

Systematic Review in Infectious Diseases

Copeptin as a marker of COVID-19 severity: A systematic review and meta-analysis

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Abstract

Introduction: Infection with SARS-CoV-2 is particularly hazardous in patients with cardiovascular pathology, diabetes or chronic lung disease. Arginine vasopressin (AVP), an antidiuretic hormone secreted in response to hemodynamic and osmotic disturbances plays a crucial role in maintenance of cardiovascular homeostasis. Copeptin has shown promising results regarding its utility in prediction of morbidity and mortality of COVID-19. Therefore, we conducted a meta-analysis to evaluate the role of copeptin in risk stratification in COVID-19.

Methods: This study was designed as a systematic review and meta-analysis. We systematically searched the following databases: Scopus, Web of Science, PubMed, EMBASE, Cochrane Library through September 10th, 2022. Methodological quality was assessed using the Cochrane risk-of-bias tool.

Results: Pooled analysis of four trials showed that mean copeptin plasma concentrations were higher in patients with severe course of COVID-19 than in patients with non-severe course of the disease (26.64 ± 13.59 vs. 16.75 ± 6.13 , respectively; MD=9.39; 95%CI: 1.38 to 17.40; I²=99%; p=0.02). Furthermore, higher copeptin concentrations in COVID-19 patients who died than in those who survived (13.25 ± 3.23 vs. 44.65 ± 26.92 , respectively; MD=-31.40; 95%CI: -42.93 to -19.87; p<0.001).

Discussion: Results from the present meta-analysis revealed that increased copeptin plasma concentrations found in COVID-19 patients are associated with the severity of the disease. Copeptin may assist in early identification of COVID-19 progression and possibly in prediction of adverse outcomes, thus its use in risk stratification could be beneficial.

Take-home message: Copeptin may assist in early identification of COVID-19 progression and possibly in prediction of adverse outcomes, thus its use in risk stratification could be beneficial.

Keywords: Copeptin; COVID-19; meta-analysis; SARS-CoV-2; severity.

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INTRODUCTION

First infections with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) were reported in Wuhan, China, in December 2019 [1]. Abrupt spread of the pathogen and systematic emergence of its new variants led to global pandemic of the COVID-19 disease [2–6]. With 600 million cases and over 6 million deaths reported by the end of October 2022 [7], COVID-19 has become an enormous challenge for the public health all over the world [8–13].

SARS-CoV-2 causes wide range of illness, from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) and eventually death. COVID-19 is primarily a pulmonary disease. However, it can lead to multiorgan involvement, e.g., cardiovascular [14–16] or renal [15,17] disorders. Critically ill patients often require admission to the intensive care unit (ICU) [18]. As they are prone to developing major complications, an appropriate follow-up care must be

provided. Especially during the pandemic, such cases may overload the health care system. Hence, patients at high risk of severe course of COVID-19 should be early identified.

Infection with SARS-CoV-2 is particularly hazardous in patients with cardiovascular pathology, diabetes or chronic lung disease [19–23]. Risk factors also include older age, current smoking status, obesity, cancer and some other chronic medical conditions. Furthermore, socio-demographic features shall be considered in predictions [2]. Besides clinical characteristics, numerous studies aimed to detect applicable biomarkers [24–28]. Correlations between COVID-19 and markers of inflammation and hemostasis have been reported [29–31]. As a robust assay for risk stratification remains unknown, novel biomarkers have been investigated [32].

Arginine vasopressin (AVP), an antidiuretic hormone secreted in response to hemodynamic and osmotic disturbances [33,34] plays a crucial role in maintenance of cardiovascular homeostasis. Disturbances in its secretion are likely to occur in COVID-19. Assessment of AVP plasma concentration may be challenging though. Thus, copeptin, simply measured C-terminal fragment of pro-AVP, serves as surrogate biomarker for AVP [35,36]. Multiple trials revealed that evaluation of copeptin levels may be beneficial in pulmonary [37,38] or cardiovascular diseases and in critical conditions [39,40]. Copeptin has shown promising results regarding its utility in prediction of morbidity and mortality of COVID-19 [24,29,41]. Therefore, we conducted a meta-analysis to evaluate the role of copeptin in risk stratification in COVID-19.

METHODS

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [42] and the guidelines described in the Cochrane Handbook [43]. Due to the character of the study, ethical approval or patient consent was not required.

Search strategy and study selection

The Scopus, Web of Science, PubMed, EMBASE, Cochrane Library databases were searched independently by two authors (M.M. and M.P.) to identify papers published in English between January 1st, 2020, and September 10th, 2022, that reported copeptin plasma concentrations in COVID-19 patients. Databases were explored using the following keywords: “copeptin” AND “covid-19” OR “corona virus disease 2019” OR “novel coronavirus” OR “SARS-CoV-2”. Search strategies were modified for each database using free text terms and controlled vocabularies.

Inclusion and exclusion criteria

Eligibility criteria for included studies were as follows:

- 1) Types of studies: randomized controlled trials or observational studies (in English language).
- 2) Types of participants: adult patients with COVID-19.
- 3) Types of prognostic factor: copeptin levels.

Case reports, conference papers, editorials, review articles and studies where no comparison was conducted were excluded from the review process as well as studies not reported in English.

Data extraction

Two authors (M.M. and M.P.) extracted the data using a standardized data collection sheet, which was checked for accuracy by a third author (A.G.). The following data was extracted from the included studies: study characteristics (first author name, year publication, country, study design,

inclusion and exclusion criteria, primary outcome(s), findings), study groups (no of participants, male sex, age) for severe and non-severe COVID-19 patients or survive vs. dead COVID-19 patients.

Risk of bias assessment

Two authors (M.M. and M.P.) independently assessed the quality of the included studies according to the Newcastle-Ottawa scale [44]. Any disagreements were resolved by discussion with third author (A.G.).

Statistical analysis

All statistical analyses were performed using Review Manager 5.4 (Cochrane Collaboration, Oxford, UK). A P-value less than 0.05 was considered statistically significant. For dichotomous data, odds ratios (OR) with 95% confidence intervals (CI) were analyzed. For continuous data, mean difference (MD) with 95% CI was analyzed. In case when data were reported as median with interquartile range, we estimated means and standard deviations using the formula described by Hozo [45]. Heterogeneity was quantified with Cochran's Q test and I-squared (I^2) statistic in all the measured outcomes. The I^2 value of 25%, 50%, and 75% as cut-off points represented low, moderate, and high degrees of heterogeneity respectively [46]. If significant heterogeneity was present ($P \leq 0.1$ and $I^2 \geq 50\%$), the random-effects model (Mantel-Haenszel) was used to combine MD and 95%CI, otherwise, otherwise the fixed effects model was employed. A funnel plot was not performed because of the limited number of studies ($n < 10$).

RESULTS

Study characteristics

The flow chart of the literature search and the study selection process is pictured in Figure 1. A total of 911 articles were identified through database search. After excluding duplicates and studies that did not meet inclusion criteria, a total of 4 studies comprising 579 patients and published between August 2021 and March 2022 were included [29,47–49]. Of the total population, 54.6% were males. Copeptin may assist in early identification of COVID-19 progression and possibly in prediction of adverse outcomes, thus its use in risk stratification could be beneficial.

Meta-analysis outcome

As shown in Table 1, pooled analysis of four trials showed that mean copeptin plasma concentrations were higher in patients with severe course of COVID-19 than in patients with non-severe course of the disease (26.64 ± 13.59 vs. 16.75 ± 6.13 , respectively; MD=9.39; 95%CI: 1.38 to 17.40; $I^2=99\%$; $p=0.02$). Furthermore, one trial found higher copeptin concentrations in COVID-19 patients who died than in those who survived (13.25 ± 3.23 vs. 44.65 ± 26.92 , respectively; MD=-31.40; 95%CI: -42.93 to -19.87; $p<0.001$).

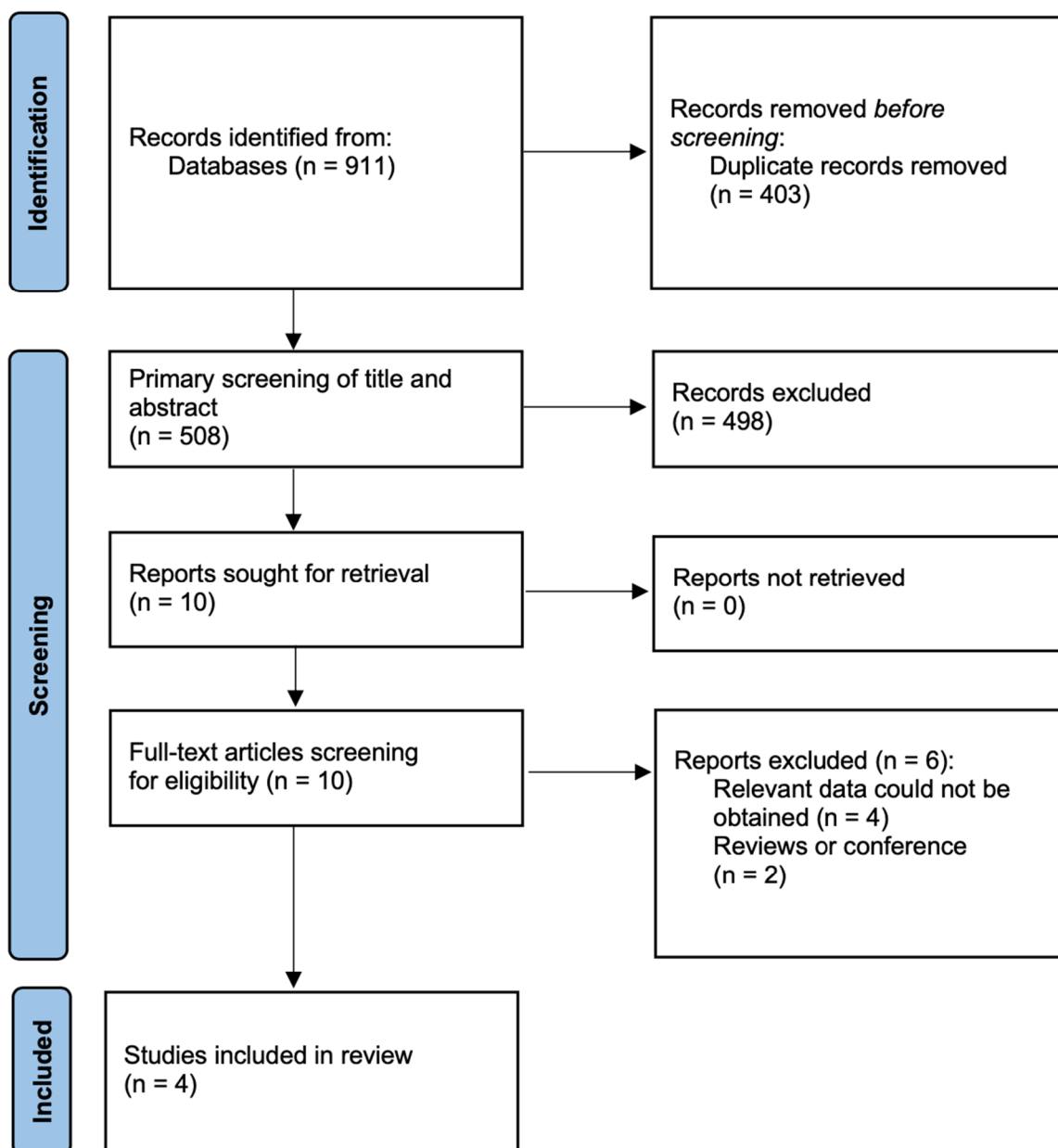


Figure 1. Flowchart detailing selection and screening of the studies included in this review.

Table 1. Baseline characteristics of included trials.

Study and year	Country	Study group	No. of patients	Age (ys)	Sex, male	Copeptin, Pmol/L	NOS score
Hammad et al, 2022 [47]	Egypt	Severe	80	62.5 ± 2.21	40 (50.0%)	30.1 ± 1.96	9
		Non-severe	80	44.7 ± 2.92	39 (48.7%)	13.7 ± 0.61	
In et al, 2021 [48]	Turkey	Severe	55	58.8 ± 16.8	35 (63.6%)	26.3 ± 10.3	8
		Non-severe	35	44.5 ± 14.9	18 (51.4%)	14.4 ± 4.9	
Indirli et al, 2022 [49]	Italy	Survive	95	NS	NS	13.25 ± 3.23	7
		Dead	21	NS	NS	44.65 ± 26.92	
Kaufmann et al, 2022 [29]	Austria	Severe (ICU)	55	72.0 ± 16.25	37 (67.3%)	38.3 ± 15.4	8
		Non-severe	158	63.5 ± 16.46	82 (51.9%)	20.7 ± 5.6	

Legend: NS: no specified.

DISCUSSION

In our meta-analysis of four studies, we found copeptin concentrations to positively correlate with COVID-19 severity. Additionally, higher copeptin levels were prognostic for subsequent mortality among COVID-19 patients.

Activation of the vasopressin system preserves homeostasis, thus helps adapt to stressful conditions, e.g., infections [50]. AVP is a nonapeptide produced in the supraoptic and paraventricular nuclei of the hypothalamus [51,52]. Initially synthesized pre-pro-AVP is subsequently cleaved into pro-AVP. Eventually, pro-AVP is split into equimolar amounts of AVP, copeptin and neurophysin-II. The latter is engaged in transport of AVP to its storage in the neurohypophysis, whereas copeptin, a 39-aminoacid glycoprotein, may assist in formation of pro-AVP [39].

AVP is released from the neurohypophysis due to hyperosmolality, hypovolemia, hypotonia, hypoxia or acidosis, as well as in response to stressors, e.g., pain or injury [48]. AVP not only has a key role in maintenance of water-electrolyte balance and regulation of circulation, but also controls the respiratory system via V1aRs receptors. AVP may act as an inhibitor or activator of ventilation. The former effect is seen in the area postrema, the latter in the carotid bodies, whereas both are observed in the brainstem. Contrary to the systemic circulation, AVP exerts a vasodilatory effect on pulmonary arteries. Overall, as a circulating hormone, AVP suppresses ventilation, thus prevents excessive increase in breathing rate under pathological conditions [50].

Infection with SARS-CoV-2 leads to hemodynamic disturbances due to widespread inflammation with cytokine storm or direct injury [24,53]. Cytokines, especially elevated interleukin 6 levels, promote AVP secretion [47]. Furthermore, SARS-CoV-2 enters a host cell through interaction between its spike glycoprotein and a cellular receptor - angiotensin-converting enzyme 2. As a result, renin-angiotensin system is disturbed and concentration of angiotensin II increases [54], what further activates AVP release. Moreover, lung injury present in COVID-19 causes hypoxic pulmonary vasoconstriction, which subsequently leads to increase in AVP levels [55]. Nevertheless, as AVP has a short half-life, is primarily bound to platelets and requires specialist assays, its availability as a biomarker is limited. Therefore, copeptin with greater stability, longer half-life and less demanding analysis, is applied as surrogate biomarker [39].

Increased copeptin levels have been reported in various pulmonary disorders. In patients with chronic obstructive pulmonary disease copeptin predicted exacerbation and all-cause mortality

[56,57]. Elevated copeptin concentrations were observed in conditions characterized by abnormal respiratory pattern, e.g., sleep apnea [58]. High prevalence of pituitary hormone alterations was seen in critically ill patients admitted to the ICU. Interestingly, among this population, higher copeptin levels were found in patients with ARDS than in those with subarachnoid hemorrhage or traumatic brain injury. High copeptin concentrations predicted unfavorable outcome in the latter condition [59]. Copeptin was shown to be applicable in diagnosis of ARDS or acute lung injury, whereas it was a stronger prognostic marker for short-term mortality than established N-terminal pro-B-type-natriuretic peptide. Furthermore, increased copeptin levels were present in patients admitted to the ICU or emergency department with acute, severe dyspnea or sepsis [60].

Rise in copeptin concentrations was also observed in infections of the lower respiratory tract [56]. In community-acquired pneumonia (CAP) copeptin was described as independent predictor of mortality, superior to traditionally used biomarkers [37,38]. Copeptin levels were reported to positively correlate with the severity of CAP and to be the highest in non-survivors [36]. Another study confirmed that increased copeptin concentrations reflected the severity of pneumonia in children and predicted further complications [61].

Elevated copeptin levels were consecutively reported in COVID-19. Whether copeptin could help distinguish COVID-19 from other pulmonary infections is uncertain. One study described higher copeptin concentrations in COVID-19 in comparison to CAP [33]. Conversely, in another trial, copeptin levels in COVID-19 and acute or severe bronchitis or pneumonia were comparable [62]. Nevertheless, association between copeptin levels and disease severity was reported in several studies. More pronounced elevation in copeptin concentrations were seen in severe than in non-severe COVID-19 cases [47]. Higher copeptin levels at admission were also observed in COVID-19 patients with in-hospital or short-term mortality. Importantly, its ability to identify non-survivors persisted after statistical adjustment for comorbidities, that worsen the prognosis and contribute to raised copeptin levels, e.g., heart failure. Therefore, copeptin was described as an independent predictor of COVID-19 severity. Moreover, one study found positive correlation between copeptin and length of hospital stay. An association with occurrence of sepsis and acute kidney injury was reported, suggesting that copeptin may not only predict mortality, but also certain complications [49].

Connections between copeptin and markers of inflammation, as well as other laboratory findings, has been investigated in COVID-19 [25,28,63,64]. Copeptin positively correlated with C-reactive protein, ferritin and D-dimers [47]. After comparison, predictive value of copeptin was superior to that of mentioned, traditional biomarkers. Conversely, negative correlation was found with leukocyte, neutrophil and platelet count [33]. Unfortunately, no association was reported with clinical parameters, e.g., oxygen saturation, need for ventilation or radiological findings on chest imaging studies.

As SARS-CoV-2 often causes additional cardiac injury, particular attention was drawn to cardiac biomarkers, emphasizing their role in prediction of morbidity and mortality in COVID-19 patients [65,66]. High sensitivity cardiac troponin I (hs-cTnI) was reported to predict adverse outcomes within 28 days from index admission. Importantly, the highest prognostic sensitivity was reached once hs-cTnI was combined with copeptin. Furthermore, individuals with increased hs-cTnI, but normal copeptin levels, were identified as low-risk patients [29]. Moreover, natriuretic peptides were shown to raise due to development or exacerbation of heart failure in course of COVID-19 [24]. Value of its

combination with copeptin in COVID-19 remains uncertain though. Conversely, measurement of copeptin together with mid-regional pro-adrenomedullin was reported to increase diagnostic accuracy of both markers [49]. Although currently available data is inconsistent, multimarker approach seems to be a promising strategy.

Some limitations of our meta-analysis are to be acknowledged. Firstly, a small number of studies was included, as limited evidence is available on the discussed topic. Consequently, our results did not reach statistical significance. Furthermore, laboratory techniques applied in measurements of copeptin levels, as well as clinical criteria for identification of COVID-19 severity and established copeptin cut-off concentrations differed per study. For this reason, considerable heterogeneity was observed between included trials. Therefore, further studies should be conducted to entirely assess copeptin performance.

CONCLUSION

Results from the present meta-analysis revealed that increased copeptin plasma concentrations found in COVID-19 patients are associated with the severity of the disease. Copeptin may assist in early identification of COVID-19 progression and possibly in prediction of adverse outcomes, thus its use in risk stratification could be beneficial.

Author Contributions: Conceptualization: MM, LS; methodology: MM, FC, LS; software: MP, LS; validation: MM, AN, MY, BNK, GN; formal analysis: LS, MM; investigation: MM, MB, MP, ZZ, AN, GN; resources: MM, MB, LS; data curation: MM, JZ, FC, MP, LS; writing—original draft preparation: MM, JZ, FC, MP, LS; writing—review and editing, all authors; visualization: MM, LS; supervision: LS; project administration: MM. All authors have read and agreed to the published version of the manuscript.

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