Prognostic Value of Serum Procalcitonin in COVID-19 Patients: A Systematic Review

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ABSTRACT

Background: This study is aimed at reviewing the published literature on the prognostic role of serum procalcitonin (PCT) in COVID-19 cases.

Data retrieval: We systematically reviewed the literature available on PubMed, MEDLINE, LitCovid NLM, and WHO: to assess the utility of PCT in prognosis of coronavirus disease. Scrutiny for eligible studies comprising articles that have evaluated the prognostic utility of PCT and data compilation was undertaken by two separate investigators. Original articles in human subjects reporting the prognostic role of PCT in adult COVID-19 patients were included. The Quality in Prognosis Studies (QUIPS) tool was utilized to assess the strength of evidence. Results were reported as narrative syntheses.

Results: Out of the total 426 citations, 52 articles passed through screening. The quality of evidence and methodology of included studies was overall acceptable. The total sample size of the studies comprised of 15,296 COVID-19-positive subjects. Majority of the studies were from China, i.e., 40 (77%). The PCT cut-off utilized was 0.05 ng/mL by 18 (35%) studies, followed by 0.5 ng/mL by 9 (17.5%). Eighty five percent ($n = 44$) studies reported statistically significant association (p value < 0.05) between PCT and severity.

Conclusion: Procalcitonin appears as a promising prognostic biomarker of COVID-19 progression in conjunction with the clinical context.

Keywords: COVID-19, Procalcitonin, Prognostic biomarker, Systematic review.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) emerged as an unanticipated emergency crisis at the beginning of year 2020 with devastating medical, social, and financial implications globally.¹ From a clinical perspective, the unknown complications, lack of availability of prophylactic and reliable therapeutic regimens, and the intricacy of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, accompanied by a rapidly evolving clinical course, puzzled the medical community worldwide.²

The clinical scientists extensively and urgently studied reliable biochemical markers related to COVID-19 disease severity aimed at high-risk stratifications and optimal resource allocation, in the already overwhelmed medical infrastructure.³ The biomarkers that were particularly explored in this context included procalcitonin (PCT), C-reactive protein (CRP), ferritin (Fer), D-dimer, interleukin-6 (IL-6), and lactate dehydrogenase (LDH).³

Preliminary studies have described pathogenetic mechanisms triggered by COVID-19 including a plethora of inflammatory processes, cytokine storms, and the stimulation of coagulation pathways; ultimately, a picture of systematic inflammation ensues with systemic vasculitis and often fatal complications.⁴ Due to the characteristic nature of PCT in bacterial vs. viral infections, this biomarker may have a role in prognosis of COVID-19.⁵

Procalcitonin is a glycoprotein calcitonin pro-hormone released by the thyroid parafollicular cells. In case of a microbial infection, PCT levels are significantly raised as it is released by all parenchymal tissue under the influence of endotoxins and pro-inflammatory cytokines.⁶ Thus, in physiological state serum PCT is recorded significantly below 0.05 ng/mL. Furthermore, keeping in view the timelines for risk stratification, PCT follows a swift course with its inclining levels detected 2–6 hours after the stimulus.⁶ However,

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highly regarded and utilized as a biomarker of bacterial infection, contrasting opinion exists on the efficacy of PCT as a prognostic tool for COVID-19.^{7,8} Moreover, cytokines released in COVID-19, particularly interferon (INF)- γ , have a negative effect on PCT levels, adding to the strength of this prognostic tool.⁹ Early studies in the wake of the pandemic have shown higher levels of PCT in severe COVID-19 cases.¹⁰ Lippi et al. have reported that the PCT levels are expected to quintuple in severe cases.¹¹ Various other authors have also supported the view that any considerable increase from baseline PCT levels reflects the onset of a critical phase of the viral infection.¹²

Given these unique characteristics, reliable kinetics, and the potential association of declining levels with resolution of infection, PCT has emerged as a promising prognostic biomarker in COVID-19.¹¹ This paper is aimed at an extensive evaluation of the published literature on the prognostic role of serum PCT in COVID-19 cases.

DATA RETRIEVAL

The team of investigators performed a systematic literature review based on Medline (PubMed interface), LitCovid NLM, and WHO: Global literature on coronavirus disease from the advent of COVID-19 in December 2019 till June 15, 2020. The strategy adopted was in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹³

Keywords and medical subject heading terms searched included Coronavirus OR "corona virus" OR coronavirinae OR coronaviridae OR betacoronavirus OR covid19 OR "covid 19" OR nCoV OR "CoV 2" OR CoV2 OR sarscov2 OR 2019nCoV OR "novel CoV" OR "wuhan virus" OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia) AND (outbreak)) OR "Coronavirus" OR "Coronavirus Infections" OR "COVID-19" OR "severe acute respiratory syndrome coronavirus 2" OR "Betacoronavirus" AND (Procalcitonin OR PCT OR Calcitonin Precursor Polypeptide OR Calcitonin-1 OR Calcitonin 1 OR Calcitonin Related Polypeptide Alpha OR Pro-Calcitonin) without language restrictions.

Nonhuman and biological model studies were not included. Moreover, two separate investigators (SA and LJ) reviewed the titles and abstracts of all articles identified for inclusion in the final analysis; alongside, the references of the scrutinized articles and the PubMed-related article feature were also explored for any additional publications of potential interest. The inclusion criteria were structured upon the following conditions: (1) study participants (adults with confirmed COVID-19); (2) single or serial measurements of serum PCT documented; (3) assessment of prognostic performance of PCT; (4) at least one outcome measure documented, i.e., severe infection requiring mechanical ventilation, needing admission to intensive care unit, and mortality; and (5) study design: cross sectional, cohort, case-control, and case series.

Studies comprising reviews, meta-analysis, letters to the editor, surveys, commentary, perspectives, opinion papers, hypothesis, viewpoints, animal studies, drug discovery, drug trials, basic sciences/nonclinical studies, studies done in pediatric population, article full text in language other than English, and abstracts only

were omitted. Full-text article versions of the abstracts included in the final study analysis were further appraised by two authors. The agreement and concordance between independent evaluations was statistically sought with κ statistic for the interrater reliability.¹⁴

The quality of evidence gathered and likely risk of bias was evaluated according to the quality in prognosis studies (QUIPS) tool.¹⁵ Scores were calculated as "low," "moderate," or "high" for 30 variables under six domains, namely study population selection, attrition rate, prognostic biomarker analysis, outcome assessment, potential confounders evaluation, statistical exploration, and delineation. High quality was defined as attainment of low or moderate risk of bias for most domains and vice versa. A third reviewer (IS) was involved to resolve the disagreement in opinions through mutual consensus.

The two reviewers autonomously compiled the data using a predesigned pro forma enlisting the region of study publication, number of study participants, time period of recruitment, PCT cut-offs utilized, and correlation of PCT with severity by the p value and descriptive results as reported by the different studies included in the final analysis.

RESULTS

The databases searched revealed a total of 426 studies. Moreover, 26 duplicate studies were excluded. Based on the stringent inclusion criteria as depicted in Flowchart 1, 52 articles were included in the final analysis based on autonomous evaluation by two investigators with an excellent agreement of κ statistic = 0.90. The accumulated sample size of the studies comprised of 15,296 cases.

Table 1 presents a comprehensive overview of the articles included in this systematic review published from January to June 2020. Different PCT cut-offs were utilized ranging from 0.05, 0.1 and 0.5 ng/mL, by 35% ($n = 18$), 9% ($n = 5$), and 17.5% ($n = 9$) studies, respectively, whereas, cut-off used was not reported by 27% ($n = 14$) studies.

Seventy-seven percent ($n = 40$) were reported from China as shown in Figure 1. Total 44 (85%) studies reported statistically significant association (p value < 0.05) between PCT and severity

Flowchart 1: Search strategy

Table 1: Summary of studies evaluated and enlisting correlation of PCT with severity

Author	Region	Date of recruitment	Year of recruitment initiation	Study design	Sample size (male:female)	Age in years, Median (range) or Mean $\pm$ SD	Cut-off used for elevated PCT (ng/mL)	PCT correlation with severity (p value = correlation coefficient)
Bhandari et al. ⁷	India	March to May	2020	Prospective cohort	21 (14:7)	43.5 (2.0–85.0)	N/R	PCT elevated in all severe cases
Cecconi et al. ¹⁶	Italy	February to March	2020	Retrospective cohort	239 (169:70)	63.9 $\pm$ 14.0	> 0.5	$p < 0.001$
Cen et al. ¹⁷	China	February	2020	Prospective cohort	1007 (493:514)	61 (49–68)	> 0.5	$p < 0.044$
Chen et al. ¹⁸	China	March	2020	Retrospective cohort	548 (313:235)	56.0 $\pm$ 14.5	> 0.5	$p < 0.001$
Chen et al. ¹⁹	China	December to January	2019	Retrospective cohort	1590 (N/R)	69 (51–86)	> 0.5	$p < 0.001$
Chen et al. ²⁰	China	January to February	2020	Retrospective cohort	203 (108:95)	54 (20–91)	> 1.0	$p < 0.04$
Chen et al. ²¹	China	January	2020	Retrospective cohort	78 (39:39)	45 (15–79)	> 0.5	$p < 0.001$
Duan et al. ²²	China	January to February	2020	Retrospective cohort	397 (233:164)	51.0 $\pm$ 15	> 0.04	$p < 0.01$
Gavin et al. ²³	USA	March	2020	Retrospective cohort	140 (72:68)	60 (48–72)	> 0.24	$p < 0.00004$
Gregoriano et al. ²⁴	Switzerland	February to April	2020	Retrospective cohort	99 (62:37)	67 (56–76)	> 0.05	$p < 0.002$
Guo, et al. ²⁵	China	January to February	2020	Retrospective case series	187 (91:96)	58.50 $\pm$ 14.66	> 0.05	$p < 0.001$
Hong, et al. ²⁶	China	January to February	2020	Retrospective cohort	75 (41:34)	46.37 $\pm$ 13.34	N/R	$p < 0.004$
Hou et al. ²⁷	China	January to February	2020	Prospective cohort	389 (200:189)	61.3 $\pm$ 13.8	N/R	$p < 0.0001$
Hu et al. ²⁸	China	January to March	2020	Retrospective cohort	95 (39:56)	57.6 $\pm$ 14.7	> 0.05	$p < 0.05$
Ke et al. ¹⁰	China	January	2020	Case series	2 (1:1)	79 and 40	> 0.05	PCT was elevated in all cases
Li et al. ²⁹	China	January to February	2020	Retrospective cohort	132 (75:57)	62 (33–89)	> 0.05	PCT had no significant changes in association disease severity
Li et al. ³⁰	China	January to February	2020	Retrospective cohort	225 (120:105)	50 $\pm$ 14	> 0.5	PCT was elevated in 10.67 % of patients
Li et al. ¹²	China	January to February	2020	Retrospective cohort	25 (10:15)	73 (55–100)	> 0.1	PCT was elevated in 90.5% of patients
Lima et al. ³¹	USA	March to April	2020	Retrospective cohort	5 (4:1)	45–68	> 0.5	PCT was elevated in two cases
Liu et al. ³²	China	January to March	2020	Retrospective observational	141 (49:91)	65.5 (54.3–73.0)	> 0.07	$p = 0.025$
Liu et al. ³³	China	February	2020	Retrospective cohort	107 (52:55)	68(61–76)	> 0.1	$p = 0.031$
Luo et al. ³⁴	China	January to February	2020	Retrospective cohort	298 (150:148)	57(40–69)	N/R	$p < 0.001$
Ma et al. ³⁵	China	January to March	2020	Retrospective cohort	37 (20:17)	62 (59–70)	> 0.1	$p < 0.001$
McRae et al. ³⁶	USA	April	2020	Retrospective cohort	160 (82:78)	63 $\pm$ 13	> 0.05	$p < 0.001$

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Author	Region	Date of recruitment	Year of recruitment initiation	Study design	Sample size (male:female)	Age in years, Median (range) or Mean $\pm$ SD	Cut-off used for elevated PCT (ng/mL)	PCT correlation with severity (p value = correlation coefficient)
Ni et al. ³⁷	China	February	2020	Prospective cohort	27 (14:13)	60 (33–83)	> 0.05	$p < 0.01$
Ortiz-Brizuela et al. ³⁸	Mexico	February to April	2020a	Prospective cohort	309 (183:126)	43 (33–54)	> 0.05	$p < 0.001$
Pan et al. ³⁹	China	January to March	2020	Case-control study	124 (85:39)	68 (61–75)	> 0.05	$p < 0.001$
Price-Haywood et al. ⁴⁰	United States	March to April	2020	Retrospective cohort	3,491 (2097:1394)	55.5 $\pm$ 18.5, 53.6 $\pm$ 16.1	> 0.25	Elevated PCT associated with in-hospital mortality HR 1.40 (1.06–1.84)
Rastrelli et al. ⁴¹	Italy	N/R	2020	Case series	31 (All males)	63 (55–66.5)	> 0.9	$p < 0.001$
Rath et al. ⁴²	Germany	February to March	2020	Prospective cohort	123 (77:46)	68 $\pm$ 15	N/R	$p < 0.002$
Sattar et al. ⁴³	USA	N/R	2020	Case report	1 (male)	67	N/R	PCT levels increased with disease progression
Shao et al. ⁴⁴	China	January to March	2020	Retrospective cohort	155 (62:93)	48 (7–96)	> 0.05	$p = 0.032$
Sun et al. ⁴⁵	China	January to February	2020	Retrospective cohort	84 (47:37)	64 (21–95)	N/R	$p < 0.001$
Tian et al. ⁴⁶	China	January to March	2020	Retrospective cohort	232 (119:113)	64 (58–69)	N/R	$p < 0.001$
Wan et al. ⁴⁷	China	January to February	2020	Case series	135 (72:63)	47 (36–55)	N/R	$p < 0.05$
Wang et al. ⁴⁸	China	January to February	2020	Prospective cohort	85 (45:40)	59 $\pm$ 15.3	N/R	$p < 0.011$
Wang et al. ⁴⁹	China	January to March	2020	Retrospective cohort	108 (72:36)	70.9 $\pm$ 10.6, 71.1 $\pm$ 10.1	N/R	$p < 0.001$
Wang et al. ⁵⁰	China	January to February	2020	Retrospective cohort	28 (21:7)	68.6 $\pm$ 9.0	N/R	$p = 0.0006$
Wu et al. ⁵¹	China	January to February	2020	Retrospective cohort	270 (139:131)	62 (50–69)	> 0.05	$p < 0.05$
Yan et al. ⁵²	China	January to February	2020	Retrospective observational	193 (114:79)	64 (49–73)	> 0.05	$p < 0.001$
Yang et al. ⁵³	China	January to February	2020	Retrospective cohort	114 (56:58)	46.05 $\pm$ 15.15	>5	$p < 0.014$
Yang et al. ⁵⁴	China	January to April	2020	Retrospective cohort	52 (28:24)	63 (34–98)	N/R	$p < 0.05$
Yang et al. ⁵⁵	China	January to February	2020	Retrospective case series	136 (66:70)	56 (44–64)	> 0.05	$p < 0.001$
Ye et al. ⁵⁶	China	January to March	2020	Retrospective cohort	349 (173:176)	62 (21:69)	N/R	$p < 0.001$
Yu et al. ⁵⁷	China	January to February	2020	Retrospective cohort	1663 (736:728)	64 (51–71)	> 0.05	$p < 0.001$
Yuan et al. ⁵⁸	China	February to March	2020	Retrospective cohort	117 (56:61)	66 (29–92)	> 0.5	$p < 0.01$
Zaninotto et al. ⁵⁹	Italy	January to March	2020	Prospective cohort	75 (56:19)	67 (56–76)	> 0.5	PCT was elevated in 2 severe cases
Zeng et al. ⁶⁰	China	January to March	2020	Retrospective cohort	461 (239:222)	45 (34.5–57)	> 0.05	$p < 0.001$

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Author	Region	Date of recruitment	Year of recruitment initiation	Study design	Sample size (male:female)	Age in years, Median (range) or Mean $\pm$ SD	Cut-off used for elevated PCT (ng/mL)	PCT correlation with severity (p value = correlation coefficient)
Zhang et al. ⁶¹	China	January to February	2020	Retrospective cohort	84 (50:34)	49 (24–80)	> 0.05	$p < 0.003$
Zhang et al. ⁶²	China	January to February	2020	Retrospective case series	221 (108:113)	55 (39–66.5)	> 0.05	$p < 0.001$
Zhang et al. ⁶³	China	December to February	2019	Retrospective cohort	289 (155:134)	57 (22–88)	> 0.1	$p < 0.004$
Zhang et al. ⁶⁴	China	January to February	2020	Retrospective cohort	140 (71:69)	57 (25–87)	> 0.1	$p < 0.001$

*Studies in alphabetic order; *N/R: not recorded; PCT, procalcitonin

Fig. 1: Countries of origin of studies

based on p values or hazard's ratio. Seven (14%) studies did not present a statistical analysis however reported elevation of PCT in severe case or mortality. Whereas, only one study did not report any significant elevation in PCT with disease progression.

Figure 2 shows the quality of evidence according to the QUIPS tool. Low to moderate risk of bias was noted for most domains whereas high risk in one or more domains was evident in only eight studies (15%). For the probable effects of the confounding variable, no adjustments in the analysis were undertaken. The statistical analysis realm had a moderate to high risk of bias in five (9%) articles. Eight (15%) studies did not report use of any statistical analysis to assess PCT's association with prognosis and only narrative results were presented while moderate to high risk was noted for the statistical analysis in five (9%) studies.

Three studies evaluated the receiver operating characteristic (ROC) curve for PCT and reported optimal cut-off and the area under the curve (AUC) for the prediction of severity.^{22,24,32} The optimal cut-offs reported alongside the AUC were 0.04 ng/mL (AUC 0.74 [95% CI: 0.69–0.78]), 0.11 ng/mL (AUC: 0.80 [95% CI: 0.71–0.90]), and 0.07 ng/mL (AUC: 0.74), respectively.

DISCUSSION

With the global medical crisis amidst the COVID-19 pandemic, the role of laboratory evaluation and early prediction of the severity of a patients' condition was markedly highlighted. Since its inception on the diagnostic platform in 1993, a significant and reliable linkage

Fig. 2: Assessment of risk of bias using QUIPS tool

between serum PCT level for severity prediction of infectious etiologies has been widely reported.⁶⁵ In context of COVID-19, the extrathyroidal secretion of PCT is thought to be massively intensified during infectious insults and, furthermore, actively precipitated by the inflammatory cytokines.³

To further substantiate this association, our results revealed 51 studies reported either a significant association between PCT and severity or markedly elevated PCT levels in the severe patients group making it a reliable prognostic biomarker. However, Li et al. reported no significant association between PCT and prognosis in COVID-19 cases, which could be due to a small proportion of critically ill ($n = 5$) and expired ($n = 11$) cases and the findings could vary if a larger cohort is evaluated.²⁹ A handful of studies presented clinical and outcome profiles of COVID-19 cases in their respective setups, accompanied with varying proportions of severe cases, whereas most studies lack homogeneity when it came to evaluation of biochemical parameters, pertaining mainly to rapidly evolving guidelines.

As the PCT release is thought to be inhibited by interferon (INF)- γ upsurge, it is expected that the PCT value would remain significantly lower than the optimal cut-off in cases with noncritical or severe infection.³ Similarly, in this review, the optimal cut-off was >0.05 ng/mL as utilized by studies, i.e., 35% ($n = 18$) to label severe cases and determine statistical association.

More than 75% of the studies revealed were conducted in Chinese population. This could be a potential confounding factor

as the expression of PCT is thought to be dependent upon the genetic framework of the population.⁶ However, a few studies in this review did include the Caucasians and south Asians and similar strong association between PCT and severity was obtained.^{7,24,43,59} This multiethnic evaluation further strengthens our proposition of PCT as a prognostic biomarker in COVID-19 cases. However, studies from various populations may be needed to understand the prognostic ability better.

As revealed by Liu et al., PCT levels greater than 0.07 ng/mL with an AUC of 0.812 and sensitivity and specificity of 73.15 and 84.85%, respectively, for the prediction of morbidity can be considered in routine clinical practice in conjunction with other biochemical markers and clinical picture.³² The prediction of cases that can potentially progress to severe stage can aid optimal resource allocation and aggressive treatment plans.

Majority of the studies in this review were inpatient based, making it more feasible to longitudinally record follow-up, which is essential to evaluate prognostic performance of PCT. Furthermore, the population evaluated by the studies in this review was multiethnic ranging from Chinese, Indian, Europeans, North and South Americans, as depicted in Table 1. A few notable limitations include exclusion of non-English publications mostly from China. Existing comorbidities including renal dysfunction, prior bacterial infection, and prophylactic antibiotic initiation that could alter PCT levels were not extensively evaluated. A meta-analysis could not be performed owing to the lack of uniformity of the statistical models adopted by various studies. Moreover, microbiological culture results for coinfecting bacterial and fungal infections were not appraised.

CONCLUSION

In spite of the several limitations, PCT seems to appear as a promising prognostic biomarker in COVID-19. Initially elevated PCT levels may be used as a prompt prognosticator of criticalness, deteriorating clinical picture, and even mortality in COVID-19. The biomarker can also serve as a risk stratification tool for intensive resource allocation and aggressive therapeutics in conjunction with clinical details and other biomarkers, in an already overoccupied medical centers globally amidst the crisis. However, to expansively evaluate the prognostic utility of PCT, large-scale cross-sectional multicenter studies are need of time.

HIGHLIGHTS

- Procalcitonin (PCT) has emerged as a promising prognostic biomarker in COVID-19.
- Various studies have supported the view that PCT levels are below the optimal cut-off in COVID-19 and any considerable increase from baseline reflects the development of a critical state.
- Given these unique characteristics, reliable kinetics, and the potential association of declining levels with resolution of infection, this is a comprehensive systematic review of studies that have evaluated PCT in COVID-19, from across the globe with a total sample size of 15,296 cases.

AUTHORS' CONTRIBUTIONS

Sibtain Ahmed performed the literature search, reviewed articles, data analysis, and write-up of the work in the first draft. Lena Jafri

conceived the idea, reviewed articles, and coordinated the writing of the paper and reviewed the final draft. Zahra Hoodbhoy helped with the tables and critically revised the article for the intellectual content. Imran Siddiqui reviewed the articles in case of conflict between Sibtain Ahmed and Lena Jafri and critically revised the article for the intellectual content. All authors have reviewed the final draft and agreed upon.

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