procedure, 64.4% of them had an episiotomy and 7.8% of them were not informed before the procedure, fundal pressure was applied to 46.4% of them and 23.6% of them were not informed before the procedure, and 1.6% of them were provided with vacuum-assisted delivery and 88.9% of them were not informed before the procedure (Table 2).

The distribution of women according to their exposure to non-confidential care during the labor process and during delivery is presented in Table 3. Accordingly, it was determined that the privacy of 95% of the women during the birth process and 95.9% of the women during delivery was protected. It was determined that 69.8% of the women did not have a companion during delivery (Table 3).

Table 3 The Distribution of Women According to Their Exposure to Non-Confidential Care During the Labor Process and During Delivery

Variables	n	%
Was your privacy considered important during the birth process?		
Yes	528	95.0
No	28	5.0
Was your privacy considered important at the time of birth?		
Yes	533	95.9
No	23	4.1
Were you free to have any companion you want with you during the birth process?		
Yes	168	30.2
No	388	69.8

The distribution of women according to their participation in decisions and their expectations during the delivery process is presented in Table 4. It was determined that 67.1% of the women were not included in the decisions during the delivery process, and that 93.9% of them asked for permission from them before the procedure to be applied during the delivery process and to be informed about the procedure (Table 4).

Table 4 The Distribution of Women According to Their Participation in Decisions and Their Expectations During the Delivery Process

Variables	n (556)	%
Participation in decisions during the birth process		
Yes I'm involved	27	4.9
I'm partially involved	156	28.0
No I'm not included	373	67.1
Obtaining permission and providing information on interventions during the birth process		
No I do not want to	11	2.0
I would partially	23	4.1
Yes I would	522	93.9

The distribution of women according to their exposure to physical abuse, non-consented care and non-confidential care during the labor process and during delivery is presented in Table 5. When the women's exposure to obstetric violence was questioned, it was determined that 37.7% of women who were exposed to physical violence had vaginal examinations less than 4 hours apart, and this rate was 95.1% for those included in the study. It was determined that oxytocin was administered in 30.8% of women exposed to Non-Consented Care, and this rate was 79.7% in those included in the study. It was determined that 13.7% of the women whose non-confidential care status were evaluated had a companion during the birth, and this rate was 31.1% in those included in the study (Table 5).

Table 5 The Distribution of Women According to Their Exposure to Physical abuse, Non-consented care and Non-confidential care

		Responses n (%)	Percent of Cases* (%)
		Yes	
Physical Abuse *(During the birth process)*	NST Implementation Status	34 (2.4)	6.1
	Fluids and oral intake	255 (18.2)	45.9
	Vaginal examination status	528 (37.7)	95.1
	Freedom of position until birth	509 (36.4)	91.7
	Freedom at the time of birth	73 (5.2)	13.2
	Total	1399 (100)	252.1
Non-Consented Care *(During the birth process)*	Shaving	17 (1.2)	3.1
	Enema	22 (1.6)	4.1
	Amniotomy	180 (12.9)	33.3
	Bladder catheter application status	124 (8.9)	22.9
	Induction of labor with oxytocin	431 (30.8)	79.7
	Episiotomy	358 (25.6)	66.2
	Fundal pressure	258 (18.4)	47.7
	Vacum assisted delivery	9 (0.6)	1.7
	Total	1399 (100)	258.6
Non-Confidential Care *(During the labor process and during delivery)*	Privacy during the birth process	528 (43)	97.4
	Privacy at the time of birth	533 (43.4)	98.3
	Freely having any companion during the birth process	168 (13.7)	31.1
	Total	1229 (100)	226.8

** MR: Multiple Response*

The distribution of women according to their exposure to physical abuse, non-consented care and non-confidential care according to some sociodemographic and obstetric characteristics is presented in Table 6. Accordingly, it was determined that the difference between the distributions of exposure to physical abuse, non-consented care and non-confidential care according to the age, education status, pregnancy week, parity, miscarriage, curettage and number of living children status of the women was not statistically significant ($p<0.05$; Table 6).

Table 6 The distribution of women according to their exposure to physical abuse, non-consented care and non-confidential care according to some sociodemographic and obstetric characteristics

	Physical Abuse (n, %)		Test[a], p value	**Non-Consented Care** (n, %)		Test[a], p value	**Non-Confidential Care** (n, %)		Test[a], p value
Age	**Yes**	**No**		**Yes**	**No**		**Yes**	**No**	
≤ 25 years	24, 2.7	208, 38.4	p=0.563	5, 0.9	216, 38.8	p=0.457	280, 37.4	13, 2.3	p>0.999
≥ 26 years	30, 3.9	294, 55.0		12, 2.2	323, 58.1		320, 57.6	15, 2.7	
Education status									
≤High school	26, 5.0	383, 74.2	p=0.664	15, 2.7	423, 76.1	p=0.546	418, 75.2	20, 3.6	p=0.344
≥University	8, 1.6	99, 19.2		2, 0.4	116, 20.9		110, 19.8	8, 1.4	
Pregnancy week									
≤ 36 w	4, 0.8	49, 9.5	p=0.769	3, 0.5	56, 10.1	p=0.410	58, 10.4	1, 0.2	p=0.344
≥ 37 w	30, 5.8	433, 83.9		14, 2.5	483, 86.9		470, 84.5	27, 4.9	
Parity									
Primigravid	20, 1.8	195, 35.6	p=0.362	9, 1.6	190, 34.2	p=0.197	186, 33.5	13, 2.3	p=0.232
Multigravid	34, 4.7	307, 57.9		8, 1.4	349, 62.8		342, 61.5	15, 2.7	
Miscarriage									
Yes	13, 0.6	80, 13.6	p=0.453	1, 0.2	79, 14.2	p=0.489	77, 13.8	3, 0.5	p=0.784
No	41, 6.0	422, 79.8		16, 2.9	460, 82.7		451, 81.2	25, 4.5	
Curettage									
Yes	12, 0.4	19, 1.7	p=0.160	1, 0.2	17, 3.1	p=0.433	18, 3.2	0, 0.0	p> 0.999
No	42, 6.2	483, 91.7		16, 2.8	522, 93.9		510, 91.7	28, 5.1	
Number of living children									
1- 2 children	31, 4.1	342, 64.3	p=0.445	11, 2.0	369, 66.4	p=0.793	358, 64.4	22, 4.0	p=0.299
≥ 3 children	23, 2.5	160, 29.1		6, 1.1	170, 30.5		170, 30.5	6, 1.1	

[a] *Fisher's Exact Test*

Discussion

The WHO's first recommendation for a positive birth experience is respectful maternal care. Respectful maternal care refers to the care provided in a way that protects the dignity, privacy and confidentiality of all women with a human rights-based approach [16]. In this study conducted to determine the components of obstetric violence, it was found that while more than one-tenth of the women underwent continuous NST, approximately half of them were restricted for oral fluid and food intake, and almost all of them underwent vaginal examination at intervals of less than four hours (Table 1, Table 5). Practices such as increased unnecessary birth interventions and the routine use of ineffective and potentially harmful practices pave the way for obstetric violence by causing disrespectful maternal care [16]. Furthermore, the implementation of unnecessary interventions causes physical abuse, which is one of the categories of disrespect and abuse in maternal care. However, contrary to the results in the study, in the World Health Organization's positive birth guide, continuous cardiotocography/NST is not recommended for the evaluation of fetal health in healthy pregnant women with spontaneous delivery, oral fluid and food intake during labor is recommended in low-risk pregnant women, and vaginal examination at least every four hours is recommended in the routine evaluation of the first stage of labor in low-risk women [16]. Furthermore, according to the Mother-Friendly Hospital Program of the Ministry of Health of the Republic of Turkey, non-evidence-based interventions should not be routinely applied. Accordingly, pregnant women should not be starved, fluid intake should not be interrupted, and touch should not be applied frequently [17]. In parallel with the result of the study, in the study conducted on women in Turkey in order to determine the pregnancy and birth experiences of puerperant women with a vaginal delivery and their views on the mode of delivery, it was determined that 12% of women underwent continuous NST and 75.07% of them were restricted for oral intake. Furthermore, while there was no difference between the experiences of pregnant women who underwent continuous NST or intermittent NST at the time of delivery, it was determined that the experiences of pregnant women with oral restriction at the time of delivery were significantly negative compared to those without oral restriction [18]. In a study conducted by Uzel and Yanıkekrem to determine the preferences of women regarding evidence-based practices in the intrapartum period, it was determined that only 0.6% of women were allowed for oral intake during delivery [19]. Despite the recommendations of international organizations, it is reported that midwives frequently perform unregistered vaginal examinations [20]. In the study conducted by Stepherd and Cheyne to determine the causes and frequency of vaginal examination during delivery, it was determined that almost 70% of the healthcare team performed vaginal examinations at intervals of more than four hours [21]. In another study conducted on Turkish women to determine their experiences of vaginal examination during the normal delivery process and the factors affecting it, it was found that women were exposed to unnecessary and frequent vaginal examination [22]. These results show that unnecessary birth interventions were highly performed for the pregnant women included in the study and that the pregnant women were not pleased with these practices.

According to the result of our study, it was determined that although the vast majority of women took the position they wanted in the first stage of labor, contrary to the

recommendations of national and international organizations, this rate changed sharply in the second stage of labor and the majority of women could not take the position they wanted (Table 1). In the positive birth guide of the World Health Organization, supporting movement in the first stage of labor, encouragement of pregnant women, and upright position are recommended in low-risk pregnant women, and in the second stage, it is also recommended to encourage the woman to adopt a birth position that she prefers, including the upright position [23]. Furthermore, nowadays, mothers being in the position where they feel most comfortable during delivery, and the mother's ability to walk in the room as they wish are among the Mother-Friendly Hospital Implementation Criteria of the Ministry of Health [17]. Except for certain circumstances, it is not beneficial for the pregnant woman to lie down during delivery, and it may even cause fetal and maternal harm in low-risk pregnancies [24-26]. As a result of the qualitative study conducted with 7 women to investigate the perceptions and experiences of mothers and midwives regarding the use of the supine position during labor and delivery, it was reported that mothers who gave birth took the position preferred by the midwife participating in delivery and that only one mother was given the opportunity to choose a position during delivery. Furthermore, the study revealed that midwives primarily performed deliveries only in the supine position [27]. In a study, it was determined that approximately half of the women were restricted in movement during delivery, and that positive perception levels of these women about delivery were lower compared to those without movement restriction [18]. In another study conducted to evaluate women's birth experience and postpartum satisfaction, it was determined that approximately half of the women gave a negative answer to the question “The staff encouraged me about the delivery method I wanted” [28].

According to another result obtained in our study, approximately half of women with perineal shaving during delivery, one-third of women who had an enema, approximately one fourth of women who had amniotomy and fundal pressure, and almost all of the women who underwent vacuum application indicated that they were not informed before the procedure (Table 2). Similar to the result of the study, in the study conducted by Meijer et al., it was determined that information was not provided to more than half of women before perineal shaving and enema application, approximately half of women who had fundal pressure, and two-thirds of women before the forceps application, which is used when intervention is required such as vacuum [29]. In the study conducted by Özmen to determine the services received by women and their expectations for nursing approaches during gynecological examination, approximately half of the women stated that the nurse did not inform them about the pre-examination procedure [30]. In the study conducted to determine the frequency of induction use in labor and its relationship with postpartum depression score, it was determined that women experienced fear of induction due to their lack of knowledge about the procedure [31]. Medical interventions that can be performed without informing the woman about the health status of herself or her unborn baby lead to cases of maltreatment and thus obstetric violence [32]. However, in practice, women cannot always get the information they need to make conscious decisions [29]. In accordance with the 2018 intrapartum care recommendations of the World Health Organization, it is recommended to establish effective communication between health care professionals and women giving birth by using simple and culturally acceptable methods for a positive birth experience [23]. In this context, it is indicated that healthcare professionals should present the information needed by women and their families in a clear, concise and understandable way, should avoid medical language and use pictorial and graphic materials when necessary, should explain the procedures to women and their families, and should ensure that verbal or, where appropriate, written informed consent is obtained for pelvic exams and other procedures [16].

According to another result of our study, almost all of the women indicated that their privacy was protected both during and at the time of delivery (Table 3, Table 5). In parallel with the result of the study, in the study conducted on Turkish women to determine the effect of birth expectations on primiparous women's perceptions of birth experience, it was determined that almost all of the women's privacy perceptions about delivery were at the expected level and above [33]. Respecting privacy is one of the patients' rights to protection [34]. In the World Health Organization's positive birth guide, it is stated that it is important to respect the wishes of all women and that cultural sensitivities should be regarded. If there are no separate rooms in the institution providing care services, in other words, if there is a ward system with more than one bed, it is emphasized that attention should be paid to ensure the privacy and confidentiality of all women with dividers such as curtains and screens [23].

In the study, it was determined that two-thirds of the women were not allowed to have any companion they wanted during the delivery process (Table 3, Table 5). Similar to the result of the study, in the study conducted by Meijer et al., it was found that approximately half of the women with a vaginal delivery were not allowed to have any companion they wanted with them during the delivery process [29]. For a positive birth experience, it is recommended that all women should be allowed to have a companion (spouse, friend, relative, healthcare worker, daula, etc.) during labor and delivery [23]. Furthermore, according to the Mother-Friendly Hospital Program of the Ministry of Health of the Republic of Turkey, pregnant women should be able to feel comfortable and at home with a suitable companion and freedom of movement should be provided [17]. The practices apart from these practices are within the scope of non-confidential care and lead to obstetric violence.

In the study, two-thirds of the women considered that they were not included in the decisions taken during labor and delivery, and almost all of them wanted to be informed about the decisions taken in their next birth (Table 4). In parallel with the result of our study, in a study on women who gave birth in Turkey, it was determined that the majority of women gave a negative answer to the question "I was involved in making decisions about my treatment and care during the delivery process" [35]. In another study on Turkish women, it was found that participants expected healthcare professionals to be friendly and informative [22].

According to the last result obtained in our study, it was determined that the difference between the distribution of exposure to Physical abuse, Non-consented care and Non-confidential care according to the age, education status, pregnancy week, parity, miscarriage, curettage and number of living children status of the women was not statistically significant (Table 6). In this case, it was determined that exposure to obstetric violence does not differ according to sociodemographic and obstetric characteristics. As a matter of fact, in a study conducted to support our study finding, discrimination and obstetric violence in maternity wards were evaluated and it was determined that there was no difference between the distribution of exposure to obstetric violence according to the sociodemographic and obstetric characteristics of women [36].

Limitations of the study

This study has some important limitations. First, the data were collected only from women who had a vaginal delivery. Therefore, the obtained results cannot be generalized to all women in the postpartum period. Although a retrospective approach is appropriate for this study, a longitudinal format may be adopted for future studies. Nevertheless, this study provides solid evidence for the determinants of physical abuse, non-consented care and non-confidential care, which are the components of obstetric violence in Turkey.

Conclusion and recommendations

According to the result of the study obtained, it was determined that women were subjected to obstetric violence due to continuous NST application, oral intake restriction, frequent vaginal examination, not being given freedom to take the desired position during delivery, not being informed about the interventions performed, and not being allowed to have a companion during delivery. Moreover, the women in the study indicated that their privacy was regarded.

These results show that some practices should be changed in order to prevent obstetric violence and provide improvements in this field. Accordingly, it is recommended that expectant mothers should be fully and accurately informed about the interventions in delivery before the procedure, should be allowed to have a companion with them and should be allowed to take the position they want, and that in-service trainings on not performing interventions unless necessary should planned and the necessary policies should be established. Furthermore, midwives are recommended to adopt the principles of respectful maternal care during delivery.

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Health related quality of life in patients with primary biliary cholangitis

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Abstract

Aim: To assess the health related quality of life (HRQOL) in patients diagnosed with primary biliary cholangitis (PBC).

Material and methods: A single-centered, prospective, cross-sectional study was conducted among patients diagnosed with primary biliary cholangitis in the Gastroenterology out-patient clinic at Gazi University Hospital, Ankara. Data was collected using a sociodemographic information form, hospital medical database and a PBC-40 questionnaire. Statistical comparison analysis was performed using Chi-square test for categorical variables and Mann-Whitney U test for continuous variables. P values less than 0.05 were considered significant.

Results: A total of 37 PBC patients were included in the study. The mean age of the participants was 54.2±8.6. When evaluating the PBC-40 questionnaire scores from each domain in terms of severity, we found that majority of patients in itch %40.4 (n=19) and social %42,6 (n=20) domains had mild severity, as for fatigue %42.6 (n=20), cognitive %36 (n=17), emotional %40.4 (n=19) and other symptoms %44.7 ((n=21) domains had moderate severity. A statistically significant difference was found between AMA positive and AMA negative patient groups in the itch domain (p=0.007).

Discussion: With this study on a Turkish based population using the PBK-40 questionnaire we were able to demonstrate that patients with PBC had a significantly impaired HRQOL and fatigue was the most seen symptom.

Key words: primary biliary cholangitis, health related quality of life, PBC-40

Introduction

Primary biliary cholangitis (PBC) is an autoimmune biliary liver disease, it predominantly affects middle-aged women and can progress to cirrhosis [1]. Most patients with PBC suffer from a variety of symptoms, including fatigue, pruritus, jaundice, sleep disturbances, cognitive dysfunction, mood disorders and depression, that can significantly impair their health-related quality of life (HRQOL) [2].

Fatigue has been shown to be the most important symptom affecting the daily activities and lives of individuals at all stages of PBC disease [3]. For this reason, research was needed to evaluate how much the disease affects the quality of life and valid scales specific to this disease were developed. PBC-40, one of which is a health-related quality of life score specific to patients with PBC. PBC-40 was developed with a focus on the course of the disease, its treatment, and its effects on the physical, emotional and functional state of patients. Studies have shown that PBC-40 is a reliable questionnaire that is useful both in research and in the clinic setting for the evaluation of fatigue, pruritus and other symptoms and indices of emotional, social, and cognitive life [4]. In our study, we aimed to evaluate the HRQOL of the disease by using the PBC-40 questionnaire in PBC patients followed up in our center.

Materials and methods

Our study was a single-centered, cross-sectional study conducted at Gazi University Medical Faculty Hospital, Gastroenterology outpatient clinic, between December 2020 and October 2021.

Forty-five patients diagnosed with PBC disease, who were regularly monitored at the outpatient clinic, were invited to participate in the study. 3 of the patients did not consent to be included in the study. 5 of them were excluded because they had one or more of the exclusion criteria of the study.

Informed consent was obtained from all patients for participation. The study was conducted in accordance

with the ethical standards stated in the Declaration of Helsinki by the World Medical Association. The study protocol was approved by Gazi University Ethics Committee (Decision no. 819) on 07.12.2020.

Inclusion and exclusion criteria for the study

Patients between the ages of 18-75 who were diagnosed with PBC were included in the study. Patients with a diagnosis of PBC who were hospitalized for any reason during the study period, those who declared that they wanted to leave the study, those with a history of liver transplantation due to PBC and those with other etiologies of liver diseases, including autoimmune hepatitis or an overlap syndrome, were excluded from the study. In addition, patients with comorbidities such as: Signs of decompensated cirrhosis, severe painful rheumatoid arthritis, severe pruritic atopic dermatitis, patients with end-stage renal disease requiring dialysis and malignant disease, because they had severe symptoms that may greatly affect HRQOL were also excluded from the study.

Method

Diagnosis of primary biliary cholangitis included two or more of the criteria; Chronic elevation in biliary liver enzymes (ALP and GGT), detectable anti-mitochondrial antibody (AMA) in the serum, and a liver histology compatible with or diagnostic of PBC.

Detailed clinical features, biochemical and imaging findings of the patients were accessed and recorded from the hospital database. These data included the date of diagnosis (in years), liver histological stage at diagnosis if liver biopsy was performed, liver biochemistry, and presence of clinical events (i.e., jaundice, ascites, edema, hepatic encephalopathy, esophageal or gastric varices and hepatocellular carcinoma).

Patients who agreed to participate in the study were asked to fill up the PBC-40 questionnaire adapted into Turkish for the evaluation of symptoms and HRQOL. PBC-40 is a patient-derived, disease specific symptom and HRQOL questionnaire consisting of 6 domains; Other symptoms, pruritus, fatigue, cognitive, social, and emotional [5]. Each domain mentioned contains 7, 3, 11, 6, 10 and 3 items respectively. And since the scores on each item range from 1 to 5 points, the score range in each domain is 7-35, 3-15, 11-55,6-30, 10-50 and 3-15 respectively.

In this study we defined the severity of each area in four categories as follows; “None” if the score is 0, “mild” if the score is between 0 and one-third of the full score, “moderate” for scores between one-third and two-thirds of full score, and “severe” for scores between two-thirds and full score (Table 1).

Table 1 Classification of PBC-40 Field Scores by Severity.

	None	Mild	Moderate	Severe
Other symptoms (7-35)	0	0-11	11-24	24-35
Pruritus (3-15)	0	0-5	5-10	10-15
Fatigue (11-55)	0	0-18	18-36	36-55
Cognition (6-30)	0	0-10	10-20	20-30
Social (10-50)	0	0-16	16-32	32-50
Emotional (3-15)	0	0-5	5-10	10-15

Statistical analysis

All statistical analyzes were performed using SPSS® Statistical version 22 (IBM). Continuous variables are presented as mean (standard deviation) if normally distributed, otherwise as median (interquartile range), categorical variables are presented as numbers and percentages. Chi-square test was used within statistical analysis between categorical variables. The Mann-Whitney U test was used for comparisons between groups for continuous variables. P value less than 0.05 was considered statistically significant.

Results

Clinical and demographic characteristics of the patients

37 patients with PBC were included in the study. 35 (94.6%) of the patients were female and 2 (5.4%) were male. The mean age of the patients was 54 (35-69). The median body mass index (BMI) of the patients was 28 (21.7-39.5) kg/m2. The mean disease duration was 6 years, the shortest disease duration was 1 year, and the longest disease duration was 16 years. Education level, marital status, habits and comorbid diseases are summarized in Table 2.

Table 2 Demographic characteristics of the patients included in the study

Variable	n (%)
Age , Mean ± SD (min–max)	54.24±8.64 (35-69)
Sex	
Female	35 (94.6)
Male	2 (5.4)
BMI, kg/m2	28.09 ±4.58 (21.7-39.5)
Duration of disease (yrs.), mean ±SD (min–max)	5.95±3.50 (1-16)
Education level	
Primary	17 (45.9)
Secondary	15 (40.5)
University	5 (13.5)
Marital status	
Married	30 (81.1)
Single	2 (5.4)
Widow	5 (13.5)
Work status	
House wife	26 (70.3)
Working	11 (29.7)
Smoking habit	
Smoker	11 (29.7)
Never smoked	22 (59.5)
Former smoker	4 (10.8)
Presence of other autoimmune disease	
Present	17 (45.9)
Absent	19(51.7)

Evaluation of biochemical parameters

In evaluating of biochemical parameters, mean values of AST, ALT, total protein, albumin, total bilirubin, international correction ratio (INR), creatinine, total IgG, erythrocyte sedimentation rate (ESR) values were within the normal limits. The mean value of ALP was 145.05±92.30 U/L and was above the normal limits. The summary of evaluation of the biochemical parameters of the patients is shown in Table 3.

When categorizing patients in terms of autoantibody positivity, 32 patients (86.5%) were found to be AMA positive, 6 patients (16.20%) anti-sp100 positive, 6 patients (16.20%) anti-gp210 positive and 19 patients (51.4%) antinuclear

antibody (ANA) positive. Liver biopsy findings of 20 patients were compatible with PBC. Three of the patients (8.1%) had compensated cirrhosis. The clinical and autoimmune markers of the patients are summarized in Table 4.

Table 3 Evaluation of biochemical variables in the study group

Variable	Mean ±SD(min-max)
ALP	145.05±92.30 (63-555)
GGT	59.03±49.95 (16-226)
AST	32.54±27.98 (15-174)
ALT	27.00±18.26 (8-92)
Total bilirubin	0.66±0.25 (0.27-1.55)
Total protein	7.53±0.48 (6.7-8.5)
Albumin	4.21±0.31 (3.5-4.8)
Creatinine	0.67±0.16 (0.33-1.05)
INR	0.97±0.10 (0.61-1.20)
ESH	31.11±14.57 (10-79)
Total Ig G	1400.59±236.50 (962-1900)

Table 4 Evaluation of clinical and autoimmune markers of patients

Variable	n(%)
AMA positive	32 (86.5)
Anti sp100 positive	6 (16.20)
Anti gp210 positive	6 (16.20)
ANA positive	19 (51.4)
Compensated cirrhosis	3 (8.1)
Liver biopsy compatible	20 (54.1)
Liver size	
Normal	31 (83.8)
>16cm	6 (16.2)

Evaluation of the patients' performance from the PBC-40 Questionnaire.

The highest and lowest mean field scores were observed in fatigue (24.35±9.47) and itching (3.93±2.80) domains, respectively. Score averages of the 6 domains of the PBC-40 are summarized in Table 5. When evaluating the PBC-40 questionnaire scores from each domain in terms of severity, we found that majority of patients in itch %40.4 (n=19) and social %42,6 (n=20) domains had mild severity, as for fatigue %42.6 (n=20), cognitive %36 (n=17), emotional %40.4 (n=19) and other symptoms %44.7 ((n=21) domains had moderate severity. Classification of the domains of PBC-40 questionnaire in terms of severity is summarized in Table 6.

Table 5 Evaluation of the PBC-40 questionnaire in the study group

Variable	mean SD (min-max)
Itching	3.93±2.80 (0-11)
Fatigue	24.35±9.47 (7-44)
Cognitive	13.59±6.31 (6-27)
Emotional	8.22±3.44 (3-15)
Social	16.86±5.85 (9-37)
Other symptom	13.24±4.60 (6-25)

Table 6 Classification of PBC-40 questionnaire domains according to severity.

Variable	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Itch	6 (12.8)	19 (40.4)	10 (21.3)	2 (4.3)
Fatigue	0 (0)	12 (25.5)	20 (42.6)	5 (10.6)
Cognitive	0 (0)	13 (27.7)	17 (36.2)	7 (14.9)
Social	0 (0)	20 (42.6)	16 (34)	1 (2.1)
Emotional	0 (0)	6 (12.8)	19 (40.4)	12 (25.5)
Other symptoms	0 (0)	15 (31.9)	21 (44.7)	1 (2.1)

Analyzing of the domains of the PBC-40 questionnaire according to the presence of antibodies is summarized in Table 7. No statistically significant difference was found between the anti gp-210 positive and negative groups among domains of the PBC-40 questionnaire (p>0.05).

When comparing between AMA positive and AMA negative groups, a statistically significant high value in itching was found in the AMA positive group (p=0.007). However, in other PBC-40 domains a statistically significant difference was not found among AMA negative and positive groups.

Table 7 Comparison of PBC-40 scale parameters according to the presence of autoimmune antibodies

	Anti gp210 +	**Anti gp210 -**	**P**	**AMA -**	**AMA +**	**P**
Itch	5 (0-11)	3.5 (0-11)	0.809	5 (3-11)	3 (0-11)	0.007
Fatigue	26 (11-43)	16.5 (6-26)	0.785	27 (7-44)	25.5 (7-36)	0.508
Cognitive	16 (6-27)	16.5 (6-26)	0.845	18 (6-27)	10.5 (6-24)	0.019
Social	15 (11-37)	19 (9-24)	0.815	14 (11-37)	15.5 (9-30)	0.679
Emotional	9 (3-15)	7 (3-15)	0.410	8 (5-15)	8 (3-15)	0.803
Other symptoms	12 (9-22)	10 (10-20)	0.969	12 (9-22)	11,5 (6-20)	0.360

Mann-Whitney U test was used, p value <0.05 was statistically significant, AMA; anti-mitochondrial antibody.

Correlation analysis evaluating the relationship between itching and biochemical parameters is summarized in Table 8. According to the evaluation, no statistically significant correlation was found between itching and any of the biochemical parameters (p>0.05).

Table 8 Evaluation of the relationship between itching and biochemical parameters

Variable	r	p
Itch		
ALP		
0.084		
0.620		
GGT	-0.060	0.806
AST	-0.042	0.806
ALT	-0.122	0.471
Total bilirubin	-0.136	0.423
Albumin	-0.239	0.155
Creatinine	-0.295	0.076
INR	0.063	0.713
ESR	-0.017	0.922
Total Ig G	0.075	0.658

Spearman correlation was used, p value <0.05 was statistically significant, ALP; alkaline phosphatase, GGT: gamma-glutamyl transferase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, INR: international normalized ratio ESR: erythrocyte sedimentation rate.

Discussion

PBC is a chronic autoimmune liver disease characterized by progressive inflammation and eventual destruction of the small intrahepatic bile ducts. Symptoms such as itching, cognitive impairment and fatigue negatively affect the quality of life in PBC patients. HRQOL in these patients can be assessed using questionnaires, which may or may not be specific to the disease. One of these questionnaires is PBC-40. PBC-40 questionnaire was developed focusing on the course of the disease, its treatment and the physical, emotional and functional status of the patients.

Studies have shown that evaluation of fatigue, itching and other symptoms, as well as emotional, social and cognitive vitality indices by the PBC-40 questionnaire to be useful and reliable both in research and clinical practice [5]. In this study, using the PBC- 40 questionnaire we evaluated the relation between the patients' quality of life and clinical findings, laboratory values, and demographic characteristics. According to our literature review, we did not come across a study evaluating HRQOL in PBC patients from Turkey.

PBC is known to be predominant in women. In our study, 95% of the patients were women. In an epidemiological study, the mean age of patients diagnosed with PBC was 51 years. As for our study, the mean age was found to be 54 years. Our findings, showed almost similar features with previous studies on PBC in terms of both gender and age [6].

Autoimmune injury is inherent in PBC. In addition, PBC may be associated with other autoimmune diseases. In our study, we found that approximately 46% of the patients had an autoimmune disease accompanying PBC. According to the literature, the distribution of autoimmune disease accompanying PBC is variable, although seen frequently, it was similar to the findings we found in our study [7,8].

ALP elevation is typical in PBC. In our study, the mean ALP was found to be 145.05 U/L and it was above the normal limits. Fatigue has been shown to be an important cause in the deterioration of quality of life in PBC patients [4]. Fatigue; Among the symptoms, as shown in other studies also, in our study it had the highest impact on HRQOL [9].

Itching, while an important symptom that affects the quality of life of PBC patients, has a less frequent effect in this study. This is more likely considered to be because of the availability and effectiveness of treatments for itching rather than the weakness of the PBC-40 questionnaire [5]. We also think that itching was less common in the patients included in our study due to the exclusion of decompensated cirrhotic patients and most of the patients were under regular treatment with ursodeoxycholic acid therapy. In this study, we performed a correlation analysis between the itching and biochemical values. However, we did not find any statistically significant correlation. In one study, a positive correlation was found between the emotional domain of PBC-40 with ALP and GGT levels [9]. In another study, itching was shown to be more common in cirrhotic patients than in non-cirrhotic patient [10].

A study found that anti-gp210 seropositivity was associated with worse itching, cognitive, social and emotional state. In the same study, no difference was found between AMA positive and negative patients among the domains of PBC-40 [10]. In our study, anti-gp210 positivity was not associated with any statistically significant difference among all domains of PBC-40. Also of note is we found that, between AMA positive and negative groups, a statistically significant higher incidence of itching in the AMA positive group.

We found a significant symptom burden and HRQOL disorder associated with PBC disease. In terms of severity, from all domains of the PBC-40 questionnaire, the least (21.3%) in itching and the most in other symptoms domain (44.7%), we found that they were moderately affected. Accordingly, we can say that half or at least a quarter of the patients lived with a significant burden of the disease in their daily life regardless of its severity.

Limitations

In the beginning of the study, we had planned to include 50 participants to the study but due to the ongoing COVID-19 pandemic the targeted number could not be reached. The limitations of our study were the few number of participants and the study being a single-centered study.

Conclusion

According to the World Health Organization, health is defined as, not only as the absence of infirmity or sickness but a state of complete physical, mental and social well-being. And if any of these is broken, the person cannot be considered healthy. Therefore, further research, specific to each community, is needed to develop modalities that will increase the quality of life in patients with PBC and minimize the negative effects of the disease.

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Structural and functional characteristics of the heart before and after CRT in patients with heart failure

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Abstract

Abstract: The aim of the study was to evaluate the clinical and hemodynamic effects of resynchronization therapy in patients with congestive heart failure.

Material and methods: Seventy-six consecutive patients underwent echocardiography, NYHA classification, 6-minute walk test and clinical assessment scale modified by Mareev, before and after cardiac resynchronization therapy. All had complete left bundle branch block, with a QRS complex duration ≥130 ms. and left ventricular ejection fraction ≤35%. Also, all patients had received optimal medical therapy for at least 3 months before inclusion to the study.

Results: We observed significant increase in left ventricular ejection fraction (35.4±3.7%, p<0.001, compared with baseline) and decrease in end-systolic volume of the left ventricle (20.2±3.0 %, p<0.001 compared with baseline). Improvement in functional class of congestive heart failure by NYHA classification by >1 was observed in 68.4% of individuals, in 26.3% of participants demonstrated no change and 5.3% of patients had worsening of CHF symptoms.

Conclusion: The response of patients with congestive heart failure to cardiac resynchronization therapy is heterogeneous. The relationship between left ventricular reverse remodeling and the functional class of the congestive heart failure was not significant.

Key words: congestive heart failure, cardiac resynchronizing therapy, optimal drug therapy

Introduction

Many different cardiovascular diseases (CVD) results in development of congestive heart failure (CHF). Despite the improvement in care, CHF remains to be a medical issue with high socio-economic burden [1-3]. Electrical disturbances, such as atrioventricular (AV) and intraventricular blocks present in most of the patients with CHF. AV conduction abnormalities lead to uncoordinated atrial and ventricular contractions, and an intraventricular contraction delay leads to uncoordinated contractions of the ventricles (ventricular dyssynchrony). Wide QRS (>120 ms) is associated with more severe CHF and is a predictor of increased overall risk of death and risk of sudden cardiac death.

Cardiac resynchronization therapy (CRT) has been used since the late 1990s to eliminate the dyssynchrony of cardiac contractions [4–7]. The number of people on CRT is growing all over the world, as well as in our country. However, there are not enough reports on the long-term clinical and hemodynamic effects of CRT, reflecting our own experience of regular follow-up of patients after the intervention.

Here we aim to evaluate the clinical and hemodynamic effects of resynchronization therapy in patients with congestive heart failure.

Material and methods

The single-center prospective observational study of consecutive unmatched patients undergoing CRT for HF between October 2019 and November 2021 evaluating clinical parameters before and after CRT. National Institute of Clinical Excellence (NICE)

criteria [8] were used to enroll patients to the study. Exclusion criteria were a recent acute coronary syndrome or acute HF decompensation (<6 weeks), end-stage renal disease (on renal replacement therapy), significant cognitive impairment or terminal illness (expected survival <1 year). Postimplantation exclusions were applied in case of procedure failure or complications resulting in unsuccessful CRT pacing (eg, lead displacement/phrenic nerve pacing). Each participant underwent a preimplantation visit and follow-up at 6 months postimplant. Participants had NewYork Heart Association (NYHA) class assessment, 6 min walk test (6MWT), the clinical assessment scale modified by Mareev [9], transthoracic echocardiography and resting 12-lead electrocardiography (ECG) at all attendances. At the time of enrollment each participant were receiving optimal medicine therapy (OMT) which includes angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor antagonists (ARA), mineralocorticoid receptor antagonists, β – blockers, antiaggregant, anticoagulants and statins for at least three months. The study protocol was approved by Institutional Research Ethic committee. All participants provided written informed consent.

Clinical assessment scale modified by Mareev

For a comprehensive analysis of the functional state of the patient and their response the clinical assessment scale (CAS) modified by Mareev V.Yu. were used [9]. This scale includes patient complaints (shortness of breath, weight changes, feeling of heart rhythm disturbances), objective data (orthopnea, cervical venous overload signs, fine crackles in the lower lobes of the lungs, gallop rhythm, liver span, edema of lower extremities), systolic and diastolic blood pressure. Summary of points corresponds to functional classes (FC): 0 points - no signs of CHF, I FC - ≤3 points, II FC - from 4 to 6 points, III FC - from 7 to 9, IV FC - ≥9 points.

Transthoracic echocardiography

All underwent transthoracic echocardiography (Vivid 7, GE Healthcare, Horten, Norway) for LV volumetric assessment performed on the same machine by the same operator for each study visit. LV ejection fraction was estimated using the biplane modified Simpson's method [10].

Statistical analysis

Basic descriptive statistics for all participants (means, standard deviations) were conducted. Continuous variables were presented using means and for categorical variables were presented using percentages. Student's t-test was used to compare continuous independent variables.

Results

Baseline characteristics

Baseline characteristics are shown in the Table 1. A total of 76 patients were enrolled to the study. 40 of them were male and 36 female. The average age at the time of enrollment was 61.1±1.2. Two thirds of patients had acute myocardial infarction and 37 patients had coronary artery disease (CAD) + arterial hypertension. Based on NYHA class assessment 15 patients had class II, 43 – class III and 18 patients had class IV. The average time of 6MWT was 238.22±11.1 minutes, and average CAS score was 9.0±0.43 points. Average QRS duration was 156.8±2.56 ms.

Table 1 Baseline characteristics

Demographics		
	Age (years, mean ±SD)	61.1 ± 10.2
	Male (n, %)	40 (53%)
Etiology (n, %)		
	Ischemic + hypertension	40 (53%)
	Hypertension	23 (30 %)
	Dilatational cardiomyopathy	13 (17%)
NYHA (n, %)		
	II	15 (19.7%)
	III	43 (56.6%)
	IV	18 (23.7%)
6MWT (M, mean ±SD)		238.22 ± 11,1
CAS score (points, mean ±SD)		9,0 ± 0,43
ECG		
	QRS duration (ms, mean ±SD)	156,8 ± 2,56 ms.
	LBBB (n, %)	76 (100%)

Table 2 Structural and functional parameters of the heart before and 6 months after CRT

Echo-parameters	Baseline	6 months after CRT	p
Left atrium, (cm, mean ±SD)	4.4 ± 0.08	4.2 ± 0.07	<0.001
LVEDD (cm, mean ±SD)	7.1 ± 0.1	6.6 ± 0.1	< 0.001
LVESD (cm, mean ±SD)	6.0 ± 0.1	5.4± 0.1	< 0.001
LVEDV (mm, mean ±SD)	262.3 ± 10.47	230.5 ± 9.76	< 0.001
LVEDVI (ml/m2, mean ±SD)	136.3 ± 5.28	119.8 ± 4.87	< 0.001
LVESV (mm, mean ±SD)	186.7 ± 8.59	144.8 ± 7.89	< 0.001
LVESVI (ml/m2, mean ±SD)	97.2 ± 4.48	75.3 ± 4.02	< 0.001
SV (mm, mean ±SD)	77.2 ± 2.35	84.8 ± 3.04	< 0.01
SVI (ml/m2, mean ±SD)	40.0 ± 1.2	44.1 ± 1.49	< 0.01
LVEF (%, mean ±SD)	27.7 ± 0.72	36.4 ± 0.91	< 0.001
ePASP (mm Hg, mean ±SD)	50.7 ± 1.8	45.4 ± 1.44	< 0.01
Mitral regurgitation (level, mean ±SD)	2.4 ± 0.07	1.9 ± 0.07	< 0.001
Tricuspid regurgitation (level, mean ±SD)	1.7 ± 0.07	1.7± 0.07	>0.01

Effects of CRT on cardiac function

Structural and functional parameters of the heart before and 6 mo. after CRT are shown in the Table 2. It is shown that the most significant changes were in LV ejection fraction (EF) (increase on average by 35.4±3.7% compared with the baseline, p<0.001) and LV end systolic volume (ESV) (decrease by 20.2±3.0% vs baseline, p<0.001).

ECG assessment

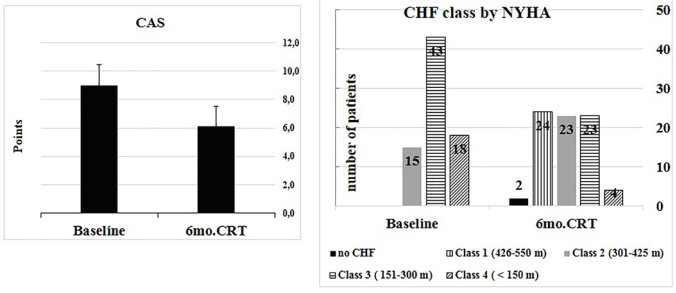
On ECG assessment, the duration of the QRS complex shortened from 156.8±2.56 ms to 128.5±2.79 ms (p<0.001), i.e. there was a significant decrease in the width of the ventricular ECG complex. Overall improvement of all indicators of the structural and functional state of the heart was more pronounced in individuals with an initially wider ventricular complex (≥150 ms) than in the group with a complex width of less than 150 ms, however, the difference was statistically insignificant.

In our study, 51 (67.1%) of 76 patients had an increase in LV EF by ≥15%, 18 (23.7%) - less than 15%, the remaining 7 (9.2%) - a decrease in this score compared to baseline. LV end-systolic volume decreased by ≥ 15% and < 15% in 40 (52.6%) and 24 (31.6%) patients, respectively, and 12 (15.8%) patients experienced an increase in ESV.

Clinical assessment

According to CAS, the average points decreased from 9.0±0.43 to 6.1±0.37 points (p<0.001) 6 months after CRT implantation. The 6-minute walk test showed that the average distance increased from 238.2±11.13 meters to 363.6±14.81 meters, i.e. by 73.44±11.56% compared with the baseline (p<0.001). It should be noted that 46 (60.52%) out of 76 subjects showed an increase in the distance by ≥25% compared with the baseline.

Figure 1 - Clinical assessment of patients before and after CRT implantation



At the follow-up clinical symptoms corresponding to NYHA class I were in 24 patients, class II - in 23, and class III - in 23, and class IV were in only 4 patients. Two patients walked more than 551 m (600 and 563), i.e. they did not have signs of heart failure according to the test criteria (Figure 1). Analysis of individual data showed that a positive response (decrease in CHF class according to NYHA ≥ 1) was observed in 52 (68.4%) of 76 individuals; 20 (26.3%) patients showed no changes in the class, and 4 (5.3%) patients had deterioration (an increase by one class of NYHA). In the group of individuals with an increase in LV EF ≥ 15%, the changes in CHF class was as follows: decrease - in 35 (68.6%), unchanged - in 15 (29.4%), increase - in 1 (2%) of 51 patients, among those with an increase in LVEF < 15% - in 13 (72.2%), 3 (16.7%) and 2 (11.1%) of 18 subjects, respectively; even among 7 individuals with a decrease in LV EF compared with the baseline, exercise tolerance was different: 4 people had a decrease (improvement) in CHF class by ≥1, 1 had an increase (deterioration) and 2 remained unchanged.

There was direct correlation between the distance in 6MWT and LVEF (r=0.338, p=0.003) and a negative correlation between the ESV and the distance in 6MWT (r=- 0.244, p=0.03).

Discussion

Based on our results, there are no uniform direction of changes in hemodynamics and the clinical condition of patients at the baseline and after CRT. There is no strict relationship between gross reverse remodeling of the left ventricle and the changes of CHF class, which is consistent with a number of previously reported studies [11, 12]. The direct correlation between the distance in 6MWT and LVEF and negative correlation between the ESV and the distance in 6MWT confirm that the responses of patients with CHF to resynchronization therapy are heterogeneous. Therefore, in our work, we avoided the concepts of "responders, non-responders, super-responders", given the relatively small number of patients and the observation period. In most cases we observed that OMT and CRT improved clinical condition of patients (68.54%), their tolerance to physical stress increased and reverse heart remodeling were observed. Especially, the LVEF (an increase by an average of 35.4±3.7 %, p<0.001) 54%) and ESV of the left ventricle (decrease by 20.2±3.0%, p<0.001) changed to the greatest extent. If patient has no changes or increase (worsening) in CHF class and insufficient reverse heart remodeling after CRT, this patient generally considered to be a "non-responder" [13-16]. Different studies consider the heterogeneity of patients by cause of CHF, the presence of myocardial scar, suboptimal (not-optimal) position of the ventricular electrode and low degree of biventricular stimulation as a reason behind the poor response to CRT. There is also no unanimity in the timing of assessment of the response to CRT, although in most published studies, 6 or 12 months were chosen as an intermediate period for determining the reliability of CRT [17-22]. The results of our study show that even with a slight LVEF or a decrease in ESV (<15% compared with baseline), the clinical condition of most patients improves, therefore, in our opinion, they should not be classified as "non-responders". Even if CHF class remains unchanged and left ventricular remodeling is not worsening, then, in our opinion, this should be considered as acceptable result and we should continue our follow-up with precise control of pharmacotherapy and echocardiogram parameters.

The ambiguity of the literature data when choosing the timing of assessment the response to CRT and insufficient positive changes of the structural and functional parameters of the heart are indicating the need for a better approach to the selection of patients and the need to establish an uniform criteria and optimal timing for determination the effectiveness of resynchronization therapy. To achieve good results, it is important to achieve a high percentage of biventricular stimulation and an optimal position of the electrode in the non-scared region of the myocardium.

Thus, the results of the study confirmed the clinical efficacy and positive changes in the parameters of the structural and functional state of the heart compared to the baseline six-month after the resynchronization therapy in patients with severe heart failure. To verify the results of resynchronization therapy, it is necessary to carefully select patients, monitor their device programming parameters, and search for new approaches to pharmacotherapy.

Conclusions

1. CRT implantation along with optimal medication therapy in patients with severe CHF (LVEF ≤ 35%) with sinus rhythm and LBBB resulted in improvement of structural and functional parameters of the heart and clinical symptoms. Especially, the LVEF (an increase by an average of 35.4±3.7 %, p<0.001) 54%) and ESV of the left ventricle (decrease by 20.2±3.0%, p<0.001) changed to the greatest extent. The decrease in CHF class by more than 1 was observed in 68.6% of patients, 26.3% of patients had no change in CHF class and 5.3% patients had worsening or increase in CHF class by 1.

2. The response of the patients to the CRT implantation was not uniform. There was no relationship between reverse remodeling of the left ventricle and CHF class changes. There was direct correlation between the distance in 6MWT and LVEF (r=0.338, p=0.003) and a negative correlation between the ESV and the distance in 6MWT (r= - 0.244, p=0.03).

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The relationship between myocardial perfusion scanning results, C-reactive protein to albumin ratio, systemic inflammatory response index and coronary angiographic findings

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Abstract

Aim: We aimed to investigate whether C-reactive protein to albumin ratio (CAR) and systemic inflammatory response index (SIRI) have an additional value in interpretation of myocardial perfusion scanning (MPS) results.

Background: MPS have high sensitivity but relatively low specificity in diagnosis of coronary artery disease (CAD).

Material and methods: 449 patients who had MPS before coronary angiography were included. Patients with and without CAD constituted study (n=227) and control (n=222) groups, respectively.

Results: Sensitivity and specificity of MPS in detecting CAD were found to be as 97.8% and 62.2%, respectively. CAR value of 1.22 and SIRI value of 1.45 predicted CAD with a sensitivity of 61.2% and 59% and specificity of 77% and 80.2%, respectively. Only 10.4 % of the CAD negative patients had positive MPS and positive CAR values, whereas 0.9% of the CAD positive patients had negative MPS and negative CAR values. 27.5% of CAD negative patients had positive MPS and negative CAR values. Likewise, having a negative MPS with negative SIRI value identified 50% of the patients who had normal coronary arteries. Positive MPS with positive SIRI value correctly identified 58.1% of patients who had CAD.

Conclusion: evaluation of CAR and SIRI might be beneficial in interpretation of MPS.

Key words: Inflammation, biomarkers, coronary artery disease, myocardial perfusion scanning.

Introduction

Coronary artery disease (CAD) has been remained as the principal cause of death worldwide [1]. Early diagnosis and treatment of CAD is utmost importance in reducing the CAD related morbidity and mortality. Various noninvasive modalities have improved our ability to diagnose CAD; these modalities include echocardiography, exercise stress testing, single-photon emission computed tomography (SPECT) myocardial perfusion scan (MPS), coronary CT angiography and cardiac MR imaging.

The principle of MPS is based on distribution of radionuclides which are taken by myocardial cells in proportion to blood flow [2]. Ischemic areas are represented by reduced tracer uptake. Patients with baseline electrocardiographic abnormalities, decreased ability to perform physical exercise and who have intermediate pretest likelihood of CAD are the best candidates for this modality. It has a prognostic value and could also be used in risk stratification of patients, selection for revascularization and CAD management. Coronary artery stenoses of more than 50% are reliably detected by MPS. Studies investigating the sensitivity and specificity of MPS have yielded mixed results with reliable information [3]. Inflammation is complicit in all phases of atherosclerotic CAD development. Inflammation

accelerates atherosclerosis by means of plaque destabilization, endothelial dysfunction and increasing arterial stiffness [4]. Diagnostic and prognostic value of inflammatory markers in CAD has been outlined in sizeable number of studies and they are attractive candidates for cardiovascular risk stratification [5]. The ability of biomarkers to reveal information about CAD risk has indicated their potential use in clinical practice.

C-reactive protein to albumin ratio (CAR) and systemic inflammatory response index (SIRI) are two easily obtainable inflammatory biomarkers that have been shown to have an association with CAD severity, adverse cardiovascular outcomes and mortality [6, 7]. Since inflammatory biomarkers could provide information about cardiovascular status of human body, in the present study we aimed to investigate whether these biomarkers) had an additional value in the interpretation of MPS results.

Material and methods

Biochemical findings and coronary angiographic recordings of the subjects who underwent angiography between November 2016 and June 2020 were retrospectively reviewed. Subjects who had MPS evaluation before coronary angiographic examination were considered appropriate for the study. Patients with acute coronary syndrome, previous percutaneous coronary intervention, coronary artery bypass graft surgery, acute infection, systemic inflammatory or rheumatological diseases, hematological diseases, malignancy, hepatic and/or renal dysfunction, thyroid abnormalities and who had missing data were excluded. A total of 3554 coronary angiography recordings were screened, 449 patients who had MPS result were included in the study. Of these patients 306 patients had abnormal MPS result, whereas 143 patients had normal MPS result. Patients who had normal MPS result were undergone coronary angiographic imaging because of clinical suspicion CAD.

Twenty four hours before MPS imaging all the medications which influence heart rate and myocardial oxygen consumption were stopped. Exercise treadmill stress test was performed for patients who could exercise. Bruce protocol was used for exercise testing (Schiller CS-200, Switzerland). Blood pressure of the patients was taken in every stage and recovery period. Exercise testing was stopped if the patient developed chest pain, dyspnea, ischemic ECG changes, hypo/hypertensive response or 85% of the maximum predicted heart rate was achieved. Maximal predicted heart rate was calculated using the formula "220-age". When the patients' heart rate reached maximal predicted heart rate, technetium 99-m methoxy-isobutylisonitrile (Tc-99m MIBI) was injected to the patients. For the patients who could not exercise, a standard dose of dipyridamole (0.142 mg/kg/min) or adenosine (0.28 mg/min) was infused over a period of 4 minutes. ECG recordings of the patients were taken before and every minute of dipyridamole infusion. Tc-99m MIBI was given to the patients three minutes after the end of the infusion. Stress/rest imaging protocols were undertaken in two days. Both rest and stress images were carried out 1 hour after dipyridamole infusion with a dose of 296 MBq and 814 MBq, respectively. All of the images were taken by DDD-CorCam SPECT system (Denmark). Interpretation of the images was based on 17-myocardial segment model [8]. Images were classified as normal or ischemic.

After an overnight fast, blood samples were collected from antecubital fossa using venipuncture method. Biochemical parameters including creatinine, fasting glucose, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), C-reactive protein (CRP), albumin, complete blood count were assessed by using Beckman Coulter LH 780 (Mervue, Galway, Ireland). Diabetes mellitus was described as fasting glucose ≥126 mg/dl or taking antidiabetic medication. Hypertension was diagnosed when patient's systolic and/or diastolic blood pressures were greater than 140 and 90 mmHg, respectively or use of antihypertensives. Hyperlipidemia was described as TC ≥200 mg/dl or taking anti-lipidemic medication. CAR, monocyte to lymphocyte ratio (MLR), systemic inflammatory index (SII) and SIRI were calculated. SII was calculated by multiplying platelet and neutrophil counts and dividing the result into lymphocyte count. SIRI was calculated by multiplying neutrophil and monocyte counts and dividing the result into lymphocyte count.

Coronary angiographic examinations of the patients were done by use of Siemens Axiom Artis Zee Cath Lab (Munich Germany) system. Right common femoral arterial access was preferred and 6F catheter was inserted into arterial system with Judkins technique. Multiplane images of each coronary artery were taken. SYNTAX score, an algorithm which is based on the measurement of anatomical variables including number of lesions, lesion location, presence of bifurcation and/or trifurcation lesions, ostial stenosis, tortuosity, lesion length more than 20 mm, calcification, thrombus, small vessel or diffuse disease, was calculated for each patient [9]. Patients who had SYNTAX score equal to zero and greater than zero were classified as control group and study group, respectively.

Statistical analysis

Normality of the patients' data was assessed by Kolmogorow-Smirnow test. According to the result of normality test, data was expressed as mean±SD or median (minimum-maximum). For the comparison of patients who had CAD and normal coronary arteries, student-t test or Mann-Whitney U test was conducted. Chi-square test was used for comparison of categorical variables. Sensitivity and specificity of MPS imaging and biochemical variables in detecting CAD were assessed by Chi-square test. In order to found out the cut-off values of biochemical variables for the presence of CAD, ROC curve analysis was conducted. Univariate logistic regression analysis was used to evaluate the independent predictors of CAD.

Results

A total of 449 subjects were included in the study. Of these patients 222 had normal coronary arteries or noncritical CAD and 227 had critical coronary artery disease. The median age of the study and control groups were 65 (31-75) years and 64 (31-62) years, respectively. Number of females, patients with hypertension, diabetes mellitus, hyperlipidemia, angiotensin converting enzyme inhibitor/angiotensin receptor blocker use, B-blocker use, statin use, acetylsalicylic acid use were significantly higher in study group than that of control group. Creatinine, CRP concentration levels, neutrophil count, monocyte count, SII, SIRI, CAR and MLR were found to be significantly higher, whereas HDL-C and albumin levels were significantly lower in the study group compared to control group. We did not find any other differences between two groups with respect to other clinical or biochemical parameters. Table 1 shows the comparison of clinical and biochemical parameters between two groups.

In the present study, sensitivity and specificity of MPS imaging in detecting CAD were found to be as 97.8% and 62.2%, respectively. According to ROC curve analysis, CAR value of

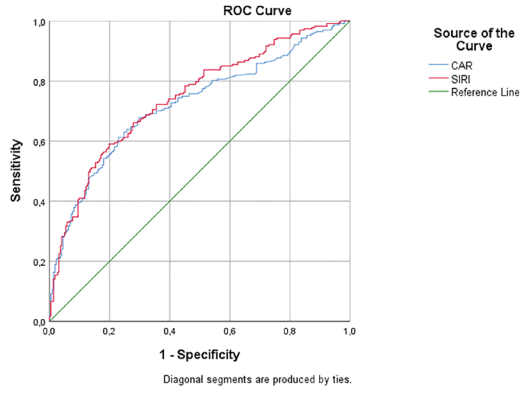
Table 1 Clinical and biochemical parameters of two groups

	Control group (n=222)	Study group (n=227)	p
Age (years)	64 (31-62)	65 (31-75)	0.058
Gender (n, %)			0.001
Female	104 (46.8)	141 (62.1)	
Male	118(53.2)	86 (37.9)	
DM, n (%)	81 (43.8)	104 (56.2)	0.042
Hypertension, n (%)	132 (41.6)	185 (58.4)	<0.001
Hyperlipidemia, n (%)	84 (33.9)	164 (66.1)	<0.001
ACEI/ARB use, n (%)	114 (40.7)	166 (73.1)	<0.001
B-blocker use, n (%)	102 (37.2)	172 (62.8)	<0.001
Ca-channel blocker use, n (%)	71 (43.8)	91 (56.2)	0.074
Diuretic use, n (%)	75 (43.6)	97 (56.4)	0.051
Statin use, n (%)	79 (34.2)	152 (65.8)	<0.001
OAC, n (%)	19 (47.5)	21 (52.5)	0.797
Anti-platelet use, n (%)	19 (13.2)	125 (86.9)	<0.001
Nitrate use, n (%)	6 (14.3)	36 (85.7)	<0.001
ASA use, (n, %)	110 (37.4)	184 (62.69	<0.001
TG (mg/dL)	124 (3.9-708)	131 (24-587)	0.264
Hgb (g/dL)	13.3 (8.5-16.7)	13.1 (8.8-17.7)	0.757
Neutrophil (103/µL)	4.20±1.21	5.15±1.42	<0.001
Platelet (×109 /l)	230 (2.9-663)	239(50-483)	0.247
Lymphocyte (103/µL)	2.1 (0.53-4.30)	2.13 (0.51-4.39)	0.879
Monocyte (103/µL)	0.55 (0.23-1.08)	0.70 (0.31-1.40)	<0.001
CRP (mg/l)	0.31 (0.05-1.83)	0.55 (0.05-2.1)	<0.001
Albumin (g/dL)	4.2 (3.2-46)	4.0 (2.89-5.30)	<0.001
CAR	0.74 (0.04-4.84)	1.44 (0.13-6.12)	<0.001
SII	430.41 (2.83-2722.07)	563.09 (70.25-2504.66)	<0.001
SIRI	1.04 (0.007-6.87)	1.69 (0.43-8.45)	<0.001
RDW (%)	13.6 (11.6-43.6)	13.6 (11.9-19.9)	0.920
PDW (%)	12.1 (8.6-25.4)	12.15 (8.8-21.5)	0.256
MPV (fL)	10.4 (8.4-14.4)	10.4 (8.7-13.2)	0.957
Plt (×109 /l)	0.24 (0.11-0.70)	0.25(0.06-0.48)	0.229
MLR	0.26 (0.12-1.00)	0.31 (1.22-1.47)	<0.001
PLR	108.27 (0.77-396.22)	113.30 (31.64-313.63)	0.358

ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, ASA: Acetylsalicylic acid, CRP: C-reactive protein, CAR: CRP to albumin ratio, DM: Diabetes mellitus Hgb: Hemoglobin, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, MLR: Monocyte to Lymphocyte ratio, MPV: Mean platelet volume, TG: Triglyceride, SII: Systemic immune inflammatory index, SIRI: Systemic inflammation response index, RDW: Red cell distribution width, PDW: Platelet distribution width, Pct: Plateletcrit, PLR: Platelet to Lymphocyte ratio, OAC: Oral anticoagulant.

1.22 predicted CAD with a sensitivity and specificity of 61.2% and 77%, respectively; SII value of 423.78 predicted CAD with a sensitivity and specificity of 50.9 % and 49%, respectively; SIRI value of 1.45 predicted CAD with a sensitivity and specificity of 59 % and 80.2%, respectively; and MLR value of 0.24 predicted CAD with a sensitivity and specificity of 84.1 % and 42.8%, respectively. ROC curve analysis of the parameters is shown in Table 2 and Figure 1.

Figure 1 - ROC curve of CAR and SIRI in predicting CAD



Since the specificity of CAR and SIRI were found to be higher than the other parameters, we further evaluated whether these biochemical parameters had an additional value in interpretation of MPS result. Only 10.4 % of the CAD negative patients had positive MPS result and positive CAR values, whereas 0.9% of the CAD positive patients had negative MPS result and negative CAR values. 27.5% of CAD negative patients had positive MPS result and negative CAR values. When both CAR and MPS results were negative the specificity of that finding reached to 98.2%, whereas when both CAR and MPS results were positive, the sensitivity of that finding reached to 85.5%.

Likewise, having a negative MPS result with negative SIRI value identified 50% of the patients who had normal coronary arteries. Although 29.7% of the patients who had normal coronaries had positive MPS result, their SIRI value was lower than the cut-off value of 1.45. Positive MPS result with positive SIRI value correctly identified 58.1% of patients who had CAD. When both SIIR and MPS results were negative, specificity of that finding was found to be as 97.4%. When both SIRI and MPS results were positive sensitivity of that finding was 88.5%. Table 3 shows the patients' clinical results with respect to their CAR, SIRI and MPS results.

Table 2 ROC curve analysis of biochemical parameters

	AUC	CI 95%	p	Value	Sensitivity	Specificity
CAR	0.722	0.674-0.769	<0.001	1.22	61.2	77
SII	0.642	0.591-0.692	<0.001	423.78	50.9	49.1
SIRI	0.744	0.699-0.789	<0.001	1.45	59	80.2
MLR	0.684	0.635-0.732	<0.001	0.24	84.1	42.8

Table 3 Assessment of biochemical and MPS results of the patients in predicting the presence of CAD

	Control group (CAD negative)	Study group (CAD positive) n (%)	Total n (%)
CAR - / MPS -	110 (49.5)	2 (0.9)	112 (24.9)
CAR - /MPS +	61 (27.5)	86 (37.9)	147 (32.7)
CAR + / MPS -	28 (12.6)	3 (1.3)	31 (6.9)
CAR + /MPS +	23 (10.4)	136 (59.9)	159 (35.4)
SIRI - /MPS -	111 (50.0)	3 (1.3)	114 (25.4)
SIRI - / MPS +	66 (29.7)	90 (39.6)	156 (34.7)
SIRI + / MPS -	27 (12.2)	2 (0.9)	29 (6.5)
SIRI + / MPS +	17 (7.1)	132 (58.1)	149 (33.2)

Table 4 Univariate logistic regression analysis for predictors of CAD

	OR	p	CI 95%
CAR	2.712	<0.001	2.070-3.551
Age	1.025	0.010	1.006-1.045
Creatinine	2.353	0.005	1.291-4.287
LDL-C	0.99	0.673	0.995-1.004
Triglyceride	1.001	0.487	0.999-1.003
HDL-C	0.954	<0.001	0.936-0.973
Hemoglobin	0.978	0.720	0.869-1.102
SII	1.002	<0.001	1.001-1.002
SIRI	3.400	<0.001	2.441-4.737
MLR	2.120	<0.001	1.954-3.758

Univariate logistic regression analysis showed that CAR, creatinine, HDL-C, SII, SIRI and MLR were the independent predictors of CAD (Table 4).

Discussion

According to our results, having both elevated CAR/SIRI values and abnormal MPS result decreased the chance of having normal coronary arteries less than 10%, whereas having both lower CAR/SIRI values with normal MPS were associated with the CAD risk of less than 2%. In the present study, considerable amount of patients (n=84, 37.8%) with normal coronary arteries had abnormal findings on MPS imaging, indicating relatively low specificity. When the MPS results were interpreted with CAR and/or SIRI values, it was seen that almost one third of the patients with normal coronary arteries had abnormal MPS findings but their CAR/SIRI values were fell into the values lower than the cut-off threshold. Besides from other parameters including creatinine, HDL-C, SII, and MLR, CAR and SIRI were found to be the independent predictors of CAD.

MPS, the most frequently used imaging modality for in our country, is applied for diagnosis, risk stratification and follow-up of CAD patients. This test allows obtaining information about myocardial perfusion and plays crucial role in clinical decision-making process. Although sensitivity of MPS imaging has been reported around 85 to 98%, its specificity in detecting CAD is relatively low [10]. A number of factors especially attenuation artifacts from diaphragm, breast or obesity could lead to false positive results. McGee et al. indicated that the specificity of MPS imaging could be as low as 54%, which was a markedly lower value compared to previous reports [11]. In our study the specificity of MPS imaging was found to be as 62.2%.

After the discovery of the role of inflammation in CAD pathogenesis, a lot of research have been conducted in order to find out the value of inflammatory biomarkers in diagnosis and management of cardiovascular diseases. Increased number of neutrophils, lymphocytes and monocytes have been shown to be associated with worsened cardiac outcomes [12-14]. CRP, an acute phase reactant, is an indicator of inflammation. Increased levels of CRP has been associated with impaired fibrinolysis, decreased nitric oxide and increased endothelin-1 release, activation of the complement system and the severity of coronary atherosclerotic lesions [15-17]. Likewise, serum albumin levels decrease in the presence of systemic inflammation and is an independent predictor of mortality in heart failure and acute coronary syndrome patients [18-20]. Combining CRP/albumin levels and neutrophil/monocyte/lymphocyte numbers into single index (CAR and SIRI, respectively) has been thought to represent higher inflammatory state and might be superior to the single parameter [21,22]. According to our results, if a patient had an abnormal MPS result with a positive CAR/SIRI values sensitivity of this finding in diagnosing CAD were 85.5% and 88.5, respectively. Conversely, having a normal MPS result with negative CAR/SIRI values, increases the specificity to 98.2% and 97.4%, respectively. However, 147 patients had abnormal MPS result with negative CAR/SIRI values in our study. Of these patients 61 (41.5%) had normal coronaries, 88 (51.5%) had CAD. When we further elucidated the characteristics of the patients, it was seen that patients with CAD had higher incidence of risk factors such as diabetes mellitus, hypertension and hyperlipidemia. Therefore cardiovascular risk factors as well as inflammatory biomarkers could help in decision-making process during interpretation of MPS result.

In conclusion, taking into consideration of biochemical markers might be beneficial in clinical decision process during interpretation of MPS imaging results. More than one third of the patients who had abnormal MPS imaging result had normal/noncritical CAD. However combining abnormal MPS imaging result with high inflammatory biomarker levels decreased false positive results almost less than 10%. This could help avoid unnecessary invasive coronary angiograms.

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Prognostic factors for the severe course of COVID-19 in the different COVID-19 peak periods in Central Kazakhstan

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Abstract

Introduction: COVID-19 has become the cause of a pandemic that has swept the entire world. Considering the genetic variability of the virus, the development and implementation of antiviral therapies, and the acquisition of a society's immune defenses through past infection or vaccination, the course of COVID-19 may change over time. The research aim was to study the prognostic significance of clinical and laboratory parameters with severe COVID-19 in 2020 and 2021 in Central Kazakhstan.

Material and methods: A cohort of 1556 patients with COVID-19 admitted to the infection hospitals of Karaganda from May to July 2020 and 2021 year was retrospectively analyzed. The association of clinical and laboratory parameters with the severe disease was analyzed using univariate and multivariate logistic regression, and independent predictors were established for each factor.

Results: The comparative analysis of the prognostic significance of demographic, clinical, and laboratory parameters in different periods of the pandemic showed a reduction in developing severe COVID-19 among hospitalized patients in 2021 compared to 2020. The essential value of comorbidity, especially chronic renal failure, and chronic heart failure remained significant against the background of decreasing prognostic significance of age, gender, and clinical and laboratory indicators of inflammation for the severe course of COVID-19.

Key words: COVID-19, coronavirus disease, prognosis, risk factors

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the cause of the coronavirus disease-2019 (COVID-19) initiated a pandemic that swept the whole world. The first cases of COVID-19 in Kazakhstan were confirmed on 13 March 2020 in Nur-Sultan and Almaty. On March 16, 2020, the government declared an emergency throughout the country [1-3].

The result of the meta-analysis shows that the frequency of severe cases of COVID-19 variated according to different researchers from 7,2 to 49,1%, deaths from 3,1% to 61,5% [4-6]. Most of the evidence-based research analysis where most participants were from China and later were published research from the USA, Europe, and other countries [7,8]. Big Kazakhstan's study which included hospitalized patients between February and April 2020 showed that the frequency of severe manifestations was about 4% [2].

For the 2020 year the predictive value of demographic, clinical, and laboratory parameters in predicting the severity of the course, the necessity for artificial lung ventilation (ALV), and patient mortality has been studied in many research [9-11]. Given the genetic variability of the virus, the development, and deployment of antiviral drugs, and the acquisition of a society's immune defenses through past infection or vaccination, it is not surprising that the course of COVID-19 can change over time. We didn't find research that studied the association of clinical and laboratory factors with the risk of developing a severe course of COVID-19 for different periods of the pandemic in Kazakhstan.

The investigation aimed to study the prognostic significance of clinical and laboratory parameters with severe COVID-19 associated pneumonia in 2020 and 2021 in Central Kazakhstan.

Materials and methods

A cohort of 1556 patients with COVID-19 from all of Central Kazakhstan (the total number of adult population of this region is 1 043 983 people [12]) admitted to the Regional clinical hospital and Medical University clinic in Karaganda from May to July 2020 and 2021 year was retrospectively analyzed. Patients with a positive nasopharyngeal PCR test for COVID-19 were included in the study. We collected data from electronic medical records for all patients: demographic data, presence or absence of active smoking, comorbidities, anthropometric parameters, blood pressure (BP), heart rate (HR), respiratory rate (RR), and oxygen saturation. Laboratory tests performed on admission included a complete blood count, and biochemical parameters (alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine, glucose, D-dimer), laboratory tests were carried out in the same certified laboratory in Karaganda. In all patients, we calculated body mass index, Charlson comorbidity index [13,14], and performed a chest CT scan. Of 1556 patients, 270 were excluded: 34 patients had no oxygen saturation data, in 122 patients - creatinine and blood glucose values, in 114 - the results of computed tomography of the lungs. In total, 1286 patients were included: 872 in 2020 and 414 in 2021. According to the WHO criteria, patients were divided into 4 groups depending on the severity: mild - 91 (7,1%), moderate - 999 (77,7%), severe - 182 (14,2%) and critically severe - 14 (1,1%). Patients with mild and moderate severity were combined into 1 group - 1090 (84,8%), and patients with severe and critically severe degrees constituted group 2 – 196 (15,2%). The study design was approved by the ethics committee of Karaganda Medical University dated April 14, 2021, No. 18.

Statistical analysis

Data were analyzed by using SPSS 21.0. The normal distribution was checked by the Kolmogorov-Smirnov test. Gender, smoking, presence of arterial hypertension (HTA), myocardial infarction (MI), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), pulmonary embolism (PE), bronchial asthma (BA), acute stroke (AS), presence of symptoms, severity, 30-day mortality were introduced as dichotomous variables. Descriptive statistics used the Mann-Whitney U-test for independent samples to compare quantitative variables; categorical variables were analyzed by Pearson's $\chi 2$. Continuous variables were reported as median (interquartile range), and categorical variables were presented as absolute frequency (relative frequency, %). We used univariate and multivariate logistic regression to establish an association of clinical and laboratory parameters and severe COVID-19 parameters of was d using, established independent predictors and odds ratios (ORs) at 95% confidence intervals (CI) for each factor. Covariates with $p<0,05$ or if they changed positive effect by ≥10% were included in multivariate analysis. Considering the strong correlation between systolic blood pressure (SBP) and diastolic blood pressure (DBP) ($r=0.604$), the variable SBP*DBP was included in the multivariate analysis, which reflects the relationship of these predictors. P-values <0,05 were considered as significant.

Results

In this study, we analyzed data from 872 and 414 hospitalized patients with COVID-19 of the first and second waves of the pandemic in two hospitals in Karaganda. The clinical characteristics of patients are presented in Table 1. In 2020 and especially in 2021, women predominated among inpatients - 54% and 60,4% respectively; the age of patients in 2020 was significantly younger: 32.3% were persons aged 45-59, in 2021 - 45.4% of patients were aged 60-74 (Table 1). The most common symptoms during both periods were complaints of general weakness, fever, cough, and shortness of breath. In 2021, complaints of myalgia were significantly more frequent than in 2020– 1,6 times (p=0,003), general weakness – 1,1 times (p=0,001), joint pain – 2,4 times (p=0,01), ageusia – 261 times (p=0,042). The Charlson comorbidity index between groups differed due to the prevalence in 2021 of patients with comorbidity 2-3 points compared to 2020; groups with severe comorbidity (3 points or more) were comparable – 14,7% in 2021 and 15,9% in 2020. In the structure of comorbidities, a higher frequency of HTA and CHF was revealed in 2021 compared to 2020, the frequency of DM, COPD, MI, CKD, and BA did not differ significantly between the groups.

In 2020, COVID-19 was characterized by a more severe course compared to 2021: 2,3 times more likely to have severe and extremely severe severity, 2,2 times more need for ventilation, 3.2 higher in-hospital mortality compared to 2021. The percentage of lung tissue damage was higher in 2020 (Me 30% Q2-Q3 (20–60) compared to 2021 – (Me 25% Q2-Q3 (12–40); p=0,0001). The frequency of MI, stroke, and PE did not differ significantly between the groups. More than a third of patients noted taking antibacterial drugs before hospitalization, anticoagulant intake ranged from 3,9 to 6,1% with no significant difference between 2020 and 2021.

Laboratory parameters are shown in Table 2. In 2020 compared to 2021, patients had higher levels of leukocytes, platelets, and NLR (neutrophil-lymphocyte ratio), from biochemical parameters - AST level. We did not find significant differences in ALT, and creatinine levels between patients in 2020 and 2021. In 2021, patients had significantly higher levels of bilirubin and glucose compared to 2020. D-dimer levels did not differ between groups.

The results of the unadjusted odds ratio for the variables showed that in 2020 the risk of developing a severe degree of the disease increased significantly with the age of the patient (odds ratio [OR]: 1,053 95% CI: 1,040 – 1,066, $p<0,0001$) and did not depend on gender (odds ratio [OR]: 1,397 95% CI: 0,993 – 1,965, $p<0,055$). In 2021, we found no predictive significance of age (p=0б323) and sex (p=0б731) for severe COVID-19 risk in univariate analysis. HTA, CHF, and diabetes mellitus prevailed in the structure of concomitant conditions. The presence of comorbid diseases such as hypertension, CHF, DM, and CKD had a significant predictive value for the severity of COVID-19 in patients in 2020 and 2021. In 2020 increased temperature, instability of blood pressure, and decreased oxygen saturation were associated with severe course of the disease, in 2021, only reduced oxygen saturation remained significant for severe COVID-19 (odds ratio [OR]: 0,727 95% CI: 0,654-0,808, p=0,0001). From laboratory parameters, the most significant increase in the risk of severe COVID-19 was associated with an increase in NLR and creatinine levels.

The results of multivariate logistic regression models for assessing the relationship of various indicators that are statistically significant in a univariate analysis with the risk of developing severe degree of COVID-19 in 2020 and 2021 are presented in Table 3. In 2020, a stratified analysis showed that the risk of severe COVID-19 is associated with age (odds ratio [OR]: 1,034 95% CI: 1,015-1,054, p=0,001), increased temperature (odds ratio [OR]: 1,527 95% CI: 1,087-2,145, p=0,015), decreased oxygen saturation (odds ratio [OR]: 0,866 95% CI: 0,840-0,893, p=0,0001) and increased NLR (odds ratio

Table 1 Clinical characteristics (% and median value (interquartile range)) of COVID19 inpatients in 2020 and 2021.

Parameter	2020 year (n=872)	2021 year (n=414)	Z	p-value
Age, years	57 (45–68)	62 (52–70)	4.038	0.0001
Age categories: 18–44 45–59 60–74 75 and older	 216 (24.8%) 282 (32.3%) 260 (29.8%) 114 (13.1%)	 74 (17.9%) 96 (23.2%) 188 (45.4%) 56 (13.5%)	4.27	0.0001
Gender: female male	 471 (54%) 401 (46%)	 250 (60.4%) 164 (39.6%)	2.151	0.031
Smoker no data	37 (4.2%) 298 (34.2%)	19 (4.6%) 215 (51.9%)	1.45	0.146
Temperature > 38 °C	635 (72.8%)	317 (76.6%)	1.432	0.152
Myalgia	81 (9.3%)	62 (15.0%)	2.97	0.003
General weakness	728 (83.5%)	373 (90.1%)	3.6	0.001
Loss of appetite	170 (19.5%)	100 (24.2%)	1.938	0.053
Sore throat	140 (16.1%)	62 (15.0%)	0.556	0.578
Cough	603 (69.2%)	295 (71.3%)	1.035	0.301
Dyspnea	309 (35.4%)	190 (45.9%)	0.975	0.330
Joint pain	14 (1.6%)	16 (3.9%)	2.589	0.010
Chest pain	106 (12.1%)	43 (10.4%)	0.932	0.351
Anosmia	53 (6.1%)	29 (4.3%)	0.635	0.525
Ageusia	20 (2.3%)	18 (4.9%)	2.032	0.042
Stomach ache	18 (2.1%)	8 (1.9%)	0.151	0.880
Stool disorders	34 (3.9%)	15 (3.6%)	1.015	0.310
Stroke	10 (1.1%)	6 (1.4%)	0.457	0.648
PE	14 (1.6%)	8 (1.9%)	0.422	0.673
MI	22 (2.5%)	17 (4.1%)	1.546	0.122
HTA	399 (45.8%)	225 (54.3%)	2.879	0.004
CHF	251 (28.8%)	149 (36.0%)	2.607	0.009
BA	11 (1.3%)	4 (1.0%)	0.461	0.645
COPD	20 (2.3%)	7 (1.7%)	0.704	0.481
CKD	41 (4.7%)	13 (3.1%)	1.304	0.192
DM	124 (14.2%)	72 (17.4%)	1.478	0.139
Comorbidity index, score 0-1 2-3 4 or more	 548 (62.8%) 185 (21.2%) 139 (15.9%)	 226 (54.6%) 127 (30.7%) 61 (14.7%)	2.154	0.031
Temperature, °C	36.8 (36.6–37.4)	36.8 (36.5–37.2)	1.972	0.049
BMI, kg/m^2	27.7 (24.6–31.6)	30.8 (27.0–34.6)	4.316	0.0001
SBP, mmHg	120.0 (120.0–130.0)	120.0 (115.0–130.0)	1.475	0.140
DBP, mmHg	80 (70-80)	80 (70-80)	4.091	0.0001
HR, beats/min	80 (76-88)	80 (76-89)	0.568	0.570
RR, in min	19 (18-22)	19 (18-20)	2.263	0.024
Sat O2, %	95 (92-97)	95 (93-97)	1.283	0.200
Severity degree 1 2	 709 (81.3%) 163 (18.7%)	 381 (92,0%) 33 (8,0%)	4.996	0.0001
Lung damage, %	30 (20-60)	25 (12-40)	5.671	0.0001
ALV	73 (8.4%)	16 (3.9%)	3.647	0.001
Mortality	75 (8.6%)	11 (2.7%)	3.985	0.0001
Bed days	11 (9-13)	10 (9-11)	4.429	0.0001
Antibiotics before hospitalization	308 (35.3%)	125 (30.2%)	1.817	0.069
Anticoagulants before hospitalization	53 (6.1%)	16 (3.9%)	1.645	0.10

Abbreviations: ALV - artificial lung ventilation, BA - bronchial asthma, BMI – body mass index
CKD - chronic kidney disease, COPD - chronic obstructive pulmonary disease, CHF - chronic heart failure, DBP - diastolic blood pressure, DM - diabetes mellitus, HR - heart rate, HTA - Arterial hypertension, MI - myocardial infarction, PE - pulmonary embolism, RR - respiratory rate, SaO2 - Oxygen saturation, SBP - systolic blood pressure

[OR]: 1,078 95% CI: 1,022-1,138, p=0,006). Of the comorbid conditions in the multivariate model for patients in 2020, the presence of CKD and COPD preserved predictive value. The presence of other comorbid conditions in 2020 lost predictive value for COVID-19 severity after correction. In 2021, after correction in the multivariate model, the presence of CHF (odds ratio [OR]: 4,580 95% CI: 1,028-20,409, p=0,046), CKD (odds ratio [OR]: 7,728 95% CI: 1,707-34,993, p=0,008) and a decrease in oxygen saturation (odds ratio [OR]: 0,724 95% CI: 0,636-0,824, p=0,0001) retained a significant association with the risk of developing severe COVID-19.

Table 2 Laboratory parameters in patients hospitalized with COVID-19 in 2020 and 2021

Parameter	2020 year (n=872)	2021 year	Z (n=414)	p-value
	Me (Q_{25}-Q_{75})	Me (Q_{25}-Q_{75})		
Leukocytes, 109/л	5.50 (4.40–7.50)	5.10 (3.97–6.37)	4,527	0.0001
Neutrophils, 109/л	3.56 (2.45–5.25)	3.20 (2.29–4.36)	3.924	0.0001
Lymphocytes, 109/л	1,28 (0,92–1,77)	1.21 (0.94 -1.66)	1.379	0.168
NLR	2.75 (1.74-4.81)	2.52 (1.72-3.73)	2.425	0.015
Platelets, 109/л	200.0 (173–259)	188 (166–214)	5.048	0.0001
ESR, mm/h	20 (10–32)	13 (9–21)	7.593	0.0001
AST, U/l	30.7 (23.0–47,0)	27 (23–37)	3.181	0.001
ALT, U/l	27.5 (19.0–40.0)	29 (21–33)	0.619	0.536
Creatinine, μmol/l	84.9 (71.0–99.0)	88.0 (78.3–96.0)	1.765	0.078
Bilirubin total, μmol/l	11.20 (9.70–14.37)	13.1 (11.8–16.0)	8.728	0.0001
Glucose, mmol/l	5.7 (5.0–7.3)	6.5 (5.50–8.0)	6.092	0.0001
D-dimer, ng/ml	315.0 (198.7–476.5)	310.0 (183.0–470.0)	0.657	0.511

Abbreviations: ALT - alanine aminotransferase, AST - Aspartate aminotransferase, ESR - Erythrocyte Sedimentation Rate, NLR - Neutrophil-to-lymphocyte ratio

Table 3 Univariate and multivariate logistic regression analyses of risk variables for association with severe COVID-19 in 2020 and 2021

Parameter	2020 (n=872)				2021(n=414)			
	unadjusted OR (95% CI)	p value	aOR (95% CI)	p value	unadjusted OR (95% CI)	p value	aOR (95% CI)	p value
Age, years	1.053 (1.040–1.066)	0.0001	1.034 (1.015–1.054)	0.001	1,012 (0,988–1,038)	0.323	-	
Male	1.397 (0.993-1.965)	0.055	-		1,135 (0,552–2,332)	0.731	-	
HTA	7.383 (4.830–11.286)	0.0001	2.141 (1.071–4.279)	0.031	2.828 (1.244–6.429)	0.013	0.360 (0.073–1.773)	0.209
CHF	6.285 (4.362–9.054)	0.0001	1.639 (0.881–3.050)	0.119	4.655 (2.150–10.078)	0.0001	4.580 (1.028–20.409)	0.046
DM	2.202 (1.436-3.377)	0.0001	1.218 (0.638-2.326)	0.549	2.623 (1.210-5.687)	0.015	1.811 (0.580-5.652)	0.307
CKD	7.846 (4.082-15.084)	0.0001	3.725 (1.441-9.625)	0.007	16.827 (5.272-53.710)	0.0001	7.728 (1.707-34.993)	0.008
COPD	5.629 (2.292-13.820)	0.0001	6.705 (1.810-24.843)	0.004	1.953 (0.228-16.726)	0.541	-	
MI	2.076 (0.832-5.177)	0.117	-	-	3.894 (1.193-12.707)	0.024	2.720 (0.645-11.469)	0.173
SBP	1.023 (1.006-1.041)	0.008	0.981 (0.957-1.005)*	0.116	1.020 (0.990-1.050)	0,192	-	
DBP	0.989 (0.967-1.010)	0.303	-		1.024 (0.971-1.080)	0.374	-	
Temperature, °C	1.749 (1.403-2.181)	0.0001	1.527 (1.087-2.145)	0.015	0.997 (0.962-1.033)	0.860	-	
SatO2, %	0.846 (0.822–0.870)	0.0001	0.866 (0.840-0.893)	0.0001	0.727 (0.654–0.808)	0.0001	0.724 (0.636–0.824)	0.0001
Platelets	1.003 (1.001–1.005)	0.004	1.002 (0.999-1.005)	0.238	0.996 (0.990–1.002)	0.244	-	
AST, U/l	1.002 (0.999–1.005)	0.181	-		1.000 (0.997-1.004)	0.910	-	
Creatinin, μmol/l	1.001 (1.000-1.003)	0.081	-		1.011 (1.003–1.020)	0.010	1.001 (0.989–1.013)	0.836
Glucose, mmol/l	1.000 (0.999-1.001)	0.740	-		1.095 (1.016–1.180)	0.016	0.985 (0.872-1.114)	0.813
NLR	1.245 (1.189-1.302)	0.0001	1.078 (1.022-1.138)	0.006	1.084 (1,011-1.163)	0.024	0.984 (0.891–1.086)	0.745

Odds ratios were given with 95% CI and p values
* variable SBP*DBP
Abbreviations: AST - Aspartate aminotransferase, CKD - chronic kidney disease, COPD - chronic obstructive pulmonary disease, CHF - chronic heart failure, DBP - diastolic blood pressure, DM - diabetes mellitus, HTA - Arterial hypertension, MI - myocardial infarction, SaO2 - Oxygen saturation, SBP - systolic blood pressure, NLR - Neutrophil-to-lymphocyte ratio

Discussion

The first wave of the pandemic in Kazakhstan began in March 2020 and quickly spread over its territory [15]. In this research for the first time, we compared the predictive value of clinical and laboratory parameters for the risk of severe COVID-19 between patients in 2020 and 2021. We found that in 2020-year patients' age, gender, presence of CKD, COPD, fever, increase in NLR, and decrease in oxygen saturation had significant predictive value for COVID-19 severity. The data obtained are consistent with numerous results of other works were shown the predictive value of age [16], gender [17], comorbidity [18-20], clinical symptoms of disease [21], and increase of NLR [22] for the prognosis of severity and death.

Interestingly, we didn't find predictive value for age and gender in COVID-19 patients in 2021. The lack of age difference cannot be attributed to the younger age of patients because the median age in 2021 is significantly higher compared to patients in 2020. We did not find a male predominance among hospitalized patients.

The predictive value of comorbid conditions for the severity of COVID-19 is supported by the results of many studies. The highest significance after correction in the multivariate model both in 2020 (odds ratio [OR]: 3,725 95% CI: 1,441-9,625, p=0,007) and in 2021 (odds ratio [OR]: 7,728 95% CI: 1,707-34,9, p=0,008) had CKD. A meta-analysis of geographical differences in the association of comorbidity with the severity of COVID-19 showed that in Asia, compared with Europe and the United States, the most common cause of COVID-19 severity was the presence of CKD [19] (68%; 95% CI: 46–87%), while liver disease (50%; 95% CI: 1–99%) in European and Latin American studies, and malignancies in US researches (38%; 95% CI: 18–60%).

Since the beginning of the pandemic, many authors have investigated the role of NLR in predicting COVID-19 and have shown its utility as a biomarker. The lack of predictive value of NLR for COVID-19 severity in 2021 cannot be fully explained by demographic differences. Our data are consistent with those of Monica Gelzo et al [23] who observed no significant difference in NLR between the WHO severity stage in COVID-19 patients during wave II in Italy (September 2020–April 2021) in contrast to the first wave of the pandemic. These differences between two wave COVID-19 patients were not associated with younger age in wave II patients, as age did not significantly affect NLR and neutrophils across different COVID-19 severity levels. The authors hypothesized that the differences between the two waves were probably related to the prescription of steroid therapy which was the only independent variable associated with NLR and neutrophils.

In our opinion, a significant decrease in the severity of the course of COVID-19, mortality, percentage of lung tissue damage in 2021 compared to 2020 in the absence of significant changes in clinical symptoms, comorbidity suggests a dependence on various factors including the introduction of various methods of therapy, the acquisition of tolerance to infection, organization and practical experience in managing the management of patients with COVID-19 infection since the beginning of the pandemic. In Kazakhstan, the first version of the guideline for diagnosing and treatment of COVID-19 was made on February 3rd 2020 year. By July 2021 in the country were held more than 10 editions which included constantly updated information on the course and treatment of the disease.

The limitations of our research were including patients from only two centers in the Karaganda region. Given the differences in the severity of the course and the prognostic significance of clinical and laboratory factors in different periods of the pandemic, an in-depth study seems relevant in future studies, depending on the therapy and the immune status of patients.

Conclusion

The COVID-19 pandemic has become a challenge for healthcare in almost all countries, including Kazakhstan due to the high incidence, severity, and mortality of patients. A comparative analysis of the prognostic significance of demographic, clinical, and laboratory parameters in different periods of the pandemic showed a decrease in the severity of the course among inpatients in 2021 compared to 2020. Against the background of a decrease in the prognostic significance of age, gender, and clinical and laboratory indicators of inflammation, the significant significance of comorbidity, especially CKD and CHF, for the severe course of COVID-19 remained. There is a relevance for future studies to assess the impact of therapy and immune status on the course and outcomes of COVID-19 infection.

Abbreviations:

ALT - alanine aminotransferase
ALV - artificial lung ventilation
AS - acute stroke
AST - Aspartate aminotransferase
BA - bronchial asthma
BP - blood pressure
CKD - chronic kidney disease
COPD - chronic obstructive pulmonary disease
COVID-19 - coronavirus disease 2019
CHF - chronic heart failure
CRF - chronic renal failure
CT - computed tomography
DBP - diastolic blood pressure
DM - diabetes mellitus
ESR - Erythrocyte Sedimentation Rate
HR - heart rate
HTA - Arterial hypertension
MI - myocardial infarction
NLR - Neutrophil-to-lymphocyte ratio
PCR - polymerase chain reaction
PE - pulmonary embolism
RR - respiratory rate
SARS-CoV-2 - Severe acute respiratory syndrome-related coronavirus 2
SaO2 - Oxygen saturation
SBP - systolic blood pressure
WHO – World Health Organization

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Preventive ultrasound diagnosis of deep vein thrombosis of the lower extremities in patients with COVID-19

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Abstract

Aim: The aim of the study was to determine the risk group for detecting early signs of thrombus formation in the veins of the lower extremities during preventive ultrasound examination in patients with COVID-19.

Materials and methods: The study included three groups of patients who were in intensive care units for COVID-19, of which 50 with acute venous thrombosis, 50 with venostasis in the veins of the lower extremities, and 50 patients without vein pathology, which constituted the control group. All patients were determined the level of D-dimer, fibrinogen and underwent duplex ultrasound scanning examination of the veins of the lower extremities.

Results: A close correlation was established between the presence of venous thrombosis and the levels of D-dimer and fibrinogen (2.33, 4.66, p=0.0001). According to the data obtained, in the examined patients values >=2.33 μg/ml for D-dimer is a sign of thrombus formation with 87.76% sensitivity and 97% specificity. For fibrinogen values 0. >=4.64 g/L are indicative of thrombus formation with 83.67% sensitivity and 83.00% specificity. The two studied parameters D-dimer (AUC area = 0.9458) and fibrinogen (AUC area = 0.9024) were a very high-quality classifier model.

Conclusion: The results of this study make it possible to form risk groups for the development of deep vein thrombosis (DVT) and to carry out timely prevention of this pathology. In patients with COVID-19 with severe respiratory failure and elevated levels of D-dimer (more than 2.33 mg/l) and fibrinogen (more than 4.64 g/l) duplex ultrasound is indicated.

Key words: preventive ultrasound diagnostics, COVID-19, deep vein thrombosis (DVT), thromboembolism

Introduction

A new coronavirus infection, now classified as COVID-19 and first identified in December 2019 in the Chinese city of Wuhan, is accompanied by an exponential increase in the number of infected people and significant mortality in many countries [1].

The ongoing COVID-19 (SARS-CoV-2) pandemic demonstrates not only the high aggressiveness of a new infectious agent, but also its ability to cause severe cardiovascular complications. One of them is the high prevalence of thrombotic complications, especially in the group of patients with a severe course of the infectious process [2].

COVID-19 predisposes to thrombosis and venous thromboembolism (VTE) due to excessive inflammation, platelet activation, endothelial dysfunction and stasis. An increase in the level of fibrinogen and factor VIII, activation of coagulation and a direct damaging effect of the virus on the endothelium play an important role in the development of thrombotic complications [3]. The incidence of DVT and pulmonary embolism (PE), according to prospective population studies is 160 and 60 cases respectively per 100,000 population per year [4, 5]. To refer to these diseases in foreign literature, the term "venous thromboembolism" (VTE) is used in the domestic literature "venous thromboembolic complications" (VTEC) [6, 7].

Deep vein thrombosis (DVT) of the lower extremities is one of the main causes of death from PE [8]. Most venous thrombi are not clinically manifested [9]. The "gold standard" for early diagnosis of DVT in COVID-19 is ultrasound using B-mode, color and power Doppler mapping as the most informative method [10]. According to the literature, the accuracy of diagnosing thrombosis of the veins of the femoral-popliteal segment is more than 90%, of the veins of the lower leg from 50 to 90%. [11].

Prevention of VTEC is one of the main problems of modern medicine, given the complexity of diagnosis the severe consequences of this pathology and significant economic losses [12]. Currently, the search for a screening method for the early diagnosis of DVT, which must meet two criteria objectivity and accessibility - is relevant. In this regard, the aim of this study was to determine the risk group for detecting early signs of thrombus formation in the veins of the lower extremities during preventive ultrasound examination in patients with COVID-19.

Material and methods

The design of the study was comparative. In working with patients, all the ethical principles required by the Declaration of Helsinki of the World Medical Association "Ethical principles of scientific and medical research involving humans (as amended in 2008) were observed. The study plan was approved by the local bioethical committee at NJSC "Astana Medical University". The study included three groups of patients who were in intensive care units for COVID-19. Patients of all groups underwent ultrasound scanning of the lower extremities, regardless of the presence of symptoms of DVT. The first (main) group consisted of 50 patients with thrombosis of the main veins of the lower extremities, the second group (comparison) included 50 patients with signs of venous stasis, and the third (control) group consisted of 50 patients without DVT. The age of the patients of the first group was from 40 to 94 years (mean age 69.18±14.50 years), in group 2 - from 40 to 92 years (mean age - 69.4±10.90 years), in group 3 - from 31 to 97 years (mean age - 69.06±12.84 years).

Duplex ultrasound was performed on LOGIQ P6 ultrasound scanners (GE Healthcare, USA) using linear transducers operating in the frequency range of 3–10 MHz. The veins from the inguinal ligament to the ankle were examined, including the common femoral vein (CFV, DFV, and SFV), popliteal vein (PV), posterior tibial vein (PTV), peroneal vein and intermuscular vein of the calf. DVT was diagnosed according to the ultrasound protocol in accordance with the recommendations of the Society of Ultrasound Sonographers for deep vein thrombosis of the lower extremities [13].

The studies were carried out in the supine position at rest, using a compression test. Duplex ultrasound examination was carried out in B mode in transverse scanning of the vein, if necessary power and color Doppler mapping mode were used. The standard criterion for assessing the patency of a vein is the level of its compressibility. Complete or partial incompressibility of the vein (indirect sign) is the only parameter required for the diagnosis of DVT. Mild progressive compression of the veins limited the risk of iatrogenic embolization. Compression testing was repeated every 2 cm over a 12 cm segment at each level [14, 15]. Signs of flotation of the thrombus head and the degree of occlusion were checked using power and color Doppler mapping. The advantages associated with 4-point ultrasound are that it is a simple, safe (i.e. no ionizing radiation) procedure, affordable, inexpensive, reliable (with sensitivity and specificity on the order of 90 to 100%) and fast (from 3 to 5 minutes), limiting potential exposure to the virus and the risk of infection.

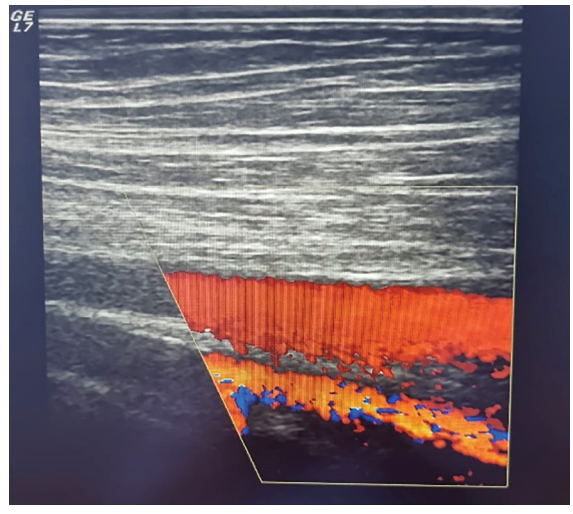
Laboratory data were collected at the first evaluation after the patients were admitted to the intensive care unit. The level of D-dimer was determined by a rapid quantitative method (D-dimer test, Finecare, China), fibrinogen on the analyzer Sysmex CA-1500 (semi-automatic coagulometer Start 4.0, Japan). Plasma samples were collected during the first 24 hours after hospitalization. The threshold value of D-dimer below 0.5 μg/ml, fibrinogen 1.8-3.5 g/l recommended by the manufacturer to exclude VTE was considered normal plasma levels.

MS Excel and Stata 14.2 (StataCorp) were used for data analysis and processing. Quantitative parameters are presented as mean, standard deviation, minimum and maximum values. To determine a statistically significant difference between groups of a continuous variable, a parametric one-way ANOVA (one-way analysis of variance) study was used if the variable was normally distributed. If not, an analog of one-way ANOVA related to the non-parametric research method the Kruskal-Wallis test was used. The difference in indicators is statistically significant at $p<0.05$.

Results

The criterion for inclusion of patients in the control group was the absence of ultrasound signs of venous pathology. The lumens of the deep veins of the lower extremities completely subsided during the compression test. Valves in the form of thin hyperechoic strips moved away from the wall of the vein during inhalation and pressed against it during exhalation. The lumen of the veins was homogeneous and anechoic (Figure 1).

Figure 1 - Ultrasound signs of the absence of thrombosis: complete staining of vein on color flow Doppler



With incomplete vein compression in obese patients and in patients with severe edema of the lower extremities, the absence of thrombosis was checked using the power and color Doppler. Full mapping of the lumen during the test with distal compression testified to the absence of thrombosis. The average values of D-dimer in the control group corresponded to the values of 0.89±0.52 [0.22-2.783] μg/ml, and fibrinogen 3.55±0.65 [1.2-4.53] g/l.

In the second group of patients with ultrasound, the "effect of spontaneous contrasting" of the lumen of the veins was observed. This effect consists in the visualization of an inhomogeneous hypoechoic lumen of the veins, due to multiple

Figure 2 - The effect of "spontaneous contrast" in the lumen of the femoral vein

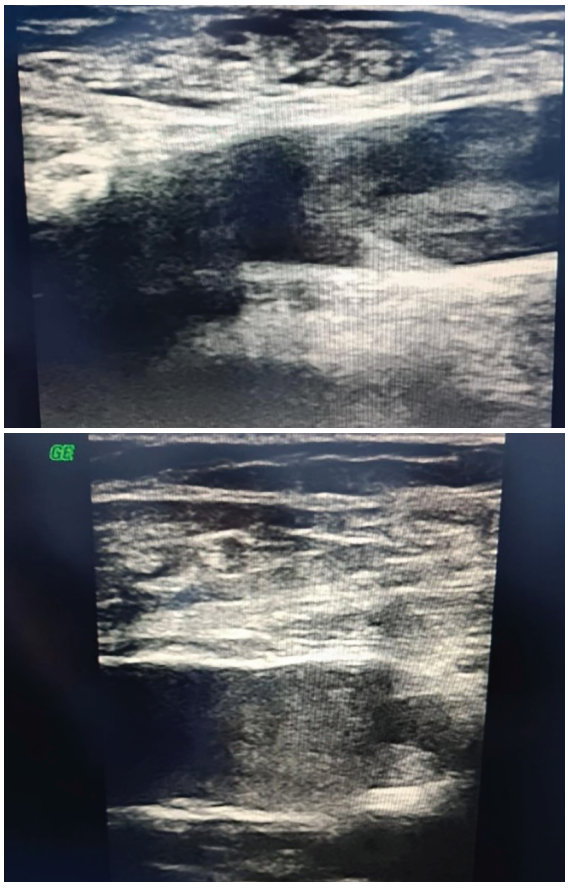


Figure 3 - Occlusive and non-occlusive thrombosis of the femoral vein

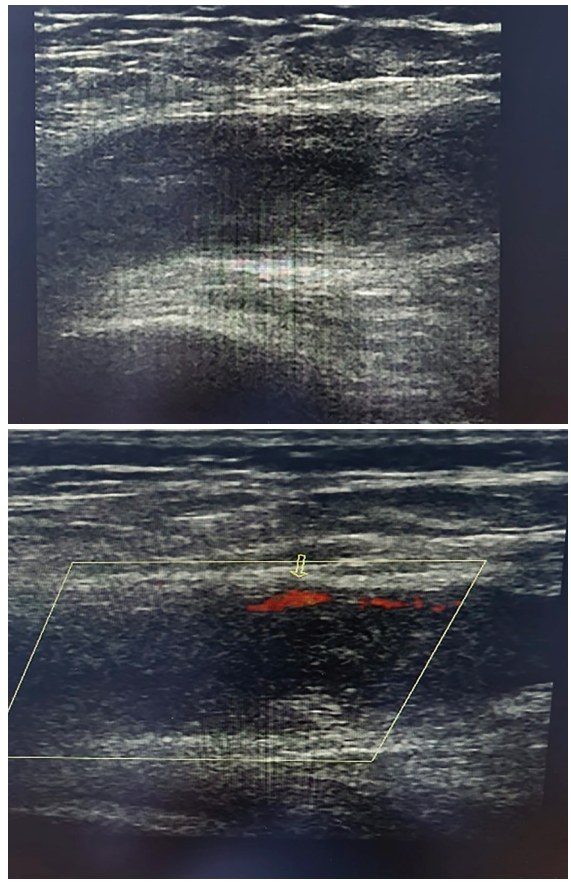


Table 1 Level of D-dimer and fibrinogen in groups of examined patients

	Group 1	Group 2	Group 3	p-value
D-dimer	4.94±2.57[0.318-10.58]	1.26±0.60 [0.396-3.8]	0.89±0.52 [0.22-2.783]	0.0001
Fibrinogen	6.07±2.53 [3.81-20.2]	4.42±0.74 [3.18-6.4]	3.55±0.65 [1.2-4.53]	0.0001

Table 2 Sensitivity and specificity of D-dimer and fibrinogen in patients with COVID-19

	AUC	Cutoff	Sensitivity	Specifity	Youden index
D-dimer	0.9458	≥ 2.33	87.76%	97.00%	0.8476
Fibrinogen	0.9024	≥ 4.64	83.67%	83.00%	0.6667

echo-positive inclusions that are displaced during a compression test. This effect is due to the accumulation of blood cells, slowing of blood flow and the phenomena of its turbulence (Figure 2). Turbulent blood flow in the area of the sinuses contributes to venostasis and in the case of an imbalance between the coagulation and fibrinolytic systems, a thrombus subsequently forms in the niche of the valvular sinus and spreads further along the vein [16, 17].

The average values of D-dimer in the 2nd group of patients with venostasis corresponded to the values of 1.26±0.60 [0.396-3.8] µg/ml, and fibrinogen - 4.42±0.74 [3.18-6.4] g/l

The group with thrombosis was characterized by the absence of compressibility of the vein heterogeneous hypoechoic thrombus masses were visualized in its lumen, which completely occluded the lumen. However, no lumen mapping was observed using the power and color Doppler mapping. Non-occlusive venous thromboses were diagnosed with incomplete compression of the vein while parietal blood flow was recorded in the color flow mode and in the power mode along the walls free from a blood clot.

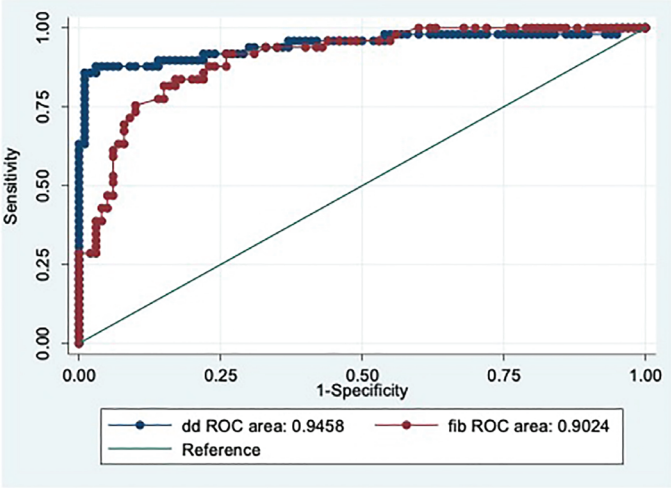
The average values of D-dimer in the group of patients with thrombosis was 4.94±2.57 [0.318-10.58] µg/ml, and fibrinogen - 6.07±2.53 [3.81-20.2] g/l.

According to the data obtained, the level of D-dimer and fibrinogen was statistically significant between the three compared groups ($p=0.0001$, $p=0.0001<0.05$, respectively) (Table 1).

To solve the problem of determining the value of the level of D-dimer and fibrinogen in homogeneous groups of patients with COVID-19 differing in outcome the presence of thrombosis, the presence of venostasis and the absence of thrombosis, the ROC analysis method was used. Using the ROC-analysis data the prognostic values of the method for determining the level of D-dimer and fibrinogen in the above groups of patients were obtained and cut-off value points were determined for the level of D-dimer and fibrinogen in each group of patients, above which an increase was observed number of outcomes (formation of thrombosis).

In the group of patients with COVID-19 and the presence of deep vein thrombosis of the extremities the D-dimer cut-off

Figure 4 - ROC curve for detecting possible thrombosis when using the level of D-dimer and fibrinogen in the laboratory diagnosis of complications in patients with COVID-19



point was determined to be 2.33 µg/ml. When using this level of the laboratory marker of venous thrombosis the area under the curve (AUC) was 0.94 (95% CI (0.899; 1.002), which means a high degree of efficiency of the classifier [18]. Sensitivity was 87.76%, specificity 97% for D-dimer (Table 2), the positive predictive value = 93.478%, diagnostic efficiency = 93.96% [19].

For fibrinogen values >=4.64 g/L were indicative of thrombus formation with 83.67% sensitivity and 83.00% specificity. For fibrinogen, positive predictive value = 70.69%, diagnostic efficiency = 83.221% [19].

Thus, the two studied parameters D-dimer (AUC area = 0.9458) and fibrinogen (AUC area = 0.9024) were a very high-quality classifier model.

Conclusion

The results of our study may allow the formation of risk groups for the development of deep vein thrombosis and timely prevention of this pathology. In patients with COVID-19 with severe respiratory failure and elevated levels of D-dimer (more than 2.33 µg/l) and fibrinogen (more than 4.64 g/L), preventive ultrasound of the veins of the lower extremities is indicated, even in asymptomatic patients.

Outside of intensive care, there is no indication for systematic screening for venous thromboembolism in patients with COVID-19 in the absence of clinical symptoms, as stated in French and European guidelines [20]. This will unnecessarily expose medical and nursing staff to the risk of infection and transmission, as well as the risk of nosocomial infections in patients. However, systematic testing of D-dimer and fibrinogen may be a valuable tool for predicting the severity of COVID-19 and the risk of thromboembolic complications.

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Surgical corrections of long ureteral defects (initial experience)

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Abstract

Introduction: Restoration of patency of ureters with long defects is one of the major problems in urology. There are cases when it is impossible to perform plastic surgery of ureter with own tissues or bladder; in these situations, appendicoureteroplasty or kidney autotransplantation can be promising solutions.

Material and methods: 4 patients underwent surgical corrections or ureter strictures: two underwent appendicoureteroplasty and two – kidney autotransplantation. To verify the diagnosis of long ureteral defects, standard research methods were used: ante- and retrograde pyeloureterography.

Results and discussion: In the early postoperative period, all patients underwent dynamic ultrasonography of the abdominal cavity and retroperitoneal space; in addition, hemodynamics parameters as well as clinical and biochemical laboratory blood parameters were monitored. The early postoperative period in three patients proceeded with no incidents and did not require serious additional studies. In one patient after appendicoureteroplasty dynamic intestinal obstruction developed on the third day post-op, which was resolved conservatively. In the late postoperative period the condition of the patients was satisfactory. There are few articles describing surgical interventions that can treat long ureteral defects, with appendiculoplasty and kidney autotransplantation being the most effective. However, each procedure has own advantages and disadvantages, as well as risks.

Conclusion: In our study, we performed these two methods with two patients for each method. Results are promising, but for a better statistical analysis and more thorough follow-up we need more patients for both appendiculoplasty and kidney autotransplantation.

Key words: ureter stricture, appendix, cecum, urodynamics, autotransplantation, kidney transplantation

Introduction

Restoration of ureteral patency in patients with long defects is one of the most difficult problems of modern urology [1,2]. According to literature, the causes of ureteral stricture include: ischemia, trauma, inflammatory diseases (including tuberculosis), periureteral fibrosis, endometriosis, prolonged exposure to a foreign body (calculus, stent, etc.), congenital developmental anomalies. More than 80% of cases of stricture are formed because of iatrogenic damage to the ureter, including burns after radiation therapy [3].

In recent years, the growth of post-radiation strictures and iatrogenic injuries of the ureters during surgical interventions on pelvis and abdominal cavity organs can be noted. In cases of impossibility of plastic surgery of the ureter with the help of own tissues or the bladder, the use of the small intestine, appendix or large intestine is the most promising. These organs have a good mucous layer and a similar structure of the muscular and serous layers of the wall, and are also functionally capable of passage due to contractile activity [4,5]. Ureteroplasty by the appendix is still a rarely performed operation. No more than a few dozen cases of using the appendix to replace long ureteral

strictures have been described in the world literature [6,7]. The development of living donor kidney transplantation has opened the possibility of kidney autotransplantation (AT), especially in patients with extended ureteral stricture with preserved kidney function. According to the literature, autotransplantation is defined as a highly effective surgical intervention for preserving an organ in various kidney pathologies [8]. Until 2013, 7 kidney autotransplantations were performed in Kazakhstan [9].

All of the above indicates that with extended defects of the ureter, there is a difficulty in resolving the issue of its surgical treatment. The main goal here is to preserve the kidney with an adequate passage of urine. The search for various solutions to this issue determines the relevance of the problem.

Aim of study: To analyze the results of the first various variants of surgical correction of long ureteral defects using the appendix and kidney autotransplantation.

Materials and methods

The results of surgical treatments performed on 4 patients for long ureteral defects were analyzed. In two cases, the appendix was used as a plastic material. In one patient, surgery of the right ureter was performed, and in the other - the left one. In two cases, patients underwent autotransplantation of the left kidneys to the right iliac vessels with the imposition of an antireflux anastomosis with the bladder.

Indications for surgery in all cases were extended strictures of the ureters, with a disturbance of the urine passage and the development of hydronephrosis. In order to resolve hydronephrosis all patients underwent percutaneous nephrostomy under ultrasound guidance. Other options of surgical treatment were not applicable in these cases, because all strictures were prolonged.

To verify the diagnosis of long ureteral defects, standard research methods were used. The main ones were ante- and retrograde pyeloureterography. To visualize kidney vessels to decide the issue of autotransplantation, computed tomography was performed in a two-vessel angio mode. Along with this, the function of the kidney and the content of pathological impurities in the urine were studied.

Figure 1 - Antegrade urography: long right ureteral stricture

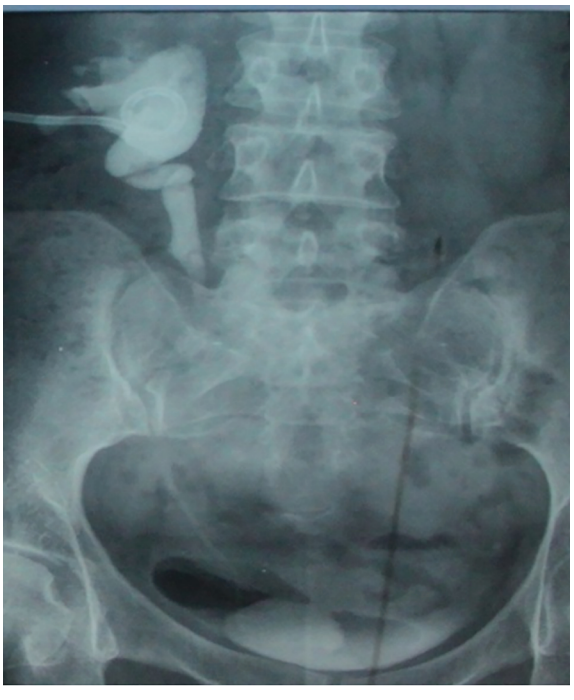


Figure 2 - CT with 3D modeling: inferior to middle-third ureter cannot be identified

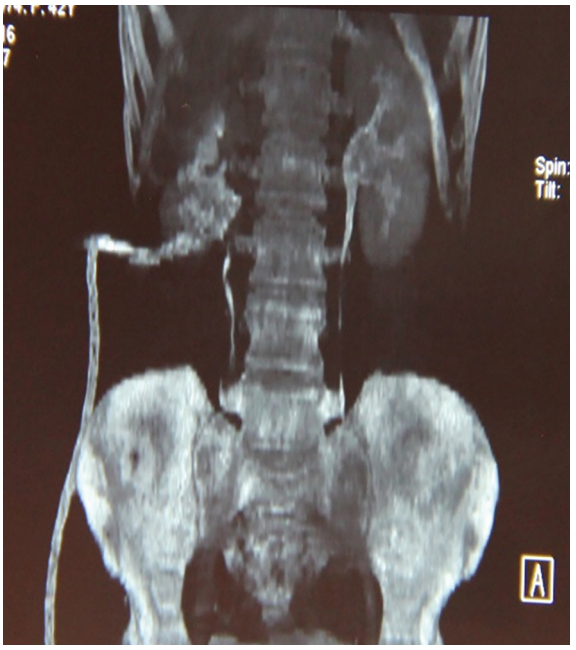
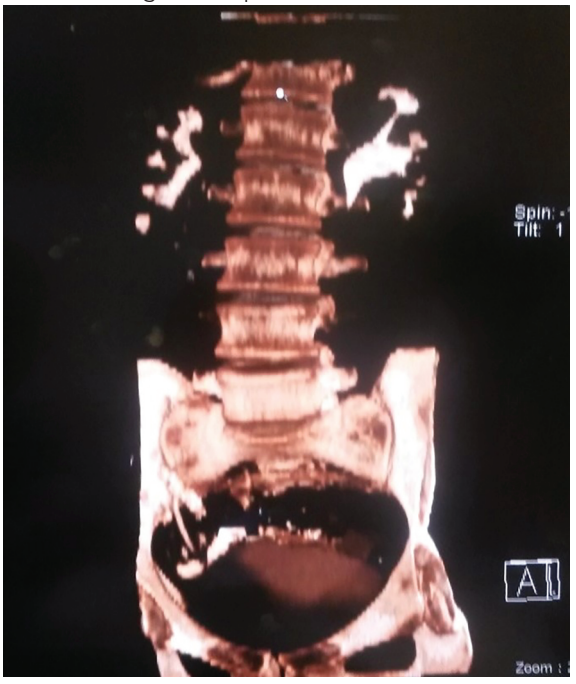


Figure 3 - CT 4 months after appendicoureteroplasty. Normalization of right renal pelvis size. Anastomosis is functional



Surgical interventions
Appendicoureteroplasty

Both patients underwent mid-lower laparotomy for appendicoureteroplasty. In the first case, the right ureter was identified by dissection of the parietal peritoneum from the right side and mobilization of the cecum and ascending colon. The ureter was isolated with technical difficulties to the ureterovesical junction. On assessing the patency of the ureter, the length of the stricture (complete obliteration) was 11 centimeters. When assessing the appendix, the latter was macroscopically without signs of inflammation, the length was 13 and the width was 1 cm. The mesentery of the appendix was mobile with diophanoscopy, the vessels of the main type, the pulsation of the appendicular artery without pathologic features. Taken into consideration a good condition and blood supply of appendix, it was decided to perform appendicoureteroplasty. The stenotic part of the ureter

Figure 4 - CT 4 months after appendicoureteroplasty. Normalization of right renal pelvis size. Anastomosis is functional

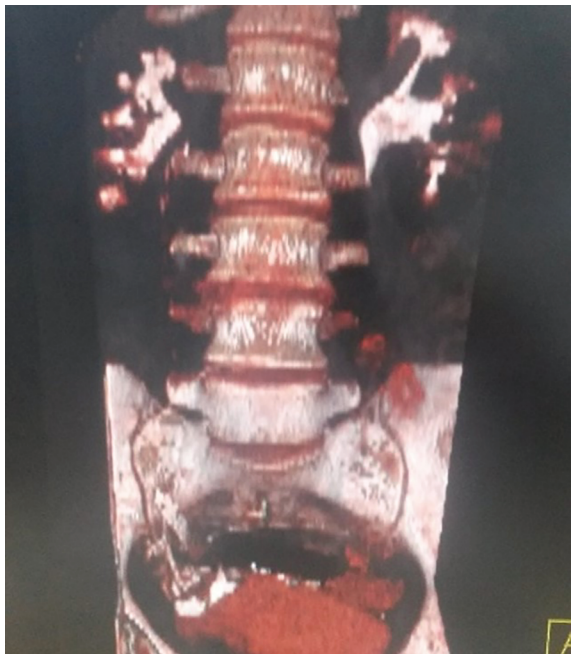
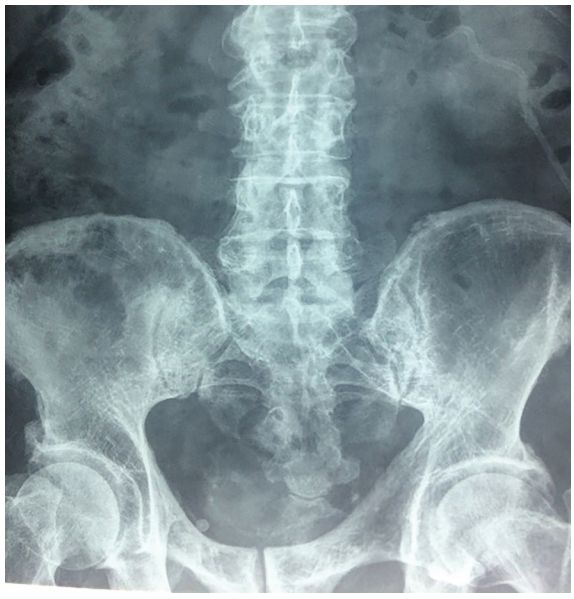


Figure 5 - Urography



was resected, with suturing of the distal end. Appendectomy was performed with double-row sutures on the wall of the cecum. Further, a cannula with a syringe was placed on the proximal end of the appendix, and the tip of the appendix was cut obliquely at an angle of 45 degrees. Sparing hemostasis with bipolar coagulator was performed. Then the lumen of the appendix was washed with dioxidine solution. When the appendix was replaced into the retroperitoneal space and an attempt was made to install it to replace the ureteral defect, tension was found in the mesentery and its vessels. To resolve this issue, the appendix was located anti-peristaltically, and ischemia of the organ was not observed. Appendicoureteroplasty was performed. Anastomoses were formed with interrupted sutures with the ureteral stent. The tip of the stent was inserted into the bladder. The abdominal cavity and retroperitoneal space were drained with elastic silicone drains. The wound healed by primary closure, the nephrostomy was removed on the 12th day after ultrasound control, the stent catheter was removed from the bladder on the 22nd day.

Figure 6 - Antegrade pyeloureterography: long left ureteral defect

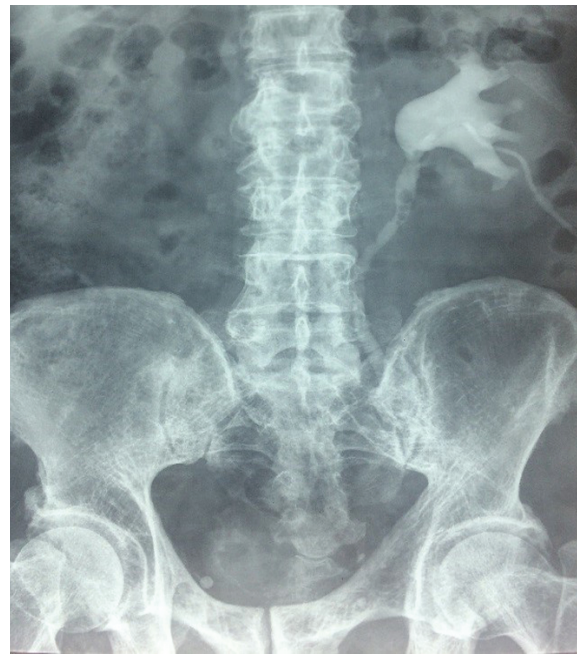
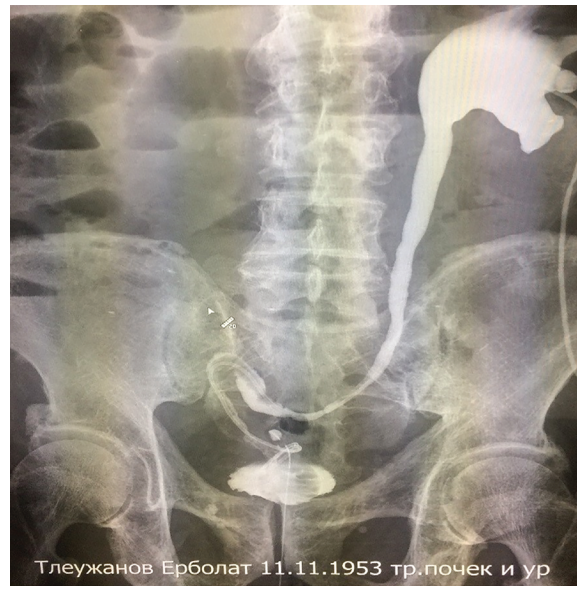


Figure 7 - Antegrade left pyeloureteropraphy



The second patient had a long ureteral defect on the left side. The technical peculiarity of the surgery was that during the revision of the abdominal organs, a medial dystopia of the caecum was found, and the vessels of the appendix derived from the branches of the lower mesenteric artery. It let us perform appendicoureteroplasty in the isoperistaltic position. Due to anatomic variation of appendix it was decided to perform appendicoureteroplsaty instead of ileoureteroplasty. The ureteral defect was 9 centimeters. The appendix was 11 long and 1.1 cm wide. The distal part was anastomosed with the proximal end of the ureter on the stent, and an anastomosis between the fundus of the bladder and the base of the appendix was formed with the stent immersed in bladder cavity. After 7 days, antegrade pyeloureterography was performed (Figure 7). The stent catheter was removed on an outpatient basis on the 24th day, and the nephrostomy was removed on the 28th day.

Kidney autotransplantation

Both patients for kidney autotransplantation ahd long defects of lest ureters. Both patients had a history of multiple surgical interventions to treat ureteral strictures, all of them were unsuccessful. That is why it was decided to perform kidney transplantation as a last resort of treatment. Pararectal incision on the left was performed in both cases with laparotomy. The parietal peritoneum along the ascending colon was dissected and the ureter was identified in the retroperitoneal space, taken on a tourniquet. With technical difficulties, it was ligated up to the wall of the bladder and transected. Both patients had nephrostomies placed before surgery, which were removed during the intervention. Next, a standard sparing nephrectomy with separate ligation of the vessels was performed. Short-term conservation of the kidney was carried out extraorganically with Custadiol solution at a temperature of + 4 degrees of Celsius until the blood cells were completely washed out (Figure 9A). Heparin solution diluted to 1:100 ml of saline solution was used as a direct anticoagulant. After conservation, condition of the ureter was assessed and resected within the healthy part: 8 cm in the first case and 11 in the second. This data correlated with preoperative findings of ante- and retrograde pyeloureterography (Figure 8 A and 8 B). After that, the kidney was transplanted with vascularization from the external iliac vessels on the right (Figure 9B). The kidney was launched into the bloodstream by standard method. In both cases, the renal blood flow was adequate, urine appeared after 5-8 minutes. After that, a stent catheter was placed up to the pelvis of kidney, and the distal end was placed into the bladder cavity through a separate incision, and an antireflux ureterocystoanastomosis formed on it. The operation was completed by draining of retroperitoneal space with two elastic silicone drains and tight suturing the abdominal cavity.

Figure 8 - Antegrade left pyelography

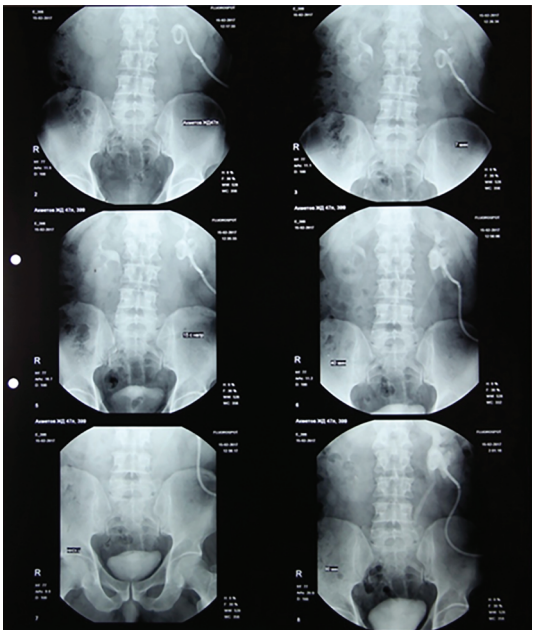


Figure 9 - Antegrade left pyelography

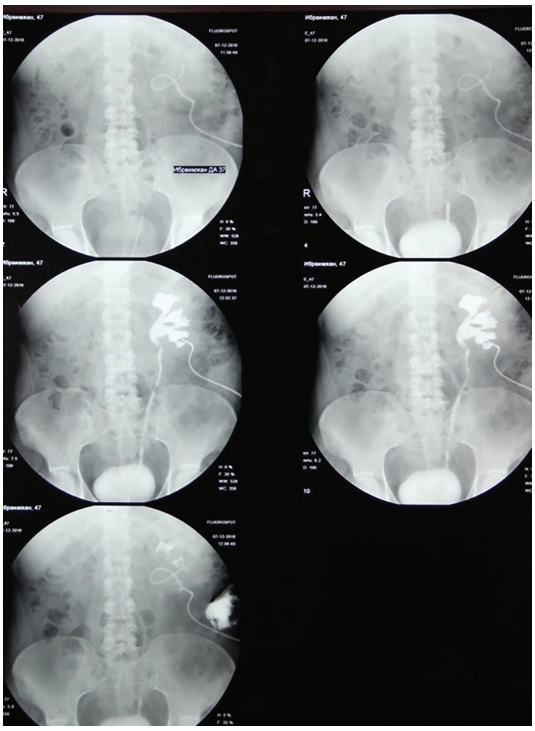


Figure 10 - Extracorporal preparation of kidney

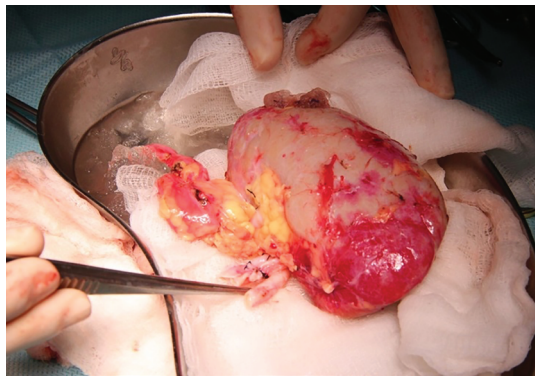
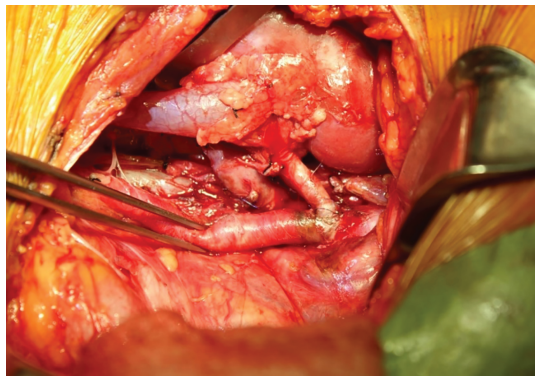


Figure 11 - Arterial and venous anastomosis formation



Results and discussion

In the early postoperative period, all patients underwent dynamic ultrasonography of the abdominal cavity and retroperitoneal space; in addition, hemodynamics parameters as well as clinical and biochemical laboratory blood parameters were monitored. Considering the specifics of the intervention, condition of the urine: gross hematuria, microhematuria, specific gravity, quantity (polyuria after kidney autotransplantation), bacterioscopy and microscopy – was of great importance.

The results of the surgical interventions performed were studied in the long-term period from 4.5 to 5 years. In addition to the general condition of patients using laboratory and instrumental methods of follow up, the condition and function of the kidneys as well as the passage of urine in patients after appendicoureteroplasty were studied.

The early postoperative period in three patients proceeded with no incidents and did not require serious additional studies. Only in one patient after appendicoureteroplasty dynamic

intestinal obstruction developed on the third day post-op, which was resolved conservatively.

In the late postoperative period, during the first two years patients underwent dynamic monitoring of the urinary functions of operated organs every 6 months and annually in subsequent years. The condition of the patients was satisfactory. Kidney function and urine passage through the newly formed ureters were without features.

The problem of ureteroplasty remains controversial nowadays due to different treatment options with no clear recommendation regarding this issue. There are few articles describing surgical interventions that can treat long ureteral defects, with appendiculoplasty and kidney autotransplantation being the most effective. However, each procedure has own advantages and disadvantages, as well as risks. For example, for appendiculoplasty the appendix should reach a ureteral defect without tension of mesentery, which is not always the case. In this situation, kidney autotransplantation can be a solution since it does not require immune suppression. The disadvantage of this method is that it requires two large incisions, and there is a risk of anastamotic leakages from vessels.

In our study, we performed these two methods with two patients for each method. Results are promising, but for a better statistical analysis and more thorough follow-up we need more patients for both appendiculoplasty and kidney autotransplantation.

Conclusion

Our first results on the correction of long ureteral defects using the formation of appendicoureteroplasty may be the method of choice for this pathology. The use of the appendix on its mesentery makes it possible to replace both part of the right and pelvic sections of the left ureter and effectively restore the urodynamics of the urinary tract. The advantage of this intervention is that the risk of stricture in the area of appendicocystoanastomosis is lower due to the formation of a wide anastomosis.

Kidney autotransplantation in case of extensive strictures of the ureter requires good practical training of the surgeon and assistants, as well as inclusion in the transplant team. The advantage of this operation is that a direct antireflux ureterocystoanastomosis is applied [7]. Therefore, this intervention is a good alternative to known methods like ureterocystoanastomosis according to Boari or Psoas hitch [7].

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