Letter to the Editor

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Presepsin value predicts the risk of developing severe/critical COVID-19 illness: results of a pooled analysis

https://doi.org/10.1515/cclm-2021-0848
Received July 30, 2021; accepted August 24, 2021;
published online September 2, 2021

Keywords: biomarkers; coronavirus; COVID-19; presepsin.

To the Editor,

The measurement of sepsis biomarkers represents now a cornerstone in risk assessment of patients with severe infectious diseases and/or sepsis, as they can help both predicting clinical progression and guiding therapeutic management [1]. Presepsin, also known as soluble CD14 subtype (sCD14-ST), is a glycoprotein fragment mainly synthesized and released by cells of the monocyte-macrophage lineage in response to a vast array of infections [2]. As opposed to other conventional sepsis biomarkers, namely procalcitonin, one theoretical advantage of measuring presepsin in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is that its circulating value may directly reflect the clinical severity of coronavirus disease 2019 (COVID-19) rather than solely mirroring the presence of co- or super-bacterial infections, which occur at high frequency (up to 34%) in COVID-19 patients with severe or critical conditions [3]. It has also been reported that fungal co- and super-infections may complicate the clinical course in up to 12% of COVID-19 patients, while the burden of viral co- and super-infections may also be as high as 15% [4], with both conditions associated with an over 3-fold higher risk of death.

Another important aspect to be considered is that the cells of monocyte-macrophage lineage can be directly infected and activated by SARS-CoV-2, triggering the release of a multitude of proteins, cytokines, and other immune mediators, including presepsin [5, 6], whose rapid and easy measurement may provide valuable clinical information on the risk of developing the so-called cytokine storm [7].

Therefore, we carried out a digital search in Medline (PubMed interface), Scopus, and Web of Science, using the keywords “presepsin” AND “coronavirus disease 2019” OR “COVID-19” OR “SARS-CoV-2” in all search fields, without applying date or language restrictions. Two authors (G.L. and F.S.G.) reviewed the title, abstract and full text of all items detected according to the keywords, finally selecting studies where presepsin values were measured and compared in at least five COVID-19 patients with or without severe/critical illness. The list of references of all manuscripts was also hand-searched for detecting other eligible studies. The mean and standard deviation (SD) of presepsin values were included in a pooled analysis, with the calculation of weighted mean difference (WMD) and its 95% confidence interval (95% CI) in COVID-19 patients with or without severe/critical illness. When the mean value and SD were not reported in the original study, we used the model proposed by Hozo et al. [8] to extrapolate these values from the sample size, median value, and range. When multiple cohorts with different degree of illness severity were provided (i.e., mild, moderate, severe, critical, death), only the two extremes were considered (i.e., typically mild vs. severe/critical or death).

For the pooled WMD analysis, we first applied a quality effects model, followed by a second analysis using a random-effects model to adjust for any heterogeneity potentially emerging across different studies. The heterogeneity was calculated using χ^2 test and I^2 statistic, and the meta-analysis was carried out according to the Preferred

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Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Material 1). The statistical analysis was carried out with MetaXL, software Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia). The study was conducted in agreement with the declaration of Helsinki and within the terms of local legislation.

The electronic search carried out according to the abovementioned criteria led to the identification of 43 documents after elimination of replicated among the three scientific repositories. Among these, 37 articles were excluded because 17 were review articles, 11 did not include presepsin measurement, 5 did not directly involve COVID-19 patients, and 2 were excluded as editorial material. An additional study was excluded as it only provided mean presepsin value without specifying the range [9], while the study by Dewi et al. was excluded since prespsin was only measured in two children [10]. There was no significant disagreement between the two reviewers.

Six studies were finally included in our pooled analysis, totaling 420 COVID-19 patients, 173 (41.2%) with a severe/critical form of illness, as summarized in Table 1 [11–16]. All studies were cross-sectional; three (50%) were conducted in Japan, and one each in France, Italy, and Turkey. The endpoints of COVID-19 severe/critical illness were respiratory distress in two studies, mechanical ventilation in two other studies, need for intensive care in one study, along with death or need for tracheostomy during hospitalization in the remaining investigation (Table 1). A wide heterogeneity of the analytical techniques used for measuring presepsin was also found among the six included studies.

The results of our pooled analysis are provided in Figure 1, showing a positive difference of presepsin values between patients with or without severe/critical COVID-19 illness in all six studies. The WMD of presepsin values in COVID-19 patients with severe/critical illness compared to those without was found to be 416.97 (95% CI, 125.03–708.90) ng/L using the quality effects model (heterogeneity, I^2=95%) (Figure 1), increasing further to 551.70 (95% CI, 309.45–793.94) ng/L with the random-effects model, respectively. Overall, presepsin values were found to be increased by 2.74-fold in COVID-19 patients with severe/critical illness compared to those without.

Two of the excluded studies deserve special mention. Schirinzi and colleagues measured presepsin values in 86 COVID-19 patients, who were stratified according to

Table 1: Summary of clinical studies which measure presepsin levels in coronavirus disease 2019 (COVID-19) patients with or without severe/critical illness.

Authors	Setting	Patient sample	Method	Endpoint	Values (severe vs. non-severe), ng/L
Domi et al. [11]	Japan	n=97; median age 68 (IQR, 58–77) years; 31% females; 22.7% severe/critical	Pathfast	Death or tracheostomy	595 ± 189 vs. 451 ± 125
Ducastel et al. [12]	France	n=159; age range 32–76 years; 42% females; 55.3% severe/critical	ST AIA	Mechanical ventilation	990 ± 328 vs. 449 ± 134
Fukada et al. [13]	Japan	n=6; median age 59 (IQR, 21–67) years; 17% females; 50.0% severe/critical	STACIA	Mechanical ventilation	605 ± 115 vs. 291 ± 44
Hasegawa et al. [14]	Japan	n=57; median age 59 (45–72) years; 42% females; 40.8% severe/critical	HISCL-5000	Respiratory distress	1,217 ± 310 vs. 563 ± 197
Kocyigit et al. [15]	Turkey	n=34; mean age 53 ± 10 years; 50% females; 55.9% severe/critical	PSPN	Respiratory distress	3,500 ± 3,300 vs. 590 ± 400
Zaninotto et al. [16]	Italy	n=75; median age 67 (IQR, 56–76) years; 25% females; 28.0% severe/critical	Pathfast	Intensive care	1,283 ± 463 vs. 419 ± 132

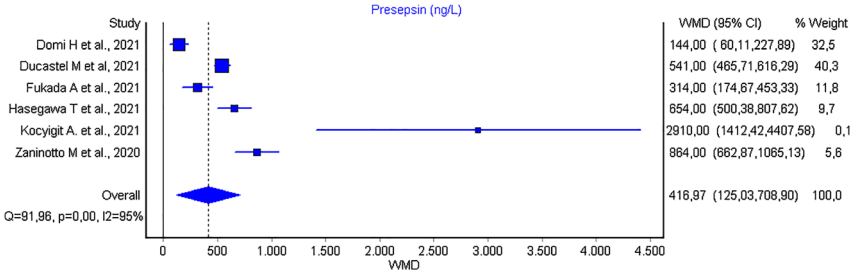

Figure 1: Weighted mean difference (WMD) and 95% confidence interval (95% CI) of presepsin values in patients with coronavirus disease 2019 (COVID-19) with or without severe/critical illness.

disease severity [9]. Notably, mean presepsin values increased progressively in parallel with clinical impairment, from 737 ng/L in COVID-19 patients with mild disease, to 1,234 ng/L in those with severe disease, up to 3,029 ng/L in patients with critical illness. Presepsin concentration was also found to be over 3-fold higher in patients who died than in those who survived (727 vs. 2,543 ng/L; p<0.0001). In receiver operating characteristics (ROC) curve analysis, presepsin displayed an area under the curve (AUC) of 0.738 (95% CI, 0.684–0.786; p<0.001) for predicting severe COVID-19 illness. Presepsin value was also measured in two children who died for COVID-19 in the study of Dewi et al. [10], and was found to be markedly elevated in both cases (range, 1,257–3,292 ng/L).

In conclusion, our pooled analysis reveals that presepsin values are significantly higher (nearly 3-fold) in COVID-19 patients with severe/critical illness than in those without (Figure 1). This is not really surprising since in the recent meta-analysis conducted by Kondo et al., the diagnostic accuracy of presepsin for diagnosing sepsis caused by mixed pathogens in critically ill adult patients was found to be even better than that of procalcitonin [17]. We hence support the conclusion that routine assessment of presepsin in COVID-19 may provide valuable clinical information for predicting adverse outcomes, as well as for guiding the clinical and therapeutic decision-making [18].

Research funding: The authors received no funding for this work.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Not applicable.

Ethical approval: Not applicable.

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Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/cclm-2021-0848).