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Prognostic value of the prognostic nutritional index in severe COVID-19 infection

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ABSTRACT

Objective: Nutritional status plays an important role in defense against infection. This study aimed to investigate the effect of the prognostic nutritional index (PNI), which consists of inflammation and nutritional markers, on prognosis and survival in patients with severe COVID-19 infection.

Material and Methods: Data were retrospectively collected by screening the files of 146 patients diagnosed with COVID-19 infection in 2020 and 2021. The PNI values of the patients were calculated using the obtained data. The cut-off value of PNI was determined with the receiver operating characteristic analysis. Multivariate and univariate analyses were undertaken to evaluate the prognostic value of PNI and its relationship with clinical features and overall survival (OS) in patients with severe COVID-19 infection.

Results: The study included a total of 146 patients, of whom 83 (60%) were male, and 55 (39.9%) were female. The mean age was 62 years. The cut-off value of PNI was 45. PNI was found to be associated with prognosis in both univariate and multivariate analyses. Survival and prognosis were statistically significantly better in the group with a PNI higher than the cut-off value (P<0.005).

Conclusion: PNI was determined to have independent prognostic value and predict OS in severe COVID-19 infection. The results showed that COVID-19 infection was more severe and had a worse prognosis in the patients with a low PNI (<45). Based on the measurement of simple, inexpensive, and easily available biomarkers, PNI can be beneficial in clinical practice.

Keywords: COVID-19, PNI, Prognosis

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2. The clinical presentation of COVID-19 varies from the asymptomatic carriage or mild acute respiratory disease to severe pneumonia, acute respiratory failure (ARDS), and multiorgan failure (1-3). COVID-19 infection is associated with immune dysregulation, and hyperinflammation. ARDS develops in approximately 25% of severe COVID-19 cases. In those developing ARDS, the rate of mortality is 60%. Risk factors for the development of severe COVID-19 include male gender, age > 65 years, presence of diabetes mellitus, and history of cardiovascular or respiratory disease (4). Severe COVID-19 infection presents with the excessive secretion of interleukin (IL)-6, IL-2, IL-7, IL-10, granulocyte colony-stimulating factor, interferon-γ-inducible protein, monocyte chemoattractant protein, macrophage inflammatory protein 1 alpha, and tumor necrosis factor-alpha.

The release of these inflammatory cytokines leads to the development of an uncontrollable inflammatory response, ARDS, and multi-organ failure. There is also an increase in lymphocytes and monocytes in the pulmonary vascular bed, endotheliitis, thrombosis, and inflammation due to angiogenesis (5-7). Tocilizumab is a monoclonal anti-IL-6 receptor-alpha blocking antibody used in patients with bilateral severe lung involvement and high IL-6 levels. Tocilizumab corrects impaired alveolo-capillary dysfunction by reducing the cytokine storm, thereby increasing oxygenation and preventing progression to pulmonary fibrosis. Clinically, mechanical ventilation requirement decreases, and lung findings improve (Figure 1) (8-11).

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In severe COVID-19 infection, individualized prognostic factors are needed to determine risk and predict survival and recovery clinically. The progression and prognosis of these patients are correlated with their inflammatory and nutritional status. The prognostic nutritional index (PNI) indicates nutritional, inflammatory, and immunological status. In many malignant diseases, systemic inflammation is a prognostic factor that is associated with malnutrition (12,13). In this study, we aimed to investigate the predictive and prognostic value of PNI in patients prescribed tocilizumab diagnosed with severe COVID 19 infection.

Figure 1: Mechanism of action of tocilizumab (8-11)

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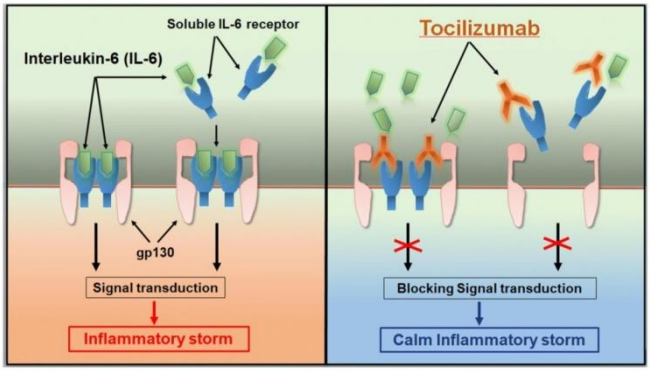

MATERIAL and METHODs

The study included patients who presented to the Internal Medicine Clinic of Yuzuncu Yil University from March 1, 2020, through September 31, 2021, with any of the complaints of fever, cough, loss of taste and smell, myalgia, shortness of breath and were diagnosed with COVID-19 based on the polymerase chain reaction test positivity and/or thorax computed tomography findings. The files of a total of 146 patients were retrospectively reviewed. Age, gender, complete blood count parameters (leukocyte, hemoglobin, and lymphocyte), alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), albumin, urea, creatinine were recorded from the hospital registration system. PNI was calculated based on the data obtained. Patients with a history of malignancy, other infections, or chronic inflammatory disease were excluded from the study. The patients were divided into two groups, with and without tocilizumab treatment. Both groups were compared in terms of clinical findings.

Onodera's PNI was calculated as follows: 10 x serum albumin level (g/dL) + (0.005 × lymphocyte count in peripheral blood (×109/L) (14).

Overall survival (OS) was defined as the time from the diagnosis of COVID-19 to death. OS was evaluated with multivariate and univariate analyses.

Statistical analysis: Descriptive statistics were presented as numbers and percentages for categorical variables, and median (minimum-maximum) and mean ± standard deviation values for numerical variables. The cut-off value of PNI was analyzed using the receiver operating characteristics (ROC) curve analysis. Visual (histogram) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) were used to determine the distribution of variables. Normally distributed parameters were compared with Student's t-test and those without a normal distribution were compared with the Mann-Whitney U test. Differences between independent groups were compared with either the chi-square or Fisher's exact test. Survival curves were obtained using the Kaplan-Meier analysis. The Statistical Package for the Social Sciences (SPSS) v. 21 and R softwares were used for statistical analyses. $P < 0.05$ was considered statistically significant.

RESULTs

The study included a total of 146 patients, of whom 83 (60%) were male, and 55 (39.9%) were female. The mean age was 62 years. The median follow-up time was two months. Of the patients, 103 (70%) were hospitalized and given combination therapy with favipiravir and prednisolone. Tocilizumab treatment was initiated in 43 (30%) patients who did not respond to the combined therapy. Leukocyte count was significantly lower in the tocilizumab group than in the group not treated with tocilizumab ($p < 0.05$). The mean lymphocyte count was significantly higher, and the platelet count was significantly lower in the tocilizumab group compared to the control group ($p < 0.05$). The blood glucose level was also significantly higher in the tocilizumab group than in the control group ($p < 0.05$). The AST level was significantly higher in the control group compared to the tocilizumab group ($p < 0.05$), but the ALT levels did not significantly differ. The CRP level was significantly higher in the tocilizumab group than in the control group ($p < 0.05$). The mean length of hospital stay was 20 days in the patients receiving tocilizumab and 7 days in the control group, indicating statistically significantly longer hospitalization in the former ($p < 0.05$). The cut-off value of PNI was determined as 45. PNI was associated with prognosis according to both the univariate and multivariate analyses. Survival and prognosis were statistically significantly better in the group with a PNI above the cut-off value ($p < 0.005$) (Table 1).

Table 1: Demographic and clinical data of the patients

Parameter		
Age, median (min-max)		62 (28-83)
Gender	Male	83 (60%)
	Female	55 (39.9%)
PNI, median (min-max)		45 (31.5-82)
Lymphocyte (/µL), median (min-max)		1,5 (0.08-7.5)
Hemoglobin (g/dl), mean ± SD		12.2 ± 1.5
Albumin (g/dl), mean ± SD		3.7 (2.6-5)
Favipiravir-steroid combined therapy		103 (70%)
Tocilizumab therapy		43 (30%)
Length of hospital stay	Tocilizumab (+)	20 days
	Kontrol (Tocilizumab (-))	7 days

DISCUSSION

In the literature, many studies investigate the prognostic value of inflammatory and nutritional parameters in many malignant or non-malignant diseases. Based on this idea, we conducted the current study to determine whether PNI, which is both a nutritional and inflammatory marker, had prognostic value and affected survival in patients with severe COVID-19 infection. We determined that a low PNI was an independent factor of poor prognosis in severe COVID-19 infection. A healthy diet is necessary for the protection against infections and formation of immune response. Individuals with severe COVID-19 infection develop malnutrition due to severe inflammation and anorexia. The European Society for Clinical Nutrition and Metabolism emphasizes that the risk of malnutrition should be identified early in those infected with COVID-19 (15,16). Liu et al. conducted a retrospective study to evaluate nutritional risks and the correlation of COVID-19 with clinical outcomes among elderly COVID-19 cases aged over 65 years. The authors showed that the Nutrition Risk Screening-2002, Mini Nutritional Assessment Short-Form, and nutritional risk index were useful and practical for screening nutritional risk in patients with COVID-19 (17). Inflammation and nutritional status significantly affect the progression and survival of inflammatory diseases (12). Local inflammation is indicative of the systemic inflammatory response. Immunomodulatory cytokines and systemic inflammatory markers (neutrophils, lymphocytes, IL-1, 6, 8, and 9, and tumor necrosis factor-alpha) in the inflammation site play an important role in the progression of infection. High metabolic rate, anorexia, and hypoalbuminemia seen in the presence of infection cause malnutrition, which then leads to the impairment of cytokine response and immune system activation. Peripheral blood cells are an indicator of inflammatory and immune response against tumors and have independent prognostic significance (16-18). However, the underlying mechanism of the relationship between PNI and the severity of COVID-19 remains unclear. PNI is a combination of peripheral blood lymphocyte count and albumin concentration and correlates nutritional status with immune response. Nutritional status is known to play a critical role in the immune response. Nutritional deficiency is associated with immunodeficiency, which manifests as the disruption of cell-mediated immunity, phagocyte function, complement system, and cytokine production (19,20). The serum albumin level is generally an indicator of malnutrition. Beside malnutrition, other pathological acute or chronic conditions presenting with inflammation (liver failure, nephrotic syndrome, and protein-losing enteropathy) decrease the serum albumin levels. Some proinflammatory cytokines also reduce albumin synthesis. Peripheral lymphocytes are also known to show the immunological and nutritional status of individuals. Therefore, PNI, calculated based on serum albumin and lymphocyte values, is more significant in terms of prognosis. Recent studies have shown that a low PNI is associated with a poor prognosis in many gastrointestinal system malignancies. In the current study, we obtained similar results. In a study by Nalbant et al., PNI was shown to be an independent prognostic factor in patients with severe COVID-19 infection followed up in the intensive care unit (21). In another study, Hu et al. reported that malnutrition was associated with severe COVID-19 infection, and patients with a low PNI had a worse prognosis (22). Wang et al. detected a relationship between PNI and mortality due to COVID-19 infection (23). In a retrospective meta-analysis of 13 studies, Hung et al. found PNI to be a predictive factor of disease severity and mortality in COVID-19 infection (24). In the literature, the cut-off value of PNI has been reported in a wide range from 40 to 55, and there is no standard threshold (25).The cut-off value of PNI varies depending on the number of patients and differences in the technical methods used.There are some limitations to our study. It had a retrospective and single-center design, which also resulted in a small sample size. In addition, the nutritional status of the patients at the time of admission could not be evaluated.

CONCLUSION

Nutrition and inflammatory markers have independent prognostic significance in COVID-19 infection. PNI is an independent prognostic factor of severe COVID-19 infection. The results of this study showed that COVID-19 infection had a more severe and clinically worse prognosis in those with a low PNI (<45). Based on the measurement of simple, inexpensive, and easily available biomarkers, PNI can be beneficial in clinical practice. Nutritional status should be improved by providing nutritional support for patients before treatment to increase the quality of life, life expectancy, and prognosis of patients during the follow-up. There are very few studies in the literature investigating the prognostic significance of PNI in COVID-19 infection. Therefore, we consider that the results of this study are important and will contribute to the literature.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Non-Invasive Clinical Research Ethics Committee of Yuzuncu Yil University Faculty of Medicine approved the study (decision date: 16/10/2020, number: 2020/07-11).

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