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Original article
Using inflammatory indices for assessing malnutrition among COVID-19 patients: A single-center retrospective study

Buthaina Alkhatib *, Huda M. Al Hourani, Islam Al-Shami

*Department of Clinical Nutrition and Dietetics, Faculty of Applied Medical Sciences, The Hashemite University, P.O. Box 330127, Zarqa 13133, Jordan

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Background: Coronavirus disease 2019 (COVID-19) causes malnutrition in infected patients. This study aimed to investigate the use of systemic immune-inflammatory index (SII), platelet-to-lymphocyte ratio (PLR), the Glasgow Prognostic Score (GPS), and neutrophil-to-lymphocyte ratio (NLR) for malnutrition assessment among COVID-19 inpatients.

Methods: This is a single-center retrospective study on 108 hospitalized COVID-19 patients; 14 were admitted to the intensive care unit (ICU). Data were collected from patients’ profiles while NLR, PLR, and SII were calculated. Inflammatory indices’ predictive power was analyzed using the receiver operating characteristic curve (ROC). A P-value of < 0.05 was considered statistically significant.

Results: Hospitalization days, neutrophils count, C-reactive protein (CRP), and serum urea levels were significantly higher in ICU patients. None of SII, PLR, and NLR were significantly different between ICU and non-ICU groups. Also, albumin and GPS showed a higher sensitivity level (100.0), followed by PLR and SII (78.57 and 71.34, respectively). Regarding ROC curves, even though NLR, PLR, and SII provided the largest area under the curve (AUC) (0.687, 0.682, 0.645; respectively), they have shown a poor discrimination ability, while GPS and albumin were ineffective in predicting malnutrition in COVID-19 patients.

Conclusion: NLR, SII, and PLR showed poor predicting ability for malnutrition among COVID-19 inpatients. Additional consideration should be taken for using inflammatory parameters (SII, PLR, GPS, and NLR) to predict malnutrition in COVID-19 inpatients.

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Introduction

Coronavirus-19 was first recognized in China, in December 2019, known globally as coronavirus disease (COVID-19) [1]. Male sex, older age, and previous related comorbidities (mainly chronic lung diseases, hypertension, and diabetes) are the most significant risk variables that link mortality, nutritional status, and the severity of COVID-19 [2,3], systemic inflammation, and malnutrition (obesity and undernutrition) [4,5]. In addition to malnutrition, trace elements and vitamins must be considered as they are crucial and involved in the modulation of immune responses and inflammatory status [5].

It has been reported that infectious respiratory diseases lead to malnutrition [6]. Similarly, studies have reported that about 50 % of COVID-19 patients describe olfactory and gustatory dysfunction, which could reduce food intake [7]. Li and colleagues showed a high prevalence of malnutrition [52.7 %] in 182 Chinese elderly COVID-19 patients [8]. Conversely, malnutrition [undernutrition and overweight or obesity] alters the immune response, leading to an increase in the risk of infections [9] such as influenza infection in mice and humans [10,11], respiratory viruses [12], and coronavirus [13].

One of the malnutrition diagnosis problems is the lack of a unified definition and standard methods for screening and diagnosis [14]. Although inflammation plays a major role in the pathophysiology of malnutrition, many clinicians assume that sudden weight loss is the most important criterion for a malnourished state in case of inflammation [15]. Albumin is the most abundant protein in human serum, it has been used as an indicator of malnutrition in patients, and systemic inflammation reduces albumin synthesis and increases its degradation [16]. There is relatively little evidence about predicting malnutrition in COVID-19 inpatients using laboratory inflammatory markers. Du and colleagues [17] have identified a composite malnutrition score based on albumin, cholesterol levels,
and lymphocyte count as an independent predictor of mortality in COVID-19 patients.

Recently, a predictable novel biomarker called systemic immune-inflammation index (SII) was proposed by Hu and colleagues [18]. SII is an inflammation-related indicator and can reflect the immune and inflammation status, based on the lymphocyte, neutrophil, and platelet counts [19]. Glasgow Prognostic Score (GPS) is another inflammatory indicator based on serum C-reactive protein and albumin levels [20]. A higher GPS was correlated with poor survival outcomes and a valid prognostic predictor in gynecologic cancer patients [21]. Also, GPS value represents a tool for evaluating metastatic or recurrent gastric cancer patient’s prognosis and should be part of a regular assessment of patients to provide timely nutrition care [22]. Maurício and colleagues (2013) found a correlation between nutritional status and GPS in colorectal cancer patients [23]. Other systematic inflammatory response indicators are the neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) [24]. A meta-analysis done by Abate and colleagues (2021) reported that the prevalence of malnutrition and mortality associated with malnutrition among COVID-19 hospitalized patients was very high [25].

There have been no studies on SII, PLR, GPS, and NLR in reflecting the prognosis of malnutrition in COVID-19 patients. As a result, the current study aimed to investigate the capacity of SII, PLR, GPS, and NLR instead of albumin to predict malnutrition in COVID-19 inpatients.

Materials and methods

Study design and data collection

This single-center prospective study included 108 patients diagnosed with COVID-19 by real-time PCR testing and hospitalized due to COVID-19 pneumonia, referred to the hospital, Amman, Jordan, between January and April 2021. The data were collected from patients’ profiles. Inclusion criteria were limited to COVID-19-admitted patients without chronic illnesses. The reported participants with chronic illnesses such as liver cirrhosis, renal issues, cardiac issues, diabetes mellitus, cancer, and hypertension were excluded. Among the selected patients from the hospital electronic database, 14 of them were admitted to the intensive care unit (ICU), and 94 were not. Demographic data and comorbidity were recorded for all patients. The hospital has accredited laboratories standardized for internal and external quality assurance measures.

The study protocol was carried out following the principles of the Declaration of Helsinki as revised in 2000. Ethical approval for this research was obtained from the Ethical Review Board at The Hashemite University (No.1/14/2020/2021).

Biochemical data and analysis

Blood samples were obtained from the peripheral vein within 24 h of hospitalization. Blood and serum were used to measure blood glucose, complete blood count, C-reactive protein (C-RP), blood proteins, and d-dimers for all COVID-19 patients, all tested parameter values were obtained from patients’ profiles. NLR ratio was calculated as the absolute count of neutrophils divided by the total count of lymphocytes. Also, the PLR was defined as the absolute count of platelets divided by the absolute count of lymphocytes. In addition, SII was calculated as the product of the neutrophil and platelet counts divided by the lymphocyte count [24]. GPS score was determined as follows: patients with both an elevated C-RP level and hypoalbuminemia (>1.0 mg/dl), <3.5 g/dl; respectively) were assigned a score of 2, patients with only one of these markers abnormalities were assigned a score of 1, and patients with neither of these abnormalities were assigned a score of 0 [26]. Patients with a GPS score ≥ 1 were classified as malnourished.

Statistical analysis

Statistical analysis was performed by using Statistical Package for Social Sciences (SPSS) software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) and MedCalc Statistical Software version 19.5.1 (MedCalc Software bv, Ostend, Belgium). Normal distribution was tested with the Shapiro–Wilk test. Continuous variables were described using means and standard deviations, and categorical variables were described using percentages. Frequencies were compared with the Chi-square test to compare ratios. Parameter differences between ICU/non-ICU were assessed using an independent samples t-test in cases of normal data distribution and the Mann–Whitney U in cases of non-normal data distribution. The receiver operative characteristic (ROC) curve with 95 confidence interval (CI) analyses was used to compare the predictive power of SII, NLR, PLR, GPS, and albumin indices area under the curve (AUC) with malnutrition in COVID-19 patients. The discrimination ability was classified based on AUC as followed: (0.9–1.0; 0.8–0.9; 0.7–0.8; 0.6–0.7 and 0.5–0.6 has excellent; good; fair; poor and failed discrimination abilities, respectively [27]. Cutoff values were determined by maximizing both specificity and sensitivity according to the Youden index. A p-value of <0.05 was considered statistically significant.

Results

The study included 108 hospitalized COVID-19 patients (14 were ICU patients). The general characteristics of selected participants are shown in Table 1.

As presented in Table 2, hospitalization days, neutrophils count, serum urea levels, and CRP were significantly higher in ICU patients vs non-ICU patients (12.71 ± 7.83 vs 7.48 ± 4.44; 87.08 ± 5.82 vs 78.65 ± 12.00; 39.21 ± 21.75 vs 30.00 ± 12.48; and 133.46 ± 94.93 vs 89.82 ± 64.59; respectively, p values <0.05). Blood sugar, NLR, PLR, SII, and GPS were not significantly different in ICU patients compared to non-ICU.

Table 3 and Fig. 1 show the areas under the ROC curve of NLR, PLR, SII, GPS, and albumin and their confidence intervals (95 %) as predictors for malnutrition in COVID-19 inpatients. The AUC of NLR, PLR, SII, GPS, and albumin were 0.687, 0.682, 0.645, 0.527, and 0.538, respectively, in predicting malnutrition among a group of COVID-19 inpatients (regardless of whether they were in ICU or not). In addition, the sensitivity level was higher in albumin and GPS (100.00), followed by significantly higher levels in PLR (78.57), and SII (71.43), and significantly lower in NLR (57.14). Overall, the AUCs of NLR, PLR, and SII showed poor predicting ability, while GPS and albumin failed to predict malnutrition among COVID-19 inpatients (Fig. 1).

Discussion

Assessment of nutritional status in COVID-19 inpatients is a challenge. However, it is difficult to assess malnutrition in COVID-19

Table 1

| General Characteristics of study participants. |
|-----------------------------------------------|
| Variables | ICU (n = 14) | Non-ICU (n = 94) | p-value |
|-----------|-------------|----------------|---------|
| Age       | 52.79 ± 13.78 | 47.04 ± 14.81 | 0.175   |
| Gender    | Male        | Female        |         |
|           | 9 (64.3)    | 5 (35.7)      | 0.682   |
|           | 55 (58.5)   | 39 (41.5)     |         |

* Values presented as mean ± S.D. or n [%]
patients by conventional nutritional screening measures \[28,29\], given the disease’s rapid progression and urgent nature \[28,30,31\].

Many studies used biochemical variables to investigate malnutrition, such as ferritin \[32\], albumin, cholesterol, lymphocyte count \[30,31\], and total protein \[33,34\]. In addition, malnutrition was assessed using inflammatory biomarkers, age, the severity of disease [ICU vs. non-ICU], and comorbidities \[17,31,35\]. Moreover, other variables were considered such as disease severity \[30\], the existence of comorbidities (diabetes mellitus, cardiovascular diseases, and hypertension) \[30\], ICU admission \[35\], hospital mortality \[5,8,17,31\], and hospitalization length \[36\].

The present study attempted to find predicting indicators for malnutrition in COVID-19 inpatients based on inflammatory indicators. Albumin and GPS failed to predict malnutrition in COVID-19 inpatients, despite the higher sensitivity level of albumin. Contrary to these findings on albumin, there is evidence of the association between COVID-19 severity and low albumin levels \[37,38\]. Bedrock et al. \[33\] reported that the prevalence of malnutrition was 66.7% in patients admitted to ICU; also, lower albumin levels were significantly associated with an increased likelihood of ICU admission. In a cross-sectional study, Li and colleagues \[34\] evaluated the nutritional status of elderly inpatients with COVID-19 using the Mini Nutritional Assessment [MNA]. Body mass index [BMI], calf circumference, albumin, hemoglobin, and lymphocyte count differ statistically between the three groups: non-malnutrition, at risk of malnutrition, and malnutrition \[33\]. Regarding, hemoglobin level and lymphocyte count, this study’s results are consistent with Li and colleagues’ findings \[34\]. The poor malnutrition prediction ability of albumin in the present data could be related to the small sample size.

Inverse to the current findings, GPS has been approved as a valuable tool for nutritional assessment in different cancers. Nei and colleagues \[21\] found that a higher GPS correlated with poor survival outcomes and a valid prognostic predictor in patients with gynecologic cancers \[21\]. The GPS level was a valuable tool for evaluating metastatic or recurrent gastric cancer patients’ prognoses and might be a part of a regular assessment to provide timely nutritional care \[22\]. Mauricio and colleagues \[2013\] found a correlation between nutritional status and GPS in colorectal cancer patients \[23\]. Also, the GPS correlated with 30-day readmission and surgical complications among the five commonly used nutrition assessment tools, it was the most prominently associated with short-term postoperative risks of all parameters in stage III gastric cancer patients \[29\]. Moreover, Lee and colleagues \[40\] found that high GPS is independently associated with both total and cardiovascular mortality in patients with acute coronary syndrome \[40\]. The present findings could differ from others; this may be due to the nature of the disease and the lack of studies that examined the same indicators for the same disease.

Our findings revealed that SII, PLR, and NLR have poor malnutrition prediction capacity in COVID-19 hospitalized patients. Previous studies indicated SII to be a predictive index for the prognosis of inflammatory diseases, obesity, pulmonary embolism, and tumors \[41–43\]. Also, Li and colleagues \[8\] found that SII might be a

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**Table 2**

Clinical outcomes in COVID-19 patients for ICU and non-ICU patients.

| Indicators | ICU (n = 14) | Non-ICU (n = 94) | p-value |
|------------|-------------|-----------------|---------|
| Hospitalization days | 12.71 ± 7.83 | 7.48 ± 4.44 | < 0.001 |
| Blood sugar (mg/dL) | 172.25 ± 63.71 | 144.68 ± 45.19 | 0.067 |
| White blood cell count (X10^3/L) | 9.21 ± 1.66 | 7.66 ± 3.39 | 0.125 |
| Neutrophil count (%) | 87.08 ± 5.82 | 78.65 ± 12.00 | 0.015 |
| Lymphocyte count (%) | 9.00 ± 4.44 | 16.62 ± 11.28 | 0.014 |
| Platelet count X10^9/L | 228.69 ± 61.03 | 235.96 ± 70.60 | 0.726 |
| Red blood cell count (X10^6/cu mm) | 4.77 ± 0.43 | 4.87 ± 0.52 | 0.523 |
| Hemoglobin (g/dL) | 13.62 ± 1.57 | 13.59 ± 1.68 | 0.941 |
| Albumin (g/dL) | 3.65 ± 0.38 | 3.68 ± 0.61 | 0.869 |
| Urea (mmol/L) | 39.21 ± 21.75 | 30.00 ± 12.48 | 0.024 |
| Creatinine (µmol/L) | 0.59 ± 0.18 | 0.64 ± 0.41 | 0.005 |
| C-reactive protein (mg/dL) | 133.46 ± 94.93 | 89.82 ± 64.59 | 0.030 |
| D-Dimer (ng/L) | 352.60 ± 218.58 | 536.25 ± 879.26 | 0.514 |
| NLR | 10.32 ± 5.20 | 7.42 ± 5.21 | 0.063 |
| PLR | 28.59 ± 10.79 | 20.95 ± 15.15 | 0.094 |
| SII | 2435.92 ± 1174.27 | 1787.68 ± 1421.66 | 0.134 |
| GPS* | 0 (0.0) | 5 (3.3) | 0.394 |
| Not malnourished (0 scores) | 14 (100.0) | 89 (94.7) |
| Malnourished (≥1 score) | 89 (94.7) | 7 (7.5) |

* n (%). NLR: Neutrophil to Lymphocyte ratio; PLR: Platelet to Lymphocyte ratio; SII: Systemic immune-inflammation index; GPS: The Glasgow Prognostic Score; ICU: intensive care unit.

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**Table 3**

AUC, Cutoff point, Sensitivity, and Specificity value for selected inflammatory indicators.

| Indicators | AUC (lower- higher) | Sensitivity | Specificity | Cutoff point | p-value | Youden index |
|------------|---------------------|-------------|-------------|--------------|---------|--------------|
| NLR | 0.687 (0.590–0.773) | 57.14 | 80.65 | > 11.13 | 0.0128 | 0.3779 |
| PLR | 0.682 (0.585–0.769) | 78.57 | 59.14 | > 19.94 | 0.0058 | 0.3771 |
| SII | 0.654 (0.547–0.735) | 71.43 | 59.14 | > 1695 | 0.0568 | 0.3057 |
| GPS | 0.527 (0.428–0.624) | 100.00 | 5.32 | ≤ 1 | 0.7468 | 0.0531 |
| Albumin | 0.538 (0.436–0.637) | 100.00 | 11.36 | ≤ 4.2 | 0.0328 | 0.1136 |
remarkable prognostic indicator to assess the mortality of in-hospitalized and ICU patients with COVID-19, and it could help in clinical risk assessment [44].

Hence, PLR and NLR have investigated health problems like malignancies, respiratory, gastrointestinal, cardiovascular, systemic diseases, or more severe forms of illness with the worst prognosis [24,35]. Also, these indicators have been used to assess the severity of COVID-19 [45]. Furthermore, Man and colleagues [46] found a positive correlation between NLR and PLR with chest computed tomography. scan severity in COVID-19 patients.

After reviewing the many studies, there were insufficient data on whether SII, NLR, GPS, and PLR play any role in prognostic abilities for malnutrition prediction in COVID-19 inpatients.

In conclusion, NLR, SII, and PLR showed poor predicting ability for malnutrition among COVID-19 inpatients.

Among the study’s limitations, the study’s retrospective design in a single center set a limit to the conviction of our study. Due to the nature of our study, the results must be explained with caution, given the possibility of confounders. Because of the limited number of COVID-19 patients, some conclusions are preliminary, especially those on the prospective impact of PLR, NLR, and SII on COVID-19. Nevertheless, as this topic’s information is scarce, we thought this to be a good starting point for future clinical trials validated in a larger population with a longer formal follow-up period. Finally, our work was lack of anthropometric data, so we could not apply any conventional malnutrition screening methods such as weight, which was not measured for the COVID-19 patients.

Ethics approval

The study protocol was carried out following the principles of the Declaration of Helsinki as revised in 2000. Ethical approval for this research was obtained from the Ethical Review Board at The Hashemite University (No.1/14/2020/2021).

Consent for publication

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Consent to participate

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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CRediT authorship contribution statement

B A; contributed to data collection, writing the first draft, and data analysis. H A; contributed to data collection and revision of the manuscript. I AS; data analysis and writing a draft.

Data availability

The database analyzed for the current study is available from the corresponding author on reasonable request.

Conflicts of interest/Competing interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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