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ORIGINAL RESEARCH

Impact of Acute Myocardial Injury on Short- and Long-Term Outcomes in Patients With Primary Intracerebral Hemorrhage

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BACKGROUND: Myocardial injury is common after brain injury; however, few studies have reported serial cardiac troponin (cTn) measurements to distinguish whether the myocardial injury is acute or chronic. The fourth Universal Definition of Myocardial Infarction introduced for the first time the criteria for acute myocardial injury (AMI). We aimed to investigate the prevalence and prognostic implications of AMI in primary intracerebral hemorrhage.

METHODS AND RESULTS: We retrospectively analyzed patients with primary intracerebral hemorrhage within 48 hours after symptom onset. All patients included had at least 2 cTn measurements: 1 obtained at the time of emergency admission and at least 1 more within the first 2 days of hospitalization. AMI was defined as an elevated cTn above the upper-reference limit (14 ng/L) along with a rise/fall >20%. Patients were followed for up to 5 years. Outcomes included major adverse cardiac events (MACEs; a composite of vascular death, nonfatal coronary events, and nonfatal stroke) and 90-day unfavorable outcomes (modified Rankin scale score ≥4). Cox proportional hazards models, multivariable logistic regression models, and Kaplan–Meier analyses were used to evaluate the association between AMI and outcomes. Of 600 patients included, 115 had AMI (19.2%). AMI independently conferred an increased risk for major adverse cardiac events (adjusted hazard ratio, 1.69 [95% CI, 1.12–2.53]) and 90-day unfavorable outcomes (adjusted odds ratio, 2.15 [95% CI, 1.26–3.67]) compared with patients without AMI.

CONCLUSIONS: AMI is relatively common in patients with intracerebral hemorrhage and is associated with both long-term major adverse cardiac events and 90-day unfavorable outcomes.

Key Words: cerebral hemorrhage ■ myocardial injury ■ prognosis ■ stroke ■ troponin

See Editorial by Rennenberg and Nolte.

Primary intracerebral hemorrhage (ICH) accounts for 10% to 15% of all stroke types. Although considerable progress has been made in the management of ICH, it remains a major clinical threat because of its relatively high morbidity and mortality rate.[1] In recent years, it has been increasingly recognized that acute brain injuries can have immediate deleterious effects on the heart, which has been described as stroke–heart syndrome.[2–4] In addition to acute neurocardiogenic alterations, the occurrence of stroke–heart syndrome is associated with long-term prognosis in patients with acute ischemic stroke, but data in patients with ICH are scarce.

An elevation in serum cardiac troponin (cTn) indicates injury to myocardial cells and is frequently detected among patients with stroke, even in the absence of acute coronary syndrome or myocardial infarction.[5,6] Acute myocardial injury (AMI) is a common

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CLINICAL PERSPECTIVE

What Is New?

- In the setting of primary intracerebral hemorrhage, the presence of acute myocardial injury is associated with an increased risk of long-term major adverse cardiovascular events, including vascular death, stroke recurrence, and nonfatal acute coronary events; however, similar results were not obtained in patients with chronic myocardial injury (ie, with stable cardiac troponin elevation).

What Are the Clinical Implications?

- Our results suggest that identifying patients with acute myocardial injury via serial cardiac troponin measurements can yield important information to refine risk stratification for both short- and long-term outcomes in primary intracerebral hemorrhage.
- Our results may provide new insights into secondary neurocardiac injury and prompt mechanism-oriented efforts to develop novel therapeutic strategies for intracerebral hemorrhage.

Nonstandard Abbreviations and Acronyms

cTn	cardiac troponin
hs-cTnT	high-sensitivity troponin T
ICH	intracerebral hemorrhage
IVH	intraventricular hemorrhage
MACEs	major adverse cardiovascular events
NIHSS	National Institutes of Health Stroke Scale
UDMI	universal definition of myocardial infarction
URL	upper reference limit

type of stroke–heart syndrome. Notably, in the clinical setting, it can be challenging to differentiate acute injury from chronic conditions if only a single cTn sampling is obtained, as stroke typically occurs among older individuals and is associated with a high burden of cardiovascular comorbidities that can lead to chronic increases in cTn values.[7,8] Previous studies have yielded conflicting results concerning the role of elevated cTn in the prognosis of ICH.[9–12] These discrepancies might be attributed to the analysis of patients with elevated cTn in general without differentiating between AMI and chronic myocardial injury. The fourth version of the universal definition of myocardial infarction (UDMI) recommended confirming a new dynamic rising or falling pattern (>20%) of cTn values above the 99th-percentile upper reference limit (URL) for defining AMI,[13] and studies on the prognosis of patients with ICH and AMI are limited. A definitive answer to this question would assist in clarifying the necessity for serial sampling for patients with ICH with asymptomatic cTn elevation.

Considering these aspects, we aimed to explore the frequency of AMI and its association with long-term major adverse cardiovascular events (MACEs) and 90-day functional independence in patients with primary ICH.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

This study was designed as a retrospective analysis of prospectively collected data from patients with ICH hospitalized at the Neurology Department, Second Affiliated Hospital of Zhejiang University. The institutional ethical committee approved the study protocol (2018083), and informed consent was obtained from all patients or their relatives.

A total of 895 patients who met the inclusion criteria were recruited between November 2016 and February 2021. The inclusion criteria included a neuroimaging-confirmed diagnosis of primary ICH and admission to the hospital within 48 hours after symptom onset. The exclusion criteria were as follows: (1) conversion to any type of surgical hematoma evacuation; (2) severe renal insufficiency with an estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2; (3) persistent or permanent atrial fibrillation; (4) symptoms and ECG findings fulfilling the criteria for myocardial ischemia; (5) history of cardiac intervention (eg, coronary artery bypass surgery or percutaneous coronary intervention) within the past 4 weeks; (6) insufficient cTn data on initial evaluation or within the following 2 days during hospitalization; or (7) loss to follow-up.

Patient Characteristics

Demographics, cardiovascular risk factors, past history of stroke, National Institutes of Health Stroke Scale (NIHSS) score, Glasgow Coma Scale score, systolic blood pressure, and diastolic blood pressure were collected at baseline via standardized data collection methods, as previously described.[14] Imaging data, including the hematoma volume, hematoma location,

and presence of intraventricular hemorrhage (IVH), were collected. The hematoma volume was measured with open-source ITK-Snap software (University of Pennsylvania, Philadelphia, PA; www.itksnap.org). ICH pathogenesis was classified as hypertension, amyloid angiopathy, or undetermined type according to the SMASH-U (structural vascular lesions, medication, cerebral amyloid angiopathy, systemic disease, hypertension, or undetermined) system.[15]

Laboratory Analysis

High-sensitivity troponin T (hs-cTnT, 99th percentile URL, 14 ng/L according to healthy reference population; limit of blank, 3 ng/L; limit of detection, 5 ng/L) levels were obtained in all included patients on emergency admission, and at least 1 more measurement was obtained within the first 2 days of hospitalization. According to the fourth UDMI, AMI was defined as at least 1 hs-cTnT value greater than the URL with a rise/fall >20% on serial measurements; if the minimum value was less than the URL, the maximum value was required to exhibit an increase of >50% of the URL (ie, 7 ng/L with our deployed assay).[13] If >2 hs-cTnT values were available, the difference between the minimum and maximum level was used. Patients who did not meet these criteria were defined as no AMI or were further categorized as no myocardial injury (all hs-cTnT values equal to URL or lower) or chronic myocardial injury (at least 1 value greater than the URL but no rise/fall >20%) for sensitivity analyses. Time from symptom onset to first, second, and peak hs-cTnT values were recorded. The other laboratory parameters collected at the time of admission included white blood cells, neutrophils, and leukocytes. The neutrophil-to-lymphocyte ratio was calculated on the basis of the differential blood count as neutrophils divided by lymphocytes. The value of total cholesterol, low-density lipoprotein cholesterol, and creatine were extracted from the results obtained in the morning the day after admission. The creatinine level was used to calculate the eGFR according to the Chronic Kidney Disease Epidemiology Collaboration equation.[16]

Study Outcomes

The study primary end point (MACEs) was a composite of nonfatal recurrent stroke (ischemic or hemorrhagic stroke), nonfatal acute coronary events (ie, unstable angina pectoris, ST-segment elevation, and non–ST-segment–elevation myocardial infarction), and vascular death.[17] The secondary end points were individual components of MACEs and 90-day unfavorable outcomes. Stroke was defined as an acute episode of focal neurological dysfunction confirmed by brain imaging (ie, computed tomography or magnetic resonance imaging). Acute coronary events were defined as acute episodes of chest pain associated with electrocardiographic evidence of myocardial ischemia and elevated levels of cardiac biomarkers, such as creatine kinase–MB or cTn, above cutoff values. Vascular death was defined as death within 30 days of stroke, death within 7 days of a nonfatal coronary event, death caused by noncerebral hemorrhage or necrosis following peripheral artery occlusion or pulmonary embolism, or death within 24 hours of a previous good and stable condition without another identifiable cause.[18] The functional outcome was measured with the modified Rankin Scale score, and an unfavorable outcome was defined as a modified Rankin Scale score ≥4. Patients were prospectively followed up after discharge at 3, 6, and 12 months and annually thereafter for up to 5 years. Each end point was obtained via structured telephone interviews by a team of independent and well-trained researchers who were blinded to the purpose of this study and not involved in the management of patients. Follow-up data were censored at the date of death, loss to follow-up, or June 2022.

Statistical Analysis

Categorical variables are summarized as n (%) and were compared via the Pearson χ^2 test. For continuous variables, the means±SDs are reported for normally distributed data, and the medians with interquartile ranges are reported for variables with skewed distributions. Continuous variables were compared via Student's *t* test or the Mann–Whitney *U* test, as appropriate. Time-to-event analyses were performed via the Kaplan–Meier method, and the results were compared via the log-rank test. Unadjusted and adjusted Cox proportional hazards regression analyses were used to compare the AMI and non-AMI groups by time to the first composite MACE end point and each individual MACE component separately. To evaluate the association between AMI status and the risk of 90-day unfavorable outcomes, logistic regression models were developed. To control for potential confounding factors, we examined variables associated with outcomes of interest in univariable analyses at a significance level of $P<0.1$, as well as variables related to outcomes of interest on the basis of clinical knowledge and literature review. Our list of candidate covariates for the risk of MACEs included age, sex, NIHSS score, ICH pathogenesis, medical history of hypertension, diabetes, prior stroke, coronary artery disease, history of smoking, eGFR values, ICH volume, lobar location, deep location, and IVH status. Our list of candidate covariates for the risk of 90-day unfavorable outcomes included age, sex, Glasgow Coma Scale score, NIHSS score, prior stroke, eGFR values, ICH volume, infratentorial location, and IVH

status. We subsequently used backward elimination procedures to arrive at a minimal model including only variables associated with the outcome of interest at $P<0.05$. The proportional hazards assumption was tested by the Schoenfeld residuals test and graphic check after fitting Cox proportional hazards models, and the proportionality assumption was not violated. The results for time to prespecified events are reported as hazard ratios (HRs) with 95% CIs, and those for 90-day unfavorable outcomes are reported as odds ratios.

Sensitivity analyses were carried out by categorizing patients into those with acute/chronic/no myocardial injury according to the fourth UDMI criteria, with patients categorized as having no myocardial injury as the reference. In addition, we repeated the analyses after including a subset of patients with a history of atrial fibrillation.

Statistical analyses were performed using R Statistical Software version 4.3.1 (R Core Team 2023). All the statistical tests were 2-sided, and $P<0.05$ was considered to indicate statistical significance.

RESULTS

From November 2016 to February 2021, 895 eligible patients were screened for our study. Of these, 295 patients were excluded: 9 underwent any type of surgical hematoma evacuation, 56 had comorbidities associated with elevated cTn, 27 had insufficient hs-cTnT data on admission, 171 had no serial cTn measurements, and 32 had no follow-up data after discharge. Finally, 600 patients (median age, 63 [interquartile range, 54–71] years, 66.3% men) who met the inclusion and exclusion criteria were included. A study flowchart is shown in Figure 1. Compared with patients who were excluded, patients who met the inclusion criteria were less likely to report a history of diabetes and were found more frequently with deep hemorrhage (Table S1).

Patient Characteristics

Two hs-cTnT measurements were obtained in 553 (92.2%) patients, 3 hs-cTnT measurements in 40 (6.7%) patients, and 4 hs-cTnT measurements in 7 (1.2%) patients. According to the fourth UDMI, 115 (19.2%) patients were classified as having AMI. Detailed patient characteristics stratified by AMI status are summarized in Table 1. Patients with AMI compared with those without AMI were older, had a higher NIHSS score and lower Glasgow Coma Scale score at admission, and were more likely to have a medical history of diabetes and coronary artery disease. In addition, patients with AMI had a greater white blood cell count and neutrophil-to-lymphocyte ratio, whereas patients without AMI had higher total cholesterol and low-density lipoprotein cholesterol levels. In terms of ICH parameters, the presence of AMI was associated with a larger hematoma volume, lobar hemorrhage, and the presence of IVH. Baseline characteristics for patients categorized in 3 groups (acute versus chronic versus no myocardial injury) are shown in Table S2.

The median time from stroke onset to first, second, and peak hs-cTnT measurement, as well as median time interval between the first and second the hs-cTnT measurements, did not differ between patients with or without AMI (all $P>0.05$; Table 2). Results remained the same after categorizing patients by presence of no myocardial injury, chronic myocardial injury, and acute myocardial injury (Table S2).

AMI and Long-Term MACEs

During the median follow-up of 3.7 (interquartile range, 2.4–4.8) years, there were 130 (21.7%) patients with MACEs (Table 2). Nonfatal recurrent stroke accounted for 85 cases, nonfatal myocardial infarction accounted for 4 cases, and vascular deaths accounted for 51 cases. In total, 10 patients had 2 events during the observation period (nonfatal recurrent stroke and vascular death in 8 patients, nonfatal myocardial infarction and vascular death in 1 patient, and nonfatal recurrent stroke and nonfatal myocardial infarction in 1 patient). No patient in the cohort had >3 events during follow-up. The cohort contributed a total person-time of 1898 person-years, equivalent to a MACE rate of 6.8 events per 100 person-years.

The primary outcome of MACEs was more frequent in patients with AMI than in those without AMI (13.8 events versus 5.6 events per 100 person-years, respectively). After adjustment for age, hypertension, prior stroke, deep location of hemorrhage, and IVH, the risk of MACEs remained greater in patients with AMI (adjusted HR, 1.69 [95% CI, 1.12–2.53]; $P=0.012$; see Table 3).

With respect to individual component of MACEs, crude event rates of vascular death (7.7 events versus 1.6 events per 100 person-years, respectively) and nonfatal recurrent stroke (8.0 events versus 3.8 events per 100 person-years, respectively) were higher in patients with AMI compared with their counterparts without AMI. The presence of AMI was independently associated with a 2.82-fold greater risk of vascular death (adjusted HR, 2.82 [95% CI, 1.51–5.25]; $P=0.001$; see Table 3). Patients with AMI exhibited a trend toward higher incidence of nonfatal recurrent stroke in comparison with patients without AMI (adjusted HR, 1.59 [95% CI, 0.95–2.67]; $P=0.070$; see Table 3). The distribution of nonfatal coronary events was 4 of 485 (0.8%)

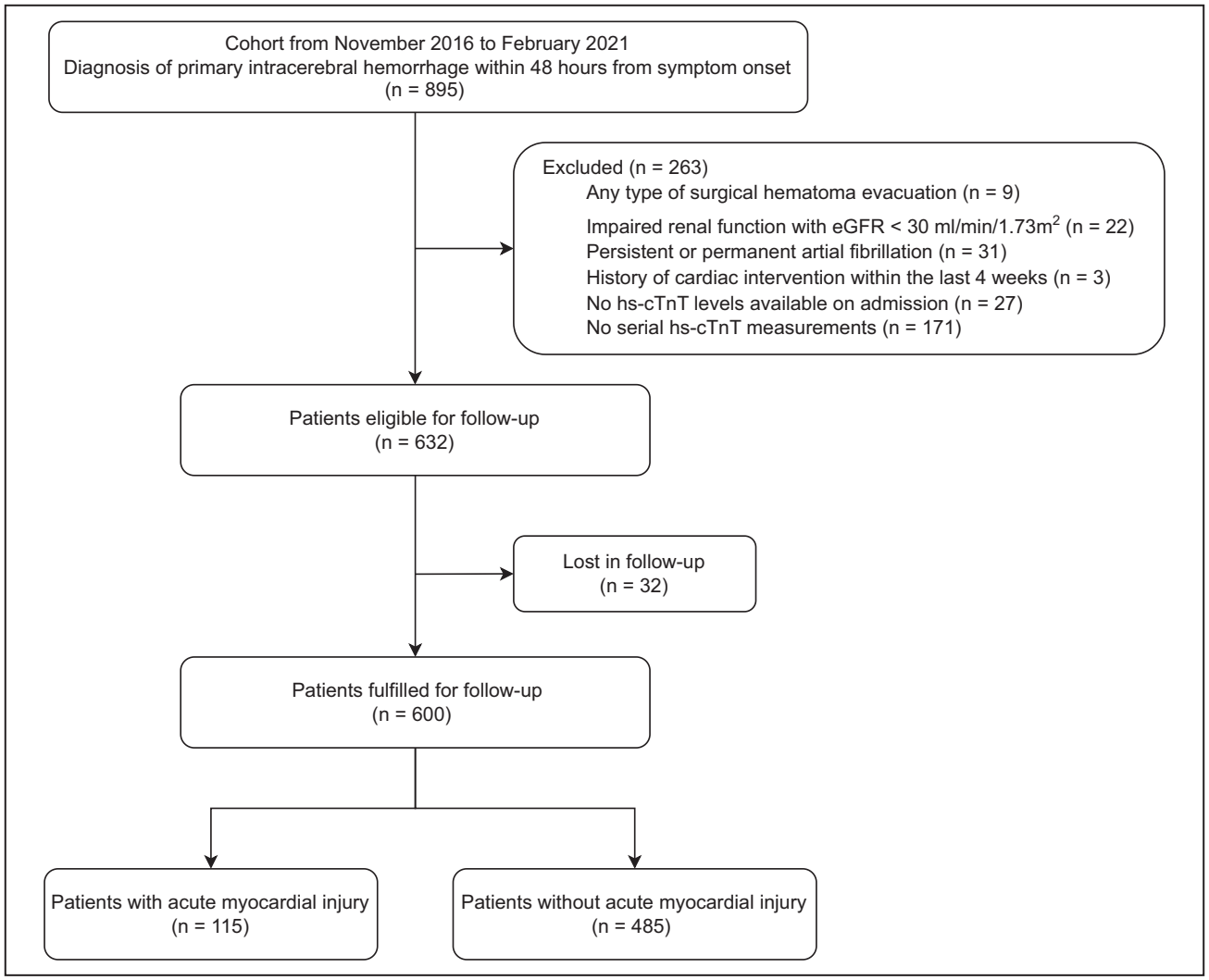

Figure 1. Selection diagram of included and excluded patients.
eGFR indicates estimated glomerular filtration rate; and hs-cTnT, high-sensitivity cardiac troponin T.

without AMI and 0 of 115 (0.0%) with AMI. Analyses were not conducted for the outcome of nonfatal coronary events because of the small number of events.

Figure 2 shows Kaplan–Meier curves depicting risk for MACEs (Figure 2A), vascular death (Figure 2B), and nonfatal recurrent stroke (Figure 2C) stratified by the presence of AMI.

AMI and 90-Day Unfavorable Outcomes

The distribution of modified Rankin Scale scores within the study cohort is presented in Figure 3. Compared with those without AMI, patients with AMI were more likely to have an unfavorable functional status at 90 days (50.4% versus 21.2%). After adjustment for age, prior stroke, baseline NIHSS score, ICH volume, and eGFR, binary logistic regression revealed that the presence of AMI was independently associated with the risk of unfavorable outcomes at 90 days after ICH (adjusted odds ratio, 2.15 [95% CI, 1.26–3.67]; *P*=0.005).

Sensitivity Analysis

Our results remained consistent after including a subset of patients with a history of atrial fibrillation (Table S3). In a second series of sensitivity analyses, we categorized patients into those with acute/chronic/no myocardial injury. Patients with no myocardial injury represented the reference group. In agreement with our main findings, the presence of AMI was independently associated with a higher risk of MACEs, vascular death, and 90-day unfavorable outcomes after adjusting for the confounding factors. The presence of chronic myocardial injury status was not associated with the risk of any outcome end point (Table S4).

Table 1. Baseline Characteristics of Patients With Primary ICH According to AMI Status

	Entire cohorts, N=600	Without AMI, N=485	With AMI, N=115	*P* value
Age, y, median (IQR)	63 (54–71)	62 (52–69)	73 (63–82)	<0.001
Male sex, n (%)	398 (66.3)	319 (65.8)	79 (68.7)	0.551
Baseline clinical assessment, median (IQR)				
Glasgow Coma Scale	15 (13–15)	15 (14–15)	14 (11–15)	<0.001
NIHSS	5 (2–10)	5 (2–10)	8 (3–15)	<0.001
Systolic blood pressure, mm Hg	160 (145–178)	160 (145–178)	162 (145–183)	0.596
Diastolic blood pressure, mm Hg	90 (80–101)	90 (80–101)	87 (74–100)	0.034
Cardiovascular risk factors, n (%)				
Hypertension	449 (74.8)	363 (74.8)	86 (74.8)	0.989
Diabetes	92 (15.3)	62 (12.8)	30 (26.1)	<0.001
Coronary artery disease	21 (3.5)	12 (2.5)	9 (7.8)	0.010
Prior stroke	99 (16.5)	75 (15.5)	24 (20.9)	0.160
Smoker	202 (33.7)	160 (33.0)	42 (36.5)	0.471
Laboratory values, median (IQR)				
eGFR, mL/min per 1.73 m^2	112 (93–133)	114 (98–135)	98 (79–122)	<0.001
Total cholesterol, mmol/L	4.7 (4.0–5.4)	4.7 (4.1–5.4)	4.3 (3.7–5.3)	0.006
Low-density lipoprotein cholesterol, mmol/L	2.4 (1.9–3.0)	2.5 (2.0–3.0)	2.1 (1.7–2.7)	<0.001
White blood cells, 10^9/L	8.5 (6.6–10.7)	8.3 (6.5–10.4)	9.4 (6.8–11.9)	0.004
Neutrophil-to-lymphocyte ratio	5.4 (3.1–9.4)	5.2 (3.0–8.5)	7.0 (3.8–14.0)	<0.001
Radiological variables				
ICH volume, mL, median (IQR)	8.8 (3.3–18.5)	8.4 (3.3–17.2)	11.6 (3.9–32.3)	0.007
ICH localization, n (%)				
Lobar	117 (19.5)	77 (15.9)	40 (34.8)	<0.001
Deep	401 (66.8)	344 (71.0)	57 (49.6)	
Infratentorial	82 (13.7)	64 (13.2)	18 (15.7)	
IVH, n (%)	197 (32.8)	141 (29.1)	56 (48.7)	<0.001
ICH pathogenesis, n (%)				
Cerebral amyloid angiopathy -related	97 (16.2)	57 (11.8)	40 (34.8)	<0.001
Hypertension	320 (53.3)	275 (56.7)	45 (39.1)	
Undetermined pathogenesis	183 (30.5)	153 (31.5)	30 (26.1)	

AMI indicates acute myocardial injury; eGFR, estimated glomerular filtration rate; ICH, intracerebral hemorrhage; IQR, interquartile range; IVH, intraventricular extension hemorrhage; and NIHSS, National Institutes of Health Stroke Scale.

DISCUSSION

In the present study, we explored the prevalence and prognostic role of AMI, according to the fourth UDMI criteria, in patients with primary ICH. The results of this study can be summarized as follows: (1) ≈19.2% of patients with primary ICH had evidence of AMI; (2) over a median follow-up of 3.7 years, patients with AMI had a significantly greater risk of composite MACEs than those without AMI; and (3) regarding the individual MACE components, AMI status was associated with an increased risk of vascular death. Moreover, there was a significant shift toward worse 90-day functional outcomes in patients with AMI.

Our findings add to the growing evidence that myocardial injury is common in patients with ICH. In previous studies, a serum cTn concentration above the 99th percentile URL was considered to indicate myocardial injury.[9–11] Considering that the myocardial injury could be acute or chronic, the 4th UDMI recommended defining AMI by confirming a newly dynamic rising and/or falling pattern (>20%) of cTn values above the 99th percentile URL.[13] Few studies have applied the current definition of AMI in patients with primary ICH. One previous study used a 30% change cutoff and reported a dynamic elevation rate of 88 of 1004 (8.8%) in patients with ICH.[19] This proportion is obviously lower than that observed in our patients. This difference seems to be related to the variance in the applied cutoff value (difference of >30% instead of >20% as applied in this analysis) and the distribution by age. Notably, the median ages of the patients in the previous and present studies were 56 and 63 years, respectively. Older age is a nonmodifiable risk factor for cTn elevation and

Table 2. hs-cTnT Values and Outcomes Categorized by Presence of AMI

	Entire cohorts, N=600	Without AMI, N=485	With AMI, N=115	*P* value
hs-cTnT values				
Having ≥3 hs-cTnT measurements, n (%)	47 (7.8)	26 (5.4)	21 (18.3%)	<0.001
First, ng/L, median (IQR)	9 (7–14)	8 (6–12)	19 (13–25)	<0.001
Second, ng/L, median (IQR)	10 (7–16)	9 (6–13)	21 (17–35)	<0.001
Time from symptoms onset to first hs-cTnT, h, median (IQR)	6.0 (3.0–11.0)	6.0 (3.0–12.0)	5.0 (3.0–9.0)	0.355
Time from symptoms onset to second hs-cTnT, h, median (IQR)	34.0 (28.0–44.0)	34.0 (28.0–44.0)	34.5 (25.5–44.0)	0.827
Time interval between first and second hs-cTnT, h, median (IQR)	24.0 (23.8–32.0)	24.0 (24.0–31.0)	28.0 (20.0–34.0)	0.279
Peak hs-cTnT value, ng/L, median (IQR)	11 (8–17)	10 (7–13)	26 (21–43)	<0.001
Time from symptoms onset to peak hs-cTnT, h, median (IQR)	25.0 (6.0–34.0)	25.0 (6.0–33.0)	24.0 (6.5–38.0)	0.273
Outcomes, n (%)				
MACEs	130 (21.7)	90 (18.6)	40 (34.8)	<0.001
Vascular death	51 (8.5)	27 (5.6)	24 (20.9)	<0.001
Nonfatal recurrent stroke	85 (14.2)	62 (12.8)	23 (20.0)	0.046
Nonfatal coronary events	4 (0.7)	4 (0.8)	0 (0.0)	1.000
90-d unfavorable outcome	161 (26.8)	103 (21.2)	58 (50.4)	<0.001

AMI indicates acute myocardial injury; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; and MACEs, major adverse cardiovascular events.

cardiac complications following stroke.[20–23] Future studies stratified by age are warranted to better understand the prevalence of AMI.

Data on the prognostic role of AMI over a long period in patients with ICH are scarce. Most studies have focused on the prognostic value of elevated cTn levels, yielding inconsistent results.[9–12] The reason for these inconsistencies may be the heterogeneity in the study population. Notably, patients with chronic conditions (ie, renal failure and structural heart disease) can have stable increases in cTn values and various long-term outcomes.[24,25] By applying the definition proposed by the fourth UDMI, we were able to differentiate acute from chronic myocardial injury and found that patients with AMI are at a significantly greater risk of MACEs than those with no myocardial injury. In contrast, we did not find a significant difference in long-term outcomes between the chronic myocardial injury and no myocardial injury groups. Our findings are partly in line with those of previous studies, which revealed that patients with a dynamic rise/fall pattern presented the worst survival outcome among patients with stroke.[19,26] Taken together, these data provide further evidence supporting the need for clinicians to perform serial cTn measurements to differentiate patients with AMI in the management of ICH.

Surprisingly, the AMI group did not have a significant increase in myocardial infarction occurrence during follow-up. Instead, the association between the presence of AMI and MACEs in our study was likely driven primarily by differences in the risk of experiencing vascular death and recurrent stroke. Considerable evidence suggests that the presence of AMI may be a reflection of neurocardiogenic injury rather than myocardial infarction. Additionally, previous observational studies have revealed that patients with subclinical myocardial

Table 3. Cox Proportional Hazards Regression: Univariable and Multivariable Analyses of MACEs, Recurrent Stroke, and Vascular Death

	MACEs		Vascular death		Nonfatal recurrent stroke	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Age	1.04 (1.03–1.05)	1.03 (1.01–1.04)	1.07 (1.04–1.09)	1.05 (1.02–1.07)	1.03 (1.01–1.05)	1.02 (1.01–1.04)
Hypertension	0.52 (0.37–0.75)	0.52 (0.36–0.74)	0.31 (0.18–0.53)	0.29 (0.16–0.50)	0.68 (0.43–1.07)	0.68 (0.43–1.09)
Prior stroke	2.12 (1.44–3.12)	1.83 (1.23–2.72)	2.01 (1.09–3.72)	1.58 (0.84–2.99)	2.43 (1.52–3.87)	2.25 (1.39–3.63)
ICH deep location	0.47 (0.33–0.66)	0.61 (0.42–0.87)	0.48 (0.27–0.82)	0.80 (0.45–1.44)	0.43 (0.28–0.65)	0.52 (0.33–0.81)
IVH	1.45 (1.02–2.06)	1.27 (0.87–1.84)	2.51 (1.45–4.34)	1.79 (0.99–3.24)	1.05 (0.67–1.66)	0.96 (0.60–1.56)
AMI	2.39 (1.64–3.47)	1.69 (1.12–2.53)	4.70 (2.70–8.15)	2.82 (1.51–5.25)	2.07 (1.28–3.34)	1.59 (0.95–2.67)

AMI indicates acute myocardial injury; HR, hazard ratio; ICH, intracerebral hemorrhage; IVH, intraventricular extension hemorrhage; and MACEs, major adverse cardiovascular events.

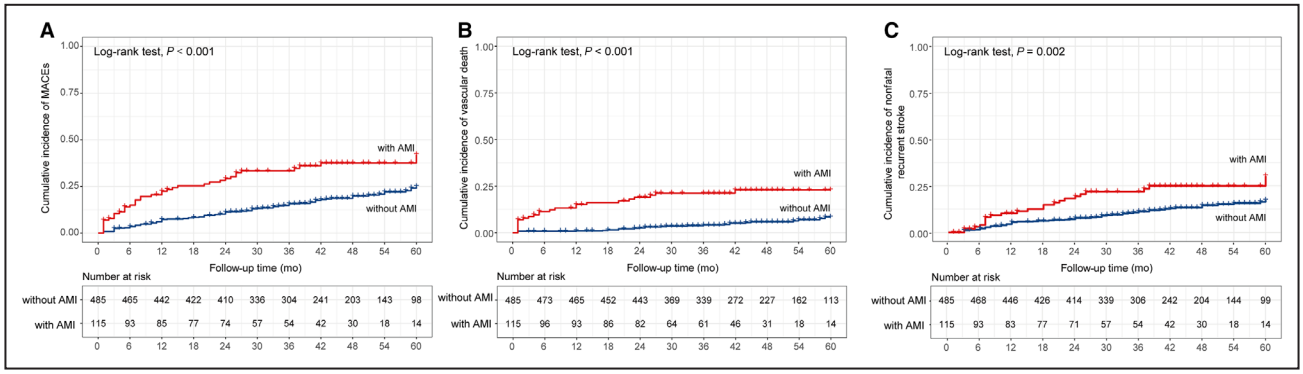

Figure 2. Kaplan–Meier curves showing cumulative incidences by presence (red) and absence (blue) of AMI in patients with intracerebral hemorrhage for (A) overall MACEs, (B) vascular death, and (C) nonfatal recurrent stroke.
AMI indicates acute myocardial injury; and MACEs, major adverse cardiovascular events.

injury in the acute phase after ischemic stroke have a greater burden of cerebral small vessel disease. The various levels of severity of vasculopathy might result in different incidences of cerebral and cardiac vascular events.[5] However, the possibility that patients with AMI are at increased risk of acute coronary events due to individual cardiac vulnerability cannot be denied.[27] On the other hand, the clinical symptoms of acute coronary events (ie, chest pain) may be absent or neglected in patients with AMI because of sensory deficits, aphasia, or a reduced level of consciousness; therefore, individuals with myocardial infarction may be classified as experiencing vascular death in the case of sudden death. This finding is supported by our finding that the neurological deficits in the AMI group were more severe than those in the non-AMI group. Additional studies are needed to evaluate whether there is a relationship between the total burden of cerebral small-vessel disease and the presence of AMI, and a longer follow-up of a larger cohort might facilitate the exploration of whether the presence of AMI is related to an increased risk of acute coronary events.

The mechanisms by which AMI influences the risk of poor outcomes are not well understood. A plausible interpretation is that AMI status is indicative of an increased systemic inflammatory response and impaired autonomic nerve activity after ICH, which can exacerbate cardiovascular injury through a prothrombotic state, inflammation-mediated injury of the endothelium, or effects on myocardial tissue.[2,4] This finding is also partially supported by our data, which revealed that patients with AMI had increased inflammatory markers, such as white blood cell counts and neutrophil-to-lymphocyte ratios. An elevated neutrophil-to-lymphocyte ratio, on the other hand, also reflects a cortisol-induced stress response with impaired autonomic activity.[28] However, extensive data on autonomic functional activity were not available in our cohort, and the interaction between autonomic functional activity and AMI status as well as systemic

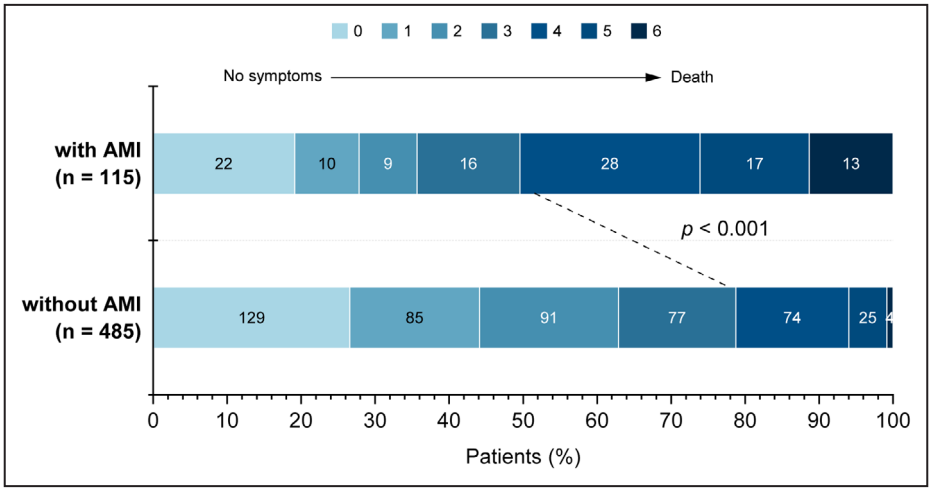

Figure 3. 90-day functional status (modified Rankin scale score) among patients grouped by AMI status.
AMI indicates acute myocardial injury.

inflammation status in patients with ICH should be a focus of future research.

Given both the short- and long-term poor prognosis, evidence of AMI should prompt a cardiac workup, including echocardiography, cardiac MRI, and multislice coronary computed tomography, to search for the underlying cause and consider feasible treatment approaches as early as possible.[29] Currently, there are no recognized guidelines on how to manage AMI in patients with hemorrhagic stroke, but some preliminary algorithms regarding ischemic stroke exist.[6,30] In the setting of ICH, because of the high risk of bleeding, a conservative strategy may be the most suitable option for patients. Moreover, in light of the possible mechanism of autonomic dysfunction and the inflammatory response in AMI, restoring autonomic balance as well as the use of anti-inflammatory agents are promising approaches that should be tested in prospective, randomized clinical trials.

The strengths of our study include the large sample size, systematic follow-up data over a long period, standardized collection of clinical information, and differentiation of patients with elevated hs-cTnT levels as having acute or chronic myocardial injury according to formal diagnostic criteria. Nonetheless, the following limitations should be considered when interpreting our findings. First, this is a retrospective analysis of prospectively collected data, which may have introduced collection bias. In addition, the single-center nature of the study may also limit the external validity of our findings. Second, the strict inclusion and exclusion criteria may have introduced selection bias; however, one thing worth noting is that most patients included have stroke of relatively mild severity (median NIHSS score, 5 [interquartile range, 2–10]). As stroke severity is strongly correlated with outcomes in patients with ICH, our results emphasize the necessity of evaluating AMI even in patients with mild clinical symptoms. Third, as the time interval between hs-cTnT sampling points is wide and varies among patients (first value was obtained at emergency admission and the next at any time within the first 2 days of hospitalization), some greatest magnitude of change may be missed, which may lead to misclassification of patients with AMI as those without AMI. On the other hand, continuous daily monitoring for a longer time may improve the AMI detection rate. Accumulating evidence demonstrates that the values of hs-cTnT usually peak within 48 hours after stroke onset and subsequently decline. Therefore, some patients with stable elevated hs-cTnT values within 48 hours may have been misclassified as chronic myocardial injury in our study because the time course of sampling may have missed the minimum troponin value. Fourth, no detailed mapping analysis for ICH localization was performed; therefore, we cannot analyze the association between the involvement or side of the insular cortex, which is engaged in the central autonomic network, and the presence of AMI and outcomes in primary ICH. Fifth, although the outcome data were confirmed by diagnostic records, the possibility of MACE underestimation could not be excluded. Indeed, if symptoms are mild, some patients may not visit the hospital for additional diagnosis. Finally, additional adjustment for medication use over time in the Cox regression models would have increased the validity of the results. Unfortunately, this was not assessed systematically in our cohort. Future studies should include the prospective recording of the use of medications, such as antiplatelet agents and anticoagulants, because they might have an impact on the risk of MACEs.

CONCLUSIONS

AMI is relatively common in patients with ICH and is associated with long-term MACEs risk and 90-day functional independence. To differentiate AMI from chronic myocardial injury, serial cTn measurements in the acute phase are warranted and would facilitate individualized prognosis and stratification strategies.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S4

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