RESEARCH

Pentraxin-3 (PTX-3) as a potential biomarker for predicting death in hospitalized patients with COVID-19

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Abstract

Background   Pentraxin 3 (PTX3) is an acute-phase protein that belongs to the pentraxin family, which plays an important role in the body's defense against pathogens. PTX3 levels have been associated with inflammatory processes, and it is a possible biomarker for the diagnosis and prognosis of different infectious diseases, including COVID-19. The objective of this study was to analyze the potential of PTX3 as a plasma biomarker for predicting death in patients hospitalized with COVID-19.

Methods   The study included a total of 312 patients with COVID-19, admitted from July 2020 to August 2021 to hospital ward and intensive care unit beds at two hospitals in the Northeast Region of Brazil. PTX3 was measured using ELISA in samples collected within 24 h after hospital admission. Maximally selected rank statistics were used to determine the PTX3 cutoff point that best distinguished patients who died from those who survived. A receiver operating characteristic (ROC) curve was used to determine the performance of the biomarker. Survival analysis was performed using a Kaplan-Meier curve, and a Cox regression model was used to determine predictors associated with death.

Results   Of the 312 patients included in the study, 233 recovered and 79 died. Patients who died had higher PTX3 levels at the time of admission, when compared to those who recovered (median: 52.84 versus 10.79 ng/mL; $p < 0.001$). PTX3 showed area under the ROC (AUC) = 0.834, higher than other markers used in clinical practice, such as C-reactive protein (AUC = 0.72) and D-dimer (AUC = 0.77). Furthermore, according to the Kaplan-Meier survival curve, patients with PTX3 concentrations above the cutoff point (27.3 ng/mL) had a lower survival rate ($p = 0.014$). In multivariate Cox regression, PTX3 > 27.3 ng/mL was an important predictor of death, regardless of other confounding factors (hazard ratio = 1.79; $p = 0.027$).

Conclusion   PTX3 can be considered as a potential biomarker for predicting death in patients hospitalized with COVID-19.

Keywords   Biomarkers, COVID-19, Innate immunity, Pentraxin, SARS-CoV-2

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Background

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China. The virus was capable of causing an infectious respiratory disease called COVID-19 [1]. Due to its high transmissibility, in March 2020, the COVID-19 pandemic was declared by the World Health Organization [2]. By April 1, 2021, there were approximately 135 million people affected and 3 million deaths, increasing to approximately 700 million confirmed cases and more than 7 million deaths by April 1, 2024 [3].

In Brazil, according to the Coronavirus Panel established by the Brazilian Ministry of Health, as of April 4, 2024, there were around 38 million confirmed cases, with approximately 700,000 deaths. The Northeast Region of Brazil holds third place in the ranking of the most affected regions with respect to the number of confirmed cases and second place with respect to number of deaths, with the states of Bahia, Ceará, and Pernambuco standing out [4].

COVID-19 has an abrupt course, ranging from the asymptomatic form to the death of affected patients [5]. In view of this, it is of fundamental importance to investigate possible markers capable of predicting the severity and clinical outcome of patients affected by COVID-19, in order to assist clinical staff in decision-making.

Pentraxins are a class of proteins of the innate immune system that have been extensively studied in relation to various pathologies, such as cardiovascular diseases [6], kidney diseases [7], and lupus erythematosus [8]. They are divided into short (C-reactive protein [CRP] and serum amyloid P) and long pentraxins (long pentraxin 3 [PTX3]) [9]. PTX3 was the first long pentraxin identified, and it differs from short pentraxins due to the N-terminal region. This protein is a pattern recognition molecule (PRM) whose expression is mainly stimulated by damage-associated molecular patterns (DAMPs), inflammatory stimuli, and inflammatory cytokines [10].

Previous studies have provided evidence regarding the role of PTX3 in the clinical course of COVID-19 [11–22]. For example, a cross-sectional study conducted in Italy demonstrated greater PTX3 concentrations in patients admitted to the intensive care unit (ICU) compared to those not in the ICU [11]. In another study conducted in Italy with two independent cohorts (96 and 54 participants), PTX3 was a strong predictor of short-term mortality in patients with COVID-19 [12].

Notwithstanding these findings, there is still a lack of studies with significant sample sizes that have the objective of evaluating the role of PTX3 as a biomarker of clinical outcome in COVID-19. Therefore, the objective of this study was to evaluate the performance of PTX3 plasma levels as a potential biomarker for predicting death in hospitalized patients with COVID-19 and to compare its performance to other markers used in clinical routine.

Methods

Ethical considerations

This study was approved by the Ethics Committee of the Hospital das Clínicas of the Federal University of Pernambuco (HC/UFPE) under protocol number CAAE: 36613520.0.0000.5640. A free and informed consent form was obtained in accordance with the requirements of the Brazilian National Research Ethics Commission (CONEP, acronym in Portuguese).

Study population

This accuracy study included 312 samples (233 recovered and 79 deaths) from patients with confirmed COVID-19 admitted between July 2020 and August 2021 at the University Hospital of the Universidade Federal do Vale do São Francisco (HU-UNIVASF) and at the Field Hospital of the City of Petrolina, Pernambuco, both references in the treatment of COVID-19 in the Vale do São Francisco region, Northeast Brazil.

Data collection

Clinical and laboratory data were acquired through analysis of electronic medical records. The characterization of patients was carried out by collecting information, such as sex, age, symptoms, comorbidities, length of hospital stay, and outcome. Laboratory tests were conducted within 24 h after admission, and they included the following: total leukocytes, platelet count, fasting blood glucose, activated partial thromboplastin time (APTT), D-dimer, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, creatinine, CRP, urea, and international normalized ratio (INR).

Sample collection and processing

Blood samples from hospitalized patients were collected in a tube containing the anticoagulant ethylenediaminetetraacetic acid (EDTA) by venipuncture, within 24 h of hospital admission, and they were sent to the Multi-User Research Laboratory (LAMUPE, acronym in Portuguese) of the HU-UNIVASF. Upon receipt, the samples were centrifuged at 3500 rpm for 10 min to obtain plasma. The plasma was then transferred to cryogenic tubes (Greiner Bio-One) and stored in a freezer at −80 °C until PTX3 measurement using commercial kits.

PTX3 quantification

PTX3 quantification was performed in plasma samples using enzyme-linked immunosorbent assay (ELISA). Patients were randomly selected according to the availability of biological material for the assay. Commercially available Human Pentraxin 3/TSG-14

Immunoassay Quantikine™ ELISA kits (R&D Systems, Minneapolis, MN, USA) were used, following manufacturer instructions.

An automatic microplate washer (Asys Atlantis®), programmed according to the instructions for the kit used, was used to wash the assay microplates. Absorbances were obtained by reading at 450 nm and corrected at 620 nm, using a Multiskan FC microplate reader (Thermo Fisher). The results were analyzed using a four-parameter logistic curve, with free software available at: https://www.bosterbio.com/biology-research-tools/elisa-data-analysis-online.

Statistical analysis

For data analysis, SPSS Statistics version 22.0 (SPSS, Inc., Chicago, IL, USA) and RStudio® version 2023.06.0+421 were used. GraphPad Prism version 9.0 (GraphPad, San Diego, CA, USA) was used to create graphs.

The MissForest package was used to impute data on laboratory variables with up to 30% missing data. MissForest is a machine learning-based data imputation algorithm that uses the random forest algorithm as its principle.

The Kolmogorov-Smirnov test was used to verify the distribution of continuous variables. Comparisons between the two groups were performed using Student's t test and/or Mann-Whitney test for parametric and non-parametric variables, respectively. For categorical variables, Pearson's chi-square test or Fisher's exact test was used. Categorical data were expressed as absolute and relative frequency (percentage). Continuous variables

were shown as median with interquartile range (IQR). The performance of laboratory tests to distinguish deaths and recoveries was evaluated using the area under the receiver operating characteristic curve (AUC).

The maximally selected rank statistics package of RStudio software was used to determine the best cutoff point for PTX3 levels to distinguish the study groups. Subsequently, survival analysis was performed using the Kaplan-Meier method (log-rank test). Baseline host variables with a p-value<0.05 in the univariate analysis were included in a Cox regression model (backward method) to determine whether PTX3 plasma levels were an important predictor of death due to COVID-19 independent of other variables and to calculate the hazard ratio (HR).

Results

The study included a total of 312 patients (233 recovered and 79 deaths). There was a prevalence of males in both groups. Participants who died were older when compared those who recovered, 62 versus 51 years, respectively ($p<0.001$). A higher prevalence of comorbidities, such as diabetes, chronic heart disease, chronic kidney disease, hypertension, and obesity, was observed in the group of patients who died ($p<0.05$ for all comparisons). The use of invasive ventilatory support was higher in the group that died compared to those who recovered (100% vs. 30%; $p<0.001$), as was the median length of stay (13 days vs. 4 days; $p<0.001$). Only 1 patient was taking an immunosuppressive drug on admission Table 1).

Table 2 summarizes the distribution of the median and IQR of laboratory data collected within 24 h after admission, among patients who died and recovered. Among the routine variables analyzed, only platelets, ALT, and total bilirubin did not show a significant difference between the groups studied. Plasma PTX3 levels, in turn, were higher in patients who did not survive COVID-19 than in those who recovered (median 52.84 versus 10.79 ng/mL), and this difference was approximately 5 times greater when comparing the groups ($p<0.001$) (Table 2).

The performance of laboratory variables with $p<0.05$ in the univariate analysis was subsequently evaluated using the AUC (Fig. 1). Among the laboratory tests evaluated, PTX3 performed best, presenting AUC=0.834.

To assess whether PTX3 levels could be influenced by host factors, we checked whether there was an association between PTX3 levels, gender and age. We found that PTX3 plasma levels were significantly higher in men than in women (median: 21.1 ng/mL vs. 11.06 ng/mL; $p=0.007$) (Figure S1). It was also observed that PTX3 levels increased with age ($p=0.008$) (Figure S2). Therefore, in order to check whether PTX3 plasma levels could perform well in predicting death regardless of possible confounding factors such as age and gender, we carried out

Table 1 Clinical data of patients who recovered and those who died due to COVID-19

Variables	All (*n*=312)	Recovered (*n*=233)	Death (*n*=79)	*P* value
Age, median [IQR]	53 [42–64]	51 [40–61]	62 [52–75]	<0.001
Sex				
Female, n (%)	115 (36.86)	85 (36.48)	30 (37.97)	1.000
Male, n (%)	197 (63.14)	148 (63.51)	49 (62.03)	1.000
Comorbidity				
Diabetes, n (%)	85 (27.24)	51 (21.88)	34 (43.03)	<0.001
Chronic heart disease, n (%)	13 (4.16)	5 (2.14)	8 (10.12)	0.002
Chronic kidney disease, n (%)	14 (4.80)	3 (1.28)	12 (15.19)	<0.001
SAH, n (%)	154 (49.35)	103 (44.20)	51 (64.55)	0.002
Obesity, n (%)	71 (22.75)	46 (19.74)	25 (31.64)	0.029
Immunosuppressive drug, n (%)	1 (0.3)	0	1 (1.26)	0.253
Invasive ventilation, n (%)	151 (48.4)	72 (30.9)	79 (100)	<0.001
Length stay, days median [IQR]	6 [3–14]	4 [3–9]	13 [8–23]	<0.001

Legend IQR: interquartile range; SAH: systemic arterial hypertension

Table 2 Median and interquartile range of laboratory variables investigated according to outcome in patients with COVID-19

Variables	All (*n* = 312)	Recovered (*n* = 233)	Death (*n* = 79)	*P* value
Total bilirubin (mg/dL)	0.36 [0.26–0.48]	0.36 [0.26–0.46]	0.35 [0.24–0.56]	0.541
Creatinine (mg/dL)	0.86 [0.70–1.07]	0.82 [0.66–0.99]	1.10 [0.70–2.20]	< 0.001
PTX3 concentration (ng/mL)	16.66 [5.87–37.80]	10.79 [4.93–22.93]	52.84 [23.32-106.26]	< 0.001
D-dimer (mg/L)	0.90 [0.55–2.49]	0.74 [0.51–1.38]	2.80 [1.00-7.10]	< 0.001
Blood glucose (mg/dL)	154.50 [125.00–215.75]	146.00 [118.00–189.00]	201.30 [150.00-258.00]	< 0.001
INR	1.19 [1.03–1.31]	1.23 [1.08–1.33]	1.06 [0.94–1.15]	< 0.001
Total leukocytes (absolute value/mm^3)	8670 [6543–11620]	8190 [5940–10960]	10,590 [7920–14940]	< 0.001
Platelets (absolute value/mm^3)	235,000 [176000 – 30875]	231,000 [175500–303500]	256,430 [179000 – 32000]	0.201
C-reactive protein (mg/L)	92.72 [50.99-183.35]	81.00 [42.88-157.35]	178.10 [92.40-264.20]	< 0.001
AST (U/L)	44.00 [28.32–63.50]	40.20 [27.00-60.50]	54.80 [38.20-71.28]	< 0.001
ALT (U/L)	42.44 [25.22–63.00]	43.80 [25.05–63.75]	35.12 [26.30-59.56]	0.317
aPTT (s)	34.2 [29.52–40.19]	36.6 [30.50–41.90]	31.01 [27.90–33.60]	< 0.001
Urea	32.30 [25.60-47.67]	30.00 [22.80–38.00]	55.90 [36.60-100.50]	< 0.001

Legend aPTT: activated partial thromboplastin time; ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio; PTX3: pentraxin 3. Values are displayed as median and interquartile range
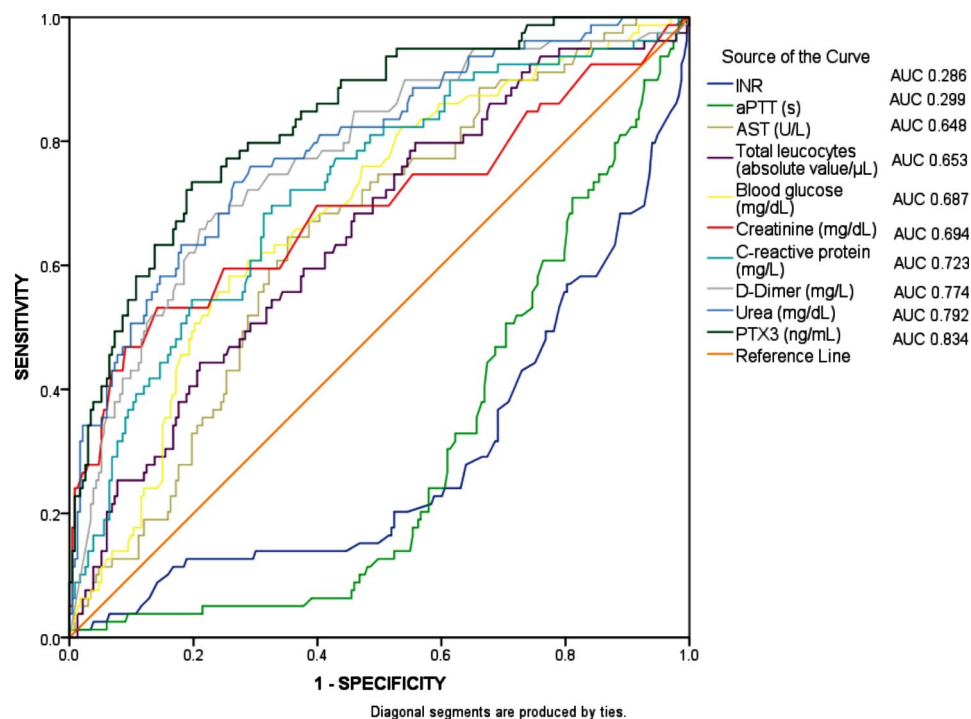

Fig. 1 Receiver operating characteristic curve (ROC) analysis for laboratory variables as predictors for coronavirus disease 2019 (COVID-19) death *Legend* aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; AUC: area under the curve; INR: international normalized ratio; PTX3: pentraxin 3

a sub-analysis of the area under the ROC curve considering only males (Figure S3A) and females (Figure S3B). For both analyses, PTX3 levels performed better than other laboratory variables (AUC=0.811 and AUC=0.879, respectively) (Figure S3). For the age analysis, we established a cut-off point at the median of our population (individuals under or over 53 years of age). PTX3 levels also showed superior performance when compared to other laboratory variables, regardless of age (AUC=0.842 and AUC=0.824, respectively) (Figure S4).

With the aim of determining the best cutoff point for PTX3 levels to differentiate patients who recovered from those who died, maximally selected rank statistics were used. The test obtained a value of 27.3 ng/mL as the best cutoff point for differentiating the groups (Fig. 2).

Survival analysis was subsequently carried out to verify the performance of the cutoff point obtained in discriminating recoveries and deaths as a function of time. Patients with PTX3 concentrations less than or equal to 27.3 ng/mL were observed to have a median survival of 28 days; on the other hand, patients with a plasma level above 27.3 ng/mL had a median survival of 20 days, according to the log-rank test ($p=0.014$) (Fig. 3).

With the aim of verifying whether plasma PTX3 level greater than 27.3 ng/mL was an important predictor of death due to COVID-19, regardless of other variables, we used a Cox regression model, inserting into the initial model all confounding factors that were statistically associated with death due to COVID-19, verified through univariate analysis in Table 1. After regression, PTX3>27.3 was demonstrated to be an important predictor of death (HR=1.79; $p=0.027$), along with diabetes ($p=0.049$) and chronic kidney disease ($p<0.001$) (Table 3).

Discussion

This study demonstrated that plasma PTX3 levels, determined within 24 h after hospital admission, may be a potential biomarker for discriminating hospitalized patients with COVID-19 at higher risk of death. PTX3 was capable of predicting the risk of death regardless of other confounding factors, and it showed superior performance to other markers used in clinical practice.
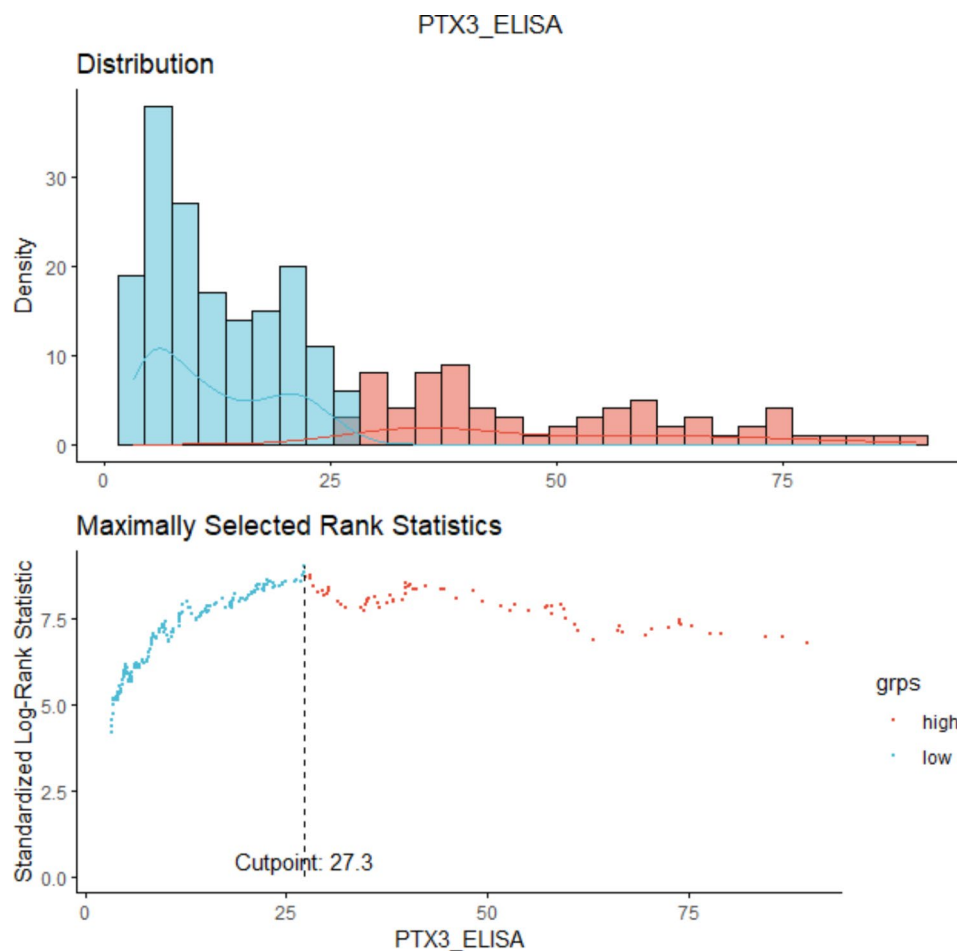

Fig. 2 Determination of the cutoff point for PTX3 plasma levels using the maximally selected rank statistics method. *Legend* ELISA: enzyme-linked immunosorbent assay; grps: groups; PTX3: pentraxin 3
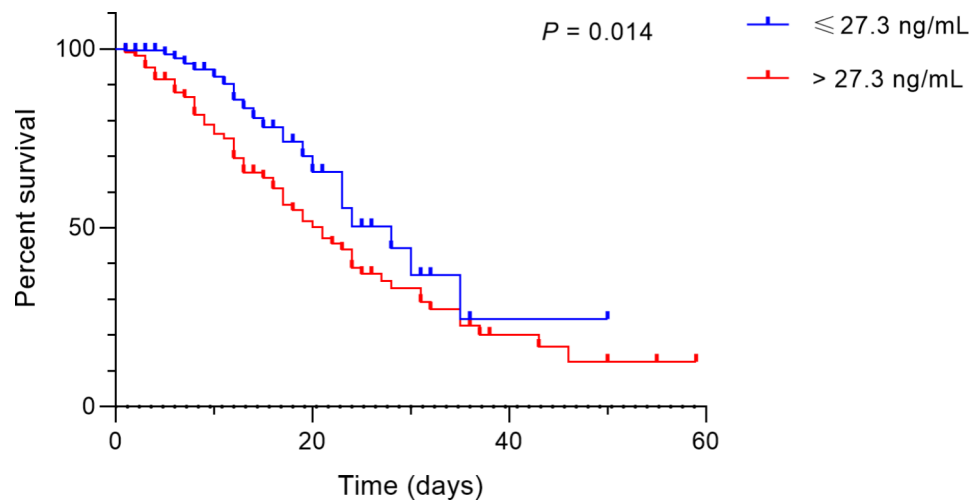
Fig. 3 Kaplan-Meier curve showing patient survival at 60 days according to plasma level of pentraxin 3

Table 3 Characteristics associated with risk of death according to the Cox's proportional hazards model

Variables	HR (95% CI)	*P* value
PTX3 > 27.3 ng/mL	1.79 (1.06–3.02)	0.027
Age (years)	1.01 (0.99–1.02)	0.063
Diabetes	1.57 (1.00–2.48)	0.049
Chronic kidney disease	4.21 (1.89–9.38)	< 0.001

Legend CI: confidence interval; HR: hazard ratio; PTX3: pentraxin 3. Variables included in the initial model: age, diabetes, chronic heart disease, chronic kidney disease, hypertension, and obesity

In the present study, the majority of laboratory tests collected within 24 h after admission were significantly different between the recovery and death groups, with emphasis on PTX3, CRP, and D-dimer, which showed higher levels in patients who died. CRP and D-dimer are routine laboratory markers used for inflammation and coagulation, respectively. During the pandemic, these tests were used in clinical practice with the aim of monitoring the risk of death in hospitalized patients with COVID-19 [23]. However, in our study, PTX3 showed better performance when associated with deaths due to COVID-19 (AUC = 0.834).

A study conducted in Italy including 75 patients with COVID-19 hospitalized in the ICU or the pulmonology division, found that, of the markers analyzed, PTX3 was the one that presented the best performance when discriminating deaths and recoveries (AUC = 0.93; 95% CI: 0.86 to 0.99) [22]. In another study conducted in Italy with 96 patients with COVID-19, PTX3 was identified as a potential marker associated with the need for ICU admission (AUC = 0.96) [11]. In contrast, a study conducted in Turkey including 88 patients with confirmed COVID-19, divided into survivors and non-survivors, demonstrated that troponin had a higher power to predict death than PTX3 [16].

It has not yet been possible to determine an ideal cutoff point for PTX3, although there are related studies in the literature [16, 20, 24, 25]. One likely reason for this is the lack of standardization in commercial kits for measuring PTX3 levels. Nonetheless, as it is an acute-phase protein, PTX3 levels in healthy individuals are known to be minimal, around 2 ng/mL [6]. In a study conducted in Denmark evaluating 261 patients admitted to the ICU and 100 healthy controls, serum PTX3 levels were correlated with severity and mortality in patients with systemic inflammatory response syndrome (SIRS) and sepsis; additionally, the study determined a cutoff point of 16 ng/mL to differentiate healthy controls and patients with SIRS. Nonetheless, the best cutoff point to discriminate high and low PTX3 levels in relation to survival was 39.3 ng/ml [24]. In relation to COVID-19, a study conducted in China with 39 patients determined a cutoff point of 5.54 ng/mL, with sensitivity of 100% and specificity of 90%, for classifying patients with greater severity based on serum D-dimer levels [25]. In Italy, in turn, a study including 152 hospitalized patients with COVID-19 identified a PTX3 cutoff point of 39.32 ng/mL for predicting mortality [20].

In our analysis, we used maximally selected rank statistics as the method to establish the best cutoff point capable of distinguishing patients who died from those who survived, based on the largest AUC. Patients with PTX3 above 27.3 ng/mL had a greater chance of death and shorter survival time, regardless of other confounding factors included in the multivariate model. PTX3 is an acute-phase protein, from the same family as CRP; therefore, its levels are proportional to the degree of inflammation, triggered by the exacerbated release of pro-inflammatory cytokines in COVID-19 [26]. A study conducted in Poland in 2022, with 254 participants, demonstrated that patients who recovered from COVID-19

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showed a decrease in PTX3 levels between the period of hospitalization and the resolution of the infection, suggesting that PTX3 has a short half-life after the interruption of the inflammatory process, which makes PTX3 a potential candidate for use as a biomarker [27]. Other studies corroborate our findings, such as the study carried out in Italy in 2021, in two cohorts with 96 and 54 patients, which found lower survival in patients with higher PTX3 levels [12]. This was also observed in a study conducted in Denmark, in which individuals with PTX3 levels greater than or equal to 29.9 ng/mL had a shorter survival time after hospitalization [18].

This study has some limitations, including the fact that it included patients from the same region. On the other hand, it is worth highlighting that this is one of the largest cohorts analyzed regarding the role of PTX3 levels in hospitalized patients, in addition to the fact that it used robust statistical methods, comparing PTX3 with other markers used in clinical practice.

Conclusion

Plasma PTX3 levels were significantly higher in the group of patients who died when compared to those who survived, and 27.3 ng/mL was the best cutoff point to differentiate the two groups. Patients with PTX3 above 27.3 ng/mL had a shorter survival time after hospitalization, regardless of other confounding factors.

Therefore, we conclude that PTX3 is a potential biomarker for predicting death in COVID-19. Further studies are needed to establish an appropriate cutoff point to differentiate cases with a higher risk of death due to COVID-19.

Abbreviations

ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
CAAE	Certificate of submission for ethical consideration
CI	Confidence interval
CONEP	Brazilian National Research Ethics Commission
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
DAMPs	Damage-associated molecular patterns
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
HC/UFPE	Hospital das Clínicas of the Federal University of Pernambuco
HR	Hazard ratio
HU-UNIVASF	University Hospital of the Universidade Federal do Vale do São Francisco
INR	International normalized ratio
IQR	Interquartile range
LAMUPE	Multi-User Research Laboratory
PRM	Pattern recognition molecule
PTX3	Long pentraxin 3
ROC	Receiver operating characteristic
SAH	Systemic arterial hypertension
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
Sirs	systemic inflammatory response syndrome

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12985-024-02501-z.

Supplementary Material 1

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital das Clínicas of the Federal University of Pernambuco (HC/UFPE) under protocol number CAAE: 36613520.0.0000.5640. A free and informed consent form was obtained in accordance with the requirements of the Brazilian National Research Ethics Commission (CONEP, acronym in Portuguese).

Consent for publication

Not applicable.

Competing interests

RFC is Senior Editor at BMC Series.

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