RESEARCH

EVALUATION OF PENTRAXIN 3 UTILITY IN PREDICTING MORTALITY IN GERIATRIC PATIENTS WITH COVID-19: A PROSPECTIVE STUDY

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Abstract

Introduction: The clinical spectrum of coronavirus disease (COVID-19) ranges from mild upper respiratory tract infections to fulminant pneumonia. Nevertheless, it is associated with high rates of morbidity and mortality in elderly individuals. The present study aimed to investigate the levels of pentraxin 3 in geriatric patients with COVID-19 and to determine whether it could serve as a marker for predicting mortality.

Materials and Method: This study included patients aged ≥ 65 years who were diagnosed with COVID-19 infection and admitted to the pandemic ward between October 2021 and march 2022. The patients were classified into two groups: survivors and nonsurvivors.

Results: Of the 95 geriatric patients included in this study, 20 (21%) died and 75 (79%) were discharged upon full recovery. There was a significant difference between male and female patients in terms of mortality. Shortness of breath was noted in 19 nonsurvivors and 9 survivors ($p < 0.05$). The median pentraxin 3 level was 5.8 ng/mL (1–20) for all patients, 3.92 ng/mL (1–19.6) for survivors, and 6.3 ng/mL (4.1–20) for nonsurvivors ($p < 0.001$). The area under the curve in the receiver operating characteristic curve analysis for pentraxin 3 was 0.596 ($p = 0.04$) to predict mortality. The likelihood ratio test revealed a cutoff value of 4.43 ng/mL (sensitivity: 57.1% and specificity: 70.5%) for pentraxin 3.

Conclusion: Pentraxin 3 was found to be a novel biomarker for predicting mortality in geriatric patients with COVID-19, and it was investigated for the first time in this special population.

Keywords: COVID-19; Geriatrics; Mortality; Acute-Phase Proteins.

INTRODUCTION

In December 2019, the World Health Organization reported pneumonia cases of unknown etiology in Wuhan, Hubei Province, China. The causative agent was identified as a new coronavirus (2019-nCoV), and the pneumonia caused by it was termed COVID-19 (1). COVID-19 has affected countries worldwide, giving rise to a pandemic associated with significant morbidity and mortality (2). Disease severity has ranged from asymptomatic clinical forms to severe clinical forms, with signs and symptoms of pulmonary parenchymal involvement (3).

Respiratory infections are among the major causes of morbidity, hospitalization, and mortality throughout the world, especially in elderly individuals. Elderly patients with infectious diseases exhibit atypical prognoses owing to chronic alterations, along with genetic and environmental factors (4). Furthermore, delayed diagnosis and a worsened prognosis are highly prevalent in this population because current symptoms may be considered a natural consequence of aging (5). Nevertheless, early diagnosis and assessment of disease severity are essential for the optimal treatment of respiratory infections (6).

While the lack of reliable means available to diagnose respiratory infections continues to be a major problem, many biomarkers, such as C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), plasminogen activation inhibitor-1, and pentraxin 3 (PTX3), have been introduced to improve diagnostic accuracy (6–8). PTXs are a family of acute-phase reactants characterized by a cyclic multimeric structure. The PTX family is classified into two subgroups—short and long—depending on the primary structure of the protein. CRP and serum amyloid-P belong to the short pentraxin subgroup, whereas PTX3 is included in the long pentraxin subgroup. It has been established that increased levels of PTX3 serve as an independent marker associated with the risk of developing certain diseases, including atherosclerosis, cancer, respiratory diseases, and central nervous system diseases (9,10).

The role of PTX3 is not yet clearly understood in the geriatric population with COVID-19. To our knowledge, this is the first study in which a new biomarker was investigated to predict mortality in geriatric patients with COVID-19. The present study aimed to investigate the levels of PTX3 in geriatric patients with COVID-19 and to determine whether it could serve as a marker for predicting mortality.

MATERIALS AND METHOD

This prospective study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Firat University with the number 3801 dated September 16, 2019. The participants were briefed about the study and their respective written consents were obtained prior to the collection of clinical information and blood samples.

Study design

Patients and Controls: This study included patients diagnosed with SARS-CoV-2 infection and admitted to the pandemic ward between October 2021 and March 2022. According to the inclusion criteria, patients aged ≥ 65 years in whom COVID-19 diagnosis was confirmed via real-time polymerase chain reaction were included in the study. Patients aged < 65 years who were suspected to have another infection and received antimicrobial therapy during the last 1 month were excluded from the study. The patients were classified into two groups—survivors and nonsurvivors.

Data collection

Clinical data: Patient data, including demographic characteristics, medical history, and the status of receiving other COVID-19 therapies (such

as anticytokine treatment), were retrieved from the hospital's electronic registration system. All the patients underwent pulmonary computed tomography at admission. Furthermore, the need for ventilators, length of hospital stay, and rate of mortality were recorded during the study.

Determination of plasma levels of pentraxin 3: At admission, venous blood (5 mL) was collected from the patients and stored in ethylenediaminetetraacetic acid-containing tubes. The blood samples were centrifuged within 40 min of their collection at 3500 rpm for 10 min. The plasma samples were kept at −80°C until examination. Serum PTX3 levels were analyzed using an enzyme-linked immunosorbent assay (ELISA) kit (human PTX3; catalog no.: 201-12-1939; Biological Technology Co., Ltd, Shanghai, China) in accordance to the manufacturer's instructions. The measurement range of the human PTX3 ELISA kit was 0.08–20 ng/mL, and the intra-assay and interassay CV values were <10% and <12%, respectively. The test results were expressed in ng/mL.

Routine biochemistry and hematology: Standard blood assays were performed as a part of the routine analyses for many parameters, including CRP levels, white blood cell count (WBC), ESR, and PCT and D-dimer levels.

Statistical analysis: SPSS v.22 package program (SPSS, Inc., Chicago, IL, USA) was used for data analysis. Visual (histograms and probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test) were used to test the variables' normality of distribution. Continuous variables with normal distribution were expressed as mean (±standard deviation), whereas data with non-normal distribution were presented as median (minimum–maximum). Categorical variables were expressed as frequency and percentage. Mann–Whitney U test or Student's *t*-test was used to compare continuous variables based on their normality of distribution. The cutoff value for PTX3 to predict mortality was calculated using ROC analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

Of the 95 geriatric patients included in this study, 42 (44%) were females and 53 (56%) were males ($p > 0.05$). The median ages of the female and male patients were 65 (65–85) and 65 (65–89) years, respectively ($p > 0.05$). Additionally, 20 (21%) patients died, and 75 (79%) were discharged upon full recovery. Of the nonsurvivors, 7 (35%) were females and 13 (65%) were males. There was a significant difference between the male and female patients in terms of mortality ($p < 0.05$). The median ages of the survivors and nonsurvivors were 65 (65–82) and 65 (65–89) years, respectively ($p > 0.05$). Shortness of breath was observed in 19 (95%) nonsurvivors and 9 (12%) survivors ($p < 0.05$).

Laboratory values in the general population were 32 (5–334) for CRP, 0.12 (0.03–93) for PCT, 554 for D-dimer (441–1620), 0.71 (0.62–1.6) for creatinine, 4.5 (1.2–16) for high-sensitivity troponin, 40 for ESR (21–123), 6,850 for WBC (2,400–24,900), 4,560 for neutrophils (1,390–22,420), 1,410 (660–6,520) for lymphocytes, 264.2 ± 137 for platelets, 265 ± 364 for ferritin, 38 ± 11 for aspartate aminotransferase, 34 ± 23 for alanine aminotransferase, 293 ± 156 for lactate dehydrogenase (LDH), and 590 ± 297 for fibrinogen. The biochemical parameters of the nonsurvivors and survivors and their relationships are provided in Table 1.

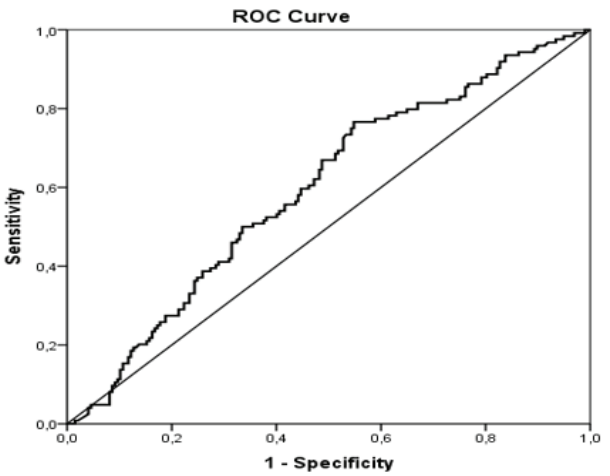
Median PTX3 levels were 5.8 (1–20) ng/mL for all the patients. The survivors and nonsurvivors had median PTX3 levels of 3.92 (1–19.6) ng/mL and 6.3 ng/mL (4.1–20) ng/mL, respectively ($p < 0.001$). The AUC for the ROC curve analysis of PTX3 was 0.596 ($p = 0.04$) to predict mortality (Figure1). When performing the LR test, the cut-off value for PTX 3 was 4.43 ng/mL (sensitivity: 57.1% and specificity: 70.5%).

Table 1. Laboratory parameters of the patients

Characteristics	Nonsurvivors (n:20)	Survivors (n:75)	P value
WBC, K/uL	1200±11700	6230±5700	0.584
Neutrophil, K/uL	1000±1190	4210±510	0.290
Lymphocyte, K/uL	810±500	2260±3360	**0.036**
Platelet count, K/uL	184.2±103.0	323.2±167.5	0.134
CRP, mg/L	75 (34-334)	21 (3-133)	0.046
Procalcitonin, ng/mL	1.15 (0.1-95)	0.10 (0.02-0.28)	0.07
ESR (>20mm/saat)	34±14	63±74	0.606
AST, U/L	48±32	40±14	0.037
ALT, U/L	35±12	42±32	0.233
LDH, U/L	312±186	310±152	0.028
Serum albumin, g/L	3.5±0.7	3.9±0.5	0.002
Kreatinin, mg/dL	0.91 (0.62-1.6)	0.72 (0.63-1.31)	0.187
Ferritin, ug/L	416±262	334±274	0.010
D-dimer, ugFEU/L	723 (441-6970)	675 (458-1620)	0.033
hsTn I, ng/L	4.9 (1.2-13.5)	4.6 (2.9-16)	0.082

CRP: C reactive protein, ESR: Erythrocyte sedimentation rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

Figure 1. ROC curves of pentraxin-3 on differentiating survive patients from nonsurvives with COVID-19



DISCUSSION

SARS-CoV-2 infection may occur in various clinical forms, ranging from mild upper respiratory tract infections to fulminant pneumonia (11), and some affected patients may experience progression to life-threatening acute respiratory distress syndrome, coagulopathy, and septic shock (12). In patients with COVID-19, the risk of progression to severe disease is 26%–32%. An increased risk of mortality is expected, especially in elderly patients, due to an increased risk of a worsening prognosis (13).

The overall rate of COVID-19-related mortality ranges from 2.3% to 14.8% depending on the demographic characteristics of the country or region, age, disease severity, and comorbidities (14). Increased

mortality was directly related to the demographic factors, including advanced age and male sex in the cohorts of the patients with COVID-19(15). The present study on the geriatric patient population supported all the foregoing results, and the overall mortality rate was found to be 21%. Furthermore, the mortality risk was higher in the male patients in our study. The most common symptoms reported by patients with COVID-19 were fever, fatigue, and dry cough (16). Nevertheless, the fever response is generally weak, especially in elderly individuals. Pulmonary involvement with shortness of breath is frequently seen in the critical patient group (17). In the present study, the incidence of shortness of breath was significantly higher in the nonsurvivors than in the survivors.

It was found that increased levels of laboratory parameters, especially CRP, ferritin, LDH, D-dimer levels, and lymphopenia were directly associated with the progression of COVID-19 (18). Critical patients exhibited leukopenia, lymphopenia, increased liver enzyme, ferritin, lactate dehydrogenase, and D-dimer levels, and increased prothrombin time (16). The mortality rate was higher in patients with high D-dimer levels and severe lymphopenia (19). In this study, significantly increased CRP, PCT, D-dimer, LDH, ferritin levels, and lymphopenia were observed in the nonsurvivors. The laboratory results reported in our study were consistent with those reported in the relevant literature.

The serum PTX3 levels are typically very low in healthy individuals (<2 ng/mL) and rapidly and highly increase in patients with various infectious and inflammatory conditions (20). The plasma PTX3 level has a diagnostic and prognostic role in many diseases, as it reaches peak concentration 6–8 h after an inflammatory stimulus (21, 22). It is well established that significantly higher PTX3 levels are observed in association with viral and bacterial diseases (23). Moreover, PTX3 has been proven to be a prognostic marker in community-acquired pneumonia (24), ventilator-associated pneumonia (25), and sepsis (23).

Genç et al. (21) reported a PTX3 level of 3.91 (1.9–23.2) in nonsurvivors, which was statistically significantly higher compared to that of the survivors in a study of 88 patients with COVID-19 aged 67 (23–95) years. In the present study, there was a significant correlation between the inflammation indicator serum PTX3 level and COVID-19-related mortality, and the cutoff value to predict mortality was 4.43 ng/mL. Also, it was suggested that increased PTX3 levels could predict increased mortality risk in geriatric patients with COVID-19, which would enable early intervention in the management of patients included in this high-risk population.

This is the first study to demonstrate the utility of plasma PTX3 levels in geriatric patients with COVID-19. However, there are certain limitations to this study. The relatively limited number of patients, examination of PTX3 levels only at admission, and lack of a healthy control group are also some limitations of the study.

In conclusion, given the increased risk of worse prognosis and mortality rate associated with COVID-19 in the high-risk geriatric patient group, early prognostic information should be obtained by the determination of PTX3 levels along with the evaluation of conventional mortality predictors, thereby improving clinical prognosis and enabling the provision of rapid individualized treatment.

Conflict of Interest: There is no conflict of interest.

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