# Clinical Utility of Circulating Pentraxin 3 as a Prognostic Biomarker in Coronavirus Disease 2019: A Systematic Review and Meta-analysis

Yani Ke · Kaihan Wu · Chenglu Shen · Yuqing Zhu · Chuchu Xu ·

Qiushuang Li · Jie Hu · Shan Liu

## ABSTRACT

*Introduction*: Pentraxin 3 (PTX3) is involved in inflammation regulation and has a certain association with infectious diseases. However, its specific correlation with infectious diseases remains controversial. This study aimed to analyze the association between them and explore the possible role of PTX3 in the prognosis of coronavirus disease 2019 (COVID-19).
*Methods*: Five databases (PubMed, Cochrane Library, Embase, Clinicaltrials.gov, and gray literature) were searched. Outcomes were expressed as a standardized mean difference (SMD) and 95% confidence intervals (CI). The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of included articles. Stata 12 and Meta-DiSc were applied to analyze the pooled data. Receiver operating characteristic (ROC) curves were conducted to determine the prognostic value of PTX3 for mortality.
*Results*: Six articles met the inclusion criteria. Circulating PTX3 levels had a nonsignificant difference between intensive care unit (ICU) and non-ICU patients with COVID-19 [SMD 1.37 (−0.08, 2.81); $I^2$ = 93.9%, $P < 0.01$], while the PTX3 levels in nonsurvival COVID-19 patients was significantly lower than those in survival patients [SMD −1.41 (−1.92, −0.91);

Yani Ke and Kaihan Wu are co-first authors of the article.

Y. Ke
Zhejiang Chinese Medical University, No 548, Binwen Road, Hangzhou 310051, Zhejiang Province, China

K. Wu · C. Shen · Y. Zhu · C. Xu
The First Clinical Medical College of Zhejiang, Chinese Medical University, No 548, Binwen Road, Hangzhou 310051, Zhejiang Province, China

Q. Li · S. Liu (✉)
Department of Clinical Evaluation Center, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), No. 54, Youdian Road, Hangzhou 310006, Zhejiang Province, China
e-mail: 20123002@zcmu.edu.cn; graystar92@163.com

J. Hu (✉)
Department of Infectious Diseases, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine), No. 54, Youdian Road, Hangzhou 310006, Zhejiang Province, China
e-mail: muhudie1106@163.com

$I^2 = 66.4\%, P = 0.051$]. Circulating PTX3 had good mortality prediction ability (area under ROC curve, $AUC = 0.829$) in COVID-19. Funnel plots and Egger's tests showed low probabilities of publication bias. Through sensitivity analysis, the results of this study were robust.

*Conclusion*: This study found that PTX3 was differentially expressed between survival and nonsurvival patients with COVID-19, while there was no significant difference between ICU and non-ICU patients. Meanwhile, circulating PTX3 may be a good biomarker for monitoring the prognosis of COVID-19, which may provide new ideas and directions for clinical and scientific research.

## Key Summary Points

PTX3 may be progressively considered as an independent strong prognostic indicator in severe infectious diseases, such as COVID-19.

No significant difference existed in circulating PTX3 levels between ICU and non-ICU patients with COVID-19.

Nonsurvival patients with COVID-19 had significantly lower circulating PTX3 levels than survival patients with COVID-19.

Circulating PTX3 may be deemed as an indicator with good diagnostic value for predicting the mortality of COVID-19.

This systematic review and meta-analysis is valuable for those interested in the relationship between PTX3 and other infectious diseases.

## PLAIN LANGUAGE SUMMARY

This study focuses on the relationship between circulating pentraxin 3 (PTX3) and coronavirus disease 2019 (COVID-19). COVID-19 can initiate the inflammatory reaction of the body, trigger a series of immune mechanisms, and cause death in severe cases. PTX3 is a soluble pattern recognition molecule (PRM) belonging to the humoral innate immune system, which may be increasingly deemed as an independent strong prognostic indicator in severe infectious diseases, such as COVID-19. Five databases (Pubmed, Cochrane Library, EMBASE, Clinical-trials.gov, and gray literature) were searched for six keywords. There was no significant difference in circulating PTX3 levels between intensive care unit (ICU) and non-ICU patients with COVID-19, while the PTX3 levels of nonsurvival patients with COVID-19 was significantly lower than those of survival patients. Circulating PTX3 may indicate good diagnostic value in predicting the mortality of COVID-19, which may be useful as an indicator for monitoring.

## INTRODUCTION

The global outbreak of coronavirus disease 2019 (COVID-19) has been widely discussed in current research, and is known for its high transmission efficiency and rapid spread worldwide. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), which affects microcirculation and causes an inflammatory response [1–3]. In patients infected by SARS-CoV-2, the disease may be asymptomatic, cause mild-to-moderate symptoms, need severe requiring intensive care unit (ICU) treatment, or even lead to death [4]. Although the general pathological mechanism of intrapulmonary [1] or extrapulmonary [5] manifestations of COVID-19 has been gradually clarified, there are still many uncertainties. It is essential to find

reasonable biomarkers to monitor and predict the prognosis of the disease.

Pentraxin 3 (PTX3) is a soluble pattern recognition molecule (PRM) belonging to the humoral innate immune system [6], and is involved in the resistance against pathogens as well as in the regulation of inflammation [6–8]. Fungal, bacterial, and viral infections [9, 10], as well as coagulation disorders [11], severe inflammatory syndrome, sepsis [12–14], and cardiovascular disease may contribute to elevate plasma PTX3 levels. In addition, de Oliveira et al. [15] found that PTX3 plays a clear role in the induction of sterile inflammation by affecting the neutrophil–endothelial cell interactions. Bonavita et al. [16] suggested that PTX3 acts as an extrinsic oncosuppressor gene in mice and humans by modulating complement-dependent, macrophage-sustained, and tumor-promoting inflammation. Deban et al. [17] elucidated that PTX3 modulates inflammation by regulating P-selectin-dependent leukocyte recruitment and complement activation. Ciancarella et al. [18] showed that PTX3 deficiency is associated with higher bacterial load, more severe outcome, and higher mortality after *Shigella flexneri* infection. It has been expounded that circulating PTX3 levels are increasingly considered as an independent strong prognostic indicator in severe [19] infectious diseases, such as COVID-19. Therefore, this study was performed to draw more accurate conclusions and evaluate the relationship between circulating PTX3 and COVID-19 comprehensively for providing a new direction for clinical practice.

# METHODS

This study was conducted in accordance with the recommendations of the Cochrane Collaboration and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. Furthermore, the study protocol was registered in PROSPERO with the number CRD42022339907 (Supplementary Material 1). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## Data Sources and Search Strategy

Two researchers searched five databases (PubMed, Cochrane Library, Embase, Clinical-trials.gov, and gray literature) to find relevant articles published up to 15 June 2022. Medical Subject Headings (MeSH) terms and free terms for literature retrieval were used, such as: ("COVID-19," "COVID19," "SARS-CoV-2," "Sars-CoV-2 infection," "2019 nCoV," "2019-nCoV infection," "coronavirus," "coronavirus disease 2019," "nCoV pneumonia," "corona-virus") and ("pentraxin 3," "ptx3," "ptx-3," "pentraxin 3," "pentraxin-3," "PTX3 protein"), and the full search strategy is detailed in Supplementary Material 2. In addition, the reference lists of the selected articles were searched for further relevant research. No language restrictions were applied, and the authors were contacted via email for the missing data.

## Inclusion and Exclusion Criteria

Each study was examined independently by two researchers. In case of any dispute, a third researcher made reasonable judgments based on the study protocol.

### Association between Circulating PTX3 and COVID-19

Inclusion criteria were as follows: (1) studies that included adult patients (aged ≥ 18 years) with COVID-19 diagnosed either by test indicators or by imaging features; (2) case–control studies or cohort studies. In case–control studies, the case group was ICU COVID-19 patients or nonsurvivors, while the control group was the non-ICU COVID-19 group or survivors. In cohort studies, one group had high levels of PTX3 and the other group had low levels of PTX3; (3) results of studies that measure circulating PTX3 levels by enzyme-linked immunosorbent assay (ELISA) in plasma or serum; (4) studies comparing circulating PTX3 levels between survivors and nonsurvivors, and ICU and non-ICU patients with COVID-19.

Exclusion criteria were as follows: (1) studies that included patients with suspected but undiagnosed COVID-19; (2) studies that included patients with other lung diseases; (3) studies that focused on other indicators but not on circulating PTX3 levels; (4) articles with incomplete data and the corresponding author could not be contacted to obtain the required data; (5) randomized controlled trials, case reports, literature reviews, or animal experimental research; (6) repetitive articles or non-English studies.

### Prognostic Value of Circulating PTX3 in COVID-19

Inclusion criteria were as follows: (1) studies in which all the patients were diagnosed with COVID-19 by the gold standard; (2) studies focused on the relationship between circulating PTX3 levels and mortality; (3) studies that were conducted using sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR); (4) sufficient data to calculate the following diagnostic values: true positive (TP), false positive (FP), false negative (FN), and true negative (TN).

Exclusion criteria were as follows: (1) studies focused on other diagnostic-related indicators but not on circulating PTX3 levels; (2) PTX3 levels not in the plasma or serum; (3) research that not focused on the relationship between mortality and circulating PTX3 levels; (4) incomplete diagnostic test data in four grids and no reply from the corresponding author; (5) case reports, literature reviews, or repetitive articles.

### Data Extraction and Quality Assessment

Two researchers independently extracted data, including the first author's last name; publication date; country of study population; Newcastle–Ottawa Scale (NOS) score; the method of COVID-19 diagnosis; number of cases and controls; basic information of cases and controls (such as age and sex); classification of control groups; circulating PTX3 level detection method; PTX3 levels; and sensitivity, specificity, and area under receiver operating characteristic (ROC) curve (AUC). The selected studies were scored on the basis of methodological quality using the NOS scale [20], with scores ranging from 0 to 9, with a set score of 0–4 as low quality and 5–9 as high quality. The quality assessment was performed independently by two researchers, and the results were crosschecked, with a third researcher assisting in judgment if there was any disagreement.

### Statistical Analysis

All statistical analyses were performed using Stata 12 (Stata Corporation, TX, USA) and Meta-DiSc. The data of normal distribution were extracted in the form of mean ± standard deviation (SD), and those with non-normal distribution were converted into mean ± SD through https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html) [21–23]. All circulating levels of PTX3 were extracted as continuous variables using standardized mean difference (SMD) and 95% confidence intervals (CI). The level of heterogeneity was determined using the $I^2$ test. When the statistical heterogeneity was significant ($I^2 \geq 50\%$), the random effect model (shown as "D + L") was selected [24, 25]. When statistical heterogeneity was not significant ($I^2 < 50\%$), the fixed effect model (show as "I – V") was selected. When high heterogeneity was found and the number of studies was greater than three, a subgroup analysis was performed. The pooled sensitivity, specificity, PLR, NLR, and diagnostic odds ratio (DOR) were calculated, and the summary ROC (sROC) was drawn in the diagnostic meta-analysis. Sensitivity analysis was carried out using the approach of omitting each study. Publication bias was assessed using the funnel plot and Egger's test ($P < 0.05$ was considered significant).

## RESULTS

### Study Selection

Five English databases (PubMed, Embase, the Cochrane Library, Clinicaltrials.gov, and gray

literature) were searched. A total of 96 articles were found, and 91 remained after excluding repetitive articles. Two different researchers and the third arbitrator finally included six articles based on the inclusion and exclusion criteria: three studies of ICU and non-ICU COVID-19 patients, two studies of survival and nonsurvival COVID-19 patients, and three studies on COVID-19 mortality. Among these studies, two were from Italy, one from Turkey, one from the USA, one from Denmark, and one from Iran (Tables 1 and 2) [19, 27–31]. The literature selection process is illustrated in Fig. 1 [26].

## Quality Evaluation

Two researchers evaluated the included articles using the NOS scale [20], and the third researcher arbitrated. The average NOS score of this study was 6.33, indicating that the included articles adopted a reasonable methodology (Table 3).

## Correlation between PTX3 and COVID-19

### *Circulating PTX3 Levels between ICU and Non-ICU COVID-19*

Circulating PTX3 levels of ICU and non-ICU COVID-19 patients are shown in Fig. 2a. Because of the high heterogeneity ($I^2$ = 93.9%, $P < 0.01$), the random-effect model was selected. The circulating PTX3 levels were not significantly different between ICU patients and non-ICU patients with COVID-19, with SMD 1.37 (−0.08, 2.81). Meanwhile, the Galbr test (Fig. 2b) was adopted to analyze the heterogeneity, and three articles were not within the reasonable range, thus indicating high heterogeneity.

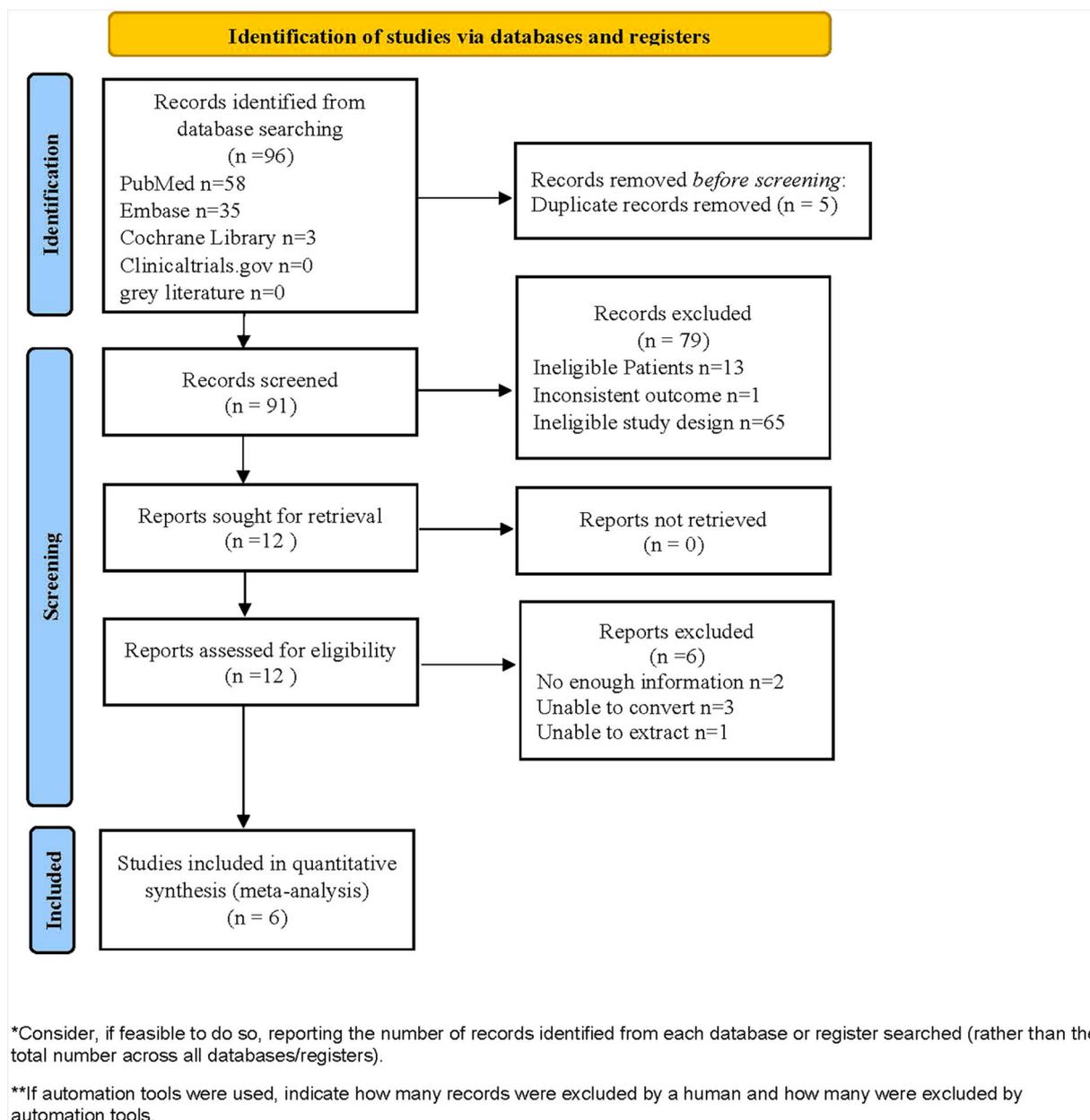### *Circulating PTX3 Levels between Survival and Non-survival COVID-19 patients*

Figure 3a shows circulating PTX3 levels of survivors and nonsurvivors with COVID-19. There was significant heterogeneity ($I^2$ = 66.4%, $P$ = 0.051) among studies, so the random-effect model was the first choice. The circulating PTX3

**Table 1** Baseline characteristics of studies included in the meta-analysis

| Study | Country | Case | | | Control | | | Diagnostic criteria | Relevant data | Type |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *Mean* | *SD* | *N* | *Mean* | *SD* | *N* | | | |
| Assandri 2022 [27] | Italy | 34.6873 | 9.7561 | 75 | 9.7429 | 3.8605 | 21 | RT–PCR | CRP, ferritin, LD | ICU and non-ICU |
| Jacobs 2022 [28] | USA | 12.4061 | 12.6975 | 23 | 3.644 | 5.358 | 19 | qPCR | CRP, ferritin | |
| Moulana 2021 [29] | Iran | 1.957 | 1.769 | 14 | 1.22 | 1.784 | 59 | RT–PCR | CRP, ferritin | |
| Hansen 2022a [19] | Denmark | 7.3042 | 7.0797 | 92 | 22.6305 | 17.6457 | 34 | / | CRP, ferritin | Survival and nonsurvival |
| Hansen 2022b [19] | Denmark | 30.0907 | 29.2033 | 96 | 61.7068 | 53.2398 | 16 | / | CRP, ferritin | |
| Schirinzi 2021 [30] | Italy | 6.217 | 4.7057 | 38 | 13.4313 | 2.5188 | 37 | / | CRP, IL6 | |

**Table 2** Main results of diagnostic trials in the included studies

| Study | Country | TP | FP | FN | TN | Diagnostic criteria | Relevant data |
|---|---|---|---|---|---|---|---|
| Genc 2021 [31] | Turkey | 19 | 21 | 10 | 38 | RT–PCR | CRP, ferritin, LDH |
| Hansen 2022 [19] | Denmark | 27 | 20 | 7 | 72 | / | CRP, ferritin |
| Schirinzi 2021 [30] | Italy | 33 | 3 | 4 | 35 | / | CRP, IL6 |



**Identification of studies via databases and registers**

Records identified from database searching (n =96)
PubMed n=58
Embase n=35
Cochrane Library n=3
Clinicaltrials.gov n=0
grey literature n=0

Records removed *before screening*:
Duplicate records removed (n = 5)

Records screened (n = 91)

Records excluded (n = 79)
Ineligible Patients n=13
Inconsistent outcome n=1
Ineligible study design n=65

Reports sought for retrieval (n =12)

Reports not retrieved (n = 0)

Reports assessed for eligibility (n =12)

Reports excluded (n =6)
No enough information n=2
Unable to convert n=3
Unable to extract n=1

Studies included in quantitative synthesis (meta-analysis) (n = 6)

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

**Fig. 1** Flow diagram of the study selection process

**Table 3** NOS score of included studies

| Number | Study | Year | Selection | | | | Comparability | Exposure | | | Total | Average |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Adequate definition | Representativeness | Selection of controls | Definition of controls | | Ascertainment of exposure | Same method | Nonresponse rate | | |
| 1 | Assandri [27] | 2022 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 6 | 6.33 |
| 2 | Jacobs [28] | 2022 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 6 | |
| 3 | Moulana [29] | 2021 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 8 | |
| 4 | Hansen [19] | 2022 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 6 | |
| 5 | Schirinzi [30] | 2021 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 6 | |
| 6 | Genc [31] | 2021 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 6 | |

levels of survival COVID-19 patients were significantly lower than those of nonsurvival COVID-19 patients, with SMD of −1.41 (−1.92, −0.91). Furthermore, the Galbr test was used to test the heterogeneity, and the result showed that all articles were within a reasonable range.

### Diagnostic Value of Circulating PTX3 for Mortality

Three studies were included to evaluate the association between circulating PTX3 levels and the mortality rate of patients with COVID-19. The pooled analysis showed that the sensitivity and specificity values were 0.79 (0.70, 0.87) and 0.77 (0.70, 0.83), respectively. The pooled values of PLR and NLR were 3.72 (1.60, 8.65) and 0.27 (0.12, 0.64), respectively. Additionally, the $I^2$ of sensitivity and specificity were 63.7% and 81.8%, respectively, indicating statistical heterogeneity. Figures are detailed in the Supplementary Material 3. No obvious threshold effect existed among the studies. However, owing to the limited number of studies included, subgroup analysis and meta-regression could not be carried out.

### Predictive Value of Circulating PTX3 for Mortality

ROC curves were used to determine the prognostic value of circulating PTX3 for mortality outcomes in the three included studies (Fig. 4). Pooled analysis revealed an overall *AUC* value of 0.829, indicating a good predictive ability of circulating PTX3 for mortality.

### Sensitivity Analysis

In this study, the method of omitting a single study was used for the sensitivity analysis, as shown in Fig. 5. By observing the interval after excluding each study, it was determined that the two parts of this study were relatively stable, and no study had an obvious impact on the overall results.

### Publication Bias

For the evaluation of publication bias, funnel plots (Fig. 6) and Egger's test were employed.
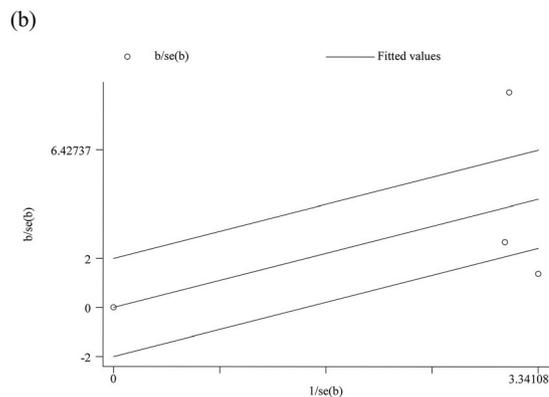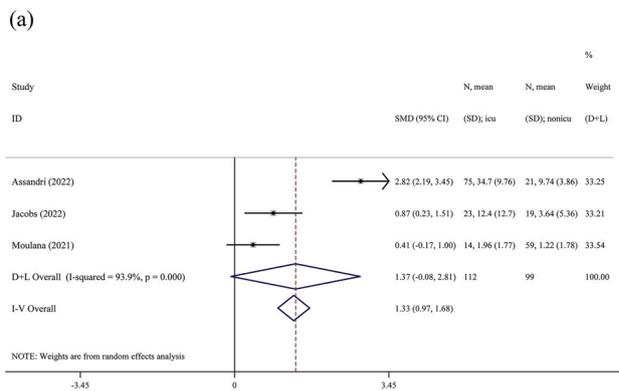
**Fig. 2 a** Forest plot of circulating PTX3 levels between ICU and non-ICU patients with COVID-19. **b** Galbr test of circulating PTX3 levels between ICU and non-ICU patients with COVID-19
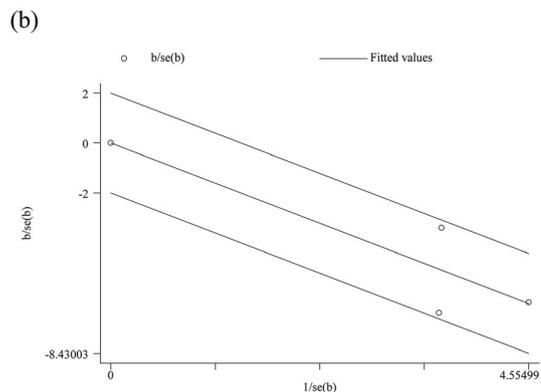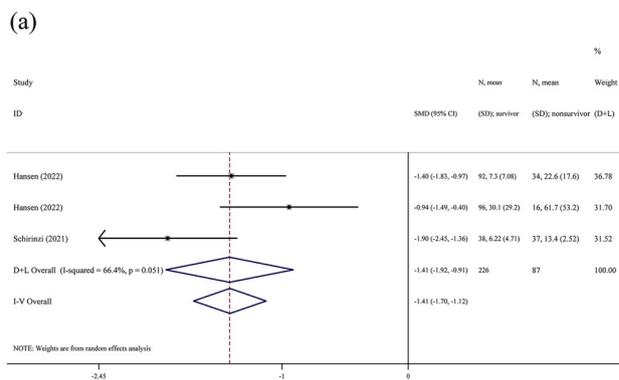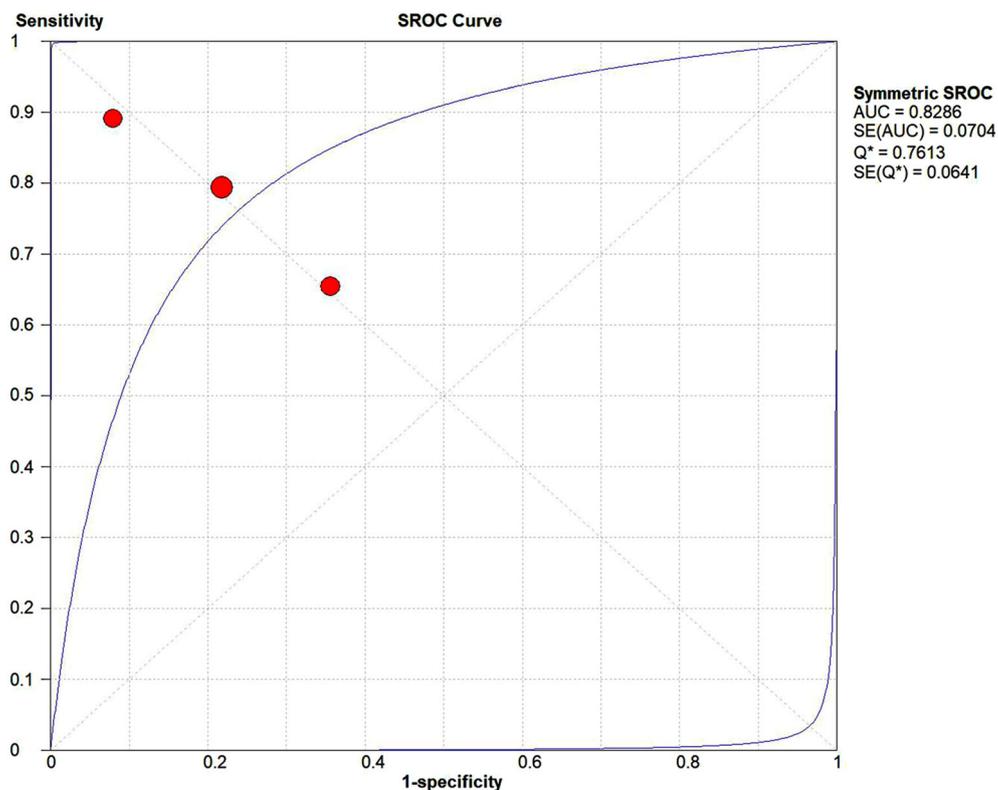


**Fig. 3 a** Forest plot of circulating PTX3 levels between survival and nonsurvival patients with COVID-19. **b** Galbr test of circulating PTX3 levels between survival and nonsurvival patients with COVID-19

Both funnel plots were symmetrical, implying nonsignificant publication bias. Moreover, Egger's tests of the two parts also showed low possibility of publication bias ($P = 0.610$ and $P = 0.966$, respectively).

## DISCUSSION

The lungs of patients with COVID-19 tend to exhibit unique vascular features, including severe endothelial damage as well as inflammation around the vessels, rupture of endothelial cell membranes, and extensive intravascular thrombosis [32, 33]. Diffuse endothelial inflammation and extensive microvascular dysfunction have become the main determinants of the pathogenesis of COVID-19 [34–36].

In addition, infection leads to a high inflammatory response, which by affecting lung tissues and blood vessels, leads to acute respiratory distress syndrome (ARDS), shock, and multi-organ failure. PTX3 is an important component of the humoral innate immune system, secreted by macrophages and myeloid dendritic cells, involved in the regulation of resistance and inflammation to specific pathogens. PTX3 also plays an irreplaceable role in systemic inflammatory diseases [37–40] as well as in vascular pathology [41–43], so it is reasonable to speculate that PTX3 could affect COVID-19 by regulating the complement system and macrophages in the inflammation response and angiogenesis. Previous studies have also found that patients with severe COVID-19 express

**Fig. 4** Receiver operating characteristic (ROC) curves of PTX3 for mortality

higher PTX3 levels. Kerget et al. [44] found that serum PTX3 levels were higher in the COVID-19 patients with macrophage activation syndrome (MAS), and the AA genotype is also more frequent in the COVID-19 group with MAS. Therefore, a meta-analysis of the associations between PTX3 and COVID-19 is of importance for both clinical prevention and scientific research exploration.
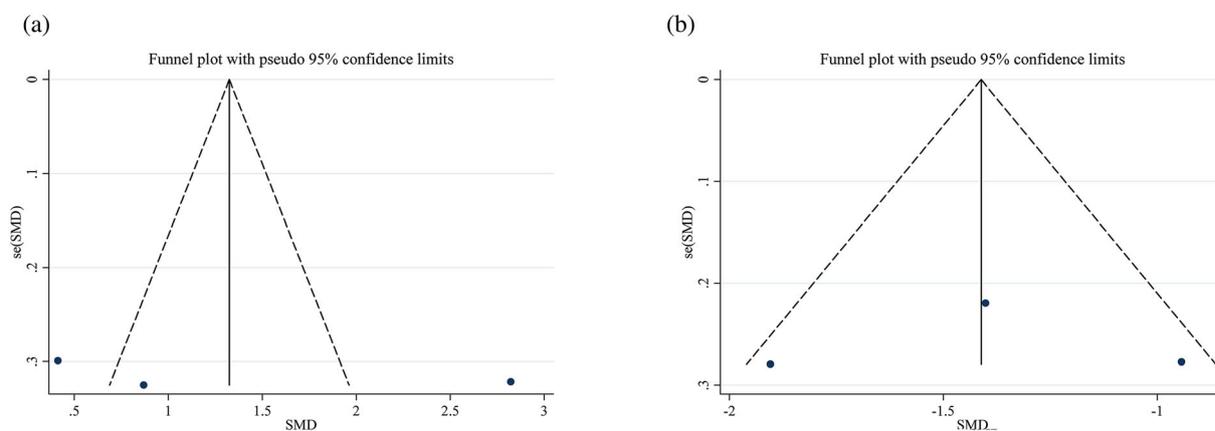
This study is divided into three parts: circulating PTX3 levels in ICU and non-ICU patients with COVID-19, circulating PTX3 levels in survival and nonsurvival patients with COVID-19, and circulating PTX3 levels and mortality in patients with COVID-19. The first part included three studies from Italy, the USA, and Iran. Two studies from Denmark and Italy were included in the second part. The three studies in the third part were from Denmark, Turkey, and Italy. None of the included studies had obvious gender and age restrictions, but on average, the patients were middle-aged and elderly. Using the NOS table for quality evaluation, the overall

reliability of the study is medium, which also suggests that the primary studies included in this meta-analysis used reasonable methodology.

The pooled analysis showed that there was no significant difference in circulating PTX3 levels between ICU and non-ICU patients with COVID-19, whereas the PTX3 levels of nonsurvival patients with COVID-19 was significantly lower than those of survival patients. There was significant heterogeneity in these two parts, but because of the limited number of included studies, subgroup analysis or meta-regression could not be conducted to explore the possible sources of heterogeneity. Sensitivity analysis and publication bias analysis revealed that the results were relatively robust. Wang et al. [45] also explored the different expression of circulating PTX3 levels in sepsis, and the results also demonstrated that the circulating PTX3 levels of nonsurvivors were significantly lower than those of survivors. Both sepsis and COVID-19 can initiate the inflammatory reaction of the
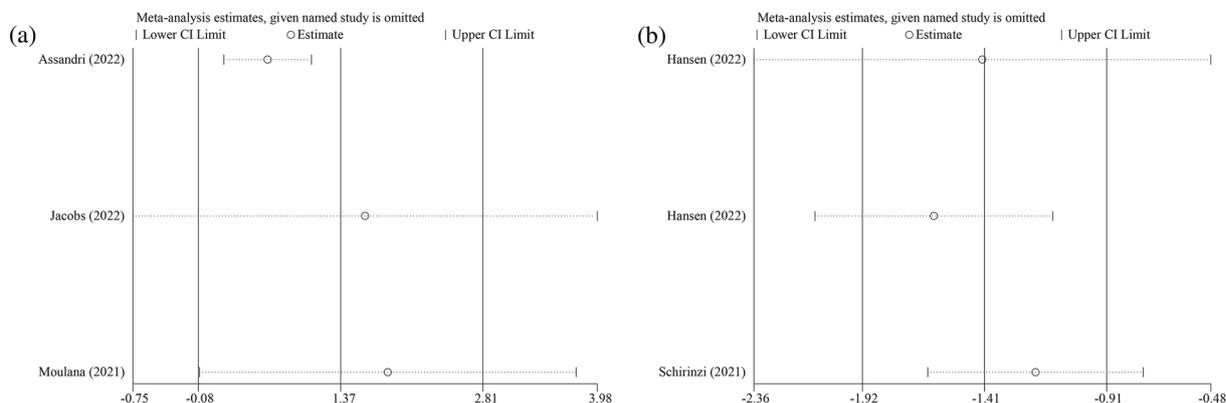
**Fig. 5** **a** Sensitivity analysis of circulating PTX3 levels between ICU and non-ICU patients with COVID-19. **b** Sensitivity analysis of circulating PTX3 levels between survival and nonsurvival patients with COVID-19



**Fig. 6** **a** Funnel plot of circulating PTX3 levels between ICU and non-ICU patients with COVID-19. **b** Funnel plot of circulating PTX3 levels between survival and nonsurvival patients with COVID-19

body, trigger a series of immune mechanisms, and cause death in severe cases. As an inflammatory factor, PTX3 is closely associated with the immune response. It may reflect the occurrence and development of infectious diseases to some extent, but the specific impact is still unclear. Combined with the research results, the difference in PTX3 levels between ICU patients and non-ICU patients was not found to be significant, but it was significant between survivors and nonsurvivors with COVID-19. Thus, whether PTX3 has diagnostic value and obvious clinical significance still needs to be determined.

Consequently, we further explored the relationship between circulating PTX3 levels and mortality in patients with COVID-19. The results of the diagnostic meta-analysis showed that circulating PTX3 level had high sensitivity and specificity in predicting mortality in COVID-19 patients, and was accompanied by *AUC* greater than 0.8, also indicating its good diagnostic value. There is still high heterogeneity among studies, but the results suggest that this heterogeneity does not result from the threshold effect. Owing to the limited number of studies included, the possible sources of this heterogeneity could not be adequately explored. Overall, circulating PTX3 levels have good diagnostic value in predicting the mortality of COVID-19 as well as sepsis. These two diseases are serious infectious diseases, so can PTX3 be considered as a predictive indicator of death and prognosis of all infectious diseases?

This also requires more clinical studies and more comprehensive meta-analyses as supporting materials.

Our study also has some limitations, and we hope that the follow-up research can pay attention to and improve on this. First of all, the number of studies included in each part was small, and some studies cannot extract the mean and standard deviation because of skewed data distribution. Meanwhile, owing to the limited number of included studies, we could not explore the possible sources of heterogeneity through subgroup analysis and meta-analysis. Secondly, in the basic meta-analysis, we discussed the difference in circulating PTX3 between ICU and non-ICU patients with COVID-19, and the difference in circulating PTX3 between survival and nonsurvival patients. Only in the second part were the results significant, so we discussed the relationship between circulating PTX3 and mortality in COVID-19. Whether circulating PTX3 is related to other conditions such as disease severity has not been discussed, and clinical recommendations cannot be given. Thirdly, these studies may come from different countries and continents, so the experimenters and experimental equipment are completely different. Although we have strictly controlled many factors in the early stage, there are still influential factors that cannot be ignored, which may also be the sources of heterogeneity and have a certain impact on the pooled results. Finally, as a highly infectious disease in recent years, COVID-19 has something in common with many clinical critical infectious diseases. Our study did not make a reasonable horizontal comparison to summarize the relationship between PTX3 and more infectious diseases to determine its possible clinical value. It is hoped that further studies will focus on the relationship between these, and conduct a more reasonable systematic analysis.

## CONCLUSIONS

This article analyzes some of the relationships between circulating PTX3 and COVID-19. No significant difference was found in circulating PTX3 levels between ICU and non-ICU patients with COVID-19, while the circulating PTX3 levels of survival COVID-19 patients were significantly lower than those of nonsurvival patients. Further diagnostic meta-analysis showed that circulating PTX3 could act as a good biomarker to predict the mortality of patients with COVID-19. There is significant heterogeneity among these studies, but owing to the small number of included studies, the source of this heterogeneity could not be determined. The publication bias and sensitivity analysis suggest that the results of this study are robust. PTX3 may participate in the pathogenesis and disease progression of COVID-19 and play a certain role in it. Recently, an increasing number of studies have also highlighted the importance of PTX3 in other infectious diseases. It is hoped that multi-center, multi-aspect, and multi-level studies will appear in the future to further clarify the biological processes and clinical value of PTX3.

## ACKNOWLEDGEMENTS

***Disclosures.*** The authors (Yani Ke, Kaihan Wu, Chenglu Shen, Yuqing Zhu, Chuchu Xu, Qiushuang Li, Jie Hu, Shan Liu) declare that there are no competing interests in this study.

***Compliance with Ethics Guidelines.*** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

***Data Availability.*** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

***Open Access.*** This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc/4.0/.

## REFERENCES

1. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. N Engl J Med. 2020;383(2):120–8. https://doi.org/10.1056/NEJMoa2015432.

2. Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. Circulation. 2020;142(1):68–78. https://doi.org/10.1161/CIRCULATIONAHA.120.047549.

3. Ostergaard L, Jorgensen MB, Knudsen GM. Low on energy? An energy supply-demand perspective on stress and depression. Neurosci Biobehav Rev. 2018;94:248–70. https://doi.org/10.1016/j.neubiorev.2018.08.007.

4. Ostergaard L. SARS CoV-2 related microvascular damage and symptoms during and after COVID-19: consequences of capillary transit-time changes, tissue hypoxia and inflammation. Physiol Rep. 2021;9(3): e14726. https://doi.org/10.14814/phy2.14726.

5. Behzad S, Aghaghazvini L, Radmard AR, Gholamrezanezhad A. Extrapulmonary manifestations of COVID-19: radiologic and clinical overview. Clin Imaging. 2020;66:35–41. https://doi.org/10.1016/j.clinimag.2020.05.013.

6. Bottazzi B, Doni A, Garlanda C, Mantovani A. An integrated view of humoral innate immunity: pentraxins as a paradigm. Annu Rev Immunol. 2010;28:157–83. https://doi.org/10.1146/annurev-immunol-030409-101305.

7. Garlanda C, Bottazzi B, Magrini E, Inforzato A, Mantovani A. PTX3, a humoral pattern recognition molecule, in innate immunity, tissue repair, and cancer. Physiol Rev. 2018;98(2):623–39. https://doi.org/10.1152/physrev.00016.2017.

8. Pepys MB. The pentraxins 1975–2018: serendipity, diagnostics and drugs. Front Immunol. 2018;9: 2382. https://doi.org/10.3389/fimmu.2018.02382.

9. Cunha C, Aversa F, Lacerda JF, et al. Genetic PTX3 deficiency and aspergillosis in stem-cell transplantation. N Engl J Med. 2014;370(5):421–32. https://doi.org/10.1056/NEJMoa1211161.

10. Reading PC, Bozza S, Gilbertson B, et al. Antiviral activity of the long chain pentraxin PTX3 against influenza viruses. J Immunol. 2008;180(5):3391–8. https://doi.org/10.4049/jimmunol.180.5.3391.

11. Tong M, Xiong Y, Zhu C, et al. Elevated serum pentraxin-3 levels is positively correlated to disease severity and coagulopathy in COVID-19 patients. Mediterr J Hematol Infect Dis. 2021;13(1): e2021015. https://doi.org/10.4084/MJHID.2021.015.

12. Caironi P, Masson S, Mauri T, et al. Pentraxin 3 in patients with severe sepsis or shock: the ALBIOS trial. Eur J Clin Invest. 2017;47(1):73–83. https://doi.org/10.1111/eci.12704.

13. Jenny NS, Arnold AM, Kuller LH, Tracy RP, Psaty BM. Associations of pentraxin 3 with cardiovascular disease and all-cause death: the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol.

2009;29(4):594–9. https://doi.org/10.1161/ATVBAHA.108.178947.

14. Perez-San Martin S, Suberviola B, Garcia-Unzueta MT, Lavin BA, Campos S, Santibanez M. Prognostic value of plasma pentraxin 3 levels in patients with septic shock admitted to intensive care. PLoS ONE. 2020;15(12): e0243849. https://doi.org/10.1371/journal.pone.0243849.

15. de Oliveira THC, Souza DG, Teixeira MM, Amaral FA. Tissue dependent role of PTX3 during ischemia-reperfusion injury. Front Immunol. 2019;10:1461. https://doi.org/10.3389/fimmu.2019.01461.

16. Deban L, Russo RC, Sironi M, et al. Regulation of leukocyte recruitment by the long pentraxin PTX3. Nat Immunol. 2010;11(4):328–34. https://doi.org/10.1038/ni.1854.

17. Bonavita E, Gentile S, Rubino M, et al. PTX3 is an extrinsic oncosuppressor regulating complement-dependent inflammation in cancer. Cell. 2015;160(4):700–14. https://doi.org/10.1016/j.cell.2015.01.004.

18. Ciancarella V, Lembo-Fazio L, Paciello I, et al. Role of a fluid-phase PRR in fighting an intracellular pathogen: PTX3 in Shigella infection. PLoS Pathog. 2018;14(12): e1007469. https://doi.org/10.1371/journal.ppat.1007469.

19. Hansen CB, Sandholdt H, Moller MEE, et al. Prediction of respiratory failure and mortality in COVID-19 patients using long pentraxin PTX3. J Innate Immun. 2022. https://doi.org/10.1159/000521612.

20. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–5. https://doi.org/10.1007/s10654-010-9491-z.

21. Shi JD, Luo DH, Wan X, et al. Detecting the skewness of data from the sample size and the five-number summary. 2020. arXiv preprint arXiv: 05749.

22. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res. 2018;27(6):1785–805. https://doi.org/10.1177/0962280216669183.

23. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135. https://doi.org/10.1186/1471-2288-14-135.

24. Schmidt FL, Oh IS, Hayes TL. Fixed- versus random-effects models in meta-analysis: model properties and an empirical comparison of differences in results. Br J Math Stat Psychol. 2009;62(Pt 1): 97–128. https://doi.org/10.1348/000711007X255327.

25. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60. https://doi.org/10.1136/bmj.327.7414.557.

26. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71. https://doi.org/10.1136/bmj.n71.

27. Assandri R, Accordino S, Canetta C, et al. Long pentraxin 3 as a marker of COVID-19 severity: evidences and perspectives. Biochem Med (Zagreb). 2022;32(2): 020901. https://doi.org/10.11613/BM.2022.020901.

28. Jacobs JL, Bain W, Naqvi A, et al. Severe acute respiratory syndrome coronavirus 2 viremia is associated with coronavirus disease 2019 severity and predicts clinical outcomes. Clin Infect Dis. 2022;74(9):1525–33. https://doi.org/10.1093/cid/ciab686.

29. Moulana Z, Bagherzadeh M, Mirzakhani M, Rostami A, Mohammadnia-Afrouzi M, Shahbazi M. Increased levels of serum pentraxin 3 in critical coronavirus disease-2019 patients. Environ Sci Pollut Res Int. 2021. https://doi.org/10.1007/s11356-021-15183-9.

30. Schirinzi A, Pesce F, Laterza R, et al. Pentraxin 3: Potential prognostic role in SARS-CoV-2 patients admitted to the emergency department. J Infect. 2021;82(4):84–123. https://doi.org/10.1016/j.jinf.2020.10.027.

31. Genc AB, Yaylaci S, Dheir H, et al. The predictive and diagnostic accuracy of long pentraxin-3 in COVID-19 pneumonia. Turk J Med Sci. 2021;51(2): 448–53. https://doi.org/10.3906/sag-2011-32.

32. Kvietys PR, Fakhoury HMA, Kadan S, Yaqinuddin A, Al-Mutairy E, Al-Kattan K. COVID-19: lung-centric immunothrombosis. Front Cell Infect Microbiol. 2021;11: 679878. https://doi.org/10.3389/fcimb.2021.679878.

33. Purohit D, Ahirwar AK, Sakarde A, Asia P, Gopal N. COVID-19 and lung pathologies. Horm Mol Biol Clin Investig. 2021;42(4):435–43. https://doi.org/10.1515/hmbci-2020-0096.

34. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure.

Nature. 2005;436(7047):112–6. https://doi.org/10.1038/nature03712.

35. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109: 102433. https://doi.org/10.1016/j.jaut.2020.102433.

36. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10(2):102–8. https://doi.org/10.1016/j.jpha.2020.03.001.

37. Lussana F, Rambaldi A. Inflammation and myeloproliferative neoplasms. J Autoimmun. 2017;85: 58–63. https://doi.org/10.1016/j.jaut.2017.06.010.

38. Gao P, Tang K, Lu Y, et al. Pentraxin 3 promotes airway inflammation in experimental asthma. Respir Res. 2020;21(1):237. https://doi.org/10.1186/s12931-020-01499-6.

39. Moalli F, Paroni M, Veliz Rodriguez T, et al. The therapeutic potential of the humoral pattern recognition molecule PTX3 in chronic lung infection caused by *Pseudomonas aeruginosa*. J Immunol. 2011;186(9):5425–34. https://doi.org/10.4049/jimmunol.1002035.

40. Polentarutti N, Bottazzi B, Di Santo E, et al. Inducible expression of the long pentraxin PTX3 in the central nervous system. J Neuroimmunol. 2000;106(1–2):87–94. https://doi.org/10.1016/s0165-5728(00)00214-9.

41. Mantovani A, Garlanda C, Bottazzi B, et al. The long pentraxin PTX3 in vascular pathology. Vascul Pharmacol. 2006;45(5):326–30. https://doi.org/10.1016/j.vph.2006.08.011.

42. Zlibut A, Bocsan IC, Agoston-Coldea L. Pentraxin-3 and endothelial dysfunction. Adv Clin Chem. 2019;91:163–79. https://doi.org/10.1016/bs.acc.2019.03.005.

43. Presta M, Camozzi M, Salvatori G, Rusnati M. Role of the soluble pattern recognition receptor PTX3 in vascular biology. J Cell Mol Med. 2007;11(4): 723–38. https://doi.org/10.1111/j.1582-4934.2007.00061.x.

44. Kerget F, Kerget B, Kahraman ÇY, et al. Evaluation of the relationship between pentraxin 3 (PTX3) rs2305619 (281A/G) and rs1840680 (1449A/G) polymorphisms and the clinical course of COVID-19. J Med Virol. 2021;93(12):6653–9. https://doi.org/10.1002/jmv.27238.

45. Wang G, Jiang C, Fang J, Li Z, Cai H. Pentraxin-3 as a predictive marker of mortality in sepsis: an updated systematic review and meta-analysis. Crit Care. 2022;26(1):167. https://doi.org/10.1186/s13054-022-04032-x.

## Publisher's Note