

The clinical and predictive value of C-reactive protein/albumin ratio in critically ill and mechanically ventilated adult patients

Klinička i prediktivna vrijednost omjera C-reaktivnog protein/albumin u kritičnih, mehanički ventiliranih bolesnika

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Summary

Introduction: CPR/albumin ratio represents a new biomarker that integrates two laboratory-tested acute phase reactants: a positive one (C-reactive protein) and a negative one (albumin), and which can be used as an indicator of the severity, progression and outcome of various illnesses, including critical illnesses. In this retrospective study, we investigated the impact of the CRP/albumin ratio on the clinical characteristics and outcome of the treatment of critically ill and mechanically ventilated adult patients.

Patients and methods: This retrospective study included 100 critically ill patients (65 % males and 35 % females; median age of 67) treated at the medical intensive care unit (ICU) which required the use of invasive mechanical ventilation. The primary diagnoses upon admission to the intensive care unit were: sepsis and septic shock (39 %), acute heart failure or worsening chronic heart failure (20 %), exacerbation of chronic obstructive pulmonary disease (16 %), pneumonia (11 %), acute kidney injury or the exacerbation of chronic kidney disease (7 %) and other conditions (7 %).

Results: Correlation analysis showed a significant moderate positive correlation between CRP/albumin ratio and the duration of mechanical ventilation measured in hours ($r = 0.48$, $p = 0.001$) and the time spent in the intensive care unit, measured in days ($r = 0.44$, $p = 0.001$). The median of the CRP/albumin ratio was 58.77 and the patients in the above-the-median group had a higher SOFA score. In terms of the outcomes, it has been determined that the surviving patients (56 %) had a significantly lower CRP/albumin ratio compared to those that had not survived (44 %), which correlates with their SOFA scores as well. In the group of survivors, the correlation between the ratio of CRP/albumin and the SOFA score is positive and statistically significant ($r = 0.29$, $p = 0.03$), in the group non-survivoris ($r = 0.45$, $p = 0.003$).

Conclusion: Based on the results of our study, the CRP/albumin ratio has proved to be a good predictor of clinical characteristics and outcomes of critically ill and mechanically ventilated patients.

Key words: C-reactive protein, albumin, critically ill, outcome, mechanical ventilation

Sažetak

Uvod: Omjer CPR/albumin predstavlja novi biomarker koji integrira dva laboratorijski ispitana reaktanta akutne faze: pozitivni (C-reaktivni protein) i negativni (albumin), a koji se može koristiti kao pokazatelj težine, progresije i ishoda raznih bolesti, uključujući kritične bolesti. U ovoj retrospektivnoj

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studiji istraživali smo utjecaj omjera CRP/albumin na kliničke karakteristike i ishod liječenja kritično bolesnih, mehanički ventiliranih bolesnika.

Bolesnici i metode: Ova retrospektivna studija uključila je 100 kritično oboljelih bolesnika (65 % muškaraca i 25 % žena, prosječne dobi 67 godina) liječenih na Jedinici intenzivnog liječenja (JIL) koji su zahtijevali primjenu invazivne mehaničke ventilacije. Primarne dijagnoze po prijemu u jedinicu intenzivnog liječenja bile su: sepsa i septički šok (39 %), akutno zatajenje srca ili pogoršanje kroničnog zatajenja srca (20 %), egzacerbacija kronične opstruktivne plućne bolesti (16 %), upala pluća (11 %), akutno oštećenje bubrega ili egzacerbacija kronične bubrežne bolesti (7 %) i druga stanja (7 %).

Rezultati: Korelacijska analiza pokazala je značajnu umjerenu pozitivnu korelaciju između omjera CRP/albumin i trajanja mehaničke ventilacije mjenenog u satima ($r = 0,48$, $p = 0,001$) i vremena provedenog u Jedinici intenzivne njege, mjenenog u danima ($r = 0,44$, $p = 0,001$). Medijan omjera CRP/albumin bio je 58,77, a bolesnici u skupini iznad medijana imali su viši SOFA rezultat. Što se tiče ishoda, utvrđeno je da su preživjeli bolesnici (56 %) imali značajno niži omjer CRP/albumin u usporedbi s onima koji nisu preživjeli (44 %), što također korelira s njihovim SOFA rezultatima. U skupini preživjelih korelacija između omjera CRP/albumin i SOFA bodovnog zbroja je pozitivna i statistički značajna ($r = 0,29$, $p = 0,03$), a u skupini preminulih ($r = 0,45$, $p = 0,003$).

Zaključak: Na temelju rezultata naše studije, omjer CRP/albumin pokazao se kao dobar prediktor kliničkih karakteristika i ishoda kritično bolesnih, mehanički ventiliranih nekirurških bolesnika.

Ključne riječi: C-reaktivni protein, albumin, kritično bolesni, ishod, mehanička ventilacija

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Introduction

The C-reactive protein/albumin ratio or CRP/albumin ratio represents a new prognostic marker, the role of which has been examined and proved in different illnesses and conditions, and which is based on well-known, basic characteristics of the C-reactive protein and serum albumins. The C-reactive protein represents a marker of the systemic inflammatory response (positive acute phase reactant), which is mostly synthesized in the liver under the influence of interleukin 6 (IL-6), increased levels of which are linked to worse clinical outcomes of various illnesses, especially in critically ill patients. Serum albumins are proteins with multiple roles (maintaining osmotic pressure, the transport of hormones, metabolites and medicines) and their levels are used as a predictive marker both in chronically and in critically ill patients, since they belong to the group of so-called negative acute phase reactants because their levels are decreased in systemic inflammatory responses.¹⁻⁴ Except in inflammatory responses, decreased values of albumins may be a consequence of malnutrition, which occurs in chronic illnesses, and of increased catabolism, which occurs in acute illnesses.^{5,6} Based on the foregoing, it would be logical to assume that CRP/albumin ratio as an indicator of the severity of inflammatory and nutritional status will be more sensitive in predicting the severity, progression and outcome of an illness than the individual levels of the two proteins. The prognostic significance of the CRP/albumin ratio has mostly been studied in malignant diseases, but its role is being increasingly studied in other illnesses as well, such as cardiovascular diseases, systemic diseases and immunological

disorders, severe infections, etc. Its predictive significance in surgical patients is also being studied. The CRP/albumin ratio has also been studied as a prognostic marker in critically ill patients; however, studies to date have focused on critically ill patients with predominantly surgical pathology (trauma, surgery) and on neurological patients.⁷⁻¹⁵ In addition, the CRP/albumin ratio may also be interesting in terms of predicting the duration of mechanical ventilation of critically ill patients, considering that one of the main factors associated with prolonged mechanical ventilation is the intensity of the systemic inflammatory response and the severity of malnutrition.¹⁶ The primary aim of this study is to investigate the relationship between the CRP/albumin ratio and clinical characteristics of the medical critically ill patients (the duration of mechanical ventilation, laboratory parameters and SOFA score). The secondary aim of the study is to examine the association of CRP/albumin with the outcome of the treatment of critically medical ill patients.

Patients and methods

This retrospective study involved 100 patients treated at the Intensive Care Unit of the Clinical Hospital Centre in Osijek over a period of three months. The study included critically ill patients who required mechanical ventilation for longer than 72 hours due to respiratory insufficiency as a result of the underlying disease (sepsis and septic shock, acute heart failure or worsening chronic heart failure, the exacerbation of chronic obstructive pulmonary disease, pneumonia, acute kidney injury or the

exacerbation of chronic kidney disease). Patients were excluded from the study if they: 1) were younger than 18 years; 2) had been mechanically ventilated for less than 72 hours; 3) had an active malignant disease; 4) had an acute surgical illness and received immediate surgical intervention; 5) had an acute neurological event. Data on the patients, methods and the course of treatment, outcomes and laboratory test results were obtained by searching the hospital information system, upon prior approval of the competent Ethics Committee (number approval R2-208/2021). For the purposes of this study, besides demographic data (age, sex), other data were used as well, such as: primary diagnosis (the reason for admission to the intensive care unit), total time spent on mechanical ventilation (the duration of mechanical ventilation) expressed in hours, time spent in the Intensive Care Unit (in days), the outcome of treatment (survival or fatality), laboratory parameters (red blood cell count, white blood cell count, lymphocyte count, platelet count, C-reactive protein, urea, creatinine, sodium, potassium, albumin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, lactates, procalcitonin, pH values and arterial blood gas tests) and the SOFA score (Sequential Organ Failure Assessment). The CRP/albumin ratio was calculated based on the standard formula:

$$\frac{\text{C reactive protein (mg/L)}}{\text{albumin (g/dL)}} \times 10$$

CRP and albumin values used in the calculation of the CRP/albumin ratio were those measured upon the arrival at the Intensive Care Unit or those measured within 24 hours after admission.

Based on the previous studies, the sample size was estimated a priori using G-power 3.1. Categorical data were presented as absolute and relative frequencies. Numeric data were described as the median and interquartile range. A correlation analysis was used for determining the correlation between the observed phenomena. The comparison of continuous variables was made by using the t-test, and the effect size of the observed phenomenon was measured by Cohen's d, which was calculated by subtracting the mean of one group from the other and dividing the result by the standard deviation. The calculated common standard deviation refers to the total sample of participants. The effect size was calculated only for statistically significant differences and was interpreted as trivial (<0.2), small (≥ 0.2), medium (≥ 0.5) and large (≥ 0.8). Statistical analysis was performed by using the MedCalc Statistical Software

version 19.1.7 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2020).

Results

This study included 100 patients, 65 (65%) males and 35 (35%) females. The patients' median age was 67 and the interquartile range was 34 to 89 years of age. The presentation of clinical characteristics is provided in Table 1.

The correlation analysis showed a significant moderate positive correlation between the CRP/albumin ratio and the duration of mechanical ventilation measured in hours ($r = 0.48$, $p = 0.001$), with patients whose CRP/albumin ratio was higher spending longer time on mechanical ventilation. Furthermore, the correlation analysis showed a significant moderately positive correlation between the CRP/albumin ratio and the time spent in the Intensive Care Unit, measured in days ($r = 0.44$, $p = 0.001$), with patients whose CRP/albumin ratio was higher staying longer at the ICU.

Those patients' median CRP/albumin ratio was 58.77 (the interquartile range was from 0.25 to 181.92), with 50 patients below and 50 above the median. Table 2 shows a comparison of patients below and above the median CRP/albumin ratio in terms of their clinical presentation and laboratory test results. As evident from (Table 2), patients in groups below and above the median CRP/albumin ratio exhibited statistically significant differences in seven elements of clinical presentation and laboratory test results. In this context, patients in the above-the-median group had a statistically significant longer stay in the Intensive Care Unit, longer mechanical ventilation, a higher SOFA score and their laboratory test results showed significantly higher levels of CRP, white blood cells and urea and significantly lower levels of albumin compared to the patients in the below-the-median group. The effect size for the identified statistically significant differences ranged from small (pertaining to white blood cells) to large (pertaining to the other elements of clinical presentation and laboratory test results).

In terms of the outcomes, it has been determined that the surviving patients (56%) had a significantly lower CRP/albumin ratio compared to those that had not survived (44%), which correlates with their SOFA scores as well. In this context, the effect sizes for both differences determined between these groups of patients were large. The effect of CRP/albumin ratio and the SOFA score on the outcome of treatment of these patients is presented in Table 3.

Table 1 Patients' clinical characteristics

Tablica 1. Kliničke karakteristike pacijenata

| Demographic data | |
|---|-------------|
| Demografski podaci | |
| Males <i>Muškarci</i> | 65 (65 %) |
| Females <i>Žene</i> | 35 (35 %) |
| Median age <i>Medijan dobi</i> | 67 |
| Primary diagnosis (reason for admission) | |
| Primarna dijagnoza po prijemu | |
| Sepsis and septic shock <i>Sepsa i septički šok</i> | 39 (39 %) |
| Acute heart failure or worsening chronic heart failure <i>Akutno srčano zatajenje / pogoršanje kroničnog srčanog zatajenja</i> | 20 (20 %) |
| Exacerbation of chronic obstructive pulmonary disease <i>Pogoršanje kronične obstruktivne plućne bolesti</i> | 16 (16 %) |
| Pneumonia <i>Pneumonija</i> | 11 (11 %) |
| Acute kidney injury / exacerbation of chronic kidney disease <i>Akutno bubrežno zatajenje / pogoršanje kroničnog bubrežnog zatajenja</i> | 7 (7 %) |
| Other conditions <i>Ostala stanja</i> | 7 (7 %) |
| SOFA* score | |
| SOFA rezultat | |
| Median SOFA score <i>Medijan SOFA bodovnog zbroja</i> | 7.68 ± 3.25 |

* SOFA - Sequential Organ Failure Assessment)

Table 2 The comparison of elements of clinical presentation and laboratory test results in patient groups above and below the median CRP/albumin ratio

Tablica 2. Usporedba elemenata kliničke prezentacije i rezultata laboratorijskih pretraga u skupinama pacijenata iznad i ispod srednjeg omjera CRP/albumin

| | Below the median (n = 50) | | Above the median (n = 59) | | Group comparison | |
|---|------------------------------------|-------|------------------------------------|--------|---------------------------------|---|
| | <i>Ispod medijana (n = 50)</i> | | <i>Iznad medijana (n = 50)</i> | | <i>Usporedba skupina</i> | |
| | M | SD | M | SD | P value* <i>P vrijednost</i> | Effect size** <i>Veličina učinka</i> |
| Time spent at the ICU (in days) <i>Vrijeme u JIL-u (u danima)</i> | 6.82 | 5.32 | 12.90 | 7.52 | 4.66 (0.001) | 0.93 |
| Mechanical ventilation (in hours) <i>Mehanička ventilacija (u satima)</i> | 76.48 | 75.44 | 240.60 | 164.40 | 6.42 (0.001) | 1.28 |
| SOFA score <i>SOFA bodovni zbroj</i> | 5.46 | 1.58 | 9.90 | 2.96 | 9.35 (0.001) | 1.87 |
| Red blood cells ($\times 10^{12}/L$) <i>Eritrociti ($\times 10^{12}/L$)</i> | 4.38 | 0.78 | 4.19 | 0.90 | 1.13 (0.25) | — |
| White blood cells ($\times 10^9/L$) <i>Leukociti ($\times 10^9/L$)</i> | 11.74 | 5.88 | 14.89 | 8.69 | 2.12 (0.04) | 0.42 |
| Lymphocytes ($\times 10^9/L$) <i>Limfociti ($\times 10^9/L$)</i> | 10.44 | 7.74 | 9.69 | 8.78 | 0.45 (0.65) | — |

| | Below the median (n = 50) <i>Ispod medijana</i> (n = 50) | | Above the median (n = 59) <i>Iznad medijana</i> (n = 50) | | Group comparison <i>Usporedba skupina</i> | |
|---|---|--------|---|---------|--|---|
| | M | SD | M | SD | P value* <i>P vrijednost</i> | Effect size** <i>Veličina učinka</i> |
| Platelets ($\times 10^9/L$) <i>Trombociti ($\times 10^9/L$)</i> | 229.24 | 106.55 | 246.28 | 102.55 | 0.81 (0.42) | — |
| RDW (%)*** <i>RDW (%)</i> | 14.47 | 2.262 | 14.52 | 2.49 | 0.12 (0.90) | — |
| C-reactive protein (mg/L) <i>C-reaktivni protein (mg/L)</i> | 76.79 | 54.92 | 258.64 | 140.34 | 8.53 (0.001) | 1.70 |
| Urea (mmol/L) <i>Ureja (mmol/L)</i> | 10.90 | 6.97 | 15.10 | 11.69 | 2.19 (0.03) | 0.43 |
| Creatinine ($\mu\text{mol/L}$) <i>Kreatinin ($\mu\text{mol/L}$)</i> | 132.30 | 112.69 | 187.96 | 177.77 | 1.87 (0.06) | — |
| Sodium (mmol/L) <i>Natrij (mmol/L)</i> | 137.16 | 8.53 | 138.80 | 7.73 | 1.00 (0.32) | — |
| Potassium (mmol/L) <i>Kalij (mmol/L)</i> | 4.17 | 0.64 | 4.22 | 0.75 | 0.34 (0.73) | — |
| Albumin (g/L) <i>Albumin (g/L)</i> | 34.30 | 6.48 | 23.77 | 5.30 | 8.89 (0.001) | 1.78 |
| Aspartate aminotransferase (U/L) <i>Asparat aminotransferaza (U/L)</i> | 236.40 | 887.41 | 235.04 | 743.99 | 0.01 (0.99) | — |
| Alanine aminotransferase (U/L) <i>Alanin aminotransferaza (U/L)</i> | 188.64 | 642.63 | 149.16 | 444.57 | 0.66 (0.72) | — |
| Lactate dehydrogenase (U/L) <i>Laktat dehidrogenaza (U/L)</i> | 545.28 | 817.10 | 690.46 | 1071.33 | 0.76 (0.45) | — |
| Lactates (mmol/L) <i>Laktati (mmol/L)</i> | 10.10 | 58.17 | 2.55 | 2.69 | 0.92 (0.36) | — |
| Procalcitonin (mg/L) <i>Prokalcitonin (mg/L)</i> | 2.60 | 9.46 | 11.04 | 31.18 | 1.83 (0.07) | — |
| pH <i>pH</i> | 7.37 | 0.10 | 7.35 | 0.16 | 0.93 (0.35) | — |
| pO ₂ (kPa) <i>pO₂ (kPa)</i> | 8.56 | 3.38 | 8.56 | 3.38 | 0.41 (0.68) | — |
| pCO ₂ (kPa) <i>pCO₂ (kPa)</i> | 5.87 | 1.77 | 5.37 | 2.09 | 1.28 (0.14) | — |

*t-test (*t-test*)**Cohen's d (*Cohen's d*) Effect size was calculated only for statistically significant differences and was interpreted as trivial (<0.2), small (≥ 0.2), medium (≥ 0.5) and large (≥ 0.8).*Cohenov d (Cohen's d) Veličina učinka izračunata je samo za statistički značajne razlike i tumačena je kao trivijalna (<0,2), mala ($\geq 0,2$), srednja ($\geq 0,5$) i velika ($\geq 0,8$).**** Red Cell Distribution Width (*Raspodjela eritrocita po volumenu*)

Table 3 The impact of CRP/albumin ratio and SOFA score on the outcome of treatment
 Tablica 3. Utjecaj omjera CRP/albumin i SOFA bodovnog zbroja na ishod liječenja

| | Survivals (n = 56) <i>Preživjeli</i> (n = 56) | | Fatalities (n = 44) <i>Umrli</i> (n = 44) | | Group comparison <i>Usporedba skupina</i> | |
|---|--|-------|--|-------|--|---|
| | M | SD | M | SD | P value* <i>P vrijednost</i> | Effect size** <i>Veličina učinka</i> |
| CRP/albumin ratio <i>CRP/albumin omjer</i> | 39.81 | 36.86 | 100.64 | 61.18 | 6.16 (0.001) | 1.20 |
| SOFA score <i>SOFA bodovni zbroj</i> | 5.71 | 2.12 | 10.18 | 2.67 | 9.39 (0.001) | 1.85 |

*t-test (*t-test*)

**Cohen's d (*Cohen's d*) Effect size was calculated only for statistically significant differences and was interpreted as trivial (<0.2), small (≥0.2), medium (≥0.5) and large (≥0.8).

Cohenov d (Cohen's d) Veličina učinka izračunata je samo za statistički značajne razlike i tumačena je kao trivijalna (<0,2), mala (≥0,2), srednja (≥0,5) i velika (≥0,8).

Discussion

Our study showed a significant moderately positive correlation between the CRP/albumin ratio and longer mechanical ventilation measured in hours (patients with a higher ratio were mechanically ventilated for a longer period of time). This is consistent with the results of Bai M. et al, who studied the prognostic role of CRP/albumin ratio in critically ill neurological patients¹⁵ and of Ozciftci Y. P. et al, who looked at the role of CRP/albumin ratio in the prognosis of critically ill patients who required urgent surgery.¹⁷ In this context, a significant moderate positive correlation was found between CRP/albumin ratio and the time spent in the intensive care unit (patients with a higher ratio spent more days in the intensive care unit), which is also consistent with the results of the mentioned papers. Both the duration of mechanical ventilation and the time spent in the intensive care unit also depend on the intensity of the inflammatory response, the metabolic response (catabolism) and the nutritional status, so it can be expected that patients with a stronger inflammatory response and increased catabolism, accompanied by a poorer nutritional status, will also have poorer outcomes (longer mechanical ventilation, longer treatment), and this is something that a higher CRP/albumin ratio indicates. Systemic inflammatory response and malnutrition have an indirect effect on the respiratory function, this ratio can be expected to serve as a good indicator in predicting the duration of mechanical ventilation in critically ill individuals.¹⁶ Considering that previous papers dealing with the correlation between clinical indicators and outcomes of critically ill patients with their CRP/albumin ratio were mostly based on critically ill surgical and

neurocritically ill patients, our study focused on critically ill patients whose primary diagnoses were those within the scope of internal medicine, including patients suffering from infectious diseases, the severity and nature of which required invasive mechanical ventilation. Moreover, patients with a higher CRP/albumin ratio exhibited a higher mortality rate in the Intensive Care Unit, and in this respect, the CRP/albumin ratio has a positive correlation with the SOFA score, as shown in Table 3 (the surviving patients' median CRP/albumin ratio was 39.81 and their median SOFA score was 5.71, whereas the median CRP/albumin ratio for the patients that did not survive was 100.64 and their median SOFA score was 10.18). This correlation between the SOFA score and the CRP/albumin ratio on the one side and mortality on the other has been tested and proved in critically ill surgical patients.¹³ By comparing the laboratory test parameters with the CRP/albumin ratio, we found a positive correlation with the white blood cell count and urea levels. The white blood cell count is expectedly elevated in conditions involving inflammatory response, whereas elevated urea values can be interpreted by the influence of anti-inflammatory mediators such as NF- α and IL-6 as the promoters of protein catabolism and increased production of urea.¹⁸ Based on our study, and by comparison with other papers dealing with surgical, traumatological and neurological patients, we see similar results, so it is safe to assume that CRP/albumin ratio can serve as a good indicator of clinical outcomes of critically ill patients (duration of mechanical ventilation, time spent in the intensive care unit and outcome - survival or fatality). Our contribution is primarily based on investigating the role of the CRP/albumin ratio in patients with primary

medical critical illness in order to contribute to the overall consideration of the predictive role of the CRP/albumin ratio in medical critically ill patients. Nevertheless, when interpreting our results, just like the results of other similar papers, one should keep several limitations in mind. Firstly, this was a retrospective study with a limited number of patients included (patients that met the inclusion criteria and were treated in the specified period). Secondly, patients with very high CRP levels (and consequently very high CRP/albumin ratio) have a much more serious clinical condition, which could end fatally very quickly, which in turn has an impact on the duration of mechanical ventilation (patients who were worse off and died sooner were ultimately mechanically ventilated for a shorter period of time), which is why we included patients treated at the Intensive Care Unit over a minimum period of 72 hours. Thirdly, when interpreting the impact of CRP/albumin ratio on these patients' outcomes, one has to consider the fact that outcome was defined as a fatality if the patient died while in the intensive care unit, and that survival in fact meant dismissal from the intensive care unit (mostly involving transfer to another ward), which can be a relatively short period of time.

Conclusion

Based on the results of our study, the value of the CRP/albumin ratio proved to be a good predictor of clinically adverse events' outcomes, such as prolonged mechanical ventilation, prolonged stay in the Intensive Care Unit, and the unfavorable final outcome of treatment in critically ill and mechanically ventilated adult patients.

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