Trends in Clinical and Medical Sciences

PSR Press

Article

Evaluation of C-reactive protein/albumin ratio as an early warning parameter in critical COVID-19 cases

Ebru Aladag[1] and Eyüp Aydogan[1,*]

[1] Anesthesiology and Reanimation Department, ALKU Alanya Training and Research Hospital, Figla, 07400 Alanya/Antalya, Türkiye.

* Correspondence: eyup.aydogan@alanya.edu.tr

Academic Editor: Dr. Muyassar Khamitovna Karimova

Received: 15 October 2022; Accepted: 28 February 2023; Published: 31 March 2023.

Abstract: Introduction: In 2019, a new coronavirus disease spread throughout the world from the city of Wuhan, China. COVID-19 is divided into four groups according to clinical symptoms and disease severity: mild, moderate, severe, and critical. Budgeted rates of CRP and albumin utilization will be used to estimate the incidence of COVID-19 cases. Based on this data, the aim of this study is to evaluate the diagnostic power of the C-reactive protein to albumin ratio in the early differentiation of severe hospitalized cases of COVID-19.
Materials and Methods: During hospitalization, cases will be classified as mild, moderate, severe, and critical according to the WHO interim guidance. The mild and moderate subgroups will be classified as non-severe (group 1), and the severe and critical subgroups will be classified as severe (group 2). Demographic data, morbidity, and mortality rates will be recorded.
Results: The exitus rates and length of hospital stay were significantly higher in group 2.
Conclusions: The C-reactive protein/albumin ratio has predictive value in severe COVID-19 patients who are candidates for ICU admission or endotracheal intubation. However, it is thought that supporting this data with a larger number of patients and multicenter studies would increase the value of the data.

Keywords: COVID-19; C-reactive protein; Albumin; Disease severity; Hospitalization.

1. Introduction

In December 2019, a new coronavirus disease (COVID-19) emerged from the city of Wuhan, China. COVID-19 is classified into four categories based on clinical symptoms and disease severity: mild, moderate, severe, and critical [1]. Although the majority of patients have mild to moderate symptoms, early diagnosis is crucial to prevent extended hospitalization and increased mortality rates [2,3]. As a result, researchers are striving to detect severe and critical cases at an early stage. The primary challenge faced by researchers at this point is the lack of clarity around the parameters that should be used for early diagnosis of critical intensive care patients. Inflammation can trigger the liver to synthesize an excessive amount of acute phase reactants, including C-reactive protein (CRP). CRP can be used as a biomarker in various conditions, including rheumatoid arthritis, cardiovascular diseases, and infection [4,5]. In severe critical cases of COVID-19, elevated CRP levels have been reported before any findings on CT scan, indicating that CRP can be used to identify severe cases at an early stage [6].

In addition, cytokine storms induced in critical COVID-19 cases can cause critical hypoalbuminemia, which increases the risk of death. Low albumin levels at the patient's hospital admission stage can independently predict disease course, irrespective of other indicators [7,8]. The utilization rates of CRP and albumin budgets (which will be used in calculating the CAR protein for osteosarcoma) will be utilized to estimate the incidence of COVID-19 cases [9,10]. Based on this data, the goal is to evaluate the diagnostic efficacy of the C-reactive protein to albumin ratio (CAR) in the early differentiation of severe hospitalized COVID-19 cases.

2. Materials and Methods

This study was designed retrospectively to include COVID-19 patients who were hospitalized at the pandemic service and intensive care unit of Usak Training and Research Hospital between April 1, 2021, and October 1, 2021. Patients were classified as mild, moderate, severe, and critical according to the interim guidance of the World Health Organization (WHO). The non-severe subgroups (mild and moderate) were categorized as group 1, while the severe and critical subgroups were categorized as group 2. Group 1 included patients without symptomatic hypoxia and with moderate pneumonia symptoms such as dyspnea, cough, fever, and room air oxygen saturation (SpO2) of at least 90%. Group 2 consisted of patients with at least one of the following: respiratory rate >30/min, severe respiratory distress, SpO2 in room air <90%, and oxygen/fraction arterial partial pressure = 300 mmHg, in addition to pneumonia symptoms such as dyspnea, cough, and fever patients requiring mechanical ventilation therapy due to respiratory failure.

Only patients over the age of 18 were included in the study. Demographic data, signs and symptoms, comorbidities, and laboratory data were collected from the hospital's electronic information system. Laboratory data obtained within the first 24 hours after hospitalization were evaluated, including complete blood count, C-reactive protein (CRP), albumin, glucose, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), direct bilirubin (DBil), total bilirubin (TBil), ferritin, troponin, prothrombin time (PT), and activated partial prothrombin time (APTT).

Sample size was calculated using G Power 3 software. The study included 24 cases in each group, which was determined to be sufficient for comparing the numerical variables between the C-reactive protein/albumin ratios of the two groups using the Mann-Whitney U test with a 5

2.1. Exclusion criteria

Patients under 18 years of age and patients with missing CRP, albumin, glucose, creatinine, ALT, AST, DBil, TBil and ferritin, troponin, PT and APTT records in the first 24 hours were not included in the study.

3. Results

No significant difference was found between demographic data. There was no significant difference between patients with chronic diseases. There was a significant difference between the length of stay in the hospital and the exitus rates. Exitus rates and length of hospital stay were significantly higher in group 2 (severe ill group) (Table 1). When the patient's symptoms were examined, no significant difference was observed except fever and dyspnea, but fever and dyspnea rates were significantly higher in group 2. When complete blood count parameters were examined, a statistically significant difference was found in lymphocyte, monocyte, and neutrophil-lymphocyte ratios. While there was a significant decrease in lymphocyte and monocyte counts in group 2, NLR was significantly higher. The CRP/Alb ratio (CAR) was found to be significantly higher in group 2 (Table 2).

Mean, standard deviation, or median (25.pers-75.pers) statistics were given for numerical variables, and frequency (percentage) statistics were given for categorical variables. Wilcoxon Rank Sum test was used in the analysis of numerical variables, and Pearson Chi-Square or Fisher's exact test was used in the analysis of categorical variables. Analytics R 4.1.3 (R Core Team 2022) done with the program. $p<0.05$ was considered significant.

4. Discussion

According to WHO data, COVID-19 disease has caused a worldwide pandemic and more than 2 million deaths [1]. Due to the large number of patients applying to health institutions at the same time, the need for management, classification, and treatment of these patients by directing them to different units according to their severity has arisen [11]. Because of this need, physicians have sought many different methods in order to predict which patients will need intensive care conditions/endotracheal intubation with milder symptoms [12]. The study it is aimed to contribute to this issue by using frequently used and easily accessible biochemical parameters (CRP, Alb). It has been reported in previous studies that high CRP values are correlated with the presence of infiltration in lung tomography imaging [6] and that CRP values increase early [10]. For this reason, in our retrospective study, in which the test results obtained at the stage without pneumonic

Table 1. Demographic Information by Health History

Variable	Good n=241	Severe n=261	p-value2
Age	74.50±6.20	75.04±7.23	>0.9
Gender			0.8
E	12 (50%)	14 (54%)	
K	12 (50%)	12 (46%)	
HT	14 (58%)	12 (46%)	0.4
CAD	14 (58%)	15 (58%)	>0.9
DM	9 (38%)	13 (50%)	0.4
CRD	0 (0%)	1 (3.8%)	>0.9
COPD	10 (42%)	7 (27%)	0.3
CVD	3 (12%)	4 (15%)	>0.9
Hospital Stay	7.83±4.07	13.77±8.38	0.007
Exitus	0 (0%)	15 (58%)	<0.001

Mean±SD; n (%)

Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 2. Biochemical Parameters by Health Condition

Variable	Good n=241	Severe n=261	p-value2
WBC	9.91±4.17	9.68±6.04	0.5
NOTR	7.57±3.39	8.45±5.21	>0.9
LENF	1.65(0.94-2.20)	0.81(0.49-1.58)	**0.015**
MON	0.64±0.34	0.35±0.20	**0.002**
PLT	242.12±107.11	269.96±81.61	0.12
NLO	3.17(2.44-6.37)	8.74(4.89-16.09)	**0.004**
LMO	2.71(2.00-3.25)	2.76(1.96-3.28)	0.9
CRP	46.62±43.91	148.70±83.71	**<0.001**
ALB	36.68±3.48	32.65±4.34	**0.001**
CAR	1.31±1.28	4.75±2.81	**<0.001**
Glucose	127.46±32.46	147.92±58.04	0.6
Creatinin	0.96(0.82-1.10)	1.30(0.89-1.98)	**0.023**
ALT	22.38±15.91	26.08±15.31	0.2
AST	23.67±9.65	36.42±19.91	**0.020**
DBIL	0.23(0.17-0.30)	0.28(0.20-0.48)	0.10
TBIL	0.50(0.40-0.80)	0.60(0.40-0.80)	0.7
Ferritin	267.96±286.52	714.40±536.41	**<0.001**
Troponin	0.01(0.00-0.03)	0.05(0.01-0.26)	**0.019**
PT	96.95±24.34	88.37±30.14	0.3
APTT	26.35±8.40	26.66±5.55	0.3
PTZ	11.10(10.70-12.12)	11.75(11.15-12.95)	0.080

Mean±SD; Median(25%-75%)

Wilcoxon rank sum test

infiltrates on the chest X-ray were evaluated, patients with oxygen saturation less than 90%, a respiratory rate more than 30/min, and pO2/FiO2 less than 300 mmHg according to arterial blood gas results showed severe disease. Group 2) and patients with milder symptoms in the other group (group 1) were classified, and the patients were retrospectively examined in terms of disease course and outcomes. According to our statistical results, the high mortality rate in group 2 and the high CRP/Alb rate we followed were considered significant.It has also been reported in previous studies that the Alb value begins to decrease before the disease progresses [8]. In addition, it has been reported that cytokines are effective in inflammation processes that are responsible for lung involvement [7,8]. Although our case number is limited and our study is retrospective, the number of cases is sufficient according to our power analysis results before the study. Considering that this rate was much lower in Group 1 and there was no mortality, it was concluded that when CRP/Alb was used predictively, consistent predictions could be made to make a significant difference in mortality and ICU admissions. There was no statistically significant difference between the demographic data of the patients and their chronic diseases. In the patients whose data were analyzed in our study, chronic disease rates were found to be similar in both groups. Considering that no statistically significant correlation could be established between the patients' previous HT, DM, or COPD and the course of the disease, the need to focus on biochemical parameters is undeniable.

On the other hand, cytokine storms induced in critical COVID-19 cases can cause critical hypoalbuminemia, and increase the risk of death, and low albumin levels at the patient's admission stage can be used to predict disease course independently of other indicators [7,8]. CRP and albumin together and the ratio of C-reactive protein to albumin (CAR) have been used to estimate the severity of COVID-19 cases, with documented benefits as an indicator of inflammation-related prognosis for diseases such as osteosarcoma [9,10].

The fact that there was a significant increase in the duration of hospital stay of the patients in Group 2 supports the clinical picture of more severe disease. Considering both the clinical sense and the high mortality rates caused by the disease severity, the increase in the CAR parameter increases the predictive value. Since the beginning of the epidemic, changes in the biochemical parameter caused by the disease are known [3]. Zuang *et al.*, reported that the risk of poor clinical outcome may increase in patients with advanced age, chronic comorbidities, blood leukocyte/lymphocyte count, procalcitonin level, and coinfections. However, according to the data of our study, higher mortality and longer hospital stays were observed in the patient group with a high CAR ratio, in groups that did not differ in terms of chronic diseases and demographic data. According to these results, biochemical parameters provided more consistent clinical prediction.

5. Conclusions

CAR has predictive value in severe covid patients who are candidates for ICU admission/endotracheal intubation. however, it was thought that supporting this data with higher numbers of patients and multicenter studies would increase the value of the data.

Author Contributions: All authors contributed equally to the writing of this paper. All authors read and approved the final manuscript.

Conflicts of Interest: "Authors declare no conflict of interests."

References

[1] WHO. (2020). Clinical management of COVID-19: interim guidance. *World Health Organization*.

[2] Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., ... & Zhong, N. S. (2020). Clinical characteristics of coronavirus disease 2019 in China. *New England Journal of Medicine*, *382*(18), 1708-1720.

[3] Zhang, G., Hu, C., Luo, L., Fang, F., Chen, Y., Li, J., ... & Pan, H. (2020). Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. *Journal of Clinical Virology*, *127*, 104364.

[4] Felger, J. C., Haroon, E., Patel, T. A., Goldsmith, D. R., Wommack, E. C., Woolwine, B. J., ... & Miller, A. H. (2020). What does plasma CRP tell us about peripheral and central inflammation in depression?. *Molecular Psychiatry*, *25*(6), 1301-1311.

[5] Sproston, N. R., & Ashworth, J. J. (2018). Role of C-reactive protein at sites of inflammation and infection. *Frontiers in Immunology*, *9*, 754.

[6] Tan, C., Huang, Y., Shi, F., Tan, K., Ma, Q., Chen, Y., ... & Li, X. (2020). C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *Journal of Medical Virology*, *92*(7), 856-862.

[7] Huang, W., Li, C., Wang, Z., Wang, H., Zhou, N., Jiang, J., ... & Wang, D. W. (2020). Decreased serum albumin level indicates poor prognosis of COVID-19 patients: hepatic injury analysis from 2,623 hospitalized cases. *Science China Life Sciences*, *63*, 1678-1687.

[8] Huang, J., Cheng, A., Kumar, R., Fang, Y., Chen, G., Zhu, Y., & Lin, S. (2020). Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. *Journal of Medical Virology*, *92*(10), 2152-2158.

[9] Li, Y. J., Yao, K., Lu, M. X., Zhang, W. B., Xiao, C., & Tu, C. Q. (2017). Prognostic value of the C-reactive protein to albumin ratio: a novel inflammation-based prognostic indicator in osteosarcoma. *OncoTargets and Therapy*, *10*, 5255.

[10] Karakoyun, I., Colak, A., Turken, M., Altin, Z., Arslan, F. D., Iyilikci, V., ... & Kose, S. (2021). Diagnostic utility of C-reactive protein to albumin ratio as an early warning sign in hospitalized severe COVID-19 patients. *International Immunopharmacology*, *91*(2021), Article No. 107285.

[11] Hernandez-Romieu, A. C., Adelman, M. W., Hockstein, M. A., Robichaux, C. J., Edwards, J. A., Fazio, J. C., ... & Auld, S. C. (2020). Timing of intubation and mortality among critically ill coronavirus disease 2019 patients: a single-center cohort study. *Critical Care Medicine*, *48*(11), e1045-e1053.

[12] Winck, J. C., & Scala, R. (2021). Non-invasive respiratory support paths in hospitalized patients with COVID-19: proposal of an algorithm. *Pulmonology*, *27*(4), 305-312.