Wien Klin Wochenschr (2022) 134:377–384
https://doi.org/10.1007/s00508-021-01999-5

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Clinical and prognostic significance of C-reactive protein to albumin ratio in hospitalized coronavirus disease 2019 (COVID-19) patients

Data on 2309 patients from a tertiary center and validation in an independent cohort

Marko Lucijanić · Josip Stojić · Armin Atić · Tomislav Čikara · Besa Osmani · Mislav Barišić-Jaman · Ana Andrilović · Petra Bistrović · Anamarija Zrilić Vrkljan · Marko Lagančić · Marko Milošević · Ivan Vukoja · Lovorka Đerek · Tomo Lucijanić · Nevenka Piskač Živković

Received: 13 October 2021 / Accepted: 18 December 2021 / Published online: 17 January 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Austria, part of Springer Nature 2022

Summary C-reactive protein (CRP) and albumin are inflammation sensitive parameters that are regulated by interleukin-6 inflammatory pathways. The CRP to albumin ratio (CAR) integrates these two into a potent clinical parameter whose clinical and prognostic association in the context of coronavirus disease 2019 (COVID-19) have not been well defined. We aimed to investigate the clinical and prognostic significance of CAR in the context of COVID-19 infection.
We retrospectively analyzed 2309 consecutive COVID-19 patients hospitalized at a tertiary level hospital in the period from March 2020 to March 2021 who had baseline data for a CAR assessment. Findings were validated in an independent cohort of 1155 patients hospitalized from March 2021 to June 2021.
The majority of patients (85.8%) had severe or critical COVID-19 on admission. Median CRP, albumin and CAR levels were 91 mg/L, 32 g/L and 2.92, respectively. Higher CAR was associated with a tendency for respiratory deterioration during hospitalization, increased requirement of high-flow oxygen treatment

Supplementary Information The online version of this article (https://doi.org/10.1007/s00508-021-01999-5) contains supplementary material, which is available to authorized users.

M. Lucijanić, MD PhD (✉)
Hematology Department, University Hospital Dubrava, Av. Gojka Suska 6, 10000 Zagreb, Croatia

School of Medicine, University of Zagreb, Zagreb, Croatia
markolucijanic@yahoo.com

M. Lucijanić, MD PhD · J. Stojić · A. Atić · T. Čikara · B. Osmani · M. Barišić-Jaman · A. Andrilović · P. Bistrović · A. Zrilić Vrkljan · M. Lagančić · M. Milošević · L. Đerek · T. Lucijanić · N. Piskač Živković
Primary respiratory and intensive care center, University Hospital Dubrava, Zagreb, Croatia

J. Stojić · A. Atić · A. Andrilović · M. Lagančić
Department of Emergency Medicine, University Hospital Dubrava, Zagreb, Croatia

T. Čikara · P. Bistrović
Cardiology Department, University Hospital Dubrava, Zagreb, Croatia

B. Osmani
Nephrology Department, University Hospital Dubrava, Zagreb, Croatia

M. Barišić-Jaman · M. Milošević
Department of Gastroenterology, Hepatology and Clinical Nutrition, University Hospital Dubrava, Zagreb, Croatia

A. Zrilić Vrkljan · T. Lucijanić
Endocrinology Department, University Hospital Dubrava, Zagreb, Croatia

I. Vukoja
Gastroenterology and nephrology Department, General County Hospital Požega, Požega, Croatia

Faculty of Medicine Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

L. Đerek
Clinical Department for Laboratory Diagnostics, University Hospital Dubrava, Zagreb, Croatia

N. Piskač Živković
Pulmology Department, University Hospital Dubrava, Zagreb, Croatia

and mechanical ventilation, higher occurrence of bacteriemia, higher occurrence of deep venous thrombosis, lower occurrence of myocardial infarction, higher 30-day mortality and higher postdischarge mortality rates. We defined and validated four CAR prognostic categories (< 1.0, 1.0–2.9, 3.0–5.9 and ≥ 6.0) with distinct 30-day survival. In the series of multivariate Cox regression models we could demonstrate robust prognostic properties of CAR that was associated with inferior 30-day survival independently of COVID-19 severity, age and comorbidities and additionally independently of COVID-19 severity, CURB-65 and VACO index in both development and validation cohorts. The CAR seems to have a good potential to improve prognostication of hospitalized COVID-19 patients.

Keywords Thromboinflammation · SARS-CoV-2 · Prognosis · IL-6 · Pneumonia

Introduction

Pneumonia and subsequent respiratory insufficiency caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are leading reasons for hospitalization and high morbidity and mortality observed in coronavirus disease 2019 (COVID-19) patients [1, 2]. Due to strong inflammatory response mediated through interleukin (IL)-6, a subset of patients develop severe or critical symptoms and experience unfavorable clinical outcomes [3]. Severe or critical disease and hospitalization rates may vary depending on the dominant circulating virus strain, number of tested individuals and vaccination status of the population [4] and were reported to be 15–20% in the large cohort of patients at the start of the pandemic [2]. Clinical deterioration in these individuals developing due to hyperinflammatory response can potentially be modified using immunosuppressive drugs [5–7].

Among other parameters that are affected by strong inflammatory response to the SARS-CoV-2 infection, C-reactive protein (CRP) and albumin are easy to obtain and widely available. Both parameters are produced in the liver and regulated by IL-6 promoted inflammation [8], although CRP is positively affected and albumin negatively affected by this process. These parameters are thus commonly deranged among other liver blood tests during the COVID-19 infection [9]. The CRP to albumin ratio (CAR) incorporates deviations of these parameters into a single direction and has been shown to be prognostic of more severe disease and higher mortality if elevated in COVID-19 patients [10–13]. These findings resemble those observed in the context of other chronic inflammatory diseases [14–17]. Nevertheless, clinical associations of CAR in COVID-19 patients outside respiratory status and death and its prognostic significance in relationship to established prognostic scores have not been investigated so far. This is the reason why we aimed to investigate the clinical and prognostic roles of CAR in a large cohort of hospitalized COVID-19 patients treated in our institution that we present in this paper.

Patients and methods

We retrospectively analyzed a total of 2309 consecutive COVID-19 patients hospitalized in our institution in the period from March 2020 to March 2021 with available data for CAR assessment on admission. We further validated our findings in an independent cohort of 1155 patients treated in our institution in period from March 2021 to June 2021.

Our institution is a clinical hospital that was repurposed as a regional tertiary COVID-19 center during the pandemic. All patients had a positive polymerase chain reaction or rapid antigen COVID-19 test prior to hospital admission. All patients were adults and of white race. Pregnant women were only occasionally treated as other institutions served as gynecologic referral centers. Patients were treated according to the contemporary guidelines. Only index hospitalizations with acute COVID-19 were investigated. Clinical and laboratory data used in this paper are a part of a hospital registry project and were obtained through analysis of electronic and written medical records. The study was approved by the Institutional Review Board.

The severity of COVID-19 on admission was graded as mild, moderate, severe and critical based on the World Health Organization (WHO) recommendations [18]. Comorbidities were assessed as individual entities and were summarized using the Charlson comorbidity index. The CRP (normal range < 5 mg/L) and albumin (normal range 40–48 g/L) concentrations were determined in addition to other hematological and clinical parameters. The CAR was calculated as CRP (mg/L) to albumin (g/L). The CAR values were stratified at median value (2.92) for the purpose of comparison with clinical characteristics and clinical outcomes presented in Tables 1 and 2. Mortality and other clinical outcomes were assessed from the start of hospitalization. The modified early warning score (MEWS) was used to quantify COVID-19 symptom severity. Confusion, urea, respiratory rate, blood pressure and 65 years of age (CURB-65) and Veterans Health Administration COVID-19 (VACO) index were used as prognostic risk scores and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used for estimated glomerular filtration rate (eGFR) estimation.

Statistical methods

Normality of distribution of numerical variables was tested using the Shapiro-Wilk test. All analyzed variables had non-normal distribution and were presented as median and interquartile range (IQR) and were compared between groups using the Mann-Whitney *U*-test or Kruskal-Wallis one-way analysis of

Table 1 Patient characteristics on admission and their relationship with CRP to albumin ratio (CAR) stratified at median

	Overall (*N* = 2309)	CAR ≤ 2.92 (*N* = 1155)	CAR > 2.92 (*N* = 1154)	*P*-value
Age (years)	73 (64–81)	72 (62–81)	73 (64–82)	*P* = 0.002 [a]
Male sex	1326 (57.4%)	616 (53.3%)	710 (61.5%)	*P* < 0.001 [a]
Day of disease on admission	5 (1–9)	3 (1–8)	6 (2–10)	*P* < 0.001 [a]
ECOG status on admission	3 (1–4)	2 (1–3)	3 (2–4)	*P* < 0.001 [a]
Pneumonia	2075 (89.9%)	965 (83.5%)	1110 (96.2%)	*P* < 0.001 [a]
Oxygen therapy	1940 (84%)	870 (75.3%)	1070 (92.7%)	*P* < 0.001 [a]
Low molecular weight heparin	2012 (87.1%)	986 (85.4%)	1026 (88.9%)	*P* = 0.011 [a]
Corticosteroids	1720 (74.5%)	795 (68.8%)	925 (80.2%)	*P* < 0.001 [a]
Remdesivir	248 (10.7%)	93 (8.1%)	155 (13.4%)	*P* < 0.001 [a]
MEWS score	2 (1–4)	2 (1–3)	3 (2–4)	*P* < 0.001 [a]
COVID-19 severity				Overall *P* < 0.001 [a]
Mild	218 (9.4%)	179 (15.5%)	39 (3.4%)	*P* < 0.001 [a]
Moderate	110 (4.8%)	79 (6.8%)	31 (2.7%)	*P* < 0.001 [a]
Severe	1611 (69.8%)	809 (70%)	802 (69.5%)	*P* = 0.775
Critical	370 (16%)	88 (7.6%)	282 (24.4%)	*P* < 0.001 [a]
Co-infection on admission	337 (14.6%)	151 (13.1%)	186 (16.1%)	*P* = 0.038 [a]
Charlson comorbidity index	4 (3–6)	4 (3–6)	4 (3–6)	*P* = 0.774
Nm. of drugs in chr. therapy	5 (3–8)	6 (3–9)	5 (2–8)	*P* < 0.001 [a]
Arterial hypertension	1621 (70.2%)	828 (71.7%)	793 (68.7%)	*P* = 0.119
Diabetes mellitus	731 (31.7%)	365 (31.6%)	366 (31.7%)	*P* = 0.953
Hyperlipoproteinemia	555 (24%)	319 (27.6%)	236 (20.5%)	*P* < 0.001[a]
Obesity	651 (28.2%)	336 (29.1%)	315 (27.3%)	*P* = 0.338
Cong. heart failure	377 (16.3%)	206 (17.8%)	171 (14.8%)	*P* = 0.049 [a]
Atrial fibrillation	415 (18%)	220 (19%)	195 (16.9%)	*P* = 0.178
Coronary artery disease	367 (15.9%)	217 (18.8%)	150 (13%)	*P* < 0.001[a]
Previous CVI	255 (11%)	129 (11.2%)	126 (10.9%)	*P* = 0.848
Previous myocardial inf	216 (9.4%)	126 (10.9%)	90 (7.8%)	*P* = 0.010[a]
Chr. kidney disease	295 (12.8%)	163 (14.1%)	132 (11.4%)	*P* = 0.054
COPD	175 (7.6%)	102 (8.8%)	73 (6.3%)	*P* = 0.023[a]
Chronic liver disease	83 (3.6%)	51 (4.4%)	32 (2.8%)	*P* = 0.034[a]
Liver cirrhosis	38 (1.6%)	26 (2.3%)	12 (1%)	*P* = 0.022[a]
Active malignancy	273 (11.8%)	130 (11.3%)	143 (12.4%)	*P* = 0.398
Metastatic malignancy	173 (7.5%)	76 (6.6%)	97 (8.4%)	*P* = 0.096
History of malignancy	434 (18.8%)	211 (18.3%)	223 (19.3%)	*P* = 0.516
Dementia	429 (18.6%)	195 (16.9%)	234 (20.3%)	*P* = 0.036[a]
Alcohol use	142 (6.1%)	66 (5.7%)	76 (6.6%)	*P* = 0.385
Smoking	141 (6.1%)	79 (6.8%)	62 (5.4%)	*P* = 0.141
IL-6 (pg/mL)	55.6 (22.3–124.7)	29.6 (14.2–72)	78.4 (34.8–159.6)	*P* < 0.001[a]
Procalcitonin (ng/mL)	0.22 (0.09–0.76)	0.12 (0.07–0.29)	0.45 (0.18–1.56)	*P* < 0.001[a]
WBC ($x10^9$/L)	8.1 (5.7–11.3)	7 (5–10)	9.1 (6.6–12–8)	*P* < 0.001[a]
Abs. lymphocytes ($x10^9$/L)	0.8 (0.55–1.2)	0.91 (0.6–1.35)	0.7 (0.5–1)	*P* < 0.001[a]
Hemoglobin (g/L)	127 (112–140)	128 (113–142)	127 (111–195)	*P* < 0.044[a]
Platelets ($x10^9$/L)	219 (161–298)	208 (153–287)	231 (171–308)	*P* < 0.001[a]
CRP (mg/L)	91.1 (43.1–153.8)	43.1 (17.8–67.2)	153.8 (120–207.2)	*P* < 0.001[a]
Ferritin (µg/L)	711 (390.8–1292)	526 (283–932)	945 (562–1614)	*P* < 0.001[a]
D-dimers (mg/L FEU)	1.4 (0.74–3.6)	1.16 (0.63–2.73)	1.64 (0.88–4.24)	*P* < 0.001[a]
CKD-EPI eGFR (ml/min/1.73 m^2)	72.7 (46.3–91.9)	75.4 (48.8–93.1)	70.2 (43.4–90)	*P* < 0.001[a]
LDH (U/L)	344 (252–468.5)	296 (220–390)	404 (297–537)	*P* < 0.001[a]

Table 1 (Continued)

	Overall (N= 2309)	CAR ≤ 2.92 (N= 1155)	CAR > 2.92 (N= 1154)	P-value
AST (U/L)	41 (29–64)	37 (25–56)	46 (32–72)	P< 0.001[a]
ALT (U/L)	31 (19–51)	28 (17–46)	34 (21–57)	P< 0.001[a]
GGT (U/L)	43 (24–85)	39 (22–75)	48 (27–96)	P< 0.001[a]
ALP (U/L)	72 (55–98)	70 (55–93)	75 (56–104)	P< 0.001[a]
Total bilirubin (µmol/L)	11.3 (8.6–15.7)	11.1 (8.5–15.6)	11.3 (8.6–15.8)	P= 0.405
Albumin (g/L)	32 (28–35)	34 (30–36)	30 (27–33)	P< 0.001[a]
PT (%)	100 (89–109)	101 (92-110)	98 (87–108)	P< 0.001[a]

Data are presented as median and interquartile range for numerical variables and as frequency and percentage for categorical variables
CAR C reactive protein to albumin ratio, *ECOG* Eastern Cooperative Oncology Group, *MEWS* modified early warning score, *nm.* number, *chr.* chronic; *cong.* congestive, *CVI* cerebrovascular insult, *COPD* chronic obstructive lung disease, *WBC* white blood cells, *abs.* absolute, *CRP* C-reactive protein, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *eGFR* estimated glomerular filtration rate, *LDH* lactate dehydrogenase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyl transferase, *ALP* alkaline phosphatase, *PT* prothrombin time
[a]Statistically significant at level P< 0.05. No P-value adjustments for multiple testing were performed

Table 2 Clinical outcomes of index COVID-19 hospitalization/postdischarge in relationship to C-reactive protein to albumin ratio (CAR)

	Overall (N= 2309)	CAR ≤ 2.92 (N= 1155)	CAR > 2.92 (N= 1154)	P-value
Length of hospitalization (days)	10 (6–16)	10 (6–17)	10 (6–17)	P= 0.407
Intensive care unit	678 (29.4%)	246 (21.3%)	432 (37.4%)	P< 0.001[a]
High-flow oxygen th	536 (23.2%)	164 (14.2%)	372 (32.2%)	P< 0.001[a]
Mechanical ventilation	512 (22.2%)	161 (13.9%)	351 (30.4%)	P< 0.001[a]
Immobilization ≥ 7 days	1098 (47.6%)	443 (38.4%)	655 (56.8%)	P< 0.001[a]
Venous thromboembolism	146 (6.3%)	64 (5.5%)	82 (7.1%)	P= 0.123
Pulmonary embolism	100 (4.3%)	49 (4.2%)	51 (4.4%)	P= 0.835
Deep venous thrombosis	56 (2.4%)	18 (1.6%)	38 (3.3%)	P= 0.007[a]
Arterial thrombosis	121 (5.2%)	76 (6.6%)	45 (3.9%)	P= 0.004[a]
Acute myocardial infarction	38 (1.6%)	27 (2.3%)	11 (1%)	P= 0.009[a]
Acute cerebrovascular insult	49 (2.1%)	29 (2.5%)	20 (1.7%)	P= 0.195
Bleeding	187 (8.1%)	97 (8.4%)	90 (7.8%)	P= 0.598
Major bleeding	74 (3.2%)	34 (2.9%)	40 (3.5%)	P= 0.481
Bacterial sepsis	276 (12%)	99 (8.6%)	177 (15.3%)	P< 0.001[a]
30-day survival rate	63.5%	75.1%	52%	P< 0.001[a]
Hospital readmission rate[b]	43 (3%)	27 (3.2%)	16 (2.7%)	P= 0.625
6-months post-discharge survival rate[b]	91.6%	93.8%	88.6%	P= 0.014[a]

Data are presented as median and interquartile range for numerical variables and as frequency and percentage for categorical variables
CAR C-reactive protein to albumin ratio, *th.* therapy
[a]Statistically significant at level P< 0.05. No P-value adjustments for multiple testing were performed
[b]Evaluated only in index hospitalization survivors (N= 1443)

variance (ANOVA) test where appropriate. Categorical variables were presented as frequencies and percentages and were compared between groups using the χ^2-test or the Fisher test where appropriate. Survival analyses were based on the Kaplan-Meier method. Univariate survival analyses were performed using the Cox-Mantel version of the log-rank test [19, 20] and the Cox regression analysis. Multivariate survival analyses were performed using the Cox regression analysis while simultaneously controlling for all included parameters. P-values < 0.05 were considered statistically significant. All analyses were performed using the MedCalc statistical software version 20.008 (MedCalc Software Ltd, Ostend, Belgium).

Results

Patient characteristics and their associations with CRP to albumin ratio

A total of 2309 hospitalized COVID-19 patients treated in the period from 3/2020 to 3/2021 were analyzed. Median age was 73 years IQR (64–81 years). There were 1326 (57.4%) males. Median Charlson comorbidity index was 4 points IQR (3–6). Majority (1981, 85.8%) of patients presented with severe or critical severity of COVID-19 symptoms on admission. During hospitalization, a total of 678 (29.4%) patients required intensive care unit treatment, 512 (22.2%) required mechanical ventilation and 866 (37.4%) died. The 30-day survival rate was 63.5%.

Median CRP, albumin and CAR levels were 91 mg/L IQR (43.1–153.8), 32 g/L IQR (28–35) and 2.92 IQR (1.33–5.23), respectively. Both CRP (HR = 1.003; $P < 0.001$) and albumin (HR 0.91; $P < 0.001$), age (HR 1.04; $P < 0.001$) and male sex (HR 1.23; $P = 0.004$) showed significant mutually independent association with 30-day survival in our cohort of patients, providing a rationale for their analysis as a ratio in the context of COVID-19. Patient characteristics stratified according to the CAR median value are shown in Table 1.

Patients with higher CAR were statistically significantly more likely to be older, of male sex, to have more severe COVID-19 on admission and worse functional status, to present later during the disease course, have pneumonia, require oxygen supplementation and to have coinfection on admission. They were also more likely to receive specific treatment (corticosteroids, LMWH, remdesivir). As expected from the CAR definition, patients with a higher CAR were significantly more likely to have a higher CRP and lower albumin concentrations. Also, patients with higher CAR had higher IL-6 concentrations (IL-6 concentrations stratified over CAR prognostic categories defined below are shown in Fig. 1a). Higher CAR was also associated with a higher procalcitonin, higher white blood cells, lower absolute lymphocyte count, higher platelets, higher ferritin, higher D-dimers, higher lactate dehydrogenase, higher aspartate aminotransferase, higher alanine aminotransferase, higher gamma-glutamyl transferase, higher alkaline phosphatase, lower prothrombin time, lower hemoglobin and lower eGFR ($P < 0.05$ for all analyses).

Charlson comorbidity index was similar regarding CAR level ($P = 0.774$); however, patients with higher CAR had a lower number of drugs in chronic treatment, were less likely to have hyperlipoproteinemia, congestive heart failure, coronary artery disease, previous myocardial infarction, chronic liver disease, liver cirrhosis and chronic obstructive lung disease but were more likely to have dementia ($P < 0.05$ for all analyses).

Clinical outcomes during and after hospitalization and their associations with CRP to albumin ratio

Associations of CAR with clinical outcomes are presented in Table 2. Median hospital stay did not significantly differ between patients with lower and higher CAR values; however, patients with higher CAR were significantly more likely to require intensive care unit treatment, high-flow oxygen therapy, and mechanical ventilation. Higher CAR was associated with prolonged immobilization (defined as ≥ 7 days without bathroom privileges) and development of deep venous thrombosis. Conversely, higher CAR patients were less likely to experience arterial thrombosis, driven by lower frequency of myocardial infarction and without significant difference in cerebrovascular insult rates. Patients with higher CAR were also more likely to experience bacterial sepsis during hospital stay. There was no significant difference in bleeding nor pulmonary embolism rates. Patients with higher CAR on admission stratified at median were significantly more likely to experience inferior 30-day survival rates (52% vs. 75%; $P < 0.001$) and lower 6-month posthospital discharge survival rates (88.6% vs. 93.8%; $P = 0.014$).

We further investigated prognostic properties of CAR for 30-day survival. When stratified at deciles, CAR showed a gradually worsening prognosis with each increasing decile (Supplementary Figure S1). By analyzing the course of survival curves and associated hazard ratios, we were able to categorize patients into 4 categories with a distinct prognosis, presented in Fig. 1b, and that corresponded to CAR values of < 1.0, 1.0–2.9, 3.0–5.9 and ≥ 6.0. Patients belonging to these groups experienced 30-day survival rates of 86%, 68%, 58% and 43%, respectively. There were mutually significant survival differences present between all four

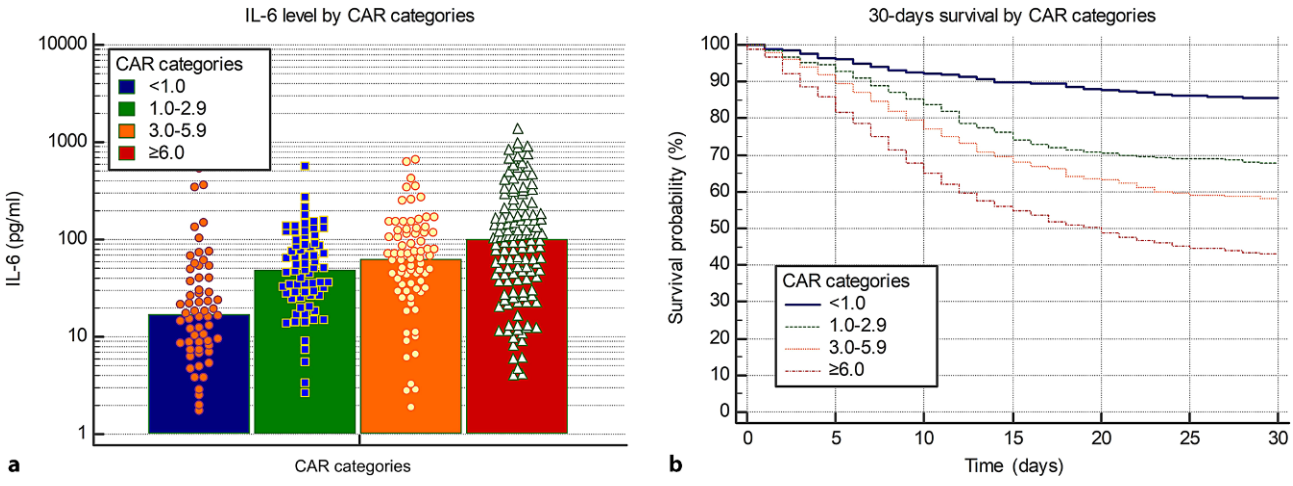

Fig. 1 **a** Median IL-6 concentrations and **b** 30 days from admission survival stratified according to the C-reactive protein to albumin ratio (CAR) prognostic categories

categories. Associated unadjusted hazard ratios in comparison to the first category were 2.47 (95% CI 1.88–3.25), 3.42 (95% CI 2.63–4.49) and 5.38 (95% CI 4.11–7.05) for 2nd, 3rd and 4th prognostic categories.

We could demonstrate robust independent prognostic properties of CAR prognostic categories in a series of multivariate Cox regression models. CAR prognostic categories remained significantly associated with 30-day survival after adjusting for age, sex, Charlson comorbidity index, COVID-19 severity and duration of symptoms on admission as shown in Supplementary Table S1. CAR prognostic categories also remained significantly associated with 30-day survival when compared to other relevant COVID-19 prognostic scores (WHO COVID-19 severity, CURB-65, VACO index) as shown in Supplementary Table S2. A similar model with prognostic indices stratified to their prognostic categories is shown in Supplementary Table S3. These analyses show that CAR prognostic properties are independent of disease severity and duration, age and comorbidities as well as of other prognostic scores.

Validation of CRP to albumin ratio prognostic properties in an independent cohort of patients

We further analyzed robustness of association of CAR prognostic categories with survival in an independent cohort of 1155 patients subsequently treated in our institution in the period from 3/2021 to 6/2021. In comparison to patients in the development cohort, patients in the validation cohort were significantly younger (median age 69 vs. 73 years; $P<0.001$), had lower Charlson comorbidity index (median 3 vs. 4; $P<0.001$), higher frequency of severe or critical COVID-19 on admission (91.5% vs. 85.8%; $P<0.001$) but were of similar sex distribution (58.4% vs. 57.4% males; $P=0.602$). The 30-day survival rate in the validation cohort was 68.3%.

Patients in the validation cohort had similar CAR levels on presentation as patients in the development cohort (median 27.8 vs. 29.2; $P=0.620$). When stratified to CAR prognostic categories defined above, significantly different 30-day survival could be observed in the validation cohort as well ($P<0.001$), with distinct survival course associated with each category as shown in Supplementary Figure S2. In the multivariate analyses, CAR prognostic categories retained statistical significance and demonstrated same prognostic properties in the validation cohort as observed in the development cohort as shown in Supplementary Table S1 and Supplementary Table S2.

Discussion

CRP and albumin seem to depict different pathophysiologic processes and different aspects of inflammation. In contrast to CRP where elevation reflects the severity of acute phase inflammatory response, decrease in albumin can reflect different processes including inflammation, nephrotic range proteinuria, damaged liver function and worse nutritional status [21]. As we demonstrate, both CRP and albumin are independent of age, sex and each other associated with adverse outcome, providing rationale to investigate their ratio as a separate parameter. In indirect comparison to CRP alone, CAR seems to have better prognostic properties achieving higher AUC values in the multivariate models presented in Supplementary Table S1 (AUC for CAR 0.768 vs. 0.764; data not shown). CAR is associated with a number of unfavorable features in hospitalized COVID-19 patients. Among them, older age, male sex, more severe COVID-19 and worse functional impairment are well known negative prognostic factors that reflect worse clinical outcomes. CAR is also associated with features of stronger inflammation (elevated IL-6, D-dimers, WBC ...) and other liver blood test derangements. It is notable, however, that higher CAR values are observed among patients with longer duration of symptoms at the time of hospital admission and no significant association with bilirubin levels are present. These findings imply that more developed inflammatory response but not functional liver injury is underlying this parameter. Thus, it seems that higher CAR patients have specific, inflammatory phenotype with more severe COVID-19 on presentation. Duration of symptoms did not affect prognostic associations of CAR as shown in the multivariate models where both factors were independently associated with worse survival (higher CAR and shorter duration of symptoms). Higher CAR patients were also more likely to receive specific therapies, probably owing to more severe disease presentation; however, after including specific drugs into multivariate analyses they did not change associations of CAR with worse clinical outcome (data not shown). Also, there was a similar comorbidity burden as assessed by Charlson comorbidity index between patients with lower and higher CAR values and this parameter seems to be less affected by comorbidities and more by acute inflammatory state induced by SARS-CoV-2 infection. Specific metabolic comorbidities associated with unfavorable clinical course of COVID-19 did not group with higher CAR but were even more frequent in patients with lower CAR values (hyperlipoproteinemia, congestive heart disease, coronary artery disease, history of myocardial infarction, chronic obstructive lung disease, chronic liver disease and liver cirrhosis). Only comorbidity associated with higher CAR was dementia, probably due to the older age of these patients.

Worse clinical course including more rapid respiratory deterioration and higher need for intensive level of care as well as higher mortality, have been previously reported to be associated with higher CAR in smaller cohorts of COVID-19 patients [10–13]. Similar observations regarding disease severity were es-

tablished in non-COVID community-acquired pneumonia patients as well [22–24]. Our paper validates these findings but also extends these observations to demonstrate that survival is gradually improved with lower CAR values. We were able to define four novel CAR prognostic categories that add up to prognostication of COVID-19 patients. These categories predict survival independently of established prognostic scores CURB-65 and VACO index as well as independently of age, comorbidity burden and COVID-19 severity on admission. We also show that CAR reflects on postdischarge mortality as well. Substantial advantage of laboratory dependent parameters in comparison to complex prognostic indices is less cumbersome procedure of calculation and ability to quickly classify patients when blinded for information regarding specific comorbidities and other included parameters. Its use in adjunction to established prognostic scores can help improve prognostication of COVID-19 patients. CAR was also shown to be predictive of worse functional impairment and higher occurrence of deep venous thrombosis and bacterial sepsis. Considering these associations, CAR could reflect more severe COVID-19 which was shown to be associated with higher occurrence of venous thrombosis [25, 26]. Conversely, probably due to a baseline association with a more favorable cardiovascular risk profile, acute arterial thromboses were less frequent in patients with higher CAR. This finding could reflect the fact that patients presenting with acute arterial thrombotic events might not have had the time to develop full inflammatory profile of their disease and presented earlier during the disease course.

Main limitations of our work are retrospective design, single-center experience and lack of longitudinal assessment of CAR. No *P*-value adjustments for multiple testing were performed when comparing characteristics and outcomes between two group of patients (higher and lower CAR values). Main strengths of our work are a large sample size and validation of findings in an independent cohort of patients treated in the same institution. This was possible due to high volume of patients and represents largest single-center cohort reporting CAR-related clinical and prognostic aspects of COVID-19 so far. Our findings are representative of tertiary center experience with high proportion of patients with severe or critical disease at the time of admission and might not be generalized to other clinical contexts.

In conclusion, among hospitalized COVID-19 patients, higher CAR at the time of hospital admission is associated with older age, male sex, parameters reflecting stronger systemic inflammation and more severe COVID-19. Higher CAR is associated with higher 30-day and postdischarge mortality. We defined and validated four CAR prognostic categories with robust prognostic properties for 30-day survival independent of disease severity, age and comorbidities. CAR seems to have a good potential to improve prognostication of hospitalized COVID-19 patients.

Acknowledgements This paper is a part of the project "Registar hospitalno liječenih bolesnika u Respiracijskom centru KB Dubrava" / "Registry of hospitalized patients in University Hospital Dubrava Respiratory center" registered on the ClinicalTrials.gov website, identifier NCT05151094.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations

Conflict of interest M. Lucijanić, J. Stojić, A. Atić, T. Čikara, B. Osmani, M. Barišić-Jaman, A. Andrilović, P. Bistrović, A. Zrilić Vrkljan, M. Lagančić, M. Milošević, I. Vukoja, L. Đerek, T. Lucijanić and N. Piskač Živković declare that they have no competing interests.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the University Hospital Dubrava Review Board.

References

1. Attaway AH, Scheraga RG, Bhimraj A, Biehl M, Hatipoglu U. Severe covid-19 pneumonia: pathogenesis and clinical management. BMJ. 2021;372:436.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239–42.
3. Mehta P, Fajgenbaum DC. Is severe COVID-19 a cytokine storm syndrome: a hyperinflammatory debate. Curr Opin Rheumatol. 2021;33(5):419–30.
4. https://www.hzjz.hr/aktualnosti/covid-19-izvjesce-hzjz-a/; Accessed 12.12.2021.
5. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693–704.
6. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med. 2021;384(1):20–30.
7. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med. 2020;383(24):2333–44.
8. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014;6(10):a16295.
9. Paštrovic F, Lucijanic M, Atic A, et al. Prevalence and prognostic impact of deranged liver blood tests in COVID-19: experience from the regional COVID-19 center over the cohort of 3812 hospitalized patients. J Clin Med. 2021;10(18):4222.
10. Karakoyun I, Colak A, Turken M, et al. Diagnostic utility of C-reactive protein to albumin ratio as an early warning sign in hospitalized severe COVID-19 patients. Int Immunopharmacol. 2021;91:107285.
11. Bannaga AS, Tabuso M, Farrugia A, et al. C-reactive protein and albumin association with mortality of hospitalised

SARS-CoV-2 patients: a tertiary hospital experience. Clin Med. 2020;20(5):463–7.
12. El-Shabrawy M, Alsadik ME, El-Shafei M, et al. Interleukin-6 and C-reactive protein/albumin ratio as predictors of COVID-19 severity and mortality. Egypt J Bronchol. 2021;15(1):5.
13. Saylik F, Akbulut T, Kaya S. Can C-reactive protein to albumin ratio predict in-hospital death rate due to COVID-19 in patients with hypertension? Angiology. 2021;72(10):947–52.
14. Lucijanic M, Galusic D, Krecak I, et al. C reactive protein to albumin ratio as prognostic marker in primary and secondary myelofibrosis. Leuk Lymphoma. 2020;61(12):2969–74.
15. Kocaturk M, Kocaturk O. Assessment of relationship between C-reactive protein to albumin ratio and 90-day mortality in patients with acute ischaemic stroke. Neurol Neurochir Pol. 2019;53(3):205–11.
16. Shibutani M, Nagahara H, Fukuoka T, et al. Prognostic significance of the C-reactive protein-to-albumin ratio in patients with metastatic colorectal cancer treated with trifluridine/thymidine phosphorylase inhibitor as later-line chemotherapy. Anticancer Res. 2019;39(2):1051–7.
17. Li YJ, Yang X, Zhang WB, Yi C, Wang F, Li P. Clinical implications of six inflammatory biomarkers as prognostic indicators in Ewing sarcoma. Cancer Manag Res. 2017;9:443–51.
18. World Health Organization. Clinical management of COVID-19: interim guidance, 27 May 2020. Geneva: World Health Organization; 2020.
19. Lucijanic M. Survival analysis in clinical practice: analyze your own data using an Excel workbook. Croat Med J. 2016;57(1):77–9.
20. Lucijanić M. An update to the custom-made MS Excel workbook performing the log-rank test with extended functionality and a new original COVID-19 training data set. Croat Med J. 2021;62(5):531–3.
21. Lucijanic M, Veletic I, Rahelic D, et al. Assessing serum albumin concentration, lymphocyte count and prognostic nutritional index might improve prognostication in patients with myelofibrosis. Wien Klin Wochenschr. 2018;130(3–4):126–33.
22. Luo B, Sun M, Huo X, Wang Y. Two new inflammatory markers related to the CURB-65 score for disease severity in patients with community-acquired pneumonia: the hypersensitive C-reactive protein to albumin ratio and fibrinogen to albumin ratio. Open Life Sci. 2021;16(1):84–91.
23. Bozkurt HB. Is there any relationship between C-reactive protein/albumin ratio and clinical severity of childhood community-acquired pneumonia. Turk J Biochem. 2021;46(6):647–53.
24. Lee JH, Kim J, Kim K, et al. Albumin and C-reactive protein have prognostic significance in patients with community-acquired pneumonia. J Crit Care. 2011;26(3):287–94.
25. Lucijanic M, Krecak I, Soric E, et al. Thrombocytosis in COVID-19 patients without myeloproliferative neoplasms is associated with better prognosis but higher rate of venous thromboembolism. Blood Cancer J. 2021;11(11):189.
26. Srivastava R, Parveen R, Mishra P, Saha N, Bajpai R, Agarwal NB. Venous thromboembolism is linked to severity of disease in COVID-19 patients: A systematic literature review and exploratory meta-analysis. Int J Clin Pract. 2021;75(12):e14910.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.