Original Research

Risk Assessment of Sepsis through Measurement of proAVP (Copeptin): a secondary analysis of the TRIAGE study

Short Title: Risk Assessment of Sepsis through Copeptin

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Keywords: copeptin, SOFA score, risk-stratification, infection, sepsis

Word count: 2734
Abstract

Objective: Systemic infections and sepsis lead to a strong activation of the vasopressin system, which is pivotal for stimulation of the endocrine stress response and in addition has vasoconstrictive and immunomodulatory effects. Our aim was to assess the significance of the vasopressor system through measurement of C-terminal proAVP (copeptin) regarding mortality prediction in a large prospective cohort of patients with systemic infection.

Design and Methods: This secondary analysis of the observational cohort TRIAGE study included consecutive, adult, medical patients with an initial diagnosis of infection seeking emergency department care. We used multivariable regression analysis to assess associations of copeptin levels in addition to the Sequential Organ Failure Assessment (SOFA) score with 30-day mortality. Discrimination was assessed by calculation of the area under the curve (AUC).

Results: Overall, 45 of 609 (7.4%) patients with infection died within 30 days. Non-survivors had a marked upregulation of the vasopressin system with a more than 4-fold increase in admission copeptin-levels compared to non-survivors (199.9 ± 204.7 vs. 46.6 ± 77.2 pmol/L). In a statistical model copeptin was significantly associated with mortality (adjusted odds ratio of 1.04, 95% CI 1.01 to 1.07, p=0.002). Regarding discrimination, copeptin alone showed an AUC of 0.82, while adding copeptin to the SOFA score significantly improved its prognostic ability (AUC 0.83 vs. 0.86, p=0.027).

Conclusion: Activation of vasopressin system mirrored by an increase in copeptin levels provided significant information regarding mortality risk and improved the SOFA score for prediction of sepsis mortality.
**Trial registration:** ClinicalTrials.gov NCT01768494. Registered January 9, 2013
Introduction

Systemic infection leading to sepsis remains a major portion of patients seeking care in the emergency department (ED) and the intensive care unit (ICU) (1, 2). Sepsis has been defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and is associated with increased use of healthcare resources and mortality (3, 4). Sepsis leads to a strong physiological activation of the vasopressin system aiming to co-stimulated the endocrine stress response and stabilize blood hemostasis through, vasoconstrictive effects and the overwhelming immune response through immunomodulatory effects (5). While pharmacological treatment of sepsis patients with vasopressin did not appear to lower mortality (6) measuring the activation of the vasopressin system could provide important prognostic information regarding the severity of infection and associated mortality risks.

Estimating severity and risk for mortality has become a main focus in the initial assessment of sepsis. It has become clear that organ dysfunction is both, a hallmark of severe systemic infection and a main prognostic indicator (7, 8). According to current guidelines, the diagnosis of sepsis thus also relies on the Sequential Organ Failure Assessment (SOFA), which reflects the individual degree of organ dysfunction (9). However, relying on SOFA still is not perfect, and there is misclassification of patients regarding their true mortality risk. Thus, improving SOFA by addition of other prognostic indictors is important. Herein, novel biomarkers mirroring fluid and endocrine activation may be helpful (1, 10-12). Hemodynamic instability including vascular tone loss, decreased arterial blood pressure and tissue perfusion occurs in sepsis and in septic shock resulting in an activation of counteracting mediators (13, 14). This includes an activation of the arginine
vasopressin (AVP) on the hypothalamic-pituitary-adrenal (HPA) axis (15-17). As AVP is hard to measure due to the instability and short half-life, the more stable pre-hormone copeptin (39-amino acid C-terminal portion of proAVP) may be measured instead (14, 18-20). Copeptin has previously been shown to provide prognostic information in patients with stroke and infection of the lung (10, 21-24) as well as for critically ill patients with sepsis (13, 25-28). However, to our knowledge, there is a lack of studies investigating whether the addition of copeptin to SOFA could improve the prognostic assessment of patients by providing information regarding activation of the vasopressin system.

Our aim was to assess the significance of the activation of the vasopressor system through measurement of copeptin in addition to SOFA regarding mortality prediction in a large prospective cohort of patients with systemic infection.
Materials and Methods

Study Design, setting and patient sample

This is a secondary analysis of the prospective TRIAGE study (1), a multi-national, observational cohort study, which recruited consecutive emergency department patients with any symptoms in Aarau (Switzerland), Paris (France), and Clearwater (FL, USA) between March 2013 and October 2014. The study protocol (29) and main results (1) have been published previously. The Institutional Review Board of all centers approved the protocol and waived the need for individual inform consent due to the observational design of the study (main Swiss IRB: Ethic Commission of the Canton Aargau: registration number: EK-2012/059). The TRIAGE study was registered at the “ClinicalTrials.gov” website (http://www.clinicaltrials.gov/ct2/show/NCT01768494, last access 19.02.2021).

For this secondary analysis, only medical patients presenting at the tertiary care hospital in Aarau (Switzerland) with a main diagnosis of infection were included. Thus, all patients had a main infection diagnosis, which was verified through their Swiss Diagnosis Related Groups (DRG) coding at discharge (from: https://www.swissdrg.org, last access 19.02.2021). Surgical and pediatric patients were not part of the study.

Data Collection and Selection

All included participants provided a medical history and underwent a physical examination including measurement of vital signs, laboratory assessment and collection of leftover blood samples. We also recorded socio-demographical data, clinical symptoms, complaints, and comorbidities. Patient' outcomes, including admission to intensive care unit (ICU) and length of hospital stay (LOS), were
collected by chart review, if necessary. Missing data was supplemented through chart abstraction and automatic export from the internal medical data system. All included patients were contacted 30 days after hospital admission via telephone interview to assess their vital status.

**Primary and Secondary Endpoints**

Consistent with the initial study, the primary endpoint of this analysis was defined as all-cause 30-day mortality. Secondary endpoints were defined as admission to the ICU within 30 days following ED admission and positive blood cultures during the hospital stay.

**Definitions of Infection at ED Admission**

For this analysis, we grouped patients into pre-specified groups based on the main focus of infection, namely respiratory tract infection (including community-acquired pneumonia, chronic obstructive pulmonary disease (COPD)-exacerbation, asthma-exacerbation, bronchitis), urinary tract infection, skin infection, gastrointestinal infection, central nervous system infection, and other types of infections.

**SOFA Score Calculation**

In order to identify organ dysfunction caused by a dysregulated host response to infection, the SOFA score as proposed by the “Third International Consensus Definitions for Sepsis and Septic Shock” was used (30). The score evaluates different organ systems (respiratory, coagulation, liver, cardiovascular, central nervous, and renal) which require laboratory and clinical variables for assessment and computation (9). Because the main entry point of the study was the ED and not all patients had an arterial blood gas analysis taken, we used an adapted score as previously proposed relying on the SO2/FiO2 -index instead of the pO2/FiO2 index (9). If the route of O2-administration was unknown, we assumed an FiO2 of 0.3 for patients with nasal O2-
administration according to previous study (31). For the cardiovascular system, 0 points were assigned for mean arterial pressure (MAP) ≥ 70 mmHg and 1 point for MAP <70 mmHg as specified in the original SOFA score calculation.

**Copeptin Measurement and other markers of the osmotic system**

For the analysis of these copeptin values, there were no new measurements performed. The analyzed copeptin data were measured during the TRIAGE-study and are original data from there. For this, left-over samples of routinely collected blood samples upon admission were immediately centrifuged, aliquoted and frozen at -20°C for later batch analysis of copeptin. Copeptin was batch-measured in plasma with a new sandwich immunoassay as described elsewhere (14, 32). The assays have analytical detection limits of 0.4 pmol/L. We also recorded other markers influencing the osmotic system such as sodium, osmolality and glomerular filtration rate (GFR) from the routine laboratory assessment.

**Statistical Analysis**

All statistical analyses were performed using STATA 15.1 (StataCorp LLC). For descriptive statistics, discrete variables are expressed as frequency (percentage) and continuous variables are expressed as mean with standard deviation (SD) or as medians with interquartile range (IQR). Imputation methods were used to complete data missing less than 10% of values. Univariable and multivariable logistic regression models with primary and secondary endpoints were used to examine the association of copeptin and other markers. Laboratory values with non-normal distribution were normalized through log-transformation before being entered into the statistical models. Odds ratios (OR), including the corresponding 95% confidence intervals (CI) were reported as a measure of association. We predefined three types of regression models, namely an unadjusted model (Model 1), a model adjusted for
age, sex, type of infection and comorbidities (Model 2), and a model adjusted for age, sex, type of infection, comorbidities and SOFA score (Model 3). The area under the receiver-operator-curve (ROC-AUC) was calculated as a measure of discrimination. Moreover, we also investigated subgroups for differences in performance based on socio-demographic factors (age and sex), type of infection and fluid balance makers.
Results

Patient Population
This analysis includes a total of 654 medical inpatients presenting with a main diagnosis of infection to the emergency department of the Cantonal Hospital Aarau (Switzerland). The median age was 61 ± 20 years and 56% (n=365) of the patients were male. The mean SOFA score was 1.5 point (±2) and 62.4% of patients had a SOFA score <2 points. Regarding focus of infection, respiratory tract infection (n=272, 41.6%) and urinary tract infection (n=154, 23.5%) were most frequent. Almost 30% of patients had chronic kidney disease (n=184). Overall, a total of 45 patients (6.9%) reached the primary endpoint of all-cause 30-day mortality. Baseline characteristics of the patient population overall and stratified according to the primary endpoint are presented in Table 1.

Association of SOFA, copeptin and Fluid Balance Markers with primary and secondary endpoints
Overall, initial SOFA score values were 3-fold higher in patients who died compared to survivors. (4.2 ± 2.7 vs. 1.3 ± 1.8, p<0.001). Also, copeptin-levels upon admission were 4-fold higher in non-survivors compared to survivors (199.9 ± 204.7 pmol/L vs. 46.6 ± 77.2 pmol/L). In an unadjusted logistic regression analysis (Model 1), we found an association of copeptin with an OR of 1.08 (95% CI 1.06, 1.10, p<0.001) for the primary endpoint 30-day mortality. These results remained robust in the multivariable Model 2 (OR 1.06 (95% CI 1.04, 1.09), p<0.001), adjusted for age, sex, type of infection and comorbidities, as well as in the multivariable Model 3 adjusted for age, sex, type of infection, comorbidities and SOFA score (OR 1.04 (95% CI 1.01, 1.07), p=0.002). Copeptin also showed an association for the two secondary endpoints - ICU-admission and blood culture positivity - in the unadjusted model.
(Model 1). However, in the two adjusted models (Model 2 and Model 3), the association was no longer significant for both secondary endpoints.

Regarding discrimination, copeptin was the strongest for 30-day mortality, with an AUC of 0.82 compared to the other fluid balance markers including sodium (AUC 0.57), osmolality (AUC 0.74) and GFR (AUC 0.75) and similar to the SOFA score (AUC 0.82). We also compared AUCs of copeptin among different predefined patient subgroups. As demonstrated in Figure 1, results were similar in the subgroup stratified by gender, type of infection, sodium concentration and osmolality. However, a significant effect modification was found for urinary tract infection and CKD stage 3 (p for interaction <0.05). We also investigated the same subgroups regarding SOFA score, where a subgroup effect was found for patients aged under 60 years (AUC 0.94) and for patients with CKD stage 4 and 5 (AUC of 0.53 (Figure 2).

In a next step, we investigated whether the combination of SOFA score with copeptin and other fluid balance markers would further improve its prognostic potential. Table 3 shows the AUC of different bivariable and multivariable models combining different parameters. Adding copeptin to SOFA significantly improved its AUC from 0.83 to 0.86 (p=0.028). Further addition of markers did only slightly provide better prognostication as assessed by improvements in AUC and none of the other markers improved the SOFA score, expect MR-proADM which showed the same improvement as Copeptin (AUC from 0.83 to 0.86, p=0.002). Also, regarding blood culture positivity, copeptin improved the SOFA score from AUC 0.65 to 0.68, while none of the other markers had a similar effect. Finally, regarding admission to ICU, osmolality but not copeptin improved the model.
Association of Copeptin ICU-Admission and Blood Culture Positivity

The SOFA score alone showed the best discrimination for the secondary endpoint of ICU admission as well (AUC 0.83) followed by copeptin with an AUC of 0.75. In contrast, regarding blood culture positivity, copeptin performed the best (AUC 0.68) followed by SOFA score (AUC 0.65) which nevertheless remained very weak. Results of the regression analysis and discrimination values are shown in Table 2.

Figure 3 illustrates the SOFA score together with copeptin, whereby stratification by age found higher AUC for 60 to 80 years (AUC 0.98) and an p for interaction of <0.05 for stage 1 and 2-CKD.
Discussion

The key findings of this analysis are twofold. First, we found that the activation of the vasopressin system mirrored by an increase in admission copeptin levels provided prognostic information regarding mortality. Second, when added to the SOFA score, this information further improved the early risk stratification of patients. The addition of fluid balance biomarkers such as osmolality or sodium did not provide such prognostic information.

Early and reliable risk stratification in patients presenting with signs and symptoms of infection and possible sepsis is important to reduce time to effective treatment and improve site of care decisions (1, 2). For this purpose, SOFA is a well-established score with high prognostic accuracy regarding mortality (8). It has been shown, that the vasoactive peptide mid-regional pro-adrenomedullin (MR-proADM) is able to improve the mortality risk stratification in patients with infection presenting to the ED beyond SOFA score alone and may further can improve initial therapeutic site-of-care decisions (33). These findings were also shown for copeptin, as already mentioned above. Moreover, we have observed a further significant improvement of discrimination when adding both, MR-proADM and copeptin to the SOFA score.

Physiopathologically, systemic infections lead to a strong activation of the vasopressin system in order to balance vasodilatation by its vasoconstrictive and volume-retention effects. Often neglected vasopressin stimulates adreno-corticotropic hormone (ACTH) secretion in synergy with hypothalamic corticotroph releasing hormone (CRH). Thus, vasopressin mediates and amplifies the hypothalamic-pituitary-adrenal stress response. Vasopressin also has immunomodulatory effects (5). Vasopressin also controls sodium balance by free water retention in the kidney. In addition to the production of vasopressin in response to volume and osmolarity...
effects (5, 34), it is also a stress hormone that increases under physiological conditions of disease including acute infections (27, 28). Physiological stress caused by infections or severe disease trigger the release of copeptin aiming to increase free water resorption in the kidney and thus maintaining blood pressure homeostasis through V2 receptors and inducing vasoconstriction of blood vessels through V1 receptors (35-37). The physiological role of copeptin is not yet known. However, this peptide may have a role during intracellular processing of provasopressin, which contributes to the correct structural formation of the AVP precursor, which in turn leads to efficient proteolytic maturation (38). Despite unknown function, copeptin has been described as a surrogate of AVP for physiological conditions and in different diseases (39). Several studies found copeptin to be increased in different types of infections and associations with short-term mortality (40, 41). Our finding of higher copeptin levels in infections as a marker and mediator of the stress response is, thus, not surprising. To our knowledge, however, this is the first large-scale study investigating the additive effects of the vasopressor system through measurement of copeptin to the SOFA score, the current gold standard for sepsis diagnosis, regarding mortality risk.

Our results are in line with previous studies showing that fluid balance markers (i.e. sodium, osmolality, GFR) may improve risk prediction for infection in addition to organ dysfunction markers (8, 12). Interestingly, patients with respiratory, gastrointestinal or hepatic infections had the most benefit when applying SOFA score together with copeptin levels. Especially remarkable is the impact of kidney function on predicting 30-day mortality when the SOFA score is combined with copeptin. Mortality prediction remains significant regardless of the stage of chronic kidney disease, indicating dysregulated fluid homeostasis, which is also in line with other
investigations (42). Taken together with other study results, this is evidence of the strong correlation of body fluid balance with infection and mortality (43).

It represents also a fluid balance marker, associated with urine osmolality and sodium, released by increased plasma osmolality, decreased arterial pressure and reductions in cardiac volume (44). Earlier investigations of copeptin focused primarily on vasopressin-dependent disorders of fluid homeostasis such as hyponatremia, polydipsia and diabetes insipidus in the outpatient setting with a generally low stress level (5, 34) or acute cardiovascular illness (45, 46).

Based on above-mentioned findings, one may hypothesize that risk stratification can be improved by assessing the SOFA score together with biomarkers such as copeptin in the initial assessment of patients with infection. One can expect better patient flow and a more adequate estimation of triage priority, which in turn may lead to lower ICU admissions and 30-day mortality rates. However, these findings must be investigated in further studies.

Our study has some limitations. First, because of the retrospective design of this analysis we did not have all laboratory parameters and characteristics available which would be of value in the context of copeptin measurement. We also used an adapted version of the SOFA score as not all patients had arterial gas analysis done upon ED admission. Second, we limited all results to admission values only and no follow-up information regarding kinetics was available. Third, we did not have a control patient population without infection to understand whether copeptin can discriminate between infection-related and non-infection-related deterioration in patients.
Conclusion

In conclusion, activation of vasopressin system mirrored by an increase in copeptin levels provided significant information regarding mortality risk and improved the SOFA score for prediction of sepsis mortality.

Abbreviations

ACTH: adreno-corticotropic hormone; AUC: area under the curve; AVP: arginine vasopressin; CI: confident interval; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; CRH: corticotroph releasing hormone; ED: emergency department; GFR: glomerular filtration rate; HPA: hypothalamic-pituitary-adrenal; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay; OR: odds ratio; MR-proADM: mid-regional pro-adrenomedullin; ROC-AUC: area under the receiver operating curve; SD: standard deviation; SOFA Score: sequential organ failure assessment score

Declaration of Interests

PS and BM received research support paid to the Institution from Thermofisher, bioMerieux, Roche Diagnostics, Nestle Health Science and Abbott Nutrition. All other authors reported no conflicts of interest.

Funding

Thermofisher provided an unrestricted research grand for the initial TRIAGE-study. PS was supported by the Swiss National Science Foundation (SNSF Professorship, PP00P3 15031/1). This TRIAGE-study was supported by the Swiss Academies of Arts and Sciences (SAMW).
Author’s Contributors

MK, CG and EH managed the data collection. MK, CG and PS performed the statistical analyses and MK and CG drafted the manuscript. EH, AK, BM and PS, amended and commented on the manuscript. All authors approved the final version.

Acknowledgments

This multidisciplinary and interprofessional trial was only possible in close collaboration of social services (Anja Keller, Regina Schmid), the nursing department (Susanne Schirlo, Petra Tobias), the central laboratory (Martha Kaeslin, Renate Hunziker), medical controlling (Juergen Froehlich, Thomas Holler, Christoph Reemts), IT (Roger Wohler, Kurt Amstad, Ralph Dahnke, Sabine Storost) of the Cantonal Hospital Aarau, Clinical Trial Unit (CTU), University Hospital Basel (Thomas Fabbro, Guido Stimimann, Patrick Simon), the department of Health Economics of the University of Basel (Stefan Felder, Timo Tondelli), as well as all participating patients, nurses and physicians. The TRIAGE study group includes members from the University Department of Internal Medicine, Cantonal Hospital Aarau, Switzerland (Ulrich Buergi, MD, Petra Tobias, RN, Eva Grolimund, MD, Ursula Schild, RN, Zeljka Caldara, RN, Katharina Regez, RN, Martha Kaeslin, Ursina Minder, RN, Renate Hunziker, RN, Andriy Zhydkov, MD, Timo Kahles, MD, Krassen Nedeltchev, MD, Petra Schäfer-Keller, PhD) the Clinical Trial Unit University Hospital Basel (Stefanie von Felten, PhD), the Institute of Nursing Science, University of Basel, Switzerland (Sabina De Geest, PhD); the Department of Psychology, University of Berne (Pasqualina Perrig-Chiello, PhD). We thank Erica Holt for native English review.
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Tables and Figures Legend

Table 1. Baseline characteristics of the overall cohort and stratified by primary endpoint.

Table 2. Univariable and multivariable logistic regression analysis for the primary and secondary endpoints.

Table 3. Association of various combinations of SOFA score with copeptin and fluid balance biomarkers for primary and secondary endpoints.

Figure 1. Prognostic performance of copeptin as predictor for 30-day mortality stratified by age-, sex-, type of infection, and fluid balance markers (sodium, osmolality and kidney function) to evaluate subgroup differences. The vertical reference line mirrors the overall AUC. AUCs to the right of the reference line indicate higher levels of discrimination, AUCs to the left of the reference line indicate lower levels of discrimination. The Forrest plot shows different levels of discrimination with their respective 95% confidence intervals by subgroups. P for interaction indicates the level of effect modification by subgroups.

Figure 2. Prognostic performance of SOFA score as predictor for 30-day mortality stratified by age-, sex-, type of infection, and fluid balance markers (sodium, osmolality and kidney function) to evaluate subgroup differences. The vertical reference line mirrors the overall AUC. AUCs to the right of the reference line indicate higher levels of discrimination, AUCs to the left of the reference line indicate lower levels of discrimination. The Forrest plot shows different levels of discrimination with their respective 95% confidence intervals by subgroups. P for interaction indicates the level of effect modification by subgroups.
**Figure 3.** Prognostic performance of SOFA score and copeptin as predictor for 30-day mortality stratified by age-, sex-, type of infection, and fluid balance markers (sodium, osmolality and kidney function) to evaluate subgroup differences. The vertical reference line mirrors the overall AUC. AUCs to the right of the reference line indicate higher levels of discrimination, AUCs to the left of the reference line indicate lower levels of discrimination. The Forrest plot shows different levels of discrimination with their respective 95% confidence intervals by subgroups. P for interaction indicates the level of effect modification by subgroups.
Table 1. Baseline characteristics of the overall cohort and stratified by primary endpoint.

|                             | All (n=654) | Survivors (n=609) | Non-Survivors (n=45) | p-value |
|-----------------------------|-------------|-------------------|----------------------|---------|
| **Sociodemographics**       |             |                   |                      |         |
| Age (years)                 | 61.0 (20.3) | 59.8 (20.3)       | 78.3 (10.2)          | <0.001  |
| Male sex                    | 365 (55.8%) | 336 (55.2%)       | 29 (64.4%)           | 0.23    |
| **Clinical presentation at ED admission** |           |                   |                      |         |
| Blood pressure systolic (mmHg) | 129.9 (22.6) | 130.7 (22.0)   | 119.3 (27.2)         | 0.001   |
| Blood pressure diastolic (mmHg) | 74.8 (15.3) | 75.5 (14.3)       | 64.6 (23.1)          | <0.001  |
| Pulse rate (bpm)            | 90.4 (19.5) | 89.8 (19.0)       | 97.7 (24.4)          | 0.010   |
| SpO2 (%)                    | 93.8 (4.5)  | 94.0 (4.3)        | 91.2 (5.6)           | <0.001  |
| O² administration           | 119 (18.3%) | 95 (15.7%)        | 24 (54.5%)           | <0.001  |
| Temperature (°C)            | 37.9 (1.1)  | 37.9 (1.1)        | 37.7 (1.0)           | 0.26    |
| GCS                         | 14.7 (1.2)  | 14.8 (0.8)        | 13.4 (3.1)           | <0.001  |
| **SOFA score at ED admission** |           |                   |                      |         |
| Total SOFA score            | 1.5 (2.0)   | 1.3 (1.8)         | 4.2 (2.7)            | <0.001  |
| SOFA score < 2 points       | 408 (62.4%) | 401 (65.8%)       | 7 (15.5%)            |         |
| SOFA score 2-5 points       | 208 (31.8%) | 187 (30.7%)       | 21 (46.6%)           |         |
| SOFA score > 5 points       | 38 (5.8%)   | 21 (3.5%)         | 17 (37.9%)           |         |
| **Origin of infection**     |             |                   |                      | 0.12    |
| Respiratory tract infection | 272 (41.6%) | 246 (40.4%)       | 26 (57.8%)           | 0.023   |
| Pneumonia                   | 135 (49.6%) | 117 (47.6%)       | 18 (69.2%)           |         |
| Asthma exacerbation, bronchitis, others | 120 (44.1%) | 115 (46.7%)     | 5 (19.2%)            |         |
| COPD exacerbation           | 17 (6.3%)   | 14 (5.7%)         | 3 (11.5%)            |         |
| Urinary tract infection     | 154 (23.5%) | 145 (23.8%)       | 9 (20.0%)            |         |
| Skin infection              | 59 (9.0%)   | 56 (9.2%)         | 3 (6.7%)             |         |
| Gastrointestinal tract infection | 39 (6.0%)   | 35 (5.7%)         | 4 (8.9%)             |         |
| Central nervous system infection | 17 (2.6%)    | 17 (2.8%)        | 0 (0.0%)             |         |
| Other infection             | 113 (17.3%) | 110 (18.1%)       | 3 (6.7%)             |         |
| **Comorbidities**           |             |                   |                      |         |
| Anemia                      | 316 (48.3%) | 279 (42.7%)       | 37 (5.7%)            | <0.001  |
| Hypertension                | 305 (46.6%) | 278 (45.6%)       | 27 (60.0%)           | 0.063   |
| Chronic renal failure       | 184 (28.1%) | 155 (25.5%)       | 29 (64.4%)           | <0.001  |
| Cancer                      | 122 (18.7%) | 106 (17.4%)       | 16 (35.6%)           | 0.003   |
| Diabetes mellitus           | 119 (18.2%) | 108 (17.7%)       | 11 (24.4%)           | 0.26    |
| Condition               | Control n (%)  | Case n (%)   | p-value |
|------------------------|----------------|--------------|---------|
| Coronary heart disease | 89 (13.6%)     | 73 (12.0%)   | 0.29    |
| COPD                   | 53 (8.1%)      | 42 (6.9%)    | <0.001  |
| Congestive heart failure | 47 (7.2%)    | 42 (6.9%)    | 0.003   |
| Dementia               | 45 (6.9%)      | 37 (6.1%)    | 0.51    |
| Substance abuse        | 27 (4.1%)      | 26 (4.3%)    | 0.87    |
| Stroke                 | 26 (4.0%)      | 24 (3.9%)    | <0.001  |

**Initial blood sample**

| Measure                        | Control Mean (SD) | Case Mean (SD) | p-value |
|--------------------------------|-------------------|----------------|---------|
| Sodium (mmol/l)                | 136.8 (4.3)       | 136.7 (4.2)    | 0.34    |
| hypernatremia (<135 mmol/l)    | 214 (32.7%)       | 199 (32.7%)    | 0.003   |
| normonatremia (136-143 mmol/l) | 414 (63.3%)       | 390 (64.0%)    | 0.003   |
| hypernatremia (>143 mmol/l)    | 26 (4.0%)         | 20 (3.3%)      | 0.003   |
| Osmolality (mosmol/kg)         | 289.1 (11.2)      | 288.4 (10.6)   | <0.001  |
| hypoosmolality (<280 mosmol/kg)| 101 (15.4%)       | 99 (16.3%)     | <0.001  |
| Normoosmolality (280-300 mosmol/kg) | 483 (73.9%) | 458 (75.2%)    | <0.001  |
| hyperosmolality (>300 mosmol/kg)| 70 (10.7%)       | 52 (8.5%)      | <0.001  |
| GFR MDRD (ml/min/1.73 m2)      | 52.2 (14.9)       | 53.4 (13.9)    | <0.001  |
| CKD Stage 1+2 (>60)           | 410 (62.7%)       | 399 (65.5%)    | <0.001  |
| CKD Stage 3 (30-60)           | 175 (26.8%)       | 158 (25.9%)    | <0.001  |
| CKD Stage 4-5 (<30)           | 69 (10.6%)        | 52 (8.5%)      | <0.001  |

**Abbreviation:** SD: standard deviation; bpm: beats per minute; mmHg: unit millimeter of mercury; SpO2: peripheral capillary oxygen saturation; GCS: Glasgow Coma Scale; SOFA Score: sequential organ failure assessment score; COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; MDRD: modification of diet in renal disease; ED: emergency department
Table 2. Univariable and multivariable logistic regression analysis for the primary and secondary endpoints.

|                | Survivors | Non-survivors | p-value | AUC | Model 1: | Model 2*: | Model 3**: |
|----------------|-----------|---------------|---------|-----|---------|----------|----------|
|                |           |               |         |     | Univariable OR (95%CI), p-value | Multivariable OR (95% CI), p-value | Multivariable OR (95% CI), p-value |
| Primary endpoint: 30-day mortality | n = 609 | n = 45 | <0.001 | 0.83 | 1.66 (1.46, 1.89), p<0.001 | 1.64 (1.38, 1.95), p<0.001 | - |
| SOFA score      | 1.3 (1.8) | 4.2 (2.7)     | <0.001 | 0.82 | 1.08 (1.06, 1.10), p<0.001 | 1.06 (1.04, 1.09), p<0.001 | 1.04 (1.01, 1.07), p=0.002 |
| Copeptin (pmol/L) | 46.6 (77.2) | 199.9 (204.7) | <0.001 | 0.57 | 1.04 (0.96, 1.11), p=0.340 | 1.01 (0.94, 1.09), p=0.776 | 1.01 (0.94, 1.09), p=0.843 |
| Sodium (mmol/L)  | 136.7 (4.2) | 137.4 (6.1)   | 0.34    | 0.74 | 1.06 (1.03, 1.08), p<0.001 | 1.03 (1.00, 1.06), p=0.033 | 1.01 (0.98, 1.04), p=0.724 |
| Osmolality (mosmol/kg) | 288.4 (10.6) | 297.6 (14.9)  | <0.001 | 0.75 | 1.05 (1.03, 1.07), p<0.001 | 1.05 (1.02, 1.08), p<0.001 | 1.01 (0.98, 1.04), p=0.579 |
| GFR MDRD (ml/min/1.73 m2) | 53.4 (13.9) | 37.2 (18.7)   | <0.001 | 0.75 | 1.04 (1.03, 1.10), p<0.001 | 1.04 (1.02, 1.08), p<0.001 | 1.01 (0.98, 1.04), p=0.579 |
| Secondary endpoint: ICU admission | n = 588 | n = 66 |         |     |         |         |         |
| SOFA score      | 1.3 (1.7) | 4.0 (2.4)     | <0.001 | 0.83 | 1.68 (1.49, 1.89), p<0.001 | 1.65 (1.43, 1.90), p<0.001 | - |
| Copeptin (pmol/L) | 51.8 (97.2) | 105.0 (106.5) | <0.001 | 0.75 | 1.04 (1.02, 1.05), p<0.001 | 1.02 (1.00, 1.05), p=0.050 | 0.99 (0.96, 1.02), p=0.417 |
| Sodium (mmol/L)  | 136.8 (4.2) | 136.4 (5.0)   | 0.46    | 0.52 | 0.98 (0.92, 1.04), p=0.455 | 1.00 (0.94, 1.06), p=0.899 | 1.01 (0.95, 1.07), p=0.791 |
| Osmolality (mosmol/kg) | 288.5 (10.7) | 294.3 (13.6)  | <0.001 | 0.65 | 1.04 (1.02, 1.06), p<0.001 | 1.02 (1.00, 1.05), p=0.083 | 1.00 (0.98, 1.03), p=0.828 |
| GFR MDRD (ml/min/1.73 m2) | 53.6 (13.5) | 40.6 (20.2)   | <0.001 | 0.70 | 1.04 (1.03, 1.06), p<0.001 | 1.04 (1.02, 1.06), p<0.001 | 1.00 (0.97, 1.02), p=0.710 |

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| blood culture positivity |  |  |  |  |  |
|--------------------------|---|---|---|---|---|
| SOFA score               | 1.7 (2.0) | 2.9 (2.5) | <0.001 | 1.28 (1.15, 1.41), p<0.001 | 1.27 (1.11, 1.45), p=0.001 |
| Copeptin (pmol/L)        | 57.2 (95.2) | 109.3 (131.9) | <0.001 | 1.04 (1.02, 1.06), p<0.001 | 1.02 (1.00, 1.05), p=0.052 |
| Sodium (mmol/L)          | 136.3 (4.3) | 136.3 (4.5) | 0.91 | 1.00 (0.94, 1.05), p=0.912 | 1.00 (0.95, 1.06), p=0.934 |
| Osmolality (mosmol/kg)   | 288.7 (11.4) | 290.3 (13.3) | 0.27 | 1.01 (0.99, 1.03), p=0.271 | 1.00 (0.98, 1.02), p=0.924 |
| GFR MDRD (ml/min/1.73 m²) | 51.4 (15.8) | 45.9 (16.1) | 0.005 | 1.02 (1.01, 1.03), p=0.006 | 1.01 (0.98, 1.03), p=0.656 |

**Abbreviation:** SOFA score: sequential organ failure assessment score, GFR: glomerular filtration rate; MDRD: modification of diet in renal disease; AUC: area under the curve; OR: odds ratio

*: adjusted for age, sex, type of infection and comorbidities

**: adjusted for age, sex, type of infection and comorbidities and SOFA score
Table 3. Association of various combinations of SOFA score with copeptin and fluid balance biomarkers for primary and secondary endpoints.

|                                | AUC (95% CI)       | p-value     |
|--------------------------------|--------------------|-------------|
| **Primary endpoint 30-day mortality** |                    |             |
| SOFA score                     | 0.83 (0.77, 0.88)  |             |
| **Change in AUC in bivariate Analysis** |                    |             |
| SOFA score & Sodium            | 0.83 (0.77, 0.88)  | 0.7448      |
| SOFA score & GFR               | 0.84 (0.78, 0.89)  | 0.0321      |
| SOFA score & Osmolality        | 0.84 (0.79, 0.89)  | 0.0861      |
| SOFA score & Copeptin          | 0.86 (0.81, 0.91)  | 0.0277      |
| SOFA score & MR-proADM         | 0.86 (0.81, 0.90)  | 0.0016      |
| **Change in AUC in multivariate analysis** |                    |             |
| SOFA score & Copeptin & Osmolality & GFR | 0.87 (0.82, 0.92) | 0.0281      |
| SOFA score & Copeptin & Osmolality & GFR & Sodium | 0.87 (0.82, 0.92) | 0.0289      |
| SOFA score & Copeptin & GFR    | 0.87 (0.82, 0.92)  | 0.0144      |
| SOFA score & Copeptin & MR-proADM | 0.87 (0.83, 0.92) | 0.0075      |
| **Secondary endpoint admission to ICU** |                    |             |
| SOFA score                     | 0.83 (0.78, 0.88)  |             |
| **Change in AUC in bivariate Analysis** |                    |             |
| SOFA score & Copeptin          | 0.82 (0.77, 0.87)  | 0.0546      |
| SOFA score & Sodium            | 0.82 (0.77, 0.87)  | 0.3127      |
| SOFA score & GFR               | 0.82 (0.78, 0.87)  | 0.4976      |
| SOFA score & Osmolality        | 0.84 (0.80, 0.88)  | 0.0155      |
| **Change in AUC in multivariate analysis** |                    |             |
| SOFA score & Osmolality & GFR & Sodium & Copeptin | 0.83 (0.79, 0.88) | 0.3516      |
| SOFA score & Osmolality & GFR & Sodium | 0.84 (0.79, 0.88) | 0.1387      |
| SOFA score & Osmolality & GFR  | 0.84 (0.79, 0.88)  | 0.0194      |
| **Secondary endpoint blood culture positivity** |                    |             |
| SOFA score                     | 0.65 (0.59, 0.72)  |             |
| **Change in AUC in bivariate Analysis** |                    |             |
| Comparison                        | Correlation Coefficient (95% CI) | p-value |
|----------------------------------|----------------------------------|---------|
| SOFA score & GFR                 | 0.64 (0.57, 0.71)                | 0.0589  |
| SOFA score & Osmolality          | 0.65 (0.58, 0.71)                | 0.7496  |
| SOFA score & Sodium              | 0.65 (0.58, 0.72)                | 0.9707  |
| SOFA score & Copeptin            | 0.68 (0.62, 0.74)                | 0.0144  |

**Change in AUC in multivariate analysis**

| Comparison                        | Correlation Coefficient (95% CI) | p-value |
|----------------------------------|----------------------------------|---------|
| SOFA score & Copeptin & Sodium & Osmolality & GFR | 0.68 (0.61, 0.74) | 0.0900  |
| SOFA score & Copeptin & Sodium & Osmolality | 0.68 (0.61, 0.74) | 0.0876  |
| SOFA score & Copeptin & Sodium   | 0.68 (0.62, 0.75)                | 0.0104  |

**Abbreviation:**
- **SOFA score**: sequential organ failure assessment score
- **GFR**: glomerular filtration rate
- **MR-proADM**: mid-regional pro-adrenomedullin
- **AUC**: area under the curve
- **CI**: confidence interval
**Copeptin (n=654)**

**Age**
- <60 (n=262): 0.99 (0.97, 1.00) 0.084
- 60-80 (n=283): 0.69 (0.56, 0.82) 0.163
- >80 (n=109): 0.78 (0.67, 0.88) 0.235

**Sex**
- male (n=365): 0.80 (0.72, 0.89) 0.508
- female (n=289): 0.84 (0.73, 0.95) 0.508

**Type of Infection**
- respiratory infection (n=272): 0.87 (0.79, 0.95) 0.068
- urinary tract infection (n=154): 0.68 (0.49, 0.87) 0.018
- gastrointestinal & hepatic infection (n=39): 0.92 (0.79, 1.00) 0.214
- skin infection (n=59): 0.78 (0.48, 1.00) 0.365
- other infection (n=130): 0.74 (0.45, 1.00) 0.412

**Sodium**
- hyponatremia (n=214): 0.74 (0.60, 0.88) 0.068
- normonatremia (n=414): 0.86 (0.78, 0.94) 0.147
- hypernatremia (n=26): 0.85 (0.65, 1.00) 0.128

**Osmolality**
- hypoosmolality (n=101): 0.72 (0.24, 1.00) 0.451
- normoosmolality (n=483): 0.79 (0.69, 0.89) 0.688
- hyperosmolality (n=70): 0.70 (0.56, 0.84) 0.308

**Kidney function**
- CKD Stage 1+2 (n=410): 0.77 (0.62, 0.92) 0.119
- CKD Stage 3 (n=175): 0.79 (0.69, 0.89) 0.019
- CKD Stage 4+5 (n=69): 0.65 (0.48, 0.82) 0.543
SOFA score + copeptin (n=654)

Age
- <60 (n=262) 0.98 (0.95, 1.00) 0.118
- 60-80 (n=283) 0.77 (0.67, 0.88) 0.096
- >80 (n=109) 0.82 (0.73, 0.91) 0.607

Sex
- male (n=365) 0.86 (0.81, 0.92) 0.425
- female (n=289) 0.86 (0.77, 0.95) 0.425

Type of Infection
- respiratory infection (n=272) 0.90 (0.85, 0.95) 0.053
- urinary tract infection (n=154) 0.76 (0.59, 0.94) 0.113
- gastrointestinal & hepatic infection (n=39) 0.93 (0.81, 1.00) 0.756
- skin infection (n=59) 0.79 (0.66, 0.92) 0.309
- other infection (n=130) 0.83 (0.66, 1.00) 0.507

Sodium
- hyponatremia (n=214) 0.79 (0.67, 0.91) 0.244
- normonatremia (n=414) 0.89 (0.84, 0.94) 0.641
- hypernatremia (n=26) 0.93 (0.83, 1.00) 0.227

Osmolality
- hypoosmolality (n=101) 0.93 (0.82, 1.00) 0.584
- normoosmolality (n=483) 0.84 (0.77, 0.91) 0.395
- hyperosmolality (n=70) 0.74 (0.60, 0.88) 0.183

Kidney function
- CKD Stage 1+2 (n=410) 0.87 (0.75, 0.99) 0.002
- CKD Stage 3 (n=175) 0.82 (0.72, 0.91) 0.062
- CKD Stage 4+5 (n=69) 0.58 (0.39, 0.77) 0.04