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Photo by Miki Veličković

Principal research fellow, primarius, Dr. Aleksandar Nedok (1925–2024), one of the most valuable reviewers and authors of the *Vojnosanitetski pregled* (VSP) journal, left us this February. With his entire professional activities, Dr. Nedok entered the history of the health care system of our country (see pp. 123–125). The Editorial Board and Editorial Staff of the VSP express the deepest respect and gratitude for Dr. Nedok's decades-long support. He published his last article, "The Oldest Apothecaries of the Serbian Armed Forces", in the December 2023 issue of the VSP journal (link).

Naučni savetnik, primarijus, dr Aleksandar Nedok (1925–2024), jedan od najdragocenijih recenzenata i autora Vojnosanitetskog pregleda (VSP), napustio nas je u februaru ove godine. Svojim celokupnim profesionalnim aktivnostima dr Nedok je ušao u istoriju zdravstvenog sistema naše zemlje (videti str. 123–125). Uredništvo i Redakcija VSP izražavaju najveće poštovanje i zahvalnost za višedecenijsku podršku dr Nedoka. Poslednji članak u VSP, *Najstariji apotekari srpske vojske*, objavio je u decembru 2023. godine (link).

ORIGINAL ARTICLES

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The significance of early-onset malignant arrhythmias in ST-elevation myocardial infarction patients treated with primary percutaneous coronary intervention and their relationship with biomarkers

Značaj ranih malignih aritmija kod bolesnika sa infarktom miokarda sa ST elevacijom lečenih primarnom perkutanom koronarnom intervencijom i njihova povezanost sa biomarkerima

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Abstract

Background/Aim. Patients who were treated with primary percutaneous coronary intervention (pPCI) and survived ventricular tachycardia (VT) and ventricular fibrillation (VF) in the first 48 hrs after ST-elevation myocardial infarction (STEMI) had, in most investigations, a similar long-term prognosis of the outcome, compared to those patients who did not have VT and VF during the first 48 hrs after STEMI. The aim of the study was to determine the association of myocardial infarction markers: creatine kinase-MB fraction (CK-MB), heart failure marker – B-type natriuretic peptide (BNP), and systemic inflammation factor – C-reactive protein (CRP) with early VT and VF onset, in relation to patient mortality during the first six months after STEMI. **Methods.** The retrospective study included 971 patients with STEMI treated with pPCI for ten years. VF and sustained VT (sVT) were detected outside of the hospital and during the first 48 hrs of hospitalization. **Results.** During the first 48 hrs from admission, 108 (11.1%) patients had life-threatening arrhythmias, of which 75 (69.4%) had VF, and 33 (30.6%) had sVT and were treated with direct current – DC shock and intravenous amiodarone. Intrahospital mortality was significantly higher in patients with VF/sVT in the first 48 hrs compared to patients without VF/sVT (14.8% vs. 5.7%, $p = 0.001$). BNP level had higher accuracy in the prediction of six-month death than the maximum blood level of CRP in patients without VF/sVT after 48 hrs. However, in patients with early-onset malignant arrhythmias, BNP showed a lower level of accuracy in predicting the six-month mortality, as did the CRP values, which had almost the same level of accuracy. Admission glycemia had a much lower predictive value in both groups of patients compared to BNP and CRP [0.705 (0.628–0.781), $p < 0.001$ and 0.662 (0.521–0.803), $p = 0.046$, respectively]. In either of the groups, maximum CK-MB levels were not significant in predicting the six-month all-cause mortality. **Conclusion.** Our study indicates that STEMI patients with early onset of VF and sVT, treated with pPCI, with a high BNP level, have a statistically significantly higher mortality rate compared to patients with a lower BNP level.

Key words:
biomarkers; mortality; percutaneous coronary intervention; prognosis; st elevation myocardial infarction; tachycardia, ventricular; ventricular fibrillation.

Apstrakt

Uvod/Cilj. Bolesnici koji su lečeni primarnom perkutanom koronarnom intervencijom (pPKI) posle infarkta miokarda sa ST elevacijom (*ST-elevation myocardial infarction* – STEMI) i koji su preživeli ventrikularnu tahikardiju (VT) i ventrikularnu fibrilaciju (VF) u prvih 48 sati imali su, u većini istraživanja, sličnu dugoročnu prognozu ishoda u poređenju sa bolesnicima koji nisu imali VT i VF tokom prvih 48 sati nakon STEMI. Cilj rada bio je da se kod bolesnika sa STEMI utvrdi povezanost markera infarkta miokarda: MB frakcije kreatin kinaze (*creatine kinase-MB fraction* – CK-MB), markera srčane insuficijencije – natriuretičkog peptida tipa B (*B-type natriuretic peptide* – BNP) i sistemskog inflamacijskog faktora – C-reaktivnog proteina (CRP) sa ranim početkom VT i VF, u odnosu na mortalitet

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bolesnika tokom prvih šest meseci nakon STEMI. **Metode**. Ovom retrospektivnom studijom obuhvaćeno je 971 bolesnika sa STEMI, lečenih primenom pPKI tokom deset godina. VF i trajna VT (tVT) su detektovane i van bolnice i tokom prvih 48 sati hospitalizacije. **Rezultati.** Tokom prvih 48 sati od prijema, 108 (11,1%) bolesnika imalo je aritmiju opasnu po život, od kojih je 75 (69,4%) imalo VF, a 33 (30,6%) tVT, a lečeni su *direct current* – DC šokom i amjodaronom intravenski. Intrahospitalni mortalitet bio je značajno viši kod bolesnika sa VF/tVT u prvih 48 sati u poređenju sa bolesnicima bez VF/tVT (14,8% vs. 5,7%, $p = 0{,}001$). Nivo BNP pokazao je veću tačnost u predviđanju šestomesečnog mortaliteta u odnosu na vrednost maksimalnog nivoa CRP u krvi kod bolesnika bez VF/tVT nakon 48 sati. Međutim, kod bolesnika sa ranim početkom malignih aritmija, BNP je pokazao niži nivo tačnosti u predviđanju šestomesečnog mortaliteta, kao i vrednosti CRP, koje su imale skoro isti nivo tačnosti. Glikemija na prijemu je imala mnogo nižu prognostičku vrednost u obe grupe bolesnika u poređenju sa BNP i CRP [0,705 (0,628–0,781), $p < 0{,}001$ i 0,662 (0,521–0,803), $p = 0{,}046$, redom]. Ni u jednoj grupi, maksimalni nivoi CK-MB nisu imali značaj u predviđanju šestomesečnog mortaliteta izazvanog bilo kojim od uzroka. **Zaključak**. Naša studija ukazuje na to da bolesnici sa STEMI, sa ranim početkom VF i tVT, lečeni primenom pPKI i sa visokim nivoom BNP, imaju statistički značajno višu stopu mortaliteta u odnosu na bolesnike sa nižim nivoom BNP.

Ključne reči:
biomarkeri; mortalitet; perkutana koronarna intervencija; prognoza; infarkt miokarda sa st elevacijom; tahikardija, ventrikulska; fibrilacija komora.

Introduction

Ventricular fibrillation (VF) and sustained ventricular tachycardia (sVT) often occur in the acute phase of myocardial infarction (MI) with ST-segment elevation (STEMI) [1, 2] and significantly increase intrahospital mortality [3, 4]. Patients who were treated with a primary percutaneous coronary intervention (pPCI) and who survived sVT and VF in the first 48 hrs after STEMI, in most studies, had similar results of long-term prognosis compared to those patients without sVT and VF during the same period after STEMI [5, 6]. Therefore, current guidelines on STEMI treatment do not recommend implantation of cardioverter defibrillators (CD) in patients with sVT and VF within the first 48 hrs after STEMI, and there is no evidence to support the use of CD in such circumstances [7, 8].

An elevated level of B-type natriuretic peptide (BNP) may indicate the presence of acute heart failure regardless of the absence of heart failure clinical signs [9]. BNP emerged as a helpful laboratory finding in the diagnosis of heart failure in patients with acute coronary syndrome (ACS) [10]. Given that the elevated BNP level in ACS is associated with left ventricular dysfunction, the prognostic significance of serum BNP level on mortality is an independent risk factor [11]. Previous studies showed that the BNP level on the hospital admittance was predictive for short-term mortality more significantly than clinical assessment like Killip classification and Thrombolysis in Myocardial Infarction (TIMI) risk score in patients with STEMI treated with pPCI [12, 13].

Based on the studies conducted so far, we aimed to estimate the prognostic significance of life-threatening ventricular arrhythmias occurring within the first 48 hrs after STEMI for intrahospital and six-month mortality.

Furthermore, having in mind that most studies have not associated the relationship between early onset of sVT and VF during the first 48 hrs of STEMI and six-month mortality, we aimed to investigate the association of MI marker creatine kinase-MB fraction (CK-MB), heart failure marker – BNP and systemic inflammation factor – C-reactive protein (CRP) with early sVT and VF onset and its repercussion on six-month mortality in STEMI patients.

Methods

This retrospective study included 971 consecutive patients with STEMI who underwent pPCI and survived within the maximum ischemic time of 24 hrs. All patients were treated in the single university center with the maximal regard of the current guidelines for the treatment of STEMI patients. The cohort represented consecutive patients treated in a period of ten years from January 2008 to January 2018 at the Clinic for Urgent Internal Medicine of the Military Medical Academy in Belgrade, Serbia. The study was approved by the Ethics Committee of the Military Medical Academy (No. 76/2023, from October 12, 2023).

Patients were on continuous echocardiography monitoring during the first 48 hrs from admission to the intensive care unit. VF and sVT were detected out of the hospital (in the ambulance) and during the first 48 hrs of hospitalization and were treated promptly with asynchronous direct current (DC) shock, cardiopulmonary reanimation, and amiodarone intravenously. All patients who did not have contraindications were treated with oral beta-blockers from admission.

Echocardiography measurements of left ventricle ejection fraction and wall motion score index were performed by the independent, experienced echocardiographer at discharge, usually 4–6 days after admission. Clinical assessments were performed one and six months after infarction at the ischemic disease outpatient facility.

Laboratory tests

Glycemia was measured on admission from the venous blood samples using the commercial Dimension® Clinical Chemistry System [reference range (RR): 3.9 mmol/L–5.6 mmol/L]. Blood samples for extended-range

CRP were taken twice in the morning of two consecutive days from admission. CRP was determined in the serum of patients using the fully automated electrochemiluminescent assay by Siemens IMMULITE 2000 Immunoassay System (Siemens Healthcare Diagnostics, Deerfield, IL, USA), (normal values < 3 mg/L). CK-MB was determined in the serum of patients by the immunoinhibition method on the commercial Dimension® Clinical Chemistry System, on admission and every 8 hrs. During the first 48 hrs, normal values (< 21 units/L) were detected. BNP was determined in plasma samples on the commercial ADVIA Centaur analyzer (Siemens Medical Solutions, Fernwald, Germany) using direct chemiluminescence immunoassay (normal values < 100 pg/mL). Patients with a total cholesterol concentration greater than 5.2 mmol/L were classified as having hypercholesterolemia.

The study is retrospective, and we did not have all the data for every patient. However, this lack of data for individual variables in patients is in a statistically acceptable range of 0.3-3.2%.

Results

During the first 48 hrs from admission, 108 (11.1%) patients had life-threatening arrhythmias, of which 75 (69.4%) had VF, and 33 (30.6%) had sVT, treated with DC shock and intravenous amiodarone. One-fourth of the patients had VF/sVT before pPCI. The basic characteristics of the patients are presented in Table 1. Interestingly, there was no difference between the age, gender, risk factors, infarct-related artery, presence of multivessel disease, and reinfarction between patients with and without early onset life-threatening arrhythmias. Patients with VF/sVT were more often present in the earlier presenter's group, had some degree of decompensation on admission, and less often had TIMI-3 flow after pPCI. Patients with life-threatening arrhythmias did not have a lower incidence of ST-segment resolution after pPCI, and there was a similar distribution of presumably new Q waves on the electrocardiographic findings on admission in both groups.

Table 1

Demographic and clinical characteristics of patients

Parameters	Ventricular fibrillation or sustained ventricular tachycardia during the 48 hrs from admission		
	no (n = 863)	yes (n = 108)	*p*
Age (years)	63 ± 12	62 ± 11	0.696
Elderly			
< 70	607 (88.6)	78 (11.4)	0.738
≥ 70	256 (89.5)	30 (10.5)	
Gender			
female	254 (89.8)	29 (10.2)	0.654
male	609 (88.5)	79 (11.5)	
Atherosclerotic risk factors			
arterial hypertension			
yes	615 (89.0)	76 (11.0)	
no	243 (88.7)	31 (11.3)	0.910
missing data	5 (0.6)	1 (0.9)	
active smoking			
yes	403 (88.4)	53 (11.6)	
no	374 (89.3)	45 (10.7)	0.748
missing data	86 (9.7)	10 (9.3)	
diabetes mellitus			
yes	224 (89.2)	27 (10.8)	0.907
no	639 (88.8)	81 (11.2)	
hypercholesterolemia			
yes	409 (88.9)	51 (11.1)	
no	309 (87.8)	43 (12.2)	0.658
missing data	145 (16.8)	14 (13.0)	
Total ischemic time			
< 4 hrs	382 (91.4)	36 (8.6)	
≥ 4 hrs	467 (86.8)	71 (13.2)	0.030
missing data	14 (1.6)	1 (0.9)	
Killip class on admission			
1	126 (83.4)	25 (16.6)	
> 1	734 (89.8)	83 (10.2)	0.034
missing data	3 (0.3)		
IRA			
LAD	359 (87.3)	52 (12.7)	
RCX	129 (87.8)	18 (12.2)	0.259
RCA	375 (90.8)	38 (9.2)	

Table 1 (continued)

Parameters	Ventricular fibrillation or sustained ventricular tachycardia during the 48 hrs from admission		
	no (n = 863)	yes (n = 108)	*p*
TIMI flow before pPCI			
0/1	759 (88.8)	96 (11.2)	
2/3	99 (90.0)	11 (10.0)	0.880
missing data	5 (0.6)	1 (0.9)	
TIMI flow after pPCI			
< 3	131 (82.9)	27 (17.1)	
3	725 (90.1)	80 (9.9)	0.012
missing data	7 (0.8)	1 (0.9)	
Multivessel disease			
yes	527 (88.3)	70 (11.7)	
no	325 (89.8)	37 (10.2)	0.526
missing data	11 (1.3)	1 (0.9)	
Previous infarction			
yes	121 (89.6)	14 (10.4)	
no	737 (88.8)	93 (11.2)	0.883
missing data	5 (0.6)	1 (0.9)	
Early ST-segment resolution			
yes	525 (89.0)	68 (11.0)	0.915
no	308 (88.5)	38 (11.5)	
missing data	30 (3.5)	2 (1.9)	
New Q waves on admission			
yes	376 (90.0)	42 (10.0)	
no	467 (87.6)	66 (12.4)	0.303
missing data	20 (2.3)		
Implantation of stent in IRA			
yes	744 (88.5)	97 (11.5)	0.369
no	119 (91.5)	11 (8.5)	
Use of GP inhibitors during pPCI			
yes	245 (83.1)	50 (16.9)	
no	616 (91.5)	57 (8.5)	< 0.001
missing data	2 (0.2)	1 (0.9)	

IRA – infarct-related artery; LAD – left anterior descending; RCX – ramus circumflex; RCA – right coronary artery; TIMI – Thrombolysis in Myocardial Infarction; pPCI – primary percutaneous coronary intervention; GP – glycoprotein.
All values are expressed as numbers (percentages) except for age which is shown as mean ± standard deviation.

Several biomarkers were determined, and their significance was compared between patients with and without VF/sVT 48 hrs after admission. Admission glycemia was available in 97.6% and 96.3%, maximum CRP in 69.5% and 78.7%, maximum CK-MB in 95.0% and 93.5%, and BNP in 52.7% and 47.2% of patients, without and with VF/sVT during the 48 hrs, respectively.

The boxplots of biomarkers are presented in Figure 1. Results are shown as median (min-max). Patients with VF/sVT, as compared to those without, had significantly higher following values: admission glycemia [8.8 mmol/L, (7.1–10.9 mmol/L) vs. 7.8 mmol/L (6.6–9.9 mmol/L), $p = 0.006$, respectively], maximum CRP during the 48 hrs period [32.0 mg/L (12.5–78.0 mg/L) vs. 17.4 mg/L (8.1–49.5 mg/L), $p = 0.003$, respectively], maximum CK-MB during 48 hrs [317.0 IU/L (170.0–454.0 IU/L) vs. 172.0 IU/L (93.0–301 IU/L), $p < 0.001$, respectively], and BNP after 24 hrs from admission [347.3 pg/mL (144.4–708.8 pg/mL) vs. 221.0 pg/mL (108.6–400.0 pg/mL), $p = 0.012$, respectively].

The Kaplan-Meier curves of six-month all-cause mortality according to the occurrence of VF/sVT at 48 hrs are presented in Figure 2. Intrahospital mortality was significantly higher in patients with VF/sVT at 48 hrs after STEMI compared to patients without VF/sVT (14.8% vs. 5.7%, $p = 0.001$, respectively). The six-month mortality rate was 15.7% and 6.8% (log-rank $p = 0.001$) in patients with VF or sVT at 48 hrs after STEMI compared to patients without malignant arrhythmias, respectively. Left ventricle ejection fraction and wall motion score index at discharge were also significantly lower in patients with VF/sVT at 48 hrs after STEMI compared to patients without arrhythmias [44.8% vs. 47.6% ($p = 0.007$); 1.50 (1.28–1.75) vs. 1.37 (1.19–1.56), ($p < 0.001$), respectively].

The receiver operating characteristic (ROC) curves of BNP and CRP depending on the presence/absence of VF/sVT at 48 hrs after STEMI are presented in Figure 3.

BNP had higher accuracy in the prediction of six-month mortality than maximum CRP blood level in patients without VF/sVT at 48 hrs. However, in patients with early onset ma-

lignant arrhythmias, BNP had lower accuracy for the prediction of six-month mortality and CRP values had almost the same accuracy [area under curve (AUC) for BNP: 0.843 (0.806–0.875) in absence of VF/sVT vs. 0.732 (0.588–0.845) in the occurrence of VF/sVT; $p = 0.308$ and AUC for maximum CRP: 0.746 (0.709–0.780) in absence of VF/sVT vs. 0.743 (0.636–0.831) in the occurrence of VF/sVT; $p = 0.975$]. Admission glycemia had a much lower predictive value in both groups of patients compared to BNP and CRP [0.705 (0.628–0.781), ($p < 0.001$) and 0.662 (0.521–0.803), respectively ($p = 0.046$)]. Maximum CK-MB levels were not predictive for six-month all-cause mortality in either of the groups.

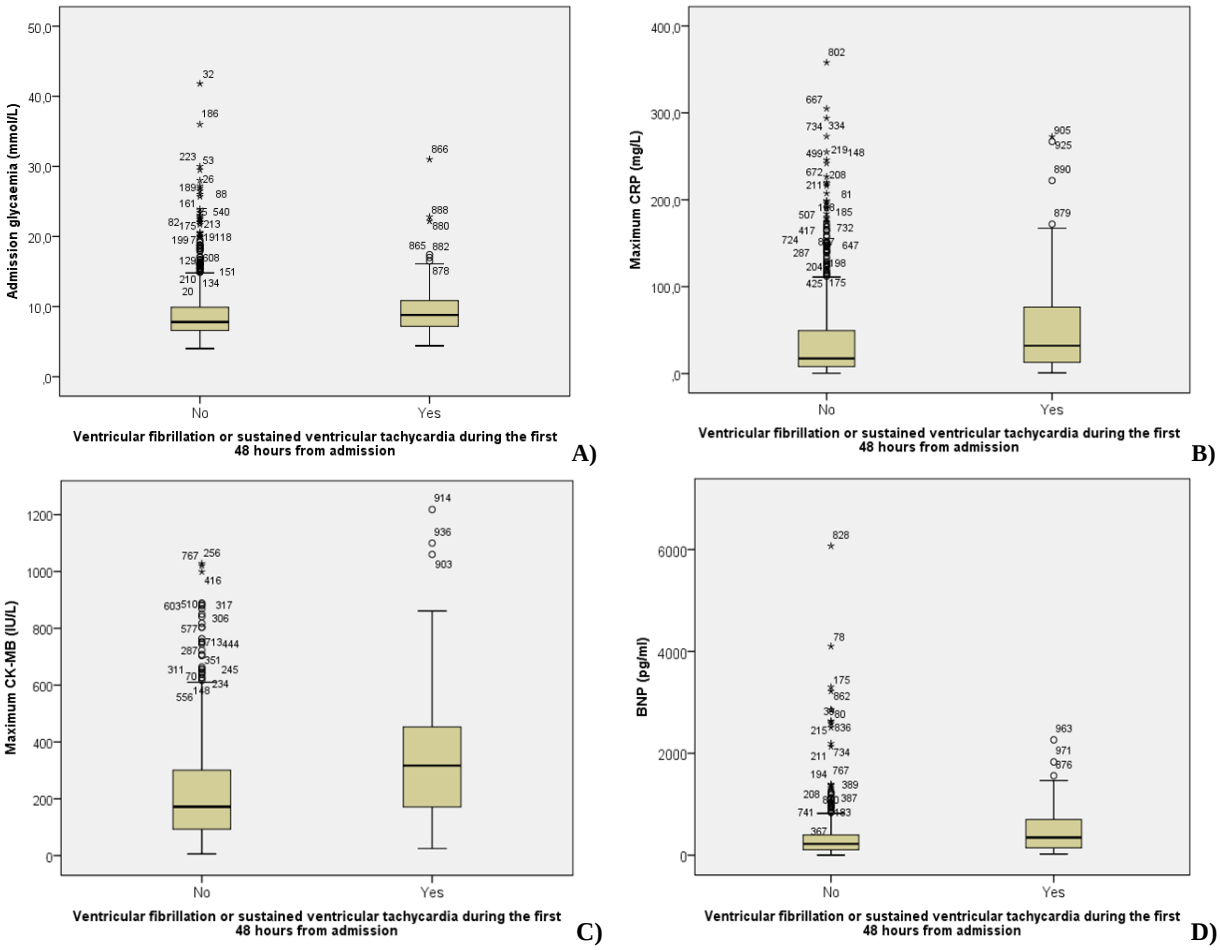


Fig. 1 – A) Admission glycemia; B) Maximum C-reactive protein (CRP); C) Maximum creatine kinase MB fraction (CK-MB); D) B-type natriuretic peptide (BNP) levels in patients with (Yes) ventricular fibrillation (VF) or sustained ventricular tachycardia (sVT) compared to the patients without (No) VF/sVT, during the first 48 hrs from admission.

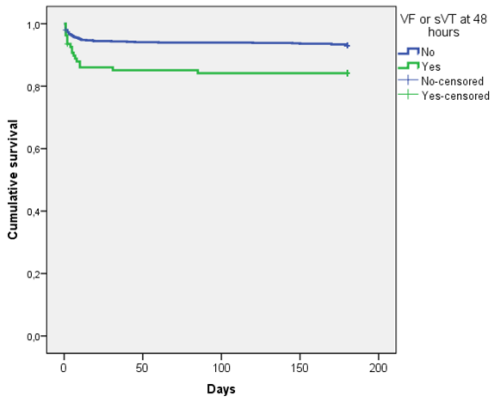
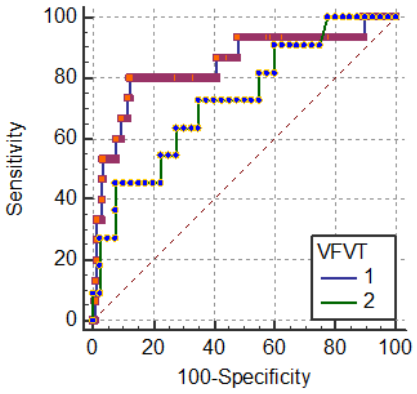
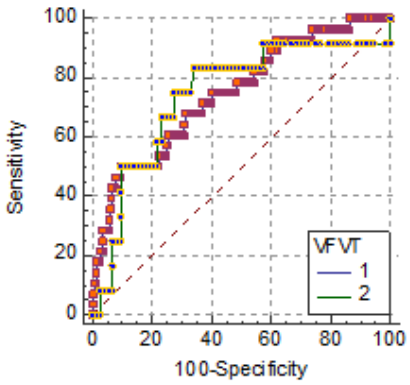


Fig. 2 – Kaplan-Meier curve of six-month survival regarding the presence (Yes) or absence (No) of ventricular fibrillation (VF) or sustained ventricular tachycardia (sVT) in the first 48 hrs from admission (log-rank $p = 0.001$).



A)



B)

Fig. 3 – The receiver operating characteristic curves for the prediction value of A) BNP in the presence (green line) and absence (blue line) of VF/sVT and B) max CRP in the presence (green line) and absence (blue line) of VF/sVT for six-month all-cause mortality.
BNP – B-type natriuretic peptide; VF – ventricular fibrillation; sVT – sustained ventricular tachycardia; CRP – C-reactive protein; z – z statistic of the test. The difference between the area under the curve (AUC) for BNP for patients with and without VF/sVT was Delta = 0.112, z = 1.019, *p* = 0.308. The difference between AUC for max CRP for patients with or without VF/sVT was Delta = 0.003, z = 0.031, *p* = 0.975.

Discussion

During the ten-year follow-up of consecutive STEMI patients treated with pPCI, we observed a greater intrahospital and six-month mortality among the patients who had VF/sVT within the first 48 hrs of hospital admission.

Patients with VF/sVT within the first 48 hrs had more often elevated markers of poor prognoses, such as hyperglycemia, CK-MB, BNP, and CRP.

Elevated levels of BNP and CRP proved to be good predictors of two-month mortality, and BNP showed greater predictive precision for this outcome [14]. Current guidelines for STEMI are based on the results of previous studies that VF which occurred during the first two days of STEMI are insignificant, regarding the long-term prognosis in case the patient survives until the discharge; no implantable CD efficacy has been demonstrated for prevention of sudden death [7].

However, most data concerning the prognostic significance of the early onset of VF/sVT for long-term outcomes was obtained during or even before the pPCI era. A few recent studies assessed VF/sVT in patients with STEMI treated with pPCI. The most important studies were Primary Angioplasty in Myocardial Infarction (PAMI) and APEX AMI [15, 16]. The APEX AMI study had the longest follow-up period, with 5,745 patients included. However, the patients were admitted to a hospital after the first six hours of STEMI, and those who had isolated posterior STEMI were excluded. Moreover, follow-up was limited to 90 days. The PAMI study assessed one-year survival, and 3,065 patients were included. At the same time, patients with chronic kidney disease, cardiogenic shock, and patients with contraindications for antithrombotic therapy were excluded.

Our study included all patients admitted to the hospital with an indication for pPCI during the period of ten years. The analysis did not exclude the most severe categories of patients, such as the patients with pre-hospital reanimation. Considering the profile of patients included in our study, differences between frequencies of malignant arrhythmias in our study (11.1%), the PAMI study (4.3%), and the APEX AMI study (5.7%) can be explained.

In research by De Jong et al. [17], 341 patients with VF and STEMI and 292 STEMI patients without VF were followed up. Demographic and infarct-related features were comparable in both groups. The follow-up median was three years. In conclusion, patients who survive the first month after primary VF have a similar prognosis to STEMI patients without VF. This is the first study that addresses this issue in the era of reperfusion therapy with pPCI.

Based on the previous studies, routine use of CD for all STEMI patients treated with pPCI and with early onset of VF/sVT is not indicated [7].

The purpose of the HORIZONS AMI [18] trial was the assessment of the risk factors and outcome of VF before and during pPCI in patients with STEMI. In this study, 5,537 patients with STEMI were included. In total, 410 patients had VF before and 88 during pPCI. Through the middle follow-up period of 4.2 years, 1,196 patients died. The logistic regression model identified younger age, anterior infarct, Killip class > 1 at the moment of hospital admission, pre-PCI fibrinolysis with TIMI flow 0–1 as significantly related to VF before pPCI, while inferior infarct thrombolysis before pPCI with TIMI flow 0–1 and Killip class > 1 at the moment of hospital admission was significantly related to VF during pPCI. In comparison, patients with VF before or during pPCI had significantly increased mortality during the first 30 days. In patients with VF before or during pPCI who survived at least 30 days, there was no increase in long-term mortality.

The aim of this investigation was the identification of a potential subgroup of STEMI patients with recorded VF/sVT during the first 48 hrs and treated with pPCI, which might have potential benefit from the implantation of CD.

Study limitations

A large number of patients was included in this monocentric study over a long period of ten years. During that period, the basic indicator of myocardial necrosis, high-sensitivity troponin, was used in almost all patients. However, different assays from different manufacturers with different reference values were used, and the concentration of this parameter could not be adequately statistically processed.

Conclusion

Previous studies did not find a relationship between VF and sVT onset during the first 72 hrs and increased mortality in patients with STEMI who underwent pPCI. Our study indicates that STEMI patients with early onset of VF and sVT, treated with pPCI, with a high BNP level, have a statistically significantly higher mortality rate compared to patients with a lower BNP level.

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Does hospital medical staff maintain hospital disaster resilience?

Da li je bolničko medicinsko osoblje sposobno da održava rezilijentnost bolnice na katastrofu?

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Abstract

Background/Aim. In the event of a disaster, it is necessary for medical personnel to demonstrate the operational component of disaster resilience, which requires certain knowledge and skills regarding disaster medical response algorithms. The aim of this study was to analyze the preparedness of hospital's healthcare staff for maintaining hospital disaster resilience. **Methods.** An anonymous survey was conducted from July to September 2019 among 295 medical staff employed in hospitals in the territory of the city of Plovdiv, Bulgaria. Pearson's Chi-square test, Student's *t*-test, and graphical analysis were used in the statistical analysis. **Results.** Most of the medical staff, i.e., 85.8%, believed that disaster drills are not held regularly in hospitals, 30.8% thought that the training period was shorter than two years, and the majority, i.e., 86.1%, did not participate in exercises. **Conclusion.** Due to the irregular implementation of exercises and the small number of participants in them, the level of preparedness for responding to disasters is not maintained at a high level in hospitals in the Plovdiv region. Therefore, it is necessary to introduce a specific training program and exercise once a year, which should have a beneficial effect on increasing the preparedness of the medical staff for disasters and improving the operational resilience of the hospital.

Key words:
bulgaria; disaster planning; hospitals; personnel, hospital; surveys and questionnaires.

Apstrakt

Uvod/Cilj. U slučaju katastrofe, neophodno je da medicinsko osoblje pokaže operativnu komponentu rezilijentnosti na katastrofu, koja zahteva određeno znanje i veštine u vezi sa algoritmima medicinskog odgovora na katastrofe. Cilj rada bio je da se analizira pripremljenost zdravstvenih radnika bolnice za održavanje rezilijentnosti bolnica na katastrofe. **Metode.** U periodu od jula do septembra 2019. godine, sprovedeno je anonimno ispitivanje 295 zdravstvenih radnika, zaposlenih u bolnicama na teritoriji grada Plovdiva, Bugarska. U statističkoj analizi podataka korišćeni su Pearson-ov χ^2 test, Student-ov *t*-test i grafička analiza. **Rezultati.** Većina medicinskog osoblja, odnosno 85,8%, smatra da se vežbe vezane za slučaj katastrofe ne održavaju redovno u bolnicama, 30,8% smatra da je period obuke bio kraći od dve godine, a većina, odnosno 86,1%, nije učestvovala u vežbama. **Zaključak.** Zbog neredovnog izvođenja vežbi i malog broja učesnika u njima, nije održavan visok nivo pripremljenosti za odgovor na katastrofe u bolnicama na teritoriji regiona Plovdiva. Stoga je potrebno uvesti poseban program obuke i vežbi jednom godišnje, što bi trebalo da ima povoljan efekat na povećanje pripremljenosti zdravstvenog osoblja za katastrofe i poboljšanje operativne rezilijentnosti bolnice.

Ključne reči:
bugarska; katastrofe, planiranje; bolnice; kadar bolnički; ankete i upitnici.

Introduction

Hospital disaster readiness includes activities, programs, and systems aimed at providing the necessary medical care to the casualties and reducing the negative impact of disasters. The hospital's activities and programs consist of coordination, approved response procedures, and medical staff training [1–5]. The planned and implemented training and drills have a significant impact on disaster response preparation and have a positive influence on human resources [6–11]. Insufficient drills are associated with slowing the reaction of medical personnel in case of a disaster and reducing the effectiveness of the disaster response, negatively affecting the operational component of disaster resilience [12, 13]. To increase knowledge and

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skills regarding specific disaster medical response algorithms, drills must be conducted routinely [14]. In order to achieve this, the plan envisages the implementation of specific training for hospital employees and contains related regulations. A hospital headquarters task is to organize disaster drills with both managers and executive medical specialists [2, 3, 7, 15–17]. The aim of this study was to analyze the preparedness of hospital medical professionals in the Plovdiv region for maintaining hospital disaster resilience.

Methods

An anonymous survey was conducted among hospital medical professionals in the Plovdiv region, Bulgaria. The study was conducted in two multidisciplinary hospitals for active treatment (MHAT) and one university multidisciplinary hospital for active treatment (UMHAT). The choice of MHAT to conduct the study is based on the role of this type of medical facility during disaster medical support. In case of a disaster, the casualties are evacuated to the nearest hospital, which can provide life-saving therapeutic and surgical assistance to casualties with multiple traumas. The hospitals listed below were included in the study: UMHAT "Plovdiv", Plovdiv; MHAT "Asenovgrad", Asenovgrad; MHAT "Dr. Kiro Popov", Karlovo. They were selected on a random (lottery) basis from a list of existing medical facilities for hospital care in the territory of the Plovdiv region. To conduct the study, written permissions were received from the heads of the hospitals: application with incoming number B-1024, dated August 6, 2019, from the executive director of UMHAT "Plovdiv", Plovdiv; application with incoming number П-800, dated July 6, 2019, from the executive director of the UMHAT "Plovdiv", Plovdiv; request with incoming number 1305, dated July 10, 2019, from the manager of MHAT "Asenovgrad", Asenovgrad; application with incoming number 748, dated July 9, 2019, from the manager of MHAT "Dr. Kiro Popov", Karlovo.

The survey was conducted from July to September 2019. The purpose of the survey and the survey card were presented to the medical personnel. After brief introductions by the interviewer, questionnaires were distributed to the medical persons who expressed willingness to participate in the study. The method of conducting was to fill in a paper form of the questionnaire. The questionnaire consisted of 55 questions. The survey was anonymous. The purpose of the conducted survey for each medical specialist was to self-determine, according to their qualification and position, the level of their awareness and medical readiness for responding in the conditions of disasters.

Stein's two-step method was used to determine the required number of observation units. In the first stage, a micro-survey was conducted on a sample of thirty medical specialists, and the age of the respondents was taken as an indicator for calculating the required standard deviation (Sx). In the second stage, 287 units of observation were determined using the formula for calculating the required number of units of observation for variation signs, with $\Delta = 0.5$ g, $Sx = 4.32$, and perceived usefulness $[P(u)] = 0.95$ as the maximum permissible error. The number of medical professionals surveyed was 310, of which 15 were dropped due to incomplete and missing data in survey cards, leaving the actual number of work units at 295. The number of medical staff who participated in the study (295 in total) constitutes 8.6% of all medical personnel (general population) in the MHAT in the Plovdiv region, and is representative in relation to the general population.

Data processing and quantitative analysis were conducted using specialized software SPSS® 21.0 (IBM Corporation®, Armonk, New York, United States of America). Descriptive statistics was used to calculate the relative percentages. Pearson's Chi-square test and Spearman's correlation were used in testing hypotheses for a statistically significant relationship between the studied factorial and performance traits. Graphic analysis was used to illustrate processes and phenomena, certain regularities, or dependencies. Microsoft Office Excel 2013 was used for tabular and graphical analysis. For all analyses, $p < 0.05$ was statistically significant.

Results

The medical professionals of hospitals in the Plovdiv region believed that disaster drills were not conducted regularly – most [253 (85.8%)] of the respondents provided a negative response (Figure 1).

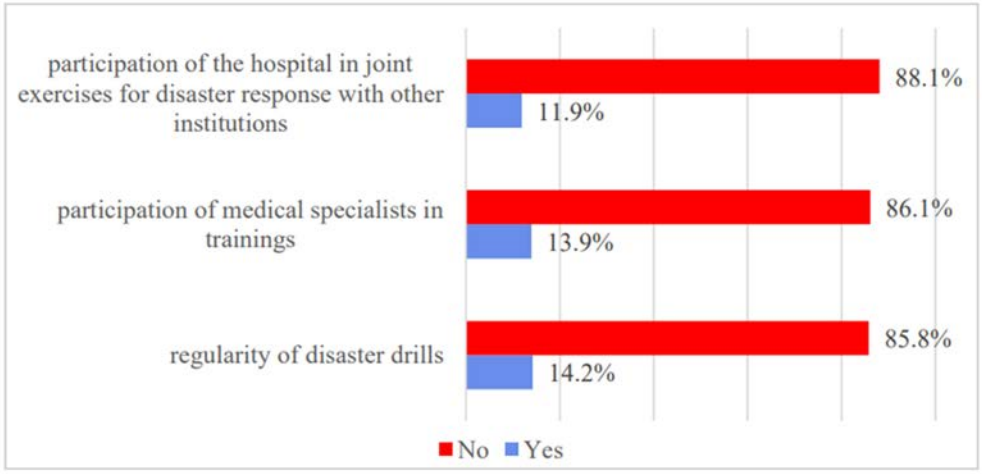

Fig. 1 – Respondents' knowledge about the regularity of hospital disaster trainings and participation in drills.

The highest percentage [9 (32.1%)] of medical specialists who believed drills to be common events was observed among managers ($p = 0.018$; $\chi^2 = 10.01$) (Figure 2).

A small number [91 (30.8%)] of hospital medical professionals have indicated that the training event period was shorter than two years. More than half [165 (55.9%)] of the respondents stated that this period was longer than five years. The relative share of respondents who noted that the classes were held over a period of 4–5 years was 19 (6.4%), and 20 (6.8%) medical specialists believed that the training event period was 2–3 years (Figure 3).

Most [254 (86.1%)] hospital medical staff in the Plovdiv region did not participate in trainings (Figure 1). Managers participated more often [11 (39.3%)] in disaster response trainings out of all participants ($p = 0.001$; $\chi^2 = 22.64$) (Figure 2). Medical specialists working in a hospital were extremely unaware of the fact whether the hospital participated in joint exercises for disaster response with other institutions – 260 (88.1%) respondents provided a negative answer (Figure 1).

Discussion

Disaster medical support requires specific theoretical and practical training, as well as the acquisition of skills that differ from daily medical practice. Therefore, it is mandatory to put into practice what has been learned through regular disaster drills [12]. The hospital medical staff in the Plovdiv region stated that disaster drills are not conducted regularly. Chimenya [15] reported that almost all of the respondents (97.8%) stated that the hospital did not perform disaster-related trainings, which coincides with the results of our study.

Although the largest number of respondents who believe that drills take place often are among managers, there are too few of them in total. In a study by Chimenya [15], only 3.0% of the superiors considered disaster trainings to be regular, which is even lower than the results in our study. Managers are responsible for planning and organizing disaster training activities. Negative statements from the hospital medical staff about training frequency indicate that the man-

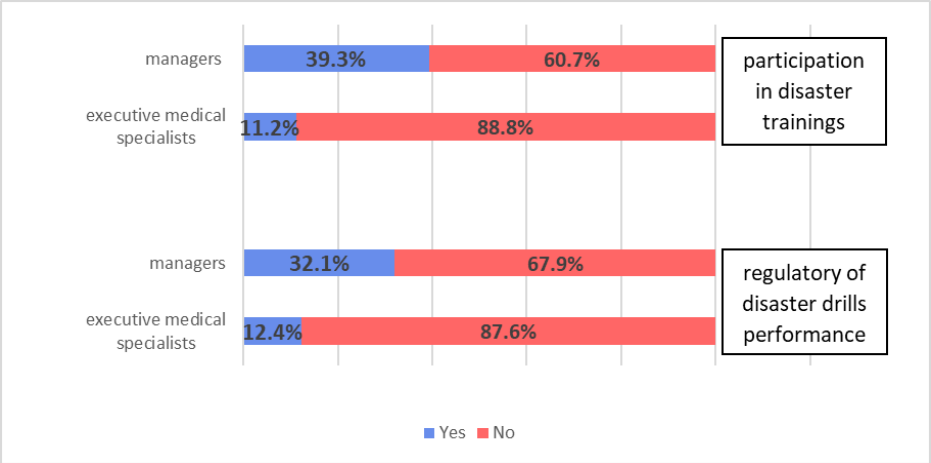

Fig. 2 – Respondents' knowledge about the hospital disaster trainings and drills according to their position held.

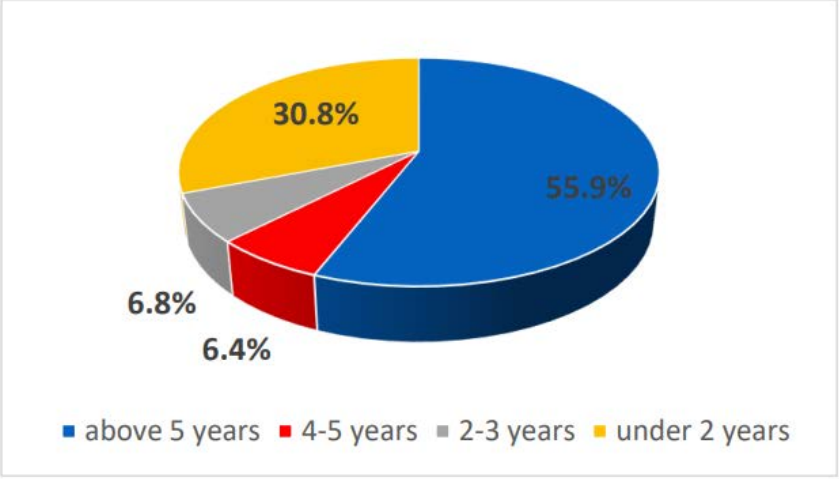

Fig. 3 – Opinion of hospital medical professionals on the training period.

agers need to consider the performance of their duties more precisely and arrange drills more frequently. Increasing drill reiteration will lead to better disaster preparedness among medical personnel and improve the operational resilience of the hospital.

Regarding regularity, according to the hospital disaster medical support plan, disaster drill performance should be held once a year. Less than 1/3 (30.8%) of medical professionals have answered that the training event period is shorter than two years. Kolev [12] reported results similar to our study. The findings of our study showed extremely unsatisfactory results and indicated that the number of conducted disaster drills by hospital medical professionals was less than it was supposed to be. As a result of the decreased frequency of the trainings, the automation and the speed of hospital staff's reactions in case of a disaster will also be decreased. This would have a negative impact on the disaster resilience of the hospital.

The hospital disaster medical support plan should include regulations for conducting disaster training and drills throughout the year. Staff disaster training is required to assess its readiness [15]. Most of the medical professionals working in hospitals in the Plovdiv region have not participated in the trainings. Managers participated more often in disaster response trainings than others. The results of this study are similar to others conducted worldwide. Chimenya [15] reported that 85.7% of medical professionals did not attend disaster-related training. In a study by Damete [18], 3/4 (76.2%) of the medical staff did not receive disaster management training. Results from research done at Alexandria University Hospitals show that 71.9% of respondents did not attend disaster-related training [19]. According to another study conducted at Amhara Regional State Referral Hospitals, Ethiopia, 65.7% of medical staff did not receive training on disaster preparedness and management [20].

Hospital staff's education and practical training on hospital disaster medical support are conducted jointly with the municipality and regional response forces of the Unified Rescue System and in accordance with the disaster medical support plan. Joint training with other structures is done to improve coordination and timing of the search, rescue, and medical activities during a disaster [12]. Hospital medical specialists are completely unaware of whether the hospital participates in joint exercises for disaster response with other institutions. To successfully deal with the challenge of disaster medical support, the Unified Rescue System elements are necessary to organize and execute continuous training for responding to disasters in cooperation among them [2, 21]. Insufficient joint training is associated with a delay in disaster response and a reduction in response effectiveness, negatively impacting disaster resilience.

Daily work of healthcare workers is associated with an increased presence of different stressors that induce an increase in psychological pressure, leading to anxiety, depression, sleep disorders, and burnout. The stress levels increase throughout crises and disaster occurrences. Hospital resilience increases the mental and physiological stamina during disasters. Psychological resilience is defined as the ability of people to tolerate increased levels of stress more easily, function adequately, and be able to adapt in emergencies and maintain or restore their mental health. The ability to mentalize is an important characteristic of resilience and represents the human ability to understand one's own and the mental states of others, which affects the general resilience of the personality, i.e., the ability to adapt successfully to challenges and stress. The process of mentalization is expressed in the interdependence between the subjective understanding of the mental states of ourselves and others, which influences our behavior and allows us to feel in control of our thinking and the way we act, as well as the way we perceive, analyze, and interpret social information from our surroundings [22–24].

Achieving higher resilience among medical specialists can be accomplished through appropriate training programs. The development of online interventions focusing on resilience and the availability of psychological support is needed to manage stress during a disaster and address the long-term consequences related to quality of life, personal functioning, and overall well-being [22–24].

Conclusion

Based on the results of the performed analyses, it must be noted that the level of preparedness for responding to disasters is not maintained at a high level in hospitals in the territory of the Plovdiv region due to the irregular implementation of exercises and the small number of participants in them. Therefore, it is necessary to introduce a specific training program and exercise once a year, which should have a beneficial effect on increasing the preparedness of the medical staff for disasters and improving the operational resilience of the hospital.

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Job satisfaction of healthcare professionals in palliative care departments and factors affecting job satisfaction during the COVID-19 pandemic

Zadovoljstvo poslom zdravstvenih radnika na odeljenjima palijativnog zbrinjavanja i faktori koji utiču na zadovoljstvo poslom tokom pandemije COVID-19

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Abstract

Background/Aim. The COVID-19 pandemic had a significant impact on the healthcare system, particularly healthcare providers such as nurses/medical technicians, who were obliged to adhere to strict procedures and manage their time effectively during shifts. The aim of this study was to identify internal strengths, weaknesses, threats, and challenges in palliative care management during the COVID-19 pandemic from the perspective of nurses/medical technicians. **Methods.** A cross-sectional study was conducted on a 100% sample of nurses/medical technicians working in hospital-based palliative care in two clinics in Belgrade (47 respondents in total). The research instrument was a Questionnaire on Employee Satisfaction. The survey was conducted during September and October 2022. **Results.** Assessing the job satisfaction of nurses/ medical technicians revealed moderate job satisfaction (3.43), which was mostly influenced by appropriate financial compensation and the implementation of measures to prevent and control the spread of the COVID-19 infection. The dimensions of management that were significantly related to respondents' satisfaction were motivation and adequacy of hygienic conditions and measures to control COVID-19 (χ^2 = 62.83, p = 0.004 and χ^2 = 36.42, p = 0.006, respectively). **Conclusion.** Nurses/medical technicians who experience stress at work in regular conditions tend to react the same way in different conditions, such as those related to COVID-19 infection. The most difficult challenge that the management faces is the recognition of the importance of the work of nurses/medical technicians by the community. Therefore, it is vital to respect and support the most important professional values of nurses/medical technicians, such as valuable achievements, the importance of professional challenges, personal growth and development, and independence in practice.

Key words:
covid-19; job satisfaction; nurses; palliative care.

Apstrakt

Uvod/Cilj. Pandemija COVID-19 je značajno uticala na zdravstveni sistem, posebno na pružaoce zdravstvenih usluga kao što su medicinske sestre/medicinski tehničari, koji su morali da se pridržavaju strogih procedura i efikasno upravljaju svojim vremenom tokom smena. Cilj rada bio je da se iz perspektive medicinskih sestara/tehničara

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identifikuju unutrašnje snage, slabosti, pretnje i izazovi u upravljanju palijativnim zbrinjavanjem tokom pandemije COVID-19. **Metode.** Studija preseka sprovedena je na 100% uzorku medicinskih sestara/tehničara koji rade na bolničkom palijativnom zbrinjavanju u dva kliničko bolnička centra u Beogradu (ukupno 47 ispitanika). Instrument istraživanja bio je Upitnik o zadovoljstvu zaposlenih. Anketiranje je sprovedeno tokom septembra i oktobra 2022. godine. **Rezultati.** Procena zadovoljstva poslom medicinskih sestara/tehničara pokazala je umereno zadovoljstvo poslom (3,43), na koje je najviše uticala odgovarajuća finansijska nadoknada za rad i sprovođenje odgovarajuih mera za sprečavanje i kontrolu širenja COVID-19 infekcije. Dimenzije menadžmenta koje su bile u značajnoj vezi sa zadovoljstvom ispitanika su motivacija i adekvatnost higijenskih uslova i mera za kontrolu COVID-19 infekcije ($\chi^2 = 62,83$, $p = 0,004$ i $\chi^2 = 36,42$, $p = 0,006$, redom). **Zaključak.** Medicinske sestre/tehničari koji doživljavaju stres na poslu u redovnim uslovima imaju tendenciju da reaguju na isti način u različitim uslovima, kao što su i oni povezani sa infekcijom COVID-19. Najteži izazov sa kojim se menadžment suočava je prepoznavanje važnosti posla medicinskih sestara/tehničara od strane društvene zajednice. Zbog toga je važno poštovati i podržavati najvažnije profesionalne vrednosti medicinskih sestara/tehničara, kao što su vredna dostignuća, važnost profesionalnog izazova, lični rast i razvoj i samostalnost u praksi.

Ključne reči:
covid-19; posao, zadovoljstvo; medicinski tehničari; nega, terminalna.

Introduction

Job satisfaction is an emotional reaction to the work performed by a person [1]. It is influenced by economic and sociological categories and indicators of employee motivation and the work environment [2]. Determining job satisfaction is significant because it can predict employees' future behavior [3]. The work environment in healthcare institutions is a complex, multifactorial phenomenon that directly affects the quality of healthcare services for providers and recipients [4]. Burnout is a common problem among healthcare professionals in the healthcare sector. High levels of job demands, long working hours, low levels of job control, and poor work-life balance are some of the factors that contribute to burnout in healthcare settings [5]. The coronavirus disease 2019 (COVID-19) pandemic has highlighted that the lack of resources, motivation, work organization, job satisfaction, and the presence of stress and work challenges affect healthcare workers, especially nurses, who are at risk of burnout and have a higher intention to leave the health sector [6–8]. During the COVID-19 pandemic, healthcare units have faced additional challenges, such as shortages of personal protective equipment, increased workload due to a higher number of patients, and fear of infection [9]. The pandemic has emphasized the essential role that nurses play by exposing themselves to COVID-19 patients [5]. Palliative care is a demanding and emotionally challenging field, that requires nurses to work with patients who are seriously ill and often nearing the end of their lives; this position has been found to affect job satisfaction [10].

Palliative care is a human right that all geriatric and oncology patients in the terminal stages of the disease should have in order to reduce their suffering and preserve their dignity.

To ensure the continuity of care, case management in palliative wards has been developed for patients with complex care requirements as an integrative part of palliative care. It consists of the assessment, planning, implementation, coordination, monitoring, and evaluation of health services and has been used for many years in psychiatry and geriatrics [11]. There are different research results on its effectiveness, models, and variations in case management [12]. However, it is difficult to compare studies due to different research methods and outcomes and unclear descriptions of case management [13–15]. Therefore, it is essential to study hospital-based palliative care management during the COVID-19 pandemic, especially for nurses who are exposed to time and obligatory procedures during their shifts.

The aim of this study was to assess the job satisfaction of nurses and medical technicians in palliative care departments during the COVID-19 pandemic and identify organizational factors that affect job satisfaction.

Methods

Study and sample type

A descriptive cross-sectional study was conducted on a sample of 47 nurses and medical technicians working in the COVID-19 zone of hospital-based palliative care at two clinics in Belgrade, Serbia: Department of Oncology of the Clinical Hospital Center Zemun (with 30 respondents) and Department of Geriatrics of the Clinical Hospital Center Zvezdara (with 17 respondents). Of the 47 nurses and medical technicians who participated in the study, seven were men and 40 were women. All (n = 47) employed nurses and medical technicians completed the questionnaire, resulting in a response rate of 100%. There were 16 nurses and medical technicians under the age of 34, 25 were aged from 35 to 54, and six were over 55. Nine respondents performed some managerial functions. Most (n = 35) of the nurses and medical technicians in this study did not have other jobs, while a minority (n = 2) worked in teaching, private practice (n = 4), and other sectors (n = 6).

Research instrument

A questionnaire on employee satisfaction, which is unique for all primary, secondary, and tertiary healthcare institutions in the Republic of Serbia, was used as a means of data collection in this study. The questionnaire consists of 24 questions classified into four thematic units.

The first group of questions (twelve questions) is related to the assessment of management in palliative care units from the aspect of resources (equipment, workspace, communication), motivation, and work organization. The respondents were asked to mark their answers on a 5-point scale ranging from 1 ("very bad") to 5 ("excellent").

The second group of questions (six questions) is related to work in the COVID-19 zone in terms of the presence of stress, work challenges, and job satisfaction. The respondents were asked to mark their answers on two 5-point scales ranging from 1 ("not at all" for questions thirteen and fourteen, and "very dissatisfied" for question eighteen) to 5 ("very much" and "very satisfied").

The third group of questions (five questions) defines the demographic and professional characteristics of the respondents. The last question in the fourth category of questions is open-ended in terms of respondents' comments and suggestions for improving the quality of work and employee satisfaction.

The questionnaire was standardized, validated, and approved by the Institute of Public Health of Serbia "Dr. Milan Jovanović Batut" and the Ministry of Health of the Republic of Serbia. It has been in use for ten years and was distributed in Serbian, supplemented by questions related to the COVID-19 pandemic, which began in March 2020 [16].

The survey was carried out during September and October 2022. It was conducted individually with each respondent according to ethical standards and principles by the researchers. Before the start of the research, approval was obtained from the Ethical Committees of the Clinical Hospital Center Zvezdara, Belgrade (No. IRB00009457, from October 5, 2022) and the Clinical Hospital Center Zemun, Belgrade (No. 151/1, from September 27, 2022), where the research was carried out. Informed consent was obtained from all subjects involved in the study.

During the first wave of the COVID-19 pandemic, there was not enough room for all patients who needed palliative care in the special departments of some of the Clinical Centers and Hospital Centers in Belgrade. At the time of the survey, Serbia was facing the seventh pandemic wave, with over 1,300 new cases a day [17], and the conditions all over the country significantly improved.

Sample of variables

The main variables of the research were extracted from the questionnaire on employee satisfaction and related to specific aspects (dimensions) of management in palliative care units. Several questions from the questionnaire were combined to form a total of five aspects of management, which are listed below: 1) Resources – It is vital to provide adequate resources, including necessary equipment and sufficient space, as well as available time for work. 2) Motivation – If we focus on motivation, it is essential to enhance motivation through promoting autonomy in work, acknowledging the value of work by superiors, providing opportunities for professional development and education, and finally ensuring appropriate financial compensation. 3) Communication – Considerable time and effort should be devoted to improving communication and cooperation among colleagues and with patients. 4) COVID-19 – It is recommended to maintain adequate hygienic conditions for work by implementing measures to prevent nosocomial infections and control the COVID-19 infection. 5) Management – The significant element is to optimize the organization of work in the palliative care unit.

Statistical analysis

The database was created using Excel, and the statistical processing was done using the PSPP program (an open-source SPSS clone). The sample size was determined using the "pwr.chisq.test" function from the R statistical package, using common values for the significance level (0.05) and power of the test (0.80). The minimum sample size obtained by this method was n = 45. Descriptive statistics methods were used to process the data, and the Chi-square (χ^2) test was used to test the significance of the hypotheses, along with the contingency coefficient to measure the strength of the relationship. A *p*-value < 0.05 was considered statistically significant. The reliability of the questionnaire was evaluated using the Cronbach's alpha method.

Results

The attitudes of respondents towards different aspects of management in palliative care units (Table 1) show that

Table 1

Respondents' attitudes on different aspects of management in palliative care units during the COVID-19 pandemic

Dimensions of management	Measures of description		
	mean ± SD	med	mod
Provision of resources (equipment for work; adequate space for work; available time for work)	3.55 ± 0.85	4.00	4
Motivation (autonomy in work; appreciation of work by superiors; opportunity for professional development and education; financial compensation)	3.55 ± 0.85	3.75	4
Communication and cooperation (with colleagues and with patients)	4.03 ± 0.72	4.00	4
Maintaining adequate hygienic conditions for work in accordance with measures to prevent nosocomial infections and implementing adequate measures to prevent and control the COVID-19 infection	3.80 ± 0.84	4.00	4
Management and organization of work	3.74 ± 1.03	4.00	4

COVID-19 – coronavirus disease 2019; SD – standard deviation; med – median; mod – most frequently occurring value.

they value communication with their colleagues and cooperation with patients the most (mean 4.03). They also value other aspects of management almost equally, including the provision of resources, motivation, maintaining adequate hygienic conditions to prevent and control COVID-19 infection, and organization of work.

Of the individual variables, financial compensation for work received the lowest rating from respondents, with an average rating of 2.76.

The biggest challenges in the work of nurses and medical technicians during the COVID-19 pandemic (Table 2) were exhaustion due to workload and working while using protective equipment.

Slightly less than half (n = 21; 44.7%) of the respondents claimed they experienced only one of the offered challenges at work. It was observed that 25 (53.2%) respondents declared that they faced more challenges at work. Eight (17%) respondents faced two challenges, nine (19.1%) respondents faced three challenges, five (10%) respondents faced four challenges, and one (2.1%) respondent indicated five challenges, while two (4.3%) respondents indicated all seven challenges. Only one (2.1%) respondent did not experience any challenges at work during the COVID-19 pandemic.

Interestingly, nurses and medical technicians from palliative care units who worked in the COVID-19 zone did not report more stress, pressure, and tension (mean 3.57) than while working under regular working conditions (mean 3.6). Specifically, nurses and medical technicians who feel greater tension, stress, or pressure in regular working conditions had the same experience and reaction mechanism while working in the COVID-19 pandemic conditions, and this relationship is statistically significant ($\chi^2 = 60.89$; $p = 0.000$).

Moreover, stress, pressure, and tension under regular and COVID-19 pandemic conditions have a high established reliability of over 0.7 (0.804).

The average value of the self-assessment of overall job satisfaction of the nurses and medical technicians in this research is 3.43 out of a maximum of 5, where a score of 5 indicates the highest possible job satisfaction and a score of 1 indicates the lowest possible job satisfaction. More than half (57.4%) of the respondents rated their job satisfaction as 3, and no respondents gave a rating of 1. About 4.3% gave a rating of 2, 29.8% of respondents gave a rating of 4, and 8.5% gave a rating of 5.

Finally, in terms of descriptive statistics, 19 (40.4%) respondents considered changing jobs in the next five years, while five (10.6%) considered moving to the private sector. Seven (14.9%) had plans to work outside of the healthcare sector in the next five years, while eight (17%) respondents had plans to work abroad.

Should we consider management in palliative care units as a whole (the sum of all 12 indicators), there is no statistically significant relationship between management and overall job satisfaction ($\chi^2 = 96.92$; df = 78; $p = 0.072$).

Regarding the relationships presented in Table 3, the motivation of respondents is most closely related to job satisfaction, followed by maintaining hygienic conditions and implementing adequate measures to prevent and control the spread of the COVID-19 infection ($\chi^2 = 62.83$, $p = 0.004$ and $\chi^2 = 36.42$, $p = 0.006$, respectively). There is a significant relationship between job satisfaction and the provision of resources in a healthcare facility ($\chi^2 = 40.96$; $p = 0.042$). However, cooperation with colleagues and relationships with patients, as well as the organization of work in the institution, did not have statistically significant values (Table 3).

If we observe the relationship between each item and job satisfaction, we can see that there is a statistically significant relationship with financial compensation ($\chi^2 = 38.33$; $p = 0.000$), followed by the implementation of adequate measures against COVID-19 ($\chi^2 = 23.98$; $p = 0.004$).

Table 2

The biggest challenges in the work of nurses and medical technicians from palliative care units during the COVID-19 pandemic

Challenges at work	Frequency distribution	
	number (%)	rank order
Work under totally new conditions	20 (42.5)	3
Exhaustion due to workload	23 (48.9)	1
Exhaustion due to work under protective equipment	21 (44.7)	2
Availability of protective equipment	5 (10.6)	7
Availability of information	14 (29.8)	4
Uncertainty and fear of infection	12 (25.5)	5
Dealing with patient experience	8 (17.0)	6

COVID-19 – coronavirus disease 2019.

Table 3

The significance of the relationship between different aspects of management in palliative care units during the COVID-19 pandemic and the job satisfaction of respondents

Parameter	Management									
	resources		motivation		communication		COVID-19		management	
Complete satisfaction at work	$\chi^2 = 40.96$ $p = 0.042$	df = 27 CC = 0.68	$\chi^2 = 62.83$ $p = 0.004$	df = 36 CC = 0.76	$\chi^2 = 28.67$ $p = 0.053$	df = 18 CC = 0.62	$\chi^2 = 36.42$ $p = 0.006$	df = 18 CC = 0.66	$\chi^2 = 16.75$ $p = 0.159$	df = 12 CC = 0.51

COVID-19 – coronavirus disease 2019; df – degree of freedom; CC – correlation coefficient; $p < 0.05$ is considered statistically significant.

A small number of respondents made remarks and suggestions for improving the quality of work and the satisfaction of nurses and medical technicians working in palliative care units. They requested a salary increase (two respondents), proposed achieving better communication between health workers (one respondent), and requested the provision of new beds in palliative care units (one respondent).

Discussion

One of the most important goals of management is to create a positive and stimulating psychosocial climate in the institution so that employees perform their jobs willingly, gladly, readily, and with quality. Indicators of an inadequate psychosocial work environment include poor financial status of employees, inadequate safety at work, inadequate communication at the workplace, poor working conditions, heavy physical and mental strain, the existence of psychosomatic illnesses among employees, and frequent absences from work [18, 19].

Factors that positively affect the psychosocial aspects of work in any health institution are adequate work requirements, a reliable and fair work environment, trust in colleagues and managers, the perception of justice, respect and social inclusion, and validation of the importance of the nurse's work [20, 21].

Our experience during the COVID-19 pandemic suggests that nurses and medical technicians in the palliative care unit value adequate communication with their colleagues and good cooperation with patients the most, indicating that they are satisfied with the nature of the work they do.

However, for their job satisfaction, the provision of resources in the health institution (extrinsic factors) [22], the implementation of adequate measures against COVID-19, and appropriate financial compensation are much more important, which is consistent with other research [23–27].

Nurses are dissatisfied with their income, which is crucial for their existence and is also a way of recognizing their investment in the work they perform [28], especially under conditions of increased stress. This is the opinion of nurses from most European countries, except Finland and the Netherlands. Nurses from Poland and Slovakia are particularly dissatisfied because their salaries cannot cover the basic costs of living [24].

Salaries greatly influence job satisfaction, and dissatisfaction may lead to increased turnover and even leaving the profession. The lowest scores of the respondents are in the domains of salary and working conditions. About 60% of respondents want to change jobs, while about 55% indicate that they experience more than one challenge in their daily work. This data is worrying, considering that many studies indicate a direct positive relationship between nurse work satisfaction and patient health outcomes [29–32].

Research conducted in Jordan discovered that nurses are mostly (67.4%) dissatisfied with their salary and the negative perception of nurses in society (62.2%). They are moderately satisfied with their work (average score around 3 out of a possible 5), while around 23.3% of respondents want to leave their workplace in the next year, and 18.1% are neutral on this issue [30]. However, as in our research, there was no statistical significance between the mentioned variables; if there was, it was quite weak. There is only a significant negative correlation between job satisfaction and salary and the intention to leave the workplace [30], while in our research, this correlation does not exist.

Research in Egypt indicated that the most significant stressor for nurses during the COVID-19 pandemic was the work environment and, above all, overtime work, frequent night shifts, unsuitable work, and rest regimes. Furthermore, nurses did not have enough time to spend with their families and loved ones [33].

About 40% of respondents in this study were completely or mostly satisfied with their jobs, but two-thirds considered changing their jobs. In a survey in Croatia, approximately 65% of nurses were completely or mostly satisfied with their job, and around 68% considered changing their job [34]. Other studies confirm this disparity. Although about 73% of nurses were satisfied with their current job and workplace, and about 82–88% with their profession, 48% of them intended to go to another workplace within the same profession field, while about 41% of respondents considered leaving the profession entirely [35].

Job satisfaction is partially related to the psychological characteristics of personality and engagement at work [36]. Nurses specializing in some type of healthcare, such as palliative care, show higher levels of job satisfaction and work engagement than general nurses because of their extensive work experiences, career identity, stronger feelings of responsibility, clear job descriptions, and a sense of mission in their work [36].

As far as psychological personality characteristics are concerned, nurse specialists have developed the following dimensions of psychological capital: self-efficacy, hope, resilience, and optimism [33, 36]. All of these personality traits are essential for the appropriate adaptation to new conditions of life and work, particularly for controlling emotions in the case of working under pressure and improving the ability to achieve work goals.

Additionally, high levels of job satisfaction and increased engagement at work have been shown by nurses who work in healthcare institutions with the following characteristics: clear rules and a proactive strategy, consistency in decision-making, the creation of a positive psychosocial atmosphere at work together with well-known ethical principles of work, clear observation of the public interest in the operation of the health institution [36–38], autonomy at work, clear job feedback, improved relationships between nurses and managers, and reduced levels of conflicts between job demands and the level of responsibilities of nurses [39].

Quality leadership, feedback from managers, and support from colleagues are important aspects of job satisfaction because they contribute to the perception of nurses belonging to the team. This consequently leads to the perception of less physical effort at work, less intensity of

work dynamics, fewer feelings of injustice, and fewer occurrences of conflicts within the team [4]. This is also supported by the fact that the nurses in our study did not work double shifts, which represents an additional risk factor for health and the perception of the workplace because they affect daily life and prevent complete rest.

The study conducted in Israel [22] found that the most essential component of occupational satisfaction is related to personal accomplishment. This means that even under the circumstances of the pandemic, the most significant occupational values of the nurses are worthwhile accomplishments, the importance of professional challenge, diversity and interest in the job, personal growth and development, and independence in their practice (intrinsic factors).

Nurses who describe their job as involving meaningful work are the ones who are highly satisfied with their jobs [40]. Research also indicates some protective effects of emotional intelligence against the adverse effects of psychosocial risks such as burnout syndrome [41].

The results of our research correlate with other research in which the importance of finding meaning in work, the importance of work and dedication to work, as well as opportunities for education and advancement are observed as significant internal factors for nurses' job satisfaction and their desire to stay at work [4]. On the other hand, the degree of nurses' commitment to work correlates with the availability of human resources and improves team performance [42]. The lack of resources in conditions of increased demands at work leads to the increased exhaustion of healthcare workers [43].

The most stressful jobs are those that involve high expectations, coercion, and low support. This was the situation created at the beginning of the COVID-19 pandemic because there were high expectations and pressures on healthcare workers that were not commensurate with their existing knowledge and abilities. At that time, there was not enough possibility to control and support employees, which generated stress [44].

In hospitals, the most significant stressors for nurses are the lack of autonomy and the high psychological and emotional demands of the job [45]. In primary health care, the absence of predictable situations and the lack of support from managers are the most significant stressors [46]. Health workers themselves believe they are among the groups most affected by the psychosocial aspects of the workplace [47]. Therefore, the identification of risks in the workplace is crucial for the motivation of employees and the improvement of working conditions. For nurses, motivation and social support are the most important protective factors for preventing the occurrence of work-related mental health disorders [48].

Interventions to reduce the stress of healthcare workers in the workplace are primarily related to the creation of an optimal psychosocial climate. These include the active participation of healthcare workers in making decisions regarding their work tasks in terms of the content and working conditions, having a choice of methods, tasks, and time for their performance, providing opportunities for advancement, perceiving the importance and significance of the work they perform, having a commitment to the workplace, transparent and open communication between colleagues and superiors, and the existence of clear levels of responsibility.

This type of organization and atmosphere should lead to increased capacities for innovation among employees, as well as the use of tools for generating original and valuable ideas and applying those ideas in practice [42]. This can only be achieved if employees are empowered, supported, and given independence at work [49, 50].

Limitations of the study

Possible bias in the sample selection was overcome by performing the study on a 100% sample. Although the sample size provides good statistical power for data analysis, generalizing the results must be cautiously approached primarily because of cultural differences. Since exposure and outcomes are measured simultaneously in this study, previous knowledge about issues or topics can affect the determining exposure or outcome, resulting in recall bias. Furthermore, this study demonstrates the relationship between two variables, but no causal inferences should be drawn from these results. Finally, despite being completely anonymous, participants tended to rate themselves better in terms of stress levels and dealing with new forms of organization in healthcare institutions. These results could be complemented by further qualitative research to obtain a broader and deeper understanding of the needs of nurses and medical technicians in the workplace, with the goal of reducing their turnover, improving the quality of healthcare, and increasing job satisfaction.

Conclusion

The greatest internal strengths in the process of providing healthcare in palliative care units during the COVID-19 pandemic are proper communication and cooperation with colleagues and patients, dedication to work, as well as opportunities for the education of nurses and medical technicians. Perceived weaknesses and threats relate to the large volume of work and the lack of human resources in a situation of increased job demands and low wages.

The biggest challenges for reducing nurse turnover in palliative care units, improving the quality of healthcare, and increasing job satisfaction are ensuring adequate redistribution of the nursing workforce to reduce workload, ensuring high-quality healthcare, enabling greater autonomy in the work of trained nurses, providing adequate resources for work, offering support and clear feedback from managers and colleagues, enabling adequate rest for nurses during and outside of working hours, promoting salary scales that reflect the complexity and the responsibility level of the work, and recognizing the importance of nurses' work by the community.

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Data availability statement

Data and research results are part of the doctoral dissertation project that will be available after the defense to the extent permitted by the regulations of the University of Kragujevac at the following link: https://eteze.kg.ac.rs/.

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Conflicts of interest

The authors declare no conflict of interest.

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The use of continuous renal replacement therapy in critically ill patients with COVID-19-related acute kidney injury

Primena kontinuirane terapije zamene funkcije bubrega kod kritično obolelih sa akutnim oštećenjem bubrega povezanim sa COVID-19

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Abstract

Background/Aim. Patients with severe clinical COVID-19 are at higher risk of developing acute kidney injury (AKI). The aim of the study was to analyze the risk factors for AKI/AKI on chronic kidney disease (CKD) and the results of treatment using continuous renal replacement therapy (CRRT) in critically ill COVID-19 patients. **Methods.** The study included 101 COVID-19 patients with AKI treated with CRRT out of a total of 293 patients with AKI. The study was conducted from March 2020 to July 2021 at the University Clinical Center of Vojvodina, Serbia. **Results.** The average age of patients was 64.69 ± 9.71 years. Out of the total number of patients, 82.2% were male, of whom 75.2% suffered from hypertension. On invasive mechanical ventilation (IMV) were 93.7% of patients, and 92.1% were on vasopressor therapy. The average length of IMV until the beginning of CRRT was 4.65 ± 4.57 days. In the first 24 hrs after starting IMV, 60% of patients had to undergo CRRT. Before administering CRRT, the average Simplified Acute Physiology Score II was 39.13 ± 14.45, creatinine 312 μmol/L [Interquartile Range (IQR) 208.0–437.5], procalcitonin 2.70 ng/L (IQR 0.62–7.20), while 10.9% of patients had SpO_2/FiO_2 index > 200 and 41.6% had anuria. The mean number of procedures was 2.01 ± 1.36. The most frequent modality was hemodiafiltration in 67.3% of patients, and 46% used the oXiris® membrane. Using binary logistic regression, including demographic parameters, comorbidities, as well as clinical parameters before CRRT, it was found that patients with previous kidney disease were 3.43 times more susceptible to developing AKI, and patients with SpO_2/FiO_2 index ≥ 200 were 69% less susceptible to developing AKI/AKI on CKD requiring CRRT in the first 24 hrs from the start of IMV. **Conclusion.** Determining the risk factors for AKI/AKI on CKD is important for planning the prevention of these conditions that require the application of CRRT with the correct choice of dialysis modality and dose, membrane/filter type, and anticoagulant dose.

Key words:
acute kidney injury; continuous renal replacement therapy; covid-19; critical illness; risk factors.

Apstrakt

Uvod/Cilj. Bolesnici sa teškom kliničkom slikom COVID-19 imaju viši rizik od razvoja akutnog oštećenja bubrega (AOB). Cilj rada bio je da se analiziraju faktori rizika od AOB/akutizacije bubrežne insuficijencije kod obolelih sa hroničnom bolešću bubrega (HBB), kao i rezultati lečenja primenom kontinuirane terapije zamene funkcije bubrega (KTZFB) kod kritično obolelih od COVID-19. **Metode.** Istraživanjem je obuhvaćen 101 COVID-19 bolesnik sa AOB, od ukupno 293 bolesnika lečenih primenom KTZFB. Istraživanje je sprovedeno od marta 2020. do jula 2021. godine u Univerzitetskom Kliničkom centru Vojvodine, Srbija. **Rezultati.** Prosečna starost bolesnika bila je 64,69 ± 9,71 godina. Od ukupnog broja bolesnika, 82,2% bilo je muškog pola, od kojih je 75,2% bilo obolelih od hipertenzije. Na invanzivnoj mehaničkoj ventilaciji (IMV) bila su 93,7% bolesnika, a 92,1% na vazopresornoj terapiji. Prosečna dužina IMV do početka KTZFB bila je 4,65 ± 4,57 dana. U prva 24 sata od početka IMV, 60% bolesnika je zahtevalo KTZFB. Pre KTZFB, prosečna vrednost *Simplified Acute Physiology Score II* iznosila je 39,13 ± 14,45, kreatinina 312 μmol/L [*Interquartile Range* (IQR) 208,0–437,5], prokalcitonina 2,70 ng/L (IQR 0,62–7,20), dok je 10,9% bolesnika imalo indeks SpO_2/FiO_2 > 200 i njih 41,6% anuriju. Prosečan broj procedura iznosio je 2,01 ± 1,36. Najčešći modalitet bio je hemodijafiltracija kod 67,3% bolesnika, a 46% je

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koristilo oXiris® membranu. Korišćenjem binarne logističke regresije, uključujući demografske parametre, komorbiditete i kliničke parametre pre KTZFB, utvrđeno je da su bolesnici sa prethodnim oboljenjem bubrega imali 3,43 puta veće šanse da razviju AOB, a bolesnici sa indeksom $SpO_2/FiO_2 \geq 200$ su imali 69% manje šanse za AOB/akutizaciju bubrežne insuficijencije u miljeu HBB, zavisne od KTZFB, u prva 24 sata od početka IMV. **Zaključak.** Utvrđivanje faktora rizika od AOB/akutizacije bubrežne insuficijencije kod obolelih sa HBB značajno je za planiranje njihove prevencije, koja zahteva i primenu KTZFB uz pravilan izbor modaliteta i doze dijalize, vrste membrane/filtera i doze antikoagulansa.

Ključne reči:
bubreg, akutna insuficijencija; bubreg, zamena funkcije, kontinuirana; covid-19; kritična stanja; faktori rizika.

Introduction

The clinical presentation of coronavirus disease 2019 (COVID-19) varies from asymptomatic to severe, the latter being present in about 5% of patients. The severe clinical presentation was accompanied by the development of acute respiratory distress syndrome (ARDS), multi-organ dysfunction (MODS), and the development of septic shock [1–5]. Patients with a severe clinical presentation of COVID-19 are at a higher risk of developing acute kidney injury (AKI). According to Chinese and American studies, AKI develops on average in 2.5–75.0% of patients [2–9]. Potential risk factors of AKI are the following: direct viral damage to tubular cells, activation of the renin-angiotensin-aldosterone system, inflammatory reaction triggered by the immune system's response to the virus, thromboembolism, and nonspecific factors such as hypotension and hypoxemia [10]. In cases of reduced or absent response to applied conservative treatment methods, renal replacement therapy (RRT) is applied. Application of RRT is necessary in 5–55% of cases [2–9]. In hemodynamically unstable patients, continuous RRT (CRRT) is indicated because this modality ensures better volume control and nutritional balance, which are very important in the treatment of patients with COVID-19 [11]. The aim of the study was to analyze the risk factors for AKI/AKI on chronic kidney disease (CKD) and the results of CRRT treatment in critically ill COVID-19 patients.

Methods

The study included 101 COVID-19 patients with AKI in the MODS who required CRRT from March 2020 to July 2021. They were hospitalized within one institution in the semi-intensive care units (SICU) and intensive care units (ICU). The study was approved by the University Clinical Center Vojvodina, Serbia, Ethics Committee (No 6-00-102, from June 1, 2023).

The following items were analyzed: demographic data; comorbidities; duration of illness, use of antibiotics before admission; first admission to the SICU/ICU; X-ray of the lungs on admission; vaccination status, need for invasive mechanical ventilation (IMV) and vasopressor therapy; AKI/AKI on CKD dependent on CRRT in the first 24 hrs from the start of IMV; duration of IMV until the beginning of CRRT; the beginning of CRRT since the hospital admission; modified index of oxygen saturation to fraction of inspired oxygen ratio (SpO_2/FiO_2), Simplified Acute Physiology Score II (SAPS II) and presence of anuria before CRRT; thromboprophylaxis therapy and dose; length of hospitalization; laboratory parameters before and after CRRT; type of CRRT modality; type of adsorptive membrane/filter; number of procedures; procedure parameters; changes in the dose of unfractionated heparin (UHF) during CRRT and reasons for ending of CRRT. A modified SpO_2/FiO_2 oxygenation index was used. Despite the arterial line being set for optimal monitoring because of a large number of patients, frequent blood sampling for arterial blood gas analysis was unnecessarily numerous during the pandemic. The SpO_2/FiO_2 index is always available as a surrogate P/F ratio [Note: P/F ratio equals the arterial pO_2 ("P") from the arterial blood gas divided by the FiO_2 ("F") – the fraction (percent) of inspired oxygen that the patient is receiving] to assess the severity of ARDS [12]. Severe COVID-19 was defined as the presence of any of the following in each patient's electronic medical record only on admission: first – results of arterial blood gas analyses, followed by sedative drugs, anesthetics, or vasopressor orders, along with diagnostic codes for ARDS and pneumonia associated with mechanical ventilators; second – procedure codes for insertion of an endotracheal tube or IMV in the course of hospitalization [13]. Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury was used to define the AKI, AKI stage, and AKI on CKD [14]. Indications for dialysis were discussed at nephrologist board meetings based on the current guidelines and adjusted individually depending on hypervolemia and/or sepsis.

The choice of CRRT modes depended on the need to remove molecules of different molecular weights and volumes and the clinical status of the patient, and it was based on the availability of resources.

Due to changes in the clinical condition of the patient and specific complications of the procedures, such as systemic coagulation, mode transitions were frequent. CRRT was performed on a Prismaflex standard high-flow Hemofilter (ST150 Gambro) with a high-flow multifiltrate filter (Kit 8 CVVHDF 1000). In septic patients, the following were used: oXiris® membrane (Gambro, membrane based on AN-69, surface treated with polyethyleneimine and heparin-grafted) and EMIC2 hemofilter (Fresenius Medical Care, Bad Homburg, Germany, surface area 1.8 m^2). UFH anticoagulation was used for the most part, whereas regional citrate anticoagulation was used in three patients, and fondaparinux-sodium was administered in one patient.

Results

The average age of the patients was 64.69 ± 9.71 years, and 82.2% of them were men. The most common comorbidity was hypertension in 75.2%, while previous kidney diseases were present in 33.7% of patients. Out of the total number of patients, 61.4% were unvaccinated. Prior to admission to the SICU/ICU, 58% of patients used one, two, or more types of antibiotics, and 66% of them were initially admitted to the ICU with radiographically confirmed pneumonia, bilateral pneumonia in 88.1% of them. On IMV were 93.7% of patients, and 92.1% were on vasopressor therapy. The average length of IMV until the start of CRRT was 4.65 ± 4.57 days. In the first 24 hrs from the start of IMV, 60% of patients had to undergo CRRT, 10.9% of patients had SpO_2/FiO_2 > 200 (Table 1), and 41.6% had anuria.

Table 1

Clinical parameters

Parameter	Values
Gender, male	83 (82.2)
Mean age (years)	64.69 ± 9.71
Comorbidities	
hypertension	76 (75.2)
diabetes mellitus	26 (25.7)
coronary disease	20 (19.8)
chronic obstructive pulmonary disease	9 (8.9)
autoimmune diseases	5 (4.9)
malignancy	5 (4.9)
previous renal disease	34 (33.7)
obesity	24 (22.7)
other	32 (31.7)
without comorbidity	8 (7.9)
Duration of illness before admission (days)	7.2 ± 4.92
Use of antibiotics before admission	
one antibiotic	29 (28.7)
two or more antibiotics	30 (29.7)
without antibiotics	16 (15.8)
unknown	26 (25.8)
Initial admission	
SICU	34 (34.0)
ICU	67 (66.0)
X-ray of the lungs on admission	
unilateral pneumonia	12 (11.9)
bilateral pneumonia	89 (88.1)
Vaccination status	
not vaccinated	62 (61.4)
incompletely vaccinated	36 (35.6)
unknown	3 (3.0)
Noninvasive mechanical ventilation	6 (5.9)
Invasive mechanical ventilation	89 (93.7)
SpO_2/FiO_2 before CRRT	
≥ 200	11 (10.9)
100–199	53 (52.5)
< 100	37 (36.6)
AKI/AKI on CKD day 1 of IMV	57 (60.0)
Duration of IMV until the beginning of CRRT (days)	4.65 ± 4.57
Vasopressors	93 (92.1)
SAPS II before CRRT	39.13 ± 14.45
Anuric patients before CRRT	42 (41.6)
Start of CRRT from admission (days)	11.16 ± 7.61
Therapy	
antivirals	13 (12.9)
steroids	70 (69.3)
tocilizumab	36 (35.6)
Dose of thrombophylaxis (dalteparin-sodium)	
2,500 IU/12 hrs	77 (76.2)
5,000 IU/12 hrs	13 (12.9)
7,500 IU/12 hrs	11 (10.9)
Length of hospital stay (days)	17.03 ± 12.44

SICU – semi-intensive care unit; ICU – intensive care unit; CRRT – continuous renal replacement therapy; AKI – acute kidney injury; CKD – chronic kidney disease; IMV – invasive mechanical ventilation; SAPS – Simplified Acute Physiology Score; SpO_2/FiO_2 – oxygen saturation to fraction of inspired oxygen ratio.
All values are expressed as numbers (percentages) or mean ± standard deviation.

The average number of CRRT procedures was 2.01 ± 1.36. The most common mode was hemodiafiltration (HDF) in 67.3% of patients, and 46.5% of patients used the oXiris® membrane (Table 2).

The mean values and differences between laboratory parameters before and after CRRT, obtained using the paired sample test, are shown in Table 3. A significant decrease in hemoglobin, platelet, urea, creatinine, sodium, aPPT, and fibrinogen values was found after CRRT. By using binary logistic regression, including demographic parameters, comorbidities, and clinical parameters before CRRT, the patients with previous kidney disease were found to have 3.43 times

Table 2

Parameters of continuous renal replacement therapy (CRRT) procedures

Parameter	Values
Type of procedure	
CVVH	1 (1.0)
CVVHD	27 (26.7)
CVVHDF	68 (67.3)
CVVHDF/CVVHD	3 (3.0)
CVVHDF + ECMO	2 (2.0)
Type of adsorptive membrane	
oXiris®	47 (46.5)
ST-150	11 (10.9)
EMIC2	27 (26.7)
Kit 8	5.9 (6)
2 membrane	9.9 (10)
Average number of CRRT	2.01 ± 1.36
Treatment parameters	
blood flow rate (mL/h)	200.3 ± 26.44
replacement flow rate (mL/h)	1,986 ± 669.37
dialysate flow rate (mL/h)	1,572 ± 456.37
dose of CRRT (mL/kg/TT)	30.89 ± 6.42
bolus dose of UFH (IU)	3,897 ± 923.52
continuous dose of UFH (IU)	1,460 ± 469.63
ultrafiltration rate (mL)	3,092 ± 2,035.64
Reasons for interruption of the CRRT	
clotting circuit	8 (7.9)
hemodynamic and/or respiratory instability	10 (9.9)
problems with vascular access	4 (3.9)
without interrupting CRRT	79 (78.2)
Change in UFH dose during CRRT	
increased dose by 1/3	40 (39.6)
increased dose by 1/2	14 (13.9)
unchanged dose	25 (24.7)
reduced dose	22 (21.9)

CVVH – continuous venovenous hemofiltration; CVVHD – continuous venovenous hemodialysis; CVVHDF – continuous venovenous hemodiafiltration; ECMO – extracorporeal membrane oxygenation; UFH – unfractionated heparin.
All values are expressed as numbers (percentages) or mean ± standard deviation.

Table 3

Differences in laboratory parameters before and after continuous renal replacement therapy (CRRT)

Parameter (NR)	Before CRRT	After CRRT	*p*
Leukocytes (4.0–10.0 × 10–9 mm^3/L)	26.72 ± 79.65	16.77 ± 8.61	0.845
Hemoglobin (120–160 g/L)	105.44 ± 20.99	98.48 ± 15.60	0.000
Platelets (140–400 × 10–9 mm^3/L)	202.42 ± 94.66	174.42 ± 88.16	0.010
C-reactive protein (< 5.0 mg/L)	155.30 ± 112.70	150.16 ± 143.72	0.709
Procalcitonin (< 2.0 ng/L)	2.70 (0.62–7.20)	1.93 (0.63–4.64)	0.170
Urea (2.5–7.5 mmol/L)	26.8 (19.65–36.50)	18.40 (13.25–25.25)	0.000
Creatinine (50–98 μmol/L)	312 (208–437.5)	233 (163.5–303)	0.000
Potassium (3.5–5.5 mmol/L)	4.8 (4–5.8)	5.4 (4.6–6.0)	0.649
Sodium (136–145 mmol/L)	141 (138–147)	140 (138–142.5)	0.000
aPTT (0.83–1.30 R)	1.07 (0.82–1.28)	1.79 (1.38–3.38)	0.000
Prothrombin time (0.83–1.30 ratio)	1.12 (1.01–1.17)	1.18 (1.06–1.31)	0.114
Fibrinogen (1.86–4.86 g/L)	5.04 (3.75–6.25)	3.90 (2.08–5.00)	0.000
D-dimer (< 0.5 mg/L)	2,145 (1,239–4,727)	3,336 (1,345–6,311)	0.144

NR – normal range; aPTT – activated partial thromboplastin time.
All values are presented as mean ± standard deviation or as mean (interquartile range).

Table 4

Association of AKI/AKI on CKD presenting on day 1 of invasive mechanical ventilation with demographic parameters, comorbidities, and clinical parameters before continuous renal replacement therapy (CRRT)

Parameters	B	Sig	Exp(B)	95% CI for EXP(B)	
				lower	upper
Female[§]	0.855	0.161	2.35	0.71	7.78
Hypertension arterialis [§]	0.007	0.990	1.01	0.33	3.04
Coronary disease[§]	-0.101	0.874	0.90	0.26	3.16
COPD[§]	-0.478	0.579	0.62	0.11	3.35
Anuria before CRRT[§]	-0.009	0.985	0.99	0.38	2.60
Vasoactive therapy[§]	-1.292	0.460	0.27	0.01	8.42
SpO_2/FiO_2 index before CRRT[#]	-1.168	0.025	0.31	0.11	0.87
Age category[¥]	0.195	0.725	1.22	0.41	3.61
Previous renal disease[§]	1.233	0.036	3.43	1.08	10.84
Diabetes mellitus[§]	-0.193	0.722	0.82	0.28	2.39

[§]Reference value for "yes"; [#]Reference value for SpO_2/FiO_2 < 100 before CRRT; [¥] Reference value for 35–59 age category.

CI – confidence interval; COPD – chronic obstructive pulmonary disease. For other abbreviations, see Table 1.

higher risks [odds ratio (OR) = 3.43; 95% confidence interval (CI) = 1.08–10.84; p = 0.036] and patients with index $SpO_2/FiO_2 \geq 200$ had a 69% lower risk (OR = 0.31; 95%CI = 0.11–0.87; p = 0.025) of developing AKI/AKI on CKD which required CRRT in the first 24 hrs from the start of IMV (Table 4). The average hospital admission was on the seventh day, IMV to CRRT on the third day, the start of CRRT was on the tenth day from admission, and 60% of patients developed AKI/AKI on CKD which required CRRT on the first day of IMV.

Discussion

This study included 34% of critically ill COVID-19 patients who required the ICU out of a total of 293 with AKI treated with conservative therapy. Namely, the incidence of AKI in COVID-19 patients varies in different studies, as well as mortality from AKI, which ranges from 35–89%, the prevalence of RRT was 5–55%, and mortality from RRT was 70–90% [2–9]. The global record covered 168 hospitals from 16 countries, with 20,608 patients, from February to November 2020, and reported an incidence of AKI in the ICU of 42.4%, mortality of 40.8% in patients on IMV alone, and 71.68% on IMV, vasopressor therapy, and RRT [8]. The same incidence of AKI of 75% was shown in two other studies: the first included 575 patients, of whom 63% required vasopressors; the second included a total of 300 patients and the need for IMV was determined in as many as 97% of patients with moderate to severe ARDS. These authors also reported the same mortality of 70% [3, 4]. It should also be noted that the need for IMV increases by ≥ 90% in critically ill patients with sepsis in KDIGO stage 3 on vasopressor therapy [15]. Our study patients were predominantly men, with an average age of 64.69 ± 9.71 years. The relation of age to unfavorable outcomes has been reported in previous studies [16–18]. The most prevalent comorbidities were hypertension 75.2% and previous stage 1–4 of CKD 33.7%, which are also mentioned in other studies [14, 19]. Namely, it has already been established that patients with existing kidney damage have a higher chance of dialysis-dependent AKI [20]. About two-thirds of the patients were initially admitted to the ICU with pneumonia, predominantly bilateral pneumonia, which was probably the reason for seeking medical help later at the healthcare facility, given that the average duration of illness until admission was 7.2 ± 4.92 days, similar to the average duration published by Doher et al. [21]. Moreover, during that period, about two-thirds of the patients were not vaccinated, and they used one or two or more antibiotics at home. Unlike other studies, all our patients were in the ICU with multiorgan failure, and 93% of them were on IMV and vasopressor therapy. A similar high percentage of patients with IMV requiring RRT was also shown by some authors [5, 14]. In other words, AKI in COVID-19 can indirectly affect other organs, such as the kidney, as part of lung-kidney cross-talk [22]. There are several reasons for the development of AKI as a consequence of respiratory insufficiency: 1) systemic hypoxia, 2) hypercapnia, 3) AKI leading to a severe inflammatory response syndrome, and 4) IMV [23]. Previous studies have shown that IMV is associated with a threefold increased risk of AKI in critically ill patients [24]. After the start of IMV, 60% of our patients already had to undergo CRRT in the first 24 hrs. Similar results have already been shown, namely that AKI/AKI on CKD requiring CRRT usually occurs at the time of intubation, which indicates the role of hemodynamic changes as a potentially important mechanism for AKI in COVID-19, as vasopressors are often initiated at the time of intubation [9, 17, 21]. Considering that previous kidney diseases were behind hypertension in terms of the representation of comorbidities with 33%, we tried to determine the number of patients undergoing CRRT on the first day of IMV and determined that it was over 50%. We compared our results with the results of an American multicenter study, which included 3,099 critically ill patients. In both studies, previous kidney disease was present in a similar percentage. However, in a multicenter study, 74% of them were dialysis dependent with median values on the third day from IMV and the onset of CRRT on the fourth day, in contrast to our patients who underwent IMV on the first day, and the median start of CRRT was on the tenth day of admission [9].

The later onset of CRRT can be explained by the absence of end-stage CKD. It should also be taken into account that before CRRT, there was a slightly higher percentage of patients on IMV and almost twice the percentage of patients on vasopressor therapy with an SpO_2/FiO_2 index of 100–199, which made our patients more hemodynamical and more unstable in terms of respiration, which indirectly indicates conclusion on the potential delayed onset of CRRT. Similar results were shown in a study by Doher et al. [21] in which AKI-RRT was predominantly present on the first day of IMV in 72% of patients, 17% of whom required RRT on day ten, i.e., three days after IMV. Strategies for initiating RRT in critically ill patients have been described in many studies [25, 26]. Some authors believe that the decision to start CRRT in COVID-19 patients with AKI should be individualized and according to the clinical context (e.g., starting CRRT due to hypervolemia in patients with severe hypoxemia) and not based only on the stage of AKI [14, 27]. The most common modality was HDF in 67.3% of our patients, and 46% of them used the oXiris® membrane. The advantages of a specific CRRT modality are not yet known, so the choice of modality depends on hospital availability and available resources [11, 14]. It is recommended that the dose of dialysis be adjusted according to the KDIGO guide and in accordance with changes in the clinical and/or metabolic state of the patient [14]. Coagulopathy in COVID-19 patients may be the cause of clot formation in the circuit of the CRRT modality and the subsequent interruption of the procedure. The aforementioned process will affect the initially applied dose of RRT, which must then be adapted to the new situation [11]. About 50% of our patients had to be administered an increase in the dose of UFH by 1/2 or 1/3, and in 7.9% of patients, CRRT was discontinued due to clotting in the circuit of the CRRT modality. In our previous work, the use of pre-diluted HDF with an antithrombin membrane (oXiris®) with doses of UFH 1/3 to 1/2 higher than recommended in patients with COVID-19, resulted in prolonged life of filters in the treatment of patients with high inflammatory parameters and D-dimer and estimated risk for the development of deep vein thrombosis [28]. On average, only two CRRT procedures were performed *per* patient due to hemodynamic instability and other complications, as reported by Bezerra et al. [15]. The need for a unique diagnostic strategy and optimization of the treatment of AKI in COVID-19 patients would contribute to determining the optimal approach to CRRT in these patients. The relation between specific laboratory values with adverse outcomes has been demonstrated in many studies [16–18]. In order to determine which parameters had the greatest influence on AKI/AKI on CKD requiring CRRT on the first day of IMV, we used a binary logistic regression model, which included demographic parameters, comorbidities, and clinical parameters before CRRT. It was found that patients with previous kidney disease had 3.36 times higher risks and 64% lower risks if the SpO_2/FiO_2 index was $\geq$ 200, and these results were comparable to the previously mentioned multicenter study [9]. By comparing studies with a similar design, it was determined that the obtained data were the following: 1) different significant predictors of AKI-RRT; 2) different modalities of RRT, anticoagulation, and other procedure parameters; 3) different testing periods which were included (in relation to the representation of vaccines and drugs); 4) the timing of the development of the AKI-RRT, which depends on the type and size of the sample, the availability of the RRT, and the organization capabilities. For these three years, we learned that the priority is the correct selection of patients for RRT, which included: age; the time period from onset of illness to admission to hospital; time from admission to presenting the patient to a nephrologist; presence of comorbidities; existence of previous kidney disease and rhabdomyolysis; the influence of nephrotoxins.

It should be emphasized that the key connection between the nephrologist and the intensivist lies in the presentation of the patient, which includes: SAPS II within 24 hrs, SpO_2/FiO_2 index, vasopressor dose, volemia state, diuresis with or without diuretic stimulation, values of nitrogenous substances, electrolytes and the presence of secondary infections.

The limitations of our study were: retrospective experience of a single center, absence of a control group, and having no complete data on volemia status and outcomes. Most patients were treated before recent clinical trials, which showed other drugs to be more effective.

Conclusion

Determining the risk factors for AKI/AKI on CKD is important for planning the prevention of these conditions that require the application of CRRT with the correct choice of dialysis modality and dose, membrane/filter type, and anticoagulant dose.

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Effect of butorphanol tartrate combined with dexmedetomidine on postoperative analgesia

Efekat kombinacije butorfanol tartarata sa deksmedetomidinom na postoperativnu analgeziju

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Abstract

Background/Aim. Since finding a safe and efficient strategy of multimodal postoperative analgesia and sedation is particularly critical, it is important that dexmedetomidine (DM) combined with opioid anesthetics can enhance that through a synergistic action. The aim of the study was to assess the effect of butorphanol tartrate (BT) combined with DM on postoperative analgesia. **Methods.** A total of 100 elderly patients undergoing general anesthesia surgery from January 2019 to June 2022 were selected. The patients were divided into two equal groups – research group (RG) and control group (CG), using the random number table method. All patients were given postoperative patient-controlled intravenous analgesia (PCIA) plus background infusion. CG patients were given 10 mg of BT, and RG patients were given 10 mg of BT and 300 μg of DM. The analgesics were diluted in 100 mL of 0.9% normal saline. The doses of rescue analgesic tramadol within 48 hrs after surgery, the number of PCIA boluses 48 hrs after surgery, and postoperative hospitalization time were recorded. The Visual Analog Scale (VAS) score, Ramsay sedation score (RSS), inflammatory and stress responses [interleukin (IL)-6, interferon (IFN)-γ, and angiotensin II (Ang-II)], and anesthesia-related adverse reactions (ARAR) were compared at different time points. **Results.** The dose of tramadol within 48 hrs after surgery, the number of PCIA boluses 48 hrs after surgery, and the postoperative hospitalization time of RG were lower than those of CG ($p < 0.05$). VAS scores at rest and during activity and serum IL-6, IFN-γ, and Ang-II levels of both groups increased at 4 and 12 hrs after surgery, then decreased at 24 hrs after surgery. The above indicators of RG were lower than those of CG at each time point ($p < 0.05$). The RSSs of the two groups increased at 4, 12, and 24 hrs after surgery, then dropped at 48 hrs after surgery. The scores of RG were lower than those of CG at each time point ($p < 0.05$). The incidence rates of ARAR had no significant difference between RG and CG ($p > 0.05$). **Conclusion.** BT combined with DM is effective for analgesia and sedation after general anesthesia surgery in elderly patients, which can reduce inflammatory and stress responses without increasing ARAR.

Key words:
analgesia, patient-controlled; anesthesia, general; dexmedetomidine; drug-related side effects and adverse reactions; pain, postoperative.

Apstrakt

Uvod/Cilj. Imajući u vidu da je pronalaženje bezbedne i efikasne multimodalne postoperativne analgezije i sedacije posebno kritično, važno je da deksmedetomidin (DM) u kombinaciji sa opioidnim anesteticima to može poboljšati sinergističkim delovanjem. Cilj rada bio je da se proceni efekat butorfanol tartarata (BT) u kombinaciji sa DM na postoperativnu analgeziju. **Metode.** Odabrano je ukupno 100 starijih bolesnika koji su bili podvrgnuti operaciji u opštoj anesteziji u periodu od januara 2019. do juna 2022. godine. Bolesnici su nasumično podeljeni u dve jednake grupe – istraživačku grupu (IG) i kontrolnu grupu (KG). Svim bolesnicima je data postoperativna intravenska analgezija koju kontroliše bolesnik (*postoperative patient-controlled intravenous analgesia* – PCIA) uz kontinuiranu infuziju. Bolesnicima KG dato je 10 mg BT, a bolesnicima IG, 10 mg BT i 300 μg DM. Analgetici su razblaženi u

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100 mL fiziološkog rastvora. Beležene su doze datog tramadola u prvih 48 sati od operacije i broj bolusa postoperativne PCIA 48 sati posle operacije, kao i dužina postoperativne hospitalizacije. Skor Vizuelne analogne skale (VAS), Remzijev skor sedacije (RSS), odgovor na inflamaciju i stres [interleukin (IL)-6, interferon (IFN)-γ i angiotenzin II (Ang-II)] i neželjene reakcije povezane sa anestezijom (NRPA) upoređivane su u različitim vremenskim tačkama. **Rezultati.** Broj doza tramadola u prvih 48 sati nakon operacije, broj bolusa PCIA 48 sati nakon operacije i dužina postoperativne hospitalizacije bili su manji u IG nego u KG ($p < 0,05$). Skorovi VAS u mirovanju i tokom aktivnosti kao i detektovani nivoi IL-6, IFN-γ, i Ang-II u serumu u obe grupe bili su povećani 4 i 12 sati posle operacije, a sniženi 24 sata posle operacije. Navedeni pokazatelji za IG bili su niži od pokazatelja za KG u svakoj tački merenja ($p < 0,05$). RSS u obe grupe povećao se 4, 12 i 24 sata posle operacije, a zatim opao 48 sata posle operacije. Skorovi za IG bili su niži od onih za KG na svakoj tački merenja ($p < 0,05$). Nije bilo statistički značajne razlike u stopi incidencije NRPA između IG i KG ($p > 0,05$). **Zaključak.** Kombinacija BT sa DM efikasna je za analgeziju i sedaciju posle operacije u opštoj anesteziji kod starijih bolesnika, što može smanjiti odgovor na inflamaciju i stress bez povećanja NRPA.

Ključne reči:
analgezija, kontrolisana od strane bolesnika; anestezija, opšta; deksmedetomidin; lekovi, neželjeni efekti i neželjene reakcije; bol, postoperativni.

Introduction

Patient-controlled intravenous analgesia (PCIA) is a common multimodal analgesic strategy following general anesthesia surgery (GAS), in which analgesics are continuously pumped into the patient at a specific speed to reduce the pain degree and keep the stability of vital signs [1, 2]. Opioids are the major analgesic substance. The analgesic effect of butorphanol tartrate (BT), a mixed agonist-antagonist opioid receptor, is 30–40 times greater than that of pethidine or about 7 times greater than that of morphine, which is beneficial for relieving visceral pain. However, postoperative high-dose use will increase gastrointestinal reactions, drowsiness, and other adverse reactions (AR) and exert little sedative effect [3, 4]. Therefore, finding a safe and efficient strategy for multimodal postoperative analgesia (PA) and sedation is particularly critical. Dexmedetomidine (DM) is a novel, highly selective α2-adrenergic receptor agonist that can effectively inhibit norepinephrine and central adrenaline levels and exert anti-sympathetic, anti-anxiety, analgesic, and neuroprotective effects [5]. It has been found that DM combined with opioid anesthetics can enhance postoperative sedation and analgesia through a synergistic action [6, 7]. However, the use of BT combined with DM in PA in elderly patients undergoing GAS is rarely reported in China and foreign countries.

In view of this, 100 patients undergoing GAS were selected in this study to assess the effect of BT combined with DM on PA.

Methods

General data

The sample size was determined according to pre-experiments. In this prospective study, a total of 100 elderly patients undergoing GAS at the Quzhou People's Hospital (Quzhou) from January 2019 to June 2022 were selected and divided into a control group (CG) and a research group (RG) (50 patients in each group) using the random number table method. This study has been approved by the Ethics Committee of Quzhou People's Hospital.

Inclusion and exclusion criteria

Inclusion criteria were as follows: 1) patients requiring PA; 2) patients in grades I and II of the American Society of Anesthesiologists (ASA); 3) patients undergoing general anesthesia; 4) patients with normal audio-visual function and intelligence before surgery; 5) patients not allergic to the drugs used in this study; 6) patients who and whose families voluntarily signed the informed consent form.

Exclusion criteria were as follows: 1) patients who used sedatives, analgesics, or antidepressants for a long time; 2) patients with a history of immunotherapy, chronic pain, or cerebrovascular disease; 3) patients accompanied by atrioventricular block or sinus bradycardia; 4) patients undergoing emergency surgery; 5) patients with uncontrolled preoperative blood pressure (BP) > 180/100 mmHg; 6) patients with infectious diseases, immune, hematopoietic, or coagulation dysfunction.

Anesthesia and analgesia methods

After the patient was sent to the operating room, venous access was established, and electrocardiogram and vital signs were routinely monitored. NICAP-18, a non-invasive continuous BP monitoring system (Zhejiang Mailian Medical Devices Co., Ltd., China), was used. The wrist splint was fixed before anesthesia induction. Subsequently, the DSA-T-C disposable non-invasive pressure sensor (Zhejiang Mailian Medical Devices Co., Ltd., China) and NICAP-18 system were put on the same level. Then, the probe automatically searched for the strongest position of the artery to perform real-time BP monitoring.

Anesthesia induction: After tracheal intubation, the anesthesia machine was connected to deliver 1.5 mg/kg propofol, 0.04 mg/kg midazolam, 0.3 μg/kg sufentanil, and 0.2 mg/kg cisatracurium besilate, and the respiration was controlled. Anesthesia maintenance: propofol (4–8 mg/kg/hr) and remifentanil (0.1–0.3 μg/kg/min) were continuously pumped, and cisatracurium besilate was intravenously injected intermittently. After the surgery, the patient was sent to the recovery room, the tracheal tube was withdrawn, and the PCIA pump was connected for PA.

PA: For CG, 10 mg of BT (Shanghai Hengrui Pharmaceutical Co., Ltd., 10 mg/mL, 1 mg of BT *per* spray) was pumped. For RG, 10 mg of BT and 300 μg of DM [Jiangsu Hengrui Pharmaceuticals Co., Ltd., China; 200 μg : 2 mL (calculated based on DM)] was pumped. The analgesics were diluted in 100 mL of 0.9% normal saline. PCIA plus background infusion were performed: PCIA dose of 1 mL/each time, background infusion rate of 2 mL/h, and lockout time of 15 min. When the Visual Analogue Scale (VAS) score was ≥ 4 points, 100 mg tramadol was injected intramuscularly for rescue analgesia. The patient returned to the ward when the Modified Aldrete Score was > 9 points.

Observation indicators

Analgesic and sedative effects: At 4, 12, 24, and 48 hrs after the surgery [8, 9], the pain degree of patients in an active state (turning over) and a resting state (lying quietly) was assessed using the VAS score. The VAS score ranges from 0 to 10 points – a lower score indicates milder pain. Meanwhile, sedation was assessed by the Ramsay sedation score (RSS) [10]: 1 point (dysphoria); 2 points (awake, quiet, and cooperative); 3 points (drowsiness but quick response to physical stimulation and instruction); 4 points (light sleep and able to be quickly awakened); 5 points (asleep and slow response to stimulation and instruction); 6 points (deep sleep and no response to any stimulation and instruction).

The dose of rescue analgesic tramadol within 48 hrs after surgery, the number of PCIA boluses 48 hrs after surgery, and postoperative hospitalization time were recorded.

Inflammatory and stress responses: 3 mL of venous blood was collected from each patient in each group before surgery (15 min before anesthesia) and at 12, 24, and 48 hrs after surgery, and centrifuged (radius: 6 cm, speed: 2,500 revolutions/min) for 10 min. Then the supernatant was harvested to measure the levels of interleukin (IL)-6, interferon IFN)-γ, and angiotensin II (Ang-II) by enzyme-linked immunosorbent assay using kits purchased from Shanghai LabEx Biotech Co., Ltd., China.

Anesthesia-related AR, including nausea and vomiting, dizziness, rash, delirium, and respiratory depression, were observed three days after the surgery.

Statistical analysis

SPSS 24.0 software (IBM Inc., USA) was used for statistical analysis. All the measurement data were subjected to the normal distribution test, and the normally distributed ones were described by mean ± standard deviation. The repeated measures data were analyzed using analysis of variance (F), and the least significant difference *t*-test was used for further pairwise comparison. The non-normally distributed measurement data were described by median (M) interquartile boundary values (P_{25}, P_{75}), and the Kruskal-Wallis rank sum test was used for comparison between groups. When there were significant intergroup differences, the Dunn's test was further employed for multiple comparisons. The count data were expressed in percentages, and the χ^2 test was performed; $p < 0.05$ was considered statistically significant.

Results

General data

There were 55 males and 45 females aged 60–81 years, with an average of 69.32 ± 3.84 years. The body mass index (BMI) was 19.34–25 kg/m^2, with an average of 22.54 ± 1.86 kg/m^2. There were 53 cases of ASA grade I and 47 cases of grade II. The surgery was conducted on the abdomen in 22 cases, the chest in 20 cases, the pelvis in 18 cases, the bone in 35 cases, and other sites in 5 cases. No significant differences were found concerning gender, age, BMI, ASA grade, and surgical site between RG and CG ($p > 0.05$) (Table 1).

Use of tramadol, number of PCIA boluses, and postoperative hospitalization time

The dose of tramadol within 48 hrs after surgery, the number of PCIA boluses 48 hrs after surgery, and the postoperative hospitalization time of RG were lower than those of CG ($p < 0.05$) (Table 2).

Analgesic and sedative effects

Both groups' resting and active VAS scores increased at 4 and 12 hrs after surgery, then decreased at 24 hrs after surgery. The above indicators of RG were lower than those

Table 1

General data of the two groups

Group	Male/Female	Age (years)	BMI (kg/m^2)	ASA grade	Surgical site
				I/II	abdomen/chest/pelvis/bone/other
Control	26/24	69.82 ± 3.45	22.86 ± 1.72	27/23	12/9/10/17/2
Research	29/21	68.82 ± 4.76	22.34 ± 1.81	26/24	10/11/8/18/3
t/χ^2	0.364	1.203	1.473	0.040	0.833
p	0.546[a]	0.232[b]	0.144[b]	0.841[a]	0.934[a]

ASA – American Society of Anesthesiologists; BMI – body mass index.
For each group the number of patients enrolled was 50.
[a] – the χ^2 test was used for the comparison of count data; [b] – the *t*-test was used for the comparison of measurement data.
All values are expressed as mean ± standard deviation or number.

of CG at each time point ($p < 0.05$). RSS of the two groups increased at 4, 12, and 24 hrs after surgery, then dropped at 48 hrs after surgery. The scores of RG were lower than those of CG at each time point ($p < 0.05$) (Table 3).

Inflammatory and stress responses

Serum IL-6, IFN-γ, and Ang-II levels of both groups increased at 4 and 12 hrs after the surgery, then decreased at 24 hrs after surgery. The above indicators of RG were lower than those of CG at each time point ($p < 0.05$) (Table 4).

Anesthesia-related adverse reactions

The incidence rates of anesthesia-related AR had no significant difference between RG (22%) and CG (28%) ($p > 0.05$) (Table 5).

Table 2

Use of tramadol, number of PCIA boluses, and postoperative hospitalization time

Group	Dose of tramadol (mg/day)	Number of PCIA boluses 48 hrs after surgery	Postoperative hospitalization time (days)
Control	62.35 ± 7.45	24.84 ± 4.02	7.85 ± 2.35
Research	54.07 ± 6.35	21.04 ± 3.54	6.02 ± 1.25
t	5.981	5.016	4.862
p	< 0.001[a]	< 0.001[a]	< 0.001[a]

PCIA – patient-controlled intravenous analgesia; For each group the number of patients enrolled was 50.
[a] – the *t*-test was used for the comparison of measurement data.
All values are expressed as mean ± standard deviation.

Table 3

Visual analog scale and Ramsay sedation scores at different time points after the surgery

Group/time point after the surgery	Visual analog scale score		Ramsay sedation score
	resting	active	
Control			
4 hrs	2.86 ± 0.28	3.32 ± 0.48	3.52 (1.25, 6.86)
12 hrs	3.37 ± 0.43	4.02 ± 0.52	3.85 (1.31, 7.35)
24 hrs	3.12 ± 0.38	3.72 ± 0.43	3.97 (1.28, 7.85)
48 hrs	2.43 ± 0.22	3.13 ± 0.28	3.42 (1.28, 7.54)
Research			
4 hrs	2.18 ± 0.32	2.76 ± 0.51	3.15 (1.18, 5.85)
12 hrs	2.86 ± 0.41	3.34 ± 0.61	3.32 (1.25, 5.89)
24 hrs	2.64 ± 0.3	3.15 ± 0.28	3.54 (1.27, 6.05)
48 hrs	2.03 ± 0.19	2.46 ± 0.33	3.51 (1.33, 6.15)
$F_{intergroup}/p_{intergroup}$ or $U_{integroup}/p_{intergroup}$	51.623/< 0.001	41.725/< 0.001	77.586/< 0.001
$F_{time\ point}/p_{time\ point}$ or $U_{time\ point}/p_{time\ point}$	81.623/< 0.001	71.824/< 0.001	153.652/< 0.001
$F_{crossover}/p_{crossover}$ or $U_{crossover}/p_{crossover}$	251.362/< 0.001	218.513/< 0.001	325.521/< 0.001

For each group the number of patients enrolled was 50.
All values are expressed as mean ± standard deviation or median [interquartile boundary values (P_{25}–P_{75})].

Table 4

Inflammatory and stress responses before and after the surgery (ng/L)

Group/time point after the surgery	IL-6	IFN-γ	Ang-II
Control			
4 hrs	21.03 ± 4.51	312.52 ± 20.16	245.26 ± 24.51
12 hrs	61.24 ± 6.35	400.12 ± 26.35	312.25 ± 32.42
24 hrs	50.18 ± 5.52	386.08 ± 31.42	281.65 ± 30.36
48 hrs	39.64 ± 4.18	348.26 ± 28.42	264.85 ± 27.65
Research			
4 hrs	20.98 ± 5.02	310.89 ± 21.42	243.32 ± 26.11
12 hrs	48.63 ± 7.81	375.62 ± 25.84	286.65 ± 30.15
24 hrs	37.26 ± 6.61	351.02 ± 21.43	266.36 ± 28.65
48 hrs	29.43 ± 5.82	322.46 ± 19.72	251.85 ± 25.16
$F_{intergroup}/p_{intergroup}$	41.526/< 0.001	38.564/< 0.001	100.251/< 0.001
$F_{time\ point}/p_{time\ point}$	96.625/< 0.001	82.512/< 0.001	154.623/< 0.001
$F_{crossover}/p_{crossover}$	99.658/< 0.001	481.623/< 0.001	602.02/< 0.001

IL-6 – interleukin 6; IFN-γ – interferon gamma; Ang-II – angiotensin II.
For each group the number of patients enrolled was 50.
All values are expressed as mean ± standard deviation or median [interquartile boundary values (P25–P75)].

Table 5

Anesthesia-related adverse reactions

Group	Nausea and vomiting	Dizziness	Rash	Delirium	Respiratory depression	Total
Control	4 (8)	7 (14)	3 (6)	0 (0)	0 (0)	14 (28)
Research	3 (6)	7 (14)	1 (2)	0 (0)	0 (0)	11 (22)
χ^2						0.480
p						0.488

For each group the number of patients enrolled was 50.
All values are expressed as numbers (percentages).

Discussion

The aim of this study was to evaluate the effect of BT in combination with DM on the PA of elderly patients undergoing GAS. We found that this method relieved inflammatory and stress responses without increasing anesthesia-related AR.

Due to the decline of various functions and low tolerance to surgery and anesthesia, elderly patients are more prone to postoperative hyperalgesia, while intense pain can cause central nervous system (CNS) excitation, improve stress responses, and even induce adverse cardiovascular events such as myocardial ischemia in severe cases [11, 12]. BT is a mixed agonist-antagonist opioid receptor with a potent analgesic effect. However, single high-dose administration may lead to deep and excessive sedation and analgesia in elderly patients and worsen the stress response, making it hard to wake the elderly patients up at any time [13, 14]. Ahsan et al. [15] found that DM plus butorphanol could exert a synergistic analgesic effect, benefitting the clinical treatment of acute nociceptive pain, which was regulated by κ-opioid receptors (KORs) and μ-opioid receptors (MORs).

In this study, the dose of tramadol within 48 hrs after surgery, the number of PCIA boluses 48 hrs after surgery, and the postoperative hospitalization time of RG were lower than those of CG. The resting and active VAS scores of both groups peaked at 12 hrs after surgery and then decreased at 24 hrs after surgery. The above indicators of RG were lower than those of CG at each time point. RSSs of the two groups increased at 4, 12, and 24 hrs after surgery, then dropped at 48 hrs after surgery. The scores of RG were lower than those of CG at each time point. Therefore, DM combined with BT can improve the analgesic effect after GAS in elderly patients and prevent agitation. Du et al. [16] found that 300 μg of DM together with 10 mg of butorphanol given by the PCIA pump after radical mastectomy could help relieve pain and reduce the times of pump pressing. Shi and Gan [17] reported that compared with 0.1 mg/kg butorphanol alone, in combination with 0.1 μg/kg/hr of DM could raise RS, lower the VAS score, and reduce the incidence of nausea, vomiting, dizziness, and other AR, which is consistent with the findings in this study. The above results verify again that DM combined with butorphanol has good postoperative analgesic and sedative effects, and its possible mechanisms are as follows: DM regulates nociceptive signaling in CNS by stimulating spinal cord α2-receptors; DM can activate presynaptic membrane α2-receptors, reduce the activation and tension of sympathetic nerves, inhibit the secretion and release of norepinephrine, and reduce the central sympathetic outflow, thereby terminating the diffusion of pain signals [18, 19]. In addition, butorphanol can antagonize or excite μ-receptors with a long duration of analgesia. It has almost no activity on δ-receptors, thus reducing anxiety and irritability [20]. As a potent and selective agonist of κ receptors, butorphanol is beneficial in relieving pain. BT can stimulate opioid receptors such as KORs and MORs, induce the hyperpolarization of the inner opioid neuron cell membrane, reduce the levels of pain-causing substances, and inhibit the release of noxious neurotransmitters such as substance P [21, 22]. Despite different mechanisms, BT combined with DM can, through a complementary and synergistic effect, enhance the sedative and analgesic effects, improve the pain threshold of patients, and reduce the sensitivity to pain and trauma.

Hyperalgesia is an important mechanism of pain, and its molecular basis lies in the synergism of neurogenic inflammatory response and the generation of pain-causing factors [23]. When stimulated by trauma, surgery, and anesthesia, the body will release a large number of pain-causing factors and nerve growth factors, thereby increasing further the permeability of the cell membrane and enhancing central sensitization, peripheral sensitization, and inflammatory cascade. As a result, pain signal transmission is facilitated. In this study, serum IL-6, IFN-γ, and Ang-II levels of both groups increased at 4 and 12 hrs after surgery, then decreased at 24 hrs after surgery. The above indicators of RG were lower than those of CG at each time point. Thus, elderly patients had inflammatory and stress responses following GAS. Nevertheless, BT combined with DM can reduce the inflammatory and stress responses, which may also be one of the analgesic mechanisms of the drug combination. In terms of safety, the incidence rate of anesthesia-related AR in RG was lower than that in CG in this study. The reason is that the incidence of adverse drug reactions is increased due to a low diffusion rate of a single drug through blood, while BT combined with DM is characterized by high metabolism speed and short onset time and can also reduce the dosage of BT and prevent overdose-induced AR. Moreover, DM can weaken gastrointestinal peristalsis through synaptic regulation, inhibit gastric secretion, and resist vomiting and nausea, thereby reducing gastrointestinal AR. However, the incidence of AR was not significantly different between the two groups.

Nevertheless, this study is limited. The sample size is small, and the follow-up time is short; hence, it is necessary to increase the sample size further and prolong the follow-up time to confirm our findings.

Conclusion

In conclusion, BT combined with DM is effective in analgesia and sedation after GAS in elderly patients, which can regulate levels of serum pain mediators and reduce inflammatory and stress responses without increasing anesthesia-related AR. This study provides novel insights into clinical treatment in the future.

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Conflict of interest

The authors declare no conflict of interest.

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Increased concentration of tumor necrosis factor alpha in the plasma of glaucoma patients

Povišena koncentracija faktora nekroze tumora alfa u plazmi bolesnika sa glaukomom

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Abstract

Background/Aim. Changes in the concentration of various mediators of inflammation in blood, aqueous humor, or eye tissues support the role of inflammation in the pathogenesis of open-angle glaucoma (OAG). Inflammatory biomarkers have a great potential for application in clinical practice. The aim of the study was to determine concentrations of tumor necrosis factor (TNF)-α in the plasma of patients with OAG and subjects without glaucoma and examine the correlation between the TNF-α concentration in plasma in glaucoma patients and specific clinical parameters. **Methods.** The study included 87 participants (87 eyes) divided into three groups: 35 subjects (35 eyes) with primary OAG (POAG) with elevated intraocular pressure (IOP) – hypertension glaucoma (HTG) (POAG-HTG), 23 subjects (23 eyes) with pseudoexfoliative OAG (XFG), and 29 subjects in the control group (healthy subjects) matched with the patient groups in terms of age and gender. We performed a complete clinical examination, including standard automated perimetry and determination of changes in the participant's repeated visual field, optical coherence tomography and determination of peripapillary retinal nerve fiber layer (RNFL) thickness. The concentration of TNF-α in participants' plasma was measured using commercial enzyme-linked immunosorbent assay – ELISA. **Results.** The concentrations of TNF-α in the plasma of glaucoma patients (POAG-HTG 2.04 ± 1.98 pg/mL and XFG OAG 2.05 ± 1.48 pg/mL) were significantly higher than in healthy subjects (1.43 ± 2.00 pg/mL, $p < 0.05$). In none of the groups of subjects suffering from glaucoma was there a statistically significant correlation of TNF-α concentration in the plasma with any of the clinical parameters, including IOP, cup/disk ratio, mean deviation, average RNFL, and RNFL in the superior and inferior quadrant. **Conclusion.** The concentration of the pro-inflammatory cytokine TNF-α in the plasma is significantly higher in glaucoma patients compared to non-glaucomatous subjects, and it confirms the role of inflammation in the pathogenesis of glaucoma as one of the non-inflammatory ocular diseases. The concentrations of TNF-α in the plasma of glaucoma patients did not correlate with any of the examined clinical parameters; hence, it cannot be considered a measure of progression and damage in glaucoma.

Key words:
biomarker; exfoliation syndrome; glaucoma, open-angle; tumor necrosis factor-alpha.

Apstrakt

Uvod/Cilj. Promene u koncentraciji različitih medijatora zapaljenja u krvi, očnoj vodici ili tkivima oka, podržavaju teoriju o ulozi inflamacije u patogenezi glaukoma otvorenog ugla (GOU). Biomarkeri inflamacije imaju veliki potencijal za primenu u kliničkoj praksi. Cilj rada bio je da se utvrde koncentracije faktora nekroze tumora alfa (*tumor necrosis factor alpha* – TNF-α) u plazmi bolesnika sa GOU i ispitanika bez glaukoma, i prouči veza između nivoa TNF-α u plazmi bolesnika sa glaukomom i određenih kliničkih parametara. **Metode.** Studijom je obuhvaćeno 87 učesnika (87 očiju) podeljenih u tri grupe: 35 ispitanika (35 očiju) obolelih od primarnog GOU (PGOU), sa povišenim

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intraokularnim pritiskom (IOP) – hipertenzivni glaukom (HTG) (PGOU-HTG), 23 ispitanika (23 oka) koji boluju od pseudoeksfolijativnog GOU (PEG) i 29 ispitanika u kontrolnoj grupi (zdravi ispitanici), sparenih po starosti i polu, sa obolelima od GOU. Urađen je kompletan oftalmološki pregled, standardna automatizovana perimetrija i određivanje promena u ponovljenom vidnom polju ispitanika, optička koherentna tomografija i određivanje debljine retinalnih peripapilarnih nervnih vlakna (*retinal nerve fiber layer* – RNFL). Koncentracija TNF-α u plazmi ispitanika merena je komercijalnim *enzyme-linked immunosorbent assay*-ELISA testovima. **Rezultati.** Koncentracije TNF-α u plazmi bolesnika sa glaukomom (PGOU-HTG 2,04 ± 1,98 pg/mL i PEG 2,05 ± 1,48 pg/mL) bile su značajno više nego kod zdravih ispitanika (1,43 ± 2,00 pg/mL, $p < 0,05$). Ni u jednoj od grupa ispitanika obolelih od glaukoma nije bilo statistički značajne korelacije koncentracije TNF-α u plazmi sa bilo kojim od ispitanih kliničkih parametara [IOP, *cup/disk ratio*, srednja vrednost devijacije (*mean deviation*), prosek RNFL (RNFL *average*), RNFL superiorni kvadrant i RNFL inferiorni kvadrant]. **Zaključak.** Koncentracija pro-inflamacijskog citokina TNF-α u plazmi je značajno viša kod bolesnika sa glaukomom u poređenju sa ispitanicima bez glaukoma i to potvrđuje ulogu inflamacije u patogenezi glaukoma, kao jednog od neinflamacijskih oboljenja oka. Koncentracija TNF-α u plazmi bolesnika sa glaukomom ne koreliše ni sa jednim od ispitivanih kliničkih parametara, zbog čega ne može biti mera progresije i oštećenja kod glaukoma.

Ključne reči:
biološki pokazatelji; eksfolijativni sindrom; glaukom, otvoreni ugao; faktor nekroze tumora alfa.

Introduction

Glaucoma is a heterogeneous group of progressive optic neuropathies in which complex genetic and other factors lead to retinal ganglion cell (RGC) death [1]. Changes in the concentration of various mediators of inflammation and immune response in blood, aqueous humor (AH), or eye tissues in glaucoma indicate the involvement of inflammation and immune system activity in the pathogenesis of open-angle glaucoma (OAG) [2]. However, the precise mechanism underlying the interaction between lymphocytes, antibodies, and cytokines in glaucoma remains unclear.

Cytokines are low-molecular-weight polypeptides involved in communication between cells [3]. Abnormal production of some cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, soluble IL-2 receptor, IL-6, and the chemokine IL-8, plays a crucial role in the pathogenesis of various inflammatory and autoimmune diseases [3, 4]. Numerous *in vivo* studies have shown that TNF-α, IL-1, IL-6, and IL-8 are significant components in the pro-inflammatory response and intraocular inflammation [4–6]. Moreover, oxidative stress is associated with many systemic inflammatory diseases, free radical production, and lipid peroxidation [7].

TNF-α belongs to the group of pro-inflammatory cytokines. TNF-α is considered a dual-function cytokine that can stimulate cell inflammation and proliferation but also induce the process of apoptosis. Genetic variations, resulting in increased production of this cytokine, are thought to be associated with the potential development of chronic diseases and increased risk of infections and may also affect the prognosis of the disease [8]. TNF-α exerts its biological effects through two TNF receptors (TNF-RI and TNF-RII). TNF-RI (CD120a, p55) is constitutive in most tissues except for erythrocytes and unstimulated lymphocytes and can be activated by both membrane-bound and soluble forms of TNF-α. TNF-RII (CD120b, p75) is exclusively found in immune system cells, and it is activated solely by membrane-bound TNF-α. Although TNF-RII exhibits a five-fold higher affinity for binding TNF-α than TNF-RI, most biological effects are achieved through TNF-RI [9].

TNF-α can initiate the process of apoptosis by external or internal activation. External activation of this signaling pathway, namely, binding of TNF-α to TNF-RI, results in a cascade activation of caspases (-3, -6, -7) through the activation of caspase-8, ultimately leading to cell death *via* apoptosis [10].

TNF-α can lead to the generation of reactive oxygen and nitrogen species by inducing the expression of the genes for inducible nitric oxide synthase and nicotinamide adenine dinucleotide phosphate oxidase. Given the effects of these metabolites on the plasma membrane, their increased concentration can disrupt the permeability of the inner mitochondrial membrane, resulting in the loss of membrane potential and release of cytochrome-c into the cytoplasm (internal pathway of apoptosis activation) [11]. In the presence of adenosine triphosphate, released cytochrome-c binds with apoptotic protease activating factor 1 and pro-caspase-9, forming a complex referred to as the apoptosome. Within the apoptosome, catalytic activation of procaspase-9 to caspase-9 and subsequent cascade activation of caspases (-3, -6, -7) occur, driving the cell to the final stage of apoptosis [10, 11].

Proteins located on the outer mitochondrial membrane regulate the internal pathway of apoptosis activation and control the translocation of certain proteins from the mitochondrial intermembrane space to the cytoplasm. These proteins fall into three categories: proapoptotic (Bak, Bax), proapoptotic facilitator (Bid, Bad, PUMA, Noxa), and antiapoptotic (Bcl-2, Bcl-X1) proteins. Upon activation of the intrinsic pathway of apoptosis, Bak and Bax proteins oligomerize, leading to the formation of pores on the mitochondrial membrane and facilitating the release of cytochrome-c. The antiapoptotic proteins bind to Bax and Bak proteins, preventing the process of apoptosis. Whether a cell will undergo apoptosis through this mechanism or survive depends on the concentration of pro- and antiapoptotic proteins [10]. TNF-α is important, both for numerous physiological and

various pathological conditions in the central nervous system (CNS) and, therefore, in the retina as well [12–15]. TNF-α has been shown to play mostly a harmful role in a wide range of neurodegenerative processes in the retina, such as glaucoma and retinal ischemia. These pathologies are primarily characterized by the loss of RGCs [14, 15]. However, TNF-α may not solely mediate cell death and toxicity; it may also promote cell survival [16].

On the other hand, astrocytes are in close contact with RGCs and provide support to neurons, typically allowing their normal function. However, in specific pathological conditions within the CNS, they are associated with neuronal loss, thereby facilitating RGC death [17–21]. Previous studies have shown that the TNF-α produced and secreted by astrocytes facilitates RGC death in cultures of RGCs and astrocytes [22].

Given that inflammatory biomarkers have a great potential for application in clinical practice and that the role of TNF-α in the glaucoma process has not yet been fully clarified, we decided, as the aim of our paper, to investigate the plasma concentrations of TNF-α in patients with OAG and non-glaucomatous controls and examine the correlation between plasma TNF-α levels of glaucoma patients and their clinical parameters.

Methods

The present study included 87 participants (87 eyes) divided into three groups: 35 subjects (35 eyes) with primary OAG (POAG) with elevated intraocular pressure (IOP) - hypertension glaucoma (HTG) (POAG-HTG), 23 subjects (23 eyes) with pseudoexfoliative OAG (XFG), and 29 subjects in the control group (healthy subjects) matched with the patient groups in terms of age and gender. Prior to the research, all participants were informed about the objectives of the study and signed informed consent to participate according to the Declaration of Helsinki. The Ethics Committee of the Faculty of Medicine in Niš (No. 01-2625-18, from April 8, 2014) and the Ethics Committee of the University Clinical Center Niš (No. 338/43, from January 13, 2015) gave their consent for conducting the research.

We performed a complete clinical examination including collection of demographic characteristics of participants, thorough the following: assessment of family, personal, and ophthalmological history; determination of visual acuity with refraction (Snellen tables); biomicroscopy of the anterior segment of the eye; determination of IOP by Goldmann applanation tonometry; gonioscopy (using a Goldmann three mirrors gonioscope) performed to assess the opening, width, and pigmentation of the chamber angle (according to the Scheie classification system); indirect ophthalmoscopy performed to determine the cup size of the optic nerve head, specifically the cup/disk (C/D) ratio, using a 90D lens, standard automated perimetry (Humphrey Visual Field Analyzer, HFA, USA, Carl Zeiss Meditec, Inc.; Threshold Test 24-2), used to track changes in the participant's repeated visual field as mean deviation (MD); optical coherence tomography (OCT) (Stratus, Carl Zeiss Meditec, Inc., Dublin, CA); measurement of peripapillary retinal nerve fiber layer (RNFL) thickness average (RNFL Avg), in both the superior (RNFL Sup) and the inferior (RNFL Inf) quadrant. Based on the most commonly used criteria for grading glaucoma damage, the Hodapp-Parrish-Anderson classification [23], patients with POAG-HTG and XFG were classified into three groups: a) early defect [MD < -6 decibels (dB)], b) moderate defect (MD < -12 dB), and c) severe defect (MD > -12 dB).

Diagnostic criteria for POAG-HTG included the following: elevated IOP (≥ 22 mmHg); a characteristic arcuate, Bjerrum's scotoma, and/or paracentral scotoma, and/or nasal, Rönne's step observed in Humphrey's computerized vision field, and other corresponding visual field defects; corresponding optic nerve excavation, and/or thinning of the nerve fiber layer on OCT; a finding of an open angle on gonioscopy, and the absence of any secondary cause of glaucomatous optic neuropathy, such as prior trauma, administration of corticosteroids, inflammation, or uveitis. Patients with a history of inflammatory eye diseases, congenital or normotensive glaucoma, inadequate fundus visualization, diabetes mellitus, and systemic factors possibly affecting the examined marker levels were excluded from the study.

The XFG group consisted of patients with already diagnosed XFG based on the established criteria: elevated IOP, visual field alterations, and thinning of the RNFL on OCT, which are also the characteristics for the POAG-HTG group. The XFG patients had pseudoexfoliation on the anterior lens capsule and/or along the pupillary rim.

The control group consisted of healthy subjects without systemic and inflammatory diseases potentially affecting the level of the examined marker and with no family history of glaucoma, matched by gender and age. In these participants, glaucoma was ruled out using the same diagnostic criteria as for the diagnosis of POAG-HTG, i.e., after undergoing the same ophthalmological examinations and procedures. Any participant with suspected normal tension glaucoma or HTG was excluded from further examination.

During the clinical examination of the participants, we collected whole blood samples for subsequent biochemical analyses, using ethylenediaminetetraacetic acid as an anticoagulant. The blood samples were centrifuged at 3,500 rpm for 10 min at a temperature of +4 °C. Subsequently, the plasma was separated and frozen at a temperature of -80 °C.

The concentration of circulating TNF-α in participants' plasma was measured by commercial sandwich enzyme-linked immunosorbent assay (ELISA), based on the competitive binding of polyclonal antibodies specific for TNF-α, following the manufacturer's guidelines (Quantikine ELISA, DTA00C, R&D Systems, Minneapolis, USA). The concentration was determined using a standard curve and reported in pg/mL. The minimum detectable dose was 1.6 pg/mL. As *per* the manufacturer's instructions, there was no significant cross-reactivity or interference with other proteins.

Statistical analysis

We used the methods of descriptive and analytical statistics to process data obtained from the research. Statistical

processing of the results was performed using the SPSS 15.0 software package (SPSS Inc., Chicago, IL, USA). Basic descriptive statistical parameters for qualitative and quantitative evaluation of the obtained results included the following: absolute and relative numbers, arithmetic mean, standard deviation, median, and an interval of variation (minimum and maximum values). We applied the Mann-Whitney *U* test or the Student's *t*-test for independent samples to assess the significance of differences (*p*-value) in tested values between two groups of participants. The Kruskal-Wallis test and analysis of variance (ANOVA) were employed to test the significance of differences among multiple groups, whereas the Student's *t*-test and ANOVA were used when continuous variables exhibited a normal distribution. To test the strength of the association between two continuous variables, we performed a correlation analysis, specifically using Spearman's rank correlation coefficient for a distribution deviating from normal. We conducted a univariate linear regression analysis to test the influence of independent predictor variables on the value of the continuous dependent variable. A value of $p < 0.05$ was used as the threshold for statistical significance.

Results

Table 1 shows the demographic characteristics of the 87 participants, divided into three groups (35 POAG-HTG + 23 XFG + 29 control), and basic clinical parameters of glaucoma (IOP, C/D ratio, MD, RNFL Avg, RNFL Sup, and RNFL Inf).

The results of the study revealed that the average age of all participants was 71.8 ± 8.2 years, with a median of 74 years. The participants' ages ranged from 51 to 88 years. The Kruskal-Wallis test indicated no significant difference in age among the examined groups, as confirmed further by the Mann-Whitney *U* test comparing each group separately. POAG-HTG and XFG were more prevalent in men (54.3% and 56.5%, respectively), while women were more prevalent (51.7%) in the control group. However, there was no significant difference between the groups nor clear dominance of one of the genders within the examined

Table 1

Demographic and clinical characteristics and plasma levels of TNF-α in glaucoma patients and the control group of subjects

Parameter	Group			Statistical analysis
	POAG-HTG (n = 35)	XFG (n = 23)	control (n = 29)	
Age (years)				
mean ± SD	70.9 ± 7.9	73.8 ± 5.8	71.8 ± 9.4	Kruskal-Wallis test
median (min–max)	70.0 (58.0–87.0)	76.0 (59.0–84.0)	74.0 (51.0–88.0)	Mann-Whitney *U* test
Gender, n (%)				
male	19 (54.3)	13 (56.5)	14 (48.3)	
female	16 (45.7)	10 (43.5)	15 (51.7)	
IOP (mmHg)				
mean ± SD	**21.86 ± 7.37**^{c***}	**23.11 ± 11.78**^{c***}	14.76 ± 2.39	Kruskal-Wallis and Mann-Whitney *U* test
median (min–max)	20.00 (10.00–48.00)	20.50 (10.00–56.00)	14.00 (8.00–20.00)	
Cup/Disk ratio				
mean ± SD	0.64 ± 0.20	0.62 ± 0.19	▫	Mann-Whitney *U* test
median (min–max)	0.60 (0.40–1.00)	0.55 (0.40–1.00)		
Mean deviation (dB)				
mean ± SD	-11.73 ± 9.05	-12.95 ± 10.98	▫	Mann-Whitney *U* test
median (min–max)	-8.46 (-0.38– -31.27)	-8.62 (-0.07– -29.69)		
RNFL Avg (μm)				
mean ± SD	78.1 ± 24.4	78.9 ± 21.2	▫	Mann-Whitney *U* test
median (min–max)	80.9 (24.5–143.7)	81.6 (45.8–103.7)		
RNFL Sup (μm)				
mean ± SD	92.4 ± 34.5	100.9 ± 37.3	▫	Mann-Whitney *U* test
median (min–max)	96.0 (26.0–180.0)	104.0 (44.0–161.0)		
RNFL Inf (μm)				
mean ± SD	94.4 ± 37.6	96.4 ± 30.8	▫	Mann-Whitney *U* test
median (min–max)	101.0 (29.0–157.0)	91.00 (57.0–144.0)		
TNF-α (pg/mL)				
mean ± SD	**2.04 ± 1.98**^{c*}	**2.05 ± 1.48**^{c*}	1.43 ± 2.00	Kruskal-Wallis and Mann-Whitney *U* test
median (min–max)	1.82 (0.00–8.41)	1.57 (0.00–6.64)	0.81 (0.00–10.19)	

POAG-HTG – primary open-angle glaucoma - hypertensive glaucoma; XFG – pseudoexfoliative glaucoma; IOP – intraocular pressure; n – number of participants/eyes; SD – standard deviation; dB – decibels; RNFL Avg – retinal nerve fiber layer (RNFL) average; RNFL Sup – RNFL thickness in the superior quadrant; RNFL Inf – RNFL thickness in the inferior quadrant; TNF – tumor necrosis factor; c – vs. control; min – minimum; max – maximum; *$p < 0.05$; ***$p <$ 0.001. Bolded values are statistically significant. ▫The values could not be determined during the sampling period.

groups. The highest IOP value was found in the eyes of participants diagnosed with XFG. Both glaucoma groups exhibited significantly higher IOP values compared to the control group ($p < 0.001$). The values of the C/D ratio were nearly identical in the POAG-HTG and XFG groups. Hence, there was no significant difference in this parameter between POAG-HTG and XFG. Although the absolute value of MD was higher in eyes with XFG, it was not significantly different from the value of this parameter in eyes with POAG-HTG. The distribution of POAG-HTG and XFG patients according to the Hodapp-Parrish-Anderson classification was even, without significant difference. The value of RNFL Avg, RNFL Sup, and RNFL Inf was higher in the eyes of patients with XFG but not statistically significant compared to the group of patients with POAG-HTG.

The lowest value of plasma TNF-α was found in the control group (1.43 ± 2.00 pg/mL), significantly differing from patients with POAG-HTG (2.04 ± 1.98 pg/mL) and XFG (2.05 ± 1.48 pg/mL), $p < 0.05$ (Table 1). Table 1 and Figure 1 present the values of the statistical parameters of TNF-α in the examined groups.

We used Spearman's linear correlation coefficient to examine the relationship between plasma TNF-α concentration and IOP, C/D ratio, MD, RNFL Avg, RNFL Sup, and RNFL Inf (Table 2). No significant correlations of TNF-α concentration with any of these clinical parameters in any of the groups of patients with glaucoma was found.

Univariate linear regression analysis indicated no effect of TNF-α plasma concentration on the values of the examined clinical parameters: IOP, C/D ratio, MD, RNFL Avg, RNFL Sup, and RNFL Inf in patients with POAG-HTG and XFG (Table 3).

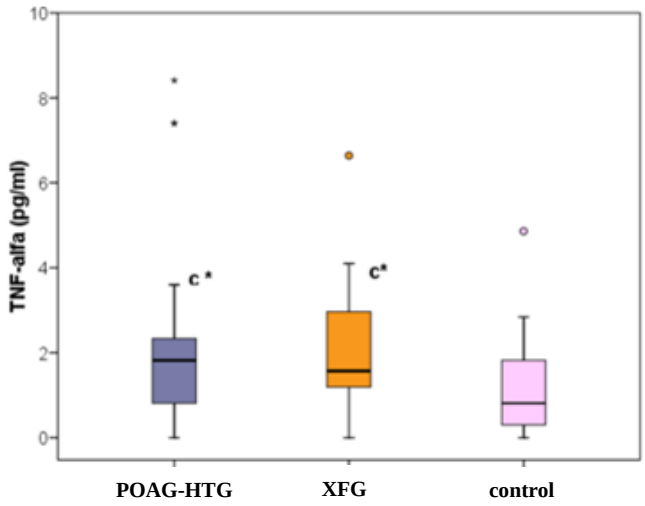

Fig. 1 – Median, minimum, maximum, and 25th and 75th percentile values for TNF-α in the plasma of participants in relation to glaucoma type and control. c – vs. control; * $p < 0.05$ (Kruskal-Wallis and Mann-Whitney *U* test). For abbreviations, see Table 1.

Table 2

Spearman's correlation coefficients of TNF-α and the clinical parameters in groups of patients with glaucoma

Group	TNF-α					
	IOP	C/D	MD	RNFL Avg	RNFL Sup	RNFL Inf
POAG-HTG	-0.03	0.02	-0.02	0.02	-0.03	-0.05
XFG	-0.08	-0.12	0.31	0.29	0.13	0.44

C/D – cup/disk ratio; MD – mean deviation; For other abbreviations, see Table 1.

Table 3

Results of univariate linear regression analysis for patients with POAG-HTG and XFG

Parameter	POAG-HTG				XFG			
	t	*p*	B	95% CI for B	*t*	*p*	B	95% CI for B
IOP	1.05	0.2971	0.52	-0.47–1.50	0.15	0.8846	0.17	-2.15–2.49
C/D	0.19	0.8538	0.00	-0.02–0.03	-0.17	0.4895	-0.03	-0.11–0.06
MD	0.26	0.7973	0.32	-2.20–2.85	1.06	0.3132	2.30	-2.49–7.09
RNFL Avg	-1.16	0.2535	-3.51	-9.64–2.63	-1.16	0.2535	-3.51	-9.64–2.63
RNFL Sup	-0.91	0.3672	-3.26	-10.50–3.98	0.57	0.5801	5.84	-17.19–28.88
RNFL Inf	-1.42	0.1661	-6.13	-14.94–2.67	1.95	0.0834	13.31	-2.16–28.78

***t* – statistical test value; *p* – statistical significance; B – regression coefficient; CI – confidence interval. For other abbreviations, see Tables 1 and 2.**

Discussion

An ischemia or increased pressure on glial cells stimulates the production of TNF-α, as shown in previous studies. This causes oligodendrocyte death and subsequent RGC apoptosis [22, 24]. In addition to nitric oxide and excitotoxicity, TNF-α has a neurotoxic effect and functions as an activator. TNF-α concentrations in plasma, cerebrospinal fluid, and brain tissue are elevated in certain CNS disorders, including Alzheimer's disease, multiple sclerosis, Parkinson's disease, and ischemic brain disorders [25]. Previous studies have demonstrated an association between some ocular diseases and increased levels of TNF-α [26–29]. In animal models with high IOP, an increase in TNF-α concentration led to the loss of RGC and oligodendrocytes. Moreover, this cell loss occurred even if TNF-α was administered without elevated IOP [30]. TNF-α exerts a negative effect on oligodendrocytes, increasing axonal susceptibility to excitotoxicity in the optic nerve head and leading to RGC death [31, 32]. When glial cells are exposed to stressors, such as high pressure or ischemia, TNF-α secretion increases, resulting in apoptosis. The apoptosis can be prevented by the administration of neutralizing anti-TNF-α antibodies [22]. These experiments are supported by the results of immunohistochemical tests on human samples conducted by Yan et al. [32] and Tezel et al. [33], demonstrating the increased level of expression of TNF-α and its receptor TNF-RI in the inner retinal layer of glaucomatous eyes compared to controls. Similar data have been published by Yuan and Neufeld [34]. The increased TNF-α expression in glaucomatous eyes suggests that this cytokine is closely associated with the neurodegenerative process. Numerous studies have investigated serum and local (aqueous) concentrations of TNF-α in XFG patients with conflicting results [35, 36]. However, only a few have examined the serum concentration of TNF-α in POAG-HTG. Currently, there is no evidence of a direct correlation between TNF-α levels in AH and serum or plasma.

In this study, we assessed TNF-α plasma levels in well-defined POAG-HTG and XFG patients and compared them with controls (subjects without glaucoma or any other ophthalmic disease). Our results revealed a significantly higher TNF-α concentration in glaucoma patients compared to healthy subjects in the control group. Although the level of TNF-α is believed to increase with age and can be a precondition for the development of atherosclerosis, diabetes, and Alzheimer's disease in the elderly [37], our control group was carefully matched for age and exhibited the lowest levels of TNF-α. Furthermore, age did not differ between groups; hence, we cannot attribute the increase in TNF-α to age or systemic diseases.

This research was conducted on a larger number of subjects, in all three groups, compared to prior studies [27, 28, 38, 39]. Our findings are in contrast to those of Huang et al. [38], who demonstrated lower serum concentrations of TNF-α in glaucoma patients in comparison to the healthy population. Sarenac Vulovic et al. [35] reported increased levels of TNF-α in the AH of patients with XFG and pseudoexfoliative syndrome but did not report elevated serum levels in the same patients. In contrast, Sorkhabi et al. [40] described an increased level of serum TNF-α as a risk factor for systemic and ocular manifestations in patients with exfoliative syndrome without glaucoma, whereas Kondkar et al. [36] reported elevated systemic levels of the inflammatory marker, TNF-α, in XFG. This suggests that the effects of systemic levels of TNF-α may be different from the effects of local levels of TNF-α in the AH [24, 41–45]. Our research did not establish a correlation of TNF-α concentration in the plasma with any of the examined clinical parameters, such as IOP, C/D ratio, MD, RNFL Avg, RNFL Sup, and RNFL Inf, that would determine the degree of development and damage in glaucoma. This is partially contradicted by the results of Huang et al. [38], as they found lower TNF-α levels in the POAG group of patients with MD < 12 dB than in the group with MD ≥ 12 dB (p = 0.0328) leading to the inference that serum TNF-α is a powerful cytokine playing a significant role in the pathogenesis of glaucoma and glaucomatous neuropathy. Kang et al. [39] demonstrated a higher serum TNF-α concentration in women than men. However, we have not replicated this finding. Our study showed elevated levels of TNF-α in the plasma of patients with POAG-HTG and XPG compared with non-glaucoma controls, indicating that elevated systemic levels of this inflammatory marker may be associated with the pathogenesis of glaucoma. Despite a lack of evidence to confirm whether plasma cytokine changes are directly correlated with AH cytokine levels, an elevated plasma TNF-α level may serve as a possible biomarker for glaucoma screening. Elevated TNF-α in plasma and AH is a clear indicator of an activated anti-inflammatory immune response.

The limitation of this study was the determination of the level of TNF-α in the plasma, which may not directly correlate with the concentration of cytokines in the AH in the anterior segment of the eye or in RGCs, which would require measuring the concentration of TNF-α in AH samples. In addition, further research should be conducted on a larger number of participants to increase the statistical power of the study.

Conclusion

The concentration of the pro-inflammatory cytokine TNF-α in the plasma is significantly higher in glaucoma patients compared to subjects without glaucoma, thus confirming the role of inflammation in the pathogenesis of glaucoma as one of the noninflammatory ocular diseases. The plasma concentration of TNF-α does not correlate with any of the examined clinical parameters; hence, it cannot be considered a measure of progression and damage in glaucoma. Nevertheless, a better understanding of this process may contribute to the development of new biomarkers for early disease detection and therapeutic strategies.

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Subcorneal pustular dermatosis: clinical characteristics and long-term follow-up of seventeen patients

Subkornealna pustulozna dermatoza: kliničke karakteristike i dugotrajno praćenje sedamnaest bolesnika

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Abstract

Background/Aim. Subcorneal pustular dermatosis (SPD) is a rare, relapsing vesiculopustular disease predominantly presenting on the flexor surfaces. Since data about the course and duration of the disease is limited, the aim of the study was to analyze the clinical features and long-term follow-up data on patients with SPD. **Methods.** A hospital database was searched for medical records of patients with SPD hospitalized at the institution between 1985 and 2014. The focus was on clinical characteristics, associated diseases, disease courses, and outcomes. **Results.** Seventeen patients with clinical features of SPD were analyzed – nine females and eight males with a median age at presentation of 45 years (range 18–90 years). Follow-up data were available for 12 patients. The median follow-up time was 9.5 years (1–28 years). In order to establish a histological diagnosis, repeated biopsies were required (on average 1.7 biopsies *per* patient). In one male patient, IgA pemphigus was diagnosed by direct immunofluorescence. In most patients, skin eruption was widespread, while in a smaller number of patients, the changes were present only on the flexor surfaces. Dysproteinemia was evident in three patients. The disease was self-limiting in three patients; five patients had mild flare-ups occurring 1–3 times a year without the need for treatment; four patients had continuous flare-ups requiring treatment. Most patients with SPD responded positively to dapsone. **Conclusion.** SPD is a rare disease, and it usually occurs in a person's fifth decade. While it is self-limiting in some patients, approximately one-third of patients require continuous therapy for continuous flare-ups.

Key words:
biopsy; dapsone; diagnosis; immunohistochemistry; skin diseases, vesiculobullous; treatment outcome.

Apstrakt

Uvod/Cilj. Subkornealna pustulozna dermatoza (SPD) je retko, relapsirajuće vezikulopustulozno oboljenje, koje predominantno zahvata fleksorne površine. S obzirom da su u dostupnoj literaturi podaci o toku i trajanju SPD veoma oskudni, cilj rada bio je da se analiziraju kliničke karakteristike i rezultati dugotrajnog praćenja bolesnika sa SPD. **Metode.** Pretraženi su medicinski kartoni iz bolničke baze podataka bolesnika sa SPD hospitalizovanih u periodu od 1985. do 2014. godine. Fokus je bio na kliničkim karakteristikama, pridruženim bolestima, toku bolesti i ishodima. **Rezultati.** Analizirano je 17 bolesnika sa kliničkim karakteristikama SPD: devet žena i osam muškaraca čija prosečna starost u trenutku manifestacije bolesti je bila 45 godina (raspon 18–90 godina). Podaci o praćenju bolesti bili su dostupni za 12 bolesnika. Srednje vreme praćenja iznosilo je 9,5 godina (1–28 godina). U cilju uspostavljanja histološke dijagnoze bile su potrebne ponovljene biopsije (u proseku 1,7 biopsija po bolesniku). Kod jednog bolesnika je direktnom imunofluorescencijom dijagnostikovan IgA pemfigus. Kod većine bolesnika kožna erupcija bila je rasprostranjena, dok su kod manjeg broja bolesnika promene bile prisutne samo na fleksornim površinama. Disproteinemija bila je prisutna kod tri bolesnika. Bolest je bila samoograničavajuća kod tri bolesnika; pet bolesnika je imalo blage relapse 1–3 puta godišnje, bez potrebe za lečenjem; četiri bolesnika imala su kontinuirane relapse, koji su zahtevali lečenje. Većina bolesnika sa SPD je pozitivno reagovala na dapson. **Zaključak.** Bolest SPD je retka, a obično se javlja u petoj deceniji života. Mada je kod nekih bolesnika samoograničavajuća, kontinuirana terapija je potrebna približno jednoj trećini bolesnika zbog čestih relapsa.

Ključne reči:
biopsija; dapson; dijagnoza; imunohistohemija; koža, vezikulobulozne bolesti; lečenje, ishod.

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Introduction

Subcorneal pustular dermatosis (SPD) is a rare, relapsing neutrophilic dermatosis first described by Sneddon and Wilkinson [1]. It can occur at any age but is more commonly observed in middle-aged and older women [2–4]. The causes and pathogenesis of SPD are still unknown. Since the disease is characterized by sterile, subcorneal accumulation of neutrophils, it has been suggested that immunologic mechanisms are involved in pathogenesis. It has been shown that tumor necrosis factor (TNF)-α, interleukin-8, and complement component C5a levels are raised in affected tissue samples [2]. In a subset of patients, intraepidermal deposits of immunoglobulin (Ig) A have been detected on direct immunofluorescence (DIF) [5, 6].

Clinical findings include discrete, oval, flaccid pustules on normal or slightly erythematous skin, predominantly distributed on the flexor surfaces and proximal limbs. Lesions may be grouped or isolated and have a characteristic appearance with the accumulation of pus in the lower half of the pustules [1, 2, 7, 8]. SPD has been described in association with IgA-paraproteinemia, IgA multiple myeloma [9–13], inflammatory bowel diseases [14, 15], rheumatoid arthritis [16, 17], Sjögren's syndrome [18], pyoderma gangrenosum [19–21], pustular psoriasis [22], and *Mycoplasma* (*M.*) *pneumoniae* infection [23, 24].

Data regarding the disease course and long-term outcomes are scarce. The aim of this study was to evaluate the clinical features, associated diseases, therapeutic options, and disease course and outcomes in patients with SPD after a long-term follow-up.

Methods

The Military Medical Academy, Belgrade, Serbia, database was searched for medical records of patients with SPD treated at the institution between 1985 and 2014. Demographic data, as well as data on clinical manifestations, associated diseases, treatments, and follow-ups, were recorded and analyzed in a retrospective study format. Diagnoses were based on clinical appearance and histopathological and DIF analysis of skin samples. Patients' records were reviewed, and cases fulfilling the diagnostic criteria proposed by Lutz et al. [7] were included in the analysis. These criteria included the onset of a pustular eruption without systemic symptoms, flaccid pustules with pus filling the lower half of lesions, absence of existing psoriasis or other stigmata of psoriasis, subcorneal neutrophilic pustule without spongiosis, and response to dapsone if challenged. Laboratory investigations encompassed the following: full blood cell count with differential, chemistry studies, quantitative serum IgA, IgM, IgG levels, urine, and serum electrophoresis, complete urinalysis, syphilis serology, microbiological examination of swabs, and other tests for excluding other specific dermatoses. Descriptive statistics were used to estimate patient characteristics and data processing.

Results

Clinical characteristics, treatments, and follow-ups of the patients are presented in Table 1. Between 1985 and 2014, 17 patients were diagnosed with SPD – nine females and eight males. Follow-up data were available for 12 patients. The median age at presentation was 45 years (range 18–90 years). The median disease duration from diagnosis was four years (range 1–28 years).

Pustular lesions were the characteristic finding in patients with SPD. Twelve patients exhibited widespread pustular eruptions, while five presented with lesions solely on flexural surfaces (Figures 1 and 2). Skin biopsies, as seen in Figure 3, were performed for all 17 patients to confirm the diagnosis. The initial biopsy confirmed SPD in 10 (58.8%) patients. For the others, multiple biopsies were required for diagnosis. DIF and indirect immunofluorescence (IIF) examinations were performed on 13 patients to rule out other autoimmune bullous dermatoses. Twelve of these patients tested negative. However, one patient displayed intercellular IgA deposits in the upper third of the epidermis, and an IIF examination verified the presence of IgA autoantibody deposits in the serum (titer of 1:20). This led to a diagnosis of IgA pemphigus, SPD type. Immunoblotting of human epidermal extracts revealed that sera clearly reacted with the 160 kD *pemphigus foliaceus* antigen.

Bacteriological examinations of pustule smears showed no bacterial growth in 11 patients. In contrast, *Staphylococcus* (*S.*) *aureus* was identified in six patients. Notably, despite this identification, the disease followed a chronic course and did not respond to short-term antibiotic treatment. This aligns with the idea that the presence of *S. aureus* was due to colonization of the diseased skin and not an active infection. Comorbidities were observed in 7 (41.2%) out of the 17 patients. Specific findings included polyclonal hypergammaglobulinemia in two patients, decreased levels of IgA in one, and benign monoclonal gammopathy (MG) IgA in one patient diagnosed with IgA pemphigus. Single instances of hypothyroidism, diabetes mellitus, and seronegative polyarthritis were also documented.

In the majority of patients, systemic treatment was necessary to control the disease, while in only one patient with mild symptoms, topical corticosteroids were sufficient to control flare-ups. Dapsone 1–3 mg/kg was used as monotherapy in 6 (35.4%) patients and in combination with systemic steroids (initial dose of 0.5 mg/kg) in six patients. Treatment with dapsone was combined with ultraviolet B (UVB) therapy in one patient. For two patients, systemic steroids were combined with etretinate and cyclosporine. In two particularly challenging cases (including the case of IgA pemphigus), multiple treatments were explored, including etretinate, a combination of psoralen and long-wave ultraviolet radiation (PUVA), cyclosporine A, colchicine, methotrexate, acitretin, and narrow-band UVB (Table 1). The median duration of active treatment for these two patients was 5.95 years.

Table 1

Clinical characteristics, treatment, and follow-up of the patients with subcorneal pustular dermatosis

Patient number	Gender / age (years)	Localization	Disease duration from the onset (years)	Disease duration from diagnosis (years)	MG	DIF	IIF	Treatment	Associated diseases	Follow-up
1	F/55	generalized	36	23	no	ND	ND	etretinate	hypergammaglobulinemia	23 years after diagnosis, continues to have a rare intermittent pustule
2	M/41	flexor surfaces	4	4	no	neg	ND	dapsone with systemic Cs	IgA hypoglobulinemia	last 8 years in remission after dapsone treatment
3	F/52	generalized	2	/	no	neg	neg	dapsone	diabetes mellitus	lost to follow-up
4	M/45	flexor surfaces	2	/	no	ND	ND	dapsone with systemic Cs	no	lost to follow-up
5	M/19	generalized	1	/	no	neg	neg	dapsone	no	lost to follow-up
6	F/40	generalized	11	3	ND	neg	1:10	dapsone	hypergammaglobulinemia	14 years of disease in remission
7	M/21	generalized	1	/	no	neg	neg	dapsone	no	lost to follow-up
8	F/35	generalized	28	28	no	ND	ND	dapsone	no	28 years after having a rare pustular lesion in the summer period
9	F/62	flexor surfaces	3	1	no	neg	neg	dapsone	angina pectoris, bronchial asthma	one year disease controlled with dapsone without new eruption during 18 years of follow-up period
10	M/19	generalized	12	/	no	neg	neg	dapsone + nbUVB	no	lost to follow-up
11	F/18	flexor surfaces	7	1	no	neg	neg	topical Cs	no	last 12 years without the occurrence of disease
12	F/54	generalized	6	3	no	neg	neg	dapsone with systemic Cs	seronegative polyarthritis	3 years after dapsone treatment very rare mild eruption once a year
13	F/68	generalized	6	6	no	neg	ND	dapsone with systemic Cs	no	6 years after diagnosis, frequent eruption of pustules
14	F/34	generalized	10	8	no	neg	neg	acitretin dapsone nbUVB cyclosporine A methotrexate	hypothyreosis	4 years after multiple treatment modalities has an occasional eruption
15	M/90	generalized	4	1,5	no	ND	neg	cyclosporine A with systemic Cs	angina pectoris	died
16	M/48	generalized	24	4	no	neg	neg	PUVA dapsone with systemic Cs	arterial hypertension	4 years on dapsone therapy with low dose Cs intermittent flares 3 times a year
17	M/50	flexor surfaces	26	8	IgA	IgA[#]	1:20	dapsone + Cs methotrexate PUVA etretinate cyclosporine A colchicine	IgA MG	last 18 years continues to have intermittent flares twice a year

MG – monoclonal gammopathy; DIF – direct immunofluorescence; IIF – indirect immunofluorescence; F – female; M – male; ND – not done; neg – negative; Cs – corticosteroids; nbUVB – narrow-band ultraviolet B; PUVA – psoralen + long-wave ultraviolet radiation. [#] – IgA in the upper epidermis.

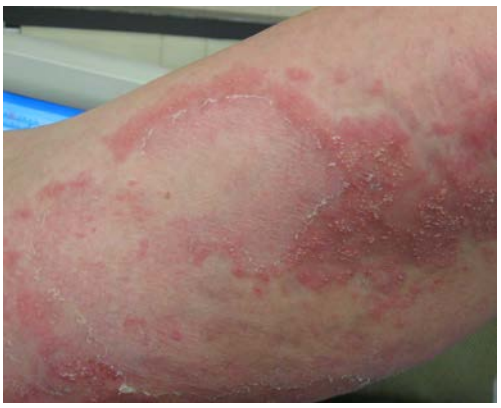

Fig. 1 – Coalescence of pustules on erythematous skin, which form a circinate pattern on the flexor side of the upper limbs.

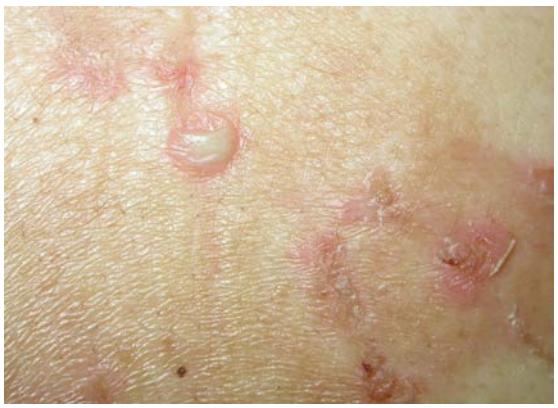

Fig. 2 – Newly formed flaccid pustule with hypopyon formation.

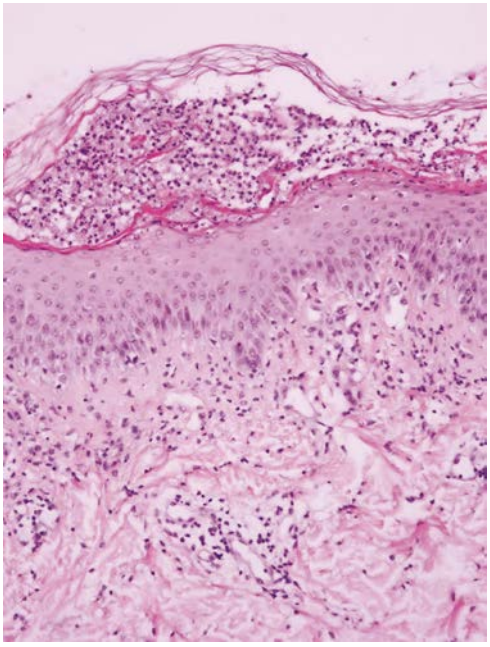

Fig. 3 – Histopathological examination shows a subcorneal accumulation of neutrophils. The dermis contains a sparse, mostly mononuclear, perivascular, and interstitial inflammatory infiltrate (hematoxylin-eosin, ×400).

A long-term follow-up spanning 1–28 years (median 9.5 years) revealed that most patients experienced lesion recurrence and needed ongoing or intermittent therapy to manage flare-ups (Table 1). Five patients had periodic flare-ups occurring one to three times a year, which were managed with intermittent topical corticosteroid treatment. Summer flare-ups were reported by one female patient. For three female patients (aged 18, 40, and 62 years), the disease spontaneously resolved, with a median duration of seven years and no relapse in the past ten years. Two patients experienced continuous flare-ups and were managed with dapsone and low-dose systemic steroids. Among the four patients diagnosed with hypo- or hyper-gammaglobulinemia, no progression to hematologic disease was observed.

Discussion

SPD is a rare but challenging clinicopathologic entity. It is a chronic, benign, pustular eruption, usually affecting adults, mostly middle-aged women. New lesions have the tendency to coalesce and often form annular or *serpiginous* patterns. Flaccid pustules or vesicles with an accumulation of pus in the lower half of lesions on clinically normal or slightly erythematous skin are characteristic. These lesions typically appear symmetrically, affecting submammary areas, axillae, groin, flexor side of the limbs, and the abdomen. No differences have been described in the clinical characteristics or prognosis of the disease in children and adults [1, 2, 7, 8].

Although previous studies have suggested that the disease affects females more frequently than males [2, 8], an equal gender distribution was found between males and females in the current analysis. Most patients in this study were middle-aged, though four were young adults aged 18–21. Follow-up data were unavailable for three of these patients. In two out of the total of three cases in whom the disease was self-limiting (an 18-year-old and a 40-year-old female), the disease lasted for seven years from the first onset without recurrence during a 12-year follow-up period.

In a recent case report of younger patients with SPD associated with *M. pneumoniae* [23, 24], it was postulated that SPD could be a self-limiting dermatosis occurring as a reaction to an infective agent in younger adult patients. Further case studies with a larger number of patients are needed to answer this question, as the available literature on follow-up data is limited. In our case series, no difference was found between patients younger and older than 40 years in relation to the clinical features, localization, or disease duration. As expected, associated diseases were more common in older patients.

The histopathologic hallmark of SPD is subcorneal pustules filled with neutrophils, occasionally eosinophils, and acantholytic cells [25]. In 1983, Sanchez et al. [22] reviewed more than 20 cases of SPD and postulated that it is clinically and histopathologically associated with psoriasis. They suggested the need for longer follow-ups to differentiate these conditions better. However, further studies did not confirm these assumptions, and SPD was classified as a neutrophilic dermatosis associated with gammopathies and inflammatory bowel disease.

There have been many case reports of SPD accompanied by IgA gammopathy [10–13], IgA myeloma [9, 19], Crohn's disease [14, 15], pyoderma gangrenosum [19–21], aplastic anemia [26], and more. In a study of 10 patients with SPD, Lutz et al. [7] found that four patients had monoclonal paraproteinemia, and three were of the IgA type. A comparison was made with a control population of 20 patients with pustular psoriasis in which no MG was detected. In the present case series, hematologic disorders were found in four patients, and of these, benign IgA MG was found in one without evidence of progression in long-term follow-up.

IgA pemphigus must be sought out in patients with the clinical appearance of SPD. A small number of cases of IgA pemphigus have been reported in the literature, with a slight prevalence of the SPD type [27, 28]. IgA pemphigus associated with MG is rare and, until now, it has beendescribed in 20% of patients. In 1992, Wallach [5] reviewed 29 cases. Six cases were associated with IgA paraproteinemia; of these, two patients had myeloma, one had B-cell lymphoma, and one could not be examined, while two patients were diagnosed with benign gammopathy. MG can appear concurrently with the skin lesions or appear between 4 to 27 years before or after them. This association was found exclusively in the SPD subtype and has never been found in the intraepidermal neutrophilic IgA dermatosis subtype.

SPD–type IgA pemphigus was found in one patient, and it was associated with IgA MG at diagnosis.

The drug of choice for SPD treatment is dapsone at a dose of 50–150 mg/d. The response is slower than in dermatitis herpetiformis but most often obtained [1, 8]. In the study of 10 patients, Lutz et al. [7] proposed that one of the diagnostic criteria for SPD should be a response to dapsone. The majority of patients in the present study had a satisfactory therapeutic effect after the administration of dapsone as monotherapy or in combination with systemic steroids, as opposed to those with IgA pemphigus, which was more resistant to dapsone therapy. Two patients, one diagnosed with the IgA pemphigus SPD variant, underwent several therapeutic regimens based on literature data, including methotrexate, etretinate [29, 30], cyclosporine A [31], colchicine [32], PUVA [33], and acitretin [13]. There is evidence that TNF-α may be involved in the pathogenesis of SPD, and, also, there is an association between SPD and inflammatory bowel disease, pyoderma gangrenosum, and rheumatoid arthritis. For the patients with recalcitrant SPD in which multiple treatments were attempted without benefit, there were few reports on patients responding to etanercept [34] and chimeric anti-TNF-α antibody (infliximab) [35, 36] .

Conclusion

After achieving long-term remission, the majority of SPD patients experienced rare recurrences that were very mild in comparison to the disease at first presentation. However, in resistant cases of the disease, the need for long-term treatment should be included in the treatment plan.

Conflict of interest

The authors declare no conflict of interest.

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CASE REPORT

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Sudden sustained monomorphic ventricular tachycardia in a previously healthy adult with many causes for it, but which is the correct one?

Iznenadna dugotrajna monomorfna ventrikularna tahikardija kod prethodno zdrave odrasle osobe sa puno uzroka za to, ali koji je pravi?

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Abstract

Introduction. Sustained monomorphic ventricular tachycardia (VT) – SMVT is a rare, underdiagnosed pathology with a very poor prognosis. Along with ventricular fibrillation, SMVT is responsible for nearly all of the arrhythmic sudden cardiac deaths (SCD). The most common cause of VT is ischemic heart disease, but there are many other reasons, among which are arrhythmogenic right ventricular cardiomyopathy (ARVD) and myocardial bridging phenomenon. Treatment options include a hybrid approach consisting of antiarrhythmic drugs, catheter ablation, and implantable cardioverter defibrillators (ICD). **Case report.** We present a case of a 46-year-old man, a military officer, who experienced chest pain, palpitations, and nausea during regular physical activity at home. Due to the symptoms described, he was examined immediately and diagnosed with SMVT. Shortly after the diagnosis, he lost consciousness and was successfully resuscitated. A complete non-invasive and invasive cardiology examination was performed. It revealed that the patient had stable coronary disease and a muscle bridge on the left anterior descending artery. An ARVD was suspected after transthoracic echocardiography and heart magnetic resonance imaging. Genetic testing for ARVD was negative, but according to the Heart Rhythm Society expert consensus criteria, we had enough for a definitive diagnosis. The patient was hospitalized for ten days and treated with drugs without recurring VT or other disorders. We implanted an implantable loop recorder before the discharge and monitored the heart rhythm for one year. During a three-year follow-up, all of his electrocardiographic findings presented sinus rhythm without heart rhythm disorders. **Conclusion.** Sudden SMVT is the most common cause of SCD. It is of inestimable importance to carry out a detailed examination and determine the immediate cause of the arrhythmia and the right therapy, which, for these patients, is a life-saving form of treatment. Therapy includes medications, electrophysiology or ICD, or a combination of these treatment approaches.

Key words:
cardiomyopathies; coronary disease; defibrillators, implantable; diagnosis; magnetic resonance imaging; myocardial bridging; tachycardia, ventricular; ultrasonography.

Apstrakt

Uvod. Dugotrajna monomorfna ventrikulska tahikardija (VT) – DMVT je retka, nedovoljno dijagnostikovana patologija sa veoma lošom prognozom. Zajedno sa ventrikulskom fibrilacijom, DMVT je odgovorna za skoro sve iznenadne srčane smrti (ISS) nastale usled aritmije. Najčešći uzrok VT je ishemijska bolest srca, ali postoje i mnogi drugi razlozi, među kojima su aritmogena kardiomiopatija desne komore (AKDK) i fenomen miokardnog „mosta“ (*bridge*). Mogućnosti lečenja uključuju hibridni pristup, koji se sastoji od antiaritmijskih lekova, kateterske ablacije i implantabilnog kardioverter defibrilatora (IKD). **Prikaz bolesnika.** Prikazujemo slučaj 46-godišnjeg muškarca, oficira u vojsci, koji je tokom redovnih fizičkih aktivnosti kod kuće osetio bol u grudima, lupanje srca i mučninu. Zbog navedenih tegoba odmah je pregledan i dijagnostikovana mu je DMVT. Ubrzo nakon postavljanja dijagnoze bolesnik je izgubio svest i uspešno je reanimiran. Sprovedena je kompletna neinvazivna i

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invazivna kardiološka dijagnostika. Utvrđeno je da je bolesnik imao stabilnu koronarnu bolest i mišićni „most“ na prednjoj descedentnoj arteriji. Nakon transtorakalne ehokardiografije i magnetne rezonance srca, posumnjano je na AKDK. Genetsko testiranje na AKDK bilo je negativno, ali prema kriterijumima konsenzusa stručnjaka *Heart Rhythm Society*, imali smo dovoljno dokaza za definitivnu dijagnozu. Bolesnik je hospitalizovan tokom deset dana i lečen lekovima, bez pojave VT i drugih poremećaja. Pre otpusta iz bolnice, ugradili smo mu implantibilni *loop* rikorder i pratili srčani ritam tokom godinu dana. Tokom trogodišnjeg praćenja svi elektrokardiografski nalazi bili su normalni. **Zaključak.** Iznenadna DMVT je najčešći uzrok ISS. Detaljan pregled je od neprocenjive važnosti, kao i utvrđivanje neposrednog uzroka aritmije i primena odgovarajuće terapije, koja za te bolesnike predstavlja vid lečenja koji spasava život. Terapija uključuje lekove, elektrofiziologiju ili IKD ili kombinaciju ovih pristupa u lečenju.

Ključne reči:
miokard, bolesti; koronarna bolest; defibrilatori, implantabilni; dijagnoza; magnetska rezonanca, snimanje; miokardni mostovi; tahikardija, ventrikulska; ultrasonografija.

Introduction

Sustained monomorphic ventricular tachycardia (VT) – SMVT is a rare, underdiagnosed pathology with a very poor prognosis [1]. Along with ventricular fibrillation, SMVT is responsible for nearly all of the arrhythmic sudden cardiac deaths (SCD) [1, 2]. SMVT demonstrates a stable QRS morphology from beat to beat when the rhythm lasts longer than 30 s or hemodynamic instability occurs in less than 30 s [3]. SMVT may be idiopathic but occurs most frequently in patients with underlying heart disease of various types, including ischemic heart disease (IHD), dilated cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic right ventricle (RV) cardiomyopathy (ARVC), myocarditis and complex congenital heart disease [4]. Other causes include myocardial bridge (MB) [5, 6], prolonged QT syndrome, infiltrative cardiomyopathy, Chagas heart disease, cardiac sarcoidosis, and left ventricular noncompaction [4, 7].

The most common cause of VT is IHD [1–3]. Another cause of VT is ARVC, a rare inherited disorder and underrecognized clinical entity manifested by ventricular arrhythmias and sudden death, especially in young athletes [8, 9]. MB or myocardial bridging is defined as the muscle overlapping the intramyocardial part of the epicardial coronary artery and is one more cause of VT [10]. The artery, which is enclosed by the myocardium, is called the “tunneled artery” [11]. In 70–98%, the tunneled artery is the left anterior descending artery (LAD) [10–11]. Autopsy studies show the frequency of MB ranging from 5% to 86%, with the largest one presenting a 26% rate [12]. Coronary angiography (CA) rates are much lower (0.5–12%) [11].

Diagnostic of all these diseases, which can lead to VT, includes medical and family history, clinical examination, laboratory analysis, 12-lead electrocardiography (ECG), and transthoracic echocardiography (ECHO) [13]. Computed tomography coronarography or invasive CA [14] and often endomyocardial biopsy, electrophysiologic testing, and cardiac magnetic resonance imaging (MRI) [15] are also needed.

Treatment of the known and variable cause of the arrhythmia can lead to its permanent cessation. If we have an unchangeable cause of the arrhythmia, like a genetic disorder or similar, treatment options include antiarrhythmic drugs, implantation of implantable cardioverter defibrillators (ICD), and catheter ablation. A hybrid approach consisting of antiarrhythmic drugs, catheter ablation, and ICD may provide an effective therapeutic approach in some situations [4, 16].

Case report

We present a case of a 46-year-old man, a military officer, who experienced chest pain, palpitations, and nausea during physical activity at home, mowing the grass. He immediately reported to the doctor at the nearest military facility. His heart rate was 245 beats/min, and his blood pressure was under 80/50 mmHg. ECG (Figure 1) demonstrated wide-QRS-complex VT consistent with sustained VT of the left bundle branch block with the superior axis. The patient was immediately transferred to the

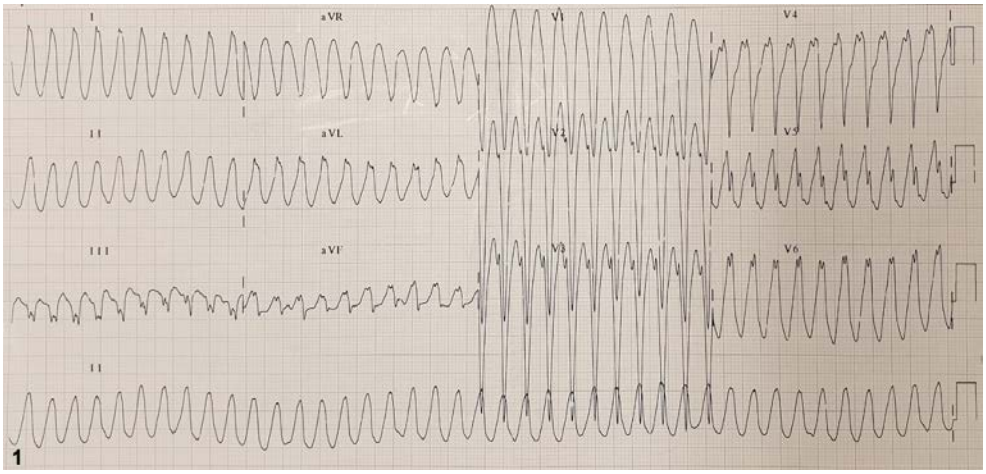

Fig. 1 – Electrocardiography during sustained ventricular tachycardia on admission.

Military Medical Academy (MMA), Belgrade, Serbia, and he was resuscitated during the transfer. Upon admission to the Emergency Unit of the MMA, he experienced a second VT occurring in a one-hour time frame, which required prompt reanimation and direct current cardioversion, after which his heart rate was 87 beats/min and blood pressure was 110/70 mmHg. The physical examination did not reveal anything extraordinary. Personal anamnesis unveiled hypertension, hyperlipidemia, glucose intolerance, active smoking for 25 years, moderate alcohol consumption, and playing recreational sports. Family anamnesis was negative for cardiovascular diseases.

Laboratory analysis revealed following increased findings on admission: leukocyte count 13.86 x 10^9/L [reference range (RR) 4–11 x 10^9/L)], glucose level 13.4 mmol/L (RR 4.1–5.9 mmol/L), creatinine 147 umol/L (RR 62–115 umol/L), creatine kinase 441 U/L (RR 32–300 U/L), and aspartate aminotransferase 51 U/L (RR 0–37 mmol/L). Electrolytes were within normal limits, and there was no suspicion of drug use. CA demonstrated non-significant stenosis of LAD in the bifurcation area with second diagonal branch and septal truncus (up to 50%) (Figure 2A), circumflex artery (ACX) in the ostial area (30–50%), and normal CA of right coronary artery (RCA) (Figure 2B). Intravascular ultrasound (US) displayed large calcified stenosis from proximal to medial part of LAD, 50–70%, with minimal luminal area (MLA) of 3.84 mm^2 (MLA < 4 mm^2 in LAD, ACX, and RCA vessels > 3 mm in diameter correlates with physiological significance) (Figure 3A), while stenosis in the ACX was 50–60% with MLA of 6.18 mm^2 (Figure 3B). Significant

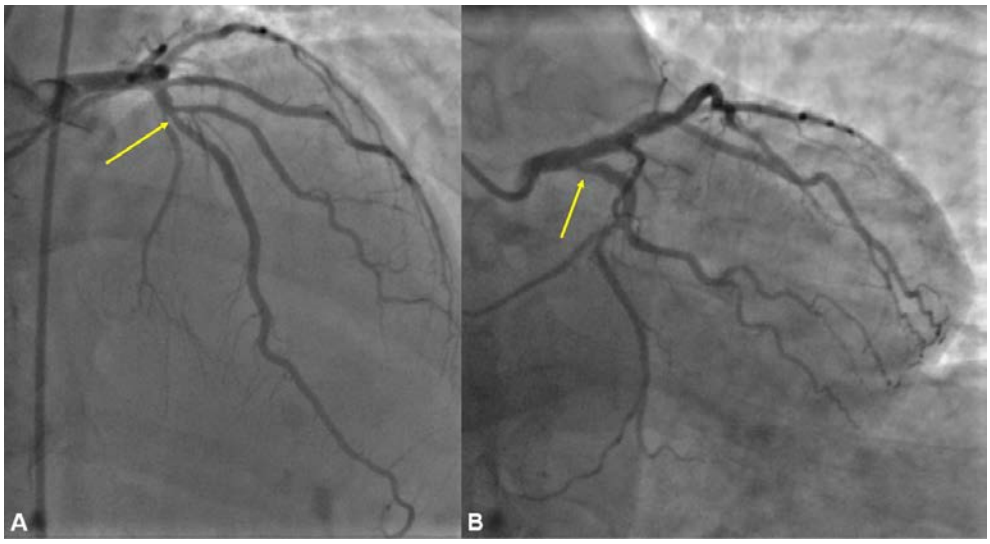

Fig. 2 – Coronary angiography of the left coronary artery reveals A) stenosis of 50–70% in the proximal part of the left anterior descending artery (yellow arrow) and B) stenosis of 30–50% in the ostial part of the circumflex artery (yellow arrow).

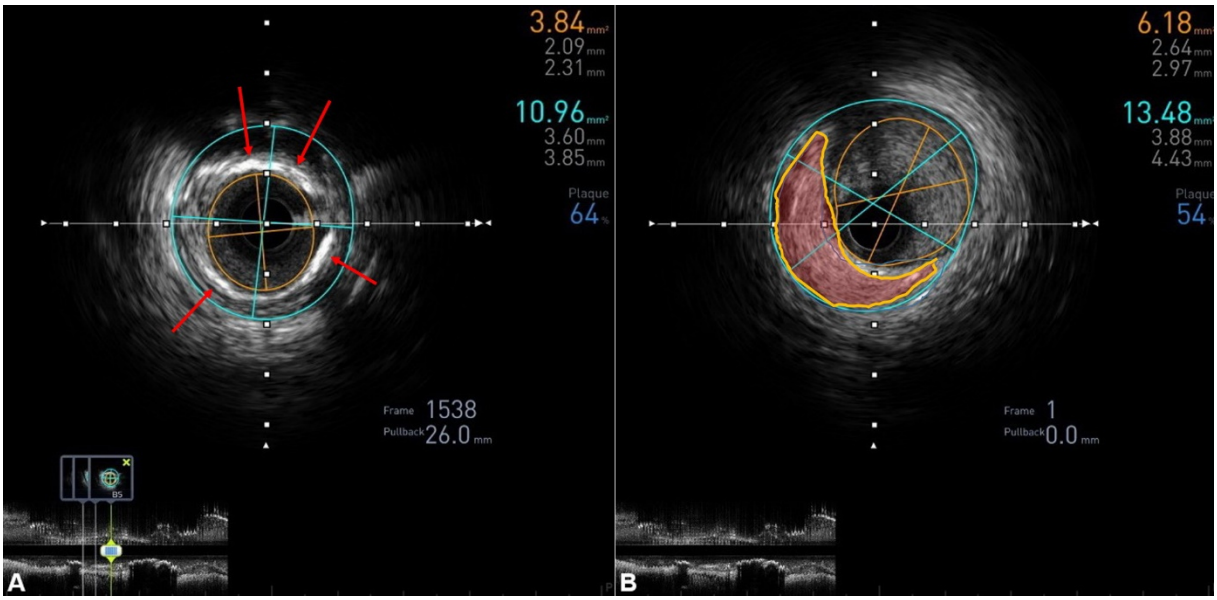

Fig. 3 – Intravascular ultrasound of left anterior descending (LAD) artery shows A) circular stenosis of 64% of mid LAD (minimal luminal area – MLA = 3.84 mm^2) with calcification (red arrows) and B) eccentric plaque of ostial part of circumflex artery with stenosis of 54% (MLA = 6.18 mm^2) (red field).

coronary compression in the mid to distal segment of the LAD was noted all along the systolic phase, attributing MB phenomenon (Figure 4A and 4B). Initially, ECHO showed unremarkable findings. Follow-up US showed good coronary flow reserve, resulting in 3.1 (reference values ≥ 2) in the LAD. Fractional flow reserve was 0.89 (reference values > 0.85) in LAD and 0.92 in ACX. The patient was hospitalized for ten days and treated with medicament therapy without recurring VT or other disorders. His therapy included the following medicaments: amiodarone 200 mg/day, bisoprolol 2.5 mg/day, valsartan 80 mg/day, aspirin 100 mg/day, rosuvastatin 40 mg/day, and trimetazidine 35 mg twice a day. Before the patient was discharged from the hospital, we implanted an implantable loop recorder and monitored the heart rhythm for one year. We performed a treadmill exercise test three months after discharge, which was negative for IHD. We did not discover any heart disturbances during the whole time of monitoring. Three years later, on ECHO, we found an enlarged RV with the greatest diameter of 4.56 cm (Figure 5A) and reduced strain of the free wall of the RV

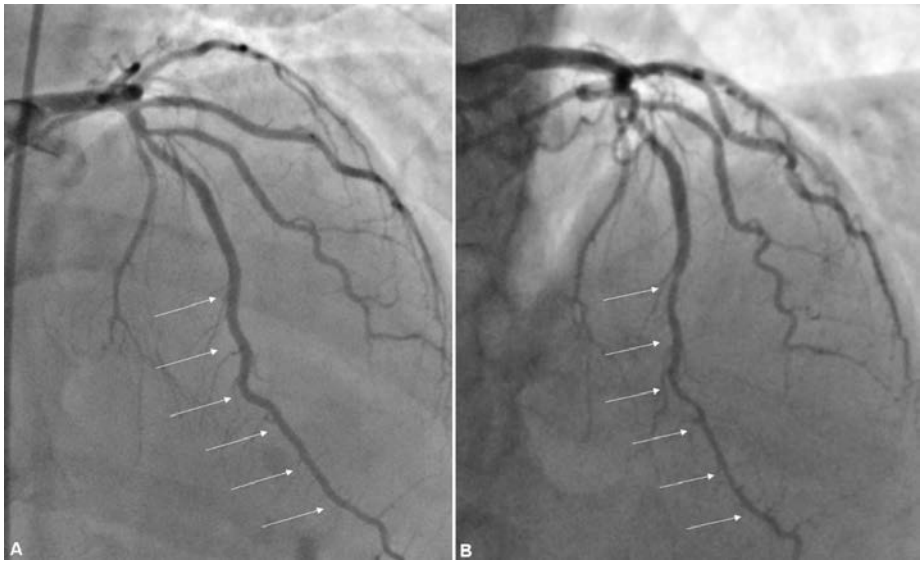

Fig. 4 – Myocardial bridge: A) left anterior descending (LAD) artery during diastole of the heart with marked part of the artery where the bridge will occur (white arrows); B) part of the LAD artery where the bridge occurred (white arrows).

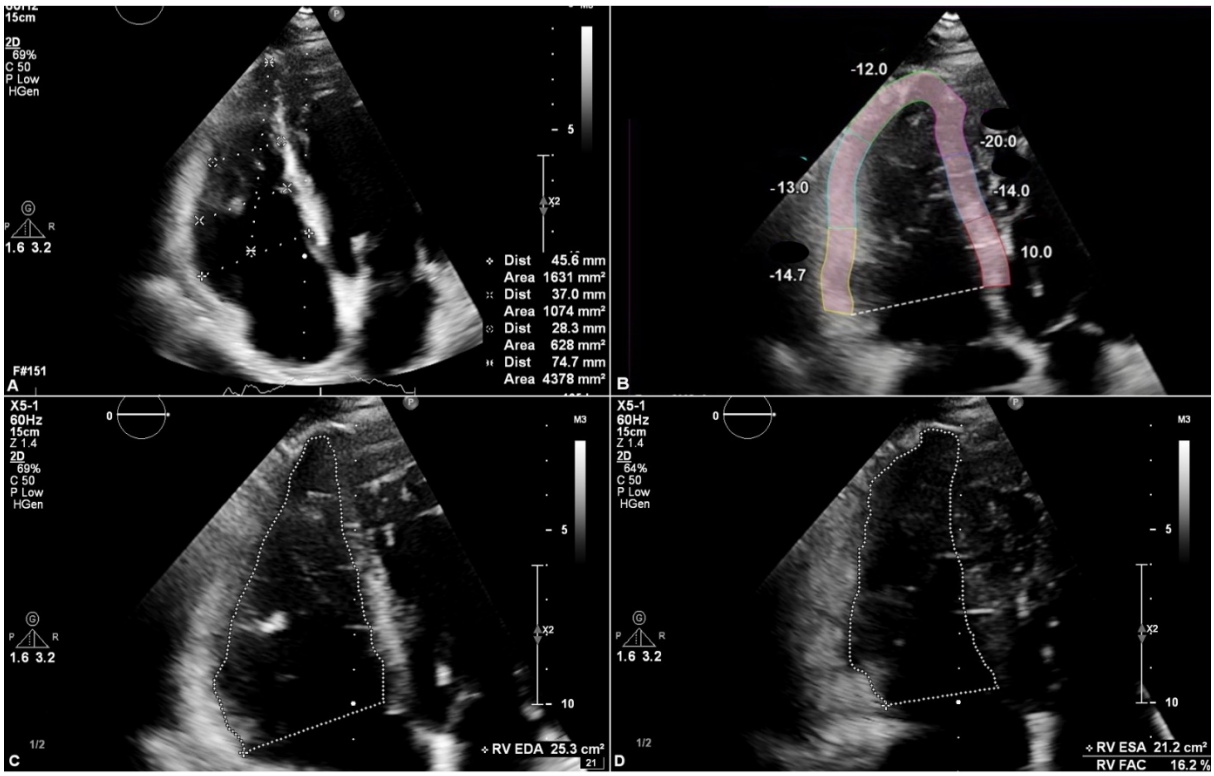

Fig. 5 – Transthoracic echocardiography: A) dimensions of the right ventricle (RV); B) the strain of the free wall of the RV (-13.3); C) right ventricular end-diastolic area; D) right ventricular end-systolic area and fractional area change (16.2%).

(-13.3) (Figure 5B). In addition, the parameter parasternal short axis – RV outflow tract was greater than 36 mm (result was 43 mm), and fractional area change was less than 33% (result was 16.2%) (Figure 5C and 5D). In the end, we decided to do an MRI of the heart. Results reveal suspicion of ARVC. Two smaller aneurysmal enlargements of RV were registered. The first was at the transition from the basal to the medial segment of the free wall forward 7.9 mm (Figure 6A), and the second was at the very apex of RV up to 6 mm in size (Figure 6B), which suggested electrophysiological testing as well as genetic screening. In order to continue with further diagnostic, according to current recommendations, we also performed genetic testing at the Institute for Molecular Genetics and Genetic Engineering, Belgrade, and the testing was negative. The patient has been followed up for three years, and all his ECG findings presented sinus rhythm without heart rhythm disorders (Figure 7). The patient's consent was obtained for this case report.

Discussion

Our case is complex, with the possibility of multiple causes for SMVT, which makes it difficult to determine the final cause of this malignant rhythm disorder.

During the examination, we diagnosed arterial hypertension, IHD, and an MB on the LAD, which were not of such a degree of severity that we could safely associate the occurrence of malignant rhythm disorders that the patient had. At this time, due to the absence of unchangeable causes for the development of malignant rhythm disorders, we made a conciliar decision to temporarily postpone the need for ICD implantation. It was also decided that severe MB is to be treated with drugs only and not surgery. During the long follow-up time, ECG as well as the exercise test were normal, but repeated ECHO revealed important changes. MRI of the heart showed suspicion for ARVD, and genetic testing on gnomAD Genomes, gnomAD exomes, and 1000 Genomes was negative, which does not rule out the existence of the disease [17, 18].

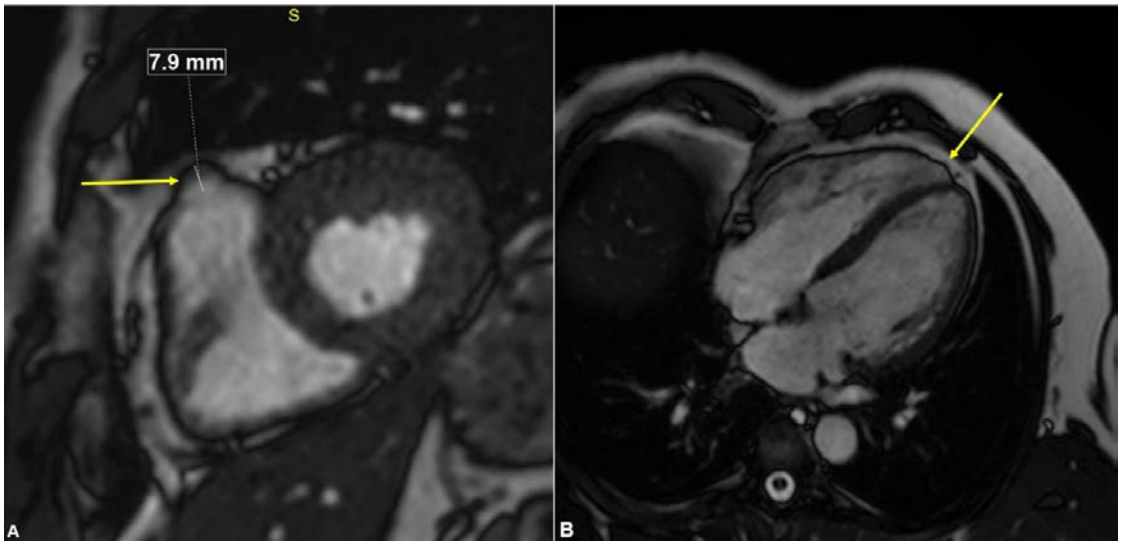

Fig. 6 – Heart magnetic resonance imaging shows A) aneurismatic dilatation of the right ventricle in the basal part with 7.9 mm (yellow arrow) and B) apex of the right ventricle (yellow arrow).

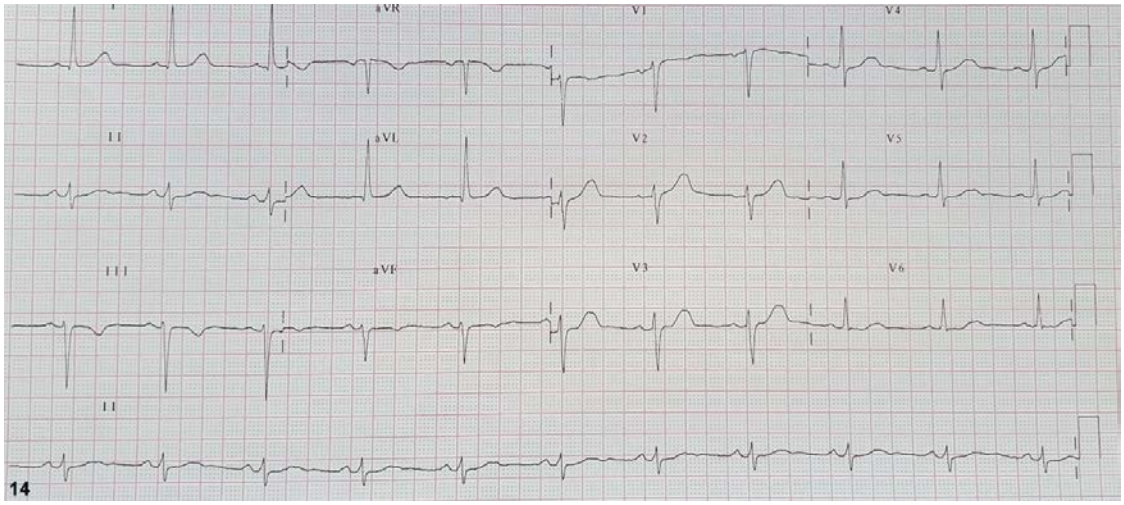

Fig. 7 – Electrocardiography three years after ventricular tachycardia shows sinus rhythm without heart rhythm disorders.

Including all these results, we had two major criteria (ECG and ECHO) for diagnosis of ARVD according to the recommendations of the Heart Rhythm Society expert consensus statement from 2019 [19]. Taking into account all the facts and based on current recommendations for the treatment of arrhythmias associated with SCD [1, 19], we decided to plan the patient's ICD implantation without previous electrophysiology testing.

Conclusion

Sudden SMVT is the most common cause of SCD. It is very difficult to diagnose, and it is often the first and last manifestation of the disease. If the disease is detected and the unwanted event is prevented, further determination of the true cause can be a problem, especially if there are several different reasons for the occurrence of the said arrhythmia. Due to the modality of treatment, which depends on the etiology of the arrhythmia, it is of inestimable importance to carry out a detailed examination and determine the immediate cause of the arrhythmia and thus determine the right therapy, which for these patients is a life-saving form of treatment. Further research in these areas will provide invaluable data for early detection and prevention of SCD.

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I N M E M O R I A M

Principal Research Fellow, Prim. Dr. Aleksandar Nedok (1925–2024)

On February 14, 2024, in Belgrade, Aleksandar Nedok, a scientific advisor, primarius, doctor of medical sciences, internist-cardiologist, and reserve major of the Serbian Army, passed away.

He was born on September 12, 1925, in Belgrade, where he finished elementary and high school. He participated in the People's Liberation War as a partisan from October 1944 until the liberation of Yugoslavia, and after that, until October 1946, he worked as an officer and youth leader in the Yugoslav Army. He left active duty because he set a goal to graduate from medical school and devote himself to the medical profession. He graduated from the Faculty of Medicine in Belgrade in 1953. After that, he worked as a General Practitioner at the Community Health Center in Paraćin. In 1961, he completed his specialization in internal medicine. From 1957, he worked at the Institute for Emergency Internal and Cerebrovascular Diseases ("St. Sava" Hospital) in Belgrade, where he was the Head of the Internal Department from 1972 to 1987, and from 1979 to 1987, he was also the director of the Institute. He founded the first Serbian and Yugoslav Coronary Unit in 1970 in Belgrade. He was the Head of the Department of Internal Diseases in the Emergency Center of the Clinical Center of Serbia in Belgrade, where he was the founder and first Head of the Department of Emergency Cardiology with a Coronary Unit from 1987 to 1990. He retired in 1990. After that, he devoted himself to historical science, his love from his high school days, studying with great success the history of the Serbian military and civilian health care.

U Beogradu je 14. februara 2024. godine umro naučni savetnik, primarijus, doktor medicinskih nauka Aleksandar Nedok, internista – kardiolog, major u rezervi Vojske Srbije.

Rođen je 12. septembra 1925. godine u Beogradu, gde je završio osnovnu školu i gimnaziju. Učestvovao je u Narodnooslobodilačkoj borbi kao partizan od oktobra 1944. do oslobođenja Jugoslavije, a posle toga je do oktobra 1946. godine radio kao oficir i omladinski rukovodilac u Jugoslovenskoj armiji. Napustio je aktivnu vojnu službu jer je sebi postavio cilj da završi Medicinski fakultet i da se posveti lekarskom pozivu. Završio je Medicinski fakultet 1953. godine u Beogradu. Posle toga radio je kao lekar opšte prakse u Domu zdravlja u Paraćinu. Specijalizaciju iz interne medicine završio je 1961. godine. Od 1957. godine radio je u Zavodu za hitna interna i cerebrovaskularna oboljenja (Bolnica „Sveti Sava") u Beogradu, gde je bio načelnik Internog odeljenja od 1972. do 1987. godine, a od 1979. do 1987. godine bio je i direktor Zavoda. Osnovao je prvu srpsku i jugoslovensku koronarnu jedinicu 1970. godine u Beogradu. U Urgentnom centru Kliničkog centra Srbije u Beogradu bio je načelnik Odeljenja za unutrašnje bolesti, gde je bio osnivač i prvi načelnik Odeljenja urgentne kardiologije sa koronarnom jedinicom u periodu od 1987. do 1990. godine. Penzionisan je 1990. godine. Posle toga se posvetio istorijskoj nauci, svojoj ljubavi iz gimnazijskih dana, proučavajući sa velikim uspehom istoriju srpskog vojnog i civilnog saniteta.

Doktorsku disertaciju pod nazivom *Bradikardije usled poremećenog stvaranja ili sprovođenja draži u akutnom infarktu miokarda* odbranio je 1978. godine. Izabran za

In 1978, he defended his doctoral dissertation on the subject *Bradycardia due to impaired generation or conduction of stimuli in acute myocardial infarction*. In 1967, Dr. Aleksandar Nedok was elected as Primarius and, in 1988, as Principal Research Fellow for the area of Cardiology at the Faculty of Medicine in Belgrade. He attended professional trainings in Paris and London and gave invited talks in Moscow, Leningrad, and Riga. He was a member of the New York Academy of Sciences and a regular member and associate of Matica Srpska in Novi Sad. He spoke English, German, and French and used Italian and Russian.

Dr. Aleksandar Nedok had an exquisite knowledge of medicine overall, but he mostly dealt with cardiology, endocrinology, and genetics in practice and theory. He published 220 research papers from several areas of internal medicine and the history of medicine in Serbian, French, American, English, and Slovenian scientific journals. He was the co-author of 10 monographs in cardiology and endocrinology and the author of 11 monographs on the history of medicine and of a large number of lexical words in the Medical Lexicon of the Yugoslav Lexicographic Institute in Zagreb and the Serbian Biographical Dictionary of Matica Srpska in Novi Sad. He published the biographies of 230 Serbian doctors who worked in the nineteenth century and in the first four decades of the twentieth century. He was quite active in researching and writing the history of medicine in Serbia until the day when he accidentally injured his hip. The treatment resulted in numerous complications, which, after almost four months, led to a fatal outcome despite the extraordinary efforts of his colleagues and other medical staff at the Intensive Care Unit of the University Clinical Center in Belgrade. The last research paper by Dr. Aleksandar Nedok on the first apothecaries in the Serbian military health care was published in the December issue of the *Vojnosanitetski pregled* journal in 2023, less than two months before his death.

Dr. Aleksandar Nedok was very active in the Serbian Medical Society (SMS): he was the president of the Section for Cardiology, one of the founders of the Section for Endocrinology and the Section for Nuclear Medicine. He made a great contribution to the formation and work of the Section for the History of Medicine, where he was the initiator of many activities and the implementer of several projects from the history of Serbian military and civilian health care. He was a reviewer in two of our eminent medical journals: *Serbian Archives of Medicine* (in which he was a member of the Editorial Board and deputy Editor-in-Chief) and *Vojnosanitetski pregled*. He is one of the founders of the journal *Cardiology*. He was elected a regular member of the Academy of Medical Sciences of the SMS in 1990. He is the holder of the most prestigious awards given by the SMS: the Great Seal and the Charter of the Serbian Medical Society, as well as the "Dr. Vladan Đorđević" Award for life's work in the field History of Medicine.

He was awarded the Medal of Merit for the People, the Order of Labor with a Silver Star, and the Order of Labor with a Golden Wreath. For his contribution to the study of primarijusa 1967, a za naučnog savetnika za oblast Kardiologija na Medicinskom fakultetu u Beogradu 1988. godine. Bio je na stručnom usavršavanju u Parizu i Londonu i držao je predavanja po pozivu u Moskvi, Lenjingradu i Rigi. Bio je član Njujorške akademije nauka i redovni član i saradnik Matice srpske u Novom Sadu. Govorio je engleski, nemački i francuski, a služio se italijanskim i ruskim jezikom.

Odlično je znao celokupnu medicinu, a u praksi i teoriji najviše se bavio kardiologijom, endokrinologijom i genetikom. Objavio je 220 stručnih radova iz više oblasti interne medicine i istorije medicine u srpskim, francuskim, američkim, engleskim i slovenačkim naučnim časopisima. Koautor je 10 monografija iz kardiologije i endokrinologije a autor je 11 monografija iz istorije medicine kao i velikog broja odrednica u *Medicinskom leksikonu Jugoslavenskog leksikografskog zavoda u Zagrebu* i *Srpskom biografskom rečniku Matice srpske u Novom Sadu*. Objavio je biografije 230 srpskih lekara koji su radili u devetnaestom veku i u prve četiri decenije dvadesetog veka. Bio je aktivan u istraživanju i pisanju istorije medicine u Srbiji sve do dana kada je slučajno doživeo povredu kuka. Prilikom lečenja, ispoljile su se brojne komplikacije, koje su, posle skoro četiri meseca dovele do fatalnog ishoda, uprkos izvanrednim naporima njegovih kolega i ostalog medicinskog osoblja u Jedinici intenzivne nege Univerzitetskog Kliničkog centra u Beogradu. Poslednji stručni članak dr Aleksandra Nedoka o prvim farmaceutima u srpskom vojnom sanitetu objavljen je u decembarskom broju *Vojnosanitetskog pregleda* 2023. godine, nepuna dva meseca pre smrti.

Dr Aleksandar Nedok bio je veoma aktivan u Srpskom lekarskom društvu (SLD): bio je predsednik Sekcije za kardiologiju, jedan od osnivača Sekcije za endokrinologiju i Sekcije za nuklearnu medicinu. Dao je veliki doprinos u formiranju i radu Sekcije za istoriju medicine, gde je bio inicijator mnogih aktivnosti i realizator više projekata iz istorije srpskog vojnog i civilnog saniteta. Bio je recenzent u dva naša eminentna medicinska časopisa: *Srpskom arhivu za celokupno lekarstvo* (u kojem je bio i član redakcije i zamenik glavnog i odgovornog urednika) i *Vojnosanitetskom pregledu*. Jedan je od osnivača časopisa *Kardiologija*. Izabran je za redovnog člana Akademije medicinskih nauka SLD 1990. godine. Nosilac je najprestižnijih priznanja koje dodeljuje SLD svojim članovima: *Velikog pečata* i *Povelje Srpskog lekarskog društva*, kao i *Nagrade „Dr Vladan Đorđević" za životno delo u oblasti istorije medicine*.

Odlikovan je Medaljom zasluga za narod, Ordenom rada sa srebrnom zvezdom i Ordenom rada sa zlatnim vencem. Za doprinos u proučavanju istorije srpskog vojnog saniteta vanredno je unapređen u čin rezervnog sanitetskog majora 30. jula 2014. godine, na dan sanitetske službe Vojske Srbije, u svojoj 89-oj godini života. To je jedinstven primer u svetu da se u visoki oficirski čin, u mirnodopsko vreme, vanredno unapredi rezervni oficir u tom životnom dobu.

U životu i radu dr Aleksandar Nedok je imao punu podršku i pomoć svoje porodice: supruge doktorke Dobrile koja je umrla 2015. godine, kćerke doktorke Olge, unuka

the history of the Serbian military health care, he was extraordinarily promoted, at the age of 89, to the rank of reserve medical major on July 30, 2014, on the Day of the Serbian Armed Forces Medical Services. It is a unique example in the world of an extraordinary promotion of a reserve officer at that age to a high officer rank in peacetime.

In his life and work, Dr. Aleksandar Nedok had the full support and help of his family: his wife, Dr. Dobrila, who died in 2015; his daughter, Dr. Olga; his grandson, Dr. Aleksandar Junior; his granddaughter, Natasha, an economist. He experienced special joy with the birth of his great-grandson, Karl-Jonathan.

Dr. Aleksandar Nedok, as a doctor, scientist, humanist, pedagogue, and historian, with his success, kindness, and honesty, earned one of the places of honor in the civilian and military health care system of the Republic of Serbia, as well as in the wider social community.

Brigadier General (ret.)
Veljko Todorović, MD, PhD

doktora Aleksandra juniora i unuke Nataše, ekonomiste. Posebnu radost doživeo je rođenjem praunuka Karla – Jonatana.

Dr Aleksandar Nedok je kao lekar, naučnik, humanista, pedagog i istoričar, svojim uspesima, dobrotom i poštenjem, zaslužio jedno od počasnih mesta u civilnom i vojnom zdravstvenom sistemu Republike Srbije, ali i u široj društvenoj zajednici.

Brigadni general u penziji
Dr sc. med. Veljko Todorović

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DiMaio VJ. Forensic Pathology. 2nd ed. Boca Raton: CRC Press; 2001.

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Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: *Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG*, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

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Balint B. From the haemotherapy to the haemomodulation. Beograd: Zavod za udžbenike i nastavna sredstva; 2001. (Serbian)

Mladenović T, Kandolf L, Mijušković ŽP. Lasers in dermatology. In: *Karadaglić Đ*, editor. Dermatology. Beograd: Vojnoizdavački zavod & Verzal Press; 2000. p. 1437–49. (Serbian)

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