Presepsin as a Predictive Biomarker of Severity in COVID-19: A Systematic Review

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ABSTRACT

Background: The aim of this review is to evaluate the global scientific literature on the utility of plasma presepsin (PSP) as a prognostic biomarker in a homogeneous group of coronavirus disease 2019 (COVID-19) positive cases.

Data retrieval: A systematic review utilizing Medline (PubMed interface), LitCovid NLM, World Health Organization (WHO)–global literature on coronavirus disease, and EBSCO CINAHL Plus was undertaken. The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group guidelines. The quality of individual evidence and possible risk of bias were assessed using the Quality in Prognosis Studies (QUIPS) tool. A narrative synthesis-based conclusion was compiled.

Results: A total of three articles passed through the predefined screening criteria and were included in the review. Methodological quality was evaluated to be acceptable. The aggregate study population was summed up to be 167 COVID-19 positive cases, who had undergone analysis of plasma PSP levels for the prediction of severity and mortality. Based on different PSP cutoffs utilized, a statistically significant association between PSP and COVID-19 severity was reported.

Conclusion: PSP appears as a promising prognostic biomarker of COVID-19 progression. As data are scarce on its utility, large cross-sectional studies are needed.

Keywords: COVID-19, Presepsin, Prognosis, Severe COVID, Systematic review.

Indian Journal of Critical Care Medicine (2021): 10.5005/jp-journals-10071-23967

INTRODUCTION

The first case of coronavirus disease 2019 (COVID-19) was detected in Wuhan, China in 2019, which spreads at an exponential rate, and hence, it was termed as a "pandemic" by the World Health Organization (WHO) by March 2020.[1] Since that time, the world faced several challenges mentally, physically, and economically as they tried to steer their way through these unchartered territories. For the medical community, it was much worse since this pneumonia of an unknown classification was difficult to diagnose and even harder to treat given the limited number of therapeutic options. These obstacles coupled with the high rate of transmission and severity of disease ranging from asymptomatic to fatal made it a pertinent topic to study and make continuous guideline improvements.[2]

Due to the overwhelming number of cases and mortality associated with COVID-19, studying reliable biomarkers to assess the severity and prognosis of the disease is crucial for medical practitioners and scientists to ensure timely diagnosis and appropriate management.[1] When the pandemic struck, the guidelines were based on basic vital signs, such as respiratory rate, oxygen saturation, and oxygen indicator (PaO$_2$/FiO$_2$). These predictors are susceptible to subjective analysis.[3] Hence, a multitude of biomarkers have been useful in the prediction of the severity of COVID-associated pneumonia as inflammatory reactions, cytokine storms, and coagulation cascades are involved in the pathogenesis of COVID pneumonia.[1] Various biomarkers have been studied over the course of this pandemic in relation to COVID-19, ranging from the widely available procalcitonin (PCT) to ferritin, and less common angiotensin-converting enzyme assays and Krebs von den Lungen 6.[1,3]

CD14, a cluster of differentiation marker protein, is found on the surface of mononuclear cells, which has a propensity for

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lipopolysaccharide (LPS), and LPS binding protein was found on the surface of pathogens. Presepsin (PSP) is a small soluble subunit of CD14 (sCD14-ST; 64 amino acids, 13 kDa) that is found on the N-terminal sequence of CD14.[4] Recent studies have shown that PSP levels rise dramatically in response to an acute infectious insult or high degree of sepsis. In the rabbit sepsis model, it was proven that phagocytosis plays a role in PSP elevation. In the lysozyme of a leukocyte, cathepsin D digests the bacteria along with CD14 creating its polypeptide subunit—PSP. This digested form of CD14 is then released into the bloodstream.[4,5] In the context of COVID-19, owing to the cytokine storm syndrome, CD14 has been linked with the presentation of LPS to Toll-like receptor. Moreover, it causes elevated plasma PSP levels through intracellular signaling leading to enhanced gene expression responsible for immune-mediated response.

The normal concentration of PSP in a healthy adult is around 250 pg/mL (upper reference rate).[5] The concentration of PSP rises significantly in sepsis or severe sepsis than in normal patients

or patients with systemic inflammatory response syndrome (SIRS) where classification for each disease severity is based upon the definitions provided by ACCP/SCCM.[6] Along with these characteristics, PSP has also shown high sensitivity and specificity for diagnosis in comparison to PCT, an otherwise frequently used biomarker.[7] Coupled with these advantages, the measurement of PSP values from blood is a quick process, measured from whole blood through point-of-care (POC) devices in labs in around 15 minutes.[5]

In severe sepsis, PSP has shown efficacy in predicting the clinical outcome in hospitalized patients with pneumonia.[8] Ugajin et al. concluded that patients who showed pneumonia severity index (PSI) class $\geq$4 with plasma PSP levels >470 pg/mL had a higher 30 day mortality ($p = 0.005$) than the milder patients with a lower PSI and PSP level, thus showing that high initial values of PSP are a good predictor for future deterioration of patients with pneumonia.[8] Various studies have concluded that the use of PSP is not only a good biomarker for predicting the prognosis of pneumonia but also helpful for early diagnosis and risk stratification.[9,10] The utility of PSP values in the case of COVID pneumonia has been shown to be predictive not only of its severity but also mortality in the limited research that has been conducted till now.

Given the limited amount of research done on PSP as a predictive marker for COVID pneumonia, prognosis and early diagnosis coupled with the positive results from the data available makes it a suitable biomarker to study further. With this perspective, this review was undertaken to systematically evaluate the globally available scientific studies that have assessed the prognostic utility of PSP in COVID-19.

DATA RETRIEVAL

In line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group, a systematic literature search was conducted. Medline (PubMed interface), LitCovid NLM, WHO–global literature on coronavirus disease, and EBSCO CINAHL Plus from the advent of COVD-19 in December 2019 till February 2021 were utilized for the search.[11]

The following Medical Subject Heading terms and keywords were searched: 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 ["presepsin protein, human" (Supplementary Concept) OR Presepsin OR PSP OR sCD14-ST], without language restrictions.

Human subject-based studies were considered only. Furthermore, the "related articles" feature in the databases was also applied to look for other potentially relevant articles, and two independent assessors from the team of authors also manually skimmed through the reference list of included articles.

In the next phase, the citations short lister were further scrutinized based on their titles and abstracts. The following inclusion criteria were applied: (1) Study population should be adult with PCR-positive COVID-19, (2) study participants must have undergone documented measurements of serum PSP, (3) study should have statistically evaluated the prognostic performance of PSP in relation to outcome, (4) outcome-based study, defining severity on the basis of the requirement of mechanical ventilation or intensive care admission or mortality, and (5) study design should be cohort or case-control or case series.

Studies comprising of reviews, perspectives, opinion papers, hypothesis, viewpoints, basic sciences/nonclinical studies, and non-English language were excluded. Subsequently, full-text versions of final inclusions were assessed by two independent reviewers. Inter-rater reliability and agreement were assessed using kappa statistics.[12]

Quality in Prognosis Studies (QUIPS) tool-based risk of bias assessment was conducted, with scores ranging from low, moderate, and high risk.[13] Six domains including case selection, attrition, PSP measurement, outcome assessment, confounders, statistical analysis, and reporting were assessed and stratified into 30 well-defined criteria. Attainment of low or moderate risk under all domains was rated as high and correspondingly.

Secondly, the extracted data were assembled in tabulated form, including the location from where the study is reported, eligible participants, timelines of recruitment, PSP levels, and correlation analysis with their respective p-value.

RESULTS

A flow diagram of the search strategy adopted and studies included is depicted in Flowchart 1. A total of 21 studies were identified, which further underwent the removal of 8 duplicate studies. The title and abstract of studies identified were further scrutinized based on the stringent exclusion criteria. Three studies fulfilled the inclusion criteria, which were included in the final analysis. The aggregate study population was summed up to be 167 COVID-19 positive cases, who had undergone analysis of plasma PSP levels for the prediction of severity and mortality. Kappa static value was yielded to be 0.90, depicting an excellent inter-investigator agreement.

Summary of the literature review is provided in Table 1.[3,9,14] Two studies were from Italy and one from Japan. All the included studies were published after January 2020. For the prediction of outcome, PSP cutoffs ranging from 250–2069 pg/mL were highlighted in the published literature. The QUIPS tool analysis yielded a low to moderate risk of bias for all studies as summarized domain-wise in Figure 2.

DISCUSSION

Clinicians and laboratorians utilized their prior experience of biomarkers linked with respiratory viral illnesses and evaluated them widely amidst the peak pandemic months. In 2004, PSP was introduced as a new biomarker with diagnostic and prognostic utility in sepsis and SIRS.[15] Since then various authors have evaluated PSP against PCT and other inflammatory biomarkers in sepsis and have reported comparable and in certain instances better performances and kinetics of PSP.[16–19] The peak concentrations that are usually attained on days 1–3 of sepsis and, therefore, on admission levels can be considered to be an effective measure to predict severity. However, as shown by this review, only a few studies evaluated PSP in relation to this novel pandemic. In a recently published systematic review, PCT was found to be significantly associated with prognosis, which was further endorsed by various subsequent publications.[20,21] Owing to its comparable performance with PCT, the need for the evaluation of PSP in COVID-19 was further justified.

The study population included Asians as well as Europeans, which adds strength to our findings as results can be generalized

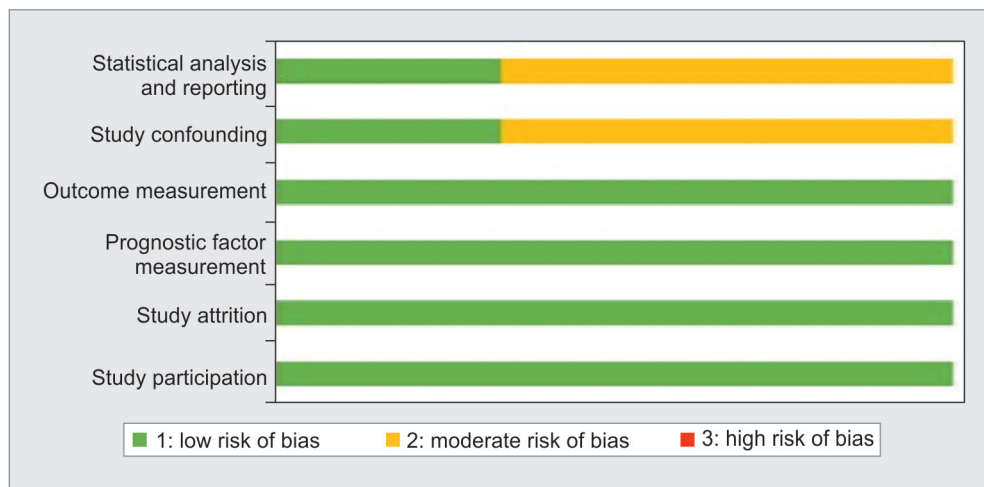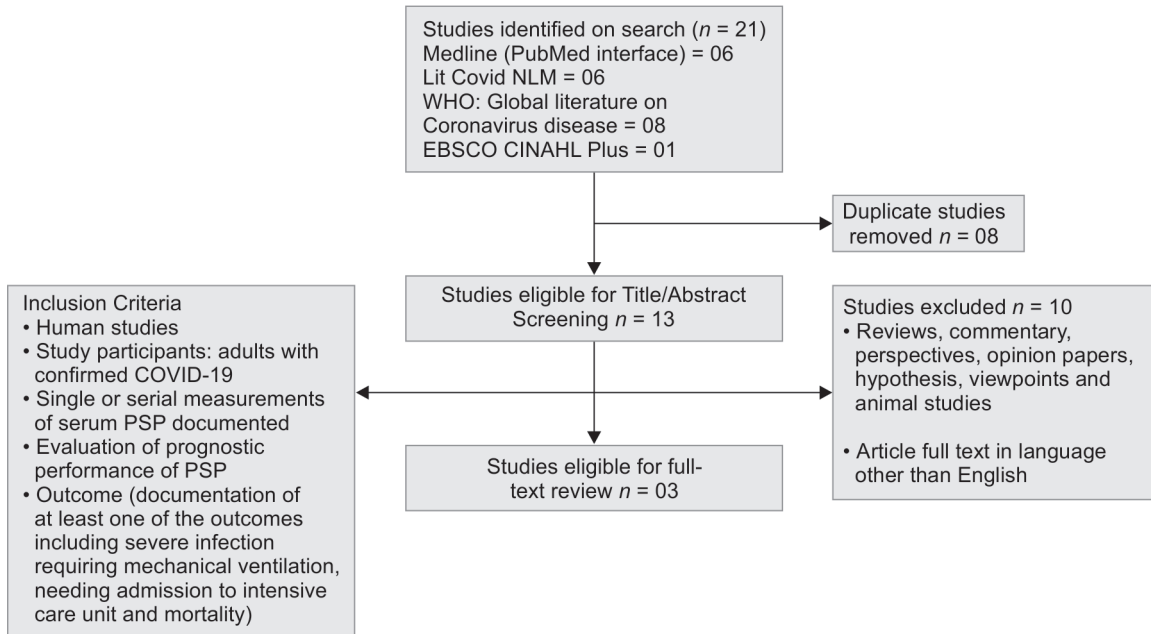**Flowchart 1:** Flow diagram of selected studies for review

Studies identified on search (*n* = 21)
Medline (PubMed interface) = 06
Lit Covid NLM = 06
WHO: Global literature on
Coronavirus disease = 08
EBSCO CINAHL Plus = 01

Duplicate studies
removed *n* = 08

Studies eligible for Title/Abstract
Screening *n* = 13

Inclusion Criteria
• Human studies
• Study participants: adults with
 confirmed COVID-19
• Single or serial measurements
 of serum PSP documented
• Evaluation of prognostic
 performance of PSP
• Outcome (documentation of
 at least one of the outcomes
 including severe infection
 requiring mechanical ventilation,
 needing admission to intensive
 care unit and mortality)

Studies excluded *n* = 10
• Reviews, commentary,
 perspectives, opinion papers,
 hypothesis, viewpoints and
 animal studies

• Article full text in language
 other than English

Studies eligible for full-
text review *n* = 03

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

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

Author	Region	Date of recruitment	Year of recruitment initiation	Study design	Sample size (male: female)	Age (years)	PSP cutoff	PSP corre-lation with severity (p value)	AUC for the prediction of severity
Fukada et al.[3]	Japan	February–March	2020	Case series	6	Not recorded	>250 pg/mL	*p* <0.05	Not recorded
Schirinzi et al.[14]	Italy	March–May	2020	Cross-sectional	86 (58:28)	Male: 67.6 ± 12.4 Female: 65.7 ± 15.4	2069 pg/mL	*p* <0.0001	0.73 (95% CI: 0.684–0.786)
Zaninot-to et al.[9]	Italy	January–March	2020	Case series	75 (56:19)	67 (IQR: 56–76)	>250 pg/mL	*p* <0.001	0.72

and are not specific to a certain genetic makeup subset. Additionally, the risk of bias was also acceptable as demonstrated by validation based on the QUIPS tool with excellent inter-rater agreement between the team of authors. Another distinct advantage offered by PSP is the availability of POC testing analyzer for rapid bedside testing that will aid rapid triage of patients.[22]

Based on a robust search, this is the first systematic review that has evaluated the utility of PSP in COVID-19, and our results

revealed a significant association between PSP and severity, suggesting its further evaluation as a reliable prognostic biomarker. In addition to the limitations of less number of studies and a small aggregated sample size, a varying degree of heterogeneity was noted across the three studies. The analysis platform was also not uniform as PATHFAST Presepsin (Mitsubishi Chemical Europe GmbH, Düsseldorf, Germany) and STACIA Presepsin (LSI Medience Corporation, Tokyo, Japan) were utilized.[3,9,14] The cutoffs used by the two studies were 250 pg/mL; however, Schirinzi et al. used a cutoff of 250 pg/mL and reported a much higher cutoff of 2069 pg/mL (AUC = 0.738) having sensitivity and specificity of 50 and 90%, respectively, for severe cases and a cutoff of 1179 pg/mL (AUC = 0.873) having sensitivity and specificity of 75 and 71%, respectively, for mild cases.[3,9,14] Serial measurements were not undertaken for PSP; however, Schirinzi et al. showed a good correlation with human epididymis secretory protein ($r = 0.621$), a potential serum inflammatory biomarker having a role in natural immunity.[14]

Additionally, some confounding factors may influence PSP concentration, such as elderly age, renal dysfunction, superimposed bacteremia, and hemophagocytic syndrome. Therefore, PSP levels should be considered an appropriate clinical context in complementation with other laboratory parameters.

Conclusion

PSP has shown acceptable performance to predict the aggravation of severity in COVID-19, which can aid clinicians to identify high-risk patients and determine treatment strategies at an early stage for optimal resource allocation in approximately 17 minutes by rapid POC assays. Further studies are high need of time to validate its utility with a large number of participants ideally in multinational and multicenter evaluations with serial measurement.

Authors' Contributions

S.A. conceived the idea, performed the literature search, reviewed articles, data analysis, and write-up of the work in the first draft. M.M. assisted in the writing of the first draft and table and reviewed the final draft. M.S.S. did the in-depth review of the literature included in the final analysis and assisted in the writing of the first draft and reviewed the final draft. I.S. reviewed the articles in case of conflict between S.A. and M.M. and critically revised the article for the intellectual content. All authors have reviewed the final draft and agreed upon it.

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