

Full length article

Emergency-transport N-terminal pro-B-type natriuretic peptide, renal function, and discharge outcome after acute stroke

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ABSTRACT

Background: N-terminal pro-B-type natriuretic peptide (NT-proBNP) is often elevated in acute stroke, but reduced estimated glomerular filtration rate (eGFR) can complicate interpretation. We examined its association with poor discharge outcome after adjustment for registry variables.

Methods: We retrospectively studied 256 emergency-transported patients with ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage. The primary outcome was discharge modified Rankin Scale (mRS) 3–6. Logistic regression estimated odds ratios (ORs) per doubling of NT-proBNP, adjusted for age, sex, eGFR, and hemorrhagic stroke. Renal-function and subtype analyses were exploratory.

Results: The primary cohort included 212 patients; 137 (64.6%) had mRS 3–6. NT-proBNP, but not eGFR, was higher with poor outcome. The adjusted OR was 1.29 (95% confidence interval [CI] 1.12–1.50; $P = 0.001$). Renal-stratum ORs were 1.18 (95% CI 0.98–1.42) for $\text{eGFR} \geq 60$ and 1.42 (95% CI 1.11–1.81) for $\text{eGFR} < 60$ mL/min/1.73 m² (interaction $P = 0.196$). Exploratory subtype-specific ORs were 1.39 (95% CI 1.17–1.66) in ischemic stroke and 0.97 (95% CI 0.74–1.28) in intracerebral hemorrhage. The hemorrhagic-versus-ischemic interaction was not significant ($P = 0.204$).

Conclusions: Early NT-proBNP was associated with poor discharge outcome after registry adjustment, without establishing independence from unmeasured confounding. Limited subgroup sizes prevented exclusion of effect modification. Predictive performance was not evaluated; the findings do not support routine clinical risk-stratification use.

1. Introduction

Stroke remains a major cause of death and long-term disability, and clinicians often need to judge early clinical risk before all imaging, neurologic reassessment, and post-acute information are available [1]. A blood test that is already available at emergency presentation can be useful if its interpretation is tied to the clinical context rather than treated as a stand-alone rule.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) reflects myocardial wall stress and is widely used in heart failure care [2]. In acute stroke, NT-proBNP may also rise through sympathetic activation, neurogenic myocardial injury, arrhythmia, heart failure exacerbation, and the broader stroke-heart syndrome [3]. At the same time, estimated glomerular filtration rate (eGFR) strongly affects NT-proBNP. In older

emergency patients, a high value may therefore be discounted as a renal-function artifact rather than read as part of the stroke presentation [4].

Associations between B-type natriuretic peptide or NT-proBNP and mortality or poor functional outcome after stroke have been reported in single-center studies, larger cohorts, and meta-analyses [5–12]. The clinical problem, however, is not only whether NT-proBNP is high in patients with poor outcomes. The practical question is whether an elevated value still carries outcome information after renal function and stroke subtype are considered. This question is especially relevant in routine emergency records, where numeric National Institutes of Health Stroke Scale (NIHSS) values are not always available at transport [13].

This study was designed as an association study, not as a clinical prediction model. We examined whether NT-proBNP measured soon

Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate.

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after emergency transport was associated with discharge functional outcome after adjustment for variables captured in the registry, including age, sex, eGFR, and stroke subtype. Because renal function is central to early interpretation of NT-proBNP, we also examined eGFR-category and eGFR-stratified analyses and tested whether the association differed according to reduced eGFR. Additional sensitivity analyses accounted for numeric NIHSS when available, documented atrial fibrillation and heart failure, nonstandard NT-proBNP entries, stroke subtype, and exclusion of the four subarachnoid hemorrhage cases. In-hospital death was examined as a secondary exploratory outcome. Discrimination, calibration, reclassification, and clinical decision thresholds were outside the scope of this study.

2. Methods

2.1. Study design and population

This was a single-center retrospective cohort study reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [14]. We screened 278 emergency-transported cases registered in the stroke registry of Fukujikai Adachi Tobu Hospital from December 25, 2023, through June 8, 2025. Because the registry also included patients initially suspected of stroke, the analytic population was restricted to patients whose final subtype was confirmed as ischemic stroke, intracerebral hemorrhage (ICH), or subarachnoid hemorrhage (SAH). Cases with unconfirmed subtype or incomplete registry information were excluded. As all eligible cases during the study period were included, no prospective sample-size calculation was performed.

2.2. Variables and measurements

We abstracted age, sex, stroke subtype, transport NIHSS, eGFR, NT-proBNP, time from transport to NT-proBNP measurement, in-hospital death, discharge modified Rankin Scale (mRS), and medical-history entries. Sex was abstracted from the electronic record as male or female; no gender-identity variable was available in this retrospective data set.

The eGFR recorded at emergency evaluation was used. At the institution, eGFR was calculated with the Japanese three-variable creatinine equation [15]. Serum creatinine itself was not retained in the research data set, so recalculation of eGFR was not performed.

Only NIHSS values recorded numerically at transport were used. Japan Coma Scale or Glasgow Coma Scale entries, delayed NIHSS reassessments, and missing entries were treated as missing for the numeric transport NIHSS variable. Because NIHSS missingness was related to the clinical recording process and could not be assumed random, NIHSS was not imputed.

2.3. Exposure and outcomes

The primary exposure was NT-proBNP measured in the first blood test after emergency transport. The primary analysis used values recorded as a single numeric measurement. The primary outcome was poor discharge functional outcome, defined as mRS 3–6; mRS 0–2 was the reference category [16]. Discharge mRS was chosen because it was the most consistently captured short-term functional measure in the registry; 90-day mRS was not available for this analysis. Discharge mRS was not treated as a substitute for 90-day outcome. In-hospital death was analyzed as a secondary exploratory outcome.

2.4. Statistical analysis

Continuous variables are reported as median [interquartile range], and categorical variables as n/N (%). Between-group comparisons used the Mann-Whitney *U* test or Fisher exact test. When a three-level eGFR

category was compared, the chi-square test was used. Correlations between NT-proBNP and age, eGFR, and NIHSS were assessed by Spearman rank correlation.

Because the NT-proBNP distribution was skewed, NT-proBNP was transformed using a base-2 logarithm after adding 1 pg/mL. Effect estimates are reported as odds ratios (ORs) per one-unit increase in the transformed value, referred to as per doubling for readability. The primary model was a complete-case logistic regression for poor discharge outcome adjusted for NT-proBNP, age, sex, continuous eGFR, and hemorrhagic stroke, defined as ICH or SAH versus ischemic stroke. SAH was included with hemorrhagic stroke in the primary model because only four confirmed SAH cases were available; a sensitivity analysis excluding these four cases was added to assess the influence of this grouping. Restricted cubic splines with 4 degrees of freedom were used to examine the functional form of NT-proBNP; the linear term was retained when likelihood-ratio testing did not show a better fit with the spline model.

Renal-function sensitivity analyses addressed the concern that reduced eGFR can raise NT-proBNP even without acute cardiac stress. First, the continuous eGFR term was replaced by eGFR < 60 mL/min/1.73 m². Second, separate models were fitted in eGFR ≥ 60 and eGFR < 60 strata, adjusted for age, sex, and hemorrhagic stroke. Third, a multiplicative interaction between transformed NT-proBNP and eGFR < 60 was added to the eGFR-category model in the full primary cohort. For both renal-function and stroke-subtype interactions, models with and without the interaction term were compared by a one-degree-of-freedom likelihood-ratio test in the same complete cases. Interaction estimates are ratios of ORs with Wald 95% confidence intervals (CIs). These exploratory tests were interpreted descriptively, not as equivalence tests for absence of effect modification.

Additional sensitivity analyses were conducted for four areas. First, numeric transport NIHSS was added in complete cases with NIHSS available. Second, atrial fibrillation and heart failure documented in the medical-history field were identified by prespecified keywords and added to the primary model. Third, nonstandard NT-proBNP entries, such as values preceded by a less-than sign or followed by comments, were parsed by extracting the leading numeric value. Fourth, subtype-stratified models for ischemic stroke and ICH adjusted for age, sex, and continuous eGFR. Separately, transformed NT-proBNP was interacted with hemorrhagic stroke (ICH or SAH versus ischemic stroke) in the primary model, retaining all 212 primary complete cases. Thus, this interaction contrast included SAH, unlike the ICH-only analysis. Missing data were summarized by available-case denominators, with complete-case sets defined separately for each outcome. Two-sided *P* values below 0.05 were considered statistically significant for the primary analysis; sensitivity-analysis *P* values were interpreted descriptively. Verification analyses used Python 3.13.5, pandas 2.2.3, statsmodels 0.14.6, scipy 1.17.0, and matplotlib 3.10.8.

During revision, ChatGPT (GPT-6 Astra Pro; OpenAI) assisted in preparing and checking Python code for analysis verification and figure generation. Estimates and figures were calculated from the registry workbook using the specified software, not generated by the language model. Aggregate outputs were checked against the submitted tables.

2.5. Ethics

This study was approved by the Fukujikai Ethics Committee (approval number 3; approval date May 11, 2026). The requirement for individual consent and the opt-out procedure followed the committee approval and institutional policy for retrospective observational research using existing clinical records.

All clinical information had been recorded during routine care before research analysis; no new data were collected for research purposes after approval. The analytic data set was prepared in a format that did not allow the investigators to directly identify individual patients.

3. Results

3.1. Cohort and baseline characteristics

Of 278 registry entries, 256 patients had confirmed acute stroke: 183 with ischemic stroke, 69 with ICH, and 4 with SAH (Fig. 1). Discharge mRS was available for 254 patients, of whom 161 (63.4%) had poor discharge outcome. A single numeric NT-proBNP value was available for 230 patients; both this value and discharge mRS were available for 228 patients. Transport NIHSS was recorded numerically for 100 patients (39.1%). Among 227 patients with timing information, NT-proBNP was measured 0.5 [0.2, 0.7] hours after emergency transport. The primary complete-case cohort included 212 patients, and 137 (64.6%) had poor discharge outcome.

Baseline characteristics of the primary analytic cohort are shown in Table 1. Patients with poor discharge outcome were older and had higher NT-proBNP values. eGFR was similar between mRS 0–2 and mRS 3–6 groups (65.4 [48.3, 82.0] vs 66.8 [44.7, 84.3] mL/min/1.73 m²; $P = 0.721$), and eGFR < 60 mL/min/1.73 m² was not more common in the poor-outcome group (42.7% vs 38.7%; $P = 0.660$). In the same group order, NT-proBNP was 291.0 [91.0, 878.0] pg/mL in the mRS 0–2 group and 666.0 [161.0, 2550.0] pg/mL in the mRS 3–6 group ($P = 0.002$), indicating higher values in the poor-outcome group. Numeric transport NIHSS was recorded less often in the poor-outcome group, but among those with numeric NIHSS, the NIHSS itself was higher in the poor-outcome group.

The 44 confirmed acute stroke cases excluded from the primary complete-case cohort are compared with included cases in Supplementary Table S1. Available characteristics were generally similar, including age, sex, subtype, eGFR, NT-proBNP, discharge outcome, and in-hospital death. Numeric transport NIHSS was recorded less often in excluded cases (22.7% vs 42.5%; $P = 0.017$).

3.2. Primary association and renal-function analyses

In the primary model, higher NT-proBNP was associated with poor discharge outcome after adjustment for variables captured in this registry, including age, sex, continuous eGFR, and hemorrhagic stroke. The adjusted OR per doubling was 1.29 (95% CI 1.12–1.50; $P = 0.001$). The restricted cubic spline did not improve fit beyond the linear term (likelihood-ratio $P = 0.544$).

The renal-function analyses are summarized in Table 2 and Fig. 2. Replacing continuous eGFR with eGFR < 60 mL/min/1.73 m² produced a similar NT-proBNP estimate (OR 1.27, 95% CI 1.10–1.47; $P = 0.001$). In the eGFR-stratified models, the adjusted OR was 1.18 (95% CI 0.98–1.42; $P = 0.077$) for eGFR ≥ 60 and 1.42 (95% CI 1.11–1.81; $P = 0.005$) for eGFR < 60. No statistically significant interaction was detected between NT-proBNP and eGFR < 60 (ratio of ORs 1.20, 95% CI 0.91–1.60; likelihood-ratio $P = 0.196$). However, the subgroup sizes and confidence intervals were insufficient to exclude clinically meaningful effect modification by renal function. Descriptive three-level eGFR strata are shown in Supplementary Table S3.

3.3. Additional sensitivity analyses

The NIHSS missingness analysis is shown in Supplementary Table S2. Patients with a numeric transport NIHSS had a better discharge mRS distribution than those without one (median 3 vs 4; $P = 0.017$), supporting possible missing not at random. Age, sex, hemorrhagic stroke, eGFR, NT-proBNP, and in-hospital death did not differ clearly by NIHSS availability. NT-proBNP correlated negatively with eGFR ($\rho = -0.46$) and positively with age ($\rho = 0.43$) and NIHSS ($\rho = 0.28$). Therefore, the NIHSS-adjusted model was interpreted as a sensitivity analysis within a selected numeric-NIHSS subset, not as a full-cohort adjustment. In that subset, the direction of association persisted after adding NIHSS (adjusted OR 1.43, 95% CI 1.04–1.96; $P = 0.026$). The adjusted OR for NIHSS itself

was 1.31 per point (95% CI 1.15–1.49; $P < 0.001$). Supplementary Figure S1 shows poor outcome rates by NIHSS severity stratum and NT-proBNP quartile as a descriptive display only.

Adding documented atrial fibrillation and heart failure to the primary model yielded a similar estimate (OR 1.28, 95% CI 1.10–1.49; $P = 0.002$). Including string-parsed NT-proBNP values also gave a similar estimate (OR 1.27, 95% CI 1.11–1.47; $P = 0.001$). Excluding the four SAH cases had little influence on the overall estimate (OR 1.28, 95% CI 1.10–1.48; $P = 0.001$), but the SAH sample was too small for any SAH-specific inference. In exploratory subtype-stratified analyses, the association was clearest in ischemic stroke (OR 1.39, 95% CI 1.17–1.66; $P < 0.001$), whereas the ICH estimate was near the null (OR 0.97, 95% CI 0.74–1.28; $P = 0.838$). The interaction estimate for hemorrhagic stroke (ICH or SAH) versus ischemic stroke was a ratio of ORs of 0.83 (95% CI 0.63–1.10; likelihood-ratio $P = 0.204$; Table 2 and Fig. 2). Subgroup power was limited, and the non-significant interaction should not be interpreted as evidence of no effect modification by stroke subtype.

3.4. Secondary exploratory in-hospital death analysis

Among 255 confirmed acute stroke patients with available death status, 19 died during hospitalization. In the complete-case death model, 13 deaths were available among 213 patients. This set included all 212 primary-cohort patients and one additional survivor with complete explanatory variables but missing discharge mRS. The events per variable (EPV) count was approximately 2.6, so the estimate was expected to be unstable and should be interpreted with explicit caution.

Higher NT-proBNP showed a same-direction association with in-hospital death (adjusted OR per doubling 1.36, 95% CI 1.03–1.78; $P = 0.029$). This result was retained as exploratory support for the main functional-outcome analysis rather than as a mortality model.

4. Discussion

In this single-center emergency-transport cohort, NT-proBNP measured soon after transport was associated with poor discharge functional outcome after adjustment for variables captured in this registry, including age, sex, eGFR, and stroke subtype. This association should not be interpreted as fully independent because prestroke mRS, echocardiographic findings, hematoma volume, and other potential confounders were unavailable, and numeric NIHSS was frequently missing and likely not missing at random. The renal-function analyses nevertheless provide context: eGFR itself was similar between outcome groups, and the NT-proBNP estimate was similar when renal function was handled as a continuous value or a clinical category. The eGFR-stratified estimates pointed in the same direction, but confidence intervals were wide and no statistically significant interaction was detected. Given the subgroup sizes, these findings cannot rule out clinically meaningful effect modification by renal function.

This distinction matters for clinical neurology and emergency cerebrovascular care. Reduced eGFR can increase NT-proBNP and may lead clinicians to regard an elevated value as a renal-function artifact [4]. The present data do not show that NT-proBNP can be read without renal context. They suggest only that renal function alone may not fully account for the observed association. The findings should therefore be viewed as a basis for further evaluation of NT-proBNP together with cardiovascular background, renal function, neurologic severity, and stroke subtype, not as support for routine risk-stratification use.

The direction of the association is consistent with earlier reports of natriuretic peptides and stroke outcomes [5–12]. The added contribution of this study is the focus on early emergency-transport measurement and the explicit handling of renal function. Because discrimination, calibration, reclassification, and decision-analytic performance were not evaluated, the study cannot establish that NT-proBNP improves clinical risk stratification beyond established clinical variables. It also does not

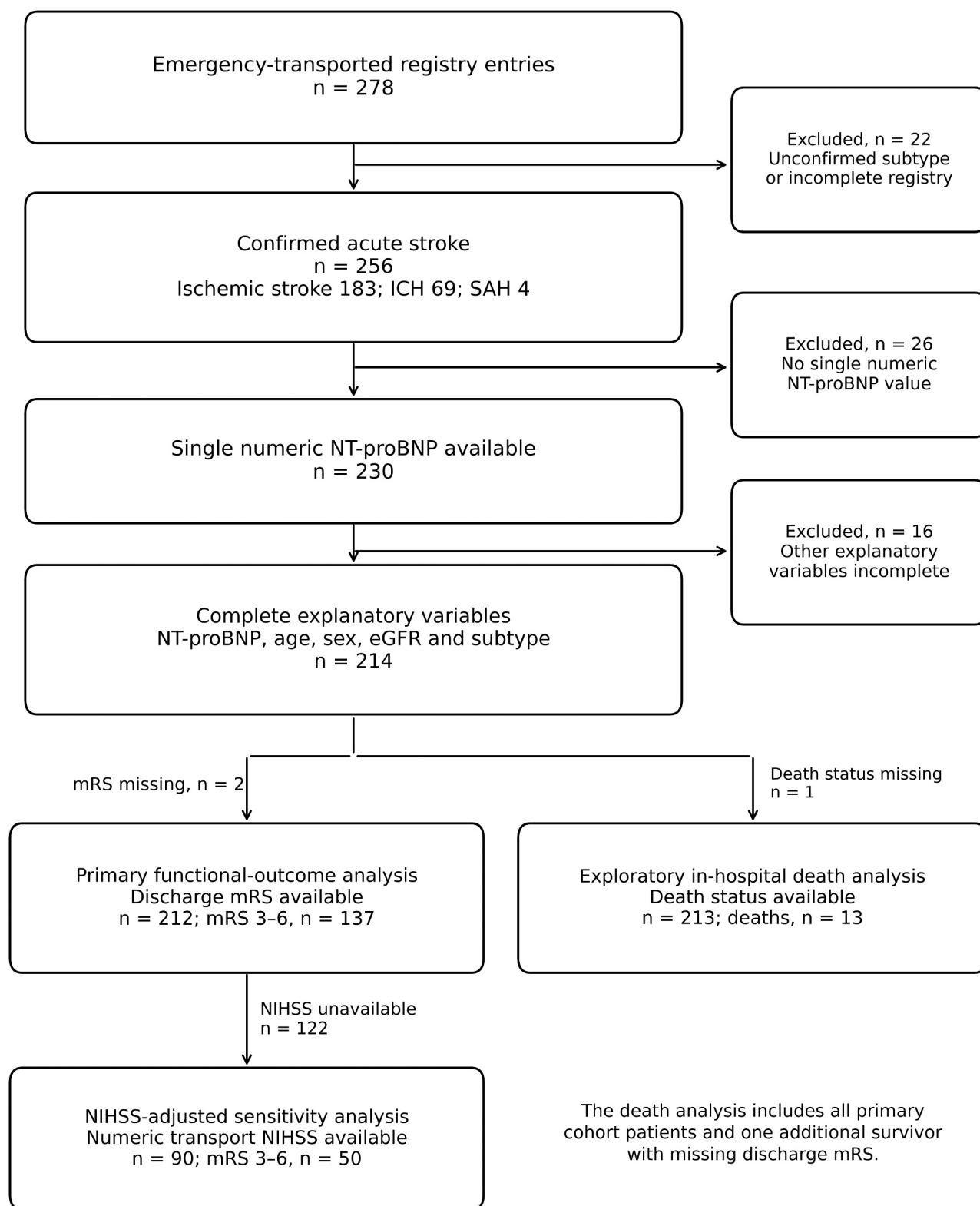


Fig. 1. Cohort selection and outcome-specific analysis sets. Of 256 confirmed stroke cases, 230 had a single numeric NT-proBNP value and 214 had complete explanatory variables. The primary functional-outcome and exploratory death analyses branch from these 214 cases after excluding missing discharge mRS ($n = 2$) or missing death status ($n = 1$), respectively. The branches overlap: all 212 primary-cohort patients are included in the 213-patient death model, together with one additional survivor whose discharge mRS was missing. Availability of discharge mRS ($n = 254$) and numeric NT-proBNP ($n = 230$) in the confirmed cohort is not sequential; both were available in 228 patients. The diagram was rendered with Python/matplotlib using code prepared with assistance from ChatGPT (GPT-6 Astra Pro; OpenAI). eGFR, estimated glomerular filtration rate; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAH, subarachnoid hemorrhage.

Table 1

Baseline characteristics of the primary analytic cohort according to discharge functional outcome.

Variable	Missing, n (%)	Overall (N = 212)	mRS 0–2 (n = 75)	mRS 3–6 (n = 137)	P value
Age, years	0 (0.0%)	80.5 [73.0, 87.0]	77.0 [66.0, 84.0]	82.0 [75.0, 89.0]	0.009
Male sex	0 (0.0%)	124/212 (58.5%)	49/75 (65.3%)	75/137 (54.7%)	0.147
eGFR, mL/min/1.73 m ²	0 (0.0%)	66.5 [46.2, 84.0]	65.4 [48.3, 82.0]	66.8 [44.7, 84.3]	0.721
eGFR < 60 mL/min/1.73 m ²	0 (0.0%)	85/212 (40.1%)	32/75 (42.7%)	53/137 (38.7%)	0.660
NT-proBNP, pg/mL	0 (0.0%)	474.0 [132.0, 1972.5]	291.0 [91.0, 878.0]	666.0 [161.0, 2550.0]	0.002
Hemorrhagic stroke (ICH or SAH)	0 (0.0%)	59/212 (27.8%)	17/75 (22.7%)	42/137 (30.7%)	0.262
Transport NIHSS, numeric cases only	122 (57.5%)	6.5 [3.0, 15.8]	3.0 [1.0, 6.0]	12.0 [6.0, 19.8]	< 0.001
In-hospital death	0 (0.0%)	13/212 (6.1%)	0/75 (0.0%)	13/137 (9.5%)	0.005
Numeric transport NIHSS available	0 (0.0%)	90/212 (42.5%)	40/75 (53.3%)	50/137 (36.5%)	0.020

Note: The primary analytic cohort included confirmed acute stroke cases with complete data for discharge mRS, NT-proBNP, age, sex, eGFR, and stroke subtype. The missing column is calculated within the primary analytic cohort. Transport NIHSS was summarized with available-case denominators. eGFR, estimated glomerular filtration rate; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAH, subarachnoid hemorrhage.

identify a treatment-changing threshold or support routine use for prognostic risk stratification. It instead addresses the narrower bedside question of whether an elevated early value remains associated with discharge outcome when eGFR is considered. The answer from these data is suggestive, but not definitive.

The subtype findings were also clinically informative. In ischemic stroke, NT-proBNP was more clearly associated with poor discharge outcome, possibly reflecting atrial fibrillation, atrial cardiopathy, heart failure, or cardioembolic mechanisms that can influence both stroke phenotype and recovery. In ICH, the association was not consistent. Short-term outcome after ICH is strongly shaped by local factors such as hematoma volume, hematoma location, intraventricular extension, early consciousness disturbance, and acute treatment decisions, which were not available in this data set. These factors may leave less room for a systemic biomarker such as NT-proBNP to explain poor outcome. The ICH group also had a high poor-outcome rate, which may have reduced outcome contrast and further limited power. Because the interaction by hemorrhagic stroke was not statistically clear, these subgroup findings should be considered hypothesis-generating.

The NIHSS analysis is important for interpretation. Numeric NIHSS was available in only 39.1% of confirmed acute stroke cases, and discharge mRS was worse in patients without a numeric NIHSS entry. This pattern suggests possible missing not at random. For that reason, the NIHSS-adjusted model cannot prove independence from neurologic severity in the whole cohort. It does, however, show that the NT-proBNP association did not disappear in the subset where numeric NIHSS was available. This is compatible with, but does not prove, the possibility that NT-proBNP contains information beyond a simple restatement of measured neurologic deficit.

The death analysis was retained because in-hospital death is

Table 2

Adjusted associations of NT-proBNP with poor discharge outcome, renal-function analyses, and exploratory in-hospital death.

Model	N	Events	Adjusted OR / ratio of ORs (95% CI)	P value
Primary model for poor discharge outcome, continuous eGFR	212	137	1.29 (1.12–1.50)	0.001
eGFR category model, eGFR < 60 vs ≥ 60	212	137	1.27 (1.10–1.47)	0.001
eGFR ≥ 60 stratum	127	84	1.18 (0.98–1.42)	0.077
eGFR < 60 stratum	85	53	1.42 (1.11–1.81)	0.005
NT-proBNP × eGFR < 60 interaction	212	137	1.20 (0.91–1.60)	0.196
SAH-excluded sensitivity	208	135	1.28 (1.10–1.48)	0.001
+Numeric transport NIHSS	90	50	1.43 (1.04–1.96)	0.026
+Documented AF and HF history	212	137	1.28 (1.10–1.49)	0.002
String-parsed NT-proBNP sensitivity	220	141	1.27 (1.11–1.47)	0.001
Ischemic stroke only	153	95	1.39 (1.17–1.66)	< 0.001
Intracerebral hemorrhage only	55	40	0.97 (0.74–1.28)	0.838
NT-proBNP × hemorrhagic stroke interaction	212	137	0.83 (0.63–1.10)	0.204
In-hospital death (secondary exploratory; EPV=2.6)	213	13	1.36 (1.03–1.78)	0.029

Note: Estimates are adjusted odds ratios (ORs) per doubling of NT-proBNP, except the two interaction rows, which report ratios of ORs. The renal interaction compares eGFR < 60 with ≥ 60 mL/min/1.73 m²; the subtype interaction compares ICH or SAH with ischemic stroke. Both interaction P values were obtained by likelihood-ratio testing, whereas other model P values and all 95% confidence intervals (CIs) are Wald-based. Non-significant interactions do not establish absence of effect modification. The primary and death models adjusted for age, sex, continuous eGFR, and hemorrhagic stroke. The eGFR-category model replaced continuous eGFR with eGFR < 60; eGFR-stratified models adjusted for age, sex, and hemorrhagic stroke. Subtype-stratified models adjusted for age, sex, and continuous eGFR. The ICH-only model excludes SAH, whereas the subtype-interaction model includes SAH and assumes common covariate effects apart from the NT-proBNP interaction. Sensitivity-analysis P values are descriptive. The death model includes all 212 primary-cohort patients and one additional survivor with complete explanatory variables but missing discharge mRS; 13 deaths give approximately 2.6 events per variable (EPV). Documented AF and HF were identified by keyword search and may be misclassified. Only four SAH cases were available; no SAH-specific inference can be made. AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; HF, heart failure; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAH, subarachnoid hemorrhage.

clinically meaningful and showed a same-direction association. However, only 13 deaths entered the complete-case model, giving an EPV of approximately 2.6. The estimate should therefore be read as exploratory support for the main functional-outcome result, not as a mortality prediction model. The main claim of this study remains the association with discharge functional outcome.

This study has limitations. It was retrospective and single-center, and testing and recording processes may have introduced selection bias. The cohort was drawn entirely from a single hospital in Japan, and eGFR was calculated using the Japanese three-variable creatinine equation; generalizability to other populations and equations is uncertain. Pre-stroke mRS was not available, so baseline disability may have amplified the observed association between NT-proBNP and discharge mRS. Reperfusion therapy, occlusion site, hematoma volume, onset-to-sampling time, echocardiographic findings, and myocardial injury markers were not included in the research data set. Numeric NIHSS was frequently missing and likely not missing at random, so the NIHSS-adjusted analysis represents a selected subset and cannot establish independence from neurologic severity. The renal-function strata were small, particularly the three-level subgroups, and the interaction analyses had limited power; therefore, non-significant interaction results

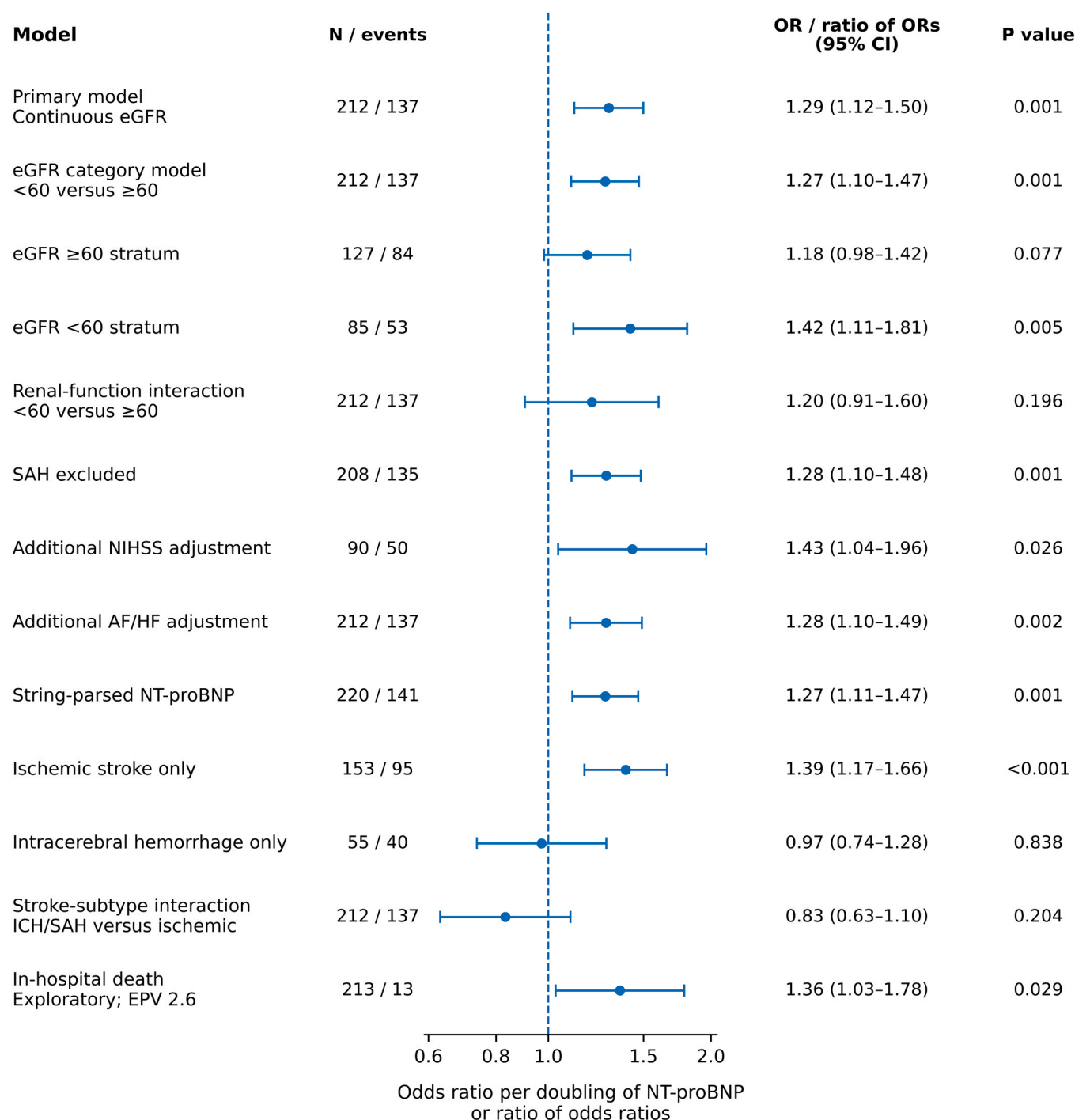


Fig. 2. Adjusted associations of NT-proBNP with poor discharge outcome, exploratory interactions, and in-hospital death. Points and error bars show adjusted odds ratios (ORs) per doubling of NT-proBNP and Wald 95% confidence intervals (CIs), except the two interaction rows, which show ratios of ORs. The renal interaction compares estimated glomerular filtration rate (eGFR) < 60 with ≥ 60 mL/min/1.73 m²; the subtype interaction compares intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH) with ischemic stroke. Both interaction P values use likelihood-ratio tests; other model P values use Wald tests. The separately fitted ICH-only model excludes SAH, whereas the subtype-interaction model includes SAH. Interaction analyses were exploratory and cannot exclude clinically meaningful effect modification. The death model includes one additional survivor with missing discharge modified Rankin Scale and is exploratory because 13 deaths correspond to events per variable (EPV) of approximately 2.6. The plot was rendered from aggregate analysis outputs using Python/matplotlib; code assistance is described in Methods 2.4. AF, atrial fibrillation; HF, heart failure; NIHSS, National Institutes of Health Stroke Scale; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

cannot exclude clinically meaningful effect modification by renal function or stroke subtype. The in-hospital death model included only 13 events and was too imprecise to support mortality prediction. Only four patients had SAH, so no SAH-specific inference can be made and the overall findings should not be applied to patients with SAH. Atrial fibrillation and heart failure were identified by keyword search of

medical-history text fields, which may have introduced misclassification. Discharge mRS was used because it was the most consistently recorded functional outcome, but 90-day mRS is the conventional endpoint for stroke prognosis. Discharge status may vary with length of stay, transfer and rehabilitation pathways, family support, and other social circumstances; it therefore represents an early hospital outcome

rather than longer-term functional prognosis. eGFR was extracted as a recorded value, and serum creatinine was not retained in the research data set, preventing recalculation. Finally, complete-case modeling may leave selection bias if missingness is related to stroke severity or outcome.

Despite these limitations, the study addresses a practical emergency-care question using the data structure that clinicians actually face. NT-proBNP was measured early, eGFR and subtype were accounted for among the variables available, and NIHSS missingness was not hidden by imputation. The findings should be interpreted as evidence of association rather than validation of a prognostic tool. Prospective studies should determine whether NT-proBNP adds predictive value when combined with standardized neurologic, imaging, renal, and cardiovascular variables.

5. Conclusions

NT-proBNP measured soon after emergency transport was associated with poor discharge functional outcome after adjustment for variables captured in this registry, including age, sex, eGFR, and stroke subtype. This does not establish independence from unmeasured confounding. The renal-function subgroup and interaction analyses were underpowered and cannot exclude effect modification, while NIHSS missingness that was likely not at random limits assessment of neurologic severity. Only four SAH cases were included, so the findings do not support SAH-specific inference. The exploratory death analysis was based on few events. Because predictive performance and 90-day outcome were not evaluated, the present data do not support routine use of NT-proBNP for clinical risk stratification. Prospective validation with systematic NIHSS recording, prestroke function, structured cardiovascular and imaging variables, 90-day outcome, and predictive-performance assessment is required.

CRedit authorship contribution statement

Akiko Ogawa: Writing – original draft, Investigation, Data curation. **Nobuo Kutsuna:** Writing – review & editing, Visualization, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Ayuka Shigemura:** Writing – review & editing, Validation, Methodology. **Yoko Tsuchiya:** Writing – review & editing, Investigation, Data curation. **Ikue Sakemi:** Writing – review & editing, Investigation, Data curation.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT (OpenAI) to translate the original Japanese manuscript into English and to assist with English-language editing. During revision, ChatGPT (GPT-6 Astra Pro; OpenAI) also assisted in preparing and checking Python code for analysis verification and figure generation. The code was executed on the registry data, and aggregate outputs were checked against the submitted results. The authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.clineuro.2026.109651](https://doi.org/10.1016/j.clineuro.2026.109651).

Data availability

Individual participant data will not be made publicly available because of privacy protection and the conditions of ethics approval. Requests for an anonymized minimum data set, variable definitions, and the main analysis code should be directed to the corresponding author and will be reviewed case by case under approval from the Fukujikai Ethics Committee and institutional data-use procedures.

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