Original Article

Minimum heart rate and mortality in critically ill myocardial infarction patients: an analysis of the MIMIC-III database

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Background: Low minimum heart rate (MHR) is common in critically ill myocardial infarction (MI) patients. However, the association between MHR and the mortality of critically ill MI patients remains unclear.

Methods: In this retrospective cohort study, a total of 2,031 critically ill MI patients were enrolled from the Medical Information Mart for Intensive Care (MIMIC)-III database. Patients were divided into a low MHR group [MHR <60 beats per minute (bpm)] and a high MHR group (MHR ≥60 bpm). A Cox proportional hazard model was used to elucidate the association between these two groups and the mortality of MI patients. The association between mortality and MHR as a continuous variable was analyzed non-parametrically using restricted cubic splines. Sensitivity analyses were conducted to determine the impact of different admission heart rate, hypertension, atrial fibrillation, and vasopressor use on our results.

Results: MI patients in the low MHR group had higher 30-day and 1-year mortality than those in the high MHR group (20.59% *vs.* 10.91%, P<0.001 and 29.76% *vs.* 19.31%, P<0.001, respectively). After adjustment, the low MHR group was significantly correlated with 30-day mortality [hazard ratio, 1.779, 95% confidence interval (CI), 1.400–2.261, P<0.001] and 1-year mortality (hazard ratio, 1.537, 95% CI, 1.272–1.859, P<0.001). This correlation remained remarkable in patients with low or high admission heart rate, with or without hypertension, and with or without atrial fibrillation. An apparent L-curve relationship was observed between the 30-day mortality or 1-year mortality and MHR as a continuous variable.

Conclusions: MHR under 60 bpm may be associated with a higher risk for both 30-day and 1-year mortality in critically ill MI patients. These findings highlight the possibility of MHR as an early risk indicator and potential therapeutic target for mortality in critically ill MI patients, which warrants further investigation.

Keywords: Minimum heart rate (MHR); myocardial infarction (MI); mortality; risk factor; intensive care unit (ICU)

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Introduction

A considerable number of critically ill myocardial infarction (MI) patients are admitted to intensive care units (ICUs), resulting in a significant health-care cost burden worldwide (1). However, not all of these patients benefit from ICU care, and thus an evaluation indicator to identify MI patients with a higher risk of mortality is crucial. Yet, several frequently used scoring systems to evaluate the prognoses of patients in ICU, such as the Simplified Acute Physiology Score (SAPS), were established according to the population excluding patients in the coronary care unit (2-5). Thus, it is necessary to determine some readily measured parameters for physicians to identify high-risk MI patients and triage this high-risk population to a standard intensive care, which may benefit MI patients in ICU and achieve a better prognosis.

Resting heart rate (HR), a physical sign of autonomic cardiac regulation and a reflection of cardiac function, such as cardiac output and sinoatrial node automaticity, is a well-established biomarker that predicts the outcomes of multiple heart disease (6,7). An elevated HR was reported to be associated with both higher short-term and longer-term mortality in acute MI patients (8,9). A positive correlation was observed between HR and mortality in patients with acute MI when they are admitted to the hospital (10). Recently, a U-shaped association was found to exist between HR and mortality in a hypertensive cohort (11), and this relationship was also observed between HR and mortality in atrial fibrillation patients (12), which indicated that a HR above or below an appropriate level may suggest poor prognosis. However, in MI patients, it is unknown whether bradycardia, which is frequently found during the first 24 hours of admission (13), confers a clinical risk in that cohort. In the present study, HR was measured at least one time per hour in the first 24-hour period, and the minimal value was defined as minimal heart rate (MHR). We aimed to understand whether MHR may also serve as a predictive value for prognosis in ICU patients.

To address this question, we conducted a retrospective cohort study and sought to determine the association between MHR and risk of mortality in critically ill MI patients based on the Medical Information Mart for Intensive Care (MIMIC-III) database. A multivariable Cox hazard ratio regression model and restricted cubic spline model were performed in our study. Furthermore, sensitivity analyses were conducted to evaluate the robustness and reliability of our results.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-21-992).

Methods

Data source and population selection

The data in this study were extracted from the MIMIC-III database (14). Briefly, the MIMIC-III database is a public critical care database that contains records from 53,423 ICU admissions to the Beth Israel Deaconess Medical Center from 2001 to 2012 (14). The establishment of this freely available database was approved by the Massachusetts Institute of Technology (MIT) and the Institutional Review Boards (IRB). The MIMIC-III database documents are comprised of charted events including demographics data, laboratory tests, fluid balance, vital status and blood gas analysis data, discharge summaries, electrocardiograph, imaging examinations, and diagnostic information such as the International Classification of Diseases, Ninth Revision (ICD-9). We included ICU patients diagnosed with MI using ICD-9 diagnosis codes, and a total of 2,031 patients were considered eligible for inclusion in this study.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

MHR and outcomes

HR was validated and documented hourly for each patient, and MHR was defined as the minimum HR during the first 24 h after admission. The participants were divided into a high MHR group (MHR ≥60 bpm) and a low MHR group (MHR <60 bpm). The primary outcome of the study was defined as 30-day mortality and 1-year mortality from the date of ICU admission.

Covariates

A large amount of admission information was collected for each patient from MIMIC-III by the Structured Query Language, including demographic data (age, gender, and race), socioeconomic factors (private insurance), nursing progress notes (weight, HR, mean arterial pressure, temperature, and ventilation), laboratory results [white blood cell count (WBC), platelet, hemoglobin, creatinine kinase, creatinine, chloride, sodium, potassium, blood urea nitrogen (BUN), and bicarbonate], medication records

(vasopressor, sedatives), clinical comorbidities (hypertension, atrial fibrillation, congestive heart failure, valvular disease, renal disease, stroke, liver disease, diabetes, sepsis, chronic obstructive pulmonary disease, and malignancy), and the severity of illness, which was defined at ICU admission using the SAPS score, sequential organ failure assessment (SOFA) score, and the Elixhauser comorbidity score.

Statistical analysis

Categorical data were presented as a number (percentages), while continuous data were presented as the mean ± standard deviation or median (interquartile range), as appropriate. The differences in categorical variables between the two groups were detected by the Chi-square test. The Student *t*-test or rank-sum test was applied to assess continuous variables between the two groups, as appropriate.

A Cox proportional hazards model was applied to determine whether MHR was independently associated with 30-day mortality and 1-year mortality after adjusting for potential confounders. Model 1 adjusted for age and private insurance. Model 2 adjusted for model 1 plus the SAPS score. Model 3 adjusted for model 2 plus HR temperature. Model 4 adjusted for model 3 plus atrial fibrillation, stroke, and liver disease. Model 5 adjusted for model 4 plus creatinine kinase, WBC, sodium, BUN, creatinine, and potassium.

The potential non-linear relationships between MHR as a continuous variable and crude hazard ratio or adjusted hazard ratio were assessed by cubic splines analysis.

Furthermore, sensitivity analysis was conducted to determine the impact of various subgroups, classified by different admission HR, hypertension, atrial fibrillation, and vasopressor use, on our results.

A P value <0.05 by two-tailed test was considered statistically significant in our study. SPSS software (version 23.0, IBM, NY, USA) and R (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis.

Results

Baseline characteristics

In total, 2,031 critically ill MI patients were included in this cohort. The low MHR group (MHR <60 bpm) and high MHR group (MHR ≥60 bpm) comprised 840 and 1,191 ICU patients, respectively. Patients in the low MHR group had significantly lower admission HR (P<0.001). The low MHR group had a significantly higher SAPS score (P<0.001) than the high MHR group, while the SOFA and Elixhauser scores were not significantly different between the two groups. Furthermore, patients with low MHR were more likely to have lower WBC, creatinine kinase, potassium and higher creatinine, sodium, and BUN. No significant difference was observed in the prevalence of comorbidities between the two groups. Importantly, the low MHR group had a higher risk for 30-day mortality (20.59% *vs.* 10.91%) and 1-year mortality (29.76% *vs.* 19.31%) (P<0.001, *Table 1*).

Association of different MHR groups with mortality

A Cox proportional hazards model was performed to evaluate the association between MHR and the outcomes of MI patients. Model 1, adjusted for age and private insurance, indicated that the low MHR group had a higher risk for 30-day mortality and 1-year mortality than the high MHR group (each P<0.05). After further adjustment for a series of covariates in model 5, the higher risk of 30-day mortality and 1-year mortality remained significant in the low MHR group with hazard ratios of 1.779 [95% confidence interval (CI), 1.400–2.261] and 1.537 (95% CI, 1.272–1.859), respectively (*Table 2*).

Non-linear association between MHR and outcome

By using restricted cubic spline analysis, we observed an apparent non-linear relationship between MHR and the outcome of MI patients in ICU (with 60 bpm as a reference). The relationship between MHR and outcome was similar in patients with or without adjusted variables, which could be characterized as a typical L-curve (*Figure 1*). Results from the cubic spline model suggested that MI patients in both groups had a higher 30-day mortality and 1-year mortality than the bottom of the curve, especially in the low MHR group.

Sensitivity analyses

To further clarify the influence of admission HR, drugs, and comorbidities on our results; admission HR over 80 bpm, hypertension, atrial fibrillation, and vasopressor use were included in the sensitivity analyses. The correlation between MHR and outcome was still statistically significant (each P<0.05) in MI patients with low or high admission HR, with

Table 1 Characteristics of participants categorized by MHR

Characteristics	low MHR group (<60 bpm)	high MHR group (≥60 bpm)	P
N	840	1,191	–
Age, years	69.76±12.73	66.64±14.47	<0.001
Male	542 (64.52)	757 (63.56)	0.656
Private insurance	276 (32.85)	446 (37.44)	0.025
White	520 (61.90)	749 (62.88)	0.652
Weight, kg	80.09±18.99	81.35±20.18	0.149
SAPS score	18.1±6.13	16.21±6.02	<0.001
SOFA score	3.00 (1.00–6.00)	3.00 (1.00–5.00)	0.156
Elixhauser score	0.00 (0.00–5.00)	0.00 (0.00–5.00)	0.060
Sedatives	260 (30.95)	401 (33.66)	0.198
Ventilation	300 (35.71)	438 (36.77)	0.624
Vasopressor	259 (30.83)	413 (34.67)	0.070
Heart rate, bpm	78.31±18.02	89.46±15.98	<0.001
MAP, mmHg	85.02±18.29	85.73±17.68	0.365
Temperature, ℃	36.24±1.05	36.42±0.90	<0.001
Hypertension	496 (59.04)	671 (56.33)	0.224
AF	233 (27.73)	277 (23.25)	0.022
CHF	310 (36.90)	468 (39.29)	0.275
Valvular disease	110 (13.09)	181 (15.19)	0.183
Stroke	50 (5.95)	48 (4.03)	0.047
Diabetes	215 (25.59)	322 (27.03)	0.468
Sepsis	181 (21.54)	221 (18.55)	0.096
Renal disease	74 (8.80)	88 (7.38)	0.244
Liver disease	44 (5.23)	36 (3.02)	0.011
COPD	78 (9.28)	114 (9.57)	0.828
Malignancy	47 (5.59)	81 (6.80)	0.271
WBC, K/μL	12.36±5.82	12.92±5.41	0.028
Platelet, K/μL	226.29±100.13	230.56±90.50	0.317
Hemoglobin, g/dL	11.71±2.08	11.75±2.14	0.663
Creatinine kinase, U/L	250.50 (51.00–964.06)	462.00 (85.00–999.85)	<0.001
Creatinine, mg/dL	1.00 (0.80–1.40)	0.90 (0.70–1.30)	<0.001
Chloride, mg/dL	104.83±5.05	104.75±4.88	0.718
Sodium, mg/dL	138.05±3.98	137.65±3.74	0.022
Potassium, md/dL	4.18±0.69	4.26±0.71	0.015
BUN, mg/dL	25.62±18.87	22.65±15.68	<0.001
Bicarbonate, mg/dL	22.91±4.31	23.08±3.89	0.354
30-day mortality	173 (20.59)	130 (10.91)	<0.001
1-year mortality	250 (29.76)	230 (19.31)	<0.001

For each variable, mean ± standard deviation, median (interquartile range), or number (percent) was reported (as appropriate). Participants were divided into two groups, a low MHR group (MHR <60 bpm) and a high MHR group (MHR ≥60 bpm). Between these two groups, continuous variables were compared using either the Student *t*-test or the rank-sum test (as appropriate). The Chi-square test was employed to compare differences in the categorical variables. MHR, minimum heart rate; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; MAP, mean arterial pressure; AF, atrial fibrillation; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; WBC, white blood cell count; BUN, blood urea nitrogen; bpm, beats per minute.

Table 2 Association between MHR group and the outcomes of MI patients

Model	30-day mortality		1-year mortality	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Model 1	1.805 (1.436–2.268)	<0.001	1.502 (1.255–1.798)	<0.001
Model 2	1.497 (1.189–1.885)	0.001	1.318 (1.100–1.579)	0.003
Model 3	1.813 (1.429–2.302)	<0.001	1.559 (1.292–1.882)	<0.001
Model 4	1.781 (1.402–2.261)	<0.001	1.524 (1.262–1.839)	<0.001
Model 5	1.779 (1.400–2.261)	<0.001	1.537 (1.272–1.859)	<0.001

Hazard ratio and 95% CI for MHR group in 30-day mortality and 1-year mortality were calculated using different Cox regression models. Compared with the high MHR group, the low MHR group had a higher risk for 30-day mortality and 1-year mortality in different models. Model 1 adjusted for age, private insurance. Model 2 adjusted for model 1 plus SAPS score. Model 3 adjusted for model 2 plus heart rate and temperature. Model 4 adjusted for model 3 plus AF, stroke, and liver disease. Model 5 adjusted for model 4 plus creatinine kinase, WBC, sodium, BUN, creatinine, and potassium. MHR, minimum heart rate; MI, myocardial infarction; CI, confidence interval; SAPS, simplified acute physiology score; AF, atrial fibrillation; WBC, white blood cell count; BUN, blood urea nitrogen.

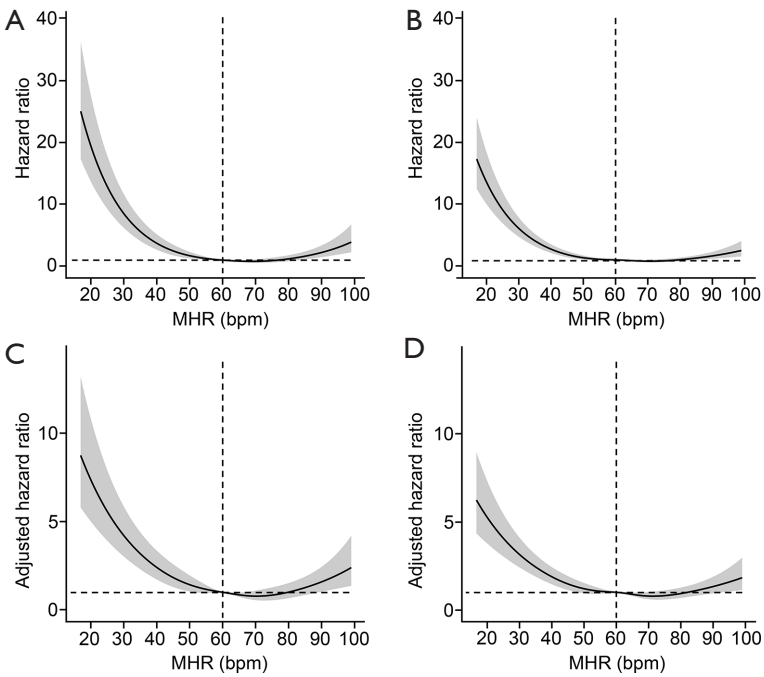

Figure 1 Association between MHR and outcomes of MI patients. Crude hazard ratio and 95% CI for MHR in 30-day mortality (A) and 1-year mortality (B). Adjusted hazard ratio and 95% CI for MHR in 30-day mortality (C) and 1-year mortality (D). The analyses used a model with restricted cubic splines. The reference (hazard ratio =1, horizontal dotted line) was an MHR of 60 bpm (vertical dotted line). Adjusted variables included age, private insurance, SAPS score, heart rate, temperature, AF, stroke, liver disease, WBC, creatinine kinase, creatinine, sodium, potassium, and BUN, namely model 5 described above. MHR, minimum heart rate; CI, confidence interval; SAPS, simplified acute physiology score; AF, atrial fibrillation; WBC, white blood cell count; BUN, blood urea nitrogen.

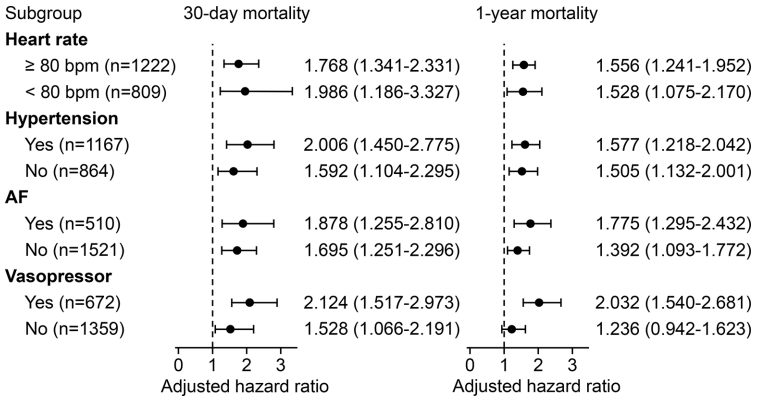

Figure 2 Association between MHR group and outcomes of MI patients in different subgroups. Adjusted hazard ratio and 95% CI for MHR group in 30-day mortality and 1-year mortality were calculated for different subgroups. Compared with the high MHR group, the low MHR group had a higher risk for 30-day mortality and 1-year mortality in different subgroups. Adjusted variables included age, private insurance, SAPS score, heart rate, temperature, AF, stroke, liver disease, WBC, creatinine kinase, creatinine, sodium, potassium, and BUN, namely model 5 described above. MHR, minimum heart rate; CI, confidence interval; SAPS, simplified acute physiology score; AF, atrial fibrillation; WBC, white blood cell count; BUN, blood urea nitrogen.

or without hypertension, with or without atrial fibrillation, and with or without vasopressor use. After adjustment of the variables, the hazard ratio of 30-day mortality and 1-year mortality was generally increased in patients with low MHR (*Figure 2*).

Discussion

This retrospective cohort study included 2,031 MI patients, which were divided into a high MHR group and a low MHR group with a cut-off point of 60 bpm. Briefly, we found that low MHR was associated with significantly higher risk for 30-day mortality and 1-year mortality compared to high MHR in MI patients. Additionally, HR has been implicated with a risk of mortality in the general population and in patients with cardiovascular disorders in previous studies (15,16). However, limited retrospective evidence was involved in the relationship between MHR and the risk of mortality. The present study showed a L-shaped curve in the restricted cubic splines, indicating a non-linear association between low MHR and 30-day and 1-year mortality. Thus, this study provides evidence for the possibility to predict critically ill MI patients with poor prognosis using low MHR, highlighting the opportunity of employing MHR as a novel, easily obtained risk marker.

Transfer timely to cardiac ICU for careful nursing was recommended for acute MI patients. And comprehensive critical care on admission or after revascularization, including continuous reassessment of hemodynamics such as HR and blood pressure, was needed to improve the prognosis of acute MI patients (17). Recently, severe Coronavirus Disease-19 patients with complex myocardial injury were reported to suffer significantly higher in-hospital mortality compared with those without myocardial injury (18). The Global Registry of Acute Coronary Events (GRACE) score was one of the most used indicators of the prognosis of acute MI (19). While HR was one of the measurements that were enrolled in the GRACE score. Notably, increased resting HR is associated with increased all-cause mortality and the risk of cardiovascular events in healthy individuals (20) or in patients with diabetes (21), atherosclerosis (22), plaque rupture (23), hypertension (24), heart failure (25,26), arrhythmia, or other cardiovascular diseases (27,28). While the negative impact of elevated HR has been confirmed in MI patients, there is still conflicting evidence in relation to the influence of bradycardia. The association between low admission HR (<60 bpm) and mortality was previously observed in patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (28). However, further data revealed that bradycardia (<60 bpm) was not an independent predictor of mortality in STEMI patients (29,30). Herein, we showed that low MHR (<60 bpm), a physiological parameter that can be easily collected at first-day admission, performs well in predicting the short-

and long-term mortality of patients with MI. We expect that MHR will work as a rapid marker to identify high-risk MI patients in ICUs.

Recently, emerging studies have focused on the non-linear relationship between HR and adverse outcomes (29,31,32). The present study showed a typical L-type curve in the restricted cubic splines, depicting an apparent non-linear relationship between MHR and 30-day and 1-year mortality, with the lowest risk around an MHR of 60 bpm. Our findings raise the possibility that MHR could rapidly provide information to physicians, and demonstrate the potential harms of an MHR that is either too high or too low. HR has been recognized as a modifiable risk factor for cardiovascular disease, and HR lowering therapy with beta-blockers (33) and ivabradine (25,34) can improve cardiovascular outcomes in patients with elevated HR, but not in those with low HR. In ICUs, pacemaker optimization had been shown to be a feasible therapeutic option for cardiogenic shock, which could help increasing cardiac output and reducing the detrimental effect of catecholamines (35). Importantly, the present study points out that controlling MHR around 60 bpm may be the optimal HR lowering therapeutic strategy for MI, which would reduce the risk of all-cause mortality in critically ill MI patients.

It was reported that age could be used to estimate the maximum HR in patients with coronary heart disease receiving beta-adrenergic blockade therapy (36). Acute myocardial infarction mortality was reported to increase exponentially with age (37). Thus, age was adjusted in most of our model. Additionally, HR can be affected easily by drugs, therapies, and changes occurring in numerous diseases, such as hypertension, atrial fibrillation, and vasopressor use. In our study, sensitivity analyses in the patients with or without admission HR over 80 bpm, hypertension, atrial fibrillation, and vasopressor use showed that the patients with lower MHR were still remarkably associated with higher mortality (after adjusting a series of covariates). Results implying that MHR acts as an early risk factor in MI patients were consistent in the sensitivity analyses, and highlighted the importance of MHR as a reliable early risk indicator, and that keeping MHR around 60 bpm may be a better HR lowering therapeutic option to minimize the risk of mortality.

Our research has several limitations that should be noted. Firstly, due to the design of retrospective cohort study, selection bias could not be excluded. Sensitivity analysis was carried out to support the consistence of our results. Further external validation would help to enhance the credibility of our results. Secondly, some relevant information about oral medications could not be found in the MIMIC-III database. However, sensitivity analyses for subgroups with hypertension or AF that might receive HR lowering medications therapy showed consistent results. Thirdly, MI patients were identified using ICD-9 codes rather than clinical diagnostic criteria, raising the possibility that a few patients might be missing.

Conclusions

In critically ill MI patients, a low MHR (<60 bpm) can indicate those at increased risk of both 30-day and 1-year mortality, and appropriate HR control strategies must be guaranteed for this high-risk population. These findings identify MHR as an easily obtained prognostic marker of critically ill MI patients during the first 24 h of ICU admission, and further validation of the potential role of MHR in risk stratification is warranted.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-21-992

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-992). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The application of the MIMIC-III database was approved by the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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