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Prognostic significance of inflammatory scoring systems in critically ill patients with COVID-19 infection

Prognostičko značenje upalnih bodovnih sustava u kritično oboljelih bolesnika s COVID-19 infekcijom

Damir Mihić, Lana Maričić, Ivana Tolj, Domagoj Loinjak, Livija Sušić, Ivana Begić*

Summary

Aim: The outbreak of novel coronavirus pneumonia that was first detected in Wuhan in December 2019 resulted in a worldwide pandemic. Approximately 25% of confirmed cases developed a severe disease and the need for intensive care unit admission. The aim of this study was to determine the role of three inflammatory scoring systems, C-reactive protein/albumin ratio, fibrinogen/albumin ratio, C-reactive protein/lymphocyte ratio and their association with survival, comorbidities, and the occurrence of additional complications in the intensive care of these patients.

Materials and methods: This retrospective study was conducted based on data collected by the Department of Respiratory Center. Ethical approval for the study was obtained from the Ethics Committee of Osijek University Hospital. This study analysed data retrospectively between October and December 2020, and included 137 critically ill patients with a diagnosis of COVID-19.

Results: Data analysis of three examined inflammatory points of the system, below and above the median found a significant association in the group below the median C-reactive protein/albumin ratio with the presence of complications (p= 0,039) in the group above the median in the study of fibrinogen/albumin ratio found a significant association with sepsis (p=0,043). In the group of participants who were above its median in terms of C-reactive protein/lymphocyte ratio, there were more of those with the development of acute kidney injury (p=0,014), and sepsis (p=0,009).

Conclusion: Inflammatory scoring systems, C-reactive protein/albumin ratio, fibrinogen/albumin ratio and C-reactive protein/lymphocyte ratio represent an independent prognostic indicator of the clinical course in critically ill patients with COVID-19 infection.

Key words: COVID-19, critically ill, C-reactive protein/albumin ratio, fibrinogen/albumin ratio, C-reactive protein/lymphocyte ratio

Sažetak

Cilj: Pojava nove pneumonije uzrokovane koronavirusom, koja je prvi put otkrivena u Wuhanu u prosincu 2019., rezultirala je pandemijom diljem svijeta. Otprilike 25% potvrđenih slučajeva razvilo je teško bolest i zahtijevalo prijam u jedinicu intenzivne njege. Cilj ovoga istraživanja bio je utvrditi ulogu tri upalna sustava, omjer C-reaktivni protein/albumin, omjer fibrinogen/albumin, omjer C-reaktivni protein/limfociti i njihovu povezanost s preživljavanjem, komorbiditetima i pojavom dodatnih komplikacije u intenzivnoj njezi ovih bolesnika.

Materijali i metode: Ova retrospektivna studija provedena je na temelju podataka koji su prikupljeni u Respiracijskom centru, Kliničkog bolničkog centra Osijek. Odobrenje za istraživanje dobiveno je od Etičkog

* **University Hospital Osijek,** Department of pulomology and intesive medicine (Damir Mihić, MD, Domagoj Loinjak, MD), Department of cardiology (Assistant professor Lana Maričić, PhD, MD), Department of nephrology (Ivana Tolj, MD), **University „Josip Juraj Strossmayer", Faculty of medicine, Osijek** (Mihić Damir, MD, Assistant professor Lana Maričić, PhD, MD, Ivana Tolj, MD, Domagoj Loinjak, MD, Livija Sušić, MD, Ivana Begić, MD); **Health Centre Osijek, Osijek** (Livija Sušić, MD)

Correspondence address / *Adresa za dopisivanje:* Assistant professor Lana Maričić, PhD, MD, internist cardiologist, University Hospital Osijek, Internal clinic, Department of cardiology, J. Huttlera 4, 10000 Osijek. E-mail: dr.lmaricic@gmail.com.hr

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povjerenstva KBC-a Osijek. Ova studija analizirala je podatke retrospektivno, između listopada i prosinca 2020., uključivši 137 kritično bolesnih bolesnika s dijagnozom COVID-19.

Rezultati: Analizom podataka tri ispitivana upalna bodovna sustava, ispod i iznad medijana, utvrđena je značajna povezanost u skupini ispod medijana omjera C-reaktivni protein/albumin s prisutnošću komplikacija (p=0,039), a u skupini iznad medijana omjera fibrinogen/albumin utvrđena je značajnu povezanost sa sepsom (p=0,043). U skupini sudionika koji su bili iznad njegova medijana, po omjeru C-reaktivni protein/limfociti, više je bilo onih s razvojem akutne ozljede bubrega (p=0,014), te sepse (p=0,009).

Zaključak: Inflamatorni bodovni sustavi, omjer C-reaktivni protein/albumin, omjer fibrinogen/albumin i omjer C-reaktivni protein/limfociti, predstavljaju neovisni prognostički pokazatelj kliničkoga tijeka u kritično bolesnih osoba s infekcijom COVID-19.

Ključne riječi: COVID-19, kritično oboljeli, omjer C-reaktivni protein/albumin, omjer fibrinogen/albumin, omjer C-reaktivni protein/limfociti

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Introduction

In December 2019, Wuhan City, the capital of Hubei province in China, became the center of an outbreak of pneumonia of unknown cause[1]. The clinical spectrum of SARS-CoV-2 infection appears to be a wide, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and even death, with many patients being hospitalized with pneumonia.[2] Since there is no specific antiviral treatment, optimized support is the most relevant factor in the patient's prognosis.[3] ICU admission has been reserved for the most severe forms, depending on the capacity of the health care system. Despite differences in culture and practices around the world, most centres report that around 25% of hospitalized patients require ICU admission.[4,5] Patients who have required critical care have tended to be older (median age ≈60 years), and 40% of them have a comorbidity, commonly diabetes and cardiac disease.[6] Given the dominance of the systemic inflammatory response in the COVID-19 infection, the study of inflammatory markers is important. A number of studies to date have addressed precisely this topic for the reason of looking for how to ensure and predict an undesirable outcome. Moreover, the systemic inflammatory response has been shown to be a useful therapeutic target in patients with COVID-19.

The C-reactive protein/albumin (CAR) ratio presents a fraction of a positive acute phase inflammatory reactant to a negative acute phase reactant and has the potential to concurrently present the host's inflammatory state and nutritional status. It was identified as a prognostic biomarker in various inflammatory states and disorders.[7,8] Albumin has been linked with both anti-inflammatory, anti-thrombotic effects, and low levels were found associated with the incidence of cardiovascular events, which also represent one leading cause of adverse events in patients with COVID-19.[9]

The Fibrinogen/albumin ratio (FAR) is an inflammatory scoring system that is associated with the occurrence of thromboembolic incidents that are significantly associated in patients with COVID-19.[10] Fibrinogen and its degradation products can interact with endothelial cells, platelets, monocytes, and lymphocytes to participate in the inflammatory response of atherosclerosis, causing thrombosis, vascular endothelial injury, and hemorheological changes.[11]

The C-reactive protein-to-lymphocyte ratio (CLR) is an important predictor factor for ICU admission and the need for intensive mechanical ventilation. An elevated C-reactive protein-to-lymphocyte ratio indicates an increase in the systemic inflammatory response and a decrease in the immune response.[12]

The aim of this study was to determine the role of these three inflammatory scoring systems, CAR, FAR, CLR and their association with survival, critical comorbidities, and the occurrence of additional complications in the intensive care of these patients.

Materials and methods

This is a retrospective study conducted on the basis of data collected by the Department of Respiratory Center of Medicine. Ethical approval for the study was obtained from the Ethics Committee of Osijek University Hospital. This study, carried out between October and December 2020, included 137 patients with a diagnosis of COVID-19 and the need for treatment in the intensive care unit due to respiratory failure. The diagnosis of COVID-19 was based on the positivity of the real-time RT-PCR results. We retrospectively collected the patient's data from the hospital's medical database. We also obtained the demographic features of the patients (age, sex), co-morbidities, medical history, treatment history for COVID-19 during hospitalization, length of intensive care unit stay, laboratory values at the onset of hypoxia (blood levels of biochemical parameters including aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, lactate dehydrogenase

(LDH), D-dimeri, fibronogen, ferritin, C-reactive protein (CRP), and hemograms), steroid treatments.

Statistical analysis

A statistical package for the Social Sciences software (version 20.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. Normally distributed variables were presented as mean and standard deviation and non-normally distributed variables as median and interquartile range. Data were compared between the two groups using either a student's t-test (normal distribution) and a chi-square or Fisher's exact test was used for the dichotomous variables. The statistical significance was set at p-values <0.05.

Results

The study included 137 critically ill patients hospitalized in the ICU, suffering from COVID-19 infection with the need for mechanical ventilation. The average age of the respondents was 68 years (IQR 38-88). 86% of the respondents hospitalized in the intensive care unit had the need for invasive mechanical ventilation, the average duration of mechanical ventilation was 151.06 hours, while non-invasive mechanical ventilation was used with the non-remaining ones. 38 (27.7%) of the 137 patients survived. Comparisons of deaths and survivors with respect to treatment, comorbidity, and drugs are presented below, using the t-test for independent samples for continuous variables and the chi-square test for dichotomous variables. Comparisons of these two groups are shown in Tables 1 and 2.

Before comparing them, it was checked whether these two groups differed with respect to age and gender, variables that may also be associated with the treatment outcomes. Although the deceased patients were on average slightly older (M = 69.08 years, SD = 10.126 years) than the survivors (M = 66.11 years, SD = 13.387 years), the t-test for independent samples did not reveal a significant difference between them with respect to age, t (133) = 1.388, p = 0.167. In addition, in each of the groups there was an equal percentage of men and women, which is why the chi-square test did not reveal significant differences between them, χ^2 (1, N = 137) = 0.038, p = 0.845. As can be seen from Table 1, the chi-square test revealed a significant difference only with respect to the application of invasive mechanical ventilation, as expected among the deceased a higher percentage of them required the application of the same.

Table 1 Comparison of surviving and deceased patients with respect to comorbidity indicators and medications
Tablica 1. Usporedba preživjelih i umrlih bolesnika s obzirom na pokazatelje komorbiditeta i lijekove

	Discharged (*n* = 38) *Otpušteni*		Died (*n* = 99) *Preminuli*		
	No/*Ne*	Yes/*Da*	No/*Ne*	Yes/*Da*	(χ^2) /FET (p)
Hypertension *Hipertenzija*	9 (23.7%)	29 (76.3%)	19 (19.2%)	80 (80.8%)	0.341 (*0.559*)
Obesity *Pretilost*	31 (81.6%)	7 (18.4%)	88 (88.9%)	11 (11.1%)	1.286 (*0.257*)
COPD	35 (92.1%)	3 (7.9%)	93 (93.9%)	6 (6.1%)	0.151 (*0.698*)
Cancer *Karcinom*	36 (94.7%)	2 (5.3%)	94 (94.9%)	5 (5.1%)	0.003 (*0.960*)
Coronary disease *Koronarna bolest*	36 (94.7%)	2 (5.3%)	86 (86.9)	13 (13.1)	1.744 (*0.187*)
Cardiomyopathia *Kardiomiopatija*	36 (94.7%)	2 (5.3%)	89 (89.9%)	10 (10.1%)	0.804 (*0.370*)
Diabetes	24 (63.2%)	14 (36.8%)	62 (62.6%)	37 (37.4%)	0.003 (*0.954*)
CKD	33 (86.8%)	5 (13.2%)	76 (76.8%)	23 (23.2%)	1.714 (*0.190*)
STATIN	30 (78.9%)	8 (21.1%)	77 (77.8%)	22 (22.2%)	0.022 (*0.882*)
ACE/ARB	21 (55.3%)	17 (44.7%)	52 (52.5%)	47 (47.5%)	0.083 (*0.774*)
ASA	35 (92.1%)	3 (7.9%)	85 (85.9%)	14 (14.1%)	0.986 (*0.321*)
OAC	34 (89.5%)	4 (10.5%)	90 (90.9%)	9 (9.1%)	0.066 (*0.797*)

COPD = chronic obstructive pulmonary disease / *kronična opstruktivna plućna bolest*; CKD = chronic kidney disease / *kronična bolest bubrega*; ACE/ARB = ACE inhibitor/angiotensin receptor blocker / *ACE inhibitor/blokator angiotenzinskih receptora*; ASA = acetylsalicyl acid / *acetilsalicilna kiselina*; OAC = oral anticoagulans / *oralni antikoagulansi*

Table 2 Comparison of surviving and deceased patients with respect to treatment
Tablica 2. Usporedba preživjelih i umrlih bolesnika s obzirom na liječenje

	Discharged (*n* = 38) *Otpušteni*		Died (*n* = 99) *Preminuli*		
	No/*Ne*	Yes/*Da*	No/*Ne*	Yes/*Da*	(χ^2) /*FET (p)*
Mechanical ventilation *Mehanički respirator*					
HFNC	21 (55.3%)	17 (44.7%)	71 (71.1%)	28 (28.3%)	3.370 (*0.066*)
NIV	34 (89.5%)	4 (10.5%)	82 (82.8%)	17 (17.2%)	0.934 (*0.334*)
IMV	15 (39.5%)	23 (60.5%)	6 (6.1%)	93 (93.9%)	23.621 (*0.001*)
Treatments *Liječenje*					
ECMO	37 (97.4%)	1 (2.6%)	99 (100%)	0 (0.0%)	2.624 (*0.105*)
Remdesivir	21 (55.3%)	17 (44.7%)	64 (66.7%)	32 (33.3%)	1.526 (*0.217*)
Dexamethasone	18 (47.4%)	20 (52.6%)	40 (41.7%)	56 (58.3%)	0.361 (*0.548*)
Methylprednisolon	16 (42.1%)	22 (57.9%)	32 (33.3%)	64 (66.7%)	0.911 (*0.340*)
Tocilisumab	38 (100%)	0 (0%)	94 (97.9%)	2 (2.1%)	0.804 (*0.370*)
IVIG	38 (100%)	0 (0%)	94 (97.9%)	2 (2.1%)	0.804 (*0.370*)
CVVH	37 (97.4%)	1 (2.6%)	96 (100%)	0 (0.0%)	2.545 (*0.111*)

HFNC = high flow nasal cannul / *nosna kanila visokog protoka;* NIV = noninvasive ventilation /*neinvazivni respirator*; IMV = invasive mehanical ventilation */ invazivna mehanička ventilacija*; ECMO = extracorporeal membrane oxygenation / *ekstrakorporalna membranska oksigenacija*; IVIG = intravenous immunoglobulin therapy / *intravenozna terapija imunoglobulina*; CVVH = Continuous Veno-Venous Hemofiltration / *kontinuirana veno-venozna hemofiltracija*

In addition, the two groups were compared with respect to oxygen saturation on admission to the hospital. Although the deceased had lower oxygen saturation (M = 352.94, SD = 378.28) than the survivors (M = 414.61, SD = 402.82), this difference was not statistically significant. However, in both groups the standard deviations are high indicating a high variability in oxygen saturation upon admission. These two groups did not differ with respect to the comorbidity as presented in Table 2.

C-reactive protein/albumin ratio (CAR)

The median CRP/albumin ratio is 50.80, with 69 participants below and 69 above the median. The two groups were compared with respect to a number of collected indicators, where for continuous variables (e.g. oxygen saturation or laboratory indicators) a t-test was used for independent samples, while for dichotomous variables (e.g. drug treatment, etc.) either hi -square test (χ^2) or Fisher's exact test (FET). As can be seen from Table 3, in the group of subjects who were above the median CAR, there were significantly more of those with coronary heart disease compared to the participants from the group below the median CAR. In contrast, in the group below the median CAR, there were significantly more of those with complications, but fewer who died. Finally, the comparison of the two groups by t-test for independent samples with respect to the duration of mechanical ventilation (measured in hours) didn't reveal a significant difference between them t (133) = 1,484, p = 0,140, although it was longer in participants above the median (M = 176.97, SD = 159.88) than those below (M = 135.84, SD = 162.18).

Fibrinogen/albumin ratio (FAR)

The median fibrinogen /albumin ratio is 0.186, with 64 participants below and 74 above the median. Similar to the median CRP / albumin ratio, the two groups were compared with respect to a number of collected indicators, with t-test for independent samples used for continuous variables and chi-square test (χ^2) for dichotomous variables or Fisher's exact test (FET). The comparisons of these two groups are shown in Table 4. In the group of participants who were above its median in terms of FAR, there were significantly more those with sepsis compared to participants in the group below the median FAR. A difference was found between the two groups of participants at the significance limit (p = 0.077) with respect to pulmonary embolism, with participants below the median FAR having a higher incidence of pulmonary embolism than those above the median of this ratio.

Table 3 Comparison of participants below and above the median CAR ratio with respect to indicators measured as dichotomous variables

Tablica 3. Usporedba sudionika ispod i iznad medijana CAR omjera s obzirom na pokazatelje mjerene kao dihotomne varijable

	Lower CAR *Niži* (*n* = 69)		Higher CAR *Viši* (*n* = 69)		
	No *Ne*	Yes *Da*	No *Ne*	Yes *Da*	(χ^2) /*FET (p)*)
Comorbidity					
Hypertension *Hipertenzija*	16 (23.7%)	53 (76.8%)	12 (17.4%)	57 (82.6%)	0.717 (*0.397*)
Obesity *Pretilost*	59 (85.5%)	10 (14.5%)	60 (87%)	9 (13%)	0.061 (*0.805*)
COPD	62 (89.9%)	7 (10.1%)	66 (95.7%)	3 (4.3%)	1.72 (*0.189*)
Cancer *Karcinom*	65 (94.2%)	4 (5.8%)	66 (95.7%)	3 (4.3%)	0.15 (*0.698*)
Coronary disease *Koronarna bolest*	66 (95.7%)	3 (4.3%)	57 (82.6%)	12 (17.4%)	6.059 (*0.014*)
Cardiomyopathia *Kardiomiopatija*	60 (87.0%)	9 (13%)	66 (95.7%)	3 (4.3%)	3.286 (*0.070*)
Diabetes	44 (63.8%)	25 (36.2%)	44 (63.8%)	25 (36.2%)	0.000 (*1.000*)
CKD	54 (78.3%)	15 (21.7%)	56 (81.2%)	13 (18.8)	0.179 (*0.672*)
Complication *Komplikacija*					
PTE	34 (49.3%)	35 (50.7%)	46 (66.7%)	23 (33.3%)	4.280 (*0.039*)
Sepsis *Sepsa*	28 (55.1%)	31 (44.9%)	29 (42.0%)	40 (58.0%)	2.350 (*0.125*)
AKI	51 (75.0%)	18 (25.0%)	47 (68.1%)	22 (31.9%)	0.797 (*0.372*)
Mechanical ventilation *Mehanički ventilator*					
HFNC	47 (68.1%)	22 (31.9%)	45 (65.2%)	24 (34.8%)	0.130 (*0.718*)
NIV	61 (88.4%)	8 (11.6%)	54 (78.3%)	15 (21.7%)	2.557 (*0.110*)
IMV	12 (17.4%)	57 (82.6%)	9 (13.0%)	60 (87.0%)	0.505 (*0.477*)
Treatments *Liječenje*					
Vasoactive drugs	34 (50.0%)	34 (50.0%)	30 (43.5%)	39 (56.5%)	0.585 (*0.444*)
Outcome *Ishod*	Died *Preminuli*	Discharged *Otpušteni*	Died *Preminuli*	Discharged *Otpušteni*	
	44 (64.7%)	24 (35.3%)	54 (80.6%)	13 (19.4%)	4.284 (*0.038*)

CAR= CRP/albumin ratio / *omjer albumina*; COPD = chronic obstructive pulmonary disease / *kronična opstruktivna plućna bolest*; CKD = chronic kidney disease / *kronična bolest bubrega*; PTE = pulmonary thromboembolism / *plućna tromboembolija* ; AKI = acute kidney injury / *akutna ozljeda bubrega*; HFNC = high flow nasal cannul / *nosna kanila visokog protoka*; NIV = noninvasive ventilation / *neinvazivna ventilacija;* IMV = invasive mehanical ventilation / *invazivna mehanička ventilacija*

By comparing the two groups by t-test for independent samples with respect to the duration of mechanical ventilation (measured in hours), a significant difference was found between them t (133) = 2,710, p = 0,008, where it was longer in participants from the group above the median (M = 191.55, SD = 183.99) than those below (M = 117.73, SD = 122.97).

Table 4 Comparison of participants below and above the median FAR ratio with respect to indicators measured as dichotomous variables

Tablica 4. Usporedba sudionika ispod i iznad medijana, omjera FAR s obzirom na pokazatelje mjerene kao dihotomne varijable

	Lower FAR *Niži* (*n* = 64)		Higher FAR *Viši* (*n* = 74)		
	No/*Ne*	Yes/*Da*	No/*Ne*	Yes/*Da*	(χ^2) /*FET (p)*
Komorbiditet					
Hypertension *Hipertenzija*	12 (18,8%)	52 (81,2%)	16 (21,6%)	58 (78,4%)	0,175 (*0,676*)
Obesity *Pretilost*	54 (84,4%)	10 (15,6%)	65 (87,8%)	9 (12,2%)	0,347 (*0,556*)
COPD	57 (89,1%)	7 (10,9%)	71 (95,9%)	3 (4,1%)	2,419 (*0,120*)
Cancer *Karcinom*	59 (92,2%)	5 (7,8%)	72 (97,3%)	2 (2,7%)	1,861 (*0,173*)
Coronary disease *Koronarna bolest*	58 (90,6%)	6 (9,4%)	65 (87,8%)	9 (12,2%)	0,275 (*0,600*)
Cardiomyopathia *Kardiomiopatija*	57 (89,1%)	7 (10,9%)	69 (93,3%)	5 (6,8%)	0,756 (*0,385*)
Hypertension *Hipertenzija*	42 (63,6%)	22 (34,4%)	46 (62,2%)	28 (37,8%)	0,178 (*0,670*)
CKD	47 (73,4%)	17 (26,6%)	63 (85,1%)	11 (14,9%)	2,904 (*0,088*)
Mechanical ventilation *Mehanička ventilacija*					
HFNC	45 (70,3%)	19 (29,7%)	47 (63,5%)	27 (36,5%)	0,714 (*0,398*)
NIV	55 (85,9%)	9 (14,1%)	60 (81,1%)	14 (18,9%)	0,583 (*0,445*)
IMV	9 (14,1%)	55 (85,9%)	12 (16,2%)	62 (83,2%)	0,123 (*0,725*)
Complications *Komplikacije*					
PTE	32 (50,0%)	32 (50,0%)	48 (64,9%)	26 (35,1%)	3,112 (*0,077*)
Sepsis *Sepsa*	37 (57,8%)	27 (42,2%)	30 (40,5%)	44 (59,5%)	4,099 (*0,043*)
AKI	49 (77,8%)	14 (22,2%)	49 (66,2%)	25 (33,8%)	2,234 (*0,135*)
Treatments *Liječenje*					
Vasoactive drugs *Vazoaktivni lijekovi*	31 (49,2%)	32 (50,8%)	33 (44,6%)	41 (55,4%)	0,291 (*0,590*)
Outcome *Ishod*	Died *Preminuli*	Discharged *Otpušteni*	Died *Preminuli*	Discharged *Otpušteni*	
	44 (69,8%)	19 (30,2%)	54 (75,0%)	18 (25,0%)	0,449 (*0,509*)

FAR = fibrinogen/albumin ratio / *omjer fibrinogena/albumina*; COPD = chronic obstructive pulmonary disease / *kronična opstruktivna plućna bolest;* CKD = chronic kidney disease / *kronična bolest bubrega*; HFNC = high flow nasal cannul / *nosna kanila visokog protoka*; NIV = noninvasive ventilation / *neinvazivna ventilacija*; IMV = invasive mehanical ventilation / *invazivna mehanička ventilacija*; PTE = pulmonary thromboembolism / *plućna tromboembolija*; AKI = acute kidney injury / *akutna ozljeda bubrega*

C-reactive protein/Lymphocyte ratio (CLR)

The median CRL is 24.97, with 57 participants below and 57 above the median. Similar to the previous ratios, the two groups were compared with respect to a number of collected indicators. As can be seen from Table 5, the two groups of participants differed statistically significantly with respect to the three indicators. In particular, in the group of participants who were above its median in terms of CLR, there were significantly more those with coronary heart disease, acute renal failure, and those

with sepsis compared to participants in the group below the median CLR. In addition, a difference was found between the two groups of participants at the significance limit with respect to the presence of diabetes (p = 0.079), with more in the group below the median than in the group above the median of the stated ratio. The group above the median had statistically significantly higher levels of CRP, Trc, fibrin and LDH, while the group below the median had significantly higher levels of lymphocytes. The magnitudes of the effects for the statistically significant differences found ranged from small and moderate for CRP and platelets respectively, and to large for fibrinogen and lymphocite. Also, a difference was found between the two groups at the significance limit with respect to D-dimers (p = 0.062). Again, the group above the median CLR had a higher level than the participants in the group below the median.

Table 5 Comparison of participants below and above the median CRL ratio with respect to indicators measured as dichotomous variables

Tablica 5. Usporedba sudionika ispod i iznad medijana CRL omjera s obzirom na pokazatelje mjerene kao dihotomne varijable

	Ispod medijana *Below median* (*n* = 57)		Iznad medijana *Above median* (*n* = 57)		
	No/*Ne*	Yes/*Da*	No/*Ne*	Yes/*Da*	(χ^2) /*FET (p)*
Comorbidity *Komorbiditet*					
Hypertension *Hipertenzija*	13 (22,8%)	44 (77,2%)	11 (19,3%)	46 (80,7%)	0,211 (*0,646*)
Obesity *Pretilost*	50 (87,7%)	7 (12,3%)	49 (86,0%)	8 (14,0%)	0,077 (*0,782*)
COPD	51 (89,5%)	6 (10,5%)	54 (94,7%)	3 (5,3%)	1,086 (*0,297*)
Cancer *Karcinom*	55 (96,5%)	2 (3,5%)	52 (91,2%)	5 (8,8%)	1,370 (*0,242*)
Coronary disease *Koronarna bolest*	55 (96,5%)	2 (3,5%)	48 (84,2%)	9 (15,8)	4,930 (*0,026*)
Cardiomyopathia *Kardiomiopatija*	50 (87,7%)	7 (12,3%)	54 (94,7%)	3 (5,3%)	1,754 (*0,185*)
Diabetes	32 (56,1%)	25 (43,9%)	41 (71,9%)	16 (28,1%)	3,085 (*0,079*)
CKD	44 (77,2%)	13 (22,8%)	48 (84,2%)	9 (15,8%)	0,901 (0,342)
Mechanical ventilation *Mehanička ventilacija*					
HFNC	42 (73,7%)	15 (26,3%)	35 (61,4%)	22 (38,6%)	1,961 (*0,161*)
NIV	47 (82,5%)	10 (17,5%)	47 (82,5%)	10 (17,5%)	0,000 (*1,000*)
IMV	8 (14,0%)	49 (86,0%)	11 (19,3%)	46 (80,7%)	0,568 (*0,451*)
Complications *Komplikacije*					
PTE	26 (45,6%)	31 (54,5%)	38 (66,7%)	19 (33,3%)	5,130 (*0,024*)
AKI	46 (82,1%)	10 (17,9%)	35 (61,4%)	22 (38,6%)	5,985 (0,014)
Sepsis *Sepsa*	35 (61,4%)	22 (38,6%)	21 (36,8%)	36 (63,2%)	6,879 (*0,009*)
Treaments *Liječenja*					
Vasoactive drugs	27 (49,1%)	28 (50,9%)	22 (38,6%)	35 (61,4%)	1,253 (*0,263*)
Outcome *Ishod*	Died *Preminuli*	Discharged *Otpušteni*	Died *Preminuli*	Discharged *Otpušteni*	
	39 (69,6%)	17 (30,4%)	45 (81,8%)	10 (18,2%)	2,235 (*0,135*)

CLR = CRP/lymh ratio /*omjer limfa*; COPD = chronic obstructive pulmonary disease / *kronična opstruktivna plućna bolest*; CKD = chronic kidney disease / *kronična bolest bubrega*; HFNC = high flow nasal cannul / *nosna kanila visokog protoka*; NIV = noninvasive ventilation/*neinvazivna ventilacija*; IMV = invasive mehanical ventilation / *invazivna mehanička ventilacija*; PTE = pulmonary thromboembolism / *plućna tromboembolija*; AKI = acute kidney injury / *akutna ozljeda bubrega*

Discussion

The period of the COVID-19 infection pandemic was characterized by a desire to find parameters that could predict patients with an increased risk of an adverse outcome as early as possible in order to direct treatment. Like this study, most studies to date are primarily based on retrospective data given the unforeseen course of the pandemic to conduct controlled randomized trials.

Previous research has shown that elevated CAR values are associated with more severe forms of COVID-19 infection.[12] In our work, unlike other studies, we analyzed critically ill patients who were treated in the intensive care unit and need for mechanical ventilation. It was found that lower values, i.e. values below the median, are associated with the existence of complications, i.e. with the occurrence of thromboembolic incidents and sepsis. The results were expected given that lower albumin values were associated with a reduced antithrombotic and anti-inflammatory response. Also in line with the previous research, which argued that higher CAR values were associated with coronary heart disease complex, this study considered only patients with severe COVID-19 infection.[13]

When we talk about the fibrinogen/albumin ratio, FAR is used as an effective marker of inflammation, and tends to be elevated in various conditions, such as severe infections and malignancies.[14] Increased FAR levels may be associated with cytokine storms caused by virus invasion. According to previous studies[6,15], elevated FAR values were associated with the expected occurrence of pulmonary thromboembolism and prolonged duration of mechanical ventilation. Analyzing the latter CLR, it can be said that higher values are expected to be associated with a stronger inflammatory response. Those with a higher ratio were also more likely to have coronary and diabetes, said in favor of a pronounced chronic inflammatory process. It is stated in accordance with similar research.[16]

In conclusion, we can say that the obtained results are in accordance with the expected, i.e. pathophysiological processes in critically ill patients with COVID-19 infection in ICU. A limiting factor is that it is a retrospective study of a center with a small sample of respondents. Certainly these inflammatory scoring systems have a role to play in assessing the movement of the clinical picture in critically ill patients with COVID-19 infection.

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