Risk factors for acute myocardial infarction in patients with acute cerebral infarction: a case-control study
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Abstract
This retrospective case-control study examined factors associated with in-hospital acute myocardial infarction (AMI) in patients hospitalized for acute cerebral infarction (ACI). In-patients with AMI following ACI (n = 33) and age- and sex-matched controls who had ACI without AMI (n = 66) were recruited in a 1:2 ratio, and their data were assessed. The results showed that the group of patients experiencing AMI after ACI exhibited a significantly higher prevalence of ischemic heart disease (p = 0.036) and heart failure (p < 0.001), had elevated fibrinogen levels (p = 0.029), presented with higher National Institutes of Health Stroke Scale (NIHSS) scores at admission (p < 0.001) and a lower proportion of them underwent thrombolytic therapy (p = 0.004) compared to the ACI-only group. The mortality rate was substantially higher in the AMI after ACI group than in the ACI-only group (18.2% vs. 1.5%, p = 0.008). Multivariable logistic regression analysis identified that higher NIHSS scores at admission (odds ratio, OR = 1.21, 95% confidence interval, CI = 1.16–1.39, p = 0.004), elevated high-sensitivity C-reactive protein (hs-CRP) levels (OR = 1.07, 95% CI = 1.001–1.14, p = 0.047) and the administration of thrombolytic therapy (OR = 0.02, 95% CI = 0.001–0.48, p = 0.015) were independently associated with AMI following ACI. In conclusion, NIHSS scores at admission, hs-CRP levels and thrombolytic therapy were found to be independent factors associated with in-hospital AMI following ACI.

Keywords
Risk factor; Acute myocardial infarction; Acute cerebral infarction; Heart failure; Mortality

1. Introduction
Acute cerebral infarction (ACI) is a significant global health issue, contributing substantially to mortality rates and standing as a primary cause of long-term adult disability [1]. Each year, an estimated 6 million individuals worldwide succumb to stroke [1], and epidemiologists have reported an increase in ACI incidence in China in recent years, with stroke emerging as a predominant cause of both morbidity and mortality among the Chinese population [2]. In China, the age-standardized incidence and prevalence rates of ACI are reported at 1115 per 100,000 persons and 247 per 100,000 person-years, respectively, with an associated mortality rate of approximately 115 per 100,000 person-years [2]. In addition, nearly 70% of all ACI cases result from ischemic strokes, primarily due to arterial occlusion, while the remaining cases manifest as hemorrhagic strokes [3, 4]. Importantly, it has been observed that stroke carries an in-hospital mortality rate of approximately 20%, thereby urging the need for immediate attention [1].

Ischemic heart disease (IHD) represents a significant contributor to global morbidity, accounting for approximately 9 million fatalities [1]. Over the past decade, the prevalence of acute myocardial infarction (AMI) in China has increased nearly fourfold, primarily attributed to population aging and shifts in lifestyle [5], and the in-hospital mortality rate for AMI has remained consistent at approximately 10% [5]. In addition, it is worth noting that ACI and AMI share common risk factors, such as hypertension, diabetes mellitus, obesity, hyperlipidemia, smoking, alcohol consumption, chronic inflammation and chronic kidney disease [5]. Consequently, individuals at risk of stroke also face an increased risk of AMI. One study even reported that one-third of ACI patients displayed more than 50% coronary stenosis [7], while a meta-analysis revealed an annual long-term risk of AMI following ischemic stroke or transient ischemic attack (TIA) of 1.67% [8].

The terms “brain-heart syndrome” and “cerebral-cardiac syndrome” (CCS) are often used interchangeably to denote the development of cardiac dysfunction as a secondary consequence of cerebral injury [9]. A related study reported that 1.6% of patients with ACI experienced AMI as a complication during their hospital stay [10]. Furthermore, patients with ACI complicated by AMI displayed a significantly higher in-hospital mortality rate in comparison to those without AMI following ACI (21.4% vs. 7.1%) [10]. Another investigation...
observed that 6.5% of ACI patients developed AMI or acute heart failure during their hospitalization, and these cardiac complications were associated with an elevated 3-month mortality rate (60.4% vs. 15.9%) [11].

Nevertheless, there remains a significant research gap regarding comprehensive data on factors that may predict the onset of AMI in hospitalized ACI patients. As a result, we performed this retrospective study to explore significant factors associated with the occurrence of in-hospital AMI in patients with ACI.

2. Materials and methods

2.1 Study participants

Patients and the general public were not involved in the design or execution of the study.

2.2 Study design and criteria

In this retrospective case-control study, the data of consecutive patients who experienced AMI following ACI during hospitalization at the Stroke Center of the Fifth Affiliated Hospital of Sun Yat-sen University between January 2018 and December 2020 were retrieved and assessed. As a control group, we also retrieved the data of patients without AMI following ACI, matched for age and sex, at a ratio of 1:2. All cases were diagnosed and managed based on a standardized protocol and care pathway in adherence to current guidelines [6, 12].

The study inclusion criteria were: (1) age exceeding 18 years, (2) ACI occurring within 7 days before hospitalization, (3) ACI diagnosis confirmed by computerized tomography and/or magnetic resonance imaging, (4) AMI diagnosis based on electrocardiography findings and cardiac troponin I levels, (5) had a modified Rankin Score of ≤2 before the stroke, and (6) availability of clinical data essential for the study analysis. Cases with dementia or severe uncontrolled mental disorder and traumatic brain injury were excluded.

2.3 Data collection and definitions

Demographic data, vascular risk factors, stroke-related information and laboratory data were extracted from medical records. These data included age, gender, smoking habits, alcohol consumption, the presence or absence of hypertension, diabetes mellitus or hyperlipidemia, a history of prior transient ischemic attack (TIA), prior ischemic stroke, ischemic heart disease, atrial fibrillation or heart failure, family history of stroke or coronary heart disease, use of antithrombotic, antihyperensive, anti-diabetic or statin medications, as well as levels of fibrinogen, high-sensitivity C-reactive protein (hs-CRP), creatinine, uric acid and homocysteine. Additionally, the patients National Institutes of Health Stroke Scale (NIHSS) score at admission, frequently utilized by neurologists to assess neurological deficits, was also recorded [13]. Dyslipidemia was diagnosed if total cholesterol levels exceeded 6.21 mmol/L, serum triglyceride levels exceeded 2.26 mmol/L, or lipid-lowering drugs were in use. Smoking was defined as patients who had smoked at least one cigarette per day for a minimum of 6 months [14].

2.4 Neuroimaging analysis

Neuroimaging data were comprehensively assessed by both a radiologist and a neurologist, and the results were confirmed through mutual consensus. The recorded neuroimaging information comprised details about the affected cerebral circulation, location of infarction and stroke subtype. The impact of stroke on cerebral circulation was categorized as anterior, posterior or affecting both. The location of infarction was classified as involving a single region (comprising cortical, subcortical white matter, deep regions such as basal ganglia, internal capsule or thalamus or subtentorial) or encompassing two or more regions. The type of stroke was categorized as large-artery atherosclerosis, cardioembolism, small-artery occlusion, stroke of another determined etiology or stroke of undetermined etiology, following the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification criteria [15].

2.5 Statistical analysis

Statistical analysis was conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as means ± standard deviation (SD) for normally distributed data and as median (interquartile range) for non-normally distributed data. Categorical variables are expressed as frequencies with their corresponding percentages. Baseline characteristics were compared between groups using appropriate statistical tests: the t-test for independent samples (for normally distributed continuous variables), the Mann-Whitney U-test (for non-normally distributed continuous variables), the chi-square test or Fisher’s exact test (for categorical variables). To identify factors associated with AMI following ACI, a multivariable logistic regression analysis was performed. Variables that exhibited statistically significant differences between groups in the univariate analyses were included in the multivariable analysis using the enter method. Adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) were also calculated. Statistical significance was defined as p < 0.05.

3. Results

3.1 Baseline clinical characteristics

Our analysis included a total of 99 patients, of whom 80 were male, and the average age was 69 years. Among these patients, 33 were categorized in the AMI after ACI group, while the remaining 66 patients were in the ACI without AMI group. Table 1 presents the baseline clinical characteristics of the study participants.

The AMI after ACI group had significantly higher proportions of patients with IHD (39.4% vs. 19.7%, p = 0.036) and heart failure (36.4% vs. 3.0%, p < 0.001) compared to the ACI without AMI group. However, there were no significant differences observed between the two groups in terms of age, sex, smoking status, alcohol consumption, prevalence of hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, history of prior TIA/stroke, family history of stroke or coronary heart disease, or the use of antithrombotic, antihypertensive, antidiabetic or statin medications (Table 1).
The results of the multivariable logistic regression analysis indicated that higher NIHSS scores at admission (OR = 1.21, 95% CI = 1.16–1.39, p = 0.004), elevated hs-CRP levels (OR = 1.07, 95% CI = 1.001–1.14, p = 0.047), and the use of thrombolytic therapy (OR = 0.02, 95% CI = 0.001–0.48, p = 0.015) were independently associated with the occurrence of AMI following ACI, as illustrated in Fig. 1.
TABLE 2. Comparison of stroke-related characteristics between patients with acute myocardial infarction (AMI) after acute cerebral infarction (ACI) and those without AMI after ACI.

<table>
<thead>
<tr>
<th>Stroke-related characteristics</th>
<th>AMI after ACI</th>
<th>ACI without AMI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS score at admission, median (IQR)</td>
<td>8 (3.5–14)</td>
<td>2 (1–4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke subtype, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>12 (36.4%)</td>
<td>24 (36.4%)</td>
<td>0.203</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>9 (27.3%)</td>
<td>10 (15.2%)</td>
<td></td>
</tr>
<tr>
<td>Small-artery occlusion</td>
<td>3 (9.1%)</td>
<td>29 (43.9%)</td>
<td></td>
</tr>
<tr>
<td>Stroke of other determined etiology</td>
<td>0</td>
<td>1 (1.5%)</td>
<td></td>
</tr>
<tr>
<td>Stroke of other undetermined etiology</td>
<td>9 (27.3%)</td>
<td>2 (3.0%)</td>
<td></td>
</tr>
<tr>
<td>Cerebral circulation affected by stroke, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior or Posterior circulation</td>
<td>23 (69.7%)</td>
<td>65 (98.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Both</td>
<td>10 (30.3%)</td>
<td>1 (1.5%)</td>
<td></td>
</tr>
<tr>
<td>Location of infarction, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One region</td>
<td>19 (57.6%)</td>
<td>55 (83.3%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Two or more regions</td>
<td>14 (42.4%)</td>
<td>11 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Thrombolytic therapy, n (%)</td>
<td>1 (3.0%)</td>
<td>18 (27.3%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Emergency PCI, n (%)</td>
<td>18 (54.5%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death during hospitalization, n (%)</td>
<td>6 (18.2%)</td>
<td>1 (1.5%)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

ACI: acute cerebral infarction; AMI: acute myocardial infarction; NIHSS: National Institutes of Health Stroke Scale; IQR: interquartile range; PCI: percutaneous coronary intervention.

FIGURE 1. Multivariable logistic regression analysis of factors associated with acute myocardial infarction following acute cerebral infarction. hs-CRP: high-sensitivity C-reactive protein; NIHSS: National Institutes of Health Stroke Scale; 95% CI: 95% confidence interval; OR: odds ratio.
4. Discussion

The key findings of this study highlight that the risk of in-hospital AMI following ACI is significantly increased in cases characterized by a higher NIHSS score at admission, elevated hs-CRP levels and the absence of thrombolytic therapy, offering valuable insights for healthcare professionals in identifying ACI patients with an increased risk of developing AMI during hospitalization, to whom more attention should be allocated to improve their treatment outcomes.

Certainly, here’s a revised version suitable for scientific publication:

CCS comprises myocardial injury resulting from cerebral conditions such as ischemic cerebrovascular disease, cerebral hemorrhage and acute traumatic brain injury [16]. Among these conditions, AMI represents the most severe manifestation of CCS and is observed in approximately 0.5%–4.5% of stroke patients, with higher incidence rates of up to 13.1%–13.8% reported in severe stroke cases [17, 18]. Previous research has found that AMI following ACI is associated with prolonged hospitalization, increased healthcare expenses, and a threefold increase in mortality rates even after active intervention [10]. Despite being relatively rare, AMI following ACI poses diagnostic and therapeutic challenges for clinicians due to the lack of consensus guidelines [19]. The early identification of ACI patients at an elevated risk of developing AMI can enable the timely implementation of preventive measures, thereby improving overall patient outcomes.

Until now, there is no widely accepted method for predicting the occurrence of AMI following ACI. In this regard, Lian et al. [20] developed the PANSAN scale, which can be used to predict the risk of cardiac injury after ischemic stroke based on factors such as age, sex, prothrombin time, activated partial thromboplastin time, neutrophil proportion, presence or absence of carotid artery stenosis and NIHSS scores [20]. Furthermore, although the results may vary, several studies have reported on factors associated with AMI after ACI. For instance, Alqahtani et al. [10] identified older age, a history of coronary artery disease, chronic renal insufficiency, mechanical thrombectomy and cardiac rhythm and conduction abnormalities as the strongest predictors of in-hospital AMI following ACI. Pana et al. [21] reported that higher blood glucose levels, total leucocyte counts and CRP levels were associated with in-hospital AMI, whereas age, hypertension, diabetes mellitus, coronary heart disease, chronic kidney disease and peripheral arterial disease were associated with AMI after discharge. Micheli et al. [11] identified a history of angina, AMI within 3 months before admission, hyperglycemia, and high NIHSS scores upon admission as factors associated with in-hospital AMI or acute heart failure. Liao et al.’s [22] analysis revealed a history of AMI, diabetes mellitus, stroke severity and peripheral vascular disease as independently associated with in-hospital ACI following ACI in their investigated cohort. We believe that the disparities among these studies could be attributed to variations in the analyzed variables and the heterogeneity among the populations investigated in these study analyses.

In this present study, the AMI after ACI group had a higher prevalence of patients with a history of IHD or heart failure, elevated fibrinogen levels, increased NIHSS scores upon admission and a lower proportion of patients undergoing thrombolytic therapy compared to the ACI without AMI group. Our multivariable logistic regression analysis indicated that higher NIHSS scores upon admission, elevated hs-CRP levels and the absence of thrombolytic therapy were associated with in-hospital AMI following ACI, thereby suggesting that pre-existing heart conditions, systemic inflammation and the severity of stroke contribute to elevated risks of AMI after ACI. It has been shown that plasma fibrinogen levels are linked to the extent and duration of occlusive thrombus formation during coronary plaque rupture. Elevated fibrinogen levels may predispose individuals to platelet aggregation through glycoprotein binding and cross-linking of activated platelets [23]. Higher NIHSS scores signify more severe strokes, a known risk factor for in-hospital AMI after ACI in previous studies [11, 22]. Strokes involving the cortical or multiple cerebral arterial territories, including both anterior and posterior circulations or multiple brain regions, are often associated with cardioembolism [24], indicating underlying structural or functional cardiac abnormalities. Moreover, thrombolysis has been reported to have a well-established role as an effective therapy for AMI [25]. Therefore, administering thrombolytic agents to stroke patients is expected to reduce the risk of developing AMI during hospitalization. Elevated CRP levels have also been linked to an increased risk of AMI in the general population [26, 27], as well as with in-hospital cardiac events post-AMI [28, 29] and mortality [30], and our findings align with related previous research findings.

Although a detailed exploration of the potential mechanisms via which ACI may induce AMI is beyond the scope of this study, it is relevant to briefly outline three plausible mechanisms. Firstly, the autonomic dysregulation and surge in catecholamines associated with ACI may exacerbate pre-existing coronary artery disease or precipitate stress-induced myocardial injury. Secondly, the development of thrombotic occlusion in a coronary vessel could potentially lead to embolization of intracardiac thrombi, although this risk is predominantly associated with large anterior ST-segment elevation myocardial infarction [31]. Thirdly, AMI might manifest shortly after a stroke due to concurrent plaque instability in the coronary and carotid vascular territories [32]. Nonetheless, it is important to acknowledge that other mechanisms, such as the activation of the hypothalamic-pituitary-adrenal axis, dysbiosis of the gut microbiome, immune responses and inflammation, may also contribute to the understanding of how ACI may induce AMI [33–35].

The leading causes of mortality following ACI include cardiovascular events, respiratory infections and early stroke-related complications, and their outcomes are often influenced by factors such as advanced age, female gender, stroke severity, stroke recurrence, seizures, as well as respiratory and cardiovascular comorbidities [1]. Our findings, consistent with prior research [10, 11, 21, 22], emphasize that in-hospital AMI significantly indeed increases the risk of death among ACI patients. In this regard, percutaneous coronary intervention (PCI) has emerged as the primary treatment for AMI, leading to a significant reduction in mortality rates [36]. Previous studies have demonstrated that the use of coronary angio-
raphy and PCI is associated with lower in-hospital mortality rates in patients who experience AMI following ACI [10]. Collectively, these underscore the importance of redoubling efforts to prevent AMI in hospitalized ACI patients.

Despite the interesting findings reported in this present work, there are several limitations that should be acknowledged. Firstly, it is important to recognize the possibility of selection and information biases inherent in the retrospective, single-center, case-matching design. Secondly, the study’s sample size was relatively small, potentially constraining our ability to identify additional significant differences between the examined groups. Thirdly, patients were not classified using the Killip classification. Lastly, differences between the examined groups. Thirdly, patients at a higher risk of AMI. Further research is still needed to uncover the mechanisms associated with AMI occurrence in ACI patients and to establish optimal management strategies for this patient group.

5. Conclusions

In conclusion, the risk of in-hospital AMI following ACI is increased in cases with elevated NIHSS scores upon admission, elevated hs-CRP levels, and the absence of thrombolytic therapy. These findings offer the potential for the future development of screening methods aimed at identifying ACI patients at a higher risk of AMI. Further research is still needed to uncover the mechanisms associated with AMI occurrence in ACI patients and to establish optimal management strategies for this patient group.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are not publicly available due to the information that could compromise the privacy of research participants, but they are available from the corresponding author.

AUTHOR CONTRIBUTIONS

JL and LZ—study concept and design; YL and YFP—acquisition of data; JLL—wrote the first draft of the manuscript; statistical analysis. All authors analysis or interpretation of data, critical revision of the manuscript for important intellectual content.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University (K239-1). Signed informed consent forms were obtained from all participants. All procedures performed in this study involving human participants were in accordance with the ethical standards of The Fifth Affiliated Hospital of Sun Yat-sen University committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES


