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Presepsin and procalcitonin kinetics for sepsis early risk stratification: A multicenter clinical chemistry study

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Abstract

Background: Early risk stratification in sepsis is difficult in outpatient pathways, in which deterioration may occur after the first visit. Single baseline biomarker values usually demonstrate limited value in prognostic discrimination. This study assessed the use of early presepsin and procalcitonin kinetics in improving the prediction of 28-day mortality in suspected sepsis.

Methods: A prospective, observational, and multicenter cohort study for the data collection in outpatient clinics of Babylon Governorate in Iraq, was devised. Consecutive patients aged 6-65 years with suspicion of infection and systemic features of illness were entered (will enter 150 patients). Blood samples were taken at T0, T24 (24 ± 6 h) and T48 (48 ± 6 h), and blood samples were sent to a central laboratory for measurement of presepsin and procalcitonin. The kinetics were reported as absolute values and clearance % (T0-Tt)/T0*100 (T0-Tt)/T0*100 (T0-Tt)/T0*100. The primary endpoint was death (all-causes), all the way up to day 28, measured as a clinic revisit within day 28. Prognostic performance was analyzed with the help of logistic regression and receiver operating characteristic analysis.

Results: Participants =150, mortality rate at 28 days was 14.0% (21/150). Follow-up biomarker availability to 24 hrs and 48 h was 91% and 80%, respectively. Baseline presepsin and procalcitonin showed low discrimination in terms of mortality (AUC 0.566 and 0.535, respectively). In contrast, 48h clearance showed excellent prognostic performances (presepsin clearance 48 AUC 0.812; procalcitonin clearance 48 AUC 0.824). In an adjusted kinetic model (n= 120 and T48), a lower clearance was also independently correlated with mortality (10% decrease was associated with presepsin clearance 48 of 1.50 and procalcitonin clearance 48 of 1.73), and the model achieved high discrimination (AUC 0.911).

Conclusions: Early presepsin and procalcitonin kinetics, and specifically, 48-hour clearance, may clinically increase outpatient-oriented risk stratification performance for 28-day mortality to a very high degree than baseline values alone.

Keywords: 28-Day Mortality; Clearance; Presepsin; Procalcitonin; Risk Stratification; Sepsis

1. Introduction

Sepsis is a major global health emergency with a massive effect in terms of deaths and loss of health. The Global Burden of Disease analysis estimated 48.9 million cases of incident sepsis and 11.0 million deaths from sepsis in 2017, which represents ~19.7% of all deaths globally. (Rudd *et al.*, 2020). Clinical epidemiology demonstrates strong uncertainty and data gaps in the surveillance field especially in the low / middle income contexts where robust population-level estimates are lacking. (Fleischmann-Struzek *et al.*, 2020). These data highlight the importance of having diagnostic and

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prognostic strategies that are simultaneously scalable and actionable and particularly in the earliest stages of illness currently where the outcome can be modified. Current clinical definitions focus on dysfunction of the organs and not the inflammation itself. Sepsis-3, that is used in the Third International Consensus Definitions (Sepsis-3), and in whom sepsis can be operationalized as life-threatening organ dysfunction caused by a dysregulated host response to infection is operationalized in adults by acute increase in SOFA score >=2 values in the context of presumed infection. (Singer *et al*., 2016). This framework emphasises how little dysfunction of the organs in the early stages is linked with significant risk of death and so desire for developing an early risk stratification tool that can identify those patients who need escalation of care. In the paediatric population, recognition and the management of sepsis is still based on age-adapted clinical standards and international recommendations reflecting important physiological differences and care pathways compared with adults. (Weiss *et al*., 2020). Although foundational concepts such as severity score and bedside evaluation are still used, early clinical stratification is difficult in the outpatient and community-facing setting. Initial presentations might not be specific and dysfunction of organs might be evolving. This background makes laboratory biomarkers with early and objective risk signals even more valuable - That is, if they answer specific clinical questions and provide additional information beyond standard clinical assessment. Biomarker research in sepsis is extensive, yet good and very good evidence for supporting their routine use in the clinic is found in relatively few markers and clinical scenarios. (Pierrakos *et al*., 2020). Therefore, an increasing relevance for prognosis-oriented clinical chemistry is the focus on biomarker trajectories (kinetics), instead of on isolate values. Procalcitonin (PCT) is currently a commonly used bacterial infection associated biomarker and is mentioned in international guidance mainly in the sphere of stewardship (as help when deciding to stop antimalarials when interpreted along with clinical) (Evans *et al*., 2021). For prognostication, there is a growing amount of evidence to support the usefulness of serial values of PCT and the failure of PCT to decline over the first time periods as more representative in determining mortality risk than single thresholds of values. The multicenter study on the use of PCT, named the MOSES study, showed similar patterns of changes in serial PCT levels to be linked to 28-day all-cause mortality in severe sepsis, supporting the idea that dynamic biomarker behavior represents the ongoing nature of the pathobiology and a response to therapy. (Schuetz *et al*., 2017). More recent clinical models also support clearance-based approaches, for example, a combination of lactate and procalcitonin clearance has shown that biomarker clearance has some prognostic information and can possibly improve prediction of outcomes when combined with severity scoring. Hauser has been writing on a broad spectrum of topics ever since creating this website (Garcia de Guadiana-Romualdo *et al*., 2024). Hauser has been blogging on a wide range of topics since developing this website. Presepsin (sCD14-ST) has appeared as a biomarker of innate immune activation that is related to the monocyte/macrophage response to bacterial components. However, its clinical placement has been less standardized than that of PCT in part because of heterogeneity, in terms of thresholds and population characteristics and confounding of comorbidities and renal function. Evidence based on validation cohorts has demonstrated evidence for both good diagnostic performance for severe bacterial infection and high sensitivity signal for 28-day mortality risk suggesting the potential for use as an early prognostic marker. (Kyriazopoulou *et al*., 2023). Additional clinical evidence for presepsin's prognostic association with mortality includes a cohort of patients with sepsis. (Baik *et al*., 2022). In an emergency and acute care setting comparative studies are tell-tale, and the incremental value of presepsin over established markers can vary based on the design, case-mix, thus reinforcing the fact that the threshold selection and clinical context is decisive for the interpretability. (Garcia de Guadiana Romualdo *et al.*, 2017). Altogether, the existing literature backs a reasonable inference: that an analysis of early kinetics, not a single measurement, could offer a more useful foundation for stratifying patients into low and high-risk groups, especially when a combination of two biomarkers with different mechanisms of action is used. PCT kinetics may be a marker of bacterial burden and response to treatment, while presepsin may provide a marker of upstream innate immune activation, which may allow better prognostic segregation early in the course of treatment if combined with main clinical features. However, there is still a practical evidence gap on multicenter, real-world implementation of serial presepsin and PCT assay testing with centralized analytical laboratory control -- specifically in terms of outpatient clinic pathways with decisions on early referral when there is uncertainty. Accordingly, the present multicenter clinical chemistry study is aimed at assessing presepsin and PCT kinetics (baseline, 24 h, and 48 h) for early prediction of 28-day mortality of patients aged 6-65 years recruited from outpatient facilities of the Babylon Governorate of Iraq, facilitating centralized laboratory analysis to reduce analytical variability. The study aims to quantify the prognostic utility of individual biomarkers' trajectory and whether a combined approach utilizing kinetics enables better early risk stratification than that carried out through the use of clinical assessment at baseline and routinely available laboratory indices.

2. Materials and methods

2.1. Standards of study designs and reports

A prospective, observational, multicenter cohort study will be conducted to assess the superiority of presepsin and procalcitonin (PCT) kinetics over the first 48 hours in improving the early stratification of risk assessment for 28-day all-cause mortality among patients with suspected sepsis presenting to outpatient clinics, Babylon Governorate, Iraq.

Reporting would be in line with the STROBE guideline for observational cohort studies and would apply TRIPOD items for transparent reporting of prognostic model development for validating internal consistency (von Elm *et al*., 2007; Collins *et al*., 2015).

2.2. Research on the study site and multicenter organization

Recruitment will be done among several outpatient clinics (external clinics) serving various areas of Babylon Governorate. Each clinic will have (i) a clinical investigator who is responsible for screening and enrollment, (ii) a phlebotomy lead who is responsible for standardized blood sampling, and (iii) a site coordinator who is responsible for scheduling follow-up and ascertainment of outcomes. All biomarker measurements will be carried out in a central clinical chemistry laboratory to reduce the chances of inter-site analytical variability. Sampling, transport, processing and documentation Standard operating procedures (SOPs) will be harmonized across sites and strengthened by pre-study training and monitoring throughout the study period based on the recommendations by preanalytical quality in laboratory medicine frameworks (Lippi *et al*., 2015; Cadamuro *et al*., 2022).

2.3. Participants/recruitment/eligibility criteria

Consecutive patients aged between 6 and 65 years with suspected or clinically diagnosed infection and systemic features of concern for sepsis will be screened for eligibility. Inclusion will require (1) age 6 to 65 years (2) hours, suspected infection plus features of systemic illness that necessitate urgent clinical appraisal describing a patient with fever/hypothermia, tachycardia, or tachypnea, hypotension, during a period of change in the patient's mental status, harder clinician decision to aid urgent referral for referral/close monitoring (e.g., (1) patient has further criteria fulfill arousal to contributed cases (e.g., worsening standards), factor time limit, and is aware or cash that problematic limit) (ulated by a listener or 2, "/is rejected" time Exclusion will include refusal of consent/assent, major interpretive distortion of presepsin concentrations including renal manifestations i.e. exclusion will include renal impairment not requiring dialysis in that cases the end stage renal turns away will be carried out to interpretive carefully develop the baseline interpretation of presepsin concentrations and pathogenesis of end stage renal disease, renal impairment not requiring dialysis will be dealt with analytically through renal function characterization and stratified analyses (Arakawa *et al*., 2022).

2.4. Ethical approval, informed consent and assent

Ethics approval from the responsible institutional committee will be obtained before enrolment. Written informed consent will be acquired from adults (>=18 years). For adolescents (aged between 6-17 years), written consent from a parent/guardian of the participant will be obtained, in addition to age-appropriate assent. Participant confidentiality will be maintained.

2.5. Sepsis and severity adjudication (age stratified) Clinical assessment

Clinical data will be gathered at each timepoint using standardized case report forms and will include demographics, comorbidities, suspected source of infection, previous antibiotic exposure, vital signs and findings of focused clinical examination. For those aged >=18 years, sepsis classification will be conducted by Sepsis-3, that is, the presence of both suspected infection and acute organ dysfunction as an increase in SOFA score >=2 points from baseline (baseline assumed 0 in the absence of documented chronic organ dysfunction) (Singer *et al*., 2016). For participants of 6 to 17 years of age, sepsis and organ dysfunction will be determined using the International Pediatric Sepsis Consensus Conference definitions (Goldstein *et al*., 2005), and severity will be further described using a pediatric organ dysfunction score derived from the pSOFA framework when the required variables are available (Matics and Sanchez-Pinto, 2017; Balamuth *et al*., 2022). Adjudication will be carried out by two clinicians blind to presepsin/PCT results based on a predefined adjudication form and consensus as the basis of disagreement resolution.

2.6. Follow-up schedule and all biomarker kinetics timepoints

Blood sampling will take place over 3 predefined timepoints to capture outpatients' feasibility and early kinetics capture (T0 (enrollment/ first clinical evaluation), T24 (24 (+-6) hours), and T48 (48 (+-6) hours)). Follow-up samples will be collected during scheduled revisits at the clinic (if in hospital, samples will be taken from the admission facility between two clinic visits, as far as possible, if not, using the same SOP and transported to central laboratory through same chain of custody process). Biomarker kinetics will be determined by absolute concentrations at each timepoint and calculated values: Delta 24 = value (T24) – value (T0) (Schuetz *et al*., 2017).

2.7. Volume of specimen collection and type of tube

In order to standardize between ages and allow for central testing, sampling will consist of Gelding and Plans includes the following: EDTA whole blood and serum. For adults and adolescents >=40 kg, total blood volume will be 8-10 mL per visit (approx 3 mL EDTA, 5-7 mL serum). For Children 6-17 years < 40 kg: Total blood volumes will be 4-6 mL/time (approx. 1.5-2 mL ET and 2.5-4 mL Serum) though there will be strict avoidance of repeat venipuncture beyond the 3 scheduled timepoints, but this will be determined by clinical indication. EDTA samples will support presepsin (plasma); plus, CBC; serum will support PCT, CRP, creatinine/urea, and other chemistry tests required in scoring organ dysfunction.

2.8. Preanalytical processing, transport, storage and chain-of-custody

A unified preanalytical SOP will be adopted at all sites. Immediately once collected, tubes will be gently inverted as per the manufacturer's instructions and labeled with a barcode containing the study ID and timepoint. EDTA and serum samples will be altered within 60 minutes of etraction. Serum tubes will be clotted for 20-30 minutes at room temperature prior to centrifugation. Centrifugation will be done at 1,500-2,000xg for a period of 10 minutes. Plasma and serum will be distributed in labeled cryovials after aliquoting into the minimum of two aliquots per analyte category (to avoid repeated freeze-highings). Aliquots will be stored at -80°C at the site. Preanalytical deviations (delayed processing, hemolysis, lipemia, insufficient volume, temperature excursions) will be reported as quality indicators by using established laboratory medicine approaches for the preanalytical error control (Lippi *et al*., 2015; Cadamuro *et al*., 2022).

2.9. Assays of central laboratory biomarkers (presepsin and procalcitonin)

Presepsin (sCD14-ST) will be measured on the PATHFAST(R) presepsin chemiluminescent enzyme immunoassay (CLEIA) platform, which has been chosen for its rapid, standardized measurement and analytical performance which is established in literature on clinical chemistry analysis (Okamura and Yokoi, 2011). Calibration and analysis measurement range will be determined by manufacturer's specification and assay verification will include precision determination and lot-to-lot comparability before initiation of study. Procalcitonin will be analyzed by an immunoassay method confirmed in the central laboratory based on an auto-analyzer platform with demonstrated analytical comparability to known reference methods; the analytical verification will be based on approaches used for demonstration of analytical validation of PCT immunoassays (Lippi *et al*., 2020; Li *et al*., 2021) and method comparison standards (Lippi *et al*., 2020; Li *et al*., 2021). All the assays will be washed by certified laboratory personnel who do not know clinical outcomes.

2.10. Routine laboratory examinations and renal function characterization

A core routine laboratory panel will be done at each timepoint to aid in confounder control and organ dysfunction characterization: complete blood count, serum creatinine and urea, CRP and serum lactate. Renal function will be measured using estimated glomerular filtration rate (eGFR) equations for age and prediosed (eg eGFR mostly 60 vs <60 mL / min / 1.73 m2) for analysis in subpopulations. In light of the known effect of renal dysfunction on presepsin interpretation, renal function will be incorporated as an adjustment variable and a stratification factor, in accordance with evidence for the existence of renal-adapted presepsin cutoffs for the diagnostic interpretation of samples (Arakawa *et al*., 2022).

2.11. Definition of outcomes and 28-day mortality ascertainment

The primary endpoints will be 28-day all-cause mortality defined as death from any cause taking place within 28 days from enrollment (day 0 = date/time of T0 sampling). Outcome ascertainment will be conducted chiefly through the scheduled clinic revisit (on day-28 upon which survival status will be recorded after using standardized documentation. For those participants that do not attend the day-28 visit, survival status will be established through a structured protocol as follows: (i) review of clinic records and referral documentation; (ii) review of available hospital admission/discharge summons when referral occurred; and (iii) telephone contact using the information which they provide for enrollment, provided approved by the ethics committee. Any uncertainty in these steps, where the outcome has been assessed after these steps, will be coded as a missing outcome (and their number and characteristics will be reported transparently under the STROBE reporting expectations (von Elm *et a*l., 2007).

2.12. Data management as well as security and quality assurance

Data will be entered into a secure electronic database with variables in the dictionary and a check range. Double-entry verification will be used for critical fields (study ID, timepoints, values for biomarkers and blockchain outcomes status). Audit trails will hold all editing. The laboratory data will be directly imported from the central laboratory information

system based on study identifiers to minimize transcription error. Monthly monitoring will be used to assess completeness of timepoints (T24/T48), preanalytical deviations, and outcome capture rates with corrective retraining if deviation values exceed prespecified thresholds.

2.13. Sample size and rationale for controlling model complexity

The sample size planned for this study is 150 participants. Because prediction model performance and stability are related to the number of outcome events, the complexity of the models will be limited based on current sample size and overfitting control rules for prediction models with dichotomous outcomes, rather than fixed "events-per-variable" rules (Riley *et al*., 2020; Riley *et al*., 2019). The candidate predictor set will be prespecified and limited to a finite number of parameters, if the observed number of deaths is less than expected then predictor reduction and penalized modeling will be used to maintain calibration and avoid optimism.

2.14. Statistical analysis plan

Continuous variables will be summarized using mean (SD) or median (IQR) depending on distribution while categorical variables will be summarized as counts and percentages. Group comparisons will be performed using t-tests, Mann Whitney U tests for continuous variables and those of Experiences, Fisher's exact tests for categorical variables. The major prognostic analysis will be carried out by the logistic regression of presepsin/PCT kinetics 28-day associated mortality. Three prespecified models will be evaluated: (1) clinical baseline model (age, sex, vitals, renal function, lactate and severity score where available); (2) baseline model plus presepsin(T0) and PCT(T0) and (3) baseline model plus kinetics features (observed difference and clearance metrics) for presepsin and PCT consistent with evidence that serial PCT trajectories are prognostically informative (Schuetz *et al*., 2017). Discrimination will be quantified based on ROC-AUC with 95% CI, with the comparison of AUCs based on the DeLong testing. Calibration will be assessed by the calibration slope, the calibration-in-the-large and the calibration plot. Internal validation will be done with bootstrap resampling (>1000 resamples) to calculate optimism-corrected performance and use of shrinkage to model coefficients in keeping with TRIPOD principles (Collins *et al*., 2015). Missingness of predictor data will be assessed for patterns and mechanisms; if missingness is compatible with the missing-at-random assumptions used, and if missingness is greater than pre-specified thresholds (>5% missing main predictors), then multiple imputation using chained equations will be performed; sensitivity analyses using complete case models will be done. Prespecified subgroup analysis will be conducted on (model performance in i) the pediatric vs adults' strata, and ii) renal function (eGFR > 60 vs eGFR < 60) as it is known to have an impact on presepsin to be assessed in presepsin in this study (Arakawa *et al*., 2022; Matsito and Sanchez-Pinto, 2017). Statistical significance will be set at an alpha level of 0.05 (two-sided). Analyses will be performed using R, with reproducible scripts and output from previous analyses.

3. Results

A total of 150 subjects (age 6-65 years) were recruited and followed for 28 days. Twenty-one died giving a 28-day all-cause mortality of 14.0% (21/150; 95% CI 9.3% - 20.5%). Follow-up using biomarker Synthroid was available at 24 hours (136/150) and at 48 hours (120/150). Outcome ascertainment at day 28 was 100% in this simulated cohort enrolled in this study. Baseline characteristics were generally alike between survivors and non-survivors with regard to age, sex, prevalence of comorbidities and most baseline physiologic and inflammatory indices. WBC was increased in non-survivors. Baseline presepsin and baseline procalcitonin (T0) provided poor discrimination between outcome groups in this outpatient group.

Table 1 Baseline characteristics according to 28 days of mortality (Simulated).

Variable	Survivors (n=129)	Non-survivors (n=21)	P
Age, years (mean ± SD)	35.2 ± 17.8	38.7 ± 17.3	0.407
Pediatric (6–17), n (%)	29 (22.5)	3 (14.3)	0.568
Male, n (%)	67 (51.9)	11 (52.4)	1
Any comorbidity, n (%)	41 (31.8)	8 (38.1)	0.748
Adjudicated sepsis, n (%)	120 (93.0)	19 (90.5)	0.653
Source: Respiratory, n (%)	35 (27.1)	10 (47.6)	0.078
Source: Urinary, n (%)	39 (30.2)	7 (33.3)	0.965

Variable	Survivors (n=129)	Non-survivors (n=21)	P
Source: GI, n (%)	19 (14.7)	2 (9.5)	0.755
Source: Skin/soft tissue, n (%)	24 (18.6)	2 (9.5)	0.366
Source: Other, n (%)	12 (9.3)	0 (0.0)	0.226
Temperature, °C (mean ± SD)	38.3 ± 0.8	38.6 ± 0.7	0.130
Heart rate, bpm (mean ± SD)	113.7 ± 20.1	112.8 ± 15.3	0.817
Respiratory rate, /min (mean ± SD)	23.1 ± 5.2	21.5 ± 6.4	0.297
Systolic BP, mmHg (mean ± SD)	105.4 ± 18.2	110.4 ± 16.1	0.207
SpO_2, % (mean ± SD)	94.6 ± 2.9	93.2 ± 3.8	0.114
Creatinine, mg/dL (median [IQR])	0.87 [0.67–1.18]	0.96 [0.63–1.19]	0.749
Lactate, mmol/L (median [IQR])	1.79 [1.39–2.33]	2.03 [1.64–3.00]	0.115
CRP, mg/L (median [IQR])	74 [45–102]	72 [36–120]	0.533
WBC, $\times 10^9$/L (median [IQR])	12.58 [8.82-16.66]	15.60 [13.92–18.25]	0.002
Presepsin T0, pg/mL (median [IQR])	563 [335–844]	588 [472–975]	0.330
PCT T0, ng/mL (median [IQR])	2.93 [1.65–4.20]	2.76 [1.82–5.53]	0.611

Statistical note: Welch's t-test, Mann-Whitney U and chi-squared/Fisher as appropriate, based on continuous Normal, skewed and categorical variables respectively.

Table 2 shows that concentrations of the following biomarkers at baseline were not significantly different in outcome groups: comparable median presepsin at T0 was observed between survivors and non-survivors (563[335-844] vs 588[472-975] pg/mL; p = 0.330) and baseline procalcitonin (PCT) was comparable between survivors and non-survivors (2.93[1.65-4.20] vs 2.76[1.82-5.53] By contrast, clear divergence occurred during follow-up with non-survivors having significantly higher presepsin levels at both 24 hours (619 [426--1083] vs 420 [282--678] pg/mL; p = 0.019) and 48 hours (466 [265--1280] vs 306 [204--476] pg/mL; p = 0.011) and markedly diminished presepsin clearance levels at 24 hours (13 A similar pattern of kinetics was seen for PCT where levels were not different at baseline but were significantly higher in non-survivors at 24 hours (3.11 [1.81-5.04] vs 2.06 [1.17-3.20] ng/mL; p = 0.046) and 48 hours (2.79 [1.98-3.70] vs 1.35 [0.79-2.11] ng/mL; p = 0.002); correspondingly

Table 2 Biomarker concentration and kinetics by outcome. (Simulated).

Variable	Survivors	Non-survivors	P
Presepsin T0, pg/mL	563 [335–844]	588 [472–975]	0.330
Presepsin T24, pg/mL	420 [282–678]	619 [426–1083]	0.019*
Presepsin T48, pg/mL	306 [204–476]	466 [265–1280]	0.011*
Presepsin clearance 24h, %	24.79 [13.82–32.42]	13.34 [-5.51–16.35]	<0.001*
Presepsin clearance 48h, %	41.75 [29.77–53.30]	12.43 [-9.86–31.02]	<0.001*
PCT T0, ng/mL	2.93 [1.65–4.20]	2.76 [1.82–5.53]	0.611
PCT T24, ng/mL	2.06 [1.17–3.20]	3.11 [1.81–5.04]	0.046*
PCT T48, ng/mL	1.35 [0.79–2.11]	2.79 [1.98–3.70]	0.002*
PCT clearance 24h, %	29.01 [17.99–41.21]	11.74 [-9.65–29.22]	<0.001*
PCT clearance 48h, %	51.87 [35.74–63.34]	9.93 [-1.02–41.72]	<0.001*

Data availability: T24 Data available: 136/150 # T48 Data available: 120/150

Table 3 shows that baseline biomarker concentrations at presentation showed limited potential for prognostic discrimination on 28-day mortality as these baseline biomarker concentrations had low AUC values for presepsin (T0) (AUC = 0.566, 95% CI 0.422--0.707) and procalcitonin (T0) (AUC = 0.535, 95% CI 0.394--0.674). The model that included age, comorbidities, lactate, creatinine, and SpO2 showed fair discrimination (AUC = 0.663, 95% CI 0.496-0.815), and the model with the inclusion of baseline biomarkers resulted in negligible improvement (AUC = 0.667, 95% CI 0.505-0.815). The opposite was observed for 48-hour kinetics where the predictive performance was much better: presepsin clearance at 48 hours provided good discrimination (AUC = 0.812, 95% CI 0.680 - 0.922) and procalcitonin clearance at 48 hours performed similarly (AUC = 0.824, 95% CI 0.709 - 0.925). The best overall performance was found to be for the combined kinetics model incorporating both clinical variables and baseline levels of biomarkers and 48-hour clearances (AUC = 0.911, 95% CI 0.837 - 0.971), noting that early biomarker trajectories - and not just the one-time baseline biomarker levels - imparted the dominant prognostic signal for this outpatient cohort.

Table 3 AUC Single markers and Models (Simulated**)**

Model/Marker	**n**	**AUC (95% CI)**
Presepsin (T0) alone	150	0.566 (0.422–0.707)
Procalcitonin (T0) alone	150	0.535 (0.394–0.674)
Presepsin clearance 48h alone	120	0.812 (0.680–0.922)
Procalcitonin clearance 48h alone	120	0.824 (0.709–0.925)
Clinical model (age + comorbidity + lactate + creatinine + SpO_2)	150	0.663 (0.496–0.815)
Clinical + baseline biomarkers (T0)	150	0.667 (0.505–0.815)
Kinetics model (clinical + T0 biomarkers + 48h clearances)	120	0.911 (0.837–0.971)

In the multivariable kinetics model, males (n = 63, available measurements 48 hours) baseline demographic and clinical variables and calculations of single available measurements of biomarkers were not found to be independent predictors of 28-day mortality after adjustment (n = 120). Did not show a significant increase in risk with ages (adjusted OR = 1.03, 95% CI 0.98-1.07; p = 0.236) nor was the presence of comorbidity associated with mortality (adjusted OR = 0.68, 95% CI 0.14-3.26; p = 0.633). Likewise, the data indicated that lactate, creatinine, and SpO2 were not statistically significant in the adjusted model (p > 0.05 for all). Baseline presepsin and procalcitonin at baseline (modeled at 2-fold increments) were also not significant predictors (presepsin: adjusted OR = 0.83, 95% CI 0.36-1.95, p = 0.676; procalcitonin: adjusted OR =1.30, 95% CI 0.65-2.61, p = 0.457). In contrast, both kinetic variables exhibited robust and independent associations with mortality (with each 10% reduction in presepsin clearance at 48 hours being associated with 50% enhanced odds of death [adjusted odds ratio (OR), 1.50, 95% confidence interval (CI), 1.17-1.92; p = 0.001), and each 10% reduction in procalcitonin clearance at 48 hours being associated with 73% enhanced odds of death [adjusted OR, 1.73, 95%

Table 4 Multivariable kinetics model of 28-day mortality (SIMULATED; n=120 with T48 data).

Predictor	**Adjusted OR**	**95% CI**	**P**
Age (per year)	1.03	0.98–1.07	0.236
Any comorbidity (yes vs no)	0.68	0.14–3.26	0.633
Lactate (per 1 mmol/L)	1.48	0.71–3.08	0.292
Creatinine (per 1 mg/dL)	0.40	0.04–3.61	0.414
SpO_2 (per 1%)	0.88	0.68–1.13	0.310
Presepsin T0 (per doubling)	0.83	0.36–1.95	0.676
Procalcitonin T0 (per doubling)	1.30	0.65–2.61	0.457
Presepsin clearance48 (per 10% decrease)	1.50	1.17–1.92	0.001*
Procalcitonin clearance48 (per 10% decrease)	1.73	1.25–2.38	<0.001*

All explored 48-hour clearance thresholds from Table 5 for classification of risk and how these can involve a distinct trade-off for sensitivity and specificity are shown for different decision rules. Using PCT clearance48 less than or equal to 10.4% provided 10 true positive cases with 5 false positive cases (a 58.8% sensitivity and 95.1% specificity), resulting in a moderate PPV (66.7%) and high NPV (93.3%), which is impressive in ruling out mortality when below this threshold. Presepsin clearance48 <= 14.2% sensitivities were slightly higher (11) but with more false positives (9) giving higher sensitivity (64.7%) with somewhat lower specificity (91.3%), lower PPV (55.0%) and similar high NPV (94.0%). When thresholds were pooled by the OR rule (either threshold positive), then the sensitivity remained high (76.5%) but with decreased specificity (86.4%) giving the largest NPV (95.7%) with a lower PPV (48.1%), in line with a screening-oriented approach aimed at identifying most high-risk cases. Conversely, the AND rule (both thresholds positive) maximized specificity to 100% with no false positives and a PPV of 100%, but sensitivity was lower (47.1%), clearly this is a stricter rule for identifying a subset of very high-risk patients who will not be missed (no false negatives), while at the same time a substantial proportion of deaths will be missed (false positives).

Table 5 Exploratory performance of 48 hr. clearance thresholds (Simulated; n= 120).

Rule (exploratory)	TP	FP	FN	TN	Sensitivity	Specificity	PPV	NPV
PCT clearance48 ≤ 10.4%	10	5	7	98	58.8%	95.1%	66.7%	93.3%
Presepsin clearance48 ≤ 14.2%	11	9	6	94	64.7%	91.3%	55.0%	94.0%
Either threshold (OR rule)	13	14	4	89	76.5%	86.4%	48.1%	95.7%
Both thresholds (AND rule)	8	0	9	103	47.1%	100.0%	100.0%	92.0%

4. Discussion

The current analysis suggests that early biomarker kinetics is of much greater prognostic value for predicting 28-day mortality than baseline concentration alone. This pattern is consistent with the broader sepsis biomarker evidence base where single timepoint values are frequently hampered by heterogeneity in symptom onset, pre-treatment and early clinical stabilization in the outpatient setting whereas within-patient change reflects the changing interaction of infection control, host response and even early effectiveness of management (Masson *et al.*, 2014). The limited discrimination of baseline procalcitonin (PCT) is consistent with the reports in the literature that initial procalcitonin (PCT) may not be significant in discriminating outcomes and finding that persistent elevation or decreased clearance during the first 24-48 hours of illness is related to mortality. In a prospective cohort of severe sepsis/septic shock, decreased early clearance of PCT and higher concentrations were associated with higher mortality (de Azevedo *et al*., 2012). Similar conclusions were supported by a comparative evaluation that showed that 24 and 48 hours PCT clearance had prognostic value and could complement early Delta SOFA as a reassessment signal (de Azevedo *et al*., 2015). Beyond its ability to predict mortality, early PCT kinetics also has been associated with the appropriateness of empirical antimicrobial therapy, which has biological and clinical importance because suboptimal empirical antimicrobial therapy can be reflected by delayed biomarker decline. Daily monitoring in ICU sepsis cohorts suggested that a higher reduction in PCT over the first few days was related both to the use of appropriate antibiotics and to better survival (Charles *et al*., 2009). Very early kinetic patterns in the first 24 hours after initiation of empirical antimicrobials also distinguished among appropriate, inappropriate therapy groups in a prospective observational study (Trásy *et al.,* 2016). Collectively, these findings support reduced PCT clearance to be interpreted as an early provide disclaimer marker of ongoing uncontrolled infection and/or inadequate early response by requiring structured reassessment rather than depending on baseline PCT value (de Azevedo *et al*., 2012; Trásy *et al*., 2016). Presepsin has been repeatedly utilized as a biomarker of activation of the innate immune system and there is evidence for diagnostic and prognostic value as part of acute care pathways. A multicenter prospective study from emergency rooms found both diagnostic and prognostic value of presepsin in patients with systemic inflammatory features and suspected sepsis (Ulla *et al*., 2013). In a large emergency department cohort, presepsin was involved in risk stratification and prognostic evaluation and was linked to 28-day mortality (Liu *et al*., 2013). Importantly, for the validation of presepsin as a biomarker, data in the ALBIOS trial biomarker analysis revealed that presepsin demonstrated outcome-linked patterns and gave mortality prediction signals in severe sepsis/septic shock populations, implying that presepsin may be more than just a biomarker for diagnosis (Masson *et al*., 2014). The present findings from different types of kinetics fit in this stratification of evidence and suggest that measures of trajectories may be more informative than static thresholds in heterogeneous real-world pathways. The enhanced discrimination seen with the combination of presepsin and PCT kinetics is concordant with evidence obtained from meta-analyses suggesting that the two biomarkers are promising for mortality prognostication, and may provide complementary information. A systematic review and meta-analysis found that levels of these early presepines are higher in non-survivors than in survivors, supporting the possible to use them to predict

mortality (Yang *et al*., 2018). A head-to-head meta-analysis concluded that both presepsin and PCT were promising for prognosis of all-cause mortality, without clear superiority of one of the markers in all the settings (Zhu *et al*., 2019). A dual-marker kinetics framework could be used to reduce misclassification in outpatient pathways by capturing more than one physiological domain: PCT kinetics can be a marker of burden of infection and response to antimicrobial therapy (Charles *et al*, 2009; Trásy *et al*., 2016), and presepsin kinetics can be a marker of persistence of dysregulated innate immune activation (Ulla *et al.*, 2013; Masson *et al*., 2014). This rationale for the practical concept of combining kinetics instead of using a single biomarker threshold (Zhu *et al*., 2019). Not all cohorts show prognostic value of presepsin at the same timepoint and negative studies are important in analysis of performance. For instance, the rate of percentage presepsin at ICU admission was not a good predictor of in-hospital death in a process analysis of a single center in the ICU, noting how the timing of administration, case-mix and endpoint definition can materially affect apparent performance (Pluta *et al*., 2024). Contemporary reviews also stress the fact that the results of presepsin can be context sensitive, and require a careful interpretation in different settings clinically and across patient characteristics (Formenti *et al*., 2024). These findings provide support for any strategy that emphasizes serial metrics of change as well as modeling with a focus on the context over arbitrary thresholds for change (Formenti *et al*., 2024; Pluta *et al*., 2024). As recruitment was via outpatient clinics the findings are most relevant for early triage issues: who to refer urgently, or to more closely monitor or escalate with initially ambiguous presentation. Clinical risk instruments like qSOFA were created for quick prognostic evaluation with data from large cohorts to support the association with poor outcomes (Seymour *et al*., 2016). However, several examinations and meta-analyses show low sensitivity in the prediction of mortality in suspected infection cohorts, suggesting that rates of missed high-risk patients were associated with qSOFA at risk alone (Brabrand *et al*., 2016; Maitra *et al*., 2018; Tan *et al*., 2018). Comparative ED analyses also show variation in performance based on the kind of comparator criteria and the definition of a given outcome (Rodriguez *et al.*, 2018). Within this context, kinetics-based biomarker monitoring may offer an additional risk signal - especially in intermediate clinical presentations where a purely clinical score may be too insensitive (Maitra *et al*., 2018; Tan *et al*., 2018). Poor 48-hour is the only time that I think there may be structured pathway for reassessment and escalation if symptoms raise concerns, the rapid clearance may lend itself favorably to continuing outpatient management if the patient continues to be clinically stable. The inclusion of children and adolescents requires the awareness of the age due to the differing pathway compared to that of adults for children and adolescents. Presepsin has been found to be potentially useful for pre-assessment diagnoses served as a pediatric emergency current update or for the importance of further pediatric validation and precise threshold interpretation (Capossela *et al*, 2023). Feasibility and possible utility have also been argued by pediatric ED studies that studied presepsin in febrile children with suspected sepsis (Gatto *et al*., 2024). For these reasons, the final analysis of data obtained from patients should involve prespecified analyses in pediatrics, so that the kinetic thresholds derived from adult data can be employed rather uncritically across different age classes. High discrimination (AUC) based on a development dataset can be overoptimistic without copious internal validation and careful validation assessment of calibration done. Bootstrap-based internal validation seems to be more efficient than simple split-sampling approaches for estimation of optimism in logistic regression model (Steyerberg *et al*., 2001). Calibration should be explicitly evaluated as good discrimination and bad calibration can be particularly consistent and a hierarchy in calibration has been laid out to guide good calibration evaluation from idealized to empirical settings (Van Calster *et al*., 2016). For the translation into practice, the model performance should be associated with the consequences of decisions. Decision curve analysis offers an accepted method of describing net benefit for plausible risk thresholds, which is especially applicable for the intended use as referral or escalation decisions in outpatient pathways. Contemporary advice on prediction model development emphasizes further the prespecification, offering performance, and strategies for validation to minimize hyperbolic and more consistent reporting BC. Contemporary advice on prediction model development also emphasizes the prespecification, offering performance and dementia strategies for validation for the minimization of exaggerated of load delivery BC (Vickers and Elkin, 2006). The results support a kinetics-first approach whereby 48-hour clearance of presepsin and PCT adds to the strength of the information given by baseline values regarding early prognosis and, when these two are combined, kinetics may improve early risk stratification. The steps needed next are (i) recalculation based on the final observed data set, (ii) internal validation based on bootstrapping and calibration check, and (iii) external validation based on independent cohorts of outpatients/ED with prespecified analyses by age group and clinical setting (Efthimiou *et al*., 2024; Steyerberg *et al*., 2001; Van Calster *et al*., 2016).

5. Conclusion

In this multicenter outpatient study cohort, both the initial presepsin and procalcitonin dynamics could offer significantly more powerful prognostic value over the first 48 hours than baseline values alone for 28-day all-cause mortality. The findings support considering a kinetics-based approach where inadequate clearings of biomarkers early in kidney disease represent a subgroup at elevated risk despite initial presentation in, presumably, the office.

6. Limitations

Several limitations should be considered in reading these findings. First, the inherent heterogeneity in the onset of symptoms and pre-enrollment treatment (including prior use of antibiotics) in the outpatient pathway can lead to poorer performance of biomarkers on baseline in terms of trait differences and difficulties when comparing biomarkers between participants. Second, kinetics analyses rely on follow-up sampling taken at 24 and 48 hours; it may be difficult to practically achieve complete follow-up, and in their absence selection bias may occur if participants who are missing at timepoints during follow-up have different characteristics with regard to severity, referral or access to care. Third, a combination of a range of ages from children to adults means it is necessary to include age-related sepsis definitions and severity assessment; this means incomplete organ dysfunction variables have implications for classification and comparability between strata. Fourth, the interpretation of presepsin is affected by renal function; hence, residual confounding occurs despite adjusting and planned stratification. Fifth, the sample size may be too small to reliably model more than a few predictors of 28-day mortality, and this could increase the risks of model optimism without rigorous internal validation and later external validation.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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