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The Level of Procalcitonin in Severe COVID-19 Patients: A Systematic Review and Meta-Analysis

25

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Abstract

There is data from individual clinical trials suggesting that procalcitonin (PCT) may be a prognostic factor in the severity of COVID-19 disease. Therefore, this systematic review and meta-analysis was performed to investigate PCT levels in severe COVID-19 patients. We searched Embase, ProQuest, MEDLINE/PubMed, Scopus, and ISI/Web of Science for studies that reported the level of PCT of patient with severe COVID-19. We included all studies regardless of design that reported the level of PCT in patients with severe COVID-19. We excluded articles not regarding COVID-19 or not reporting PCT level, studies not in severe patients, review articles,

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editorials or letters, expert opinions, comments, and animal studies. Nine studies were included in the analysis. The odds of having more severe COVID-19 disease was higher in subjects with elevated PCT (≥0.05 ng/mL) compared with those having low procalcitonin (<0.05 ng/mL) [n = 6, OR(95% CI) = 2.91(1.14, 7.42), p = 0.025). After estimating the mean and standard deviation values from the sample size, median, and interquartile range, a pooled effect analysis indicated higher serum PCT concentrations in patients with severe versus less severe disease [n = 6, SMD(95% CI) = 0.64(0.02, 1.26), p = 0.042]. The results of this study showed that PCT is increased in patients with severe COVID-19 infection.

Keywords

Coronavirus · Procalcitonin · Meta-analysis · SARS-CoV-2 · COVID-19 · Viral infection

25.1 Introduction

Patients with unexplained pneumonia were initially reported in Wuhan, China, in December 2019. A novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in samples of the lower respiratory tract of the infected patients, and the disease was termed COVID-19 (coronavirus-2019) [1]. This disease is rapidly spreading across the world [2] and has turned into a pandemic [3]. Globally, approximately 5,311,624 confirmed cases of COVID-19 have been reported, including an estimated 342,105 deaths in approximately 209 countries (as of May 23, 2020) [4]. It is presently the greatest health challenge worldwide [5], and the World Health Organization (WHO) has declared the outbreak a global public health emergency [6].

Currently the gold standard for the diagnosis of COVID-19 is reverse transcription polymerase chain reaction (RT-PCR) testing, but, in many countries, testing has been limited due to time and resource issues, and in the early stage of the disease, the positive rate of the test was relatively low [7]. Therefore, there is an urgent need to identify reliable biomarkers that may help predict the risk for illness severity so that appropriate care can be allocated earlier [8].

One of the most studied biomarkers in this field is procalcitonin (PCT), which has both diagnostic and prognostic utility [9]. PCT has become a promising biomarker for early detection of bacterial infections in modern clinical practice [10]. However, the expression of this biomarker may differ in severe COVID-19 infection with some studies reporting that PCT is increased in patients with severe COVID-19 [11, 12] and others reporting that PCT in these patients is normal [13, 14]. These differences could reflect the fact that the clinical characteristics differ in those patients with mild versus severe COVID-19 infections [9].

We have aimed to resolve this issue by carrying out a systematic review of PCT levels in COVID-19 cases.

25.2 Methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. We aimed to compare the levels of PCT in patients with severe versus non-severe COVID-19 infections, to determine if it can be used as a biomarker to predict disease course. A threshold level of 0.05 ng/mL PCT was taken to discriminate between severe and non-severe infection for each study.

25.2.1 Search Strategy

We searched, Embase, ProQuest, MEDLINE/PubMed, Scopus, and ISI/Web of Science for studies that reported the level of PCT in patients with COVID-19 infections. A date limit was set from December 2019, and the search was performed up to April 5, 2020. The reference list of articles was reviewed using forward and back-

ward citation tracking to identify other eligible documents. No language limits were applied.

25.2.2 Selection Criteria

We included all studies regardless of study design, targeting prospective or retrospective studies that met the following criteria:

1. Reported the level of PCT in COVID-19 patients displaying serious symptoms
2. Reported the level of PCT in COVID-19 patients displaying non-serious symptoms

We excluded:

1. Articles not regarding COVID-19 or not reporting PCT level
2. Studies not including both severe and non-severe COVID-19 patients
3. Review articles, editorials or letters, expert opinions, comments, and animal studies

At least two reviewers independently evaluated titles and abstracts and selected relevant studies for inclusion. If this could not be done reliably using the title and abstract of an article, the full text version was retrieved for detailed analysis. Any disagreement was resolved by a third independent reviewer. The reasons for exclusion of studies were recorded.

At first we searched databases that included Scopus (7), Embase (9), ProQuest (14), PubMed (2), and Web of Science (2) and identified 31 total studies. In the next step we removed the duplicate articles and retained 19 records to include Scopus (7), Embase (2), ProQuest (10), PubMed (1), and Web of Science (2). Subsequently, the records were screened by title and abstract and six further studies were excluded. The remaining 16 records were screened further using the full text, and this left nine articles that met all requirements for inclusion in the study.

25.2.3 Data Extraction

Data were extracted independently by at least two reviewers and included authors, year of publication, clinical setting, sample size, sample type, and levels of PCT. Disagreements on the extracted data were resolved by consensus.

25.2.4 Quality Assessment

The methodological quality assessment of studies was performed independently by two authors using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria, as recommended by the Cochrane Collaboration [16]. Disagreements about inclusion criteria, data extraction, and quality assessment were resolved by consensus.

25.2.5 Data Synthesis and Statistical Analysis

We applied random-effects meta-analyses with inverse variance weighting to calculate pooled estimates and 95% confidence intervals (CIs). We estimated the sample mean and standard deviation (SD) from the sample size, median, and interquartile range via the Wan et al. approach [17] to compute a meta-analysis of outcomes and demonstrate effectiveness. In addition, we used odds ratios (ORs) and 95% CIs to compare the rates of disease severity. Heterogeneity (I^2 statistics) was assessed and reported using Cochran's Q-test [18]. We also plotted Galbraith graphs to display heterogeneity. Egger's test and a visual inspection of funnel plots were carried out to evaluate publication bias between studies [19]. In general, a PCT concentration ≥ 0.05 ng/mL was considered as being high in our analysis. Values below 0.05 ng/mL were considered normal or low. Two groups of patients with either low or high disease were also examined. STATA version 14.0 (Stata Corp, College Station, TX) and R version 3.6.3 were used to conduct the analyses.

25.3 Results

A summary of study selection process and characteristics of the included studies are summarized in Fig. 25.1 and Table 25.1, respectively.

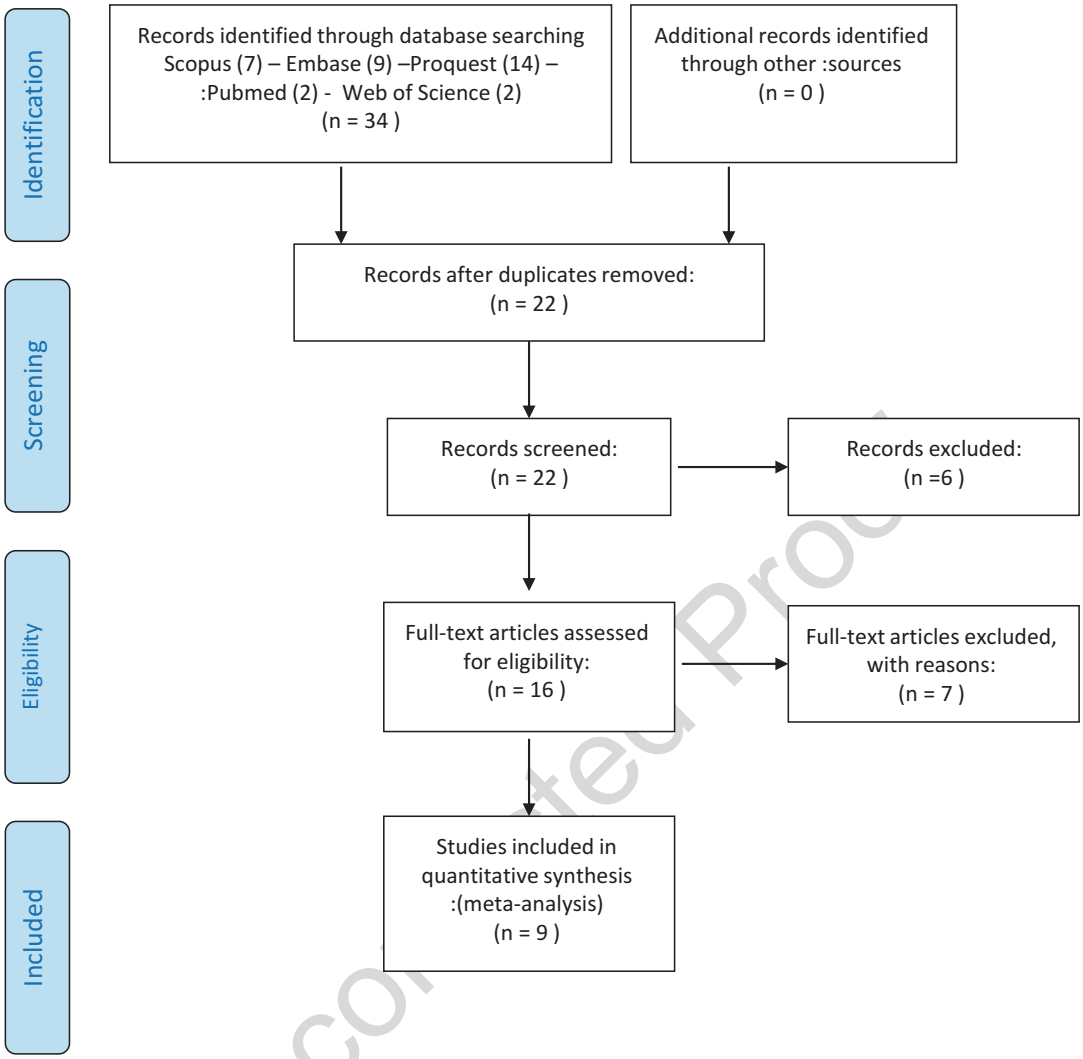

Fig. 25.1 PRISMA flow diagram summarizing the study selection process

25.3.1 Results of PCT Analyses Using Odds Ratios

Results were obtained for PCT with an odds ratio in 6 out of the 9 studies which met the selection criteria. A randomized effect analysis showed significant risk according using a forest plot to visualize the results (Fig. 25.2). The odds of having more severe COVID-19 disease was higher in subjects with elevated PCT compared to those with low PCT levels ($n = 6$, OR(95% CIs) = 2.91 (1.14, 7.42), $p = 0.025$) (Fig. 25.3).

The Q-test showed a significant variations in odds ratios attributable to heterogeneity of the procalcitonin data ($I^2 = 73.5\%$, $p = 0.002$), which can also be seen in the Galbraith plot (Fig. 25.3). There was no publication bias in the PCT studies according to results of Egger's test analyses and by using a funnel plot visualization ($p = 0.434$) (Fig. 25.4).

Table 25.1 Final studies included in meta-analysis

No	Authors	Year	Procalcitonin		Sample size	Setting	Samples	Study design
			Patients with worse condition	All Patients				
1	Qiu et al. [20]	2020	*N* = 19 0.32 (0.19)	*N* = 36 0.24 (0.17)	36	Three hospitals in Zhejiang province, China	Children with coronavirus disease 2019	Retrospective
2	Zhang et al. [12]	2020	*N* = 56 0.1 (0.06–0.3)	*N* = 138 0.07 (0.04–0.1)	138	No. 7 hospital of Wuhan	Patients diagnosed as COVID-19	Prospective
3	Wang et al. [21]	2020	*N* = 36 27 (75.0)	*N* = 138 49 (35.5)	138	Zhongnan Hospital of Wuhan University	Patients with confirmed NCIP	Retrospective
4	Guan et al. [22]	2020	*N* = 173 16/117 (13.7)	*N* = 1099 35/633 (5.5)	1099	552 hospitals in 30 provinces, autonomous regions, and municipalities in mainland China	Patients with laboratory-confirmed COVID-19	Retrospective
5	Huang et al. [13]	2020	*N* = 13	*N* = 41	41	Wuhan, China	Patients with laboratory-confirmed 2019 nCoV infection	Prospectively
			0.1 (0.1–0.4)	0.1 (0.1–0.1)				
6	Liu et al. [23]	2020	*N* = 69	*N* = 80	80	Department of Infectious Diseases, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	Patients with severe type COVID-19	Retrospective
			2/69 (2·90)	2/80 (2·50)				
7	Shi et al. [16]	2020	*N* = 82	*N* = 416	416	Renmin Hospital of Wuhan University, located in Wuhan, Hubei province, China, was assigned responsibility for the treatment of patients with severe COVID-19 by the Wuhan government	Severe patients admitted to Renmin Hospital of Wuhan University with laboratory-confirmed COVID-19	Retrospective
			0.06(0.03–0.10)	0.07(0.04–0.15)				
8	Peng et al. [24]	2020	*N* = 16 0.20(0.15–0.48)	*N* = 96 0.11(0.06–0.20)	112	Wuhan Union Hospital West Hospital	Patients with cardiovascular diseases infected with new coronavirus pneumonia	Retrospective
9	Zhou et al. [16]	2020	*N* = 11 0.21(0.11–0.42)	*N* = 9 0.05(0.03–0.06)	20	West District of Union Hospital of Tongji Medical College	In-hospital severe patients with COVID-19	Retrospectively

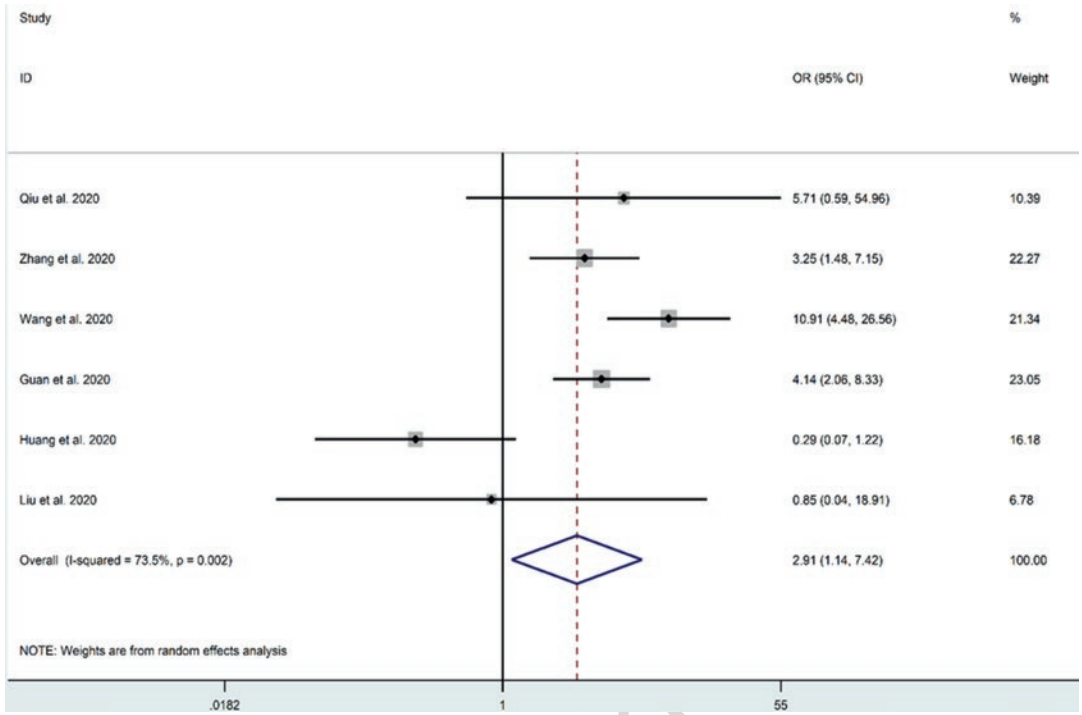

Fig. 25.2 Forest plot results for odds ratio of procalcitonin laboratory data

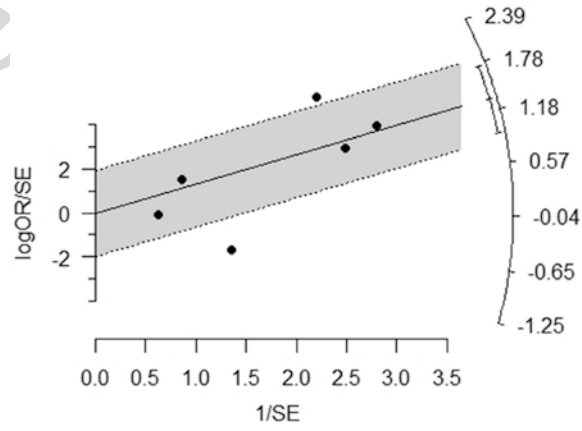

Fig. 25.3 Galbraith (radial) plot for odds ratio of trials used by procalcitonin laboratory data

25.3.2 Results of PCT Analyses Using Standardized Mean Difference

All PCT results included in the six studies were analyzed using the standardized mean difference (SMD). For most studies (except the study by Qiu et al. [20]), the median and interquartile range of PCT were reported instead of the mean and standard deviation. After estimating the values of the mean and standard deviation from the sample size, median, and interquartile range, a pooling effect analysis indicated a significantly higher PCT level (n = 6, SMD(95% CI) = 0.64(0.02, 1.26), p = 0.042) in subjects with severe versus less severe COVID-19 disease (Fig. 25.5).

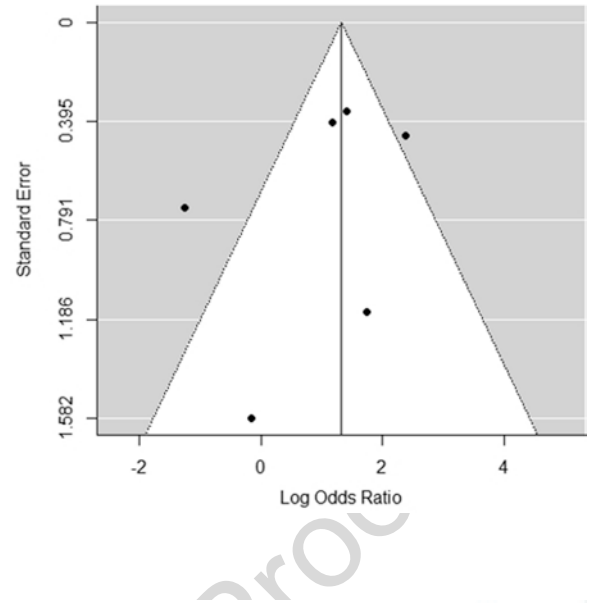

Fig. 25.4 Funnel plot for verification of publication bias in the meta-analysis of odds ratio of procalcitonin laboratory data

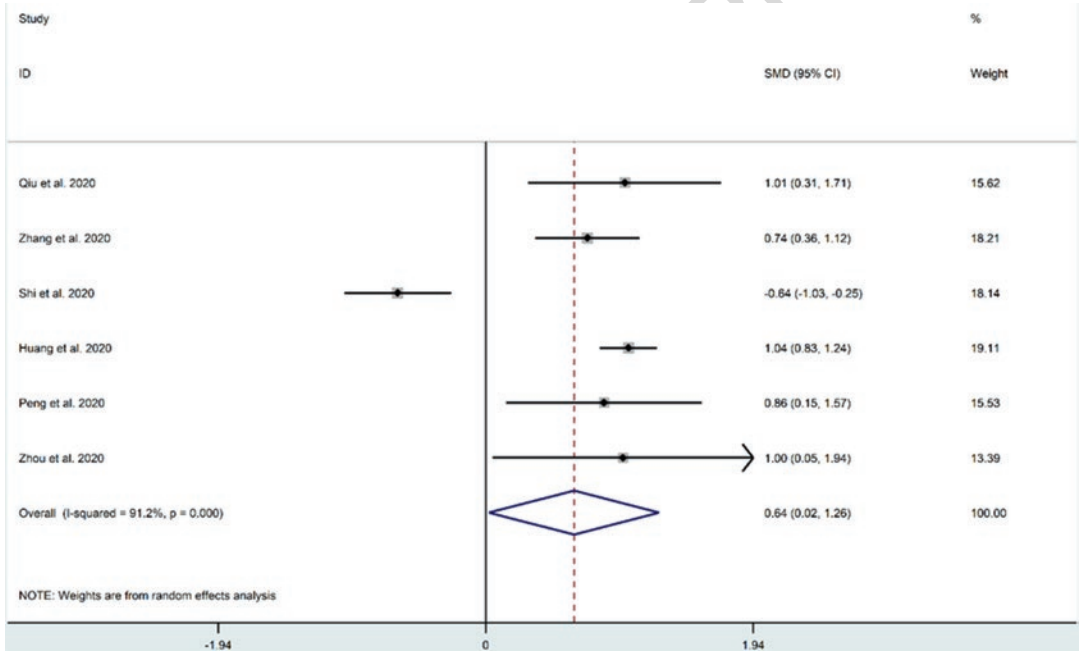

Fig. 25.5 Forest plot results for standardized mean difference of procalcitonin laboratory data

Next, we applied a random effects analysis since there was heterogeneity between the studies for PCT based on the Q-test and radial plot results ($I^2 = 91.2\%$, $p < 0.001$) (Fig. 25.6). Additionally, according to Egger's test and visualization with a funnel plot, there was no publication bias in the results of the meta-analysis ($p = 0.711$) (Fig. 25.7).

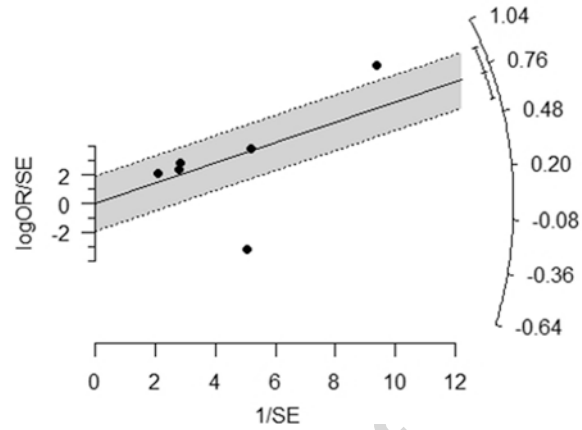

Fig. 25.6 Galbraith (radial) plot for standardized mean difference of trials using procalcitonin laboratory data

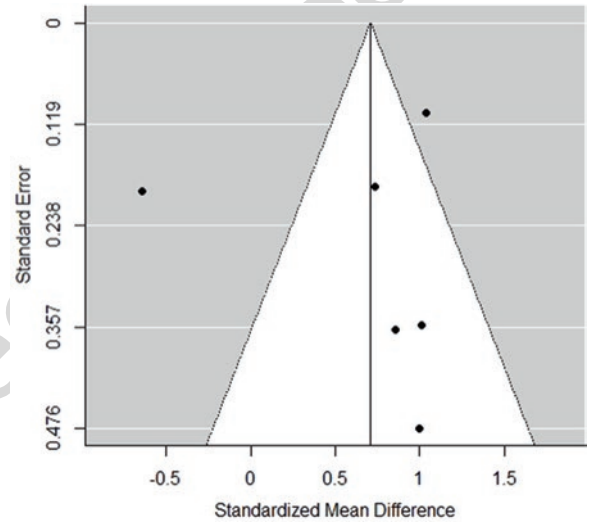

Fig. 25.7 Funnel plot for verification of publication bias in the meta-analysis of standardized mean difference of procalcitonin laboratory data

25.4 Discussion

This study demonstrated that high levels of PCT are associated with disease severity in patients infected with COVID-19. PCT is known to be elevated in bacterial infections and is currently used for diagnosis and decision-making regarding antibiotic treatment duration in respiratory infections [25]. Its synthesis is upregulated in bacterial infections and downregulated in viral infections [26]. PCT is produced by the thyroid C cells in healthy people. In the presence of bacterial infections, PCT production is activated in all parenchymal tissues and its level increases rapidly. PCT production by these tissues is stimulated both directly by bacterial endotoxins and lipopolysaccharides and indirectly by inflammatory mediators that include tumor necrosis factor-alpha (TNF-a), interleukin (IL)-1, and IL-6. However, mediators of viral infection such as interferon-gamma (IFN-γ) decrease the PCT level, which makes it a more specific marker for bacterial infections [26]. Nevertheless, the finding of this study showed that PCT is increased in patients with severe COVID-19. This suggests that in some severe COVID-19 cases, there is a bacterial co-infection that increases their PCT levels. This hypothesis is supported by the work of Zhou et al. in which it was reported that the most of severe COVID-19 patients have viral

infection and secondary bacterial infection [16]. Bacterial co-infection is a poor prognostic feature in these patients [27] and may contribute to the death of these patients [28]. Thus, a PCT level determination, in addition to helping with identification of severe patients, may guide physicians in determinations of bacterial co-infection. This would allow them to initiate early antibiotic therapy that may prevent further deterioration of health.

The results of this study are contrary to the results of the study by Lippi and Plebani, which reported that the PCT value would remain within the reference range in severe coronavirus-infected patients [29]. However, the meta-analysis in the present study was of wider scope, including multiple studies that would have accounted for more patient variables. Nevertheless, further studies are required to address this issue.

25.5 Conclusion

The results of this study showed that PCT in patients with severe COVID-19 disease is increased, which suggests that it may play an important role in predicting severity and outcome of infection. Therefore, a PCT level determination may guide physicians in cases of suspected bacterial co-infection to initiate early antibiotic therapies that may prevent further deterioration of health and death.

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Conflict of Interests None.

Funding None.

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