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Prognostic Association and Incremental Predictive Value of NT-proBNP in Emergency Department Patients With Sepsis

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Abstract

Background

N-terminal pro–B-type natriuretic peptide (NT-proBNP) is frequently elevated in sepsis and may reflect cardiac stress, cardiorenal dysfunction, and acute illness severity. However, its adjusted prognostic association and incremental predictive value beyond routinely available clinical information in emergency department (ED) patients with sepsis remain uncertain.

Methods

We conducted a retrospective cohort study of adults admitted through the emergency department with suspected infection between November 1, 2018, and February 28, 2026, who met Sepsis-3 criteria and had an eligible NT-proBNP measurement within 24 hours after hospital admission. The primary outcome was in-hospital mortality. NT-proBNP concentrations were log2-transformed, and odds ratios (ORs) represented associations per doubling of NT-proBNP concentration. Logistic regression models were sequentially adjusted for demographic characteristics, comorbidities, and Sequential Organ Failure Assessment (SOFA) score. Quartile-based analyses, tests for trend, restricted cubic spline analyses, and sensitivity analyses were performed. Incremental predictive value was assessed by comparing a prespecified base clinical model with an NT-proBNP–extended model using the area under the receiver operating characteristic curve (AUC), Brier score, calibration measures, bootstrap internal validation, and decision curve analysis.

Results

Among 2,994 included patients, 567 died during hospitalization (18.9%). The median NT-proBNP concentration was 1,382 pg/mL (interquartile range, 391–5,133 pg/mL), and the median interval from hospital admission to NT-proBNP measurement was 4.0 hours (interquartile range, 2.0–8.0 hours). In the primary adjusted model, each doubling of NT-proBNP was associated with higher odds of in-hospital mortality (OR, 1.074; 95% CI, 1.027–1.123; P = 0.002). Compared with the lowest NT-proBNP quartile, the highest quartile was associated with higher mortality odds (OR, 1.653; 95% CI, 1.204–2.275; P = 0.002; P for trend = 0.003). Restricted cubic spline analysis showed an overall association (P = 0.014) without evidence of nonlinearity (P = 0.487). Findings were directionally consistent in timing-restricted analyses, after exclusion of values at the assay reporting boundary, and when NEWS replaced SOFA.

The base clinical model had an apparent AUC of 0.705 (95% CI, 0.681–0.728), compared with 0.710 (95% CI, 0.687–0.733) after addition of NT-proBNP (ΔAUC, 0.0050; 95% CI, −0.0002 to 0.0102; P = 0.059). The apparent Brier score decreased from 0.1410 to 0.1407 (ΔBrier, −0.0003); after bootstrap optimism correction, the AUC difference was 0.0045 and the Brier-score difference was −0.0001. Calibration was similar between models. The NT-proBNP–extended model showed small and nonuniform apparent net-benefit differences across decision thresholds.

Conclusions

Higher NT-proBNP concentrations were associated with in-hospital mortality after adjustment for measured clinical factors, but added little to prediction beyond routinely available information. These findings do not support routine use of NT-proBNP for mortality risk stratification in unselected ED patients with sepsis.

Introduction

Sepsis is a life-threatening syndrome characterized by dysregulated host responses to infection and acute organ dysfunction.[1] Despite advances in early recognition, antimicrobial therapy, source control, hemodynamic support, and critical care, mortality among patients with sepsis remains substantial.[2, 3] Patients presenting through the emergency department (ED) are clinically heterogeneous, and early risk stratification remains challenging.[4] Recent prospective research and contemporary reviews have highlighted the potential value of integrating host-response biomarkers with clinical severity scores to improve early identification, diagnostic classification, and triage of patients with suspected sepsis in the ED setting.[5, 6] Routinely available indicators of physiologic derangement, including organ dysfunction scores, lactate concentration, and hemodynamic variables, provide important prognostic information; however, their ability to capture the complex cardiovascular, renal, and inflammatory consequences of sepsis may be incomplete.[1, 4]

N-terminal pro–B-type natriuretic peptide (NT-proBNP) is commonly used in the evaluation of cardiac wall stress and heart failure. In sepsis, NT-proBNP concentrations may increase through several nonexclusive mechanisms, including myocardial dysfunction, ventricular wall stress, fluid loading, renal dysfunction, altered peptide clearance, pulmonary vascular strain, systemic inflammatory activation, and the effects of early hemodynamic interventions.[7–9] Accordingly, elevated NT-proBNP concentrations are common in critically ill patients with sepsis, including those without previously documented chronic heart failure.[7, 8] Previous observational studies have reported associations between elevated BNP or NT-proBNP concentrations and adverse outcomes in patients with severe sepsis or septic shock.[10–13] Systematic reviews and meta-analyses have further suggested that elevated natriuretic peptide concentrations are associated with short-term mortality in sepsis.[14–16] However, reported prognostic performance and proposed cutoff values have varied across studies according to patient setting and illness severity, biomarker timing, assay methods, outcome definitions, and adjustment for preexisting cardiac disease, renal dysfunction, and acute illness severity.[14–16] Limited evidence from the prehospital setting further suggests that NT-proBNP may complement clinical severity scores for identifying patients at risk of sepsis-related mortality, although its value in ED-based sepsis cohorts remains uncertain.[17]

An important distinction is required between prognostic association and incremental prediction. A biomarker may be independently associated with mortality after adjustment for clinical factors but still provide limited improvement in individual risk prediction when added to an established clinical model.[18–20] Therefore, evaluating NT-proBNP in ED patients with sepsis requires both assessment of its adjusted association with mortality and examination of whether it meaningfully improves model

discrimination, calibration, overall prediction error, and decision-analytic net benefit beyond routinely available clinical information.[19–23]

To address these gaps, we examined the adjusted association between early NT-proBNP concentration and in-hospital mortality in ED patients with sepsis, recognizing that NT-proBNP may reflect overlapping cardiorenal dysfunction, hemodynamic disturbance, treatment intensity, and overall illness severity. We then evaluated whether measuring NT-proBNP added clinically useful predictive information beyond routinely available clinical variables. The latter question was considered the principal clinical objective because a statistically adjusted association alone does not establish utility for risk stratification or management decisions.

Methods

Study Design and Setting

This retrospective cohort study utilized data from a large tertiary Class A general hospital in China, comprising approximately 3,000 inpatient beds and an annual outpatient and ED volume of nearly 8 million visits. Data were extracted from the hospital electronic medical record system, including demographic information, admission records, diagnoses, vital signs, laboratory test results, treatments, and in-hospital outcomes.

The study protocol was approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (Approval No. ZE2026-278-01), and the requirement for informed consent was waived due to the retrospective nature of the study. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[24] The prediction-model component was reported with reference to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidance.[25]

Study Population

Patients aged 18 years or older who were admitted through the ED with suspected infection between November 1, 2018, and February 28, 2026, were screened. Sepsis was defined according to Sepsis-3 criteria as documented or suspected infection accompanied by an acute increase in the Sequential Organ Failure Assessment (SOFA) score of at least 2 points.[1] Suspected infection was operationalized as concomitant blood culture sampling and antibiotic administration within 24 hours, adapting an electronic health record–based approach used in Sepsis-3 validation studies.[4] The SOFA score was calculated using the worst physiological and laboratory values within the first 24 hours after hospital admission. For patients without documented pre-existing organ dysfunction, baseline SOFA was assumed to be zero.[1]

For patients with more than one eligible hospitalization, only the index eligible hospitalization was retained. Patients were excluded if in-hospital mortality status was unavailable, if no NT-proBNP measurement was obtained within 24 hours after hospital admission, or if withdrawal of active treatment at the request of the patient or family was documented. This exclusion was applied because subsequent in-hospital outcomes could be substantially influenced by goals-of-care decisions in addition to underlying clinical severity.

NT-proBNP Measurement and Exposure Definition

The primary exposure was serum NT-proBNP concentration measured from the first blood sample obtained within 24 hours of admission. NT-proBNP was detected using the Elecsys proBNP II assay (Roche Diagnostics), with a measurement range of 5–35,000 pg/mL and an inter-assay coefficient of variation of less than 3%. Because NT-proBNP had a right-skewed distribution, it was log2-transformed before analysis. Therefore, the odds ratio for log2-transformed NT-proBNP represents the change in odds of in-hospital mortality associated with each doubling of NT-proBNP.

For descriptive and categorical analyses, NT-proBNP concentrations were categorized into quartiles based on their distribution in the analytic cohort, with the lowest quartile as the reference group. Quartile cut points are reported with the study results. Baseline characteristics were summarized according to NT-proBNP quartiles, and additional regression models were fitted using quartile-based NT-proBNP categories.

The assay reporting boundary for NT-proBNP was ≥ 35,000 pg/mL. Values reported at this upper boundary were retained as recorded in the primary analysis and were considered right-censored at the upper reporting limit. An analysis excluding these values was prespecified to assess the potential influence of assay-boundary censoring.

Outcome

The primary outcome was in-hospital mortality, defined as death occurring during the index hospitalization. Outcome status was ascertained from the electronic health record.

Covariates

Prespecified demographic covariates included age and sex. Comorbidities included hypertension, coronary artery disease, chronic heart failure, diabetes, chronic kidney disease, chronic lung disease, cerebrovascular disease, and malignancy.

Illness severity was assessed using the SOFA score.[1] SOFA was derived from the worst available values during the first 24 hours after hospital admission, according to the database definition. Septic

shock was identified using the prespecified clinical or electronic health record definition applied in the study cohort.

Additional clinical and laboratory variables used in selected sensitivity and prediction analyses included lactate, creatinine, albumin, C-reactive protein (CRP), procalcitonin (PCT), white blood cell count, platelet count, troponin, blood culture status, and infection source. The National Early Warning Score (NEWS) was used as an alternative illness-severity measure in an exploratory analysis restricted to patients with complete NEWS data.[26]

Statistical Analysis

Descriptive Analyses

Baseline characteristics were summarized overall and across NT-proBNP quartiles. Continuous variables were described as medians with interquartile ranges (IQRs), and categorical variables as numbers and percentages. Percentages were calculated among patients with available data for each variable.

Differences across NT-proBNP quartiles were assessed using the Kruskal-Wallis test for continuous variables and Pearson chi-square test or Fisher exact test for categorical variables, as appropriate. No P values were calculated for NT-proBNP because quartiles were defined using this variable.

Association Between NT-proBNP and In-Hospital Mortality

Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between log2-transformed NT-proBNP and in-hospital mortality. The primary effect estimate represented the OR for in-hospital mortality associated with a doubling of NT-proBNP concentration.

Five regression models were specified:

Model 1 included log2-transformed NT-proBNP only.

Model 2 included log2-transformed NT-proBNP, age, and sex.

Model 3 included log2-transformed NT-proBNP, age, sex, hypertension, coronary artery disease, chronic heart failure, diabetes, chronic kidney disease, chronic lung disease, cerebrovascular disease, and malignancy.

Model 4 included log2-transformed NT-proBNP and SOFA score.

Model 5, the primary association model, included log2-transformed NT-proBNP, age, sex, hypertension, coronary artery disease, chronic heart failure, diabetes, chronic kidney disease, chronic lung disease, cerebrovascular disease, malignancy, and SOFA score.

Model 4 was specified as a parallel model evaluating adjustment for SOFA score alone and was not treated as a nested extension of Model 3.

In categorical analyses, NT-proBNP quartiles were entered as indicator variables, with the lowest quartile as the reference category. To test for trend, participants were assigned the median NT-proBNP concentration of their quartile. These quartile-specific median values were log2-transformed and entered as a continuous variable using the covariate set of Model 5.

Dose-Response Analysis

Restricted cubic spline logistic regression was used to evaluate the shape of the association between NT-proBNP and in-hospital mortality. Restricted cubic splines enable flexible assessment of potentially nonlinear exposure–outcome associations without imposing a linearity assumption.[27] NT-proBNP was modeled on the log2 scale, and the spline model was adjusted for the covariates included in Model 5.

The median NT-proBNP concentration in the analytic cohort was used as the reference value. Restricted cubic splines with four knots, placed at the 5th, 35th, 65th, and 95th percentiles of the log2-transformed NT-proBNP distribution, were used. The spline curve was displayed between the 1st and 99th percentiles of the observed NT-proBNP distribution to reduce the visual influence of sparse observations in the extreme tails. Overall association and nonlinearity were assessed using Wald tests.

Sensitivity Analyses

Several analyses were conducted to assess the robustness of the primary association.

First, analyses were restricted to patients with NT-proBNP measured within 6 hours and within 12 hours after hospital admission. Second, patients with NT-proBNP values reported at the assay reporting boundary (≥ 35,000 pg/mL) were excluded.

Third, in patients with complete NEWS data, NEWS replaced SOFA score while all other covariates from Model 5 were retained. This was considered an exploratory analysis because it was restricted to patients with complete NEWS data.

Additional biomarker-adjusted sensitivity analyses used an alternative covariate set comprising log2-transformed troponin, age, sex, SOFA score, septic shock, chronic heart failure, chronic kidney disease, lactate, creatinine, albumin, CRP, PCT, white blood cell count, platelet count, blood culture status, and infection source.

For analyses involving variables with missing values, complete-case estimates were compared with estimates obtained after multiple imputation by chained equations. Twenty imputed datasets were generated. The imputation model included in-hospital mortality, log2-transformed NT-proBNP, all variables included in the corresponding analysis model, and additional available variables considered informative for missingness. Estimates from imputed datasets were combined using Rubin’s rules.[28]

Prediction Models and Incremental Predictive Value

Association analyses and prediction analyses were conducted for distinct purposes. Association analyses evaluated the relationship between NT-proBNP and in-hospital mortality after covariate adjustment. Prediction analyses assessed whether NT-proBNP provided incremental predictive information beyond a predefined clinical model.[18–20]

The base clinical prediction model included age, sex, hypertension, coronary artery disease, chronic heart failure, diabetes, chronic kidney disease, chronic lung disease, cerebrovascular disease, malignancy, SOFA score, and septic shock. The extended model included all predictors in the base model plus log2-transformed NT-proBNP.

Model discrimination was assessed using the area under the receiver operating characteristic curve (AUC). Apparent AUCs were reported with 95% CIs. The apparent difference in AUC between the base and extended models was evaluated using a paired DeLong test.[29] A patient-level paired bootstrap procedure was additionally used to estimate the 95% CI for the apparent difference in AUC.

Overall prediction error was assessed using the Brier score, with lower values indicating better prediction accuracy. Calibration was assessed using the calibration intercept and calibration slope. Apparent calibration was examined graphically by dividing patients into deciles of predicted risk separately for each model and comparing mean predicted risk with observed mortality. Wilson 95% CIs were calculated for observed mortality within each decile.

Evaluation of discrimination alone is insufficient to characterize prediction-model performance. Therefore, calibration, overall prediction error, and clinical utility were assessed in addition to AUC.[19–22]

Internal validation was performed using 2,000 bootstrap resamples. In each resample, both models were refitted and evaluated to estimate optimism. Optimism-corrected AUC, Brier score, calibration intercept, and calibration slope were calculated for each model. Bootstrap internal validation was selected because it provides an efficient approach for estimating optimism in prediction model development studies.[20, 30]

Decision Curve Analysis

Decision curve analysis was used to compare the apparent net benefit of the base and NT-proBNP-extended models across threshold probabilities ranging from 0.05 to 0.60. Treat-all and treat-none strategies were included as reference strategies. Decision curve analysis evaluates the net clinical benefit of risk-based decisions across a range of threshold probabilities by incorporating the relative harms of false-positive and false-negative classifications.[23]

For decision curve analysis, “treat” denoted the prespecified model-guided clinical action or escalation strategy applied when a patient’s predicted in-hospital mortality risk equaled or exceeded a selected

threshold probability; it did not refer to treatment with NT-proBNP. Because decision curves were derived in the development cohort, net-benefit estimates were considered apparent and were not optimism-corrected.

Missing Data

The completeness of each study variable was summarized before analysis. Variables included in the primary association model were complete. Biomarker and laboratory variables had varying degrees of missingness and were handled using complete-case analysis and multiple imputation, as described above.[28]

Statistical Software

All statistical tests were two-sided, with a P value of less than 0.05 considered statistically significant. Statistical analyses were performed using R (version 4.4.3) with the following packages: mice, rms, pROC, ggplot2, dplyr, and broom.

Results

Cohort selection and characteristics

Among 14,027 adults admitted through the emergency department with suspected infection between November 1, 2018, and February 28, 2026, 4,520 met Sepsis-3 criteria (Fig. 1). After exclusion of duplicate hospitalizations (n = 23), patients without in-hospital mortality data (n = 134), those without an eligible NT-proBNP measurement or with measurement outside the prespecified time window (n = 982), and those with treatment withdrawal at the request of the patient or family (n = 387), 2,994 patients were included in the primary association analysis. Overall, 567 patients died during hospitalization, corresponding to an in-hospital mortality of 18.9%.

The median NT-proBNP concentration was 1,382 pg/mL (IQR, 391–5,133 pg/mL). The median interval from hospital admission to NT-proBNP measurement was 4.0 hours (IQR, 2.0–8.0 hours) and did not differ across NT-proBNP quartiles (P = 0.300) (Table 1). Values reported as ≥ 35,000 pg/mL were retained at the assay reporting boundary; therefore, the upper tail of the NT-proBNP distribution was right-censored.

Table 1
Selected baseline characteristics of emergency department patients with sepsis according to NT-proBNP quartiles

Characteristic	Overall, N = 2,994[1]	Q1, N = 749[1]	Q2, N = 749[1]	Q3, N = 748[1]	Q4, N = 748[1]	P value[2]
NT-proBNP quartile definition, pg/mL	—	≤ 391	> 391 to ≤ 1,383	> 1,383 to ≤ 5,133	> 5,133	
NT-proBNP, pg/mL, median (IQR)	1,382 (391–5,133)	172 (85–259)	738 (556–1,030)	2,551 (1,847–3,562)	12,954 (7,589–27,866)	
Age, years	73.0 (61.0–83.0)	65.0 (53.0–75.0)	73.0 (63.0–83.0)	77.0 (67.0–86.0)	77.0 (66.0–85.0)	< 0.001
Male sex	1,852 (61.9%)	520 (69.4%)	462 (61.7%)	470 (62.8%)	400 (53.5%)	< 0.001
Coronary artery disease	602 (20.1%)	73 (9.7%)	117 (15.6%)	168 (22.5%)	244 (32.6%)	< 0.001
Chronic heart failure	734 (24.5%)	53 (7.1%)	120 (16.0%)	222 (29.7%)	339 (45.3%)	< 0.001
Chronic kidney disease	329 (11.0%)	19 (2.5%)	34 (4.5%)	79 (10.6%)	197 (26.3%)	< 0.001
SOFA score	4.0 (3.0–7.0)	3.0 (2.0–5.0)	4.0 (3.0–6.0)	4.0 (3.0–7.0)	6.0 (4.0–9.0)	< 0.001
Septic shock	607 (20.3%)	86 (11.5%)	124 (16.6%)	180 (24.1%)	217 (29.0%)	< 0.001
Lactate, mmol/L	1.9 (1.4–3.0)	1.8 (1.3–2.6)	1.9 (1.4–2.9)	1.9 (1.3–2.9)	2.1 (1.4–3.4)	0.002
Creatinine, µmol/L	100.0 (71.0–167.0)	82.0 (63.0–107.0)	86.0 (64.0–127.5)	103.0 (74.0–155.0)	178.0 (106.0–303.0)	< 0.001
CRP, mg/L	81.4 (31.8–157.2)	57.0 (19.1–121.2)	88.0 (38.4–164.7)	89.9 (36.6–160.5)	92.2 (39.4–170.6)	< 0.001
PCT, ng/mL	1.1 (0.3–7.7)	0.4 (0.1–1.5)	1.1 (0.3–5.1)	1.8 (0.3–12.6)	3.2 (0.5–24.2)	< 0.001
White blood cell count, ×10^9/L	11.1 (7.3–16.0)	9.6 (6.4–14.2)	11.4 (7.3–16.5)	11.7 (7.8–16.5)	11.7 (7.9–17.3)	< 0.001
Platelet count, ×10^9/L	176.0 (112.0–249.0)	177.0 (106.0–253.0)	178.0 (115.0–248.0)	181.0 (118.0–257.0)	169.5 (107.0–235.0)	0.094

Characteristic	Overall, N = 2,994[1]	Q1, N = 749[1]	Q2, N = 749[1]	Q3, N = 748[1]	Q4, N = 748[1]	P value[2]
Troponin, µg/L	0.04 (0.02–0.11)	0.02 (0.01–0.03)	0.03 (0.02–0.05)	0.04 (0.03–0.10)	0.12 (0.06–0.39)	< 0.001
Positive blood culture	331 (11.1%)	52 (6.9%)	82 (10.9%)	93 (12.4%)	104 (13.9%)	< 0.001
Infection source						0.400
Pulmonary	1,498 (50.0%)	357 (47.7%)	380 (50.7%)	385 (51.5%)	376 (50.3%)	
Intra-abdominal	853 (28.5%)	226 (30.2%)	217 (29.0%)	212 (28.3%)	198 (26.5%)	
Urinary tract	423 (14.1%)	98 (13.1%)	102 (13.6%)	103 (13.8%)	120 (16.0%)	
Undetermined	157 (5.2%)	50 (6.7%)	38 (5.1%)	34 (4.5%)	35 (4.7%)	
Other specified sources	63 (2.1%)	18 (2.4%)	12 (1.6%)	14 (1.9%)	19 (2.5%)	
Time from hospital admission to NT-proBNP measurement, h	4.0 (2.0–8.0)	4.0 (2.0–8.0)	4.0 (3.0–8.0)	4.0 (3.0–9.0)	4.0 (3.0–9.0)	0.300
In-hospital death	567 (18.9%)	97 (13.0%)	130 (17.4%)	140 (18.7%)	200 (26.7%)	< 0.001

[1]Continuous variables are presented as median (interquartile range [IQR]), and categorical variables as n (%). Percentages were calculated among patients with available data for each variable. Missing data are summarized in eTable 2.

[2]P values were calculated using the Kruskal–Wallis test for continuous variables and Pearson chi-square test or Fisher exact test for categorical variables, as appropriate.

NT-proBNP quartiles were defined using original recorded NT-proBNP concentrations in the analytic cohort. Values reported as ≥ 35,000 pg/mL were retained at the assay reporting boundary and were not re-estimated. Accordingly, the upper tail of the NT-proBNP distribution was right-censored at the assay reporting boundary. P values are not shown for NT-proBNP because quartiles were defined using this variable. SOFA indicates Sequential Organ Failure Assessment; CRP, C-reactive protein; PCT, procalcitonin.

Baseline characteristics according to NT-proBNP quartiles are shown in Table 1, with additional characteristics reported in eTable 1. Compared with patients in lower NT-proBNP quartiles, those in higher quartiles were older, less frequently male, and had higher prevalences of coronary artery disease, chronic heart failure, and chronic kidney disease (all P < 0.001). Higher NT-proBNP quartiles were also associated with greater illness severity, including higher SOFA scores, a higher frequency of septic

shock, and higher lactate and creatinine concentrations. Concentrations of C-reactive protein, procalcitonin, white blood cell count, and troponin also differed across quartiles, whereas platelet count and infection source did not differ significantly. Crude in-hospital mortality increased from 13.0% in the lowest NT-proBNP quartile to 26.7% in the highest quartile (P < 0.001).

Association between NT-proBNP and in-hospital mortality

Higher NT-proBNP concentrations were associated with higher odds of in-hospital mortality across all logistic regression models (Table 2). In the unadjusted model, each doubling of NT-proBNP was associated with an OR of 1.141 (95% CI, 1.100–1.184; P < 0.001). The association remained statistically significant after adjustment for age and sex (Model 2: OR, 1.149; 95% CI, 1.107–1.193; P < 0.001), as well as after adjustment for demographic characteristics and comorbidities (Model 3: OR, 1.177; 95% CI, 1.128–1.227; P < 0.001).

Table 2
Association of log2-transformed NT-proBNP with in-hospital mortality in logistic regression models

Model	Covariates included	N	Deaths	OR (95% CI) per doubling of NT-proBNP	P value
Model 1	log2(NT-proBNP) only	2,994	567	1.141 (1.100–1.184)	< 0.001
Model 2	log2(NT-proBNP), age, and sex	2,994	567	1.149 (1.107–1.193)	< 0.001
Model 3	log2(NT-proBNP), age, sex, hypertension, coronary artery disease, chronic heart failure, diabetes, chronic kidney disease, chronic lung disease, cerebrovascular disease, and malignancy	2,994	567	1.177 (1.128–1.227)	< 0.001
Model 4	log2(NT-proBNP) and SOFA score	2,994	567	1.064 (1.024–1.105)	0.002
Model 5	log2(NT-proBNP), age, sex, hypertension, coronary artery disease, chronic heart failure, diabetes, chronic kidney disease, chronic lung disease, cerebrovascular disease, malignancy, and SOFA score	2,994	567	1.074 (1.027–1.123)	0.002

Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression. The OR represents the association with in-hospital mortality per 1-unit increase in log2-transformed NT-proBNP, corresponding to a doubling of the original NT-proBNP concentration. Model 4 was a parallel model adjusted for SOFA score alone and was not a nested extension of Model 3. Model 5 was the primary association model. SOFA, Sequential Organ Failure Assessment; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

In the parallel model adjusted for SOFA score alone, each doubling of NT-proBNP was associated with an OR of 1.064 (95% CI, 1.024–1.105; P = 0.002). In the primary Model 5, adjusted for age, sex, hypertension, coronary artery disease, chronic heart failure, diabetes, chronic kidney disease, chronic lung disease, cerebrovascular disease, malignancy, and SOFA score, each doubling of NT-proBNP was associated with 7.4% higher odds of in-hospital mortality (OR, 1.074; 95% CI, 1.027–1.123; P = 0.002).

Quartile-based and dose–response analyses

In quartile-based analyses, the highest NT-proBNP quartile was associated with higher adjusted odds of in-hospital mortality compared with the lowest quartile (OR, 1.653; 95% CI, 1.204–2.275; P = 0.002) (Table 3). The associations for the second and third quartiles did not reach statistical significance (Q2: OR, 1.271; 95% CI, 0.942–1.718; P = 0.118; Q3: OR, 1.245; 95% CI, 0.917–1.692; P = 0.161). Nevertheless, there was evidence of an overall trend across quartiles when quartile-specific median NT-proBNP concentrations were modeled continuously (OR per doubling, 1.076; 95% CI, 1.025–1.130; P for trend = 0.003).

Table 3
Association of NT-proBNP quartiles with in-hospital mortality

Quartile	N	NT-proBNP range, pg/mL	Deaths, n (%)	Model 5 adjusted OR (95% CI)	P value
Q1	749	≤ 391	97 (13.0%)	Reference	—
Q2	749	> 391 to ≤ 1,383	130 (17.4%)	1.271 (0.942–1.718)	0.118
Q3	748	> 1,383 to ≤ 5,133	140 (18.7%)	1.245 (0.917–1.692)	0.161
Q4	748	> 5,133	200 (26.7%)	1.653 (1.204–2.275)	0.002
Quartile-specific median NT-proBNP, per doubling	—	—	—	1.076 (1.025–1.130)	0.003

Estimates were adjusted for age, sex, hypertension, coronary artery disease, chronic heart failure, diabetes, chronic kidney disease, chronic lung disease, cerebrovascular disease, malignancy, and SOFA score. The observed NT-proBNP range in the analytic cohort was 5 to ≥ 35,000 pg/mL. P for trend was estimated by assigning each participant the median NT-proBNP concentration of their quartile, log2-transforming this value, and modeling it as a continuous variable.

Restricted cubic spline analysis showed a statistically significant overall association between NT-proBNP and in-hospital mortality (P for overall association = 0.014) (Fig. 2). There was no evidence of nonlinearity (P for nonlinearity = 0.487), indicating that the observed dose–response pattern was compatible with an approximately linear positive association over the displayed range of NT-proBNP concentrations.

Sensitivity analyses

The direction of association between NT-proBNP and in-hospital mortality was consistent in timing-restricted and assay-boundary sensitivity analyses (Fig. 3). Among 1,990 patients with NT-proBNP measured within 6 hours of hospital admission, each doubling of NT-proBNP was associated with an OR of 1.099 (95% CI, 1.040–1.161; P < 0.001). Among 2,656 patients with measurement within 12 hours, the corresponding OR was 1.081 (95% CI, 1.031–1.134; P = 0.001).

After excluding 150 patients with NT-proBNP values at the assay reporting boundary, the association remained statistically significant (OR per doubling, 1.090; 95% CI, 1.038–1.145; P < 0.001). In the exploratory analysis restricted to 1,272 patients with complete NEWS data, replacement of SOFA with NEWS yielded an OR of 1.197 per doubling of NT-proBNP (95% CI, 1.109–1.293; P < 0.001). Although the magnitude of the association was larger in the NEWS-based analysis, its direction was consistent with that in the primary model.

Additional biomarker-adjusted complete-case and multiple-imputation sensitivity analyses, based on 20 imputed datasets, are shown in Fig. 3. Missingness was most frequent for troponin (9.9%), albumin (7.4%), lactate (7.1%), and CRP (5.8%), whereas the variables included in the primary Model 5 were complete (eTable 2).

Incremental predictive value of NT-proBNP

The base clinical prediction model had an apparent AUC of 0.705 (95% CI, 0.681–0.728) for in-hospital mortality (Table 4). Addition of log2-transformed NT-proBNP increased the apparent AUC to 0.710 (95% CI, 0.687–0.733), corresponding to an apparent ΔAUC of 0.0050 (95% CI, − 0.0002 to 0.0102; P = 0.059). The paired bootstrap 95% CI for the apparent ΔAUC was similarly compatible with no difference (− 0.0004 to 0.0103).

Table 4
Apparent and bootstrap optimism-corrected performance of the base clinical model and the extended model including NT-proBNP for in-hospital mortality

Metric	Base model	Base model + NT-proBNP	Difference (extended – base)
Apparent performance			
AUC (95% CI)	0.705 (0.681–0.728)	0.710 (0.687–0.733)	0.0050 (95% CI, – 0.0002 to 0.0102); P = 0.059
Brier score	0.1410	0.1407	-0.0003
Calibration intercept	0.0000	0.0000	—
Calibration slope	1.000	1.000	—
Bootstrap optimism-corrected performance			
AUC	0.695	0.700	0.0045
Brier score	0.1420	0.1419	-0.0001
Calibration intercept	0.0006	0.0006	—
Calibration slope	0.953	0.950	—

The base model included age, sex, hypertension, coronary artery disease, chronic heart failure, diabetes, chronic kidney disease, chronic lung disease, cerebrovascular disease, malignancy, SOFA score, and septic shock. The extended model included all predictors in the base model plus log2-transformed NT-proBNP.

AUC indicates area under the receiver operating characteristic curve. Lower Brier scores indicate lower overall prediction error. The ideal calibration intercept and calibration slope are 0 and 1, respectively.

Bootstrap internal validation was based on 2,000 bootstrap resamples, with refitting of both models in each resample. The patient-level paired bootstrap 95% CI for the apparent ΔAUC was − 0.0004 to 0.0103.

After bootstrap optimism correction, the AUC was 0.695 for the base model and 0.700 for the NT-proBNP–extended model, with a corrected ΔAUC of 0.0045. The apparent Brier score decreased from 0.1410 to 0.1407 after inclusion of NT-proBNP, while the optimism-corrected Brier score decreased from 0.1420 to 0.1419. Thus, the observed improvements in discrimination and overall prediction error were numerically small.

Apparent calibration was broadly similar for the base and extended models (Fig. 4; eTable 3). Bootstrap optimism-corrected calibration intercepts were 0.0006 for both models, and calibration slopes were 0.953 for the base model and 0.950 for the extended model. Observed mortality according to clinically defined predicted-risk categories is reported in eTable 4.

In apparent decision curve analysis, the NT-proBNP–extended model showed marginally higher net benefit than the base model across selected threshold-probability ranges, including approximately 7.5% to 16.0%, 18.5% to 21.5%, and 34.0% to 41.0% (Fig. 5; eTables 5 and 6). However, the absolute incremental net benefit was small and not uniform across thresholds. For example, the incremental net benefit was 0.0024 at a threshold probability of 10%, 0.0027 at 15%, and 0.0036 at 20%, but was −0.0028 at 25%. Overall, addition of NT-proBNP provided limited incremental predictive information beyond the base clinical model.

Discussion

The main finding of this study is that higher early NT-proBNP concentrations were statistically associated with in-hospital mortality after adjustment for measured demographic characteristics, comorbidities, and early organ dysfunction. However, this adjusted association did not translate into meaningful improvement in individual risk prediction beyond routinely available clinical information. Although each doubling of NT-proBNP was associated with a 7.4% increase in the adjusted odds of in-hospital death, addition of NT-proBNP increased the apparent AUC by only 0.0050, produced minimal change in the Brier score, and yielded small and inconsistent differences in apparent net benefit. Thus, NT-proBNP should be interpreted as a marker correlated with adverse clinical status rather than as a biomarker that materially improves routine mortality prediction in this cohort.

The dose-response pattern was broadly linear on the log2 scale, without evidence of a clinically useful threshold. This finding argues against dichotomizing NT-proBNP at a single cut-point for routine prognostic use. Previous meta-analyses have reported heterogeneous optimal BNP and NT-proBNP thresholds across sepsis studies, likely reflecting variation in case mix, biomarker timing, assay platforms, outcome definitions, and covariate adjustment.[14–16]

The association between NT-proBNP and mortality was directionally consistent across analyses restricted to measurements obtained within 6 and 12 hours of hospital admission and after exclusion of values at the assay reporting boundary. These findings suggest that the primary association was not solely explained by delayed biomarker measurement or by accumulation of observations at the upper reporting limit. The exploratory analysis in which NEWS replaced SOFA also showed a positive association, although the estimated effect size was larger than in the primary model. Because the NEWS analysis was restricted to patients with complete NEWS data, differences in effect magnitude may reflect both use of an alternative severity measure and differences in the analyzed population.[26, 28]

NT-proBNP may reflect several interrelated features of acute illness in sepsis. In addition to chronic heart failure, elevated concentrations may be associated with myocardial wall stress, sepsis-associated cardiac dysfunction, renal dysfunction, altered peptide clearance, pulmonary vascular stress, systemic inflammation, and early hemodynamic management.[7–9, 31–38] Sepsis-related myocardial dysfunction has long been recognized as a potentially reversible phenomenon in septic shock, although its prevalence, echocardiographic phenotype, prognostic significance, and response to treatment are

variable across studies.[31–36] More recent systematic evidence suggests that sepsis-induced cardiomyopathy occurs in approximately one-fifth of patients with sepsis or septic shock and is associated with increased short-term mortality.[37] Contemporary mechanistic reviews further emphasize that sepsis-induced cardiomyopathy is multifactorial, involving systemic inflammation, mitochondrial dysfunction, oxidative stress, microcirculatory abnormalities, dysregulated calcium handling, and altered autonomic and adrenergic signaling.[34–36, 38]

In this cohort, patients in higher NT-proBNP quartiles were older and had higher prevalences of coronary artery disease, chronic heart failure, and chronic kidney disease. They also had higher SOFA scores, more frequent septic shock, and higher lactate and creatinine concentrations. These patterns underscore that NT-proBNP should not be interpreted as a cardiac-specific marker in sepsis. Rather, it may integrate information related to preexisting cardiorenal disease and the severity of acute physiologic derangement.

Our findings are broadly consistent with prior observational studies showing that elevated BNP or NT-proBNP concentrations are associated with poor short-term outcomes in severe sepsis and septic shock.[10–13] The present study extends this literature by evaluating a large ED-based cohort, modeling NT-proBNP continuously on a log2 scale, examining potential nonlinearity, and separately assessing adjusted prognostic association and incremental prediction. This distinction is important because the clinical implications of an independent association differ from those of a meaningful improvement in individual risk classification or clinical decision-making.[18–20]

The attenuation of the association after adjustment for SOFA score is also clinically informative. The unadjusted association was stronger than the association observed in the fully adjusted model, suggesting that a substantial proportion of the prognostic information represented by NT-proBNP overlaps with illness severity and comorbidity burden. Nevertheless, NT-proBNP remained associated with mortality in the primary model. This residual association may indicate that the biomarker captures aspects of cardiovascular or cardiorenal stress not completely represented by routinely measured clinical characteristics and SOFA score. However, this interpretation remains prognostic rather than causal. The present observational design cannot distinguish whether NT-proBNP is a mediator, marker, or consequence of greater illness severity or treatment intensity.

The categorical and continuous analyses should be interpreted together. Crude mortality increased from 13.0% in the lowest NT-proBNP quartile to 26.7% in the highest quartile. In adjusted quartile analyses, only the highest quartile was statistically significantly associated with mortality relative to the lowest quartile, whereas the second and third quartiles were not. This pattern does not necessarily imply a biological threshold because categorization of continuous predictors reduces statistical information, lowers precision, and can obscure the true dose-response relationship.[39] The significant trend test and the absence of evidence for nonlinearity in the restricted cubic spline analysis favor a broadly monotonic, approximately linear association on the log2 NT-proBNP scale rather than a clearly defined threshold effect.

An important finding of this study is the distinction between prognostic association and incremental predictive value. Although NT-proBNP was associated with in-hospital mortality, adding it to the predefined clinical prediction model yielded only a small numerical improvement in discrimination. The apparent AUC increased from 0.705 to 0.710, with an apparent ΔAUC of 0.0050 that did not reach conventional statistical significance by paired DeLong testing. After bootstrap optimism correction, the difference in AUC was 0.0045, and the reduction in Brier score was minimal. Calibration was broadly similar between the base and NT-proBNP-extended models. Therefore, the observed association of NT-proBNP with mortality did not translate into a substantial improvement in overall individual-level risk prediction beyond the clinical variables already included in the base model. Such discordance is well recognized in biomarker research: a statistically significant adjusted OR does not necessarily establish meaningful incremental predictive value.[18–20]

Decision curve analysis provided a similarly cautious interpretation. The NT-proBNP-extended model showed marginally higher apparent net benefit than the base model across selected threshold-probability ranges, particularly within some lower-to-intermediate risk thresholds. However, the absolute differences in net benefit were small and not consistent across all evaluated thresholds. These results do not support using NT-proBNP alone to trigger escalation of care or other management decisions. Rather, if externally validated, NT-proBNP may be considered a complementary prognostic biomarker within a broader clinical assessment framework. Its potential usefulness is likely to depend on the intended decision, the risk threshold used, and the benefits and harms of the associated clinical action. [20, 23, 40]

This study has several strengths. It included a relatively large ED-based sepsis cohort with 567 in-hospital deaths, permitting evaluation of NT-proBNP as both a continuous and categorical exposure. The analysis incorporated sequentially adjusted association models, restricted cubic splines, measurement-time restrictions, exclusion of values at the assay boundary, and an alternative illness-severity analysis using NEWS. In addition, the prediction analyses evaluated discrimination, overall prediction error, calibration, internal bootstrap validation, and decision-analytic net benefit. Finally, the study explicitly separated association analyses from prediction analyses, avoiding the assumption that a statistically significant prognostic association necessarily confers clinically meaningful incremental predictive performance.[18–23]

Limitations

This study should be interpreted in light of several limitations. First, the retrospective observational design supports estimation of prognostic associations but does not permit causal inference. Residual confounding from incompletely measured or unmeasured factors, including baseline cardiac function, prehospital clinical status, severity of infection before admission, and treatment decisions, cannot be excluded.

Second, this was a single-center study conducted in a tertiary hospital in China. Patient case mix, access to NT-proBNP testing, laboratory platforms, sepsis-management practices, and thresholds for intensive care may differ across institutions and healthcare systems. Therefore, the generalizability of the observed associations and predictive performance requires confirmation in other settings. Prediction-model performance may change across populations because of differences in baseline risk, predictor distributions, predictor measurement, clinical practice, and outcome ascertainment.[21, 25, 40]

Third, NT-proBNP was not measured in all patients with sepsis but was obtained as part of routine clinical care. Restricting the cohort to patients with an eligible early NT-proBNP measurement may have introduced selection bias because clinicians may have been more likely to order NT-proBNP for patients with suspected cardiac dysfunction, dyspnea, volume-status uncertainty, renal impairment, or greater perceived illness severity. Patients with chronic renal insufficiency may have been more likely to undergo BNP rather than NT-proBNP testing in some clinical circumstances. Such testing patterns may have influenced the composition of the analytic cohort, particularly among patients with cardiorenal disease.

Fourth, patients with documented withdrawal of treatment at the request of the patient or family were excluded. This exclusion was intended to reduce the influence of goals-of-care decisions on in-hospital mortality; however, these patients may have differed systematically from included patients in illness severity, comorbidity burden, NT-proBNP concentrations, and underlying prognosis. Selection bias related to this exclusion cannot be excluded, and its direction and magnitude are uncertain. If excluded patients were disproportionately represented among those with very high NT-proBNP concentrations and poor prognosis, the association at the upper end of the NT-proBNP distribution may have been attenuated.

Fifth, the time of ED arrival was not available. The exposure window was therefore anchored to hospital admission rather than ED presentation. Although analyses restricted to NT-proBNP measurements within 6 and 12 hours after hospital admission showed directionally consistent findings, the actual interval from ED arrival, symptom onset, early sepsis recognition, or initiation of resuscitation could not be determined. NT-proBNP concentrations may have been influenced by early ED care, including fluid administration, vasopressor therapy, oxygen supplementation, ventilatory support, diuretic therapy, or other interventions before blood sampling.[7–9, 34, 36, 38]

Sixth, SOFA score was calculated using the worst available values during the first 24 hours after hospital admission. Consequently, the measurement window for SOFA may have overlapped with, or occurred after, NT-proBNP measurement. Adjustment for SOFA was intended to account for early organ dysfunction severity, but this temporal overlap may complicate interpretation of the fully adjusted association. In particular, SOFA could partly reflect clinical deterioration or treatment-related changes occurring after biomarker measurement. For the prediction component, the model should therefore be interpreted as an early in-hospital model rather than a strictly ED-arrival model, because not all SOFA components may have been available at the exact time of initial NT-proBNP measurement.[20, 25, 41]

Seventh, NT-proBNP values reported as at least 35,000 pg/mL were retained at the assay reporting boundary, resulting in right censoring at the upper tail of the distribution. Although exclusion of these

patients did not materially alter the direction of the association, the precise shape of the mortality association among patients with extremely high NT-proBNP concentrations could not be fully assessed.

Eighth, this study focused on a single early NT-proBNP measurement. Serial measurements and changes over time may provide different or potentially more informative prognostic signals than a single measurement.[12] Similarly, systematic echocardiographic data were not incorporated, preventing direct assessment of the relation between NT-proBNP concentration and specific measures of left or right ventricular function, filling pressures, or sepsis-associated myocardial dysfunction.[32–38] This limitation is particularly relevant because sepsis-induced cardiomyopathy is heterogeneous in phenotype and likely reflects multiple dynamically evolving pathophysiological pathways rather than a single uniform ventricular abnormality.[35–38]

Ninth, detailed treatment-related information, including precise fluid balance, vasopressor dose and duration, mechanical ventilation settings, and other time-varying interventions, was not fully incorporated in the primary association model. These factors may be related to both NT-proBNP concentrations and patient outcomes.

Finally, the prediction models were evaluated using bootstrap internal validation only. Because prediction models tend to perform better in the cohort used for their development, apparent performance metrics—including AUC, Brier score, calibration, and decision-curve net benefit—may overestimate performance in new patients, despite bootstrap optimism correction.[20, 30] Given that the incremental improvement attributable to NT-proBNP was already small in the development cohort, its practical value may be further attenuated in external populations with different case mixes, comorbidity profiles, or sepsis-management practices. External validation, model updating where necessary, and prospective impact evaluation of a prespecified NT-proBNP-informed decision strategy will be needed to determine whether clinically meaningful benefit can be achieved.[25, 40, 41]

Conclusion

In this cohort of ED patients with sepsis, higher early NT-proBNP concentrations remained associated with in-hospital mortality after adjustment for measured comorbidities and early organ dysfunction. This adjusted association should not be interpreted as evidence of a causal or mechanistically independent effect.

More importantly, NT-proBNP added little to individual mortality prediction beyond routinely available clinical information: discrimination improved by less than half a percentage point, overall prediction error changed minimally, and apparent decision-curve differences were small and inconsistent. These findings do not support routine use of NT-proBNP as an add-on test for mortality risk stratification in unselected ED patients with sepsis. Future studies should evaluate serial NT-proBNP measurements and predefined NT-proBNP-informed decisions in clinically selected populations with detailed cardiac, renal, hemodynamic, and treatment data.

Abbreviations

AUC, area under the receiver operating characteristic curve; BNP, B-type natriuretic peptide; CI, confidence interval; CRP, C-reactive protein; ED, emergency department; IQR, interquartile range; NEWS, National Early Warning Score; NT-proBNP, N-terminal pro–B-type natriuretic peptide; OR, odds ratio; PCT, procalcitonin; SOFA, Sequential Organ Failure Assessment; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TRIPOD, Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis.

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (Approval No. ZE2026-278-01). The requirement for informed consent was waived by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine due to the retrospective nature of the analysis and the use of de-identified data. The study was conducted in accordance with the Declaration of Helsinki.

Data availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of interest: The authors declare no conflicts of interest.

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Author contributions: Jin Wang and Shijun Guo contributed equally to this work. Jin Wang and Shijun Guo designed the study, extracted and cleaned the data, performed the analyses, interpreted the results, and drafted the manuscript. Yonglin Li, Qiang Li, Guowei Li, Gongna Chen, and Baijian Chen contributed to patient screening, data collection, laboratory data verification, clinical variable definition, statistical support, literature review, and manuscript revision. Dawei Wang and Xiaotu Xi supervised the study, contributed to the study design and analytic strategy, obtained resources and funding, interpreted the findings, and critically revised the manuscript. All authors reviewed and approved the final manuscript. Jin Wang, Dawei Wang, and Xiaotu Xi are the corresponding authors and take responsibility for the integrity of the data and the accuracy of the analysis.

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Figures

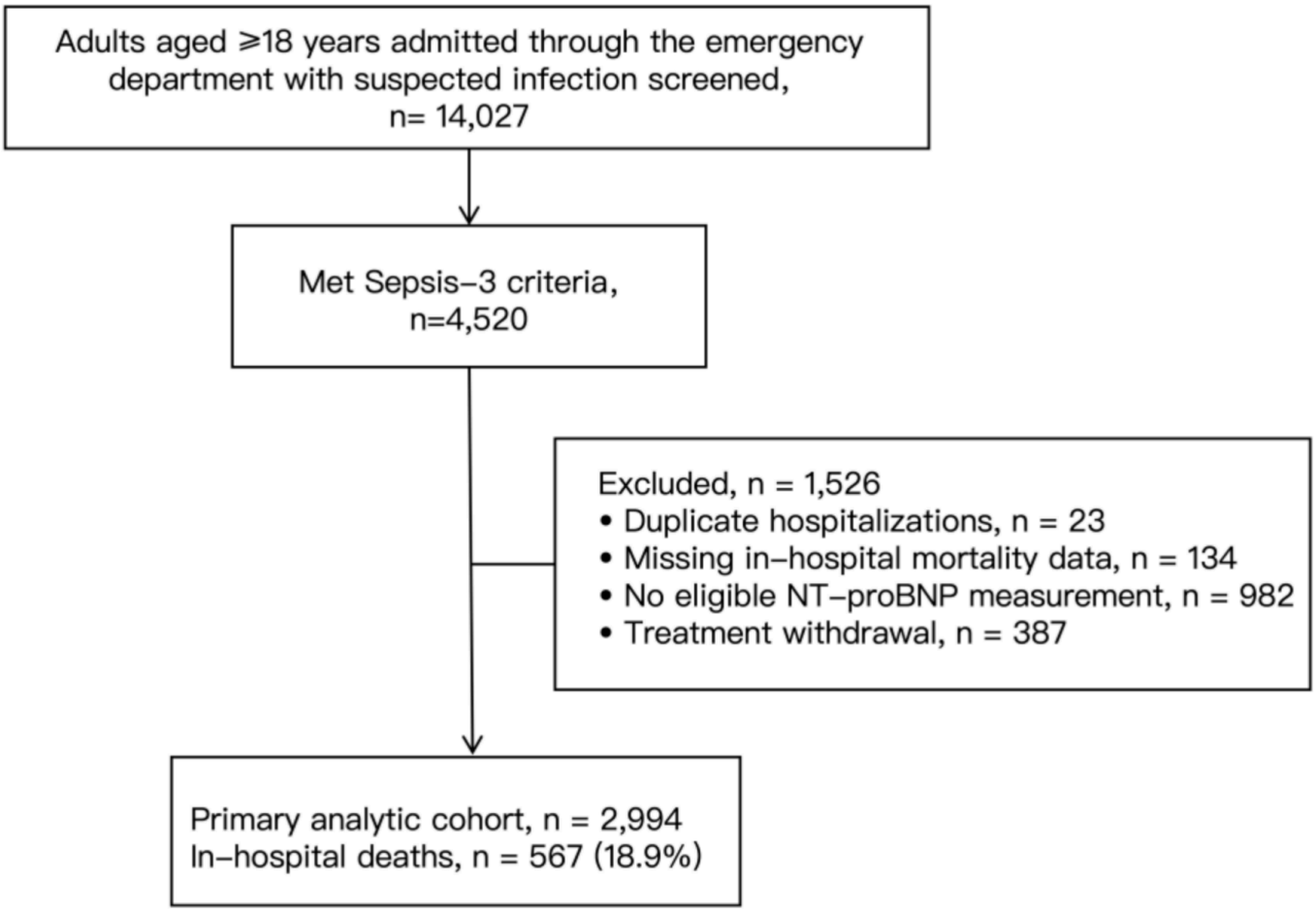

Figure 1

Flow diagram of patient selection. Sepsis was defined according to Sepsis-3 criteria. NT-proBNP indicates N-terminal pro–B-type natriuretic peptide.

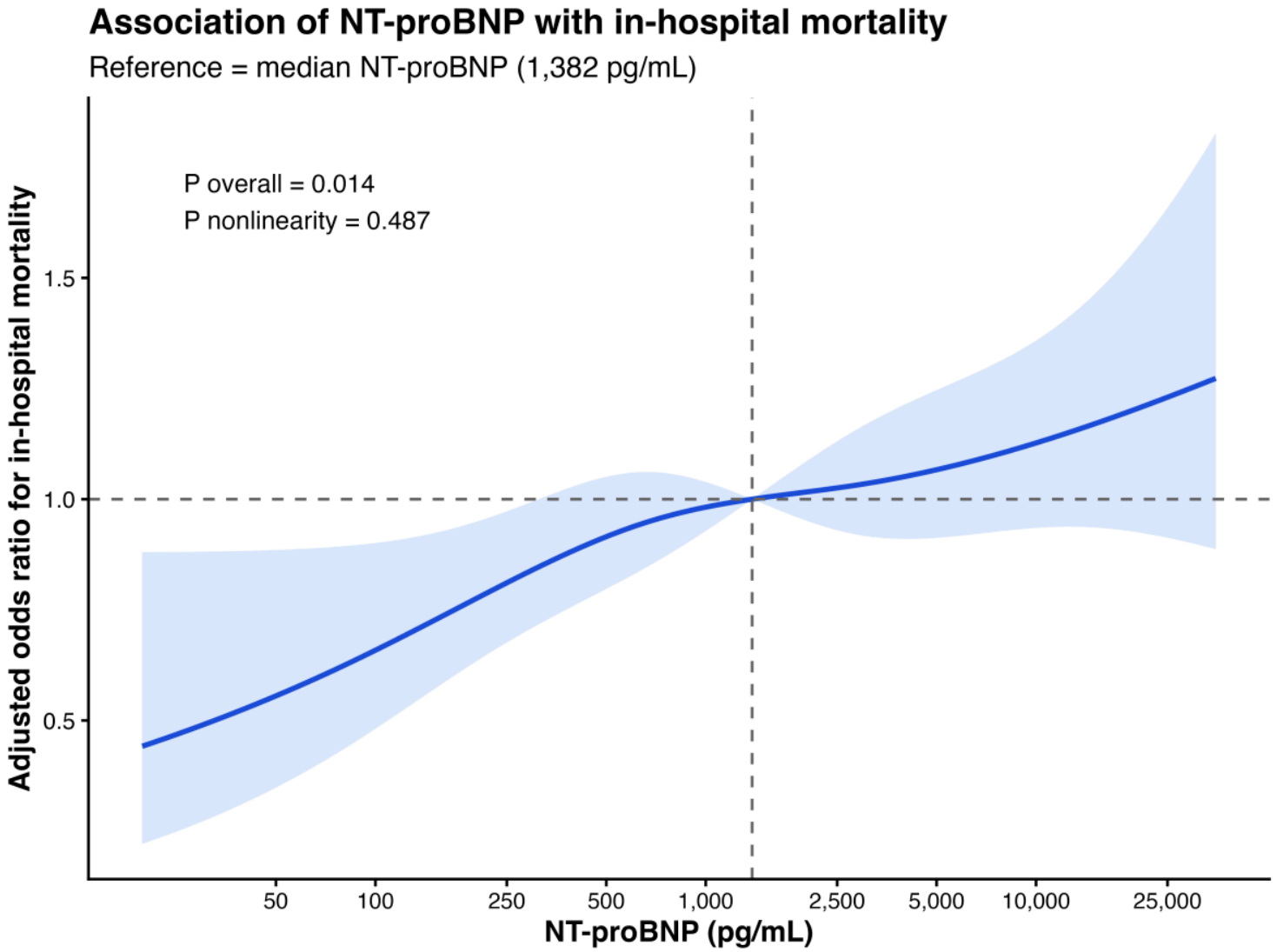

Figure 2

Restricted cubic spline analysis of the association between NT-proBNP and in-hospital mortality. The solid line indicates adjusted odds ratios and the shaded area indicates 95% confidence intervals. The reference value was the median NT-proBNP concentration (1,382 pg/mL). NT-proBNP was modeled on the log2 scale; for clinical interpretability, the x-axis displays original NT-proBNP concentrations with logarithmic spacing. The model was adjusted for age, sex, hypertension, coronary artery disease, chronic heart failure, diabetes, chronic kidney disease, chronic lung disease, cerebrovascular disease, malignancy, and SOFA score. P for overall association = 0.014; P for nonlinearity = 0.487. The curve was displayed between the 1st and 99th percentiles of the NT-proBNP distribution. Four knots were placed at the 5th, 35th, 65th, and 95th percentiles of the log2-transformed NT-proBNP distribution.

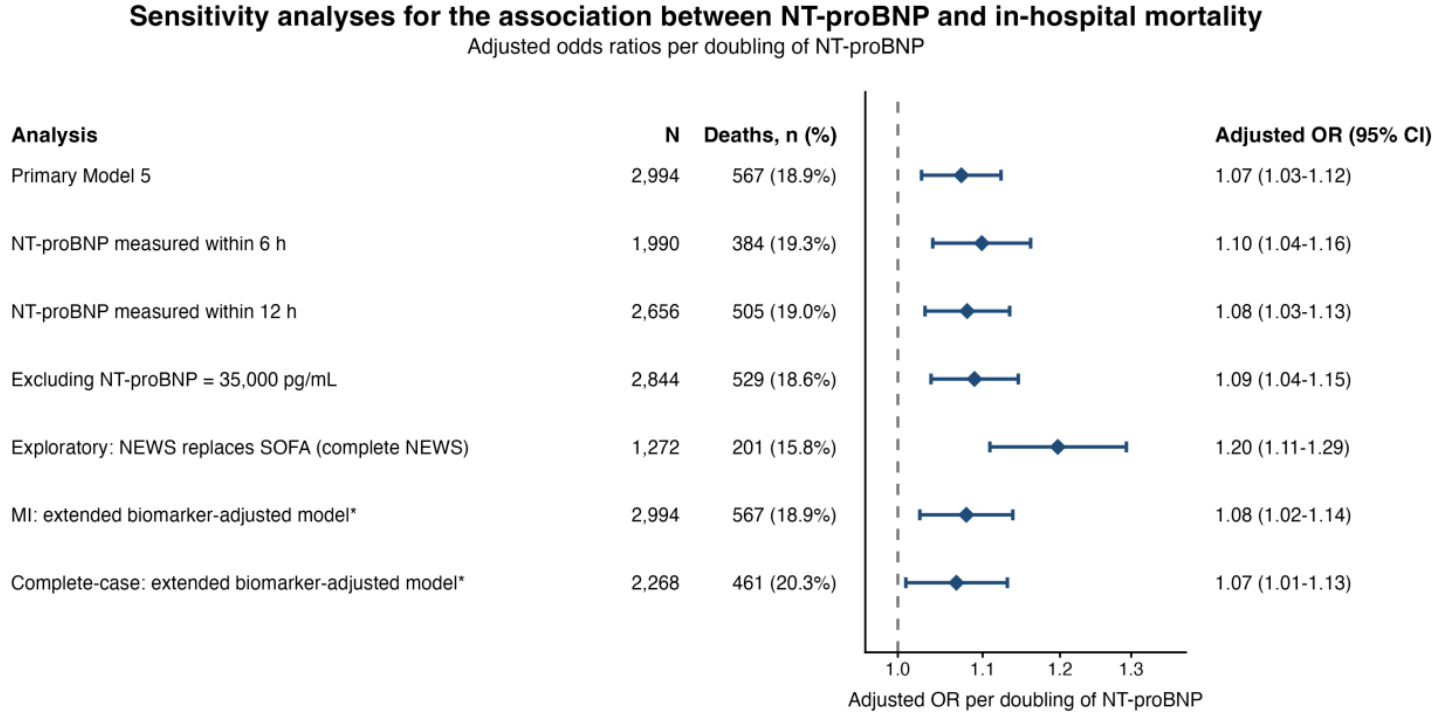

Figure 3

Sensitivity analyses for the association between NT-proBNP and in-hospital mortality. Diamonds indicate adjusted odds ratios (ORs), and horizontal bars indicate 95% confidence intervals (CIs), expressed per doubling of NT-proBNP concentration. The dashed vertical line indicates an OR of 1.0. The primary Model 5 and the timing-restricted and upper-limit exclusion analyses were adjusted for age, sex, hypertension, coronary artery disease, chronic heart failure, diabetes, chronic kidney disease, chronic lung disease, cerebrovascular disease, malignancy, and SOFA score. In the exploratory NEWS analysis, NEWS replaced SOFA score, with all other Model 5 covariates retained. *Biomarker-adjusted sensitivity models included log2-transformed troponin, age, sex, SOFA score, septic shock, chronic heart failure, chronic kidney disease, lactate, creatinine, albumin, C-reactive protein, procalcitonin, white blood cell count, platelet count, blood culture status, and infection source. The multiple-imputation analysis used 20 imputed datasets.

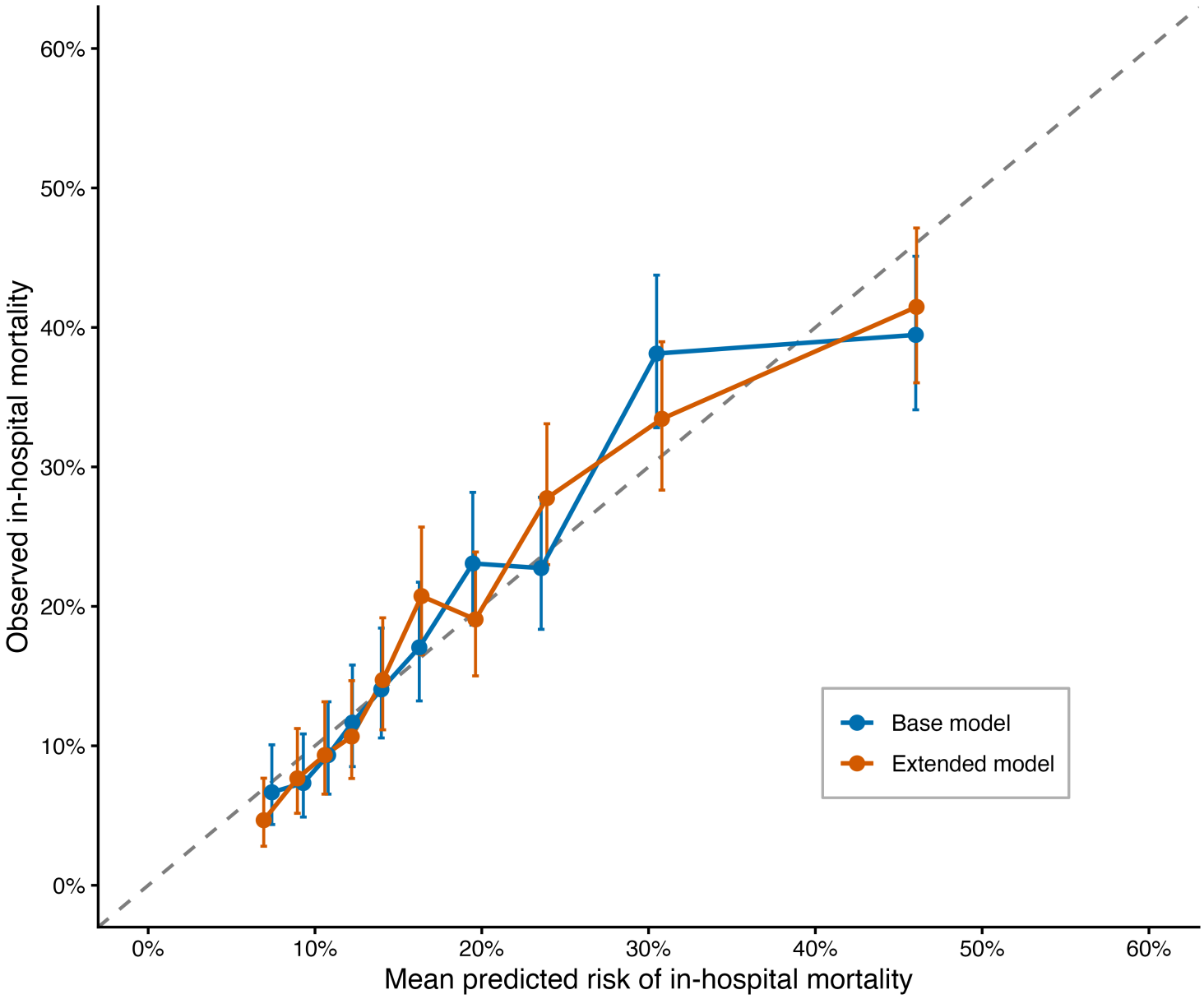

Figure 4

Apparent calibration of the base clinical model and the NT-proBNP–extended model for in-hospital mortality. Points represent observed in-hospital mortality within deciles of predicted risk for the base clinical model and the extended model including log2-transformed NT-proBNP. Vertical error bars indicate Wilson 95% confidence intervals for observed mortality. The dashed diagonal line represents perfect calibration. This figure shows apparent calibration in the development cohort and should not be interpreted as a bootstrap-corrected calibration curve. Bootstrap optimism-corrected calibration intercepts were 0.0006 for both models, and calibration slopes were 0.953 for the base model and 0.950 for the extended model.

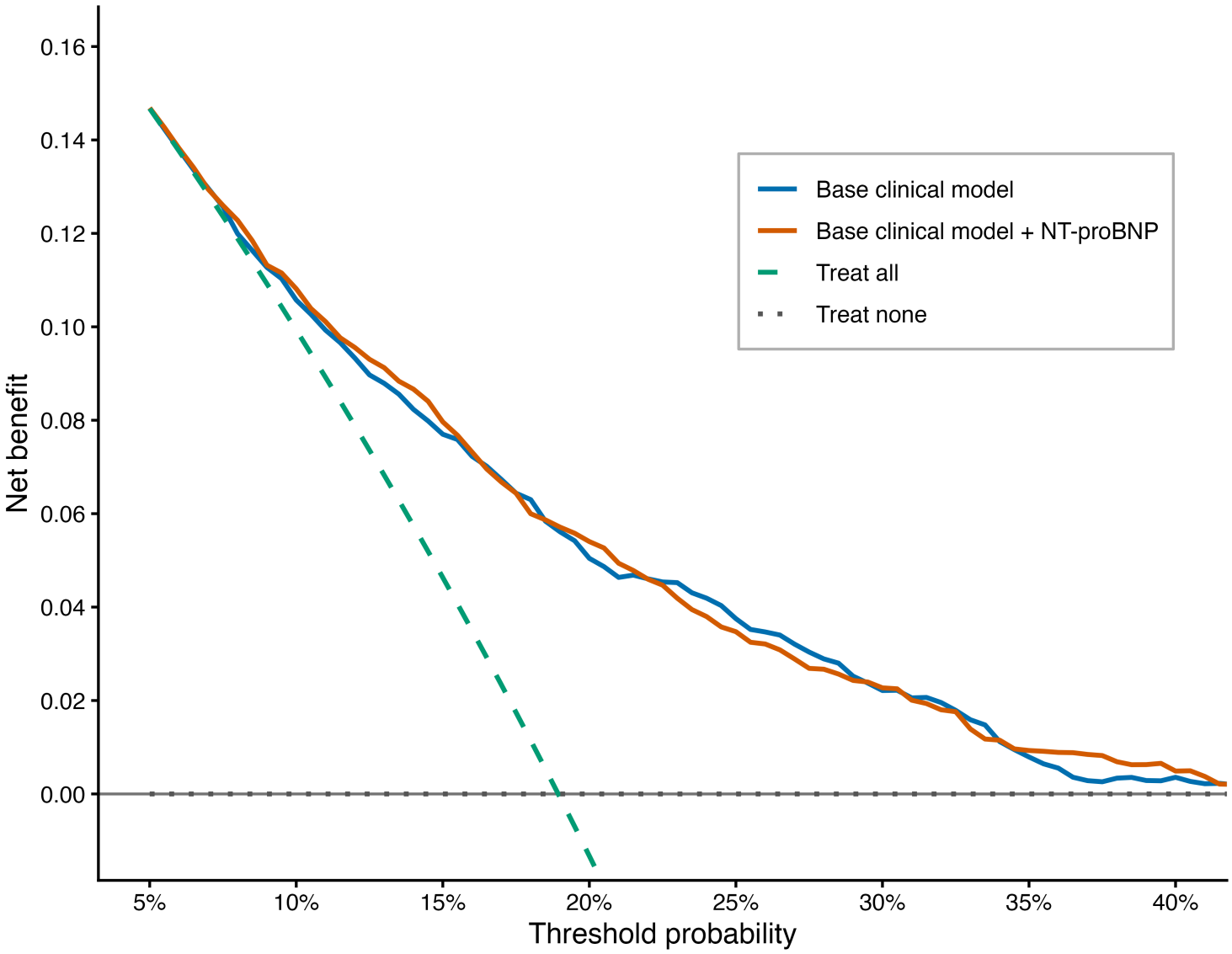

Figure 5

Apparent decision curve analysis for prediction of in-hospital mortality. The base clinical model included age, sex, hypertension, coronary artery disease, chronic heart failure, diabetes, chronic kidney disease, chronic lung disease, cerebrovascular disease, malignancy, SOFA score, and septic shock. The extended model additionally included log2-transformed NT-proBNP. Decision curves were calculated in the development cohort across threshold probabilities from 0.05 to 0.60. To improve visualization of the lower-to-intermediate threshold range, the main figure displays threshold probabilities from 0.05 to 0.40; the full range is shown in *Supplementary Figure S2*. The curves represent apparent net benefit and were not bootstrap optimism-corrected. Treat-all and treat-none strategies are shown for reference.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx