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Association between 30-day mortality and peak procalcitonin levels or early procalcitonin kinetics in patients with markedly elevated procalcitonin: a single-center retrospective study

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Abstract

Background

Procalcitonin (PCT) is commonly utilized in the diagnosis and management of sepsis; however, its absolute concentration may have limited prognostic value. The prognostic value of peak PCT concentrations and early PCT kinetics among patients with markedly elevated PCT concentrations remains uncertain.

Methods

This single-center retrospective study included patients with sepsis admitted to the intensive care unit (ICU) or high care unit (HCU) between April 2022 and October 2024, with a peak PCT concentration of ≥ 40 ng/mL during hospitalization. All 145 eligible patients were included in the analysis of peak PCT concentrations. Of these, 94 patients with PCT measurements on ICU/HCU admission (Day 0) and Day 3 were included in the PCT kinetics analysis. Receiver operating characteristic analysis with the Youden index for 30-day mortality was employed to identify cutoff values for peak PCT and the percentage reduction in PCT from Days 0 to 3 (ΔPCT). Subsequently, patient characteristics were compared between the two groups. Furthermore, 30-day survival was assessed using Kaplan–Meier analysis, whereas factors associated with 30-day mortality were evaluated using logistic regression.

Results

The area under the curve for the peak PCT was 0.655, with an optimal cutoff of 96 ng/mL. Patients with peak PCT ≥ 96 ng/mL exhibited significantly lower 30-day survival rates than those with concentrations ranging from 40 to 95.9 ng/mL. For ΔPCT, the area under the curve was 0.829, with 」 」 survival rates than those with a ΔPCT ≥ 70%. In the multivariable analysis, higher Sequential Organ Failure Assessment (SOFA) scores were independently associated with increased odds of 30-day mortality, whereas greater ΔPCT values were independently associated with lower odds of mortality. Contrarily, peak PCT concentration showed no independent association with 30-day mortality.

Conclusions

Among patients with sepsis and markedly elevated PCT concentrations, early PCT reduction by Day 3 exhibited an independent association with 30-day mortality, whereas peak PCT concentrations did not. Assessment of early PCT kinetics alongside the degree of organ dysfunction may offer greater prognostic value than considering absolute peak PCT concentration alone.

Keywords: sepsis; procalcitonin; procalcitonin kinetics; biomarker; 30-day mortality; intensive care

Background

Procalcitonin (PCT), a precursor peptide of calcitonin, is released by parenchymal cells throughout the body in response to inflammatory signals associated with bacterial infections. Serum PCT concentrations increase early following bacterial infection and relatively decrease rapidly when the infection is controlled. Accordingly, PCT is commonly employed as an adjunctive marker for sepsis diagnosis, treatment response monitoring, and antimicrobial stewardship. However, the absolute PCT concentration is influenced by various factors, including the timing of measurement relative to infection onset, infection site, causative microorganisms, organ dysfunction, renal function, and surgical stress. A single PCT measurement may be insufficient for assessing disease severity and prognosis; therefore, serial changes should also be considered.

Previous studies have suggested that initial or maximum PCT concentrations are associated with disease severity and mortality; however, the prognostic value of the absolute PCT concentration alone remains limited. Meanwhile, inadequate PCT reductions following treatment initiation have been associated with poor outcomes [1-5]. Most previous studies examining the prognostic value of PCT have included broad populations of patients with sepsis, in whom PCT concentrations were

generally below levels considered clinically markedly elevated. In particular, clinicians frequently encounter critically ill patients with septic shock or multiple organ dysfunction and markedly elevated PCT concentrations in the intensive care unit (ICU) or high care unit (HCU). Therefore, it remains unclear whether findings from populations comprising many patients with relatively lower PCT concentrations can be directly extrapolated to critically ill patients with markedly elevated concentrations, highlighting the need to investigate this high-risk population.

This study investigated patients meeting the Sepsis-3 criteria who were admitted to the ICU or HCU and had a peak PCT concentration of ≥ 40 ng/mL during hospitalization. The associations of peak PCT and PCT reduction by Day 3 following ICU/HCU admission with 30-day mortality were evaluated. This study aimed to determine the prognostic value of absolute peak PCT concentrations and early PCT kinetics among patients with sepsis and markedly elevated PCT concentrations.

Methods

Study design and ethical considerations

This retrospective, single-center observational study was conducted at Kawasaki Medical School General Medical Center. Medical records and laboratory data of patients with sepsis admitted to the ICU or HCU between April 2022 and October 2024 were retrospectively reviewed. The study adhered to the principles of the Declaration of Helsinki and received approval from the Ethics Committee of Kawasaki Medical School (approval no. 6549-01). Given the retrospective nature of the study and its reliance on existing clinical information, the requirement for written informed consent was waived. Instead, an opt-out procedure was implemented, whereby study information was publicly disclosed and patients were provided with the opportunity to decline participation. The study was reported in accordance with the STROBE guidelines.

Study population

Patients with sepsis who were admitted to the ICU or HCU during the study period and whose maximum serum PCT concentrations were ≥ 40 ng/mL during the index hospitalization (peak PCT) were considered eligible.

All 145 eligible patients were included in the analysis of the association between peak PCT concentrations and 30-day mortality. The analysis of PCT kinetics included 94 patients with available PCT measurements on ICU/HCU admission and on Day 3 to evaluate the association between changes in PCT concentrations over time and 30-day mortality. A total of 51 patients were excluded from the PCT kinetics analysis, including 12 who died within 3 days of ICU/HCU admission and 39 for whom Day 3 PCT measurements were unavailable.

Data collection

Demographic, clinical, laboratory, and outcome data were extracted from electronic medical records, including age, sex, height, body weight, comorbidities, surgical status, PCT concentrations, Sequential Organ Failure Assessment (SOFA) score, ICU/HCU length of stay, and clinical outcomes. The comorbidities assessed included hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, chronic heart failure, chronic liver disease, and renal dysfunction. The day of ICU/HCU admission was designated as Day 0, and PCT concentrations measured from Days 0 to 3, alongside PCT measurements obtained during the index hospitalization, were collected. The SOFA score was determined based on clinical and laboratory data obtained at ICU/HCU admission. Sepsis was diagnosed in accordance with the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Serum PCT concentrations were measured using the Alinity i chemiluminescent immunoassay system (Abbott Japan LLC, Tokyo, Japan). PCT concentrations on Days 1 to 3 were obtained from blood samples

collected during routine morning laboratory testing. Peak PCT was defined as the highest PCT concentration recorded during the index hospitalization.

Patient classification according to PCT

The discriminative performance of peak PCT for predicting 30-day mortality was assessed using receiver operating characteristic (ROC) curve analysis. The optimal cutoff value was determined by identifying the value that yielded the highest Youden index. Using the resulting cutoff of 96 ng/mL, patients were categorized into two groups:

- H group: peak PCT ≥ 96 ng/mL
- L group: peak PCT ≥ 40 ng/mL and < 96 ng/mL

Baseline characteristics, comorbidities, PCT concentrations at ICU/HCU admission, SOFA scores, ICU/HCU length of stay, serial PCT concentrations, and 30-day survival outcomes were compared between the groups.

Among the 94 patients included in the PCT kinetics analysis, the percentage change in PCT concentration between ICU/HCU admission and Day 3 (ΔPCT) was calculated as follows:

$$PCT\ reduction\ (\%) = [(PCT\ on\ Day\ 0 - PCT\ on\ Day\ 3) / PCT\ on\ Day\ 0] \times 100$$

The ability of ΔPCT to predict 30-day mortality was assessed using ROC curve analysis. The optimal cutoff was determined as the value that maximized the Youden index. Using the resulting cutoff of 70%, patients were stratified into two groups:

- Class I: ΔPCT < 70%
- Class II: ΔPCT ≥ 70%

Baseline characteristics, comorbidities, surgical status, SOFA scores, ICU/HCU length of stay, serial PCT concentrations, and 30-day survival outcomes were compared between the two classes.

Outcomes

The primary outcome was all-cause mortality within 30 days following ICU/HCU admission. The secondary and exploratory outcomes included ICU/HCU length of stay, SOFA score at ICU/HCU admission, and serial changes in PCT concentration from Days 0 to 3.

Statistical analysis

Continuous variables with a normal distribution were expressed as mean ± standard deviation and compared between the two groups using unpaired Student's *t*-test. Contrarily, continuous variables with a non-normal distribution were expressed as median [interquartile range] and compared using the Mann–Whitney U test. Categorical variables were expressed as number and percentage and compared using the chi-squared test or Fisher's exact test, as appropriate. Serial PCT concentrations from Days 0 to 3 were descriptively summarized as medians with interquartile ranges at each time point. No statistical between-group comparisons were conducted to evaluate longitudinal changes in PCT concentrations. The discriminative ability of peak PCT and ΔPCT for 30-day mortality was assessed using ROC curve analysis, with the corresponding area under the curve (AUC) calculated. The optimal cutoff was determined as the value that yielded the highest Youden index. Furthermore, 30-day survival was analyzed using the Kaplan–Meier method, with between-group differences assessed using the log-rank test. Hazard ratios and their corresponding 95% confidence intervals (CIs) were estimated using univariable Cox proportional hazards regression. The proportions of 30-day mortality were also compared between the groups, with unadjusted odds ratios (ORs) and corresponding 95% CIs calculated.

Among the 94 patients included in the PCT kinetics analysis, logistic regression was conducted using 30-day mortality as the dependent variable. Age was included in the multivariable model as a clinically important potential confounder, alongside the SOFA score, peak PCT, and ΔPCT, all of which demonstrated significant associations in the univariable analysis. The OR for the SOFA score

was calculated per 1-point increment, whereas that for ΔPCT was calculated per 10-percentage-point increment. ORs, 95% CIs, and *p*-values were reported for each explanatory variable.

All tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using JMP version 18.2.2 (SAS Institute Inc., Cary, NC, USA).

Results

Study population

A total of 145 patients with sepsis who were admitted to the ICU/HCU between April 2022 and October 2024 and had a PCT concentration of ≥ 40 ng/mL were considered eligible. The patients were classified into the H and L groups according to peak PCT. Among them, 94 who had PCT measurements at ICU/HCU admission and on Day 3 were included in the PCT reduction analysis, whereas 51 were excluded. A flowchart of the study population is presented in Figure. 1.

The baseline and clinical characteristics of the H and L groups are presented in Table 1. The H group comprised 68 patients, whereas the L group consisted of 77 patients. Patients in the L group were older than those in the H group, although the difference did not reach statistical significance (78.6 ± 14.0 vs. 74.1 ± 14.0 years, $p = 0.055$). No significant between-group differences were observed in sex, height, body weight, hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, chronic heart failure, chronic liver disease, renal dysfunction, or surgical status. PCT concentration at ICU/HCU admission was significantly higher in the H than in the L group (163.5 [103.4–234.3] ng/mL vs. 50.7 [40.1–63.9] ng/mL, $p < 0.001$). Furthermore, the SOFA score was significantly higher in the H group (9.2 ± 4.1 vs. 6.9 ± 3.5, $p < 0.001$), indicating greater severity at ICU/HCU admission. ICU/HCU length of stay tended to be

longer in the H group, but the difference did not reach statistical significance (11.9 ± 9.9 vs. 9.1 ± 10.5 days, $p = 0.092$).

Table 1

Baseline characteristics of patients stratified by peak PCT (<96 ng/mL vs. ≥96 ng/mL).

Variable	H group (n = 68)	L group (n = 77)	*P*-value
Age, years	74.1 ± 14.0	78.6 ± 14.0	0.055
Sex, male/female	41/27 (60/40%)	47/30 (61/39%)	0.927
Height, cm	158.9 ± 9.9	156.8 ± 10.5	0.219
Body weight, kg	53.4 ± 13.2	51.2 ± 13.2	0.319
Hypertension	44 (65%)	52 (68%)	0.720
Diabetes mellitus	25 (37%)	21 (27%)	0.283
Coronary artery disease	8 (12%)	8 (10%)	0.798
COPD	9 (13%)	7 (9%)	0.441
Chronic heart failure	14 (21%)	14 (18%)	0.834
Chronic liver disease	15 (22%)	14 (18%)	0.678
Renal dysfunction	56 (82%)	61 (79%)	0.678
Surgical	14 (21%)	19 (25%)	0.557
PCT at ICU admission, ng/mL	163.5[103.4-234.3]	50.7[40.1-63.9]	<0.001
SOFA score	9.2 ± 4.1	6.9 ± 3.5	<0.001
ICU length of stay, days	11.9 ± 9.9	9.1 ± 10.5	0.092

Data are expressed as mean ± standard deviation (SD), median [interquartile range], or n (%), as appropriate. Abbreviations: COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; PCT, procalcitonin; SOFA, Sequential Organ Failure Assessment.

The baseline and clinical characteristics of Class I and II patients are presented in Table 2. No significant between-class differences were observed in age, sex, comorbidities, surgical status, or ICU/HCU length of stay. The SOFA score tended to be higher in Class I, although the difference did not reach statistical significance (9.1 ± 3.5 vs. 7.9 ± 4.0, p=0.109). PCT at ICU/HCU admission

was significantly higher in Class II than in Class I (155.2 [64.9–234.3] ng/mL vs. 51.9 [36.1–109.5] ng/mL, $p < 0.001$).

Table 2

Baseline characteristics of patients stratified by PCT reduction rate (<70% vs. ≥70%).

Variable	Class I group (n = 50)	Class II group (n = 44)	*P*-value
Age, years	77.5 ± 15.6	74.6 ± 15.9	0.369
Sex, male/female	31/19 (62%/38%)	25/19 (57%/43%)	0.676
Height, cm	157.8 ± 9.9	157.7 ± 9.9	0.957
Body weight, kg	53.8 ± 13.4	49.5 ± 13.9	0.134
Hypertension	35 (70%)	25 (57%)	0.204
Diabetes mellitus	18 (36%)	10 (23%)	0.182
Coronary artery disease	4 (8%)	5 (11%)	0.729
COPD	7 (14%)	3 (7%)	0.327
Chronic heart failure	8 (16%)	5 (11%)	0.564
Chronic liver disease	11 (22%)	6 (14%)	0.421
Renal dysfunction	42 (84%)	34 (77%)	0.442
Surgical	16 (32%)	10 (23%)	0.316
PCT at ICU admission, ng/mL	51.9[36.1−109.5]	155.2[64.9−234.3]	<0.001
SOFA score	9.1 ± 3.5	7.9 ± 4.0	0.109
ICU length of stay, days	14.0 ± 10.6	11.9 ± 10.6	0.346

Data are expressed as mean ± standard deviation (SD), median [interquartile range], or n (%), as appropriate. Abbreviations: COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; PCT, procalcitonin; SOFA, Sequential Organ Failure Assessment.

Association of PCT with 30-day mortality

ROC analysis was conducted to evaluate the association between peak PCT and 30-day mortality. The AUC was 0.655, and the optimal peak PCT cutoff for predicting 30-day mortality was 96

ng/mL (Figure 2). Therefore, patients were classified into the high-PCT group (H group: peak PCT ≥ 96 ng/mL; n = 68) and low-PCT group (L group: peak PCT 40–95.9 ng/mL; n = 77). Kaplan–Meier analysis revealed significantly better 30-day survival in the L than in the H group (HR 2.97, 95% CI 1.45–6.07; $p = 0.0029$; Figure 2). Thirty-day mortality was significantly more frequent in the H than in the L group, occurring in 22 (32.4%) and 9 (11.7%) patients, respectively, with an unadjusted OR of 3.6 (95% CI: 1.53–8.55). Serial PCT concentrations from ICU/HCU admission to Day 3 in both groups are presented in Figure 4. The PCT concentrations were consistently higher in the H than in the L group from ICU/HCU admission to Day 3, with this difference persisting on Day 3. However, both groups exhibited a similar declining trend over time.

Subsequently, ROC curve analysis was conducted to evaluate the ability of PCT reduction from ICU/HCU admission to Day 3 to predict 30-day morality among the 94 patients included in the PCT kinetics analysis. The AUC was 0.829, with an optimal cutoff value of 70% (Figure 3). Patients who exhibited a PCT reduction < 70% were classified as Class I (n = 50) and those with a reduction ≥ 70% as Class II (n = 44). Kaplan–Meier analysis revealed significantly better 30-day survival in Class II than in Class I (HR 16.85, 95% CI 2.23–127.13; $p < 0.001$; Figure 3). Thirty-day mortality was significantly higher in Class I than in Class II, occurring in 16 (32.0%) and 1 (2.3%) patient, respectively, with an unadjusted OR of 20.2 (95% CI: 2.55–160.33). Serial PCT concentrations from ICU/HCU admission to Day 3 in Classes I and II are presented in Figure 4. The PCT concentrations showed little overall change in Class I. The median PCT concentration at ICU/HCU admission was higher in Class II than in Class I but subsequently decreased markedly and was lower in Class I by Day 3.

Logistic regression analysis

Logistic regression analysis was conducted among the 94 patients included in the PCT kinetics analysis, with 30-day mortality as the dependent variable (Table 3). Age, alongside the SOFA score,

peak PCT, and ΔPCT, which exhibited significant association in the univariable analysis, was incorporated into the multivariable logistic regression model. The SOFA score remained an independent predictor of 30-day mortality, with a 1-point increment corresponding to a 1.43-fold increase in the odds of mortality (adjusted OR 1.43, 95% CI 1.14–1.79; $p = 0.002$). ΔPCT also remained independently associated with 30-day mortality; each 10-percentage-point increment in ΔPCT was associated with an approximately 9% decrease in the odds of mortality (adjusted OR 0.91, 95% CI 0.84–0.99; $p = 0.022$). Contrarily, age and peak PCT exhibited no independent association with 30-day mortality.

Table 3

Univariable and multivariable logistic regression analyses.

Variable	Univariate OR	*P*-value	95% CI	Multivariate OR	P value	95% CI
Age, per 1-year increase	1.01	0.651	0.97–1.04	1.04	0.14	0.99-1.11
SOFA score, per 1-point increment	1.47	<0.001	1.21–1.78	1.43	0.002	1.14–1.79
Peak PCT, per 1 ng/mL increase	1.04	0.042	1.00–1.08	1.001	0.662	0.996-1.007
ΔPCT, per 10% increase in PCT reduction	0.91	0.002	0.84–0.96	0.91	0.022	0.84–0.99

Abbreviations: CI, confidence interval; OR, odds ratio; PCT, procalcitonin; SOFA, Sequential Organ Failure Assessment. ΔPCT was defined as percentage reduction in PCT from ICU/HCU admission to Day 3. An OR < 1.0 indicates that a greater reduction in PCT was associated with lower odds of 30-day mortality.

Discussion

This study investigated the prognostic value of the absolute PCT concentration and short-term PCT kinetics in patients meeting the Sepsis-3 criteria who required ICU/HCU admission and exhibited markedly elevated peak PCT concentration of ≥ 40 ng/mL during hospitalization. The major finding of this study was the strong association between the percentage reduction in PCT from Days 0 to 3 (ΔPCT) and 30-day mortality, with higher survival rates among patients whose PCT declined by ≥ 70% than among those who exhibited a < 70% reduction. Furthermore, ΔPCT remained independently associated with 30-day mortality following adjustment for age, SOFA score, and peak PCT. Contrarily, patients with peak PCT concentrations ≥ 96 ng/mL exhibited poorer unadjusted survival than those with lower peak concentrations; however, the ability of peak PCT concentration to predict 30-day mortality was only moderate. These findings indicate that, among patients with markedly elevated PCT concentrations, a ≥ 70% reduction over the subsequent 3 days may offer greater prognostic value than the absolute peak PCT concentration alone.

Schuetz et al. assessed patients with sepsis in whom the mean PCT concentration at enrollment in the derivation cohort was 32.6 ± 40.6 ng/mL [3]. A prospective study conducted by Pieralli et al. reported a mean PCT concentration of 28.06 ± 63.29 ng/mL at admission in the overall population [4]. Jensen et al. investigated 472 ICU patients and found that elevated PCT concentrations were associated with an increased risk of 90-day mortality [6]. However, the highest PCT category in their study covered a wide range of 50–1,000 ng/mL, limiting the characterization of prognostic risk specifically among patients with markedly elevated PCT concentrations. Given that the mean initial PCT concentrations reported in previous studies were approximately 28–33 ng/mL and that the highest category in Jensen et al.'s study began at 50 ng/mL, the PCT inclusion threshold of ≥ 40 ng/mL in the present study was intended to identify a population with more pronounced PCT elevation than that observed in conventional sepsis cohorts. A key feature of this study is that,

within the same population of patients with markedly elevated PCT, both PCT-based risk stratification and early PCT kinetics through Day 3 were examined.

Regarding peak PCT, the H group had higher SOFA scores and greater 30-day mortality, with an unadjusted HR of 2.97. Regarding the association between PCT and organ dysfunction, Castelli et al. demonstrated a weak but significant positive correlation between PCT concentrations and SOFA scores in a study involving serial measurements in ICU patients ($r = 0.254$, $p < 0.001$), with particularly high PCT concentrations observed in those with SOFA scores > 12 [7]. Similarly, Shi et al. demonstrated a significant positive correlation between peak PCT concentrations and sepsis severity ($r = 0.731$, $p = 0.002$) [8]. Regarding peak PCT and clinical outcomes, Rau et al. reported a significantly higher maximum PCT concentration in nonsurvivors than in survivors with secondary peritonitis (25.3 vs. 5.7 ng/mL, $p = 0.02$) [9]. Bloos et al. also reported that maximum PCT concentration predicted 28-day mortality in patients with severe pneumonia, with a mortality OR of 5.7 at a cutoff value of 7.8 ng/mL [10]. These findings support a potential association between higher peak PCT and poor outcomes. Contrarily, Ryu et al. reported that the initial peak PCT, determined using measurements from the day before ICU admission to ICU Day 2, was not associated with 28-day mortality in patients with severe sepsis or septic shock, whereas PCT clearance was associated with outcome [11]. Therefore, although peak PCT may predict disease severity and mortality risk, the absolute peak concentration alone has limitations as an independent prognostic marker.

Our findings on PCT kinetics are consistent with previous evidence indicating that serial changes in PCT concentration provide useful prognostic information in patients with sepsis. A meta-analysis conducted by Liu et al. revealed that the prognostic performance of initial PCT concentrations was limited, whereas PCT non-clearance was associated with a higher mortality risk (pooled risk ratio 3.05, 95% CI 2.35–3.95; summary ROC AUC 0.79) [1]. Karlsson et al. reported lower in-hospital

mortality among patients who exhibited PCT reduction of > 50% within 72 h than among those who showed a reduction of < 50% (12.2% vs. 29.8%, $p = 0.007$). However, this association was not significant in the multivariable analysis (OR 0.99, 95% CI 0.96–1.02, $p = 0.47$) [2]. Contrarily, Schuetz et al. reported that the 72-h PCT kinetics were independently associated with ICU and in-hospital mortality following adjustment for illness severity. In their derivation cohort, the adjusted ORs per 10-percentage-point change in PCT were 1.30 (95% CI 1.10–1.50, $p = 0.001$) for ICU mortality and 1.30 (95% CI 1.10–1.40, $p = 0.001$) for in-hospital mortality [3]. Similarly, in the multicenter MOSES study, failure to achieve a PCT reduction of > 80% by Day 4 was independently associated with higher 28-day mortality following adjustment for clinical severity and other potential confounders (adjusted HR 1.97, 95% CI 1.18–3.30, $p < 0.01$) [5]. Although these studies used different PCT reduction thresholds, observation periods, and outcome measures, their findings generally suggest that inadequate PCT reduction is associated with poor outcomes in patients with sepsis. Consistent with these findings, our study demonstrated that, even among patients with markedly elevated peak PCT concentrations of ≥ 40 ng/mL, a PCT reduction of ≥ 70% from Days 0 to 3 was associated with lower 30-day mortality. Furthermore, ΔPCT remained independently associated with 30-day mortality following adjustment for age, SOFA score, and peak PCT concentration, with a 10-percentage-point increment in PCT reduction associated with approximately 9% lower odds of 30-day mortality (adjusted OR 0.91, 95% CI 0.84–0.99, $p = 0.022$). Contrarily, peak PCT was not independently associated with mortality. These findings indicate that serial assessment of PCT kinetics may provide additional prognostic information beyond the absolute peak PCT concentration, even among patients with markedly elevated PCT concentrations.

Limitations

This study has several limitations. First, the single-center retrospective observational design and relatively small sample size, including a limited number of mortality events, may have introduced unmeasured confounding and selection bias. Consequently, the generalizability of the findings to other institutions or patient populations may be limited. Second, the PCT kinetics analysis included only 94 of the 145 eligible patients, as 12 patients who died within 3 days and 39 patients without PCT measurement on Day 3 were excluded. As patient classification depended on survival until the Day 3 PCT measurement could be obtained, this approach may have introduced survivor bias through the systematic exclusion of early mortalities. Third, peak PCT was defined as the highest concentration recorded during hospitalization; however, the frequency and timing of blood sampling, as well as the length of hospitalization, were not standardized. Consequently, ascertainment bias could not be ruled out, as patients with more frequent PCT measurements may have had a greater likelihood of having higher peak concentrations detected. Fourth, given its observational design, the present study cannot establish that PCT reduction itself improves survival or determine whether the treatment interventions guided by PCT kinetics are effective. Furthermore, the study exclusively focused on 30-day mortality and did not evaluate long-term survival, recovery from organ dysfunction, or other patient-centered outcomes. Thus, the findings should be considered hypothesis-generating and cautiously interpreted when being applied to prognostic risk stratification among patients with sepsis and markedly elevated PCT concentrations.

Conclusion

Among patients with sepsis and markedly elevated PCT concentrations (≥40 ng/mL), those with higher peak PCT concentrations had higher SOFA scores and greater 30-day mortality; however, peak PCT concentration itself was not an independent prognostic factor. Contrarily, patients who exhibited a greater reduction in PCT concentrations by Day 3 following ICU/HCU admission had

lower 30-day mortality. This association remained significant after adjustment for disease severity and other potential confounding factors. These findings suggest that prognostic assessment in patients with sepsis and markedly elevated PCT concentrations should incorporate not only the absolute peak PCT concentration but also the degree of organ dysfunction and early changes in PCT concentrations. Further investigation through larger, multicenter prospective studies is warranted to validate the findings.

List of abbreviations

PCT: procalcitonin

ΔPCT: percentage reduction in procalcitonin

ICU: intensive care unit

HCU: high care unit

SOFA: sequential organ failure assessment

COPD: chronic obstructive pulmonary disease

ROC: receiver operating characteristic

AUC: area under the curve

OR: odds ratio

CI: confidence interval

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Kawasaki Medical School (approval no. 6549-01). Because this was a retrospective observational study using existing clinical information, individual written informed consent was not obtained. Study information was publicly disclosed, and an opt-out approach was used to provide patients with the opportunity to decline participation.

Consent for publication

Not applicable.

Availability of date and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

KK and HM designed and conceived this study. KK collected data. KK, IO, TY, MM,YY, MH, YO and HK performed the measurements. HM supported statistical analyses. KK analyzed and interpreted the results and drafted the manuscript with support from HM. All authors read and approved to the published the final manuscript.

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Figure Legends

Figure 1： Flowchart of patient selection and classification according to procalcitonin (PCT) levels.

A total of 145 patients with sepsis admitted to the ICU or HCU with a peak PCT concentration ≥ 40 ng/mL were included in the study. They were classified into the H group (peak PCT ≥ 96 ng/mL; n = 68) and the L group (peak PCT ≥ 40 and <96 ng/mL; n = 77). Of these, 94 patients with PCT measurements available at ICU/HCU admission (Day 0) and on Day 3 were included in the PCT kinetics analysis. The remaining 51 patients were excluded because they died within 3 days (n = 12) or lacked a Day 3 PCT measurement (n = 39). The 94 patients were further classified into Class I (PCT reduction < 70%; n = 50) and Class II (PCT reduction ≥ 70%; n = 44).

Abbreviations: ICU, Intensive care unit; HCU, High care unit; PCT, Procalcitonin

Figure 2： Receiver operating characteristic curve and 30-day Kaplan–Meier survival analysis according to peak procalcitonin levels.

The upper panel shows the ROC curve for peak PCT concentration for predicting 30-day mortality. The AUC was 0.655, and the optimal cutoff value determined using the Youden index was 96 ng/mL. The lower panel shows Kaplan–Meier survival curves comparing patients with a peak PCT ≥ 96 ng/mL (H group; n = 68) with those with a peak PCT ≥ 40 and < 96 ng/mL (L group; n = 77). Thirty-day survival was significantly lower in the H group than in the L group (HR = 2.97, 95% CI = 1.45–6.07; log-rank p = 0.0029). Numbers at risk are shown below the survival curves.

Abbreviations: AUC, area under the curve; CI = confidence interval; HR, hazard ratio; ROC, receiver operating characteristic; PCT, Procalcitonin

Figure 3： Receiver operating characteristic curve and 30-day Kaplan–Meier survival analysis according to procalcitonin reduction rate.

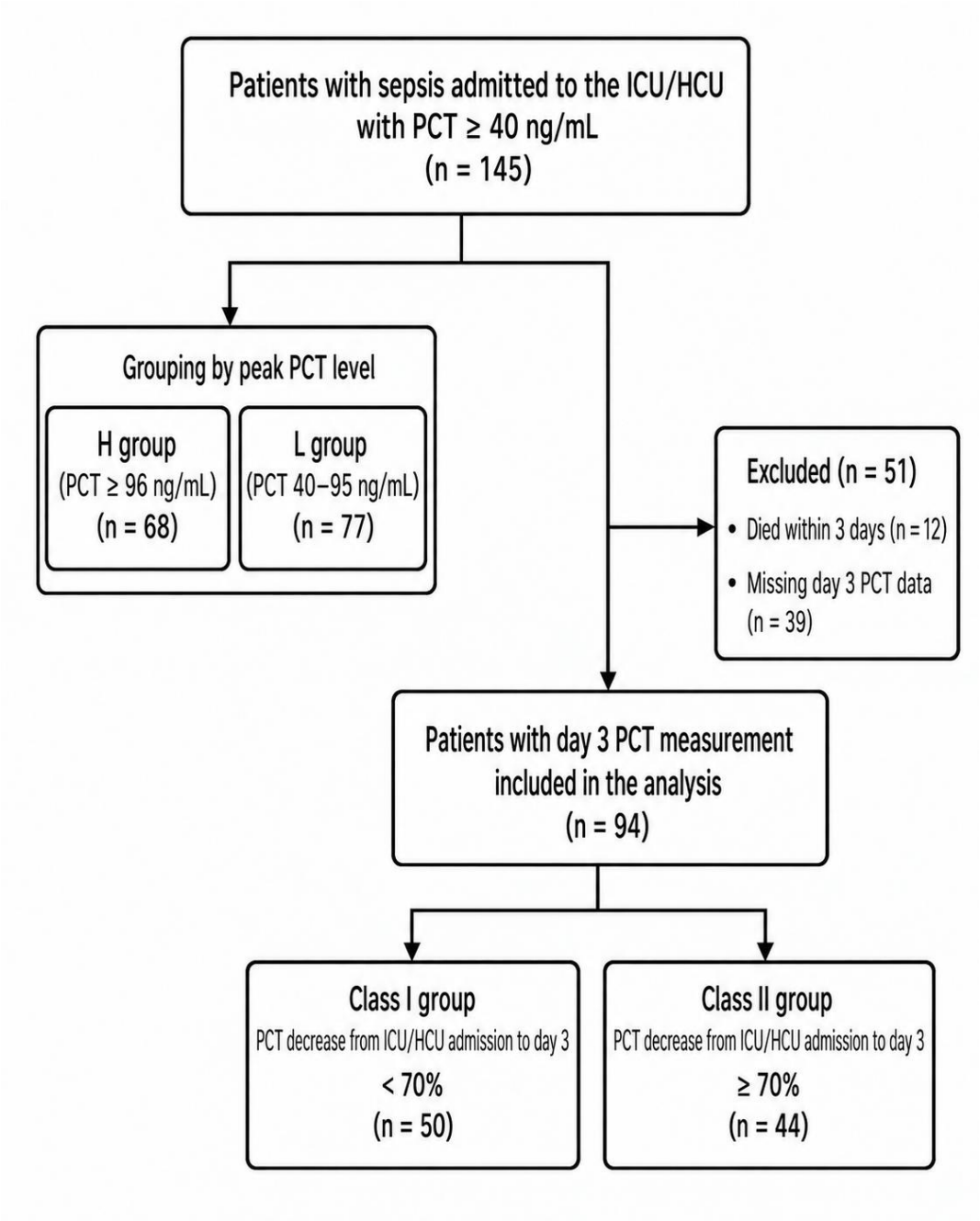
The upper panel shows the ROC curve for the percentage reduction in PCT from ICU/HCU admission (Day 0) to Day 3 (ΔPCT) in predicting 30-day mortality. ΔPCT was calculated as [(PCT on Day 0 − PCT on Day 3) / PCT on Day 0] × 100. The AUC was 0.829, and the optimal cutoff value determined using the Youden index was 70%. The lower panel shows Kaplan–Meier survival curves comparing patients with ΔPCT < 70% (Class I; n = 50) with those with ΔPCT ≥ 70% (Class II; n = 44). Thirty-day survival was significantly lower in Class I than in Class II (HR = 16.85, 95% CI = 2.23–127.13; log-rank p < 0.001). Numbers at risk are shown below the survival curves.

Abbreviations: AUC, area under the curve; CI = confidence interval; HR, hazard ratio; ICU, Intensive care unit; HCU, High care unit; PCT, Procalcitonin; ROC, receiver operating characteristic

Figure 4： Serial procalcitonin levels according to peak PCT levels and day-3 PCT reduction rates. Serial changes in serum PCT concentrations from admission to the ICU/HCU (Day 0) through Day 3 are shown. The upper panel compares patients with a peak PCT ≥ 96 ng/mL (H group) with those with a peak PCT ≥ 40 and < 96 ng/mL (L group). The lower panel compares patients with a PCT reduction of <70% from Day 0 to Day 3 (Class I) with those with a reduction of ≥70% (Class II). Data are presented as medians with interquartile ranges (25th–75th percentiles). The vertical axes are displayed on a logarithmic scale.

Abbreviations: PCT, procalcitonin; ICU, intensive care unit; HCU, high care unit

Figure 1


Patients with sepsis admitted to the ICU/HCU with PCT ≥ 40 ng/mL (n = 145)
Grouping by peak PCT level
H group (PCT ≥ 96 ng/mL) (n = 68)
L group (PCT 40–95 ng/mL) (n = 77)
Excluded (n = 51)
• Died within 3 days (n = 12)
• Missing day 3 PCT data (n = 39)
Patients with day 3 PCT measurement included in the analysis (n = 94)
Class I group
PCT decrease from ICU/HCU admission to day 3
< 70%
(n = 50)
Class II group
PCT decrease from ICU/HCU admission to day 3
≥ 70%
(n = 44)

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480 **Figure 2**

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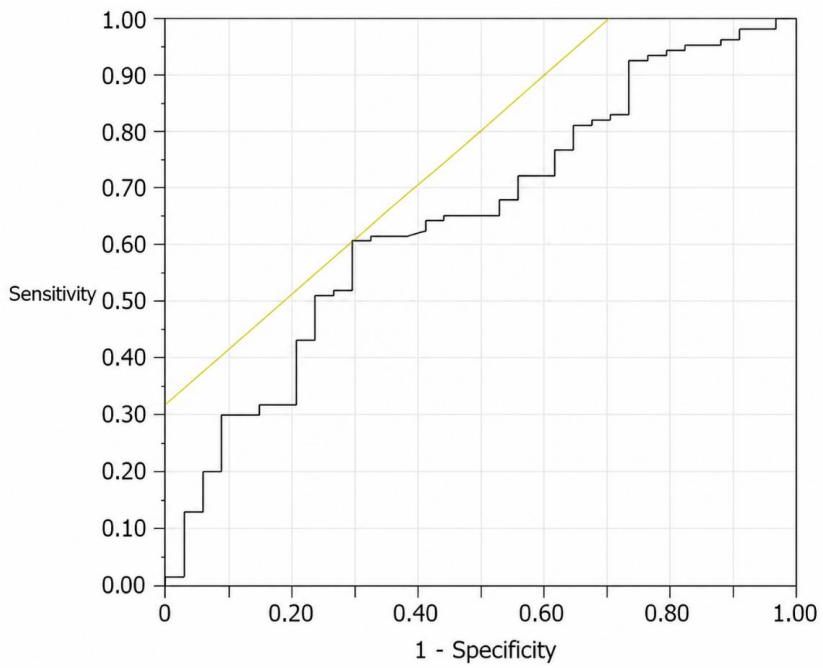

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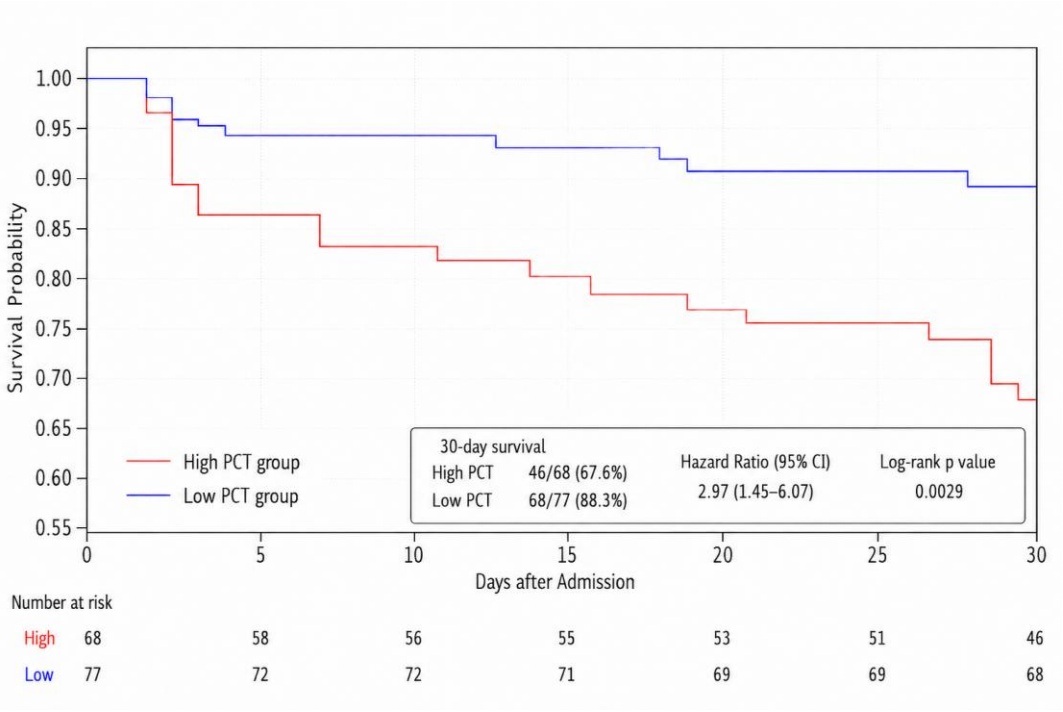

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487 **Figure 3**

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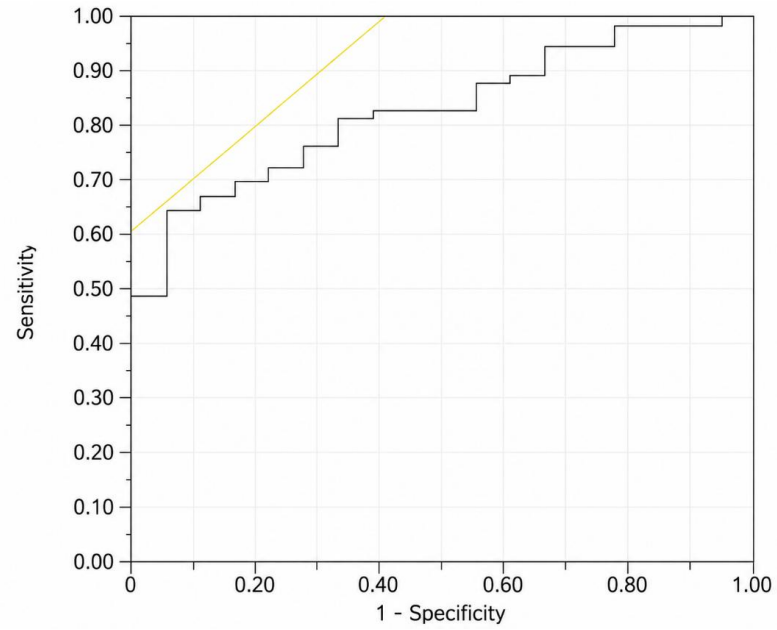

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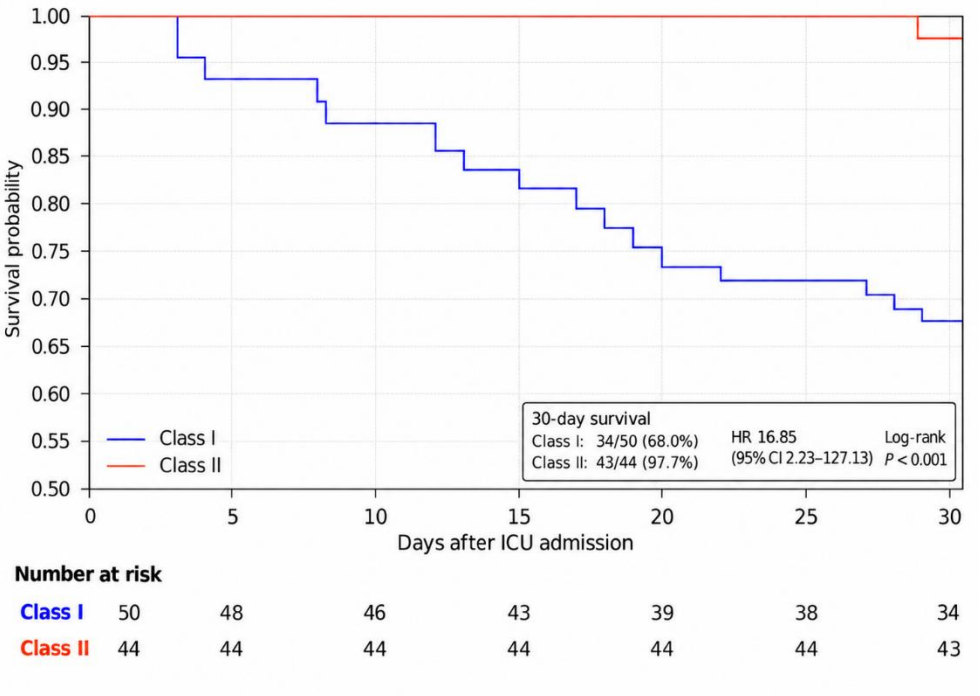

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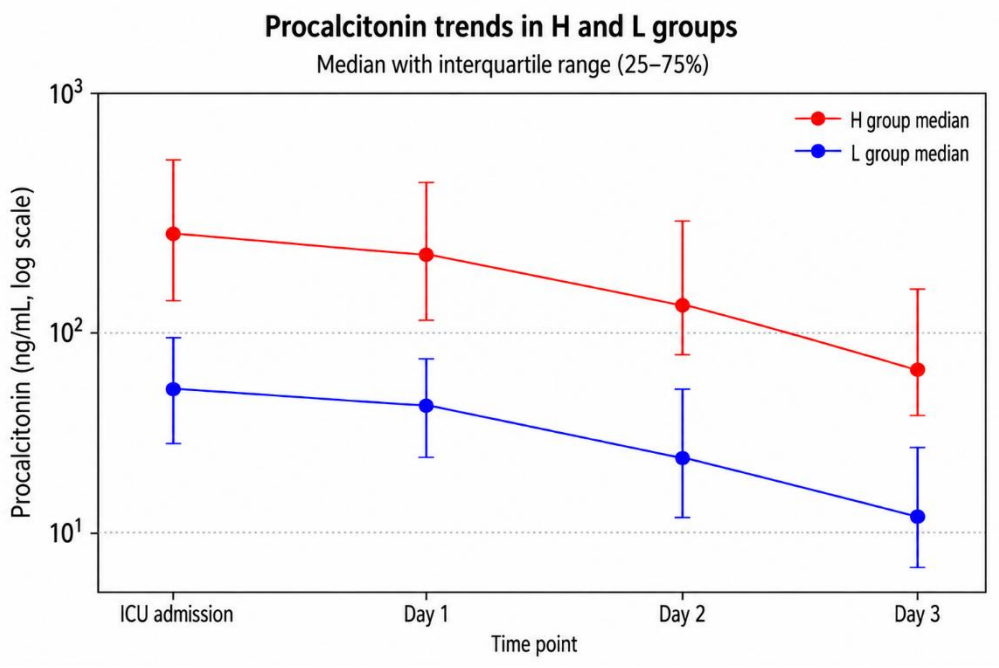
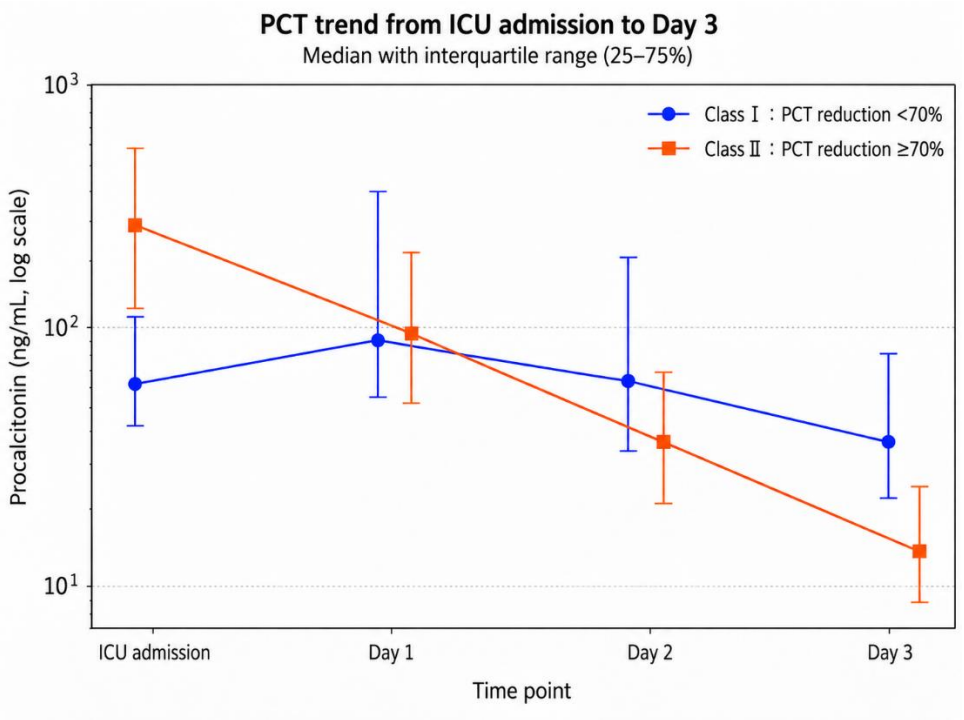
Figure 4


Procalcitonin trends in H and L groups
Median with interquartile range (25–75%)
H group median
L group median
Procalcitonin (ng/mL, log scale)
10^3
10^2
10^1
ICU admission
Day 1
Day 2
Day 3
Time point


PCT trend from ICU admission to Day 3
Median with interquartile range (25–75%)
Class Ⅰ：PCT reduction <70%
Class Ⅱ：PCT reduction ≥70%
Procalcitonin (ng/mL, log scale)
10^3
10^2
10^1
ICU admission
Day 1
Day 2
Day 3
Time point