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Assessment of Neutrophil to Albumin Ratio and C-reactive Protein with the Mortality in Patients with COVID-19 in Medical City Complex

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is a new viral disease that affected multiple organs in the body.

Aims: to investigate the role of neutrophil count to albumin ratio (NAR) and serum level of C-reactive protein (CRP) in predicting mortality in patients with COVID-19.

Patients and Methods: This was a prospective study including 100 patients with SARS-CoV-2. Patients demographics (age and gender) were collected through direct interview. Laboratory parameters (total white blood cell count, absolute neutrophil count, hemoglobin concentration, serum albumin, CRP titer, CT scan findings were gathered from patient's records. The neutrophil albumin ratio (NAR) was calculated by dividing the absolute neutrophil count by serum albumin concentration. Patients were followed-up for one month.

Results: Mortality rate was 53%. The mean age of the survivors and non- survivors was 44.72±16.71 years and 51.04±12.87 years, respectively with a significant difference. 83.02% of non-survivors had sever lung lesion compared with only 31.91% of survivors who had such lesions. The median NAR and CRP in non-survival patients was 450 and 175 mg/L, respectively compared with 246.5 and 140 mg/L, respectively in survivors with highly significant differences. The sensitivity and specificity of CRP in predicting mortality were 59% and 60%, respectively, at a cut-off value of 55.5 mg/L, while the sensitivity and specificity of NAR were 80% for both, at a cut-off value of 358.85.

Conclusions: Inflammatory markers including CRP, are significantly associated with high mortality rate. The neutrophil albumin ratio showed a significant association with mortality with a sensitivity and specificity of 80% for both, at a cut-off value of NAR = 358.85.

Key Words: Neutrophil , C-reactive protein, Albumin, Ratio, Mortality

Introduction

1.1 Background

COVID-19 (Coronavirus disease 2019) is an infectious inflammatory disease caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), a new type of coronavirus identified in China in December 2019 after several patients were diagnosed with nonspecific pneumonia [1].

Coronaviruses are single-stranded RNA viruses that are characterized by having corona-like projections on their surface.

Human-to-human transmission occurs through direct contact or respiratory droplets from infected individuals, whether symptomatic or asymptomatic [2]. Several reports have suggested that other forms of transmission, such as the fecal-oral route [3], and intrauterine vertical transmission, may also happen [4]. However, more studies need to be carried out to confirm this form of transmission.

The clinical features of COVID-19 may appear after an incubation period of around 5–14 days. Some early symptoms resemble those of other viral respiratory infections, such as those caused by influenza viruses. However, dyspnea and high fever define the main clinical difference between COVID-19 and common cold [5]. Additionally, when compared to the influenza virus, SARS-CoV-2 infection presents greater chances of progressing to severe and critical infections, which require oxygen therapy and ventilatory support [6]. Elderly patients and those with chronic conditions have higher risks of rapid progression to acute respiratory distress syndrome (ARDS) and multiple organ failure, often resulting in death. These features demonstrate a systemic aspect of this infection, which is accompanied by an intense inflammatory process [7].

1.2 Clinical Classification

According to the clinical manifestations, confirmed patients are divided into mild, moderate, severe, and critical types [8].

- Mild infection: Mild clinical symptoms include fever <38℃ with or without cough, no dyspnea, no gasping, no chronic disease. No imaging findings of pneumonia.
- Moderate infection: Fever, respiratory symptoms, imaging findings of pneumonia.
- Severe infection: There is a respiratory distress, respiratory rate ≥30 breaths/min, oxygen saturation (SpO2) <93% at rest, partial pressure of oxygen/ fraction of inspired oxygen (PaO2/FiO2) ≤ 300 mmHg. Patients showing a rapid progression (>50%) on CT imaging within 24- 48 hours should be managed as severe.
- Critical infection: there will be a respiratory failure, need mechanical assistance, shock, extrapulmonary organ failure and intensive care unit (ICU) is needed.

1.3 Neutrophils in COVID-19

Neutrophils are the most abundant immune cells in human blood. They account for approximately 50–70% of all leukocytes. Besides serving as first responders to many infections, neutrophils have critical homeostatic functions being also implicated in chronic inflammatory diseases [9]. These polymorphonuclear cells play a protective role during bacterial or fungal infections; however, their role in viral infections is not fully understood. Although the evidence is limited, it has been suggested that neutrophils enhance

antiviral defenses by interaction with other immune cell populations, virus internalization and killing mechanism, cytokines release, degranulation, oxidative burst, and neutrophil extracellular traps (NETs) [10].

Persistently activated neutrophils contribute to maintaining the inflammatory state in the lungs by cytokine release, as observed in MERS and SARS-CoV-1 infections. These molecules secreted by PMN can cause severe damage in alveolar tissue, independently of the virus cytopathic effect [11].

Studies have been reported an elevated level of NETs in patients with COVID-19, and an increased plasma NETs is correlated with increased COVID-19 severity, besides contributing to lung injury and microvascular thrombosis [12].

1.4 Levels of C Reactive Protein and COVID- 19 Evolution

C-reactive protein has been used for a long time as an indicator of acute phase inflammation; however, in the current Covid-19 pandemic it is related to tissue damage and poor prognosis of the disease. In this regard, high levels of CRP in the early stage of Covid-19 have been associated with lung damage and the severity of the disease [13].

CRP induces apoptosis by several mechanisms: (1) induction of pro- apoptotic cytokines such as TNF-α and IL-1-β and induction of reactive oxygen species through activation of Fc-γ receptors [14]. (2) Induction of p53 up- regulation altering the cell cycle through activation of Fc-γRII [22] .(3) Activation of genes related to the expression of adhesion molecules and chemotactic cytokines. (4) Induction of GADD153 gene expression related to cell cycle arrest and DNA damage.

1.5 Hypoalbuminemia: an indicator of the severity and prognosis of COVID-19 patients

Lower serum albumin can be indicative of malnutrition, underlying disease, or infectious processes [15]. Albumin was also regarded as a reliable indicator of the prognosis of patients with severe COVID-19 infection [16]. Hypoalbuminemia is very frequently noticed in patients with conditions like diabetes, hypertension and chronic heart failure, and these patients are statistically most vulnerable to SARS-CoV2 infection [17]. For each unit increase in serum albumin, the chance of death reduced 14% [18]. Patients with concomitant hypoalbuminemia have higher mortality rates and longer hospital stays [27]. In a recent study on COVID-19 patients, hypoalbuminemia was found to be an independent risk factor for death, and the risk of death in patients with

hypoalbuminemia was 6.394 times higher than that in patients with normal albumin [19]. Huang et al. found that lower albumin levels on admission can predict the outcome of COVID-19 independent of other known indicators such as lymphocyte count or co-morbidities [20]. Coagulopathy and vascular disease have been linked in COVID-19 patients because albumin encompasses anticoagulant properties and heparin-like action [21]. Reduction in colloid oncotic pressure due to hypoalbuminemia contributes to lung injury, renal failure might be mitigated as a known factor in sepsis and ARDS [22].

Patients and Methods

2.1 Design and Settings

This was a prospective study including 100 patients with SARS-CoV-2 who were admitted and treated in ICU at Baghdad Medical City (Al-Shifaa crisis center) during the period from 1st April to 1st September 2021. Patients were diagnosed after nasopharyngeal swab examination of SARS-CoV-2 RNA by real-time polymerase chain reaction. Clinical diagnosis in patients with a negative real time polymerase chain reaction (RT-PCR) was made in collaboration with infection disease specialists if the patient had typical symptoms and typical findings on a computed tomography scan with no other explanation of the symptoms (i. e, bacterial infection). The study was approved by the Iraqi Council of Medical Specializations.

2.2 Inclusion Criteria

- All adult patients confirmed with SARS-CoV-2 infection.

2.3 Exclusion criteria

- Patients who refused to participate in the study.
- Age <18 years.
- Patients with chronic disease such as diabetes mellitus (DM), chronic kidney disease (CKD), heart failure (HF).

2.4 Ethical consideration

A written consent from each participant was obtained prior to data collection after explaining the aim of study. Each patient was given the complete unconditioned choice to withdraw anytime. The confidentiality of data throughout the study was guaranteed and the patients were assured that data will be used for research purpose only.

2.5 Data Collection

Patients demographics (age and gender) were collected through direct interview. Laboratory parameters (total white blood cell count, absolute neutrophil count, hemoglobin concentration, serum albumin, C-reactive protein titer, CT scan findings were gathered from patients records. The neutrophil albumin ratio (NAR) was calculated by dividing the absolute neutrophil count by serum albumin concentration.

2.6 Follow up

Patients were followed-up for one month after admission. The outcome of the patients (survival or death) was recorded regardless the baseline data. Accordingly, patients were divided into broad categories: survived and died

2.7 Statistical Analysis

The quantitative data with were expressed as mean ± standard deviation. Binomial data were presented as frequency percentages. Comparison between quantitative were performed by the parametric Student *t*-test, while the comparison between binomial data was done by the Chi square test. The prognostic value of NAR and CRP titer was calculated using receiver operating characteristics (ROC) curve. All data were analyzed with SPSS for windows, v.25.0; IBM Corp, Armonk, New York, USA.

Results

3.1 Demographic and clinical Characteristics of the Patients

The patients' average age was 48.07±15.06 years (range 18-80 years). Sixty-four patients (64%) were men. a minority of patients (14%) had mild COVID-19 infection, (27%) moderate, while the majority (59%) had severe COVID-19 infection. The absolute neuropil counts were 12.53±4.52 $\times 10^3$/mL and 10.0±4.34 $\times 10^3$/mL, respectively, Finally, the serum albumin level was 30.12±6.61g/L (Table 3-1).

Table (3-1): Patients' clinical characteristics and demographic data (n=100)

Variables	Values
Age, Years **Mean±SD Range**	 **48.07±15.06** **18-80**
Gender **Male Female**	 **64(64%)** **36(36%)**
Neutrophil Count ×10^3/Ml **Mean±SD Median Range**	 **10.0±4.34** **10.56** **0.02-25.2**
Serum Albumin (G/L) **Mean±SD Median Range**	 **30.12±6.61** **30.5** **15.0-46.0**

3.3. Patients Outcome

Forty-seven patients (47%) survived the COVID-19 sickness, whereas (53%) died (Figure 3-1). Most patients were admitted and treated in intensive care units . Figure (3-1).

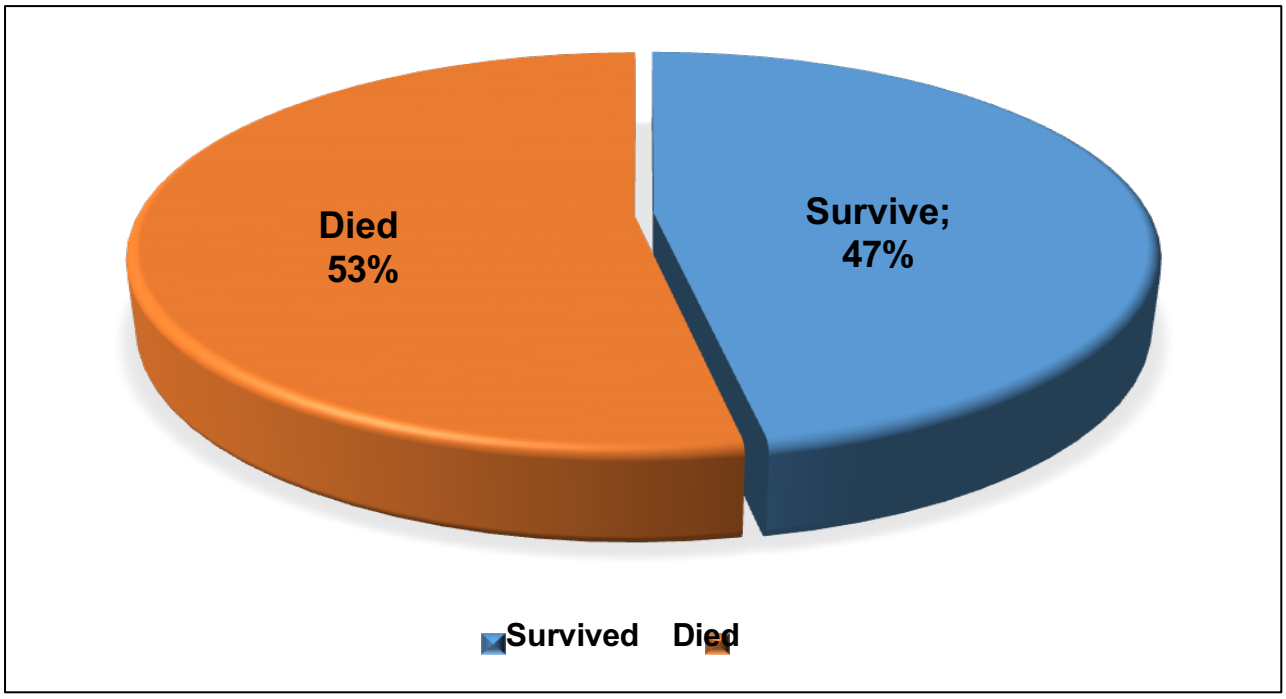

Figure (3-1). The fate of the hospitalized patients

3.3. Predicating Value of neutrophil/albumin ratio for Mortality in Patients with COVID-19

The AUC for NAR was 0.822, 95% CI= 0.735-0.909, p = 0.001. The test's sensitivity and specificity were 80% for both r, at a cut-off value of NAR

= 358.85 (Figure 3-2)

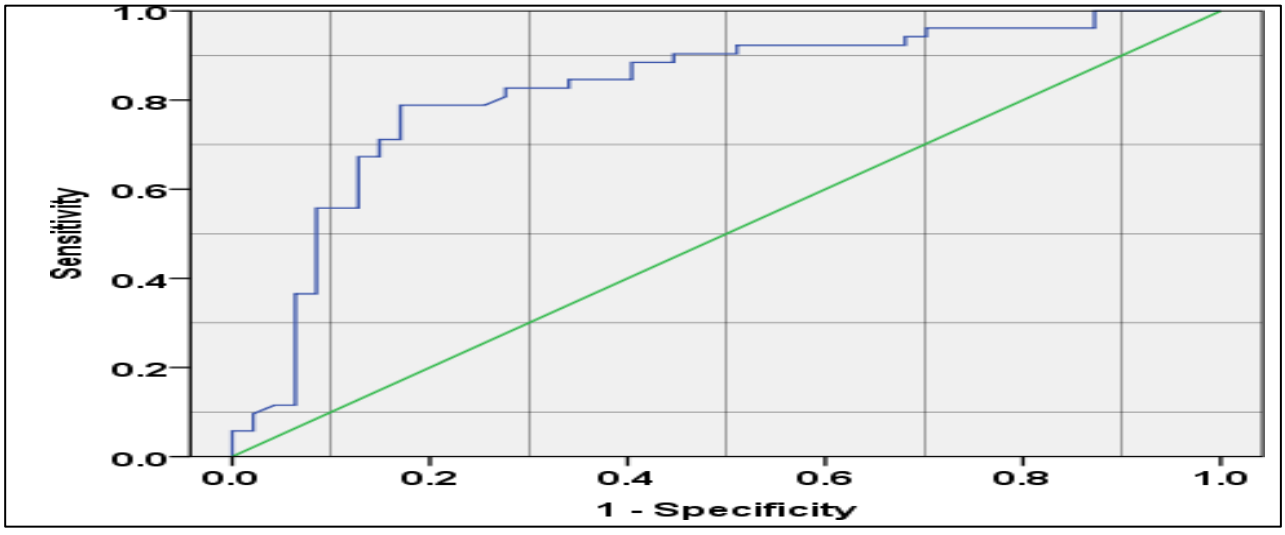

Figure (3-2) . Receiver operating characteristic curve for NAR in predicting mortality in patients with COVID-19

Discussion

The present study of severe covid-19 who were admitted to ICU the mortality rate was 53% which is slightly higher than that reported in many other studies that investigated COVID-19 patients admitted to ICU.

Armstrong et al. [23] analyzed data from 24 studies with a total of 10150 patients admitted to ICU. The mortality rate in those with a completed ICU stay was 41.6% (34.0–49.7%)%.

In a British study including 5715 patients in an ICU, the 30-day mortality was 42.0% [24]. However, in a Canadian study,117 patients were admitted to the ICU with a confirmed diagnosis of COVID-19 . After 20 days followed up, 15.4% of patients had died, and 10.3% remained in the ICU [25].

Also in this study, older age and the percentage of lung involvement were significantly associated with increased mortality rate (p value < 0.036). These results expand the previous finding by many investigators.

In the present study, all included inflammatory markers were significantly associated with increased mortality rate. Which is the sensitivity and specificity of CRT titer was (59% - 60%) , respectively .In fact, there is almost a general agreement between all previous studies about the role of inflammatory markers in predicting mortality in patients with COVID-19 whether in ICU or in hospital ward [26-28].

In a meta-analysis, showed that elevated serum CRP, procalcitonin (PCT), D-dimer, and serum ferritin levels were associated with an increased composite poor outcome that comprises mortality, severe COVID-19, ARDS, and the need for ICU care in patients with COVID-19 [28].

According to the results of the present study, the AUC for NAR was 0.822, 95% CI= 0.735-0.909, p = 0.001. The test's sensitivity and specificity were 80% for both, at a cut-off value of NAR = 358.85 which indicate a very good predictive value of this marker.

Very few studies investigated the role of NAR as predictor for mortality in patients with COVID-19. In a Turkish study, Varim et al. [29] performed a ROC analysis for NAR values, and basal NAR greater than 201.5 had 71.1% sensitivity and 71.7% specificity in predicting the mortality of patients with a COVID-19 infection. Aziz et al. [30] made a meta-analysis of 11

studies that examined serum albumin levels in patients with COVID-19, an inverse proportion was found between low serum albumin levels and the severity of the disease. In another study, serum albumin levels were found to be significantly lower in patients with COVID-19 than in healthy individuals16. In a study by Mishra et al [31]. Albumin levels reflect nutritional status and organ function, and the underlying inflammatory state give rise to a decrease of albumin production in liver by increasing inflammatory factors, the primary cause of hypoalbuminemia that occurs early

in sepsis [32-33], On the other hand, neutrophilia is a hallmark of the severe cases of COVID-19 [34]. Thus, it is reasonable to assume that severe case demonstrating higher NAR. Therefore, based on our findings, NAR, a new biomarker composed of neutrophil percentage and albumin that closely related to the inflammatory response, can significantly predict the prognosis of COVID-19.

Conclusions and Recommendations

5.1 Conclusions

1. There is a relatively high mortality rate among COVID-19 patients admitted to ICU at Al-Shifaa crisis center compared with global rate
2. Advanced age and severe involvement of the lung are risk factors for increased mortality rate in those patients
3. Inflammatory markers including CRP, ferritin and LDH and hypercoagulability marker (high level of D-dimer) are significantly associated with high mortality rate.

5.2 Recommendations

1. Older age patients and those with high severe lung involvement should direct clinicians to effectively prioritize resources for patients at high risk of mortality and to implement more aggressive treatments at an earlier phase to save patients' lives especially in the poor settings.
2. Neutrophil albumin ratio is an easy and cost effective test which could be routinely used for prognosis of patients with COVID-19 admitted to ICU.
3. The neutrophil albumin ration showed a significant association with mortality with a sensitivity and specificity of 80% for both, at a cut-off value of NAR = 358.85.

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