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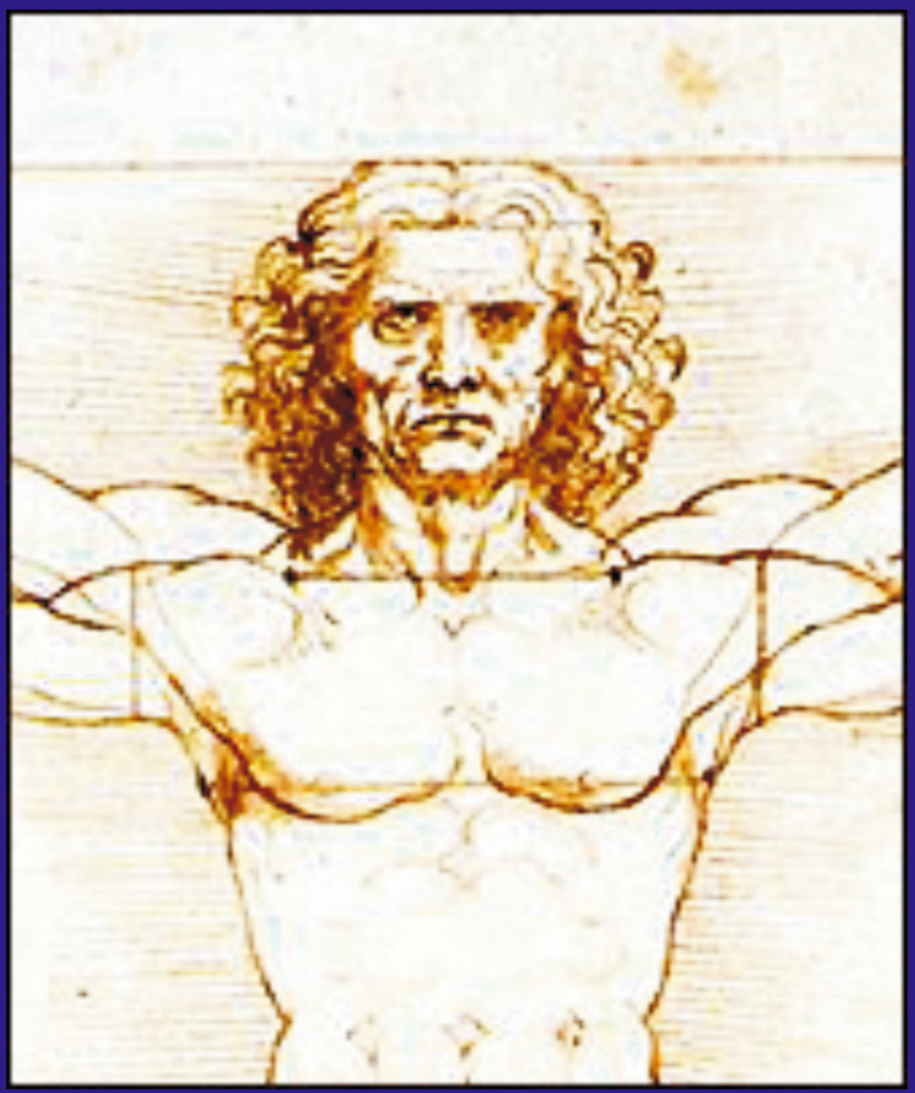

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PHYSICIAN BURNOUT LEVELS AND ASSOCIATED FACTORS IN THE COVID-19 PANDEMIC

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Abstract: **Introduction:** Burnout, characterized by emotional exhaustion, depersonalization, and low personal accomplishment, is frequently observed in physicians.

Aim: The purpose of this study was to determine burnout levels and associated factors in physicians during the pandemic.

Material and Method: This cross-sectional study was performed online with 288 physicians from various fields in Erzurum**.** Sociodemographic questions and the Maslach Burnout Inventory represented the data collection tools. The data were collected online in May and June 2021.

Statistical analysis: Descriptive statistics**,** Student's t and ANOVA tests And Multiple ordinal logistic regression analysis were used. p values < 0.05 were regarded as significant. Analysis was performed on SPSS 22.

Results: Physicians' mean emotional exhaustion, depersonalization, and personal accomplishment component scores were 20.1 ± 8.3, 6.7 ± 4.5, and 21.1 ± 4.5, respectively. Analysis showed that 49.7% of physicians exhibited moderate-high emotional exhaustion, 35.8% high-moderate depersonalization, and 69.8% signs of low personal accomplishment. Job title, regret concerning selecting the medical profession, satisfaction with the working environment, number of additional monthly out-of-hours shifts worked, regular sporting activity, and assessment of the physical conditions in the working environment emerged as factors affecting burnout components at regression analysis.

Conclusion: The participants' burnout levels were high. The planning of effective interventions addressing individual and work-related factors with a holistic approach is essential to halt this rapidly growing epidemic.

Keywords: Burnout, Physicians, COVID-19, Pandemic, Maslach Burnout Inventory.

INTRODUCTION

The concept of occupational burnout, first introduced by Freudenberg in the 1970s, has been defined as a state of exhaustion resulting from excessive demands on individuals' energy, strength, or resources (1). Maslach et al. conceptualized burnout under three dimensions (emotional exhaustion, depersonalization, and low personal accomplishment). Emotional exhaustion occurs when a worker has no more emotional resources to give to others. Depersonalization, characterized by a negative and mocking attitude, emerges in association with the exhaustion of emotional resources. The third component of the concept of burnout is that the individual develops a tendency to evaluate himself negatively in the context of his work, in other words, loss of personal accomplishment (2).

Burnout emerges as a result of work-related stress among workers with close interaction with other people and in high-intensity occupations (1). Burnout is therefore common among health sector workers, particularly physicians, and nurses (3). Prevalence figures for burnout reported among physicians vary widely, from 0% to 80.5% (4, 5).

Burnout is linked to a series of problems including organizational and personal factors (5, 6). In addition to certain demographic variables, studies have described mental fatigue and stress resulting from workload, an excessive burden of responsibility, extensive and complex medical record procedures, long and irregular working hours, compromise of work-life balance, malpractice anxiety, unsatisfactory salaries, time pressure, and high patient expectations as the principal causes of burnout (6–8).

Physician burnout must be considered due to its impacts on the health system, patient care, and doctor health (9). Research has linked physician burnout to

loss of productivity, lack of job satisfaction, and early departure from the profession (6, 9).

In addition to its deleterious effects on physician health, burnout is also an important factor requiring investigation due to its impacts on patient care and health systems. The determination of burnout levels becomes even more important in conditions involving heavy working conditions for many physicians, such as the COVID-19 pandemic.

The purpose of this study was to evaluate physician burnout levels and the direct and interactive roles of associated factors.

MATERIAL AND METHODS

The study population of this cross-sectional study consisted of physicians working in Erzurum.

The study sample was calculated for a 75% emotional burnout frequency (10), 5% error, and 95% confidence level on Epi-Info software, and we planned to contact 275 participants by applying 10% correction.

In the study, a 27-item personal information form investigating the sociodemographic characteristics of the participants and the Maslach Burnout Inventory (MBI) to measure their burnout levels were used as data collection tools. In addition to demographic questions, the personal information form consisted of questions about sports, vacation, habits, field of specialization, title, length of work in the profession, shift, thoughts about career choice, working environment, in-service training and congress activities, and academic publications.

Maslach Burnout Inventory was developed by Maslach and Jackson (2) and adapted into Turkish by Ergin (11). This Likert-type scale (1 = never, 2 = very seldom, 3 = sometimes, 4 = usually, 5 = always) consists of 22 items. Burnout is evaluated under three subdimensions; The emotional exhaustion (EE) dimension is evaluated in items 1, 2, 3, 6, 8, 13, 14, 16, and 20, depersonalization (DP) in items 5, 10, 11, 15, and 22, and personal accomplishment (PA) in items 4, 7, 9, 12, 17, 18, 19, and 21. The EE and DP dimensions consist of negative statements and the PA dimension of positive statements. High EE and DP scores and low PA scores are associated with higher levels of burnout. Scores obtained on the scale are associated with burnout at three different levels – EE, low ≤ 20, moderate 21-27, and high ≥ 28, DP - low ≤ 8, moderate 9-12, and high ≥ 13 and PA - low ≤ 23, moderate 24-27, and high ≥ 28 (12).

The study data were collected in May-June 2021.

Approval for the study was obtained from the Atatürk University Non-Interventional Clinical Research Ethical Committee. Participants completing the data collection tool sent to them electronically were regarded as consenting to take part. No personal information was collected within the scope of the study, and all data were kept secret.

Data analysis was performed on Statistics Package for Social Sciences (version 22). Categorical variables were presented as numbers and percentages, and numerical variables as mean ± standard deviation. Normality of the distribution of numerical variables was evaluated using the Kolmogorov-Smirnov test, z values calculated for skewness and kurtosis, and chart methods. Student's t-test and One-Way ANOVA, the Kruskal Wallis and Mann Whitney U tests, and the Mann Whitney U test with Bonferroni correction at posthoc analyses were employed in the analysis of continuous variables, while chi-square tests were applied in the analysis of categorical variables. Spearman's rho correlation analysis was applied to investigate relationships between continuous variables. Ordinal logistic regression analysis was applied to evaluate the independent variables affecting the probability of inclusion of participants in the EE, DP, and PA groups determined based on defined cut-off points. p values < 0.05 were regarded as significant for all analyses.

RESULTS

The mean age of the 288 physicians included in the study was 38.1 ± 8.6, and 147 (51%) were women. The physicians; mean EE, DP, and PA dimension scores were 20.1 ± 8.3, 6.7 ± 4.5, and 21.1 ± 4.5, respectively. The distribution of burnout dimensions of physicians according to cut-off points is presented in Table 1.

Male and female participants exhibited similar mean EE, DP, and PA scores (p > 0.05). Married physicians (73.3%) and those with children (63.9%) exhibited significantly lower DP scores (p = 0.030 and p = 0.012, respectively), while their PA scores were significantly higher (p = 0.029 and p = 0.002, respec-

Table 1. *Distribution of physicians' burnout dimensions by cut-off points*

Dimension	Categories		
	Low n (%)	Moderate n (%)	High n (%)
Emotional Exhaustion	145 (50.3)	88 (30.6)	55 (19.1)
Depersonalization	185 (64.2)	76 (26.4)	27 (9.4)
Personal Accomplishment	201 (69.8)	65 (22.6)	22 (7.6)

Table 2. *Distribution of some personal characteristics according to physicians' burnout dimension scores*

	n (%)	**EE** Mean ± SD / Median (Q_1-Q_3)	**DP** Mean ± SD / Median (Q_1-Q_3)	**PA** Mean ± SD / Median (Q_1-Q_3)
Gender		p = 0.474	p = 0.415	p = 0.255
Male	141 (49.0)	19.7 ± 8.7	6.4 ± 4.8	21.4 ± 4.4
Female	147 (51.0)	20.4 ± 7.9	7.0 ± 4.2	20.8 ± 4.5
Marital status		p = 0.238	**p = 0.030**	**p = 0.029**
Married	211 (73.3)	19.7 ± 8.4	6.4 ± 4.5	21.5 ± 4.4
Single/Widowed/Divorced	77 (26.7)	21.0 ± 8.0	7.7 ± 4.5	20.2 ± 4.8
Possession of children		p = 0.150	**p = 0.012**	**p = 0.002**
Yes	184 (63.9)	19.6 ± 8.0	6.2 ± 4.3	21.8 ± 4.3
No	104 (36.1)	21.0 ± 8.6	7.6 ± 4.7	20.0 ± 4.6
Monthly income		p = 0.733	p = 0.307	**p = 0.001**
5001-10.000 TL	103 (35.8)	19.9 ± 8.7	6.6 ± 4.2	19.9 ± 4.1[a, b]
10.001-15.000 TL	133 (46.2)	20.5 ± 7.9	7.1 ± 4.2	21.6 ± 4.7[a]
> 15.000 TL	52 (18.1)	19.5 ± 8.3	6.0 ± 4.4	22.5 ± 4.2[b]
Regular sporting activity		**p = 0.007**	**p = 0.001**	**p < 0.001**
Yes	45 (15.6)	16.0 (10.0-25.0)	4.0 (2.0-8.0)	25.0 (20.0-27.0)
No	243 (84.4)	21.0 (16.0-27.0)	7.0 (3.0-10.0)	21.0 (18.0-24.0)
Taking vacations		p = 0.166)	p = 0.666	p = 0.352
Every year	33 (11.5)	20.0 (13.0-25.0)	6.0 (3.0-10.0)	22.0 (18.0-25.0)
Occasionally	112 (38.9)	21.5 (16.0-27.5)	7.0 (3.0-10.0)	22.0 (18.0-25.0)
Never	143 (49.7)	18.0 (13.0-26.0)	8.0 (1.0-10.0)	20.0 (17.0-23.0)
Chronic disease		p = 0.352	p = 0.466	p = 0.255
Yes	67 (23.3)	20.9 ± 8.0	6.4 ± 4.0	21.7 ± 4.8
No	221 (76.7)	19.8 ± 8.3	6.8 ± 4.6	21.0 ± 4.4
Smoking status		p = 0.158	p = 0.260	p = 0.893
Smoker	65 (22.6)	22.0 (16.0-27.0)	7.0 (3.0-11.0)	21.0 (18.0-25.0)
Quit	36 (12.5)	23.0 (18.0-27.5)	8.0 (4.0-10.0)	20.0 (18.0-24.0)
Never smoked	187 (64.9)	19.0 (13.0-25.0)	7.0 (3.0-9.0)	21.0 (18.0-25.0)
Alcohol consumption status		p = 0.111	p = 0.288	p = 0.576
User	7 (2.4)	25.0 (18.0-35.0)	8.0 (7.0-16.0)	19.0 (16.0-25.0)
Occasional use	67 (23.3)	21.0 (16.0-27.0)	8.0 (4.0-10.0)	21.0 (19.0-25.0)
Non-user	214 (74.3)	20.0 (13.0-26.0)	6.0 (2.0-10.0)	21.0 (18.0-25.0)

[a, b, c]: Category pairs that differ significantly in terms of the relevant dependent variable at post hoc analysis.
EE: Emotional Exhaustion, DP: Depersonalization, PA: Personal Accomplishment

tively). There were significant differences between physicians' PA scores according to their income levels (p = 0.001), and PA increased with income level. Physicians who had regular sporting activity (15.6%) registered significantly lower EE and DP scores and significantly higher PA scores (p = 0.007, p = 0.001, and p < 0.001, respectively) (Table 2).

It was observed that the score distributions of the physicians for all three dimensions of burnout were similar according to the branches (p > 0.05 for all). EE and DP scores were significantly higher in physicians (51.7%) who were actively working in shifts (p < 0.001). The distribution of scores for all three dimensions of burnout differed significantly according to the physicians' regret about their choice of profession (p < 0.001 for all) (Table 3). In addition, the score distributions for all three burnout dimensions were significantly different according to their satisfaction with the working environment and physical conditions, attending various training meetings, and following academic publications (p < 0.001 for all) (Table 3).

The results of multiple rank regression analysis applied to determine the factors affecting the burnout dimensions are presented in Table 4. In the EE dimension, female gender, low income, job title, regret about the choice of profession, and satisfaction with the working environment, were found to be significantly related factors (p < 0.05 for all). On the other hand, the

Table 3. *Distributions of physicians' burnout dimension scores according to occupational and workplace environment factors*

	n (%)	**EE** Mean ± SD / Median (Q_1-Q_3)	**DP** Mean ± SD / Median (Q_1-Q_3)	**PA** Mean ± SD / Median (Q_1-Q_3)
Job title		**p < 0.001**	**p = 0.030**	**p = 0.001**
General practitioner	60 (20.8)	23.5 (15.0-30.5)[a]	7.5 (4.0-10.0)	21.0 (19.0-24.0)
Research assistant physicians	57 (19.8)	21.0 (17.0-26.0)[b]	8.0 (4.0-11.0)[a]	19.0 (17.0-22.0)[a]
Specialist physician	96 (33.4)	23.0 (16.0-27.0)[c]	7.0 (3.0-9.0)	20.0 (17.5-24.0)[b]
Academic	75 (26.0)	16.0 (10.0-20.0)[a, b, c]	5.0 (2.0-8.0)[a]	23.0 (20.0-26.0)[a, b]
Branch of specialization		p = 0.100	p = 0.440	p = 0.152
Basic	26 (9.0)	18.5 (10.5-21.3)	7.0 (2.8-10.0)	20.0 (18.0-22.3)
Internal	135 (46.9)	20.0 (15.0-25.0)	6.0 (3.0-9.0)	21.0 (18.0-25.0)
Surgical	67 (23.3)	22.0 (16.0-26.0)	8.0 (2.0-11.0)	22.0 (18.0-25.0)
Out-of-hours shifts		**p < 0.001**	**p < 0.001**	p = 0.263
Yes	149 (51.7)	22.0 ± 8.0	7.7 ± 4.6	20.9 ± 4.7
No	139 (48.3)	18.1 ± 8.1	5.7 ± 4.1	21.4 ± 4.2
Regret about choice of profession		**p < 0.001**	**p < 0.001**	**p < 0.001**
No	90 (31.3)	14.5 (9.0-20.0)[a, b]	4.0 (2.0-8.0)[a]	23.0 (20.0-26.0)[a, b]
Sometimes	128 (44.4)	21.0 (16.0-25.5)[a, c]	7.0 (4.0-9.0)	21.0 (18.0-24.0)[a]
Frequently	70 (24.3)	27.0 (22.0-32.0)[b, c]	9.0 (4.0-11.0)[a]	19.0 (16.0-22.0)[b]
Satisfaction (with working environment)		**p < 0.001**	**p < 0.001**	**p < 0.001**
Yes	78 (27.1)	13.0 (8.0-18.0)[a, b]	4.0 (2.0-8.0)[a, b]	23.0 (20.0-26.0)[a, b]
Slightly	150 (52.1)	23.0 (18.0-27.0)[a]	7.0 (4.0-10.0)[a]	20.0 (17.0-23.0)[a]
No	60 (20.8)	24.5 (20.5-32.5)[b]	8.0 (4.0-10.5)[b]	20.0 (18.0-22.5)[b]
Evaluation of physical working conditions		**p < 0.001**	**p < 0.001**	**p < 0.001**
Adequate	81 (28.1)	16.0 (8.0-23.0)[a, b]	4.0 (2.0-7.0)[a, b]	23.0 (20.0-26.0)[a]
Slightly adequate	146 (50.7)	20.0 (16.0-26.0)[a, c]	7.5 (4.0-10.0)[a]	20.5 (18.0-24.0)
Inadequate	61 (21.2)	25.0 (20.0-30.0)[b, c]	8.0 (5.0-12.0)[b]	19.0 (17.0-23.0)[b]
Participation in training sessions, seminars, and congresses		**p < 0.001**	**p = 0.023**	**p < 0.001**
Yes	140 (48.6)	18.0 (12.5-32.5)	6.1 ± 4.3	22.0 (19.0-28.0)
No	148 (51.4)	23.0 (16.0-35.0)	7.3 ± 4.6	20.0 (17.0-29.0)
Reading academic publications		**p < 0.001**	**p < 0.001**	**p < 0.001**
Yes	131 (45.5)	18.0 (11.0-30.0)	5.0 (2.0-13.0)	22.0 (19.0-30.0)
No	157 (54.5)	23.0 (18.0-35.0)	8.0 (5.0-16.0)	20.0 (17.0-27.0)

[a, b, c]: Refers to category pairs that differ significantly in terms of the relevant dependent variable at post hoc analyses.
EE: Emotional Exhaustion, DP: Depersonalization, PA: Personal Accomplishment

number of non-working shifts, regular sporting activity, and regret about profession choice were factors related to the DP dimension. Regular sporting activity, regret about the choice of profession, and physical working conditions were significantly associated with the ranking categories of the PA dimension ($p < 0.05$ for all).

DISCUSSION

Burnout is a cognitive process emerging from the interaction of personal and work-related factors. This study produced a general framework in terms of burnout levels among physicians and related factors during the COVID-19 pandemic, which involved difficult working conditions for many physicians. The study also yielded results concerning the interactive role of factors associated with burnout.

Moderate-high EE was observed in almost half the physicians in this study. Moderate-high DP was present in one-third of the physicians, and moderate-low PA levels in more than two-thirds. Our findings generally show high levels of burnout in physicians working in our region. High prevalences of burnout are reported for physicians in the majority of studies, although

Table 4. *Results of multiple ordinal logistic regression analysis evaluating factors determining the probability of physicians being in the different burnout dimension categories*

Dimensions	Variables	Categories	Estimate	SE	OR	CI 95% for OR		Wald	*p*
						Lower	Upper		
EE	Gender	Female Male	0.542	0,274	1.719 1	1.005	2.942	3.913	**0.048**
	Regular sporting activity	No Yes	0.263	0.432	1.301 1	0.558	3.034	0.369	0.543
	Monthly income	5000-10,000 TL 10,001-15,000 TL ≥ 15,001 TL	-1.312 -0.605	0.428 0.404	0.269 0.546 1	0.116 0.247	0.623 1.205	9.388 2.245	**0.002** 0.134
	Out-of-hours shifts	No Yes	-0.522	0.304	0.593 1	0.327	1.077	2.947	0.086
	Job title	General practitioner Research assistant physician Specialist Academic	2.066 1.292 1.043	0.503 0.516 0.42	7.893 3.640 2.838 1	2.945 1.324 1.246	21.155 10.008 6.464	16.899 6.277 6.163	**< 0.001** **0.012** **0.013**
	Regret about choice of profession	No Sometimes Frequently	-1.936 -1.233	0.407 0.316	0.144 0.291 1	0.065 0.157	0.320 0.541	22.588 15.177	**< 0.001** **< 0.001**
	Satisfaction	Yes Some No	-2.49 -0.765	0.491 0.327	0.083 0.465 1	0.032 0.245	0.217 0.883	25.692 5.461	**< 0.001** **0.019**
	Reading academic publications	No Yes	0.355	0.334	1.426 1	0.741	2.745	1.129	0.288

Model fitting: $\chi^2 = 136.605$, $p < 0.001$; Cox&Snell R^2: 0.378, Nagelkerke R^2: 0.434

DP	Number of out-of-hours shifts		0.228	0.074	1.256	1.086	1.452	9.38	**0.002**
	Marital status	Single Widowed / Divorced Married	0.894 0.986	0.603 1.12	2.445 2.680 1	0.750 0.298	7.972 24.076	2.199 0.775	0.138 0.379
	Children	No Yes	-0.713	0.588	0.490 1	0.155	1.552	1.475	0.225
	Regular sporting activity	No Yes	1.891	0.923	6.626 1	1.085	40.451	4.202	**0.040**
	Job title	General practitioner Research assistant physician Specialist Academic	1.333 0.164 -0.35	0.779 0.687 0.623	3.792 1.178 0.705 1	0.824 0.307 0.208	17.459 4.529 2.389	2.924 0.057 0.315	0.087 0.811 0.575
	Regret about choice of profession	No Sometimes Frequently	-0.608 -1.614	0.56 0.481	0.544 0.199 1	0.182 0.078	1.632 0.511	1.182 11.261	0.277 **0.001**
	Evaluation of physical conditions	Adequate Slightly adequate Inadequate	-0.129 0.668	0.518 0.568	0.879 1.950 1	0.318 0.641	2.426 5.937	0.062 1.382	0.803 0.240

Model fitting: $\chi^2 = 44.251$, $p < 0.001$; Cox&Snell R^2: 0.266, Nagelkerke R^2: 0.313

PA	Age		-0.044	0.052	0.957	0.864	1.060	0.713	0.398
	Length of time in the profession		0.061	0.052	1.063	0.960	1.177	1.383	0.240
	Marital status	Single Widowed / Divorced Married	-0.718 0.569	0.414 0.635	0.488 1.766 1	0.217 0.509	1.098 6.132	3.009 0.802	0.083 0.370
	Monthly income	5000-10,000 TL 10,001-15,000 TL ≥ 15001 TL	-0.811 0.208	0.443 0.371	0.444 1.231 1	0.187 0.595	1.059 2.548	3.343 0.314	0.068 0.575
	Regular sporting activity	No Yes	-1.061	0.377	0.346 1	0.165	0.725	7.914	**0.005**
	Regret about choice of profession	No Sometimes Frequently	1.422 0.447	0.416 0.404	4.145 1.564 1	1.834 0.708	9.369 3.452	11.695 1.222	**0.001** 0.269
	Evaluation of physical conditions	Adequate Slightly adequate Inadequate	-0,71 -0,175	0,322 0,411	0.492 0.839 1	0.262 0.375	0.924 1.879	4.865 0.181	0.057 0.671

Model fitting: $\chi^2 = 63.172$, $p < 0.001$; *Cox&Snell* R^2: *0.197, Nagelkerke* R^2: *0.249*

EE: Emotional Exhaustion, DP: Depersonalization, PA: Personal Accomplishment,
SE: Standart error, OR: Odds Ratio, CI: Confidence Interval

the results vary widely (3, 4, 10, 13). The prevalence of general and subdimension burnout may vary in association with regional, national, and cultural effects, the health system, human factors, and patients' levels of education. The methodology and measurement tools employed may also affect the results.

Mean age was negatively correlated with DP levels in this study and positively correlated with PA. However, no association was observed between EE categories and age. On the other hand, Koşan and Özkula reported low EE scores in the young physician group and high PA scores in the elderly physicians (10, 14). In a study of 2576 Chinese physicians investigating the relationship between organizational and patient factors and burnout, Cheng et al. observed the highest level of burnout in the 35-44 age group (13). Ashraf's study of physicians from Pakistan reported similar findings (15). According to Maslach, age is the demographic variable most consistently associated with burnout, with younger physicians having a higher risk of burnout (6).

Burnout component scores in the present study were similar between male and female physicians. However, the female gender was associated with higher EE levels in the regression model (OR = 1.7). Our findings are compatible with the previous literature (6, 10, 14, 15). However, it is clear that female doctors working in departments where workplace conflicts, workload, and stress are intense, are victims of burnout at higher levels than men (9, 16, 15). The gender differences observed in terms of burnout may be attributable to the greater responsibilities assumed by women outside their working lives compared to men, and the variation in this depends on prevailing social structures.

Married physicians registered significantly lower DP scores and higher PA scores in the present study. DP scores were lower among married physicians, but the difference was not statistically significant. These results are consistent with the local literature (14). In terms of marital status, non-married participants are known to be more disposed to burnout than married physicians (6, 17). However, some studies have also reported no association between marital status and burnout (18). The inconsistency in the results for burnout may be due to factors such as the nature of society and the meaning that individuals attach to the institution of marriage.

Physicians with children in this study registered lower DP scores and significantly higher PA scores. EE scores were lower among physicians with children, although the difference compared to those without children was not statistically significant. In a study of 324 general practitioners performed in 2019, Uyar et al. also reported significantly lower DP scores among participants with children (19). However, other studies have linked having children to high burnout levels. In their study of 1811 Chinese neurologists, Tian et al. reported a lower risk of burnout among participants with no children (17). Having children can sometimes affect burnout levels due to the psychological support it provides in terms of commitment to life and sometimes due to the various responsibilities it imposes on parents.

PA scores in the present study were significantly higher in the high-income physician group, and PA scores were correlated with income. Unsatisfactory physician salaries are regarded as one of the determinants of work-related stress factors and thus, burnout (6, 7). Although some studies have linked low wages to high burnout levels (13, 15), others have found no link between pay and burnout (17). It appears that physicians' satisfaction with their pay varies between countries and exhibits show differing relationships with burnout levels.

EE and DP scores were lower, while PA scores were higher, among physicians who engaged in regular sporting activity in this study. Similar findings have been reported in other studies from our region (10, 20). Regular sporting activity may be a means of coping with stress and preventing burnout.

No relationship was found in the present study between burnout and taking vacations, the presence of chronic disease, smoking, or alcohol use. However, Koşan reported a higher risk of burnout among physicians who did not take vacations and those who smoked (10). Burnout may increase the prevalence of alcohol use among troubled physicians (21–23).

Significant differences were observed in this study in burnout component scores depending on physicians' job titles. Being on the lower rungs of the career ladder appears to be associated with higher burnout levels. Being a general practitioner was found to be a significant predictor of being in a higher EE category compared to being an academic (OR = 7.9). Other risk factors increasing EE levels compared to academics were being a research assistant physician (OR = 3.6) or a specialist (OR = 2.8). Our findings are compatible with other studies from our region (10). In Dyrbye et al.'s study of 3574 general practitioners evaluating the factors associated with burnout symptoms and regret over career choice, burnout was reported in almost half of the participants (21). However, some studies have reported a low prevalence of burnout among general practitioners (3). The differences in burnout figures in career terms may derive from countries' different health systems.

Physicians who worked out-of-hours shifts registered significantly higher EE and DP scores in this study. A significant correlation was observed between the number of monthly out-of-hours shifts worked and component scores. Monthly out-of-hours shift numbers also emerged as an independent variable determining DP levels (OR = 1.2). Koşan also noted a high prevalence of burnout among physicians with extra shift duties and working more than six of these a month (10). Özkula reported significantly lower EE and DP scores among physicians not working out-of-hours shifts but observed no variation in terms of the number of monthly out-of-hours shifts worked (14). There are results in the literature that support our findings (24). Intensive working hours also involving night shifts may exacerbate burnout levels due to loss of concentration, risk of error, and possibly also an increase in anxiety levels.

Physicians who frequently experienced regret over their choice of career exhibited the lowest EE and DP scores and the lowest PA scores in this study. Physicians with no regrets concerning their choice of profession have a much lower likelihood of low EE levels. However, occasional feelings of regret over career choice appear to be significantly associated with the likelihood of being in the low DP category. Similar findings have also been reported in previous studies (17, 21).

In addition to personal factors, environmental factors are also associated with burnout (9, 23). In the present study, physicians who were not satisfied with their working environment in general and found their physical conditions inadequate registered significantly higher EE and DP scores, and significantly lower PS scores. However, the likelihood of being in the higher DP category was significantly lower among physicians who were satisfied or slightly satisfied with their working environment. Our findings are consistent with those of Koşan (10). The positive effects of physician- and family-friendly institutional environments on physician well-being and burnout levels are important issues emphasized in the literature (25).

EE and DP scores were significantly lower, while PA scores were significantly higher, among physicians who had taken part in such activities as training sessions, seminars, and congresses in the previous year and who read academic publications in their fields. In contrast, Cheng reported that regular clinical gatherings adversely impacted physicians' burnout levels (13). It appears that physicians regard occasional training activities as an opportunity to socialize and get away from the work environment and that these can thus positively affect burnout levels.

CONCLUSIONS

This study identified significant relationships between burnout levels and personal and work-related factors. Burnout is damaging for physicians, patients, and applications performed. In conclusion, burnout is an important condition that must be carefully evaluated from all dimensions, and holistic approaches addressing individual and organizational factors are needed to combat it.

There are several limitations to this study. In particular, problems deriving from the study's cross-sectional

methodology need to be considered in terms of determining causality. This study focused more on individual determinants of burnout, and further studies are now needed to identify potential organizational and work environment-related determinants. In addition, the fact that the study data were collected online may have limited the representation capacity of the study population.

Study Information

Department of the study: Atatürk University Faculty of Medicine, Department of Public Health

Working place: Erzurum/Turkey

Abbreviations

DP — Depersonalization
EE — Emotional exhaustion
MBI — Maslach Burnout Inventory
PA — Personal accomplishment

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Sinan Yılmaz: Planning, Data collection, Statistical analysis, Article writing, Reduction, Editing; **Zahide Koşan:** Data collection, Article writing, Reduction, Editing; **Ezel Bilge Yerli:** Data collection, Article writing, Reduction, Editing;**Esra Çınar Tanrıverdi:** Data collection, Article writing, Reduction, Editing; **Sibel İba Yılmaz:** Data collection, Article writing, Reduction, Editing.

Sažetak

NIVOI BURNOUT SINDROMA I POVEZANI FAKTORI KOD LEKARA TOKOM PANDEMIJE KOVID-19

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Uvod: Sagorevanje na radu (burnout) koje karakteriše emocionalna iscrpljenost, depersonalizacija i niska lična dostignuća, često se primećuje kod lekara.

Cilj: Svrha ove studije bila je da se utvrdi nivo sagorevanja i povezani faktori kod lekara tokom pandemije.

Materijal i metode: Ova studija preseka je sprovedena onlajn sa 288 lekara iz različitih oblasti u Erzurumu. Sociodemografska pitanja i Maslaš upitnik za procenu sindroma sagorevanja na poslu su predstavljali alate za prikupljanje podataka. Podaci su prikupljeni onlajn u maju i junu 2021.

Statistička analiza: korišćena je deskriptivna statistika, Student t i ANOVA testovi i višestruka ordinalna logistička regresiona analiza. p vrednosti < 0,05 smatrane su značajnim. Analiza je obavljena na SPSS 22.

Rezultati: Prosečni rezultati emocionalne iscrpljenosti, depersonalizacije i ličnog postignuća lekara bili su 20,1 ± 8,3, 6,7 ± 4,5 i 21,1 ± 4,5, respektivno. Analiza je pokazala da je 49,7% lekara ispoljilo umereno-visoku emocionalnu iscrpljenost, 35,8% visoko umerenu depersonalizaciju, a 69,8% znake niskog ličnog postignuća. Titula, žaljenje zbog izbora medicinske profesije, zadovoljstvo radnim okruženjem, broj dodatnih mesečnih radnih smena van radnog vremena, redovna sportska aktivnost i procena fizičkih uslova u radnoj sredini pojavili su se kao faktori koji utiču na sagorevanje.

Zaključak: Nivoi sagorevanja učesnika su bili visoki. Planiranje efikasnih intervencija koje se bave individualnim faktorima i faktorima u vezi sa poslom sa holističkim pristupom je od suštinskog značaja za zaustavljanje ove brzo rastuće epidemije.

Ključne reči: Burnout, Lekari, COVID-19, Pandemija, Maslaš upitnik za procenu sindroma sagorevanja.

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Original article

EARLY DETECTION OF ACUTE KIDNEY INJURY IN PRETERM NEWBORNS WITH PERINATAL ASPHYXIA USING SERUM CYSTATIN

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Abstract: **Introduction:** The diagnosis of acute kidney injury (AKI) in preterm newborns with perinatal asphyxia based on increased serum creatinine (sCr) value and oliguria/anuria is usually delayed. The **Aim** of this paper is to evaluate serum cystatin C as an early predictor of AKI.

Materials and methods:The study included 42 preterm newborns (24-37 weeks) with perinatal asphyxia (Apgar score (AS) ≤ 3 at 5 minutes of life or blood pH on admission ≤ 7.00). The sCr and sCys-C levels were measured on the 1st, 3rd, and 7th day of life. According to KDIGO criteria, the newborns were classified into groups, and sCr and sCys-C values were compared.

Results: The mean gestational age was 29.9 ± 3.0 weeks. AKI was diagnosed in 62.8% of patients. Of these patients, 81.5% belonged to AKI 1 group, and 18.5% to AKI 2 group. No newborns had the criteria for AKI 3. On day 7 the mean sCr values were significantly higher in AKI (65.4 ± 21.8) compared with the non-AKI group (168.4 ± 38.2) ($p < 0.001$), but not on day 1 and 3 ($p = 0.322$, 0.012, respectively). The sCys-C values were significantly higher in the AKI group on day 3 (AKI vs. non-AKI group, 0.69 ± 0.22 vs. 1.22 ± 0.20; $p < 0.001$) and day 7 (AKI vs. non-AKI group, 0.62 ± 0.41 vs. 1.68 ± 0.20; $p < 0.001$). The sCys-C was also an earlier marker of a more severe stage of AKI than sCr.

Conclusion: The sCys-C was elevated earlier than sCr, making it a valuable diagnostic tool for AKI in preterm newborns.

Keywords: preterm newborn, perinatal asphyxia, acute kidney injury, biomarkers, cystatin C.

INTRODUCTION

The improvement in the treatment of preterm newborns significantly raised their survival rate, but the residual morbidity and mortality are still very high. Various pathological conditions caused by perinatal asphyxia are called Oxygen Radical Diseases of Prematurity (ORDP) (1). One of the most common conditions in this category is acute kidney injury (AKI) of the newborn. There are various clinical criteria for the diagnosis and classifying of AKI, including the RIFLE (2), AKI Network (AKIN) (3), and Kidney Disease Improving Global Outcomes (KDIGO) (4). RIFLE classifies AKI based on the elevation of sCr value in relation to the basal value and reduction of diuresis in 3 stages (Risk, Injury, Filure) and two clinical outcomes (Loss of kidney function, End-stage renal disease) (2). Some studies indicated deficiencies in RIFLE criteria. They showed that even a slight increase (0.3-0.5 mg/dl) sCr increased mortality three times, while an increase higher than 0.5 mg/dl increased mortality up to eighteen times (3). Therefore, the working group of nephrologists and intensivists under the name Acute Kidney Injury Network (AKIN) proposed its definition of AKI (3). Significant changes made by the AKIN system concerning the RIFLE criteria are: a) the interval for the first assessment of any AKI stage is 48 hours (7 days in the RIFLE system); b) stage 1 is extended to sCr value 0.3 mg/dl, and c) patients treated with any methods of renal replacement therapy are classified in stage 3 regardless of sCr values or diuresis (3). The introduction of another classification system complicated the diagnosis, grading, prevention, and treatment

Table 1. *Neonatal AKI staging – KDIGO 2012 (4)*

Stage	SCr (mg/dl)	Urine output (ml/kg/h)
0	No change in SCr or rise < 0.3 mg/dl	≥ 0.5 mL/kg/h
1	S Cr rise ≥ 0.3 mg/dl within 48 h or SCr rise ≥ 1.5-1.9×reference SCr	< 0.5 mL/kg/h for 6-12
2	SCr rise ≥ 2.0-2.9×reference SCr	< 0.5 mL/kg/h for ≥ 12h
3	SCr rise ≥ 3×reference SCr orSCr ≥ 2.5 mg/dl	< 0.3 mL/kg/h for ≥ 24h or anuria for ≥ 12h

Scr- serum creatinine

of AKI, especially in the pediatric population. To find a compromise and reconcile the differences between AKIN and RIFLE criteria, a global organization developing and implementing evidence-based clinical practice guidelines in kidney diseases – KDIGO, introduced a unique definition and grading of AKI (Table 1). Still, all these classification systems are based on the values of serum creatinine and/or urine output. In the first days of life, the usefulness of these parameters is limited by the influence of maternal sCr level, developing renal physiology, and unreliable assessment of diuresis. On the other hand, sCr and diuresis do not provide any information about the site of kidney disease. There is also a practice of following diuresis without other parameters of renal function, which can be dangerously misleading in identifying patients with a neo-oliguric type of AKI (5). This makes sCr and diuresis insufficient in the diagnosis of AKI in newborns. There is a constant search for biological markers that can be used in diagnosing AKI, especially in its early phase. Among the first biomarkers discovered in urine was cystatin-C, a cysteine protease inhibitor that is synthesized and released into the blood at an almost constant rate by all nucleated cells. It is freely filtered in the glomeruli, completely reabsorbed in the proximal, and not secreted in the distal tubule, which makes it a promising endogenous biomarker of glomerular filtration (GF) (6).

In this study, we wanted to estimate if serum cystatin C (sCys-C) can be used as a diagnostic tool for AKI in preterm newborns.

MATERIAL AND METHODS

This was a prospective study of premature asphyxiated newborns 24-32 weeks of gestation admitted to the Neonatal Intensive Care Unit University Medical Center Sarajevo between October 2020 and October 2022. This study was conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, October 2013) and the General Data Protection Regulation (GDPR). Informed parenteral consent was given for all participating newborns.

The indicator of perinatal asphyxia was AS ≤ 3 in the fifth minute of life or blood pH on admission ≤ 7.00. The premature newborns included in the study also met the following criteria: (1) absence of congenital anomaly of the kidneys and urinary tract; (2) absence of a congenital anomaly of the heart or large blood vessels; (3) absence of any genetic disease, metabolic disease or any other anomaly. AKI was diagnosed based on an increase in the value of serum creatinine compared to the basal value and urine output (Table 1.). The lowest previous value of sCr served as its basal value.

The sCr and sCys-C levels were measured on the 1st, 3rd, and 7th day of life (the date of birth was equal to postnatal day 1). SCr was determined using the Jaffe kinetic spectrophotometric method. The sCys-C level was measured with the ELISA assay and the reference interval was calculated nonparametrically to be 0.53-0.95 mg/L. Diuresis was measured in all included preterm newborns. They did not receive diuretics in the first 48 hours of life.

According to KDIGO criteria, the newborns were classified into two groups AKI or non-AKI group. That was the primary division, and then the AKI group, according to the standards of the KDIGO classification, was divided into subgroups (AKI 1 or AKI 2). In our study, there were no registered AKI 3 cases.

The laboratory tests were blinded to the clinical outcomes.

Statistical analysis was performed using IBM SPSS statistics version 20.0 and P values less than 0.001 were considered significant. The groups were compared using the Student *t*-test and Mann–Whitney test. Multivariate logistic regression was used to assess the development of AKI.

RESULTS

All newborns were divided into two groups: the AKI group, a larger group of newborns who developed AKI 27 (64.3%), and the non-AKI group, a smaller group of 15 (35.7%) newborns without AKI. There were no significant differences between AKI and non-AKI, as well as AKI 1 and AKI 2 groups regarding sex and gestation age (GA). Values of pH in the AKI and AKI 2 groups were lower than in the non-AKI and

Table 2. *The basic clinical features and values of sCr and sCys-C of included premature newborns*

	Total (n = 42) n (%)	Non- AKI (n = 15) n (%)	AKI (n = 27) n (%)	p	AKI 1 (n = 22) n (%)	AKI 2 (n = 5) n (%)	p
Sex (male)	23 (54.8)	13 (56.52)	10 (43.48)	0.144	14 (51.85)	13(48.1 5)	0.132
GA, wk (mean, ± SD)	28.8 ± 4.0	29.4 ± 2.4	28.5 ± 3.0	0.181	28.1 ± 3.2	29.1 ± 3.5	0.024
Inotropes	30 (71.43)	6 (40)	24 (88.89)	< 0.001	20 (90,91)	4 (80)	0.014
Blood pH on admission	6.95 ± 0.4	7.0 ± 0.5	6.84 ± 0.3	0.102	6.92 ± 0.3	6.97 ± 0.2	0.123
sCr Day 1	108.4 ± 21.2	88.7 ± 16.2	115.4 ± 28.2	0.322	98.4 ± 21.2	105.7 ± 26.2	0.422
sCr Day 3	138.4 ± 41.2	80.4 ± 30.2	128.4 ± 38.2	0.012	140.4 ± 31.2	178.4 ± 41.2	0.002
sCr Day 7	150.4 ± 36.8	65.4 ± 21.8	168.4 ± 38.2	< 0.001	154.0 ± 33.9	218.4 ± 36.3	< 0.001
sCys-C Day 1	0.79 ± 0.85	0.73 ± 0.35	0.81 ± 0.20	0.355	0.80 ± 0.43	0.83 ± 0.13	0.145
sCys-C Day 3	0.85 ± 0.25	0.69 ± 0.22	1,22 ± 0.20	< 0.001	1,01 ± 0.26	1.38 ± 0.48	0.001
sCys-C Day 7	0.88 ± 0.	0.62 ± 0.41	1.68 ± 0.20	< 0.001	1.81 ± 0.55	1.61 ± 0.32	0.001

GA, gestational age; nCPAP, sCr, serum creatinine, sCys-C, serum cystatin C
P < 0.001 is considered statistically significant

AKI 1 groups, respectively, but the difference was not statistically significant.

AKI was associated with significantly higher mortality. 5 of 27 newborns (18.51%) with AKI died versus 1 of 15 (6.67%) without AKI (odds ratio (OR) 6.97, 95% confidence interval (CI), 4.3–15.0; P < 0.001]. Only one newborn of the AKI 2 group survived.

On days 1 and 3, the mean sCr values were not significantly higher in AKI compared to non AKI group (p = 0.322, 0.012, respectively). The mean sCr values became significantly higher in the AKI group on day 7 (P <0.001). When comparing AKI 1 and AKI 2 groups, the difference in mean sCr values was statistically significant only on day 7.

The mean sCys - C in the AKI group was not significantly higher compared to non AKI group only on day 1 (p = 0.355). On days 3 and 7, the mean sCys-C values were significantly higher in AKI compared to non AKI group (P <0.001). The difference in sCys-C values between AKI 1 and AKI 2 was not significant only on day 1 (p = 0.145). On days 3 and 7, the mean sCys-C values were significantly higher in AKI 2 compared to AKI 1 group (P <0.001) (Table 2.).

DISCUSSION

AKI in preterm newborns is a severe clinical syndrome with a high mortality rate (7). Both, serum creatinine and diuresis are late consequences of kidney injury and not a marker of the injury itself. The physiological characteristics of the preterm newborn make the interpretation of these parameters challenging (8,9). The general belief is that newborns have non-oliguric AKI (10), but this may be misleading in the absence of knowledge about the normal diuresis of the newborn, which changes with tubule maturation (10).

Neonatal AKI has long been considered a reversible syndrome. But recently, the long-term prognosis of AKI has been studied more seriously. In one study, out of 126 neonates who were followed up to three years after an episode of AKI, 10% developed a chronic kidney disease (CKD), which was directly correlated with AKI (11). One study evaluated the long-term AKI consequences in the newborn population (12), but generally, the evaluation studies of CKD after an AKI episode are missing. The early diagnosis of AKI in preterm newborns is crucial for early initiation of therapy, starting diuretic therapy in oliguric patients, and adjusting medication doses and fluid intake to sustain or achieve the homeostatic balance. That way, we could minimize the long-term consequences of AKI (13,14). With that goal, the difficulties with timely diagnosis of AKI are trying to be solved with new biomarkers of AKI. They are expected to have a prominent importance in newborns. Recent research efforts have led to the development of prospective studies of biomarkers for the early detection of AKI, but the number of studies on newborns is still limited (15,16,17). Our study showed that the diagnosis of AKI based on conventional biomarkers is delayed by 48-72 hours compared with sCys.C. Our ability to diagnose AKI early may improve more by combining several biomarkers, which would improve therapeutic and preventive measures and AKI prognosis.

CONCLUSION

The sCysC level was found to have a statistically significant association with the development of AKI in

preterm neonates with perinatal asphyxia, and it elevated earlier than sCr. This makes it a good predictive marker for AKI in preterm newborns. New biomarkers of neonatal AKI need to be introduced into the standard diagnostic protocol in pediatric intensive care units and neonatology wards.

Abbreviations

AKI — acute kidney injury
AKIN — Acute Kidney Injury Network
GA — gestational age
KDIGO — Kidney Disease Improving Global Outcomes
nCPAP — nasal continuous airway pressure
RIFLE — Risk Injury and Failure Classification
sCr — serum creatinine
sCys-C — serum cystatin C

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Sažetak

RANO OTKRIVANJE AKUTNOG OŠTEĆENJA BUBREGA KOD NEDONOŠČADI S PERINATALNOM ASFIKSIJOM PRIMENOM SERUMSKOG CISTATINA

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Uvod: Dijagnoza akutnog oštećenja bubrega (AOB) kod nedonoščadi s perinatalnom asfiksijom na osnovu povećane vrednosti serumskog kreatinina (sCr) i oligurije/anurije obično se kasni. **Cilj** ovog rada je procena vrednosti serumskog cistatina C kao ranog prediktora AOB.

Materijali i metode: Studija je obuhvatila 42 nedonoščadi (24-37 sedmica) sa perinatalnom asfiksijom (Apgar skor (AS) ≤ 3 na 5 minuta života ili pH krvi pri prijemu ≤ 7,00). Nivoi sCr i sCys-C mereni su 1, 3 i 7 dana života. Prema KDIGO kriterijumima novorođenčad su klasifikovana u grupe i upoređene su vrednosti sCr i sCys-C.

Rezultati: Prosečna gestacijska dob bila je 29,9 ± 3,0 sedmice. AOB je dijagnostikovan kod 62,8 % pacijenata. Od ovih pacijenata, 81,5% je pripadalo grupi AOB 1, a 18,5% grupi AOB 2. Nijedno novorođenče nije imalo kriterijume za AOB 3. Sedmog dana srednje vrednosti sCr bile su značajno veće kod AOB (65,4 ± 21,8) u poređenju sa ne-AOB grupom (168,4 ± 38,2) ($p < 0,001$), ali ne 1. i 3. dan ($p = 0.322$, 0.012, respektivno). Vrednosti sCys-C bile su značajno veće u AOB grupi 3. dana (AOB naspram ne-AKI grupe, 0,69 ± 0,22 naspram 1,22 ± 0,20; $p < 0,001$) i 7. dana (AOB naspram grupe bez AOB, 0,62 ± 0,41 vs. 1,68 ± 0,20; $p < 0,001$). SCys-C je takođe bio raniji marker ozbiljnijeg stadijuma AOB od sCr.

Zaključak: SCys-C je povišen ranije od sCr, što ga čini vrednim dijagnostičkim sredstvom za dijagnostikovanje AOB kod nedonoščadi.

Ključne reči: nedonošče, perinatalna asfiksija, akutno oštećenje bubrega, biomarkeri, cistatin C.

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DIFFERENCES BETWEEN BIOCHEMICAL, HEMATOLOGICAL AND COAGULATION PARAMETERS AMONG PATIENTS WITH MILD AND SEVERE COVID-19

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Abstract: **Introduction**: COVID-19 is an infectious disease caused by the severe acute respiratory syndrom coronavirus 2 and causes a series of respiratory symptoms. Considering the appearance and development of symptoms, the course of COVID-19 can go from mild to severe. Depending on the course of COVID-19, the laboratory parameters change a lot, trying to defend the organism against the foreign pathogen and all the changes it causes.Therefore, the aim of this study is to observe the differences between biochemical, hematological and coagulation parameters depending on the disease stage of COVID-19 patients. **Material and methods**: We conducted cross-sectional study which included 160 COVID-19 patients from Sarajevo, Bosnia and Herzegovina. Biochemical, hematological and coagulation analyzes were performed. **Results:** COVID-19 patients with a severe clinical course have higher average values of fibrinogen (6.53 ± 4.47, $p < 0.001$), D-dimer (6.89 ± 7.81, $p < 0.001$), APTT (32.05 ± 5.96, $p = 0.002$), eosinophil (0.66 ± 0.09, $p = 0.002$) and CRP (93.42 ± 75.86, $p = 0.023$), and lower values of lymphocytes (1.04 ± 0.98, $p < 0.001$), monocytes (0.45 ± 0.3, $p < 0.001$), compared to COVID-19 patients with a mild clinical course. COVID-19 patients with a severe clinical course had higher average values of neutrophils (10.12 ± 5.80, $p = 0.002$) and lower values of reactive lymphocytes (0.02 ± 0.03, $p < 0.001$) compared to COVID-19 patients with a mild clinical course. **Conclusion**: Biochemical, hematological and coagulation parameters can be a sensitive and specific biomarker for distinction of mild and severe COVID-19.

Keywords: COVID-19, laboratory parameters, clinical course.

INTRODUCTION

COVID-19 is an infectious disease caused by the severe acute respiratory syndrom coronavirus 2 and causes a series of respiratory symptoms. All symptoms, depending on the severity of the disease, are accompanied by different reactions of our body (1). Increased coagulability is one of the basic mechanisms of the disease and the main cause of death of severe COVID-19 patients. Severe COVID-19 patients may have prothrombotic complications of the disease, such as venous thrombosis and pulmonary embolism. A more frequent occurrence of cardiovascular and thromboembolic complications and death has also been proven (2). Standard diagnostics of the SARS-CoV-2 virus is based on the detection of its nucleic acid by the rt-PCR method or the detection of its spike glycoprotein by various rapid tests (3). The development of the disease, a physician can monitor the course of the disease with various general and specific laboratory tests and imaging techniques. Basic laboratory tests that can be used

to monitor the course of the disease are complete blood count, C-reactive protein and D-dimer, which can be used to identify the development of secondary, bacterial infection and thrombosis (4).

During the automatic processing of samples from patients with the confirmed presence of the SARS CoV-2 virus, the concentration of C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), liver enzymes, total bilirubin (BIL), creatinine, high-sensitivity cardiac troponin T (hs-TnT) is mostly increasing. Previous research has observed a significant higher value of CRP in COVID-19. A steady increase in C-reactive protein in COVID-19 positive patients is noted during the period of hospitalization, with higher values measured in patients placed in the intensive care unit (5). Thus, this observation of its values confirms the usefulness of C-reactive protein as an early inflammatory biomarker, and studies have proven that CRP is associated with progression and predicting the severe clinical course of COVID-19.

The hematological abnormalities that most often accompany SARS CoV-2 positive patients upon admission to the hospital are: lymphocytopenia, to the greatest extent, followed by thrombocytopenia and leukopenia. These hematological changes are more pronounced in patients with a severe clinical course compared to patients with a mild clinical course. One of the salient features of SARS-CoV-2 infection is lymphopenia (6). Fibrinogen and D-dimer were generally high in 80-100% of patients immediately upon admission to the hospital. In patients placed in the intensive care unit, higher D-dimer levels were recorded after admission and after 14 days of hospitalization, where its value was more than 20 times higher than in patients not placed in that unit. APTT and PT/INR were slightly high (7). Therefore, the aim of this study is to observe the differences between biochemical, hematological and coagulation parameters depending on the disease stage of COVID-19 patients.

MATERIAL AND METHODS

This cross-sectional study included 160 subjects positive for SARS CoV-2, who were divided into two groups: mild and severe COVID-19 patients. Study was conducted at the "JU Dom zdravlja KS" and at the Faculty of Health Studies, University in Sarajevo in Sarajevo, Bosnia and Herzegovina in the period from February to April in 2021. Venous blood of COVID-19 patients was used as material. Blood samples were obtained by venipuncture from in a tube with EDTA anticoagulant. Then peripheral blood smears were prepared and stained with May Grunwald Giemsa staining using the Pappenheim method. A sufficient amount of blood, 5-10 mL of blood, plasma or serum was taken to perform all required tests. Advia 2120i, Siemens hematology analyzer was used to obtain a complete and differential blood count of the patients, Dimension EXL 200, Siemens for C-reactive protein and Sysmex CA 660, Siemens for coagulation tests (APTT, INR, fibrinogen and D-dimer).The number of reactive lymphocytes was obtained by examining a peripheral blood smear from a blood sample collected from an EDTA tube.

This study was approved by Ethics Committee of "JU Dom zdravlja KS" and Ethics Committee od Faculty of Health Studies, University of Sarajevo.

The statistical analysis of the collected data were performed using the statistical package IBM Statistics SPSS version 23.0, where Microsoft Office programs were used to prepare and display the results. Data were analyzed using Mann-Whitney U test, Chi-squared test and Spearman's rank correlation coefficient. Stastictical significance was assumed at $p < 0,05$.

RESULTS

Of the total number of patients (n = 160), the number of male respondents was 89 (56%), while 71 (44%) were female, aged between 18-87 years. The group of patients with mild COVID-19 consisted of 60, while the group with severe COVID-19 consisted of 100 patients.

According to the Man-Whitney U test, a statistically significant difference in the average values of fibrinogen, D-dimer, APTT, CRP, and the average number of neutrophils, lymphocytes, monocytes, eosinophils, and reactive lymphocytes was shown. COVID-19 patients with a severe clinical course have higher average values of fibrinogen ($p < 0.001$), D-dimer ($p < 0.001$), APTT ($p = 0.002$), eosinophil ($p = 0.002$) and CRP ($p = 0.023$), and lower values of lymphocytes ($p < 0.001$), monocytes ($p < 0.001$), compared to COVID-19 patients with a mild clinical course. COVID-19 patients with a severe clinical course had higher average values of neutrophils ($p = 0.002$) and lower values of reactive lymphocytes ($p < 0.001$) compared to COVID-19 patients with a mild clinical course.

According to the Chi-squared test, an association between leukopenia, normal values of leukocytes, and leukocytosis was shown ($p = 0.027$), whereby a significant number of COVID-19 patients had leukocytosis.

According to Spearman's correlation coefficient (rho), there were numerous positive and negative correlations between the examined parameters. Some of them are expected due to the direct mutual dependence of the parameters, e.g. significant positive correlation between INR and APTT and D-dimer. The inflam-

***Table 1**. Differences in the values of hematological, coagulation, and inflammatory parameters between COVID-19 patients with a severe (n = 100) and COVID-19 patients with a mild (n = 60) clinical course*

	Patient group	Mean	Std. Deviation	Mean Rank	Sum of ranks	Mann-Whitney U	p-value
INR	Mild	1.172	0.5436	83.35	5001.00	2829.000	0.534
	Severe	1.078	0.0245	78.79	7879.00		
Fibrinogen (g/l)	Mild	4.802	1.0479	61.65	3699.00	1869.000	**< 0.001**
	Severe	6.536	4.4744	91.81	9181.00		
D-dimer (mg/l)	Mild	2.5857	2.06999	62.23	3733.50	1903.500	**< 0.001**
	Severe	6.8987	7.81699	91.47	9146.50		
APTT (sec)	Mild	29.668	5.8051	65.78	3947.00	2117.000	**0.002**
	Severe	32.054	5.9610	89.33	8933.00		
WBC ($x10^9$/l)	Mild	11.7348	6.50023	88.88	5332.50	2947.500	0.077
	Severe	10.7989	8.47225	75.48	7474.50		
Neutrophils ($x10^9$/l)	Mild	7.746	5.8171	71.68	5712.00	2118.000	**0.002**
	Severe	10.123	5.8068	95.20	7168.00		
Lymphocytes ($x10^9$/l)	Mild	1.795	3.9917	92.12	9212.00	1838000	**< 0.001**
	Severe	1.042	0.9812	61.13	3668.00		
Monocytes ($x10^9$/l)	Mild	1.7132	6.50559	98.20	9819.50	1230.500	**< 0.001**
	Severe	0.4505	0.30208	51.01	3060.50		
Eosinophils ($x10^9$/l)	Mild	0.0544	0.17793	68.68	4120.50	2290.500	**0.012**
	Severe	0.661	0.09731	87.60	8759.50		
Basophils ($x10^9$/l)	Mild	0.0573	0.05909	72.97	4378.00	2548.000	0.110
	Severe	0.1185	0.38517	85.02	8502.00		
RBC ($x10^9$/l)	Mild	4.477	0.60980	83.79	5027.50	2802.500	0.486
	Severe	4.3646	0.74618	78.53	7852.50		
Hgb (g/l)	Mild	135.663	20.4663	84.22	5053.00	2777.000	0.432
	Severe	131.846	21.1496	78.27	7827.00		
Hct (%)	Mild	40.071	6.0091	84.73	5083.50	2746.500	0.372
	Severe	38.521	6.4362	77.97	7796.50		
MCV (fl)	Mild	89.555	6.1867	84.39	5063.50	2766.500	0.411
	Severe	88.861	5.9762	78.17	7816.50		
Thrombocytes ($x10^9$)	Mild	214.92	104.698	82.00	4920.00	2910.000	0.751
	Severe	207.93	108.137	79.60	7960.00		
MPV (fl)	Mild	7.4788	1.49805	79.75	4785.00	2955.000	0.874
	Severe	7.7312	2.04058	80.95	8095.00		
CRP (mg/l)	Mild	64.278	49.9850	69.73	4148.00	2354.000	**0.023**
	Severe	93.426	75.8690	86.96	8696.00		
Reactive lymphocytes	Mild	0.1005	0.03451	125.94	7556.50	273.500	**< 0.001**
	Severe	0.0290	0.03189	53.24	5323.50		

Abbreviations: **INR** – international normalized ratio, **APTT** – activated partial thromboplastin time, **WBC** – white blood cells, **RBC** – red blood cells, **Hgb** – hemoglobin, **Hct** – hematocrit, **MCV** – mean corpuscular volume, **MPV** – mean platelet volume, **CRP** – C-reactive protein.

Table 2. *Differences between leukocyte count in mild and severe COVID-19 patients*

	Mild COVID-19 N (%)	Severe COVID-19 N (%)	Chi-squared	p-value
Leukopenia $< 4*10^9/l$	3 (1.88)	10 (6.25)	7.193	**0.027**
Normal value $4–10*10^9/l$	20 (12.5)	50 (31.25)		
Leukocytosis $> 10*10^9/l$	37 (23.13)	40 (25)		

Table 3. *Correlations between the tested parameters of the total number of patients (n = 160)*

	INR	Fibrinogen (g/l)	D-dimer (mg/l)	APTT (sec)	CRP (mg/l)
Fibrinogen (g/l)	-,103 ,195				
D-dimer (mg/l)	**226**** **,004**	,076 ,338			
APTT (sec)	**,238**** **0,002**	,058 ,467	,005 ,955		
CRP (mg/l)	,078 ,327	**,247**** **,002**	,084 ,289	**,185*** **,019**	
Reactive lymphocytes	,084 ,292	**-,279**** **,000**	**-,221**** **,005**	**-,193**** **,014**	**-,253**** **,001**

Abbreviations: **INR** – international normalized ratio, **APTT** – activated partial thromboplastin time, **CRP** – C-reactive protein.

matory parameter CRP has a significant positive correlation with fibrinogen (rho = 0.247, p = 0.002) and APTT (rho = 0.185, p = 0.019). Reactive lymphocytes show significant negative correlations with fibrinogen (rho = -0.279, p < 0.001), D-dimer (rho = -0.221, p = 0.005), APTT (rho = -0.193, p = 0.014) and CRP. (rho = -0.253, p = 0.001).

DISCUSSION

In our study, we proved that the examined biochemical, hematological and coagulation parameters of COVID-19 patients affect the severity of the clinical course, and that, by monitoring the other parameters, we can assess the severity of the disease course and react therapeutically in a timely manner. Given that the total examined population (n = 160) was divided into two groups, when monitoring the parameters of these two groups and comparing the values in the group of patients with a severe and mild clinical course, significant differences were observed in the average values of fibrinogen, D-dimer, APTT -a, CRP and the average number of neutrophils, lymphocytes, monocytes, eosinophils and reactive lymphocytes. Higher average values of fibrinogen (p < 0.001), D-dimer (p < 0.001), aPTT (p = 0.002), lymphocytes (p < 0.001), monocytes (p < 0.001), eosinophils (p = 0.002) and CRP (p = 0.023) compared to COVID-19 patients with a mild clinical course. On the other hand, COVID-19 patients with a severe clinical course had lower average values of neutrophils (p = 0.002) and reactive lymphocytes (p < 0.001) compared to COVID-19 patients with a mild clinical course.

Khourssaji M et al. in their research highlighted significant changes in biochemical and hemostasis parameters in COVID-19 positive subjects. They state that at the admission of patients, an elevated level of CRP was one of the most common results, increased in as many as 100% of respondents. Long-term follow-up of these parameters revealed that CRP levels were significantly different (p < 0.05) between intensive care patients and non-intensive care patients at least 14 days after admission. A continuous increase in CRP values was even observed for ICU patients during the first two weeks. Fibrinogen and D-dimer were elevated in more than 83% (1.3 times) and 100% (2.7 times) of patients with COVID-19 at admission. In ICU patients, higher D-dimer levels after admission was recorded until the fourteenth day of hospitalization, where it was 25 times higher than in the non-ICU population (8). Guan WJ et al. showed that CRP was elevated in 56.4% of patients with mild and in 81.5% of COVID patients with severe disease (9). Elevated values of APTT and fibrinogen were associated with mortality in patients

with moderately severe COVID-19 showed Jamil SW et al. in their study (10). Meta-analysis of 13 studies in 1,807 COVID-19 patients showed that the serum D-dimer concentrations in patients with severe forms of the disease were significantly higher than those in patients with milder forms. D-dimer concentrations might be helpful to rapidly identify COVID-19 patients with high risk of pulmonary complications and venous thromboembolism, facilitating the early initiation of effective therapies (11). Our presented values follow the results of these studies and we notice significantly higher values of fibrinogen, APTT and D-dimer in severe COVID-19 patients.

It has been proven that low platelet values in COVID-19 patients are associated with the severity of the clinical picture, leading to coagulopathy. Lippi G et al. proved the association of lower platelet values with worse prognosis and death of patients (12). Our results showed that thrombocytes were lower in severe patients, but their MPV was higher in that patients.

Rostami-Far Z et al. showed in their study that erythrocytes, hemoglobin and hematocrit were significantly decreased in severe COVID-19 patients (13). Yuan et al. showed that severe and critical COVID-19 patients had significantly lower values ofhemoglobin and erythrocytes (14) and all these results follow our findings.

The association between leukopenia, normal values of leukocytes and leukocytosis was not shown in the study by Layla KN et al., while they compared these values among mild, moderate and severe COVID-19 patients (15), while in our study this association was statistically significant. Neutrophilia, which was shown in our study in severe COVID-19 patients, is a characteristic of a severe form of the disease and a poor prognosis (16, 17), which is explained by the fact that neutrophilia is associated with hyperinflammatory and cytokine events, which characterizes the mechanism of the development of the COVID-19 infection. Activation of neutrophils and release of contents from granules represent one of the more active cellular mechanisms as a result of the immune response, but their significance in virus destruction has not been proven (18). The most important parameter of the blood count is the decreased number of lymphocytes, which is observed in more than 80% of patients with severe clinical course. A changed number of lymphocytes and their subtypes has been described in many viral infections, and it is assumed that the mechanisms of viral infections and changes in lymphocyte subtypes are related. It is assumed that binding of the virus and damage to the immune system leads to a reduced number of lymphocytes. Also, a reduced number of lymphocytes can also interfere with their migration into the lung parenchyma (19). In our study, lymphopenia was present in severe COVID-19 patients, which follows the results of other studies (20-22), which confirms the fact that lymphopenia is one of the main laboratory parameters for monitoring the prognosis of COVID-19.

This study has some limitations. First of all, our study included smaller number of patients compared to other studies and data come only from one institution and one region in Bosnia and Herzegovina, it is single-center study.

CONCLUSION

In our study, we showed that a mild clinical course is characterized by higher values of INR, WBC, lymphocytes, monocytes, RBC, Hgb, Hct, MCV, platelets and reactive lymphocytes. A severe clinical course is accompanied by higher values of fibrinogen, D-dimer, APTT, neutrophils, eosinophils, basophils, MPV and CRP.

Ethics approval: This study was approved by Ethics Committee of "JU Dom zdravlja KS"' (04-7-72/21(02-3-614/11)) and Ethics Committee od Faculty of Health Studies, University of Sarajevo (01-06-5847-3/20).

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Licensing

Sažetak

RAZLIKE BIOHEMIJSKIH, HEMATOLOŠKIH I KOAGULACIONIH PARAMETARA MEĐU PACIJENTIMA SA BLAGOM I TEŠKIM OBLICIMA COVID-19

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Uvod: COVID-19 je infektivna bolest uzrokovana teškim akutnim respiratornim sindromom koronavirus 2 i uzrokuje niz respiratornih simptoma. S obzirom na pojavu i razvoj simptoma, tok COVID-19 može ići od blagog do teškog. Zavisno od toka COVID-19, laboratorijski parametri se dosta menjaju, pokušavajući odbraniti organizam od stranog patogena i svih promena koje on uzrokuje. Stoga je cilj ovog istraživanja uočiti razliku između biohemijskih, hematoloških i koagulacijskih parametara u zavisnosti od stadijuma bolesti kod pacijenata obolelih od COVID-19. **Materijal i metode:** Proveli smo presečnu studiju koja je obuhvatila 160 pacijenata obolelih od COVID-19 iz Sarajeva, Bosna i Hercegovina. Urađene su biohemijske, hematološke i koagulacijske analize. **Rezultati:** COVID-19 pacijenti sa težom kliničkom slikom imaju više prosečne vrednosti fibrinogena ($6,53 \pm 4,47$, $p < 0,001$), D-dimera ($6,89 \pm 7,81$, $p < 0,001$), APTT ($32,05 \pm 5,96$, $p = 0,002$), eozinofila ($0,66 \pm 0,09$, $p = 0,002$) i CRP ($93,42 \pm 75,86$, $p = 0,023$), te niže vrednosti limfocita ($1,04 \pm 0,98$, $p < 0,001$), monocita ($0,45 \pm 0,3$, $p < 0,001$), u poređenju sa COVID-19 pacijentima sa blažom kliničkom slikom. COVID-19 pacijenti sa težom kliničkom slikom imali su više prosečne vrednosti neutrofila ($10,12 \pm 5,8$, $p = 0,002$) i niže vrednosti reaktivnih limfocita ($0,02 \pm 0,03$, $p < 0,001$) za razliku od COVID-19 pacijenata sa blažom kliničkom slikom. **Zaključak:** Biohemijski, hematološki i koagulacijski parametri mogu biti osetljivi i specifični biomarkeri za razlikovanje blagog i teškog oblika COVID-19 ili blage i teške kliničke slike COVID-19

***Ključne reči**:* COVID-19, laboratorijski parametri, klinička slika.

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Original article

THE EFFECTS OF CLINICAL, LABORATORY, AND ANGIOGRAPHIC FACTORS ON STENT THROMBOSIS AND MAJOR ADVERSE CARDIAC EVENTS IN PACLITAXEL ELUTING STENTS

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Abstract: **Background**: Drug-eluting stents (DES) have higher marked efficacy and lower revascularization requirements compared to bare metal stents (BMS).We aimed to determine the mid-term outcomes of patients implanted with a first-generation DES "paclitaxel-eluting stents" (PES).

Methods: Patients with at least 1 PES implanted in our cardiology clinic were received in the non-randomized group. Inclusion criteria were all patients undergoing percutaneous coronary intervention and PES implantation. The mean follow-up time was 35.14 + 13.4 months.

Results: A total of 302 patients (401 lesions and 337 PES) were enrolled in the study. The mean age was 61.86 + 10.27 years. Major adverse cardiac and cerebrovascular events (MACE) occurred at 17.9%, and the stent thrombosis rate was 4%. Independent predictors of stent thrombosis were serum creatinine levels [OR 1.59; 95% CI, 1.03-2.46, p = 0.03] and mean platelet volume [OR 1.59; 95% CI, 1.03–2.46, p = 0.03]. Also, poor functional capacity [OR 2.46: 95% CI, 1.42- 4.26, p < 0.001] and positive ischemia test [OR 3.43: 95% CI, (1.73-6.82), p < 0.001] were predictors of MACE's.

Conclusions: We have demonstrated that PES is safe and effective in the mid-term for use in coronary artery disease.

Keywords: Paclitaxel, restenosis, thrombosis, real-world.

INTRODUCTION

Stents are frequently applied by an interventional cardiologist and constitute more than 80% of all interventional procedures (1). Drug-eluting stents (DES) has reduced restenosis compared with bare metal stents (BMS) in different patients and lesion types (2, 3, 4). Although DES leads to a decrease in restenosis and repeats revascularization rates caused safety concerns such as higher stent thrombosis (ST) rates (2, 3).In the present work, we evaluated the frequency of Major adverse cardiac and cerebrovascular events (MACE) and ST with paclitaxel-eluting stents (PES). We planned a retrospective study to evaluate the effect of patients' clinical, angiographic, laboratory, and procedural variables on these parameters.

MATERIAL AND METHODS

Study population

A total of 302 patients who underwent PES in Kocaeli University Training and Research Hospital between April 2003 and July 2008 were analyzed retrospectively. Patients treated with at least 1 PES were included in the non-randomized group. Inclusion criteria were "all comers" for routine or emergency percutaneous coronary intervention and had native or graft vessel disease with > 18 years of age. The basic clinical and demographic features of the patients on admission are shown in Table 1. Patients who gave written informed consent to this work, without restriction on target vessel and a number of lesions, were included. Laboratory values, including complete blood counts and biochemical parameters (homocysteine, hs. CRP, fasting blood glucose, fibrinogen, fasting lipid panel, creatinine, and uric acid), were obtained from the hospital's electronic database system.

The procedures were applied following the current guidelines, and the stent placement strategy, pre-dilatation, post-dilatation, and use of Gp IIb-IIa were left to the operator's discretion. Dual antiaggregant therapy

(clopidogrel and acetylsalicylic acid) was started for all patients before the procedure. ST was defined with the Academic Research Consortium definitions (5) (Table 2).

ST segment elevation myocardial infarction (STMEI) was defined based on the ST-elevation in 2 or more contiguous leads ≥ 0.2 mV or new left bundle-branch block associated with new onset chest pain (6). Non-ST segment myocardial infarction (NSTEMI) was diagnosed according to the European Society of Cardiology criteria, as acute chest pain with the rise of cardiac markers without permanent ST-segment elevation (7). MACEs are defined as myocardial infarction (MI), stroke, heart failure, and/or death from cardiovascular disease (8). According to the Declaration of Helsinki, the present study was reviewed and approved by the local ethics committee.

Statistic

Data were analyzed in SPSS for Windows 17 statistical software program. Numerical variables were described as a mean ±standard deviation, and classified variables were expressed as a number and percentages. The patients were classified according to the development of thrombosis and MACE. Student t-test and Mann Whitney U test were used to compare continuous variables with normal and without normal distribution respectively. Classified variables were compared by Chi-square or Fisher's exact test. Parameters were analyzed with univariate and multivariate logistic regression analyses. Enter method was used in univariate analysis and parameters with p-values below 0.1 were included in the multivariable logistic regression model. The backward method used multivariate logistics regression analysis and p value < 0.05 was accepted as statistical significance. The appropriate cut-off values for the parameters found to be significantly different for the development of ST were determined by ROC curve analysis, which could be used to determine the event development. Kaplan Meier and long-rank analyses were used for the analysis of event-free survival.

RESULTS

A total of 302 patients; 230 men (76.2%) and 72 women (23.8%), aged between 34-88 (61.86 ± 10.27 years**)** were analyzed**.** The average follow-up time was 35.14 + 13.4 months. The patients were categorized as silent ischemia, stable angina, unstable angina, NSTEMI, and STMEI according to their clinical status (Table 1).

Coronary angiographic findings

Stenting was applied to a total of 401 lesions, 337 of which were PES and 63 BMS. The average per-

Table 1. *Basal demographic and clinical findings of study population*

Variables	**N**	**% or mean ± SD**
Male gender	230	76.2
Weight (kg)		78 ± 11
Obesity$^{\mu}$	69	22.8
Diabetes	116	38.4
Hypertension	209	69.3
Hyperlipidemia	270	89.4
Prior CABG	24	7.9
PVD	9	3
MI history	37	12.3
Family history	77	5.5
PCI history	29	12.9
Smoking$^{\alpha}$	51	16.9
Atrial fibrillation	12	4
Clinical features		
Silent ischemia	50	16.6
Stable angina	45	14.9
Unstable angina	107	35.4
NSTEMI	32	10.6
STEMI	68	22.5

Abbreviations: CABG: coronary artery by-pass graft, kg: kilogram, STEMI: ST segment elevation myocardial infraction, MI: Myocardial infraction, NSTMEI: Non ST segment elevation myocardial infraction, μ: BMI > 30 kg/m², α: active smoking, PVD: peripheral vascular disease, PCI: Percutaneous coronary intervention.

Table 2. *Stent thrombosis classification*

Stent thrombosis in Academic Research Consortium definitions	
According to time	
·Acute	0-24 hours
·Subacute	24 hours- 30 day
·Late	30 day- 1 year
·Very late	> 1 year
Definite stent thrombosis	
· Thrombus in stent or 5 mm distal-proximal segments in angiography	
· Acute ischemic symptoms onset at rest	
· New ischemic ECG changes supporting ischemic symptoms	
· Typical elevation of cardiac biomarkers	
· Non-occlusive, occlusive thrombus: Intracoronary thrombus	
Probable stent thrombosis	
· Unexplained death within the first 30 days after stent replacement	
· Any MI with documented signs of ischemia, independent of time after stenting, without a obviously cause	
Possible stent thrombosis	
· Unexplained death from day 30 post stent implantation to end of study follow-up	

Abbreviations: ECG: Electrocardiography, MI: myocardial infraction

***Table 3**. Main demographic, clinical, angiographic and laboratory feature in thrombosis groups*

Variable	Thrombosis (-) N = 290	Thrombosis (+) N = 12	P	Variable	Thrombosis (-) N = 290	Thrombosis (+) N = 12	P
Demographic				***Angiographic***			
Age (mean)	61.97+10.22	59.42+11.62	0.40	Slow flow-No reflow	10 (%3.4)	2 (%16.7)	0.02
Male gender	219 (%75.5)	11 (%91.7)	0.30	Lesion type A	24 (%8.3)	0 (%0)	0.60
HT	200 (%69)	9 (%75)	0.76	type B	126 (%43.4)	5 (%41.7)	0.90
DM	111 (%38.3)	5 (%41.7)	1.0	type C	140 (%48.3)	7 (%58.3)	0.49
HL	259 (%89.3)	11 (%91.7)	1.0	TIMI 3 flow	258 (%89)	12 (%100)	0.62
Family history	74 (%25.5)	3 (%25)	1.0	LAD lesion	150 (%51.7)	5 (%41.7)	0.49
Cigarette$^{\alpha}$	48 (%16.6)	3 (%25)	0.43	Cx lesion	69 (%23.8)	5 (%41.7)	0.17
MI history	35 (%12.1)	2 (%16.7)	0.64	RCA lesion	71 (%24.5)	2 (%16.7)	0.73
PCI history	38 (%13.1)	1 (%8.3)	1.0	LMCA lesion	1 (%0.3)	0 (%0)	1.0
CABG history	23 (%7.9)	1 (%8.3)	1.0	Bifurcation	16 (%5.5)	0 (%0)	1.0
PVD history	7 (%2.4)	2 (%16.7)	0.04	Graft lesion	3 (%1)	0 (%0)	1.0
< 6 mount clopidogrel use	32 (11%)	4 (33.3%)	0.04	Stent restenosis	22 (%7.6)	1 (%8.3)	1.0
				Thrombus	5 (%1.7)	0 (%0)	1.0
				PSS length	21.50 + 7.08	19.25 + 6.62	0.27
				Total stent length	26.55 + 12.16	23.08 + 12.82	0.33
Clinical findings				***Laboratory Findings***			
Silent ischemia	50 (%17.2)	0 (%0)	0.22	FBG	102+56	105+45	0.31
Stable Angina	43 (%14.8)	2 (%16.7)	0.69	MPV	9.38 + 1.61	8.41 + 1.38	0.04
Stabil CAD	93 (%32.1)	2 (%16.7)	0.35	Homocysteine	15.99 + 8.21	19.86 + 10.73	0.26
Un-stable Angina	102 (%35.2)	5 (%41.7)	0.76	Creatinine	1.06 + 0.53	2.09 + 3.28	0.04
NSTEMI	30 (%10.3)	2 (%16.7)	0.37	Uric acid	5.65 + 1.63	6.77 + 2.32	0.08
STEMI	65 (%22.4)	3 (%25)	0.73	Total cholesterol	206.94 + 40.74	202.92 + 37.19	0.73
				HDL-C	41.07 + 10.3	36.75 + 8.02	0.15
				TC/HDL-C	5.25 + 1.48	5.81 + 1.83	0.21
				LDL-C	133.50 + 34.65	132.58 + 30.09	0.92
				Fibrinogen	4.46 + 1.53	4.80 + 2.25	0.71
				Hs-CRP	2.26 + 3.56	3.07 + 4.84	0.39

Abbreviations: ACS: Acute coronary syndrome, DM: diabetes mellitus, CABG: coronary artery by-pass graft, CAD: coronary artery disease, FBG: Fasting blood glucose, HL: Hyperlipidemia, HT: Hypertension, TC: Triglyceride, STEMI: ST segment elevation myocardial infraction, MI: Myocardial infraction, Non-STMEI: Non ST segment elevation myocardial infraction, α: active smoking, PVD: peripheral vascular disease, PCI: Percutaneous coronary intervention.

centage of stenosis intervention in coronary angiography was 87.53 ± 9.39 % (60%-100%). Single-vessel coronary artery disease was detected in 182 patients (60.3%), two vessel in 82 (26.8%), and three vessel in 39 patients (12.9%). While the average number of stents per procedure was 1.33 ± 0.53, a maximum of 4 stents were applied. The average total stent length was 26,41 ± 12,18 mm, the shortest size was 8 mm, and the longest was 68 mm.

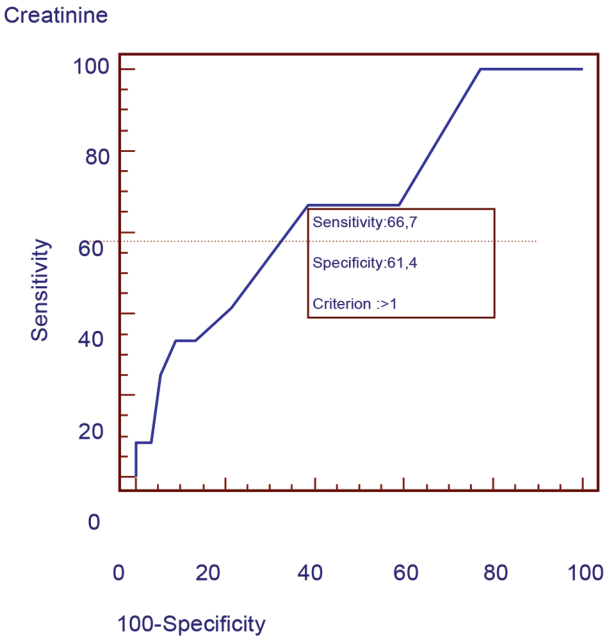
Risk Factors Associated with Thrombosis

ST occurred in 12 patients (%4). Definite ST was detected in 8 and probable ST in 4 patients**.** While subacute thrombosis was being seen in 1, late 5, and very late in 6 patients, acute thrombosis was not detected. Platelet count and creatinine values were higher, and mean platelet volume was lower detected in the thrombosis group (Table 3). Risk factors predicting ST in the multivariate logistics regression analysis were found as serum creatinine levels (Table 4). The appropriate cut-off value for creatinine by ST was automatically determined as 1 mg/dl by ROC curve analysis (Figure 1). In the ST group, a history of peripheral vascular disease (PVD), slow-flow and no-reflow phenomenon, and P2Y12 receptor blockers use for less than six mounts was more frequently observed (Table 3).

Table 4. *Univariate and multivariate logistic regression analysis examining factors that may be associated with thrombosis and MACE*

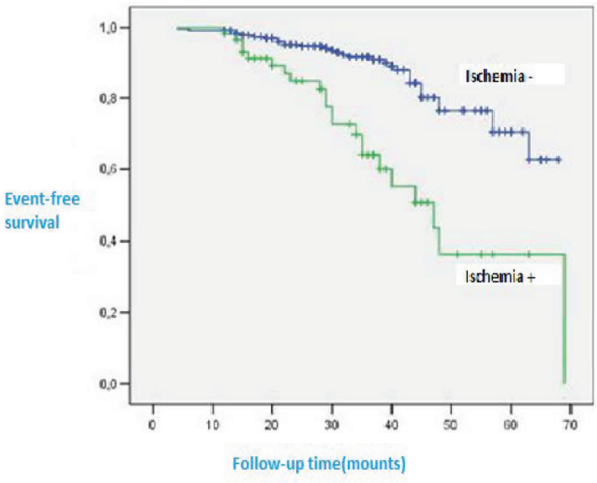
Variable	Uni-variable OR (95%CI)	P	Multi-variable OR (95%CI)	P
Thrombosis				
PVD	8.08 (1.48-43.96)	**0.01**	1.20 (0.01-85.44)	0.93
< 6 ay clopidogrel use	4.03 (1.14-14.14)	**0.02**	2.04 (0.21-19.90)	0.53
Hematocrit	0.90 (0.81-1.01)	0.07	1.01 (0.83-1.20)	0.95
Platelet	1.00 (1.00-1.10)	0.07	1.01 (0.99-1.10)	0.57
MPV	0.61 (0.38-0.98)	**0.04**	0.83 (0.42-1.64)	0.60
Creatinine	**1.53 (1.06-2.21)**	**0.02**	**1.59 (1.03-2.46)**	**0.03**
Uric acid	1.37 (0.95-2.00)	0.09	1.28 (0.82-1.99)	0.26
Slow-flow + no-reflow	5.6 (1.08-28.98)	**0.04**	5.30 (0.35-78.84)	0.22
MACE				
Poor functional capacity	2.58 (1.55-4.28)	< 0.01	2.46 (1.42- 4.26)	**< 0.01**
< 6 mount clopidogrel use	2.28 (1.04-4.98)	**0.03**	2.67 (1.14-6.23)	**0.02**
Multi-vessel disease	2.10 (1.43-3.09)	< 0.01	1.81 (1.19 – 2.73)	**< 0.01**
Positive ischemia test	3.92 (2.05-7.47)	< 0.01	3.43 (1.73-6.82)	**< 0.01**
Creatinine	1.34 (0.95-1.88)	0.08	1,22 (0.81-1.83)	0.32
Hematocrit	0.92 (0.87-0.98)	< 0.01	1.01 (0.93-1.10)	0.82
Lesion type	1.62 (0.98-2.68)	0.05	1.39 (0.77-2.48)	0.26
Stent diameter	0.45 (0.18-1.10)	0.08	0.55 (0.19-1.54)	0.25

Abbreviations: MPV: Mean platelet volume, PVD: peripheral vascular disease.



Area	0,670
Standard error	0,0872
95% CI	0,614 - 0,723
z statistic	1,949
p	0,05

Figure 1. *ROC curve analysis for creatinine in predicting stent thrombosis*



	Chi - Square	df	Sig.
Log Rank (Mantel- Cox)	23,180	1	,000

Figure 2. *Kaplan-Meier curve in patients with and without positive ischemia test during follow-up*

Major adverse cardiovascular events (MACE)

The frequency of MACE was observed in 54 patients (% 17.8). 16 deaths, 4 strokes, 18 myocardial infarctions, and 16 hospitalizations for heart failure were

Table 5. *Clinical, laboratory and angiographic variables in patients grouped by MACE development*

Variable	MACE (-) n = 248	MACE (+) n = 54	p
Single vessel disease	162 (%65.3)	20 (%37)	**< 0.01**
Multiple vessel disease	86 (%34.7)	34 (%63.0)	**< 0.01**
Hemoglobin	13,96 + 1,71	13,21 + 1,90	**< 0.01**
Hematocrit	40,59 + 4,76	38,60 + 5,67	**< 0.01**
Creatinine	1,05 + 0,45	1,33 + 1,71	**0.02**
Stent restenosis	15 (%6)	8 (%14.8)	**0.04**
NYHA I	189 (%76.2)	29 (%53.7)	**< 0.01**
NYHA III	4 (%1.6)	5 (%9.3)	**0.01**
< 6 month clopidogrel use	25 (%10.1)	11 (%20.4)	**0.03**
Positive ischemia test	37 (%14.9)	22 (%40.7)	**< 0.01**

observed during this follow-up period. Hemoglobin and hematocrit values were lower in the MACE group, while creatinine values were higher (table-5). Patients with a positive ischemia test had significantly lower event-free survival and a higher risk of MACE (Figure 2). Risk factors predicting MACE in the multivariate logistics regression analysis were poor functional capacity, use of P2Y12 receptor blockers for less than six months, positive ischemia test at follow-up, and multi-vessel disease (Table 4).

DISCUSSION

Stent application is widely used over the world, and it seems that new treatment methods will not replace this application in the near future. We determined the rates of ST and MACE after PSS was applied in our clinic. Accordingly in a mean follow-up of about three years, ST was found to be 4% and MACE 17.9%. In the DESIRE registry study (6), which had a similar protocol to our study, the long-term development of MACE was evaluated in 2084 patients**.** In this study, in which the follow-up period was around 31 months, the MACE was 8.5%, target lesion revascularization (TLR) was 3.3%, and ST was detected at a rate of 1.6%. Also, diabetes mellitus (DM), presentation with acute MI, calcific lesion, graft disease, and post-procedure residual stenosis were found as MACE-related risk factors. Compared to our study, the development of MACE occurred at a lower rate in this study, and this difference may be due to the difference in stent types, follow-up time, and new P2Y12 receptor blockers usage times. In the REAL registry study, in the DES-administered group (patients while PSS was used in 36.71% of them), TLR was 7.3% at the end of two years. In the REAL registry, DM, renal failure, and reference vessel diameter indicated an increased risk of TLR (9, 10). Comparing the use of on-label and off-label PSS in the ARRIVE 1 study, MACE rates were 5.8% in the TLR on-label group and 9.4% in the off-label group at the end of two years (11). In SIRTAX (VERY LATE) trial, MACE was attenuated at 1 year at 11%, at 5 years at 20.8 %, and 32.5 % at 10 years, respectively (12). The risks of MACE were similar between sirolimus-eluting stent (SES) and PES groups. In this study, they showed the risks of TLR and ST significantly reduced 5 years after stent implantation. Galløe et al demonstrated that on years follow-up MACE occurred at 33.1%, ST at 13.3% in the PES group (13). There was a statistically non-significant trend toward increased rates of MACE and ST in PES than in SES. In the study of Räber et al, which compared the first-generation DES, they found more frequency of MACE rate in the PES group in the first year after the stent was implanted, but this adverse outcome decreased in the subsequent years (14).

In a recent study by Simsek et al, SES and PES decreased the frequency of MACE compared to the BMS, but no significant difference was found in all-cause mortality/MI at 6-year follow-up. Also in this study, very late ST was more common in first-generation DES patients than BMS (15). Park et al. showed that in patients with left main coronary artery lesions, there was no significant difference in clinical outcomes at 10-year follow-up between those treated with SES and PES groups (16). Also, ISAR-DESIRE 3 trial found that within 10 years, PES stents significantly reduced target vessel revascularization compared with a plain balloon (17). Thuijs et al reported that at a 10-year follow-up period, no significant difference existed in all-cause death between coronary artery bypass grafting compared to percutaneous coronary intervention (PCI) using PES in patients with three-vessel and left main coronary artery disease (18).

In our study, poor functional capacity, positive follow-up ischemia test, multivessel coronary artery

disease, and P2Y12 receptor blockers use for less than six months were found to be associated with the development of MACE**.** The increase in revascularization rates in these patients contributes to the frequency of MACE. Multivessel disease and poor functional capacity are the most commonly used factors in prognosis assessment in daily practice.

The important risk factor of ST is the discontinuation of antiplatelet therapy in the early period. Autopsy studies indicated delayed healing of thrombosed DES specimens, degeneration of the metal alloy, poor endothelialization, stent malposition, and vessel remodeling as possible factors leading to late /very late ST (19).

In our group, ST was 4%, and it was found to be higher compared to the previous studies. However, the development of defined ST occurred at 2.6% and can be considered similar. In the ESFORA study, definite ST was reported in 2% of 23500 patients after 3 years (20). In this study, subacute and late ST predictors as DM, chronic kidney disease, myocardial infarction, and left anterior descending artery (LAD) lesion. In the ARRIVE 1 registry study, definite and probable ST was 2.2% in patients who underwent PSS at the end of two years (11). In the PREMIER registry study, the discontinuation of clopidogrel after one month was associated with increased mortality (21). In the BASKET-LATE study, clopidogrel was discontinued after six months, and thereafter, a higher rate of death and MI was found in the DES group than BMS group (22). In another real-world study, the TYCOON registry study, the use of clopidogrel for 12 months and 24 months were compared, and less ST was found in 24 months (23). In a single-center study by Slottow et al., it was shown that clopidogrel use was less in the group with ST (24). In parallel, Spertus et al. reported that thienopyridine discontinuation 30 days after DES treatment were more likely to die during the next 11 months (7.5% versus 0.7%) (18).In the AUTAX study in which 441 PSS implanted patients were followed for 2 years, rates of ST were < 1 % (25). This trial showed multiple PSS implantation was safe for patients with multivessel coronary artery disease, with a low incidence of ST rate. Also in SIRTAX (VERY LATE) study, the risk of late ST decreases annually over an extended period at a ten-year follow-up. (12). In the DESET trial, independent clinical correlates of late ST were younger age, current smoking, multivessel disease, longer stented length, overlapping stents, vein graft lesions, and LAD lesions (26). Bundhun et al. observed 16.724 patients, and there was no difference between SES and PES for ST. They noted both SES and PES are expected to be equally effective (27). In addition, very late ST (> 10 years) has been found in the literature in patients treated with PES (28).

The new generation P2Y12 inhibitors (ticagrelor and prasugrel) were not used in our study population which may have affected the incidence of ST and MACEs. In this study, in accordance with the guidelines (29), the mean recommended duration of P2Y12 receptor blockers was approximately 12 months, but the use of P2Y12 inhibitors for less than 6 months increased the incidence of thrombosis**.** We found that the most important parameter for ST is serum creatinine levels. In addition, a history of PVD, slow-flow or no-reflow phenomenon development, higher mean platelet count, and lower mean platelet volume were found associated with thrombosis.

Limitation of the study

When compared to similar studies, there was no relationship between classical thrombosis risk factors and ST because our population was not randomized. Also, our study was single-center, and the number of total patients was low. The absence of a control group also caused us problems in determining the benefit experienced by the patients who underwent PSS. The fact that the follow-up periods of the patients were not fixed, prevented us from reflecting on the events that may develop in the future of the study. In addition, the actual frequency may be higher in patients who cannot be contacted, since the development of adverse cardiac events cannot be learned. Also, intravascular ultrasound imaging was not performed after stent replacement, so stent malposition or incomplete stent dehiscence could not be evaluated. Furthermore, the effect of 63 BMS applications on study end-points is not clearly unexplained.

CONCLUSION

Patients who underwent PSS in our clinic have similar procedural success and complication rates in the early and long-term when compared to other publications. According to our findings, silent ischemia, angina, and positive ischemia test are associated with poor prognosis. Therefore, ischemia examination can be considered in all patients with or without symptoms in the determination of prognosis. Our study also confirms safetyand efficacy of the PES-treated patients as in other studies.

Abbreviations

BMS - Bare metal stents
DES - Drug-eluting stents
LAD - Left anterior descending artery
MACE - Major adverse cardiac and cerebrovascular events

MI - Myocardial infraction

NSTEMI - Non-ST segment myocardial infraction

PES - Paclitaxel-eluting stents

PVD - Peripheral vascular disease

SES - Sirolimus eluting stent

ST- Stent thrombosis

STMEI - ST-segment elevation myocardial infraction

TLR - Target lesion revascularization

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Licensing

Sažetak

EFEKTI KLINIČKIH, LABORATORIJSKIH I ANGIOGRAFSKIH FAKTORA NA TROMBOZU STENTA I NEŽELJENI KARDIOVASKULARNI DOGAĐAJI U STENTOVIMA OBLOŽENIM PAKLITAKSELOM

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Uvod: „Drug-eluting stents“ (DES) su efikasniji i i imaju smanjenju naknadnu potrebu za ponovnom revaskularizacijom u poređenju sa metalnim stentom. Cilj nam je bio da utvrdimo srednjoročne ishode pacijenata sa implantiranim DES-om prve generacije „stentovi obloženi paklitakselom (PES)“.

Metode: Pacijenti sa najmanje 1 PES implantiranim u našoj kardiološkoj klinici su primljeni u nerandomizovanu grupu. Kriterijumi za uključivanje bili su svi pacijenti koji su podvrgnuti perkutanoj koronarnoj intervenciji i implantaciji PES-a. Prosečno vreme praćenja bilo je 35,14 + 13,4 meseca.

Rezultati: Ukupno 302 pacijenta (401 lezija i 337 PES) su bila uključena u studiju. Prosečna starost je bila 61,86 + 10,27 godina. Veliki neželjeni srčani i cerebrovaskularni događaji (MACE) javili su se u 17,9%, a stopa tromboze stenta bila je 4%. Nezavisni prediktori tromboze stenta bili su nivoi serumskog kreatinina [OR 1,59; 95% CI, 1,03-2,46, p = 0,03] i srednja zapremina trombocita [OR 1,59; 95% CI, 1,03–2,46, p = 0,03]. Takođe, slab funkcionalni kapacitet [OR 2,46: 95% CI, 1,42-4,26, p < 0,001] i pozitivan ishemijski test [OR 3,43: 95% CI, (1,73-6,82), p < 0,001] bili su prediktori MACE-a.

Zaključak: Pokazali smo da je PES bezbedan i efikasan u srednjoročnom periodu za primenu u koronarnoj arterijskoj bolesti.

Ključne reči: paklitaksel, restenoza, tromboza, stvarni svet.

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5-YEAR CLINICAL RESULTS OF 1073 PATIENTS WITH VARICOSE VEINS TREATED USING RADIOFREQUENCY ABLATION, ENDOVENOUS LASER ABLATION AND CYANOACRYLATE EMBOLISATION

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Abstract: **Background:** There is little research on the long-term outcomes of radiofrequency ablation, endovenous laser ablation, and cyanoacrylate embolization. This study retrospectively examined the clinical results of radiofrequency ablation, endovenous laser ablation, and cyanoacrylate embolization methods.

Materials and Methods: The population of the study consisted of 1256 patients who applied to the clinic with the diagnosis of chronic venous insufficiency between the specified dates and were treated with endovenous varicose veins. Sample: 431 patients in the cyanoacrylate embolization group, 230 patients in the radiofrequency ablation group, 412 patients in the endovenous laser ablation group, a total of 1073 patients. Bilateral cyanoacrylate embolization, radiofrequency ablation, and endovenous laser ablation were not applied to the patients in the same session.

Results: When the 1-year occlusion rates were examined, it was determined as 97.57%, 98.26%, and 95.59% in the endovenous laser ablation, radiofrequency ablation, and cyanoacrylate embolization groups, respectively. There was no significant difference in Venous Clinical Severity Score scores between the groups before and after the procedure. Pain, paresthesia, ecchymosis, pigmentation, induration, burn, deep vein thrombosis, and phlebitis were significantly more common in the endovenous laser ablation group.

Conclusions: Complications were seen in the cyanoacrylate embolization group. Endovenous laser ablation, radiofrequency ablation, and cyanoacrylate embolization applications have similar long-term results. Therefore, cyanoacrylate embolization is recommended for chronic venous insufficiency patients who want to get rid of varicose veins and improve their quality of life.

Keywords: Radiofrequency ablation, Endovenous laser ablation, Cyanoacrylate embolization, Clinical results.

INTRODUCTION

Venous insufficiency and varicose veins are common conditions of significant concern for patients (1). In recent years, there have been significant advances in the diagnosis and treatment of venous insufficiency. Some of the methods that are alternative to surgical treatment are radiofrequency ablation (RFA), endovenous laser ablation (EVLA), and cyanoacrylate embolization (CAE).

Color Doppler ultrasonography (RDUSG) has been a common method for diagnosing and treating venous insufficiency. This technique has paved the way for thermal ablation methods (EVLA and RFA), which involve local anesthesia under ultrasonography (USG) guidance. Those methods have replaced surgical treatments worldwide (1).

Radiofrequency ablation and EVLA are minimally invasive procedures. Their short- and medium-term outcomes are excellent, with high occlusion rates and rare side effects (2, 3). In endovenous laser ablation, the veins causing reflux are closed up with heat (ablation) under local anesthesia by a laser fiber placed inside the lumen. Then the laser fiber is eliminated by the body through fibrosis. Some advantages of this method are that it is a painless procedure performed under local anesthesia, it leaves no scar or incision, and the patient can stand up and walk immediately after the procedure. Therefore, endovenous laser ablation has become an important option for treating venous insufficiency. Endovenous laser ablation both eliminates the cause of

varicose veins and reduces or eliminates the symptoms of venous insufficiency (pain, cramping, swelling, etc.). Involving radiofrequency (RF) or laser energy as a heat source, EVLA is an important method for treating saphenous insufficiency as well. Radiofrequency thermal ablation has largely replaced surgery because it is a safe and effective procedure with a few side effects and does not require general anesthesia and hospitalization (4, 5). New methods are being developed for high success rates, fewer complications, and higher quality of life. Cyanoacrylate embolization (CAE) has been one of the most popular nonthermal ablation methods in recent years. The advantage of CAE is that it is a short procedure that does not require tumescent anesthesia and does not cause labor loss. Cyanoacrylate embolization poses less risk for nerve damage because it does not involve thermal energy, and its mid-term results are superior to those of ultrasound-guided foam sclerotherapy (6).

Varicose veins cause signs and symptoms and serious cosmetic concerns that affect the quality of life. Invasive endovenous techniques are becoming more popular because they are easy-to-apply methods with successful results and because patients avoid surgical incisions (7). The primary objective of lower extremity varicose vein treatment is to eliminate patient complaints (pain, itching, burning, paresthesia, bleeding, ulceration, etc.) by considering aesthetic concerns and to minimize post-procedure complications (paresthesia, burn, air embolism, headache, pulmonary embolism, deep vein thrombosis (DVT), pigmentation, etc.). We should know the results of varicose vein treatment methods before informing patients about them.

There is little research on the long-term outcomes of CAE, RFA, and EVLA. This study retrospectively examined the clinical results of CAE, RFA, and EVLA methods. We think that the results will contribute to the literature.

MATERIALS AND METHODS

Research design

This retrospective study presented the outcomes of the procedures performed in the cardiovascular surgery clinic of a private hospital in Osmaniye in the south of Turkey. No sampling was performed. In the study, the results of the patients who underwent the procedure between February 2011 and April 2016 were evaluated. 1256 patients who were diagnosed with chronic venous insufficiency (CVI) and treated for endovenous varicose veins at this time constituted the population of the study. The sample consisted 431 patients in the cyanoacrylate embolization group, 230 patients in the radiofrequency ablation group, 412 patients in the endovenous laser ablation group, a total of 1073 patients. Bilateral cyanoacrylate embolization, radiofrequency ablation, and endovenous laser ablation were not applied to the patients in the same session. The inclusion criteria were as follows:

1. Aged between 18 and 70 years,
2. Great saphenous vein (GSV) ≥ 5.5 mm and vessel diameter ≤ 15 mm
3. Great saphenous vein reflux > 0.5 seconds
4. CEAP (Clinical-Etiological-Anatomical-Pathophysiological) classification between C2 and C5
5. Attending follow-up exams

The exclusion criteria were as follows:

1. History of deep vein thrombosis,
2. Deep venous insufficiency,
3. Active superficial phlebitis,
4. Great saphenous vein (GSV) aneurysm > 12 mm,
5. Lymphedema,
6. Peripheral arterial disease,
7. Pregnant or breastfeeding patients,
8. Immobility.

Data Collection

The data were recorded in patient files and then evaluated five years later.

The CEAP (Clinical-Etiological-Anatomical-Pathophysiological) classification was used to determine CVI severity. Venous Clinical Severity Score (VCSS) was used to evaluate clinical findings.

During the 5 years, patients' histories were attained from the medical records, and all patients underwent a clinical examination before treatment. Afterward, GSV deficiencies were detected using RDUSG. Venous insufficiency was assessed while the patient was standing. Operational decisions were made according to the CEAP classification and clinical complaints in addition to the GSV insufficiency and the GSV diameter at the planned level of intervention. Venous reflux flow was checked when insufficiency was suspected due to increased diameter or its association with varicose veins. Diameters exceeding 5.5 mm in the superficial femoral veins and 3.5 mm in the perforating veins while standing were accepted as criteria for venous insufficiency.

CEAP classification and VCSS were evaluated after clinical examinations in the first month, first year, and fifth-year post-intervention. Procedural success and post-procedure symptoms and complications were determined using RDUSG.

CEAP classification

The CEAP classification was developed by the American Venous Forum (1994). C0: no visible or palpable signs, C1: telangiectasias or reticular veins, C2: varicose veins, C3: edema, C4: secondary skin alter-

ations, C4a: pigmentation or eczema, C4b: lipodermatosclerosis or white atrophy, C5: healed venous ulcer, C6: active venous ulcer (8).

Venous Clinical Severity Score (VCSS)

The Venous Clinical Severity Score (VCSS) is a dynamic scoring system that evaluates ten components: pain, varicose veins, edema, pigmentation, inflammation, induration, ulcer size, the number of ulcers, ulcer duration, and compression. The components are scored on a scale of 1 to 3. (1 = Mild, 2 = Moderate, 3 = Severe). The total score ranges from 0 to 30. The VCSS is a user-friendly scoring system designed to assess the patient's clinical condition. Higher scores indicate worse clinical conditions (9).

Procedures

CAE, RFA, and EVLA were performed.

Endovenous laser ablation was performed under tumescent anesthesia. A laser with a 1470 nm radial fiber was used. After EVLA, the catheter was removed, and the puncture site was closed. The leg was wrapped with an elastic bandage. After the procedure, the patient received medical treatment and used compression stockings for three months.

Radiofrequency ablation (RA)

All patients underwent tumescent anesthesia around the saphenous vein ablation line. A sheath was inserted into the great saphenous vein (GSV) from the knee (RDUSG), and an RA catheter was placed with its tip 2-3 cm distal to the saphenofemoral junction. Following tumescent anesthesia, each 7 cm segment was exposed to 120 °C for 20 seconds. During the procedure, the patient was placed in the Trendelenburg position to apply compression to the saphenous vein line. After the operation, pressure dressing was applied to the patients, who then put on compression stockings.

Cyanoacrylate embolization (CAE)

Under the guidance of RDUSG, a puncture was performed under local anesthesia using the Seldinger technique from a suitable area at the knee level, and then a sheath was placed. InvamedVenaBLOCK embolizing agent system was used in all patients. The catheter of the system was advanced to approximately 3 cm distal to the saphenofemoral junction. The patient was placed in the Trendelenburg position and then suppressed and collapsed using a saphenofemoral junction RDUSG probe. In about 30 seconds, CA was injected continuously along the saphenous vein tracing, and external pressure was applied simultaneously. Compressions were terminated 3-4 minutes after the injection. Afterward, the reduction in vein diameter and the increase in echogenicity in the vein wall were checked using RDUSG. None of the patients received an elastic bandage and put on compression stockings.

Ethical considerations

The study was approved by the Scientific Research and Publication Ethics Committee of Osmaniye Korkut Ata University (11.11.2022/2022-9-7). Permission was obtained from the hospital.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) at a significance level of 0.05. Mean ± standard deviation and median (minimum-maximum) were used for continuous data. Frequency (n) and percentage (%) were used for categorical variables. A one-way ANOVA test and chi-square test were used to compare the groups.

RESULTS

Table 1 shows the participants' gender, age, GSV diameter, and CEAP classification.

Table 1. *Participants' Characteristics (n = 1073)*

Variables	Total n (%)	EVLA n (%)	RFA n (%)	CAE N (%)	p
Gender					
Woman	854 (79.59)	314 (76.21)	183 (79.56)	357 (82.83)	0.07
Man	219 (20.41)	98 (23.79)	47 (20.44)	74 (17.17)	0.06
Pre-procedural CEAP classification					
Class 2	378 (35.23)	155 (37.62)	56 (24.35)	167 (38.75)	0.11
Class 3	531 (49.49)	181 (43.93)	128 (55.65)	222 (51.51)	0.09
Class 4	141 (13.14)	68 (16.51)	39 (16.96)	34 (7.89)	0.06
Class 5	23 (2.24)	8 (1.94)	7 (3.04)	8 (1.85)	0.07
GSV diameter	6.99 ± 1.24	7.14 ± 1.07	7.23 ± 1.11	6.73 ± 1.67	0.07
Age (year)	43.36 ± 9.13	46.24 ± 11.31	41.56 ± 10.22	42.21 ± 8.02	0.08

GSV; great saphenous vein, RFA; radiofrequency ablation, EVLA; endovenous laser ablation, CAE; cyanoacrylate embolization.

Table 2. *Procedures (n = 1073)*

	EVLA n : 412	**RFA n : 230**	**CAE n : 431**	**p**
GSV ablation length (cm)	30.22 ± 5.21	31.13 ± 6.11	31.41 ± 6.24	0.82
Duration of the procedure (min)	16 (12-24)	11 (10-13)	8 (6-10)	0.01
Amount of tumescent anesthesia (ml)	300 (60-600)	260 (50-540)	–	0.08
Occlusion rate				
1. month	408 (99.02%)	229 (99.56%)	426 (98.83%)	0.12
1. year	402 (97.57%)	226 (98.26%)	412 (95.59%)	0.06
5. year	396 (96.11%)	221 (96.08%)	397 (92.11%)	0.05

GSV; great saphenous vein, RFA; radiofrequency ablation, EVLA; endovenous laser ablation, CAE; cyanoacrylate embolization.

Table 3. *Mean VCSS Scores (n = 1073)*

	EVLA (n : 412)	RFA (n : 230)	CAE (n : 431)	Anova	p
VCSS					
Before procedure	8.45 ± 1.87	8.56 ± 1.73	8.63 ± 1.81	24.45	0.07
1. month	4.53 ± 1.04	4.78 ± 1.08	4.47 ± 1.01	12.22	0.06
1. year	1.19 ± 1.06	1.26 ± 1.05	1.13 ± 1.01	11.56	0.14
5. year	1.53 ± 1.04	1.22 ± 1.03	1.88 ± 1.03	17.43	0.08

VCSS; venous Clinical Severity Score, RFA; radiofrequency ablation, EVLA; endovenous laser ablation, CAE; cyanoacrylate embolization.

Table 4. *Complications (n = 1073)*

Complication	**EVLA n (%)**	**RFA n (%)**	**CAE n (%)**	**P**
Paresthesia				
1. month	76 (18.44)	21 (9.13)	15 (3.48)	0.02
1. year	2 (0.48)	0	0	0.06
5. year	0	0	0	
Pain				
1. month	152 (36.89)	61 (26.52)	57 (13.22)	0.03
1. year	13 (3.15)	0	2 (0.46)	0.06
5. year	0	0	0	
Pigmentation				
1. month	53 (12.86)	12 (5.22)	0	0.00
1. year	1 (0.24)	0	0	0.06
5. year	0	0	0	
Phlebitis				
1. month	26 (6.31)	12 (5.22)	14 (3.25)	0.05
1. year	0	0	0	
5. year	0	0	0	
Ecchymosis				
1. month	105 (25.49)	42 (18.26)	5 (1.16)	0.01
1. year	0	0	0	
5. year	0	0	0	
Induration				
1. month	14 (3.40)	3 (1.30)	0	0.04
1. year	1 (0.24)	0	0	0.06
5. year	0	0	0	
Burn				
1. month	8 (1.94)	2 (0.87)	0	0.04
1. year	0	0	0	
5. year	0	0	0	
DVT				
1. month	7 (1.70)	2 (0.87)	0	0.05
1. year	0	0	0	
5. year	0	0	0	0.14

DVT; deep vein thrombosis, RFA; radiofrequency ablation, EVLA; endovenous laser ablation, CAE; cyanoacrylate embolization.

The majority of the participants were women (79.59%). Most participants belonged to CEAP 2 and CEAP 3 classes (84.72%). The EVLA group consisted of 314 women and 98 men (412 in total). The RFA group consisted of 183 women and 47 men (230 in total). The CAE group consisted of 357 women and 74 men (413 in total). The EVLA, RFA, and CAE groups had a mean age of 46.24 ± 11.31, 41.56 ± 10.22, and 42.21 ± 8.02, respectively ($p \geq 0.05$). The EVLA, RFA, and CAE groups had a mean GSV diameter of 7.14 ± 1.07, 7.23 ± 1.11, and 6.73 ± 1.67, respectively ($p \geq 0.05$) (Table 1).

Table 2 shows the procedures the patients underwent.

The EVLA, RFA, and CAE groups had a mean ablated vein length of 30.22 ± 5.21 cm, 31.13 ± 6.11 cm, and 31.41 ± 6.24 cm, respectively. The EVLA and RFA groups had a mean tumescent anesthesia volume of 300 ml (60-600 ml) and 260 ml (50-540 ml), respectively. The EVLA, RFA, and CAE groups had a mean procedure duration of 16 min, 11 min, and 8 min, respectively ($p < 0.01$). The RDUSG examination showed that the procedures were successful in all groups. The target vessel segments were closed entirely. In the next period, > 5 cm partial recanalizations were observed within one year. The EVLA, RFA, and CAE groups had a mean 1-year occlusion rate of 97.57%, 98.26%, and 95.59%, respectively ($p \geq 0.05$).

Table 3 shows the pre- and post-procedure VCSS values of the groups.

There was no significant difference in pre- and post-procedure VCSS scores between the groups ($p \geq 0.05$).

Table 4 shows the post-procedure complications.

While the highest number of complications was observed in the first month in all groups, there was a significant decrease over time. No complications developed in the patients in the fifth year. Paresthesia, ecchymosis, pain, pigmentation, induration, burn, phlebitis, and DVT were significantly more common in the EVLA group. The complications were least common in the CAE group ($p \leq 0.05$).

DISCUSSION

Varicose veins reduce people's quality of life because they are visually unappealing and cause physical signs and symptoms. They also cause significant workforce losses. EVLA, RFA, and CAE are the most common types of treatment for CVI.

In the present study, the majority of the patients were women (79.59%). Most patients belonged to CEAP 2 and CEAP 3 classes (84.72%). The EVLA, RFA, and CAE groups had a mean age of 46.24 ± 11.31, 41.56 ± 10.22, and 42.21 ± 8.02, respectively. The groups were homogenous in terms of age, CEAP classification, and gender, which is consistent with the literature (3, 10, 11). Güven et al. (6) reported that 318 (180 women and 138 men) patients had a mean age of 43.6 ± 12.78 years. Gücü et al. (12) recruited a sample of 48% men (mean age: 42.1 ± 13.4) and 52% women (mean age: 44.68 ± 10.6).

The EVLA, RFA, and CAE groups had a mean GSV diameter of 7.14 ± 1.07, 7.23 ± 1.11, and 6.73 ± 1.67, respectively ($p \geq 0.05$), which is consistent with the literature (10, 12, 13).

In the present study, CAE took shorter than EVLA and RFA, which is consistent with the literature (10, 14).

There was no significant difference in occlusion rates in the first month between the groups. The EVLA and RFA groups had higher occlusion rates in the fifth year than the CAE group. However, there was no significant difference in occlusion rates in the fifth year between the EVLA and RFA groups. Yang et al. (15) focused on 3-year occlusion rates in CAE and RFA patients and reported that CAE and RFA had a midterm treatment success of 100% and 99%, respectively. Ovalı et al. (16) investigated 1-year occlusion rates in CAE and RFA patients and found that the majority of the CAE (99.5%) and RFA (96.6%) groups had complete occlusion of the GSV in the twelfth month. Morrrison et al. (17) looked into 3-year occlusion rates in CAE and RFA patients and determined that the CAE and RFA groups had a GSV occlusion rate of 94.4% and 91.9%, respectively. Almeida et al. (18) observed the 3-year CAE occlusion rate as 94.7%. Lawaetz et al. (19) evaluated the 5-year outcomes of treatment with RFA, EVLA, UGFS, and high ligation and stripping (HL/S). They determined that the need for recanalization in the RFA, EVLA, UGFS, and HL/S groups were 5.8%, 6.8%, 31.5%, and 6.3%, respectively. Ay et al. (20) followed up 217 patients for a year and compared surgery, CAE, and RFA. The surgery group had a significantly higher occlusion rate than the CAE and RFA groups. Eroğlu et al. (3) followed up 525 patients for two years and compared RFA, EVLA, and CAE. The RFA, EVLA, and CAE groups had occlusion rates of 90.9%, 91.5%, and 92.6%, respectively. Morrison et al. (21) followed up 89 patients for five years. In month 60, the GSV was completely closed in 100% (33/33) veins in the RFA group and 93.6% (44/47) veins in the CAE group. In their meta-analysis, Chen et al. (22) have reported no significant difference in occlusion rates between CAE and RFA patients. El Kilic et al. (14) compared RFA, EVLA, and CAE in 232 patients. In the five-year follow-up, the RFA and CAE groups had higher occlusion rates than the EVLA

group. Koramaz et al. (10) reported similar rates of occlusion in CAE (98.6%) and EVLA (97.3%) patients. Proebstle et al. (23) observed a 98.6% occlusion rate in CAE patients. Morrison et al. (13) found that CAE and RFA had 99% and 96% occlusion rates, respectively. Güven et al. (6) determined that the saphenous vein was recanalized in 16 patients at the 6-month RDUSG. Tural et al. (5) reported an occlusion rate of 97.4% in CAE patients in month 12.

In the present study, CAE and RFA caused fewer complications than EVLA. The EVLA group had higher rates of ecchymosis, paresthesia, pigmentation, pain, phlebitis, burn, and DVT in the first month than the CAE and RFA groups. However, there was a significant reduction in complications in all groups in the first and fifth years. Koramaz et al. (10) compared EVLA and CAE and reported no paresthesia, burn marks, and pigmentation in CAE patients. Yang et al. (15) found that superficial phlebitis was the most common complication in the mid-term follow-up in the 5% and 15% of CAE and RFA patients, respectively. Ovalı et al. (16) reported skin burn only in one RFA patient (0.8%). They also found that pain, ecchymosis, and tenderness were more common in the RFA group than in the CAE group. Morrrison et al. (17) examined the three-year outcomes of CAE and RFA and observed stable improvement in symptoms and quality of life in both groups. They determined that the two groups had similar complication rates in the 24th and 36th months. Eroğlu et al. (3) found that the level of periprocedural pain was significantly lower in the SAE group than in the RFA and EVLA groups and that ecchymosis and phlebitis were more common in the RFA group than in the SAE and EVLA groups. Balcı et al. (24) compared the 6-month effectiveness of CAE and RFA (n=398) and detected that the CAE group had higher rates of ecchymosis and higher post-procedure comfort than the RFA group. Morrison et al. (21) reported sustained improvement in CAE patients' symptoms and quality of life over five years. Chen et al. (22) found that CAE patients had a lower risk of ecchymosis and paresthesia than RFA patients. In their meta-analysis, Garcia et al. (25) have concluded that CAE patients have less interventional pain and fewer minor complications than EVLA patients. El Kilic et al. (14) determined that EVLA patients had significantly higher complication rates than RFA and CAE patients. Güven et al. (6) detected thrombophlebitis in six patients and ecchymosis at the puncture site in 12 patients during early outpatient checkups.

In the present study, all groups had similar pre- and post-procedure VCSS scores during the five-year period. Ay et al. (20) reported that the surgery and RFA groups had higher VCSS scores than the CAE groups. Eroğlu et al. (3) determined that the RFA, EVLA, and CAE groups had the same mean pre-procedure VCSS scores. There was a reduction in VCSS scores in all groups in the sixth month. The drop continued in the first and second years. The CAE group had a significantly lower mean VCSS score in the sixth month and second year than the RFA and EVLA groups. Chen et al. (22) reported no significant difference in VCSS scores between CAE and RFA patients. El Kilic et al. (14) also found no significant difference in VCSS scores between EVLA, RFA, and CAE patients. Güven et al. (6) found that CAE patients had a significantly lower mean VCSS score in the post-procedure period than in the pre-procedure period. Poulose et al. (26) found that patients with CVI had a mean VCSS score of 11.47.

CONCLUSION

This study investigated the five-year results of CAE, RFA, and EVLA in 1073 patients. The results show that CAE, RFA, and EVLA are minimally invasive treatment options preferred by most patients. Patients prefer EVLA and RFA because those two methods have satisfactory long-term results despite early side effects, such as procedure site pain, ecchymosis, hematoma, and paresthesia. In recent years, CAE has become a popular treatment option because it has a high success rate in the early period, causes fewer complications, takes shorter to apply, and requires no anesthesia and no compression. CAE, RFA, and EVLA have similar long-term results. Therefore, CAE is recommended for patients with CVI who want to get rid of varicose veins and improve their quality of life.

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Sažetak

PETOGODIŠNJI KLINIČKI REZULTATI LEČENJA 1073 PACIJENTA SA PROŠIRENIM VENAMA, LEČENIH RADIOFREKVENTNOM ABLACIJOM, ENDOVENSKOM LASERSKOM ABLACIJOM I EMBOLIZACIJOM CIJANOAKRILATOM

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Uvod: Malo je istraživanja o dugoročnim ishodima radiofrekventne ablacije, endovenske laserske ablacije i cijanoakrilatne embolizacije. Ova studija je retrospektivno ispitala kliničke rezultate radiofrekventne ablacije, endovenske laserske ablacije i metoda cijanoakrilatne embolizacije.

Materijali i metode: Ukupan broj pacijenata u ovoj studiji koji su se javili u Kliniku, sa dijagnozom hronične venske insuficijencije između navedenih datuma i lečeni od proširenih vena bio je 1256. Uzorak: 431 pacijent u grupi cijanoakrilatne embolizacije, 230 pacijenata u grupi radiofrekventne ablacije, 412 pacijenata u grupi endovenske laserske ablacije, što je ukupno 1073 pacijenta. Bilateralna cijanoakrilatna embolizacija, radiofrekventna ablacija i endovenska laserska ablacija nisu primenjene kod pacijenata u istoj sesiji.

Rezultati: Kada su ispitane jednogodišnje stope okluzije, utvrđene su kao 97,57%, 98,26% i 95,59% u grupama endovenske laserske ablacije, radiofrekventne ablacije i cijanoakrilatne embolizacije. Nije bilo značajne razlike u skoru venske kliničke ozbiljnosti između grupa pre i posle procedure. Bol, parestezija, ekhimoze, pigmentacije, induracija, opekotina, duboka venska tromboza i flebitis bili su značajno češći u grupi koja je primala endovensku lasersku ablaciju.

Zaključak: Komplikacije su uočene u grupi koja je primala cianoakrilatnu embolizaciju. Primene endovenske laserske ablacije, radiofrekventne ablacije i embolizacije cijanoakrilatom imaju slične dugoročne rezultate. Zbog toga se cijanoakrilatna embolizacija preporučuje pacijentima sa hroničnom venskom insuficijencijom koji žele da se otarase proširenih vena i poboljšaju kvalitet života.

Ključne reči: Radiofrekventna ablacija, Endovenska laserska ablacija, cijanoakrilatna embolizacija, Klinički rezultati.

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Case report

BILATERAL AVASCULAR NECROSIS OF FEMORAL HEAD FOLLOWING COVID-19 INFECTION: CASE SERIES

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Abstract: **Introduction**: Despite having a substantial impact on survivors' mobility and leading to morbidity, musculoskeletal involvement was the post-COVID-19 infection sequelae area that received the least attention in the literature. Reviewing the COVID-19 histories of patients who visited a tertiary health center, the research is aimed at finding an association between COVID-19 infection and avascular femoral head necrosis, a condition brought on by insufficient blood flow. Avascular necrosis of the femoral head is a condition characterized by a restricted range of motion, pain, and disturbance of gait. It is brought on by insufficient blood flow. **Case reports:** We discussed several examples in which COVID-19 caused individuals to develop bilateral femoral head necrosis. When COVID-19 infection is the only factor present, and corticosteroids are used to treat it, avascular necrosis of the femoral head may become more prevalent. Detecting avascular necrosis of the femoral head in its early stages, hip MRI might reduce the patient's disability and need for continuous treatment. **Conclusion:** Early identification and treatment of AVN patients reduce the need for surgery and the chance of disabilities.

Keywords: Avascular necrosis (AVN), sedimentation rate of erythrocytes (ESR), C-reactive proteins (CRP), White blood cells (WBC), Steroid-induced AVN femoral head (SANFH).

INTRODUCTION

COVID-19 patients suffer a range of symptoms, including fever, sore throats, acute respiratory distress syndrome, thrombotic events, and acute myocardial infarction. These symptoms are only a few of the significant problems that result from the virus's systemic hyper-inflammation (1). According to the case report series by Agarwala et al, a lack of blood flow to the bone tissue causes avascular femoral head necrosis, which is characterized by bone marrow necrosis and osteocyte loss (2, 3). For COVID-19 treating patients with hip pain, diagnostic information, and imaging recommendations are not yet available. Here, we present 3 cases of symptomatic femoral head necrosis that developed following COVID-19 treatment.

Case report No 1

On April 13, 2021, a 28-year-old female patient was diagnosed with COVID-19, for which she was admitted to an intensive care Karnataka Institute of Medical Science, India. She received 80 mg per day of intravenous methylprednisolone for a week while in the hospital. She had right hip joint ache four months after COVID-19. A local doctor treated her with analgesics for three months. She subsequently developed both hip and joint pain. AVN with oedema was seen in Magnetic Resonance Imaging (MRI) (Figure 1, 2, 3). She had a hybrid total hip replacement.

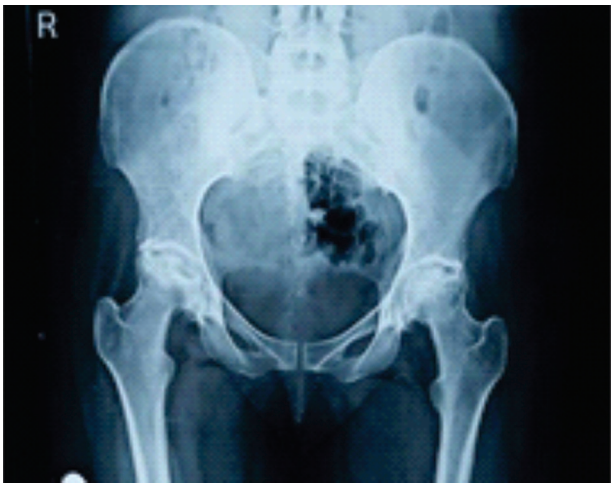

Figure 1. *X-ray of pelvis and both hips AP view*

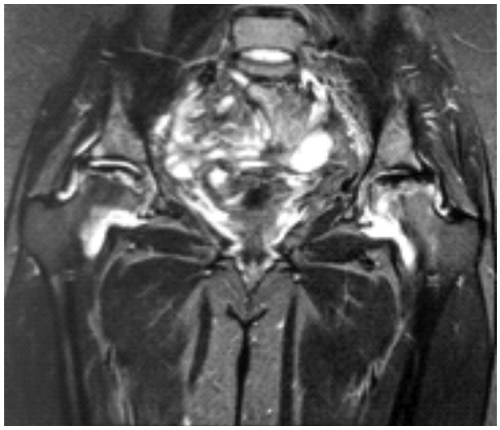

Figure 2. *Coronal view of Magnetic resonance imaging of bilateral femoral heads*

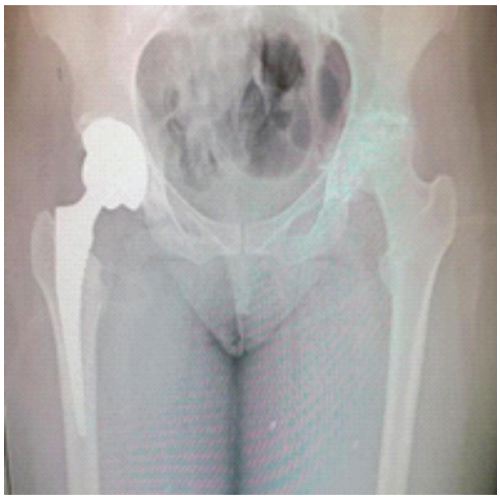

Figure 3. *Post-operative x-ray of the pelvis and both hips - AP view*

Case report No 2

On June 24, 2021, a male patient, 32 years old, was diagnosed with COVID-19 and was thereafter admitted to the hospital. He received intravenous (IV) methylprednisolone 80 mg/day for a week while in the hospital. He started experiencing right hip joint pain six months later. A nearby physician treated him with analgesics for eight months. He later developed both hip joint pain and stiffness as a result. Magnetic Resonance Imaging (MRI) revealed both femoral heads to have AVN. He underwent an uncemented total hip arthroplasty (Figure 4 and 5).

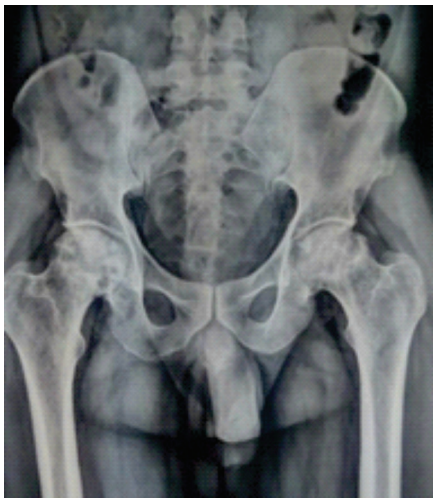

Figure 4. *X-ray of pelvis and both hips - AP view*

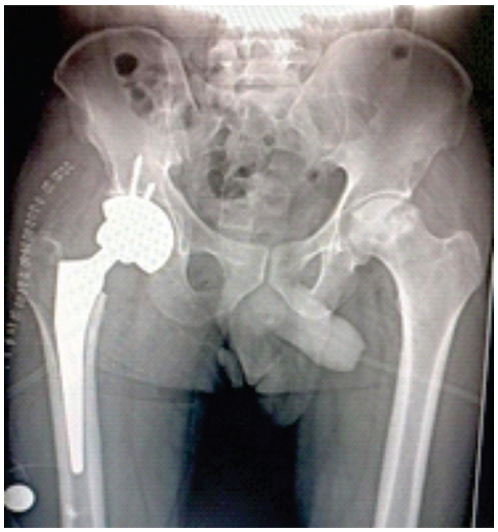

Figure 5. *Post operative-ray of the pelvis and both hips - AP view*

Case report No 3

On July 16, 2021, a male patient, 28 years old, was diagnosed with COVID-19 and was thereafter admitted to the Karnataka Institute of Medical Science and Hospital, India. He received intravenous (IV) methylprednisolone 80 mg/day for a week while in the hospital. He started experiencing right hip joint pain 14 months later. He later developed both hip and joint pain as a result. Magnetic Resonance Imaging (MRI) revealed both femoral heads to have AVN. He underwent core decompression with bone marrow aspirate infiltration (Figure 6 and 7).

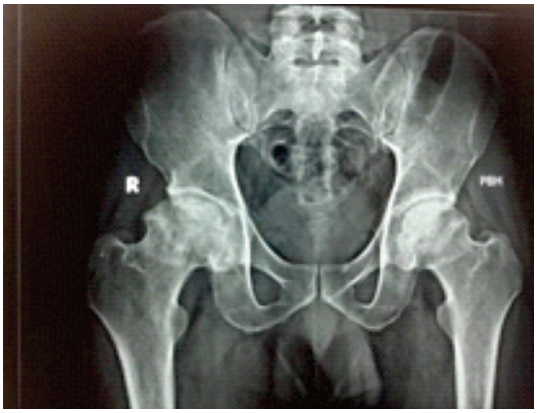

Figure 6. *X-ray of PBH - AP view*

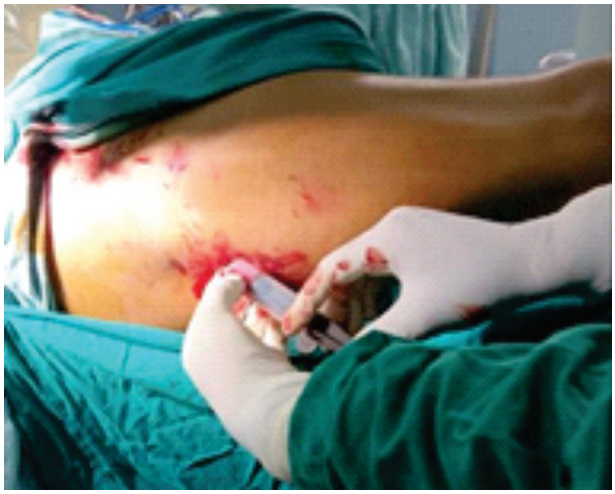

Figure 7. *Intra-operative bone marrow infiltration*

Physical examinations of all three patients showed that hip joint flexion or rotation worsened the preexisting discomfort. There was a limited range of motion because of discomfort in both hips, particularly the right hip. With the exception of the hip, no other joints were painful to move, and the range of motion was within normal ranges. Muscle strength was normal in the patient, and reflexes in the deep tendons were normal. Neither of the three patients had any particular risk factors, such as alcohol use, smoking, sickle cell anemia, trauma, or systemic lupus erythematosus, that may have led to AVN of the femoral head. Nevertheless, a SARS-CoV-2 PCR test allowed for the patient's COVID-19 diagnosis.

All three patients who came to our outpatient clinic complaining of severe hip pain were first evaluated with conventional radiographs and subsequently with an MRI. An MRI was used to diagnose AVN, and a senior musculoskeletal radiologist for interpretation. T-1-weighted MRI pictures showing a single density "bandlike" lesion with a low signal intensity rim around necrosis. The diagnosis of AVN was made using T-2 weighted MRI images showing a "double line sign" made up of an inside high signal intensity rim and an outward low signal intensity rim. Using Ficat and Arlet grading, the AVN was staged in radiographs. "Mitchell classification" was used to stage the AVN based on the MRI signal inside the lesion's epicenter. The necrotic angle severity was calculated using the mid-coronal and mid-sagittal images from the MRI, and it was then categorized using the modified "Kerboul angle" stages -1 (200°), stage 2 (200°-249°), stage 3 (250°-299°), and stage 4 (> 300°) (4). Examples of laboratory parameters include erythrocyte sedimentation rate, C-reactive protein, and total white blood cell count.

To exclude concomitant septic arthritis, hip aspiration was performed on patients who presented with increased inflammatory markers. Total hip arthroplasty was performed on both of our patients.

DISCUSSION

Ages 40 and under were the most often affected age group in this case series investigation, affecting all three individuals. The majority of COVID-19 infection patients are asymptomatic, but some have mild to severe symptoms that can affect several organ systems and lower quality of life. A hypercoagulable condition is brought on by COVID-19, which raises the possibility of thrombosis. Pro-inflammatory cytokines such as Interleukin (IL-1, IL-6, IL-17) and tumor necrosis factor-alpha, are increased according to immunological investigations (5). Vascular wall fragmentation, endothelial cell pyknosis, and karyorrhexis are the distinctive pathological characteristics. Small and medium-sized blood arteries are typically affected by neutrophilic infiltrates, which are the typical histological findings of vasculitis (6). Glucocorticoids impair the blood vessels' ability to respond to vasoactive chemicals, which results in vascular constriction that affects the femoral head and causes further femoral head ischemia. "Micro RNA (miR)-596" is discovered to be up-regulated in instances of steroid-induced avascular necrosis femoral head (SANFH), which hinders the healing of osteonecrotic bone by preventing bone stromal cell proliferation and osteogenic differentiation (7). However, in the case report series of Agarwala et al., they reported that avascular femoral head necrosis developed in three patients who received corticosteroids in the treatment of COVID-19. The average time between the COVID-19 diagnosis to the start of AVN symptoms was 58 days (2). Li et al. looked into 1406 COVID-19 patients. One patient who had 1960 mg of methylprednisolone was found to have bilateral femoral head necrosis. According to observations in the literature, the average time it takes for AVN to manifest following corticosteroid medication is between 6 and 12 months (8). When 23 patients with AVN following COVID-19 were studied by Daltro et al., they discovered that 66% had moderate to severe COVID-19 infections and had received corticosteroid treatment. The remaining 33% had a mild COVID-19 past without using corticosteroids. Overall, they reported that in these 23 individuals, the median interval between COVID-19 infection and the start of AVN was 132.8 days (between 64 and 180) (9).

CONCLUSION

Since COVID-19 infection alone and corticosteroid medication administered in its treatment may increase the incidence of AVN, clinicians should be cau-

tious about the early detection and treatment of AVN in post-COVID patients presenting with hip and thigh discomfort.

Learning objective

► Steroids are "life-saving in the treatment of COVID-19".

► Individuals with COVID-19 infection are more likely to develop avascular femoral head necrosis at minimal steroid dosages, and early presentation.

► Magnetic resonance imaging of the hips can be used to confirm a diagnosis if someone complains of hip and thigh discomfort.

► Advanced stage avascular femoral head necrosis can be effectively treated in individuals receiving total hip arthroplasty.

Declaration:

Human subjects: All participants in this study provided informed consent or waived it. The ethics committee of the KARNATAKA INSTITUTE OF MEDICAL SCIENCES approved 728/2021-22. The institutional ethics committee gave its approval to the project.

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Author contributions.

Dr. S F Kammar: Organising, collecting evidence, performing statistical analysis, drafting an article, reducing, and editing. DR.CHANDRASHEKAR MUDGAL: Statistical analysis, article authoring, and data gathering Planning, data gathering, statistical analysis, and article writing are each performed by Dr. Mahuchandra R. DR. AKASH KUMAR. Planning, data gathering, statistical analysis, writing, reducing, and editing an article.

Sažetak

BILATERALNA AVASKULARNA NEKROZA GLAVE BUTNE KOSTI NAKON INFEKCIJE COVID-19: PRIKAZ SLUČAJA

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Uvod: Uprkos tome što ima značajan uticaj na mobilnost preživelih i dovodi do morbiditeta, zahvaćenost mišićno-skeletnog sistema bila je oblast posledica infekcije posle KOVID-19 kojoj se u literaturi posvetilo najmanje pažnje.

Pregledom istorija KOVID-19 pacijenata koji su posetili tercijarni zdravstveni centar, istraživanje je imalo za cilj pronalaženje veze između infekcije KOVID-19 i avaskularne nekroze glave butne kosti, stanja izazvanog nedovoljnim protokom krvi.

Prikaz slučaja: Analizirali smo nekoliko primera u kojima je KOVID-19 prouzrokovao da pojedinci razviju bilateralnu nekrozu glave butne kosti. Kada je infekcija KOVID-19 jedini prisutni faktor, a za lečenje se koriste kortikosteroidi, avaskularna nekroza glave butne kosti može postati češća. Otkrivanjem avaskularne nekroze glave butne kosti u ranim fazama, MRI kuka može smanjiti invaliditet pacijenta i potrebu za kontinuiranim lečenjem. **Zaključak**: Rana identifikacija i lečenje pacijenata sa AVN smanjuje potrebu za operacijom i mogućnost invaliditeta.

Ključne reči: Avaskularna nekroza, brzina sedimentacije eritrocita, C-reaktivni proteini, Bela krvna zrnca, Steroidom indukovana AVN femoralna glava.

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Review article

BENEFITS OF BREASTFEEDINIG FOR MOTHER AND CHILD

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Abstract: Breastfeeding is the best way to feed a child from the first six months until the end of the second year. The unbreakable bond during pregnancy between a mother and her child continues during the lactation process, providing numerous benefits for both the mother and the child.

Due to the effects of many hormones after childbirth, lactation offers numerous advantages for the mother. Oxytocin causes reduction of the uterus and bleeding, absence of menstruation, faster return of body weight, lower risk of cancer of the reproductive organs, and prevents the occurrence of osteoporosis and the development of the metabolic syndrome. Breastfeeding certainly ensures a better emotional bond with the child. Specificity in the composition of human milk provides the newborn with short-term and long-term protective effects. Thanks to human oligosaccharides, immunoglobulins, and polyunsaturated fatty acids that influence the composition of the microbiome of the newborn's intestine, as well as the formation of its immune response, breastfed children suffer less from respiratory and digestive infections, food allergies, autoimmune diseases and have been proven to have a higher IQ.

Breastfeeding is the best form of feeding for mother and child. The specificity of the composition of human milk ensures optimal growth and development of the child and a healthier life for its mother.

Keywords: breast milk, breastfeeding, benefits of breastfeeding, mother, oxytocin, human oligosaccharides, newborn.

INTRODUCTION

Numerous international organizations involved in the promotion of breastfeeding give recommendations that mother's milk nutrition is optimal for a child, especially in the first six months of life, and as a supplement until the end of the second year (1-3). All the nutritional needs of the newborns can be fulfilled with the mother's milk. Its principal role is adequate and optimal growth and development. It is also known to have an imminent role in preventing the development of numerous diseases in the newborn, as well as to participate in the emotional connection between mother and child, **Tables 1** and **2** (4).

Table 1. *Benefits of breastfeeding for the mother (5)*

	Mother's benefits
1.	Reduction of uterus and bleeding
2.	Reduction of body mass
3.	Postpartum amenorrhea
4.	Absence of stress, relaxation, and calmness of the mother
5.	Absence of depression
6.	Lower incidence of breast cancer
7.	Lower frequency of cancer of reproductive organs (ovaries, uterine endometrium)
8.	Lower risk for osteoporosis
9.	Lower risk of Alzheimer's disease
10.	Lower risk of developing metabolic syndrome
11.	Lower risk of cardiovascular disease
12.	Lower risk of developing rheumatoid arthritis
13.	Lower risk of developing multiple sclerosis

Human milk is a living, biological substance that enables and maintains the unbreakable bond between a mother and her child even after childbirth (6).

To promote and popularize breastfeeding there are numerous recommendations and guides explaining the advantages of breastfeeding for mothers and children. It plays a key role in the early initiation of breastfeeding and its application during the child's stay in the maternity hospital. Great importance is given to

Table 2. *Benefits of breastfeeding for a child (3)*

The benefits of a child are lower risks for	
1.	inflammation of the middle ear
2.	infections of the upper and lower respiratory organs
3.	child's asthma
4.	occurrence of atopic dermatitis
5.	NEC
6.	obesity
7.	celiac disease
8.	type 1 and type 2 diabetes
9.	inflammatory bowel diseases
10.	leukemia (AML)

pediatricians and gynecologists who work in maternity hospitals as educators of mothers and promoters of breastfeeding through their daily practice. It is necessary to acquaint future parents with the advantages of breastfeeding that both mother and child will have, as well as the entire social community (3).

Benefits of breastfeeding for the mother

Oxytocin is a neuropeptide hormone synthesized in the supraoptic and paraventricular nuclei of the hypothalamus. During the breastfeeding process, the stimulation of the breast nipple affects the increased secretion of oxytocin and the production of milk. Under the influence of hormones, the mother will create positive emotions. She has a feeling of happiness and satisfaction, a positive facial expression, stress, and anxiety are reduced, and positive feelings towards the child increase. It is believed that the changes in oxytocin concentrations that accompany the breastfeeding process are actually a protective mechanism in the psychological changes that occur in mothers (7).

The released oxytocin supports the postpartum contractility of the uterus and its faster return to the state before childbirth. There is a decrease in bleeding, which prevents the occurrence of postpartum anemia. High concentrations of oxytocin ensure a higher pain threshold for the mother, preparing her for faster postpartum recovery (5). Two years after giving birth, changes in the brain structure were recorded in women. The postpartum decrease in the volume of the gray matter of the brain represents an additional protective mechanism for the woman, preparing her for motherhood (8).

Breastfeeding is important for maintaining a mother's mental health. The positivity of breastfeeding will influence the establishment of a better cycle of sleep and wakefulness, providing mothers with adequate rest and relaxation. Studies show that breastfeeding reduces the incidence of postpartum depression. If depression does occur, early recognition of the symptoms and seeking professional help will reduce the possibility of early termination of breastfeeding your child (9).

Mothers who exclusively or predominantly breastfed their children compared to those who did not or partially breastfed have a higher chance of continued lactational amenorrhea (10). The absence of menstrual cycles during breastfeeding, interruption of ovulation, and thus protection against possible new pregnancies, can be explained by high concentrations of prolactin (5).

The protective effect of breastfeeding on ovarian and breast cancer is reflected in the suppression of gonadotropin production and lower estrogen concentrations. The cumulative effect of breastfeeding for more than a year significantly affects the reduction of estrogen concentration levels and the suppression of the proliferation and differentiation of cancerous cells. The positive influence of breastfeeding on the occurrence of possible cancerous cell mutations and malignant transfers in the female reproductive organs has also been demonstrated (11).

During pregnancy and the period of lactation, due to a greater need for calcium, increased bone absorption may occur. The daily production of up to 800 ml of milk per day can cause a loss of up to 200 mg of calcium in the mother. Low concentrations of estrogen during lactation inhibit the formation of periosteal bone less, resulting in the formation of denser bone mass. In about a year after the cessation of breastfeeding, thanks to adaptive mechanisms, bone mass is restored, and the protective mechanism for the occurrence of osteoporosis remains for many years (5, 10).

The breastfeeding process requires about 2100 kcal/day, so the weight of the mother, which was accumulated during pregnancy, will be gradually lost during the lactation period. Higher caloric consumption during lactation was proven mainly in mothers with normal weight, but not in obese mothers, who had a BMI > 35 kg/m^2. Ethnicity, BMI, nutrition, physical activity, and education of mothers are often cited as confounding factors in the correlation between weight loss and breastfeeding (3, 11, 12). Cardiologists suggest that breastfeeding has a protective effect on the development of coronary artery disease. Breastfeeding in the mother can cause changes in fat and sugar metabolism, as well as regulation of blood pressure values. The release of oxytocin during lactation contributes to faster glucose metabolism, which reduces the onset of insulin resistance and type 2 diabetes, as well as the amount of visceral fat (11). The develop-

ment of maternal metabolic syndrome is inversely proportional to the length of lactation. This syndrome is characterized by central obesity, hypertension, insulin resistance, dyslipidemia, and high risks for cardiovascular disease and mortality (5).

The reduction in the onset of Alzheimer's disease in nursing mothers is attributed to the effect of estrogen on receptors located in the brain. A lower risk of developing autoimmune diseases, such as multiple sclerosis, was associated with the length of breastfeeding in mothers. Studies have also shown a lower risk for the development of rheumatoid arthritis unrelated to the length of time mothers are breastfeeding (5).

Benefits of breastfeeding for a child

The composition of human milk includes human oligosaccharides (HMO), which are indigestible carbohydrates. Their composition and amount in milk are influenced by the stage of lactation, environmental factors, and genetic factors. Their role is to establish adequate micro colonization of the intestinal tract of newborns, thereby contributing to the development of the child's immune function. Their special role is reflected in stimulating the growth of Bifidobacteria, which affects the modulation of the immune response of newborns. The better immune system of breastfed children provides a lower risk of upper and lower respiratory tract infections. The protective effect of mother's milk on middle ear infections in the first two years of life has been demonstrated. Studies have also proven that the length of breastfeeding affects the lower severity of respiratory infections, and thus the reduced rate of hospitalization and mortality (11, 13).

The protective role of breastfeeding in the occurrence of diarrhea is especially pronounced during the first six months in exclusively breastfed children. The protective role breastfeeding has on the development of gastrointestinal infections is achieved due to the specificity of the ingredients of human milk, but also due to the avoidance of contamination of dishes during other forms of feeding (11).

Breast milk has a special role in regulating the microbiome of the newborn. The mother's microflora, primarily Bifidobacteria, and Lactobacteria, is transferred into the secreted milk and affects the microflora of the nursing infant. The association between the increase in the incidence of type 1 diabetes in children and the decrease in the amount of Bifidobacteria (*Bifidobacteriumlongum subsp. infantis* (*B. Infantis*)) in the microbiome of newborns has been shown. Microorganisms from the intestinal flora that form a symbiosis with the enterocytes of the newborn maintain an intact intestinal barrier, break down HMO from breast milk, stimulate the production of immunoglobulins, and increase the concentration of short-chain fatty acids (SCFA). This interaction of the microbiome and enterocytes maintains an adequate immune barrier in breastfed infants providing them with protection if they are genetically predisposed to type 1 diabetes. Breastfeeding in children can affect the development of an adequate microbiome of the newborn with a predominance of *Bifidobacterium spec*. that would prevent pancreatic beta cell autoimmunity and type 1 diabetes in early childhood (14, 15).

In its latest revised guidelines, the European Academy of Allergy and Clinical Immunology (EAACI) suggested avoiding supplementation with cow's milk formulas in breastfed infants during the first week of life. The recommendations are given to avoid the possibility of later allergy to cow's milk proteins (16). To avoid food allergies in breastfeeding children, mothers are suggested to use potential allergens in their diet during pregnancy and breastfeeding (17). Breastfeeding in the first four months provides protection against the onset of atopic diseases until the end of the child's second year, and protection against asthma until the child's fifth year of life (18).

The pathogenesis of the development of Necrotic Enterocolitis (NEC), although still incompletely investigated, suggests that breastfed infants have been protected thanks to the specificity of the composition of the mother's milk. Immunoglobulin A, growth factors, probiotics, and HMO, with their influence on the immune response, represent protective factors for the integrity of intestinal enterocytes and prevent the development of NEC, especially in premature infants.

Thanks to the components from mother's milk in breastfed premature babies, there is less possibility of developing sepsis and invasive fungal infections, and thus the resulting neurodevelopmental disorders (19).

Breastfeeding will have a protective role in the development of celiac disease in predisposed individuals. It was concluded that the effect of breastfeeding is pronounced if gluten is introduced into the diet while the child is still breastfeeding (20).

Breastfeeding as a way of feeding infants had positive effects on metabolic, anthropometric, and genetic factors. Components of breast milk can influence epigenetic changes in the earliest life of the newborn. They initiate the process of DNA methylation, modify histones, and remodel chromatin, thereby participating in the control of gene expression in metabolic pathways and preventing obesity (21). Numerous studies confirm the positive relationship between breastfeeding and its protective role in the development of obesity during the child's life. Breastfeeding can be a protective factor in the rapid growth of a child during

the first year of life, which will prevent obesity from the second year and later in life (22). It affects the reduction of the prevalence of obesity during the period of adolescence, especially if brestfeeding lasted longer than one year (23). Breastfeeding that lasts at least four months has been suggested as a measure to prevent obesity and numerous chronic diseases, especially type 2 diabetes, in children as well as in their mothers. A positive effect for both was observed in the period from the second to the fifth year after childbirth (24).

Although the recommendations are that you should exclusively breastfeed for at least six months, there is evidence to support that even a shorter duration of breastfeeding can have a positive impact on the cognitive development of the child (25). The positive impact is primarily reflected in the emotional connection between mother and child during the breastfeeding process. The levels of certain hormones of the mother allow her to be calm, relaxed, and more attached to the child. The positivity of the parent's attitude towards the child will greatly influence the development of his cognitive abilities (26). In premature babies, substances from breast milk can affect the structural development of the brain. Polyunsaturated fatty acids (LCPUFA), especially docosahexaenoic acid (DHA), are considered to play an important role. Numerous hormones and growth factors that primarily affect the growth of glial cells and myelination, increasing the volume of the white young mass, are also highlighted. Research has shown that the development of the white matter of the brain is directly responsible for the intellect in humans. Children who have been breastfed, especially boys, show faster development and a larger volume of the brain's white matter. This suggests that breastfed children will have better cognitive and other intellectual functions later in life (27).

CONCLUSION

Under the auspices of the World Alliance for Breastfeeding Action (WABA), every year during the first week of August, the public's attention is drawn to the importance and importance of breastfeeding. This year's slogan "Stand up for breastfeeding, educate and support" additionally supports the fact that breastfeeding is an important public health issue, the promotion of which should be especially promoted by pediatricians and gynecologists. Breastfeeding is the best, easiest, most economical, most accessible, cleanest, safest, and most beautiful form of feeding for mother and child. The specifics of the composition of human milk, together with the mother's hormones, offer numerous advantages necessary for the optimal growth and development of the child and the healthier life of its mother.

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Sažetak

KORISTI DOJENJA ZA MAJKU I DETE

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Dojenje je najbolji način ishrane deteta tokom prvih šest meseci života, pa do kraja druge godine. Neraskidiva veza koja je postojala tokom trudnoće između majke i njenog deteta, nastavlja se i tokom procesa laktacije, dajući brojne benefite kako za majku tako i za dete.

Zahvaljujući dejstvu mnogih hormona nakon porođaja, laktacija nudi brojne prednosti za majku. Oksitocin uzrokuje smanjenje materice i krvarenja, izostanak menstruacije, brži povratak telesne mase, manji rizik za nastanak karcinoma reproduktivnih organa, sprečava nastanak osteoporoze kao i razvoja metaboličkog sindroma. Dojenje svakako obezbeđuje i bolju emocionalnu vezu sa detetom. Specifičnost u sastavu humanog mleka novorođenčetu pruža kratkoročna i dugoročna protektivna dejstva. Zahvaljujući humanim oligosaharidima, imunoglobulinima, polinezasićenim masnim kiselinama koji utiču na sastav mikrobioma creva novorođenčeta, kao i na formiranje njegovog imunog odgovora, dojena deca manje obolevaju od respiratornih i digestivnih infekcija, alergija na hranu, autoimunih bolesti dokazano imaju veći koeficijent inteligencije.

Dojenje predstavlja oblik hranjenja koji je najbolji za majku i dete. Specifičnost sastava humanog mleka obezbeđuje optimalan rast i razvoj deteta i zdraviji život njegove majke.

Ključne reči: majčino mleko, dojenje, korist dojenja, majka, oksitocin, humani oligosaharidi, novorođenče.

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Review article

IMPROVEMENT OF MEDICAL WASTE STORAGE PROCEDURES

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Abstract: Medical waste is all waste generated by healthcare institutions related to the performance of medical-technical actions in the field of diagnostics, therapy, or research activities. The adequate disposal of medical waste is an issue for virtually all South-eastern European countries primarily because these countries lack the necessary capacities for removing medical waste. The paper aims to review the results and experiences of treating medical waste, as well as the potential risks to patients and medical and non-medical personnel. Implementing a safe medical waste management system could significantly improve the quality of healthcare services and the health of patients, and preserve the environment. The use of steam sterilization has been suggested to reduce the content of biological agents in the waste to an acceptable level by thermal treatment, that is, to achieve biological inactivation.

Keywords: medical waste, storage, procedures, sterilization.

INTRODUCTION

Medical waste includes four types of waste: infectious waste, biohazard waste, pharmaceutical waste, and radioactive isotopes. Infectious waste includes all items that have been in contact with patients' blood (needles, syringes, bandages, gauze, scalpels, *etc.*), while biohazard waste includes organs, tissues, and amputated body parts, which are stored in cold storage and buried in city cemeteries under the supervision of sanitary inspection. Medicinal products returned from health institutions, as well as those that have expired, are classified as pharmaceutical waste. Radioactive isotopes are the remains of substances used in diagnostics and therapy and which, although unusable, contain a smaller or larger quantity of radioactivity (1).

The increase in the number of inhabitants in the European Union (EU) has been accompanied by an increasing amount of waste. EU countries discard 1.3 billion tons of waste annually, of which 40 million tons belong to the category of hazardous waste, while more than 700 million tons originate from agriculture. This is a big challenge faced by EU countries, with a clear task to ensure the treatment and disposal of waste without any negative effects on human health and the environment (2).

The overall opinion is that waste generated in healthcare institutions is a mixture of municipal waste and hazardous medical waste resulting from the provision of healthcare services. Hazardous waste has the following characteristics that distinguish it from municipal waste: harmfulness, toxicity, carcinogenicity, and infectivity.

Harmfulness is reflected in a substance or waste that, when swallowed or inhaled or when it penetrates the skin, can cause danger to human health.

Toxicity means a substance or product that may contain toxic ingredients, which in case of inhalation, ingestion, or skin penetration, can cause severe, acute, and chronic health risks, even death.

Carcinogenicity encompasses substances or products that, if inhaled, swallowed, or when they penetrate the skin, can cause cancer or increase its spread.

Infectivity means substances or waste containing living microorganisms and their spores or toxins that we know or suspect cause disease in humans and other living organisms (3).

Ugrinov and Stojanov (3) indicate that medical waste includes all types in solid and liquid form, from hospitals, clinics, research institutions, and laboratories working within a health system. However, it should be noted that between 70 and 90 percent of medical waste is actually municipal waste.

The projection of the creation of medical waste in the Republic of Serbia depends on many factors, but the expected amount by 2030 is around 5 000 tons (4).

In most healthcare institutions, infectious waste, used needles, tampons, gauze, infusion systems, *etc.*, are

not separated from conventional garbage but are thrown together into plastic baskets and/or stronger polyethylene bags. Veterinary stations and clinics generate a certain quantity of biohazardous waste, which is disposed of in pits or burned in an uncontrolled manner (5).

It is necessary for the personnel in charge of medical waste management in healthcare institutions to acquire new knowledge and skills continuously, and to influence a reduction in medical waste, its classification, collection, storage, transport, processing, and temporary or final disposal. This means that, among other things, they must be provided with professional instructions and recommendations regarding the application of adequate methods and techniques for waste management. An important segment of their work is timely and comprehensive risk assessment, as well as the application of adequate prevention measures.

Appropriate management of medical waste can reduce total generated waste, as well as hazardous waste generated during the performance of healthcare activities. Therefore, medical waste is generated during diagnosis, treatment, or provision of medical care, but also during research conducted at health institutions. In this respect, we mean all waste generated, both in healthcare institutions and outside them, for example, during home care, in institutions for the accommodation of the elderly, or in institutions that provide any form of medical care.

Contamination of the environment by radioactive substances implies the presence of radionuclides in concentrations that exceed certain values. The level of radioactive contamination in imported food, medicines, medical aids, items in general use, and other goods must not be higher than that permitted for similar household items (5).

CLASSIFICATION OF MEDICAL WASTE

There are several criteria for sorting waste, but the most commonly used division is into non-risky and hazardous waste. Sorted medical waste is packed in accordance with the space that regulates the storage, packaging and labeling of hazardous waste. For certain types of medical waste, the packaging is managed in the following manner (6):

- communal waste - in black bags;
- sharp objects - in yellow containers (the bag is filled up to ¾, after which it is closed);
- pathoanatomical waste - in brown bags;
- infectious waste - in yellow bags or containers (the bag is filled up to ¾, after which it is closed);
- waste contaminated with blood and bodily fluids - in double bags or yellow containers.

Non-hazardous waste

A characteristic of non-hazardous waste is its similarity to waste generated in households. These include, for example, paper, glass, plastic, food, and wood (recyclable materials).

Hazardous waste

Hazardous waste is all waste with one of the above characteristics: explosiveness, flammability, corrodibility, and toxicity, which represents an additional risk to health and the environment. This also includes waste from radiology.

The World Health Organization divides medical waste into several groups (7):

1. Infectious: Complete waste contaminated with body fluids and especially blood, as well as infectious agents resulting from laboratory activities and waste from patients with infections;

2. Sharp objects: Any object that is used to pierce the skin and comes into contact with biologically hazardous substances as scalpels, needles, wires, lancets, blades, *etc.*;

3. Pathological: This group refers to samples taken from patients for laboratory analysis as organs or fluids, human tissues, body parts, and contaminated animal carcasses;

4. Radioactive: This includes products contaminated with radionuclides;

5. Chemicals: Healthcare facilities use a variety of chemicals to ensure adequate sanitation. Chemical waste such as solvents and reagents used for laboratory preparations, disinfectants, sterilization agents, and heavy metals contained in medical devices and batteries;

6. Pharmaceutical products: This category of waste includes used and unused medicines, vaccines, injections, as well as expired medicines and contaminated medicines;

7. Cytotoxic/genotoxic properties:This category represents one of the most dangerous forms of medical waste: it contains substances with genotoxic properties meaning that they are mutagenic, teratogenic, or carcinogenic;

8. Non-hazardous general waste: It is waste that does not potentially a risk to human health.

According to data from the World Health Organization, due to inadequate disposal of needles and syringes, 21 million people in the world were infected with the Hepatitis B virus, of which 32% were newly discovered cases, while two million were diagnosed with Hepatitis C, of which 40% were newly discovered, and 250 000 with a confirmed HIV infection, which is 5% of all newly diagnosed cases (8).

The amount of hazardous medical waste increases annually and threatens to seriously endanger the environment. This is one of the most important reasons that ever more attention is being paid to the disposal of medical waste. Thanks to scientific and technological discoveries, as well as raising environmental awareness to a higher level, significant progress has been made with three objectives in mind:

- To avoid, *i.e.*, reduce medical waste;
- To be used, *i.e.*, recycled and
- To be processed and finally disposed of in a safe manner.

The World Health Organization recommends incineration as a method of medical waste disposal. This method is promoted because it reduces its volume by 90% and destroys microorganisms. Savings are achieved due to a reduction in transport costs while the energy obtained this way can be used for heating (space, water, *etc.*). In addition to the above, a significant benefit is reflected in the efficiency of the method as incineration safely neutralizes the potential danger of infection.

However, it should be noted that incineration as a method also carries certain dangers, which are reflected in the emission of harmful and dangerous gases, while in some cases, improper disposal of ashes is a danger considering that ashes can have the properties of hazardous waste.

With the support of the European Union, a project was implemented at the Clinical Center of Kragujevac that marked a turning point in the treatment of medical waste, *i.e.*, the application of steam sterilization in a vacuum under pressure. This method transforms medical waste into harmless waste for human health and the environment, and it is achieved by the process of heat treatment up to the level of acceptable reduction of biological agents in the waste (inactivation of spores defined by the test at 4 $\log^{10}$ or a higher level of reduction). Only after that process, medical waste is acceptable for sanitary disposal, provided that its origin cannot be recognized (9).

CATEGORIES OF MEDICAL WASTE FROM THE EUROPEAN CATALOG

The European Commission adopted a single European waste catalog to introduce common terminology and improve waste management (Council directive No. 2000/532/EC, 1994). This document is a list of waste and is not final but is periodically supplemented and changed.

In the European Catalog of waste, medical waste is defined as waste generated in medicine and veterinary medicine during the provision of health care and bears the number 18 00 00 with subsets (10).

Subsection No. 18 01: Waste from hospitals and/or health centers, waste generated during diagnosis, treatment, or preventive health services for people (in human medicine).

Subsection 18 02: Waste generated during the provision of veterinary healthcare.

Source: (11)

The European Waste Catalog defines each type of waste through a six-digit numbering (example 18 01 03). In the case of some categories of waste, in addition to the classification number of six digits, an asterisk from the numbers is categorized as hazardous waste (example: 18 01 03*, Infectious waste).

Table 1. *Waste generated in healthcare institutions (human medicine)*

18 01 01*	Sharp objects (not included 18 01 03)*)
18 01 02	Body parts and organs, bags with blood and blood derivatives (not included 18 01 03*)
18 01 03*	Infectious waste is waste that is subject to special requirements to prevent the spread of infection
18 01 04	Non-infectious waste
18 01 06*	Chemical waste with hazardous substances
18 01 07	Other chemical waste
18 01 08*	Cytotoxic drugs and cytostatics
18 01 09	Medicines except those from 18 01 08
18 01 10	Amalgam waste in use in dentistry

Table 2. *Waste generated by veterinary institutions*

18 02 01	Sharp instruments (not included18 02 02)
18 02 02*	Waste is subject to special requirements due to infection
18 02 03	Waste that is not subject to special requirements to prevent infection
18 02 05*	Chemicals that contain or are hazardous substances
18 02 06	Different chemicals compared to 18 02 05
18 02 07*	Cytotoxic and cytostatic drugs
18 02 08	Other medications from those listed in 18 02 07

MEDICAL WASTE STORAGE

Before organizing the transport, treatment, or handing over of hazardous medical waste, it is required that this waste be stored in a location that is predetermined and arranged only for that purpose.

The location for the storage of medical waste must be fenced in and must represent a separate area or facility known to the personnel involved and intended exclusively for that purpose. The storage space should meet the following conditions:

1) to be of adequate size in relation to the quantity of waste produced and its frequency of collection and removal;

2) to have water supply and drainage for cleaning and maintenance purposes;

3) to be clearly and visibly marked with a notification of the purpose of the space, prohibition of entry by unauthorized persons, as well as a warning about the possibility of endangering people's health;

4) to be built to have impermeable and resistant floor surfaces, as well as smooth wall surfaces that are easy to clean and disinfect;

5) to be easily accessible to health service personnel in charge of waste management;

6) to be locked, that is, to prevent access to unauthorized persons;

7) to be easily accessible to carts and waste collection containers inside health service and waste transport vehicles;

8) to be inaccessible to animals and other carriers of infectious agents;

9) to be well-lit and equipped with natural or artificial ventilation;

10) to ensure protection from atmospheric influences;

11) to be sufficiently removed from fresh food storage and food preparation areas, patient and visitor routes;

12) to have fire protection in accordance with separate regulations.

The place for storing infectious waste must be disinfected at least once a week and more often, if necessary. Pharmaceutical waste is always stored separately from other types of medical waste, and unused medicines from facilities where health care is provided should be stored in a separate area or a room in those facilities. To avoid unwanted chemical reactions, chemical waste of different compositions should be stored separately. Cytotoxic and cytostatic waste is stored in separate rooms, spaces, or facilities, separate from other types of medical waste. Spilled, contaminating drugs, as well as packages containing drug residues from facilities where health care is provided, are packed in adequate packaging, at the place of origin, before storage (12).

The issue of treating household medical waste is particularly important. Namely, home care services are crucial for helping patients who, for objective reasons, are unable to go to a health facility on their own, and in this sense, there is a continuous need to protect medical staff, patients, and their families. The results of research carried out in Brazil between December 2020 and January 2021 warn that the main weaknesses are the lack of training of healthcare workers and the absence of instructions that should be shared with patient caregivers regarding the treatment of medical waste. In addition to sharp waste, all other households' medical waste management practices have also been shown to be inadequate and pose a threat (13).

European Union legislation in the field of medical waste management

The countries of the European Union are the largest exporters, but also importers of waste categorized as non-hazardous, before the USA and China, and therefore it is one of the relevant topics to which great attention is paid. Therefore, it is expected that other important goals are recognized through the shipment of waste, such as ensuring maximum safety for people and the environment, and it applies to all international shipments for all purposes, inside or outside the EU. The European Union incorporated the Basel Convention on the Control of Transboundary Movement of Hazardous Waste and its Disposal. In this way, the convention is applied in all EU member states (14).

The modern medical waste management system is based on a strictly defined treatment of waste: from its origin to the location designated for disposal. Implementing the complete management of a large amount of municipal waste could require fewer funds for disposing of medical waste, which is the task of the legal framework and concrete implementation in practice.

European Union's foundation for waste management policy is the Resolution of the Council of Europe on waste management strategy (97/C76/01), which is based on the framework waste directive (75/442/EEC) and other regulations on waste management in the EU.

Five basic principles were established (15):

- Hierarchy of waste management;
- Self-sustaining disposal facilities;
- The technology that is the most adequate in the given circumstances;
- Proximity to waste disposal;
- Manufacturer's responsibility.

The European Union has ambitions to regulate as many activities as possible that affect its function-

ing with laws and regulations. That is precisely why today in the EU legislation, we have legislation that effectively regulates the situation and directs waste management. In this context, five profiled categories are differentiated, where the first is the General Framework, which includes strategies and measures related to the reduction of certain types of waste, and decisively states the types of landfills, as well as methods for continuous disposal control. Other categories are focused on the characteristics of waste and its management.

Specificity waste category deals with the treatment and disposal of oil, metal and packaging waste, old tires, sewage water, batteries and accumulators, electrical and electronic waste, as well as PVC, which is seen not only through the problem of a long half-life, but and because of its composition.

The hazardous waste category defines the process of managing that waste, specifying the actions of waste separation, treatment, and disposal. The segment of the Regulation on the transport of said waste, known as the Basel Convention, is particularly emphasized here.

Although treated as hazardous waste, *radioactive waste and radioactive substances* are separately separated, given that this type of waste is subject to special legislation, from the management of waste nuclear fuel and radioactive waste, to the transportation of such waste and to rigorous control to protect against ionizing radiation.

The incineration of the waste category is considered the method of choice in the final treatment of waste, and the reason is that it ensures the most significant reduction in the volume of waste and toxic substances and is also considered the most beneficial for human health and the environment (16).

CONCLUSION

Pollution from healthcare institutions can be dangerous for the health of those who work in those institutions, the patients, as well as for the environment. Precisely due to the potential danger, a strict obligation to properly handle medical waste has been imposed.

The method of disposal and storage of medical waste represents one of the biggest challenges, as it must be safe and efficient and should not endanger the environment. Concern for the safe management of medical waste should be the most important guide when collecting, storing, disposing, and transporting waste.

Of crucial importance is the obligation to create rehabilitation programs that offer technologically safe and environmentally acceptable solutions for all future locations. It is necessary to further affirm the approach according to which rehabilitation is carried out at the location itself, whereby it is expected that the rehabilitation program is harmonized with the spatial and urban plans of the local community within whose territory the disposal area is located.

In addition, it is necessary to create as many opportunities as possible for the reuse of materials, as well as to establish a concept of continuous site monitoring accompanied by regular reporting.

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Sažetak

UNAPREĐENJE PROCEDURA ZA SKLADIŠTENJE MEDICINSKOG OTPADA

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Pod medicinskim otpadom podrazumevamo celokupan otpad nastao u zdravstvenim ustanovama, a koji je u vezi sa obavljanjem medicinsko-tehničkih radnji u oblasti dijagnostike, terapije ili istraživačkih aktivnosti. U gotovo svim zemljama jugoistočne Evrope odlaganje medicinskog otpada ne obavlja se na odgovarajući način, pre svega jer ne postoje potrebni kapaciteti za uklanjanje medicinskog otpada. Cilj rada je sagledavanje rezultata i iskustava u tretmanu medicinskog otpada, kao i potencijalnih rizika za pacijente, medicinsko i nemedicinsko osoblje. Implementacija bezbednog sistema upravljanja medicinskim otpadom moglo bi značajno da unapredi kvalitet zdravstvenih usluga, zdravlje pacijenata i sačuva okruženje. Sugeriše se upotreba sterilizacije parom, kako bi se termičkom obradom na prihvatljiv nivo sveo sadržaj bioloških agenasa u otpadu, odnosno dostigla biološka inaktivacija.

Ključne reči: medicinski otpad, skladištenje, procedure, sterilizacija.

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