International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

The Inflammation-Presepsin Score as a Predictor of Mortality in Elderly Sepsis Patients (≥75 Years): A Pilot Study

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Purpose: The clinical diagnosis and risk stratification of sepsis are particularly challenging in extremely elderly patients (≥75 years) due to atypical presentation and potential diagnostic unreliability of standard scores. This study investigated whether a composite score —presepsin combined with the Prognostic Index (iPS-PI)—offers potential prognostic utility over presepsin alone as a predictor of 28-day mortality, thereby providing a reliable tool for early clinical decision-making in this vulnerable population.

Patients and Methods: Eighty-three adult sepsis patients were prospectively examined and stratified into over 75 (n = 41) and under 75 (n = 42) age groups. Presepsin levels and total composite scores (iPS-PI) were calculated upon ICU entry. Statistical analyses, including ROC curve analysis and Cox proportional hazard models, focused on the over 75 group.

Results: The 28-day mortality rate was 21.7% (18/83) overall (over 75 group: n = 12 [29.3%]; under 75 group: n = 6 [14.3%]). The areas under the curve (AUCs) of presepsin and iPS-PI for predicting mortality were higher (0.82) in the over 75 group than in the under 75 group. iPS-PI achieved a high AUC (0.82) in the over 75 group with a cutoff value of 2. Furthermore, in a sub-analysis focused on the over 75 group, iPS-PI (Hazard Ratio 14.22, P=0.031) was suggested as a potential independent predictor of mortality, whereas presepsin alone was not (P=0.656).

Conclusion: iPS-PI may be superior to presepsin alone as an independent predictor of mortality in extremely elderly sepsis patients. This finding strongly advocates for the use of iPS-PI as a time-sensitive "rule in" tool for early risk stratification, facilitating immediate and tailored aggressive therapeutic interventions by geriatric and critical care clinicians. iPS-PI also directly addresses the diagnostic challenges unique to geriatric sepsis management.

Plain Language Summary: Sepsis is a life-threatening condition, particularly for elderly patients. Diagnosing and predicting outcomes in patients over age 75 years can be difficult due to atypical symptoms. This study investigated a new scoring system called the "inflammation-presepsin score combined with the Prognostic Index (iPS-PI)" to determine whether it could better predict mortality in this age group. We examined 83 sepsis patients and found that the iPS-PI score was a more accurate predictor of death within 28 days than measuring presepsin levels alone. This new scoring system could help doctors identify high-risk elderly patients earlier and start life-saving treatments sooner.

Keywords: inflammation-presepsin score, iPS, presepsin, mortality, septic shock, geriatric sepsis

Introduction

Sepsis is a pathological condition of lethal organ dysfunction with a high mortality rate in critically ill patients.[1–3] In older adults, sepsis often presents with non-specific or atypical symptoms such as delirium, falls, or general weakness, leading to delayed diagnosis and treatment initiation, a key driver of poor outcomes.[4]

The clinical context of sepsis is complex, particularly in the aged population. In Japan, the "Act on Securing Medical Care for the Elderly" defines the elderly as being 65 years and older, and further divides this group into "early-stage

https://doi.org/10.2147/IJGM.S585341
Received: 29 November 2025
Accepted: 28 January 2026
Published: 2 February 2026

elderly" for those aged 65–74, and "late-stage elderly" for those aged 75 and above. The interpretation of biomarkers may also differ with age. Incidence rates of sepsis and septic shock are much higher in extremely elderly sepsis patients (≥75 years) than in younger patients,[5,6] largely due to immunosenescence.[7–9]

To address the challenges of diagnosing sepsis, novel biomarkers such as NGAL and presepsin have been reported. Presepsin (sCD14-ST) is secreted into circulation during systemic infection[10] and has been established as a valuable tool for sepsis diagnosis, prognosis, and monitoring due to its high specificity.[11–13] It also has the advantage of being measurable in less than 17 minutes using a compact fully-automated immunoanalyzer.[14] Its accuracy has been demonstrated to be superior to procalcitonin (PCT) and C-reactive protein (CRP).[15,16] However, single biomarkers may not fully capture the complex, multi-faceted pathophysiology of sepsis, particularly when overlaid with age-related immune dysfunction (immunosenescence). This has led to a growing interest in the use of composite scores that combine multiple biomarkers and clinical indicators.[17,18] Among these, inflammation-based prognostic scores, including the Prognostic Index (PI), are commonly used.[19]

Here we examined the hypothesis that the accuracy of predicting mortality is significantly improved by combining presepsin levels with inflammation-based prognostic scores (eg, inflammation-presepsin score (iPS)-PI). We posit that iPS-PI offers improved prognostic value as a more reliable, independent predictor of mortality over presepsin alone, providing a much-needed robust, practical tool for early risk stratification in this high-risk population, thereby directly assisting geriatric clinical decision-making.

Methods

Patients and Study Design

This study was a single-center prospective study conducted in a 16-bed ICU. The study protocol was approved by the Ethics Committee of Osaka Medical College (Osaka, Japan). In total, 83 adult patients older than 18 years who were diagnosed with sepsis according to the Sepsis-3 definition[1] and admitted to the ICU were prospectively examined from December 2017 to August 2019 (Table 1 and Figure 1). Informed consent was obtained from all patients enrolled in this study or their families. Patients who exhibited clinical evidence of anti-inflammatory conditions were excluded, including

Table 1 Patient Baseline Characteristics

Variable	n=83	
Age (years)	74.0	(65.5–78.5)
Sex (male) (%)	51.0	(61.4)
Cancer (%)	40.0	(48.2)
Coronary artery disease (%)	4.0	(4.8)
Diabetes mellitus (%)	10.0	(12.0)
Hypertension (%)	21.0	(25.3)
Albumin (g/dL)	2.3	(1.8–3.0)
CRP (mg/dL)	10.4	(3.7–17.5)
WBC ($\times 10^9$ L^{-1})	10.9	(5.4–15.4)
Neutrophil count ($\times 10^9$ L^{-1})	8.7	(3.56–13.29)
Lymphocyte count ($\times 10^9$ L^{-1})	0.5	(0.299–0.927)
Platelet count ($\times 10^4$ mm^{-3})	17.8	(11.5–26.5)
Fibrinogen (mg/dL)	609.0	(378–711)
Non - survivors, n (%)	26.0	(31.3)
AKI (%)	38.0	(45.8)
ARDS (%)	13.0	(15.7)
Shock (%)	48.0	(57.8)
DIC (%)	30.0	(36.1)
Presepsin on Day 1 (pg/mL)	1051.5	(569–1819.3)
Presepsin on Day 2 (ng/mL)	1016.5	(538–2156)
Presepsin on Day 3 (ng/mL)	802.0	(480.5–1825)

(*Continued*)

Table 1 (Continued).

Variable	n=83	
Presepsin on Day 5 (ng/mL)	1043.0	(480–1616)
ΔPresepsin Day 2 - Day 1 (pg/mL)	−21.50	(−246.5–274.75)
ΔPresepsin Day 3 - Day 1 (pg/mL)	−38.50	(−748.5–304)
ΔPresepsin Day 5 - Day 1 (pg/mL)	−59.50	(−745.75–635.5)
GPS	1.0	(1–2)
NLR	12.6	(4.53–26.35)
PLR	321.9	(195.63–543.69)
PI	1.0	(1–2)
PNI	26.6	(21.26–33.72)
SOFA	8.0	(5–11)
qSOFA	2.0	(1–3)

Abbreviations: CRP, C-reactive protein; WBC, white blood cell; AKI, acute kidney injury; ARDS, acute; respiratory distress syndrome; DIC, disseminated intravascular coagulation; GPS, Glasgow; Prognostic Score; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PI, Prognostic Index; PNI, Prognostic Nutritional Index; SOFA, Sequential Organ Failure Assessment; qSOFA, quick SOFA.

those undergoing immunosuppressive therapy (eg, chemotherapy, chronic steroid use, autoimmune disease treatment) within 1 month of the study (Figure 1). Analyses were stratified into two age groups: elderly patients aged 75 years and above (over 75 group) and patients under 75 years (under 75 group).

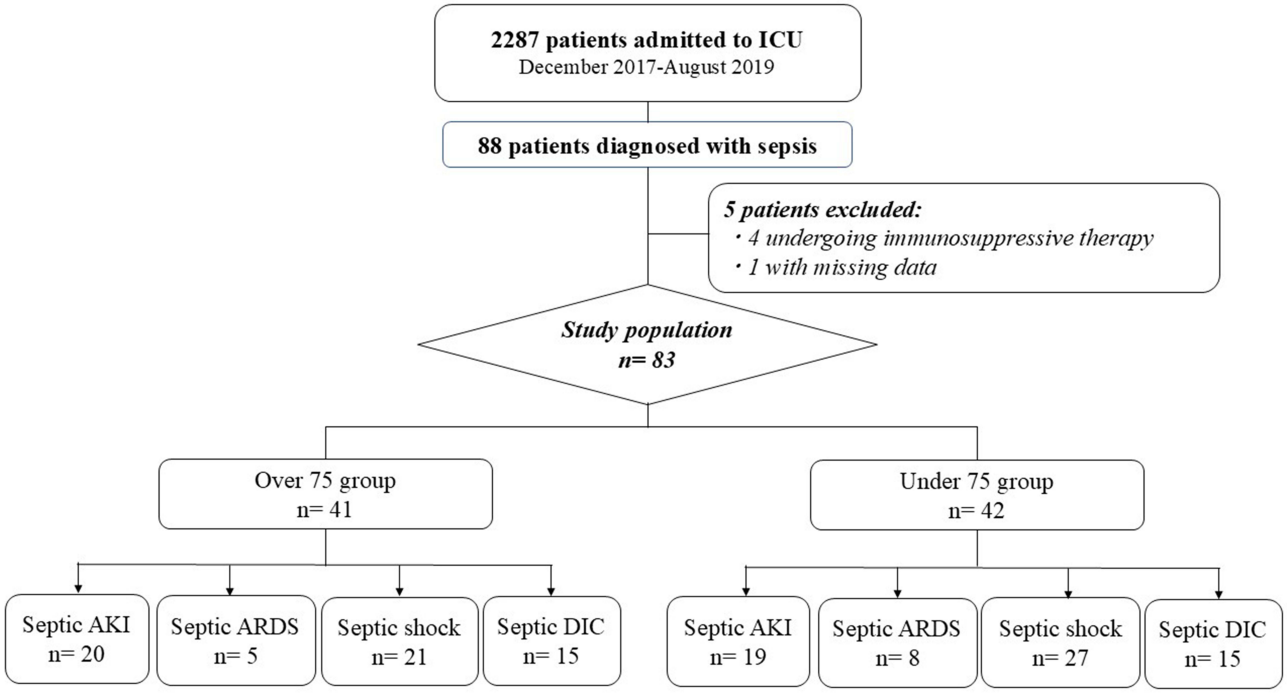

Figure 1 Study Flow Chart for Patient Selection and Grouping. The flow chart illustrates the process of identifying eligible patients with sepsis admitted to the Intensive Care Unit (ICU) and their subsequent stratification. A total of 2287 patients were initially admitted to the ICU between December 2017 and August 2019. Eighty-eight patients met the criteria for sepsis. Five patients were excluded from the final analysis due to either receiving immunosuppressive therapy (n = 4) or having missing data (n = 1), resulting in a final study population of 83 patients. These 83 patients were stratified into the extremely elderly group (age ≥75 years; n = 41) and the under 75 group (n = 42). The number of patients developing specific organ dysfunctions (septic ARDS, septic AKI, septic shock, septic DIC) within the final 83-patient cohort is also shown, stratified by age group.
Abbreviations: ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; DIC, disseminated intravascular coagulation; ICU, Intensive Care Unit.

Data Collection and Biomarker Measurement

Patients' clinical, demographic, and laboratory data were prospectively collected upon ICU admission. Arterial blood samples were collected from each patient, and presepsin values were measured immediately after ICU admission (baseline) and on Days 2, 3, and 5 after ICU admission. Presepsin concentration was measured by chemiluminescent enzyme immunoassay (CLEIA) (PATHFAST; Mitsubishi Chemical Medience Corporation, Tokyo, Japan), which produces assay results within 17 min.[14] This assay has a systemic infection (sepsis)-suggestive cut-off range of 300 pg/mL to 500 pg/mL.[20,21]

Inflammation-Based Prognostic Scores and iPS Calculation

The following inflammation-based prognostic scores were examined at baseline: Glasgow Prognostic Score (GPS), Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), Prognostic Nutritional Index (PNI), and PI.[19]

For category classification, a total score, hereafter called the "iPS," was calculated. A score of 1 was assigned if presepsin values and inflammation-based prognostic scores immediately after ICU entry were above the cut-offs determined by receiver operating characteristic (ROC) curves for 28-day mortality. A score of 0 was assigned if the values were below the cut-offs, for a total score range of 0 to 2 points.

For the composite score used in the main analysis, the two component variables were presepsin and the Prognostic Index (PI), with the final score being designated as iPS-PI. Among these scores, PI was selected for the composite model because it effectively reflects the host's chronic inflammatory and nutritional status, which are critical prognostic factors in the elderly.

Definitions

The key definitions used in this study were based on established criteria. Sepsis was defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, in accordance with the Sepsis-3 definition.[1] Septic acute kidney injury (AKI) was defined as Stage 1 or higher kidney disease according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification.[22] Septic acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition,[23] while septic disseminated intravascular coagulation (DIC) was defined according to the Japanese Association for Acute Medicine DIC diagnostic criteria.[24] Septic shock was defined in accordance with the Sepsis-3 definition.[1]

Statistical Analysis

Categorical data are shown as percentages and were compared by Fisher's exact test. Continuous data are shown as medians with interquartile ranges and were compared by the Mann–Whitney-*U* test. ROC curves were generated for presepsin levels, inflammation-based prognostic scores, and iPS, and areas under the curve (AUCs), cut-off values, sensitivities, and specificities were calculated. Presepsin levels immediately after ICU entry and variables with $P<0.005$ in the univariate analysis (inflammation-based prognostic scores, iPS, Sequential Organ Failure Assessment (SOFA) score, and quick SOFA (qSOFA) score) were examined further by multivariate logistic regression analysis with a Cox proportional hazard model for the prediction of 28-day mortality. In addition, the Log rank test was used to compare the prognostic ability of presepsin levels and variables with $P<0.005$ in the univariate analysis. As sub-analyses, multivariate logistic regression analysis with a Cox proportional hazard model and the Log rank test were performed for patients with septic complications (AKI, ARDS, shock, and DIC) in the over 75 and under 75 groups. $P<0.05$ was considered statistically significant. JMP software version 11.0.0 (SAS Institute Inc, NC) was used for all statistical analyses.

Results

Patient Characteristics (Tables 1 and 2)

Baseline characteristics for the patient cohort (n=83) are shown in Table 1. The overall mortality rate was 31.3%, while the 28-day mortality rate was 21.7%. There were no significant differences in age, sex, and underlying conditions between the over 75 group and under 75 group (Table 2). Among all candidate variables examined, including established clinical scores such as SOFA and qSOFA and all other composite scores, iPS-PI was the only predictor that demonstrated a P-value of less than 0.005 in the univariate analysis for 28-day mortality within the septic shock sub-analysis ($P=0.0045$, Table 2).

Table 2 Predictors of 28-Day Mortality (Univariate Analysis)

Variable	Over 75 Group		Under 75 Group	
	Non-Survivors: n = 12		Non-Survivors: n = 6	
	U-value	P value	U-value	P value
Main analysis:				
Age	147.5	0.441	64.5	0.135
Sex	-	1.000	-	1.000
Cancer	-	0.325	-	0.679
Coronary artery disease	-	1.000	-	0.386
Diabetes mellitus	-	0.543	-	1.000
Hypertension	-	0.694	-	0.143
Albumin	90.0	0.016	63.0	0.316
CRP	100.0	0.034	89.0	0.555
WBC	159.0	0.667	93.0	0.658
Neutrophil	153.0	0.547	81.0	0.376
Lymphocytes	149.0	0.474	78.0	0.319
Platelet count	154.0	0.567	87.0	0.507
Fibrinogen	105.0	0.429	54.0	0.483
AKI	-	0.181	-	0.377
ARDS	-	0.139	-	0.009
Shock	-	1.000	-	0.388
DIC	-	0.300	-	0.393
Presepsin on Day 1	61.0	0.001	42.0	0.020
Presepsin on Day 2	29.0	0.047	62.0	0.516
Presepsin on Day 3	3.0	0.005	37.0	0.455
Presepsin on Day 5	0.0	0.003	35.0	0.808
GPS	156.0	0.564	78.0	0.300
NLR	159.0	0.667	93.0	0.658
PLR	142.0	0.359	88.0	0.531
PI	121.0	0.105	78.0	0.265
PNI	82.0	0.008	65.0	0.140
iPS-GPS	100.0	0.022	64.5	0.104
iPS-NLR	85.5	0.005	80.0	0.326
iPS-PLR	62.0	< 0.001	85.0	0.423
iPS-PI	62.0	0.001	79.5	0.303
iPS-PNI	159.0	0.580	87.0	0.434
SOFA	143.5	0.380	61.0	0.103
qSOFA	162.5	0.730	69.0	0.163
Sub-analysis:				
AKI				
Presepsin on Day 1	-	0.013	-	0.167
GPS	-	0.861	-	0.281
NLR	-	0.537	-	0.750
PLR	-	0.877	-	1.000
PI	-	1.000	-	0.069
PNI	-	0.090	-	0.671
iPS-GPS	-	0.035	-	0.256
iPS-NLR	-	0.031	-	0.532
iPS-PLR	-	0.002	-	0.601
iPS-PI	-	0.008	-	0.720
iPS-PNI	-	0.104	-	0.907

(*Continued*)

https://doi.org/10.2147/IJGM.S585341

Table 2 (Continued).

Variable	Over 75 Group		Under 75 Group	
	Non-Survivors: n = 12		Non-Survivors: n = 6	
	U-value	P value	U-value	P value
SOFA	-	0.269	-	0.082
qSOFA	-	0.297	-	0.648
ARDS				
Presepsin on Day 1	-	0.564	-	0.564
GPS	-	0.221	-	0.495
NLR	-	0.564	-	0.386
PLR	-	0.564	-	0.386
PI	-	0.128	-	0.096
PNI	-	0.564	-	0.149
iPS-GPS	-	0.221	-	0.647
iPS-NLR	-	0.197	-	0.752
iPS-PLR	-	0.128	-	0.647
iPS-PI	-	0.221	-	0.495
iPS-PNI	-	0.197	-	0.222
SOFA	-	0.076	-	0.456
qSOFA	-	0.197	-	0.040
Shock				
Presepsin on Day 1	-	0.043	-	0.018
GPS	-	0.254	-	0.461
NLR	-	0.533	-	0.720
PLR	-	0.119	-	0.182
PI	-	0.589	-	0.653
PNI	-	0.087	-	0.345
iPS-GPS	-	0.015	-	0.078
iPS-NLR	-	0.221	-	0.183
iPS-PLR	-	0.006	-	0.483
iPS-PI	-	0.005	-	0.130
iPS-PNI	-	0.370	-	1.000
SOFA	-	0.740	-	0.163
qSOFA	-	0.625	-	0.160
DIC				
Presepsin on Day 1	-	0.125	-	0.139
GPS	-	1.000	-	0.843
NLR	-	0.555	-	0.815
PLR	-	0.479	-	0.312
PI	-	0.724	-	0.271
PNI	-	0.059	-	0.484
iPS-GPS	-	0.158	-	0.617
iPS-NLR	-	0.203	-	0.559
iPS-PLR	-	0.010	-	0.608
iPS-PI	-	0.084	-	1.000
iPS-PNI	-	0.765	-	0.498
SOFA	-	0.036	-	0.479
qSOFA	-	0.617	-	0.709

Abbreviations: CRP, C-reactive protein; WBC, white blood cell; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; GPS, Glasgow Prognostic Score; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PI, Prognostic Index; PNI, Prognostic Nutritional Index; SOFA, Sequential Organ Failure Assessment; qSOFA, quick SOFA.

Predictive Performance and Age-Dependent AUCs (Table 3)

The AUCs of presepsin, iPS-PLR, and iPS-PI for predicting mortality were higher (0.82) in the over 75 group than in the under 75 group (Table 3). iPS-PI achieved a high AUC (0.82) in the over 75 group (Table 3).

Table 3 Receiver Operating Characteristic Curve Analysis (28-Day Mortality)

Variable	AUC	Cut-Off	P value	Sensitivity	Specificity
Main analysis:					
Over 75 group					
Presepsin on Day 1 (pg/mL)	0.82	1340.00	< 0.001	0.83	0.79
Presepsin on Day 2 (pg/mL)	0.77	1581.00	0.051	0.83	0.76
Presepsin on Day 3 (pg/mL)	0.96	1819.00	< 0.001	1.00	0.89
Presepsin on Day 5 (pg/mL)	1.00	3011.00	< 0.001	1.00	1.00
GPS	0.66	2.00	0.046	0.67	0.62
NLR	0.54	22.99	0.706	0.50	0.62
PLR	0.59	387.90	0.365	0.58	0.69
PI	0.65	1.00	0.063	0.92	0.41
PNI	0.76	25.55	0.001	0.75	0.69
iPS-GPS	0.81	1.00	< 0.001	1.00	0.48
iPS-NLR	0.75	1.00	< 0.001	0.92	0.48
iPS-PLR	0.82	1.00	< 0.001	1.00	0.52
iPS-PI	0.82	2.00	< 0.001	0.67	0.86
iPS-PNI	0.54	2.00	0.614	0.17	0.93
Under 75 group					
Presepsin on Day 1 (pg/mL)	0.80	1275.00	0.004	0.83	0.66
Presepsin on Day 2 (pg/mL)	0.59	1186.00	0.567	0.67	0.56
Presepsin on Day 3 (pg/mL)	0.61	1156.00	0.496	0.60	0.68
Presepsin on Day 5 (pg/mL)	0.63	760.00	0.539	0.75	0.67
GPS	0.62	2.00	0.291	0.67	0.56
NLR	0.56	10.13	0.683	0.67	0.51
PLR	0.58	384.11	0.513	0.83	0.43
PI	0.63	1.00	0.099	1.00	0.31
PNI	0.69	15.61	0.234	0.67	0.91
iPS-GPS	0.69	2.00	0.134	0.50	0.86
iPS-NLR	0.62	1.00	0.287	0.83	0.43
iPS-PLR	0.60	1.00	0.370	0.83	0.40
iPS-PI	0.62	2.00	0.245	0.50	0.66
iPS-PNI	0.59	0.00	0.585	0.33	0.97
Sub-analysis:					
AKI: Over 75 group					
Presepsin on Day 1 (pg/mL)	0.83	1373.00	0.001	0.88	0.83
GPS	0.52	1.00	0.863	0.50	0.58
NLR	0.58	9.50	0.602	0.63	0.67
PLR	0.52	387.90	0.888	0.38	0.83
PI	0.50	1.00	1.000	0.88	0.33
PNI	0.73	20.41	0.068	0.50	1.00
iPS-GPS	0.75	2.00	0.006	0.38	0.92
iPS-NLR	0.77	1.00	0.009	0.88	0.58
iPS-PLR	0.88	1.00	< 0.001	1.00	0.67
iPS-PI	0.83	2.00	< 0.001	0.75	0.83
iPS-PNI	0.68	1.00	0.056	1.00	0.25

(*Continued*)

Table 3 (Continued).

Variable	AUC	Cut-Off	P value	Sensitivity	Specificity
AKI: Under 75 group					
Presepsin on Day 1 (pg/mL)	0.73	1679.00	0.226	0.75	0.71
GPS	0.65	2.00	0.302	0.50	0.77
NLR	0.55	15.01	0.757	0.75	0.50
PLR	0.50	384.11	1.000	1.00	0.36
PI	0.78	1.00	0.003	1.00	0.50
PNI	0.57	13.76	0.744	0.50	0.93
iPS-GPS	0.68	2.00	0.317	0.50	0.86
iPS-NLR	0.60	2.00	0.548	0.50	0.64
iPS-PLR	0.58	1.00	0.635	0.75	0.36
iPS-PI	0.55	2.00	0.727	0.50	0.57
iPS-PNI	0.52	0.00	0.927	0.25	0.93
ARDS: Over 75 group					
Presepsin on Day 1 (pg/mL)	0.67	1567.00	0.655	1.00	0.50
GPS	0.75	2.00	0.317	1.00	0.50
NLR	0.67	9.50	0.617	0.67	1.00
PLR	0.67	387.90	0.617	0.67	1.00
PI	0.92	2.00	< 0.001	0.67	1.00
PNI	0.67	21.79	0.617	0.67	1.00
iPS-GPS	0.75	2.00	0.317	1.00	0.50
iPS-NLR	0.83	1.00	0.074	1.00	0.50
iPS-PLR	0.92	2.00	< 0.001	0.67	1.00
iPS-PI	0.75	2.00	0.317	1.00	0.50
iPS-PNI	0.83	1.00	0.074	1.00	0.50
ARDS: Under 75 group					
Presepsin on Day 1 (pg/mL)	0.63	1275.00	0.584	0.75	0.50
GPS	0.63	2.00	0.513	0.75	0.50
NLR	0.69	27.53	0.399	0.50	1.00
PLR	0.69	356.94	0.444	0.75	0.75
PI	0.81	1.00	0.012	1.00	0.50
PNI	0.81	15.61	0.114	0.75	1.00
iPS-GPS	0.59	2.00	0.671	0.50	0.75
iPS-NLR	0.56	1.00	0.773	0.75	0.50
iPS-PLR	0.59	1.00	0.671	0.75	0.50
iPS-PI	0.63	1.00	0.513	0.75	0.50
iPS-PNI	0.75	0.00	0.190	0.50	1.00
Shock: Over 75 group					
Presepsin on Day 1 (pg/mL)	0.79	1373.00	0.007	0.83	0.73
GPS	0.64	2.00	0.229	0.67	0.60
NLR	0.59	4.57	0.653	0.50	0.93
PLR	0.72	387.90	0.084	0.67	0.80
PI	0.57	1.00	0.487	1.00	0.33
PNI	0.74	21.06	0.034	0.67	0.80
iPS-GPS	0.82	2.00	< 0.001	0.50	0.93
iPS-NLR	0.66	1.00	0.210	0.83	0.40
iPS-PLR	0.87	1.00	< 0.001	1.00	0.60
iPS-PI	0.87	2.00	< 0.001	0.83	0.87
iPS-PNI	0.58	2.00	0.386	0.17	0.93

(*Continued*)

Table 3 (Continued).

Variable	AUC	Cut-Off	P value	Sensitivity	Specificity
Shock: Under 75 group					
Presepsin on Day 1 (pg/mL)	0.85	1679.00	0.003	0.80	0.81
GPS	0.60	2.00	0.465	0.60	0.57
NLR	0.55	5.54	0.739	0.80	0.52
PLR	0.70	356.94	0.126	0.80	0.52
PI	0.56	1.00	0.585	1.00	0.19
PNI	0.64	14.03	0.487	0.60	0.95
iPS-GPS	0.74	2.00	0.123	0.60	0.90
iPS-NLR	0.68	1.00	0.170	0.80	0.52
iPS-PLR	0.60	1.00	0.460	0.80	0.43
iPS-PI	0.70	2.00	0.065	0.60	0.71
iPS-PNI	0.50	0.00	1.000	0.20	0.95
DIC: Over 75 group					
Presepsin on Day 1 (pg/mL)	0.74	1567.00	0.080	0.83	0.67
GPS	0.50	2.00	1.000	0.50	0.44
NLR	0.59	6.17	0.647	0.50	1.00
PLR	0.61	214.15	0.525	0.83	0.56
PI	0.55	1.00	0.734	0.83	0.22
PNI	0.80	25.55	0.014	0.67	0.78
iPS-GPS	0.69	2.00	0.107	0.33	0.89
iPS-NLR	0.69	1.00	0.179	0.83	0.44
iPS-PLR	0.86	1.00	< 0.001	1.00	0.67
iPS-PI	0.74	2.00	0.050	0.67	0.78
iPS-PNI	0.53	2.00	0.782	0.17	0.89
DIC: Under 75 group					
Presepsin on Day 1 (pg/mL)	0.79	4560.00	0.187	0.67	1.00
GPS	0.53	2.00	0.867	0.33	0.73
NLR	0.55	15.01	0.867	0.67	0.55
PLR	0.70	295.53	0.164	1.00	0.64
PI	0.70	1.00	0.161	1.00	0.36
PNI	0.64	13.76	0.628	0.67	0.91
iPS-GPS	0.59	1.00	0.670	0.67	0.45
iPS-NLR	0.61	2.00	0.634	0.67	0.64
iPS-PLR	0.59	2.00	0.697	0.33	0.91
iPS-PI	0.50	1.00	1.000	0.67	0.45
iPS-PNI	0.62	1.00	0.586	0.67	0.45

Abbreviations: AUC, area under the curve; GPS, Glasgow Prognostic Score; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PI, Prognostic Index; PNI, Prognostic Nutritional Index; iPS, inflammation-Presepsin score; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation.

Independent Predictors of Mortality (Table 4)

In the sub-analyses focused on extremely elderly septic shock patients, iPS-PI (Hazard Ratio 14.22, P=0.031) was suggested as a potential independent predictor of mortality in the Cox proportional hazard model, whereas presepsin alone was not (P=0.656) (Table 4).

Survival Analysis (Figure 2 and Table 4)

The Log rank test demonstrated that patients stratified by iPS-PI showed a highly significant difference in survival curves (P=0.003) in extremely elderly septic shock patients (Figure 2 and Table 4).

Table 4 Predictors of 28-Day Mortality in the Over 75 Group (Multivariate Analysis, Log Rank Test, Septic Shock Patients)

Variable Non-survivors n=6	Odds (Hazard) Ratio	95% CI		*P* value
Logistic regression analysis				
Presepsin on Day 1	1.00	1.00	1.00	0.483
iPS-PI	66.60	1.30	3402.88	0.036
Cox proportional hazard model				
Presepsin on Day 1	1.00	1.00	1.00	0.656
iPS-PI	14.22	1.27	159.30	0.031
Log rank test				
Presepsin on Day 1				0.151
iPS-PI (Chi-square=8.56, df=1)				0.003

Abbreviations: CI, confidence interval; iPS, inflammation-presepsin score; PI, Prognostic Index.

Predictive Performance of uNGAL (Tables 5 and 6)

As an additional investigation within the same patient cohort, a comparative study was performed with urinary NGAL (uNGAL), a widely recognized early kidney injury biomarker.[7] uNGAL levels were a more accurate predictor of septic AKI in the over 75 group than in the under 75 group. Specifically, uNGAL levels on Days 1 to 4 were significant predictors of septic AKI in the over 75 group ($P<0.05$ in univariate analysis), with AUCs being significantly higher (>0.8) in the over 75 group. In particular, uNGAL levels on Day 2 showed the highest predictive capability for 28-day and 60-day mortality in the over 75 group (AUC, 0.85; cut-off, 851.2 ng/mL; Table 5). However, the multivariate analysis for both AKI development and mortality prediction did not establish uNGAL as a significant independent predictor (Table 6).

Discussion

Prognostic Value of iPS-PI: Integrating Robustness and Accuracy

The central finding that iPS-PI (AUC 0.82, Table 3) is the most robust prognostic marker among those assessed in extremely elderly sepsis patients confirms its age-specific clinical relevance. The clinical utility of iPS-PI over other

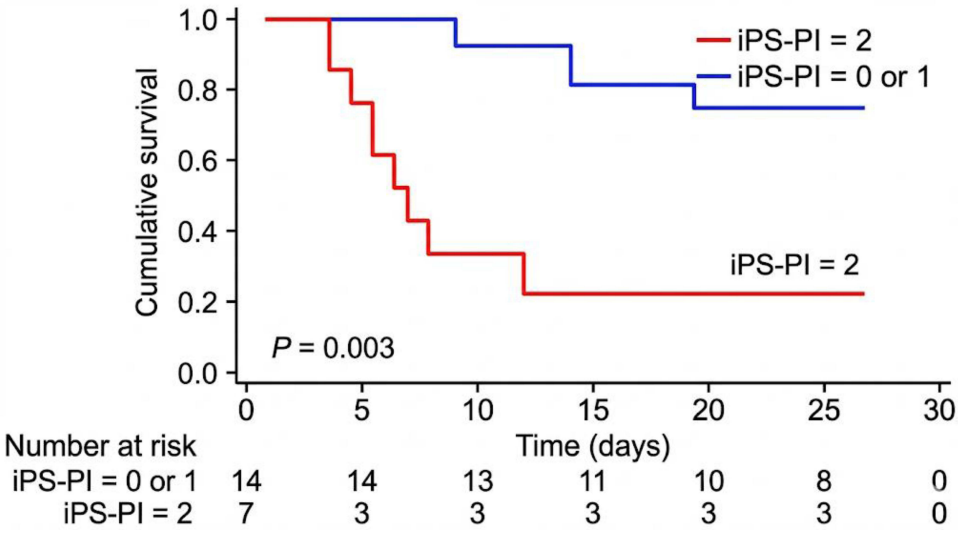

Figure 2 Kaplan–Meier Survival Curve for the Extremely Elderly Septic Shock Patients (Age ≥75 Years) Stratified by the Composite Inflammation–Presepsin Score–Prognostic Index (iPS-PI). The Kaplan–Meier curve compares 28-day survival between extremely elderly septic shock patients (age ≥75 years) with a high iPS-PI (≥2) and those with a low iPS-PI (<2). The high iPS-PI group demonstrated significantly lower 28-day survival compared to the low iPS-PI group.
Abbreviations: iPS-PI, Inflammation–Presepsin Score-Prognostic Index.

Table 5 Receiver Operating Characteristic Curve Analysis for 28-Day Mortality in the Over 75 Group

Variable	AUC	Cut-Off	P value	Sensitivity	Specificity
Over 75 group 28-day mortality: NGAL on Day 2 (ng/mL)	0.85	851.20	0.002	1.00	0.73

Abbreviations: AUC, area under the curve; NGAL, Neutrophil gelatinase-associated lipocalin.

Table 6 Predictors of 28-Day Mortality in Extremely Elderly Septic Shock Patients (≥75 Years) (Multivariate Analysis of iPS-PI and NGAL Day 2)

Variable	Hazard Ratio	95% CI		*P* value
Cox proportional hazard model				
NGAL on Day 2	1.00	1.00	1.01	0.307
iPS-PI	0.02	0.00	44.92	0.316

Abbreviations: CI, confidence interval; NGAL, Neutrophil gelatinase-associated lipocalin; iPS, inflammation-presepsin score; PI, Prognostic Index.

scores is rooted in its ability to integrate acute infection status (presepsin) with the patient's underlying host inflammatory response (PI score). This dual assessment is critical in the geriatric population, where outcomes depend not only on the initial infection but also on the patient's underlying frailty and chronic inflammation.

Clinical Imperative: Independent Predictive Power for Intervention

The most clinically compelling result of this study is that iPS-PI was suggested to be a potential independent predictor of mortality, whereas presepsin alone was not, in extremely elderly septic shock patients (Table 4). This suggests that iPS-PI may address the potential confounding and instability noted with single biomarkers.[25] A high iPS-PI should trigger time-critical, aggressive therapeutic protocols,[4,26] or prompt an accelerated review for appropriate goals of care, making it an essential "rule in" tool immediately after ICU admission. iPS-PI directly addresses the need for a reliable, early objective marker to circumvent the diagnostic ambiguity often encountered in geriatric sepsis.

The clinical utility of iPS-PI is further confirmed by our separate investigation into the same patient cohort (Shimoyama et al, unpublished data). While iPS-PI used in this study was derived using 28-day mortality as the primary cut-off endpoint, its robust predictive power aligns with the findings of our previous study (Shimoyama et al, unpublished data), where iPS-PI was derived using the progression from septic subclinical AKI to overt AKI as the ROC endpoint. This concordance suggests that iPS effectively captures a fundamental, broad inflammatory state relevant to multiple severe outcomes in the elderly. In our previous multivariate analysis of the present study's cohort for AKI development, while presepsin levels alone were not a significant independent predictor for AKI development, iPS-PI was a robust, significant independent predictor (P=0.028) (Shimoyama et al, unpublished data). This dual predictive power (mortality and the progression of severe complications) underscores the robustness of iPS-PI for assessing time-sensitive risk in extremely elderly patients.

Comparison with Neutrophil Gelatinase-Associated Lipocalin (NGAL)

uNGAL, a single, organ-specific biomarker, was not established as a significant independent predictor of mortality or AKI development in the multivariate analysis (Table 6). It is notable that the independent predictive value of iPS-PI was attenuated in this multivariate analysis (P=0.316) (Table 6). This result should be interpreted in the context of temporal assessment; although uNGAL on Day 2 showed high predictive capability for mortality (AUC, 0.85; Table 5), the measurement was performed 24 hours later than the measurement for iPS-PI on Day 1. Therefore, uNGAL on Day 2 acts as an extremely powerful downstream prognostic factor (confounder) within the model, reflecting the unique and critical

impact of severe renal injury in the highly vulnerable elderly population. Importantly, this finding does not contradict our main conclusion regarding the utility of iPS-PI over presepsin alone. Instead, it reaffirms iPS-PI's role as a readily measurable, general systemic risk indicator available immediately upon ICU admission, which is distinct from and complementary to a later-stage marker of isolated organ failure like uNGAL on Day 2.

Limitation

Given the limited number of events, the potential for overfitting in the multivariate models should be acknowledged. A limitation of this study is the small, single-center cohort size. Specifically, the sub-analysis of septic shock patients (Table 4) was based on a very small number of non-survivors (n=6), and thus, the strong association observed (HR 14.22), which was accompanied by a very wide 95% confidence interval (1.27–159.30), should be interpreted as preliminary and warrants further validation in a larger, multicenter cohort. The observed higher cut-off values for presepsin in the over 75 group suggest the need for higher age-specific cut-off values,[20,21] a biological difference supported by studies showing altered hematopoietic differentiation, particularly of the monocyte/macrophage lineage which produces the CD14 precursor of presepsin, in aging.[27,28]

Conclusions

Presepsin and iPS-PI are more useful as predictors of mortality in extremely elderly sepsis patients than in younger sepsis patients, reflecting an age-dependent shift in biomarker utility. Furthermore, iPS-PI may be a more robust, independent predictor of mortality than presepsin alone in extremely elderly septic shock patients. iPS-PI is a promising tool for early risk stratification, providing a clear and immediate signal to guide timely, individualized, and aggressive therapeutic interventions in this vulnerable demographic, thereby addressing the diagnostic challenge unique to geriatric sepsis management.

Abbreviations

iPS, Inflammation-Presepsin Score; PI, Prognostic Index; HR, Hazard Ratio; AUC, Area Under the Curve; ICU, Intensive Care Unit; NGAL, Neutrophil Gelatinase-Associated Lipocalin; uNGAL, Urinary Neutrophil Gelatinase-Associated Lipocalin; PCT, Procalcitonin; CRP, C-reactive protein; GPS, Glasgow Prognostic Score; NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; PNI, Prognostic Nutritional Index; ROC, Receiver Operating Characteristic; SOFA, Sequential Organ Failure Assessment; qSOFA, quick Sequential Organ Failure Assessment; AKI, Acute Kidney Injury; ARDS, Acute Respiratory Distress Syndrome; DIC, Disseminated Intravascular Coagulation; CLEIA, Chemiluminescent Enzyme Immunoassay; KDIGO, Kidney Disease: Improving Global Outcomes.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Written informed consent was obtained from all patients enrolled in this study or the next of kin if it was difficult to obtain consent from patients at the time of ICU admission (eg, patients under sedation or those with impaired consciousness). The study protocol was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University in Osaka, Japan (No. 2206), and was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). All methods were carried out in accordance with relevant guidelines and regulations.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded solely by institutional and/or departmental sources and personal research expenses of Osaka Medical and Pharmaceutical University, and the funders had no role in the study design, data collection, data analysis, manuscript preparation, or decision to publish.

Disclosure

The authors report no conflicts of interest in this work.

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