Initial in-hospital heart rate is associated with long-term survival in patients with acute ischemic stroke

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Abstract
Aims Increased heart rate has been associated with stroke risk and outcomes. The purpose of this study was to explore the long-term prognostic value of initial in-hospital heart rate in patients with acute ischemic stroke (AIS).
Methods We analyzed data from 21,655 patients with AIS enrolled (January 2010–September 2018) in the Chang Gung Research Database. Mean initial in-hospital heart rates were averaged and categorized into 10-beat-per-minute (bpm) increments. The primary and secondary outcomes were all-cause mortality and cardiovascular death. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using multivariable adjusted Cox proportional hazard models, using the heart rate < 60 bpm subgroup as the reference.
Results The adjusted HRs for all-cause mortality were 1.23 (95% CI 1.08–1.41) for heart rate 60–69 bpm, 1.74 (95% CI 1.53–1.97) for heart rate 70–79 bpm, 2.16 (95% CI 1.89–2.46) for heart rate 80–89 bpm, and 2.83 (95% CI 2.46–3.25) for heart rate ≥ 90 bpm compared with the reference group. Likewise, heart rate ≥ 60 bpm was also associated with an increased risk of cardiovascular death (adjusted HR 1.18 [95% CI 0.95–1.46] for heart rate 60–69 bpm, 1.57 [95% CI 1.28–1.93] for heart rate 70–79 bpm, 1.98 [95% CI 1.60–2.45] for heart rate 80–89 bpm, and 2.36 [95% CI 1.89–2.95] for heart rate ≥ 90 bpm).
Conclusions High initial in-hospital heart rate is an independent predictor of all-cause mortality and cardiovascular death in patients with AIS.
Graphical abstract

Initial in-hospital heart rate is associated with long-term survival in patients with acute ischemic stroke

Study Design and Participants

21,655 AIS patients in admission
Mean heart rate (first 3-days)
Jan-2010 Follow-up period Sep-2018

<60 bpm  7.8%
60–69 bpm  26.9%
70–79 bpm  36.5%
80–89 bpm  18.6%
≥90 bpm  10.2%

Results

All-cause mortality
CV death

Introduction

Despite improvements in secondary prevention treatment, the incidence rates of mortality and recurrent cardiovascular events post-stroke remain high [1–3]. This indicates that many risk factors have yet to be identified.

A slower heart rate is associated with greater longevity in many mammal species [4]. Heart rate is a vital sign which varies according to the physical needs of the body. Heart rate also reflects the balance between sympathetic and parasympathetic tone to the heart, and it has been shown to be a predictor of cardiovascular and all-cause mortality in the general population and in patients with cardiovascular disease [5–12]. In a review article of 18 epidemiological studies, Aboyans and Criqui reported an increase in mortality rate of 30–50% for every 20-beat-per-minute (bpm) increase in resting heart rate [13]. However, the importance of heart rate is often overlooked. Although experimental studies have suggested that lowering the heart rate may protect against cerebral ischemia by reducing oxidative stress and improving endothelial function [14], whether a lower initial in-hospital heart rate is associated with a better prognosis in patients with acute ischemic stroke (AIS) has yet to be elucidated. Therefore, the objective of this study was to evaluate the relationship between mean initial in-hospital heart rate and long-term...

Keywords Heart rate · Acute ischemic stroke · Mortality · Survival

Abbreviations

bpm  Beats per minute  
AIS  Acute ischemic stroke  
ICD-10  International Classification of Diseases, 10th Revision, Clinical Modification  
SSI  Stroke severity index  
eNIHSS  Estimated National Institutes of Health Stroke Scale  
SBP  Systolic blood pressure  
DBP  Diastolic blood pressure  
ALT  Alanine aminotransferase  
HbA1c  Glycated hemoglobin  
eGFR  Estimated glomerular filtration rate  
CKD  Chronic kidney disease  
CI  Confidence interval  
HTN  Hypertension  
DM  Diabetes mellitus  
AF  Atrial fibrillation  
CHF  Congestive heart failure  
TG  Triglyceride  
BMI  Body mass index
mortality in a large population of AIS patients with an extended follow-up.

Methods

We conducted this retrospective cohort study using data from the Chang Gung Research Database [15], the largest multi-institutional electronic medical records collection in Taiwan. All patients who had an AIS (International Classification of Diseases, 9th Revision, Clinical Modification codes 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91; International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10] code I63) in the first two discharge diagnoses [16, 17] between January 2010 and September 2018, and were admitted to one of the seven branch hospitals of Chang Gung Healthcare System were accrued consecutively in this study. Key demographic and clinical characteristics were collected, including stroke severity as assessed using the claims-based stroke severity index (SSI). The SSI was then converted to the National Institutes of Health Stroke Scale score using the equation: estimated National Institutes of Health Stroke Scale (eNIH SS) = 1.1722 × SSI − 0.7533 [18]. Measurements of height, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, creatinine, alanine aminotransferase (ALT), glycated hemoglobin (HbA1c), and lipid profiles were obtained from the records of the enrolled patients. Heart rate, SBP, and DBP were measured with the patients recumbent after 5 min rest and were recorded using an automated oscillometric device (DINAMAP ProCare 100, GE Medical Systems, Milwaukee, WI, USA) or a bedside patient monitor (IntelliVue MP60, Philips Medical System, Boeblingen, Germany). If the pulse was irregular, heart rates were measured by palpating the radial pulse over a period of 60 s. The mean heart rate was derived from recorded vital sign values in the first 3 days of hospitalization. Estimated glomerular filtration rate (eGFR) was determined using the Modification of Diet in Renal Disease equation as follows: eGFR (mL/min/1.73 m²) = 186 × (serum creatinine)^−1.154 × (age)^−0.203 × 0.742 (if female) [19]. Chronic kidney disease (CKD) was classified into five stages: stage 1 (eGFR ≥ 90), stage 2 (eGFR 60–89), stage 3 (eGFR 30–59), stage 4 (eGFR 15–29), and stage 5 (eGFR < 15) (all eGFR in mL/min/1.73 m²) [20].

The original cohort consisted of 41,241 patients aged ≥ 18 years. The exclusion criteria were patients: (1) hospitalized for less than 3 days; (2) admitted to a rehabilitation unit; (3) admitted through outpatient clinics; (4) with recurrent stroke during the study period; and (5) with less than one record of heart rate per day in the first 3 days of hospitalization. In addition, those without catastrophic illness cards were also excluded (beneficiaries of the National Health Insurance system in Taiwan would have been given a catastrophic illness card for 1 month because of their AIS; the National Health Insurance system in Taiwan covers more than 99.9% of the entire population) [21]. Finally, the data of 21,655 patients were used for the analysis (Fig. 1). The study was conducted in accordance with the Declaration of Helsinki and local ethical approval was obtained.

Outcomes

The primary outcome was all-cause mortality, and the secondary outcome was cardiovascular death. We linked to the National Registry of Deaths Database provided by the Ministry of Health and Welfare in Taiwan from January 1, 2010 to December 31, 2018. The database includes death certificates coded using ICD-10 codes. Cardiovascular diseases were classified as ICD-10 codes I00–I99.

Fig. 1 Flowchart of patient selection
Statistical analysis

Descriptive statistics are presented as number (percentage) for categorical data and mean (standard deviation) and median (interquartile range) for continuous data. The patients were classified into five subgroups according to mean heart rate (heart rate < 60, 60–69, 70–79, 80–89, and ≥ 90 bpm). Differences between the groups were tested using the Kruskal–Wallis rank test for continuous data and the Chi-square test for categorical data. In addition to crude hazard ratios (HRs), adjusted HRs and 95% confidence intervals (CIs) were calculated with reference to the lowest risk group and estimated after adjusting for potential confounding factors in the Cox proportional hazard models. Model 1 included age, sex, and eNIHSS, and model 2 included age, sex, eNIHSS, history of hypertension (HTN), diabetes mellitus (DM), dyslipidemia, atrial fibrillation (AF), congestive heart failure (CHF), cancer before admission, smoking status, beta blocking agents, body mass index (BMI), total cholesterol, triglycerides (TGs), CKD stage, ALT, HbA1c, mean SBP, and mean DBP.

Data analysis was conducted without imputing missing data. Variables with missing data were classified into a missing data category to minimize the effect of the missing data in the analysis.

Interactions between mean heart rate and age, sex, eNIHSS, history of HTN, DM, dyslipidemia, AF, CHF, cancer before admission, smoking status, beta blocking agents, BMI, total cholesterol, TGs, CKD stage, ALT, HbA1c, mean SBP, and mean DBP at baseline were tested. Subgroup analyses were performed with heart rate as a continuous variable and when interactions were significant even after adjusting for the same variables as in the Cox proportional hazard model (model 2). HRs and 95% CIs for each subgroup were calculated for every one standard deviation increment in mean heart rate. A Cox model with restricted cubic spline smoothing technique was used to explore the overall trend of risks through the range of mean heart rate values. All analyses were performed with SAS (version 9.4, Cary, NC, USA) and R (version 4.0).

Results

Baseline characteristics

A total of 21,655 adult patients with AIS were included in the analysis (mean age, 67.37 ± 12.92 years; 61.88% males). The mean SBP and DBP were 151.04 ± 19.64 and 84.81 ± 11.17 mmHg, respectively, and the mean heart rate was 74.84 ± 11.27 bpm. There were 436,376 measurements of heart rate in this study. The median number of measurement per patient was 13 (interquartile range 9–18). The demographic data and baseline characteristics of the overall patient cohort and for each 10-bpm-increment heart rate subgroup are given in Table 1. After a median follow-up of 3.2 years (interquartile range 1.4–5.6 years), 6345 patients (29.3%) met the primary outcome (all-cause mortality) and 2584 patients (11.9%) met the secondary outcome (cardiovascular death). Compared to the patients with a higher mean heart rate, those with a lower mean heart rate were more likely to be male, current smokers, without using beta blocking agent, to not have HTN or DM, and to have dyslipidemia, lower eNIHSS score, lower baseline incidence of AF and CHF, lower prevalence of cancer, and lower baseline eGFR level.

Clinical outcomes according to mean heart rate

Crude and adjusted HRs for mean heart rate are given in Fig. 2. Compared with the reference group (mean heart rate < 60 bpm), the adjusted HRs for the all-cause mortality in model 2 was 1.23 (95% CI 1.08–1.41) for mean heart rate 60–69 bpm, 1.74 (95% CI 1.53–1.97) for mean heart rate 70–79 bpm, 2.16 (95% CI 1.89–2.46) for mean heart rate 80–89 bpm, and 2.83 (95% CI 2.46–3.25) for mean heart rate ≥ 90 bpm.

Besides a high mean heart rate, age, male sex, eNIHSS, DM, CHF, history of cancer before admission, and CKD stages 2–5 were all positively associated with the risk of all-cause mortality. Conversely, a history of dyslipidemia, higher BMI, total cholesterol, ALT, and mean DBP levels showed a protective effect (Table 2).

Compared with the reference group (mean heart rate < 60 bpm), the adjusted HRs for cardiovascular death in model 2 were 1.18 (95% CI 0.95–1.46) for mean heart rate 60–69 bpm, 1.57 (95% CI 1.28–1.93) for mean heart rate 70–79 bpm, 1.98 (95% CI 1.60–2.45) for mean heart rate 80–89 bpm, and 2.36 (95% CI 1.89–2.95) for mean heart rate ≥ 90 bpm (Fig. 2). In addition to a higher mean heart rate, age, male sex, eNIHSS, AF, CHF, and CKD stages 2–5 were still associated with cardiovascular death. A history of dyslipidemia, higher BMI, total cholesterol, ALT, and mean DBP levels showed a protective effect (Table 2).

Even after multiple adjustments for potential confounding factors, no J-shaped curve was found for the occurrence of the primary and secondary outcomes. A higher mean heart rate was significantly and continuously associated with increased HRs of all-cause mortality and cardiovascular death (Fig. 3).

Subgroup analysis

Interaction analyses are presented in Supplementary Table 1. Significant effect modifications of age, sex, eNIHSS, HTN, DM, AF, CHF, history of cancer before delivery, smoking status, and beta blocking agents were observed in the interaction analyses.
### Table 1: Demographic and baseline characteristics of the overall cohort stratified by mean heart rate

| Demographic/Baseline | Number of patients | Mean heart rate | p value |
|----------------------|--------------------|-----------------|---------|
|                      | (N=21,655)         | < 60 bpm (N=1680) | 60–69 bpm (N=5834) | 70–79 bpm (N=7914) | 80–89 bpm (N=4027) | ≥ 90 bpm (N=2200) |
| Age (year)           | 21,655             |                |                  |                   |                    |                   |
| Mean (SD)            | 67.37 (12.92)      | 67.84 (11.53)   | 66.76 (12.27)    | 66.73 (12.91)     | 67.88 (13.59)      | 69.96 (14.02)     |
| Median (Q1, Q3)      | 68.00 (59.00, 77.00) | 68.00 (60.00, 76.00) | 67.00 (59.00, 77.00) | 67.00 (58.00, 78.00) | 69.00 (59.00, 81.00) | 72.00 (61.00, 81.00) |
| Male                 | 21,655             | 13,400 (61.88%) |                  |                   |                    |                   |
| Stroke severity      | 21,655             |                |                  |                   |                    |                   |
| Mild (eNIHSS < 6)    | 14,393 (66.47%)    |                |                  |                   |                    |                   |
| Moderate (eNIHSS 6–13)| 3886 (17.95%)      |                |                  |                   |                    |                   |
| Severe (eNIHSS > 13) | 3376 (15.59%)     |                |                  |                   |                    |                   |
| Body mass index (kg/m²) | 14,966          | 24.84 (4.24)   | 24.79 (3.78)     | 24.97 (4.01)      | 25.02 (4.31)       | 24.73 (4.39)      |
| Mean (SD)            | 24.49 (22.06, 27.18) | 24.55 (22.43, 27.06) | 24.65 (22.37, 27.17) | 24.68 (22.23, 27.40) | 24.34 (21.87, 26.75) | 23.81 (21.19, 26.67) |
| Hypertension         | 22,149             | 12,276 (56.69%) | 895 (53.27%)     | 3191 (54.70%)     | 4469 (56.47%)      | 4469 (56.47%)      |
| Mean (SD)            | 8680 (40.08%)      | 468 (27.86%)   | 2013 (34.50%)    | 3362 (42.48%)     | 1879 (46.66%)      | 1879 (46.66%)      |
| Diabetes mellitus    | 22,149             | 9396 (43.39%)  | 827 (49.23%)     | 2791 (47.84%)     | 3545 (44.79%)      | 1591 (39.51%)      |
| Mean (SD)            | 3551 (16.40%)      | 186 (11.07%)   | 666 (11.42%)     | 1071 (13.53%)     | 894 (22.20%)       | 734 (33.36%)       |
| Dyslipidemia         | 22,149             | 1168 (5.39%)   | 59 (3.51%)       | 214 (3.67%)       | 385 (4.86%)        | 271 (6.73%)        |
| Mean (SD)            | 21,655             | 1452 (6.71%)   | 103 (6.13%)      | 307 (5.26%)       | 494 (6.24%)        | 299 (7.42%)        |
| Congestive heart failure | 22,149            | 5967 (27.55%)  | 618 (36.79%)     | 1885 (32.31%)     | 2087 (26.37%)      | 902 (22.40%)       |
| History of cancer before admission | 21,655 | 5974 (18.81%) | 230 (13.69%) | 999 (17.12%) | 1448 (18.30%) | 845 (20.98%) |
| Total cholesterol (mmol/L) | 19,576           | 4.63 (1.12)    | 4.56 (1.01)     | 4.64 (1.03)      | 4.67 (1.10)        | 4.63 (1.26)        |
| Mean (SD)            | 4.53 (3.88, 5.25)  | 4.50 (3.88, 5.12) | 4.55 (3.96, 5.22) | 4.58 (3.93, 5.30) | 4.53 (3.83, 5.28) | 4.32 (3.62, 5.12) |
| Triglyceride (mmol/L) | 19,572            | 1.51 (1.13)    | 1.39 (0.89)     | 1.49 (0.92)      | 1.55 (1.17)        | 1.57 (1.30)        |
| Mean (SD)            | 1.24 (0.90, 1.77)  | 1.22 (0.88, 1.67) | 1.26 (0.91, 1.76) | 1.29 (0.93, 1.83) | 1.24 (0.89, 1.84) | 1.11 (0.80, 1.59) |
| CKD                  | 21,655             | 5430 (25.08%)  | 366 (21.79%)     | 1442 (24.72%)     | 1991 (25.16%)      | 1050 (26.07%)      |
| Stage 1              | 6323 (29.20%)      | 548 (32.62%)   | 1810 (31.03%)    | 2261 (28.57%)     | 1090 (27.07%)      | 614 (27.91%)       |
| Stage 2              | 4838 (22.34%)      | 290 (17.26%)  | 1021 (17.50%)    | 1689 (21.34%)     | 1095 (27.19%)      | 743 (33.77%)       |
| Stage 3–5            | 20,873             | 25.57 (25.73) | 25.33 (20.98)   | 26.22 (21.82)     | 26.24 (20.91)      | 27.04 (35.60)      |
| ALT (U/L)            | 21,655             | 26.21 (16.00, 29.00) | 21.00 (16.00, 28.00) | 21.00 (16.00, 29.00) | 20.00 (15.00, 29.00) | 21.00 (15.00, 31.00) |
| HbA1c (%)            | 11,365             |                |                  |                   |                    |                   |
| Mean (SD)            | 6.14 (1.13)        |                |                  |                   |                    |                   |
| Median (Q1, Q3)      | 6.00 (0.99, 6.39)  |                |                  |                   |                    |                   |
admission, Beta blocking agent, total cholesterol, CKD stage, ALT, HbA1c, and mean SBP at baseline were detected on the relationship between mean heart rate and the primary outcome. An association between mean heart rate and long-term mortality was found in all analyzed subgroups (Fig. 4).

### Table 1 (continued)

| Number of patients | Mean heart rate (bpm) | All-cause mortality | Cardiovascular death |
|--------------------|-----------------------|---------------------|----------------------|
|                    | Mean (SD)             | Median (Q1, Q3)     | Mean (SD)            | Median (Q1, Q3) |
| Total (N = 21,655) | <60 bpm               | 6.89 (1.89) 6.37 (1.28) 6.68 (1.71) 6.93 (1.89) 7.17 (2.10) 7.15 (2.16) |
|                    | 60–69 bpm             | 6.10 (5.70) 5.90 (5.60) 6.00 (5.70) 6.20 (5.70) 6.30 (5.70) 6.30 (5.70) |
|                    | 70–79 bpm             | 6.30 (5.70) 7.00 (7.60) 6.70 (7.60) 6.70 (7.60) 7.90 (7.90) |
|                    | 80–89 bpm             | 21,622 < 0.001 21,622 < 0.001 21,622 < 0.001 21,622 < 0.001 21,622 < 0.001 |
|                    | ≥ 90 bpm              | 21,622 < 0.001 21,622 < 0.001 21,622 < 0.001 21,622 < 0.001 21,622 < 0.001 |
|                    | Mean SBP (mmHg)       | 151.04 (19.64) 154.0 (20.27) 151.95 (19.52) 150.73 (19.13) 151.58 (20.01) 146.91 (19.98) |
|                    | Mean DBP (mmHg)       | 84.81 (11.17) 82.56 (10.97) 84.38 (10.94) 85.21 (10.69) 86.02 (11.67) 84.01 (12.28) |

Fig. 2 Forest plots of crude and adjusted hazard ratios (95% CIs) of the primary outcome (all-cause mortality) and secondary outcome (cardiovascular death) by mean initial in-hospital heart rate increments. The analyses were adjusted for age and estimated National Institutes of Health Stroke Scale score in model 1, and all of the variables in the fully adjusted model (model 2), including age, sex, estimated National Institutes of Health Stroke Scale score, history of hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, congestive heart failure, cancer before admission, smoking status, beta blocking agent, body mass index, total cholesterol, triglycerides, chronic kidney disease stage, alanine aminotransferase, glycated hemoglobin, mean systolic blood pressure, and mean diastolic blood pressure. N number; HR hazard ratio; CI confidence interval; bpm beats per minute

Discussion

In this study of 21,655 patients with AIS, we found that the mean initial in-hospital heart rate was a predictor of all-cause mortality and cardiovascular death, independently of other known risk factors such as age and stroke severity.
Table 2 Multivariable Cox regression models for all-cause mortality and cardiovascular death

| Variables                                      | All-cause mortality | Cardiovascular death |
|------------------------------------------------|---------------------|----------------------|
| Mean heart rate (ref: <60 bpm)                 |                     |                      |
| 60–69 bpm                                      | 1.23                | 0.95–1.46            |
| 70–79 bpm                                      | 1.74                | 1.28–1.93            |
| 80–89 bpm                                      | 2.16                | 1.60–2.45            |
| ≥ 90 bpm                                       | 2.83                | 1.89–2.95            |
| Age                                            | 1.04                | 1.034–1.043          |
| Male (ref: female)                             | 1.38                | 1.24–1.48            |
| eNIHSS                                         | 1.085               | 1.110–1.125          |
| HTN (ref: without HTN)                         | 0.99                | 0.99–1.17            |
| DM (ref: without DM)                           | 1.17                | 0.84–1.02            |
| Dyslipidemia (ref: without dyslipidemia)       | 0.73                | 0.76–0.92            |
| AF (ref: without AF)                           | 0.99                | 1.05–1.27            |
| CHF (ref: without CHF)                         | 1.33                | 1.22–1.58            |
| Cancer (ref: without Cancer)                   | 2.13                | 0.84–1.16            |
| Smoker (ref: non-smoker)                       | 0.98                | 0.88–1.10            |
| Beta blocking agents user (ref: non-user)      | 0.98                | 0.98–1.18            |
| BMI (ref: ≥ 18.5, < 24)                        |                     |                      |
| < 18.5                                         | 1.40                | 1.17–1.65            |
| ≥ 24, < 27                                     | 0.78                | 0.72–0.92            |
| ≥ 27, < 30                                     | 0.74                | 0.74–1.01            |
| ≥ 30                                           | 0.68                | 0.67–1.01            |
| Missing                                        | 1.07                | 1.13–1.38            |
| Total cholesterol (ref: ≤ Q1)                  |                     |                      |
| > Q1, ≤ median                                 | 0.87                | 0.79–0.98            |
| > median, ≤ Q3                                 | 0.86                | 0.72–0.92            |
| > Q3                                           | 0.88                | 0.75–0.98            |
| Missing                                        | 1.08                | 0.58–2.59            |
| Triglyceride (ref: ≤ Q1)                       |                     |                      |
| > Q1, ≤ median                                 | 0.96                | 0.87–1.08            |
| > median, ≤ Q3                                 | 0.96                | 0.86–1.09            |
| > Q3                                           | 0.98                | 0.82–1.09            |
| Unknown                                        | 0.75                | 0.31–1.40            |
| CKD (ref: stage 1)                             |                     |                      |
| Stage 2                                        | 1.13                | 1.11–1.39            |
| Stage 3–5                                      | 1.79                | 1.61–2.01            |
| Unknown                                        | 0.87                | 0.68–0.91            |
| ALT (ref: ≤ Q1)                                |                     |                      |
| > Q1, ≤ median                                 | 0.79                | 0.69–0.86            |
| > Median, ≤ Q3                                 | 0.77                | 0.68–0.85            |
| > Q3                                           | 0.88                | 0.74–0.93            |
| Unknown                                        | 0.86                | 0.72–1.14            |
| HbA1c (ref: ≤ Q1)                              |                     |                      |
| > Q1, ≤ median                                 | 0.95                | 0.89–1.21            |
| > Median, ≤ Q3                                 | 1.03                | 1.03–1.40            |
| > Q3                                           | 1.11                | 0.98–1.41            |
| Unknown                                        | 1.13                | 1.11–1.40            |
| Mean SBP (ref: < 130 mmHg)                     |                     |                      |
| ≥ 130, < 140 mmHg                              | 0.87                | 0.74–0.97            |
| ≥ 140, < 150 mmHg                              | 0.87                | 0.73–0.96            |
The size of the study cohort allowed us to adjust for two of the strongest predictors of mortality in the multivariable model: age and stroke severity. In the subgroup analysis according to different age and stroke severity groups, the association between initial in-hospital heart rate and long-term mortality was consistent (Fig. 4). The impact of increasing heart rate on all-cause mortality seemed to be more pronounced in the patients younger than 75 years and in those with mild-to-moderate stroke (Fig. 4).

Epidemiological studies have consistently shown that resting heart rate is a predictor of all-cause and cardiovascular mortality in the general population and in patients with cardiovascular disease [22–24]. However, the previous studies have reported inconsistent results about the relationship

| Variables | All-cause mortality | Cardiovascular death |
|-----------|---------------------|----------------------|
|           | HR 95% CI p value   | HR 95% CI p value    |
| ≥ 150, < 160 mmHg | 0.93 0.85–1.03 0.151 0.86 0.74–1.00 0.045 |
| ≥ 160 mmHg | 1.09 0.99–1.20 0.091 1.01 0.87–1.18 0.882 |
| Unknown   | 1.08 0.23–5.13 0.921 0.89 0.14–5.57 0.899 |

Mean DBP (ref: < 70 mmHg)

| HR 95% CI p value | HR 95% CI p value |
|-------------------|-------------------|
| ≥ 70, < 80 mmHg | 0.83 0.77–0.91 < 0.001 0.86 0.75–0.97 0.018 |
| ≥ 80, < 90 mmHg | 0.69 0.62–0.75 < 0.001 0.77 0.67–0.89 < 0.001 |
| ≥ 90, < 100 mmHg | 0.67 0.60–0.75 < 0.001 0.79 0.66–0.94 0.008 |
| ≥ 100 mmHg | 0.61 0.52–0.71 < 0.001 0.78 0.62–0.99 0.044 |
| Unknown | 0.39 0.09–1.71 0.212 0.59 0.11–3.13 0.531 |

HR hazard ratio; CI confidence interval; ref reference; bpm beats per minute; eNIHSS estimated National Institute of Health Stroke Scale; HTN hypertension; DM diabetes mellitus; AF atrial fibrillation; CHF congestive heart failure; BMI body mass index; Q quartile; CKD chronic kidney disease; ALT alanine aminotransferase; HbA1c glycated hemoglobin; SBP systolic blood pressure; DBP diastolic blood pressure
between heart rate and the clinical outcomes of patients with AIS. The Prevention Regimen for Effectively Avoiding Second Strokes study reported that heart rate was a risk factor for mortality in stroke patients, and, importantly, that a low heart rate was associated with better functional outcomes and lower rates of cognitive impairment after an AIS [25]. In addition, the Gutenberg Health Study reported that both a higher and lower heart rate were associated with a higher risk of mortality [26]. However, Ritter et al. reported that significant tachycardia or bradycardia in AIS did not independently predict the clinical course or outcomes [27]. A higher resting heart rate at admission has also been reported to be independently associated with in-hospital mortality in AIS patients without AF [28]. In addition, Lee et al. reported that in patients with AF hospitalized for AIS, the mean heart rate during the acute period was not associated with stroke recurrence, but was associated with mortality (nonlinear, J-shaped association) [29]. In the present study, mean initial in-hospital heart rate was associated with long-term all-cause and cardiovascular mortality in the overall cohort (Fig. 2), and in the patients with and without AF (Fig. 4). However, the effect of heart rate on long-term mortality seemed to be more pronounced in the patients without AF than in those with AF (Fig. 4). We also found that the long-term survival progressively declined as the level of mean initial in-hospital heart rate increased; however, there was no significant association with mortality in the patients with AF.
no clear evidence of a J-curve relationship between the mean initial in-hospital heart rate and long-term mortality (Fig. 3).

In the multivariable Cox regression analysis, history of dyslipidemia, higher total cholesterol levels, and higher BMI are associated with improved long-term survival after AIS (Table 2). Although dyslipidemia and high BMI are well-known risk factors for cardiovascular disease, this has not been the case for post-stroke mortality. From several large cohorts, blood lipid levels and BMI have generally been inversely associated with post-stroke mortality [30–32]. There may be unknown protective factors associated with dyslipidemia and high BMI.

Although heart rate is traditionally considered to be a risk factor for cardiovascular disease [33], we found that high initial in-hospital heart rate was a risk factor for both cardiovascular death and all-cause mortality after AIS in the current study. In the long-term follow-up of this study, cardiovascular death and cancer were the leading and secondary causes of death (40.7% and 17.1% of total mortality), respectively. Benetos et al. reported that heart rate was a predictive factor for non-cardiovascular mortality in both men and women in a French population [34]. Another prospective population study also reported that an increased mortality risk associated with a high heart rate was related mainly to diseases of non-cardiovascular or non-malignant origin [35]. However, many studies have demonstrated an association between an elevated heart rate and increased risks of cancer recurrence and mortality [36–38]. For example, a previous meta-analysis found that a higher resting heart rate was associated with increased risks of coronary heart disease, sudden cardiac death, heart failure, AF, stroke, cardiovascular disease, total cancer, and all-cause mortality [39].

Heart rate has been associated with plaque vulnerability, sympathetic hyperactivity, and atherosclerosis [40–42], and therefore, the role of arterial stress related to heart rate in the underlying mechanisms of the progression and clinical manifestations of cardiovascular diseases has gained increasing attention. In this study, the patients with a higher resting heart rate had more cardiovascular risk factors than those in the lowest group (Table 1). Some investigators have also indicated that many cardiovascular risk factors are also related to sympathetic hyperactivity [43–45]. Reduction of heart rate has been shown to delay the progression of coronary atherosclerosis in monkeys [46, 47], and reduce the rate of increase in carotid intima-media thickness in asymptomatic patients [48]. In a model of dyslipidemic mice, chronic heart rate reduction via ivabradine maintained cerebral endothelial function and prevented cerebral artery remodeling [49]. However, whether beta-blockers, calcium-channel blockers, or If channel inhibitor are associated with survival benefit in patients with coronary artery disease is still inconclusive [50–52]. In addition to the above agents, cholinesterase inhibitors can also slow the heart rate via increasing cholinergic effect and show some potential in improving the lifespan [53–55]; however, further studies are needed to investigate whether they can improve survival after AIS. We hope that using appropriate medications to reduce heart rate may play a role in improving the long-term survival after AIS in the future.

Limitations of this study

The current study has a large sample size and addresses the prognostic implications of initial in-hospital heart rate. However, as with all observational studies, this study has several limitations. First, to collect the vital signs for the first 3 days of hospitalization, patients who were hospitalized for less than 3 days were excluded from the study, and so some patients with mild stroke may have been missed. Second, the link between mean initial in-hospital heart rate and death may not necessarily imply a cause–effect relationship. Third, this study was performed with a population of patients with AIS; therefore, our results may not be applicable to patients with other cardiovascular diseases.

Conclusion

Heart rate is a simple measurement with important prognostic implications in patients with AIS, and it should no longer be neglected in risk flowcharts.

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Author contributions J.L. and T.L. designed the research, collected data, analyzed and interpreted data, and wrote the manuscript; Y.K analyzed and interpreted data and contributed to subsequent manuscript discussion; C.L. performed statistical analysis and contributed to subsequent manuscript discussion; Y.H and M.L. performed the research and contributed to subsequent manuscript discussion.

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Availability of data and materials The data supporting the findings of the article are available in the Chang Gung Research Databank at Chang Gung Memorial Hospital, Chiayi Branch. These data can be available after obtaining approval from our local IRB.

Code availability Not applicable.
Declarations

Conflict of interest  The authors declare that they do not have any conflicts of interest.

Ethics approval  The study was approved by the local Institutional Review Board of Chang Gung Memorial Hospital, Chiayi Branch, Taiwan (202001990BC501). All methods were carried out in accordance with relevant guidelines and regulations.

Consent to participate  Before being released for analysis, the clinical data are anonymized and de-identified to ensure confidentiality; thus, the need for informed consent was waived.

Consent for publication  All authors read and consented to the final manuscript version for publication.

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