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Research Article

Impact of Hyperuricemia on the Prognosis in Patients with Acute Myocardial Infarction and Atrial Fibrillation

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ABSTRACT

Background: Hyperuricemia (HUA) is associated with poor prognosis in patients with Acute Myocardial Infarction (AMI). However, its prognostic value in patients with AMI and coexisting Atrial Fibrillation (AF) is not clear.

Methods: We retrospectively studied patients admitted to three hospitals in Beijing, China with the diagnoses of both AMI and AF at discharge/death. HUA was defined as serum uric acid levels ≥ 6.8 mg/dl. The endpoint of the study was in-hospital all-cause mortality. The relationship between HUA and the endpoint was analyzed by multivariate logistic regression. Subgroup analyses were done in patients categorized by sex and in those who underwent Coronary Angio Graphy (CAG).

Results: After excluding those with missing data, a total of 651 patients were included in the study with the median age of 76 and 40.25% were women. Patients with HUA counted up to 40.40% of the study population and 15.51% of the patients died during hospitalization. HUA was shown to be an independent predictor of in-hospital mortality after adjusting for confounding factors (Adjusted Odds Ratio (OR) 2.09, 95% Confidence Interval (CI) 1.29-3.40, p=0.003). Subgroup analysis categorized by sex showed similar results for HUA in male patients (Adjusted OR 2.02, 95% CI 1.04-3.95, p=0.039) but not in female patients. HUA was also not included in the final adjusted model in patients who underwent CAG.

Conclusion: HUA was an independent predictor of in-hospital all-cause mortality in patients with AMI and coexisting AF. Similar conclusion could be drawn in male patients but not in female patients and patients who underwent CAG.

Keywords: Hyperuricemia; Acute myocardial infarction; Atrial fibrillation; Mortality

INTRODUCTION

Although treatment strategies keep improving, the mortality of Acute Myocardial Infarction (AMI) remains high [1]. As a result, searching for better predictive factors of adverse outcomes is an issue of interest. While some risk factors have been well identified, such as advanced age, Diabetes Mellitus (DM), prior Myocardial Infarction (MI) and renal insufficiency, there are still debates on the new emerging factor Uric Acid (UA) [2-8]. Some studies showed that adding UA to the prognosis predictive models improved their discriminatory power in patients with acute coronary syndrome including AMI [9-11]. While some other studies showed no association between UA and cardiovascular mortality [12,13].

Actually, patients suffering both AMI and Atrial Fibrillation (AF) are not rare in clinical practice [14]. Known as the most common sustained arrhythmia, AF increases rapidly and leads to severe complications such as stroke and heart failure [15]. Although associated with atrial thrombosis, it is unclear whether UA is of prognostic value for AF patients [16,17]. Furthermore, some studies have shown adverse impact of coexisting AF on the outcomes of AMI patients, which makes this population at even higher risk of death [18-20]. However, prognostic predictors of such patients have not been fully studied. UA was considered to be related to both AMI and AF, but less studied and with more debate than other well-established factors. Therefore, our study aimed to explore the role of UA in the mortality of patients with AMI and AF.

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METHODS

Study population and design

The study population was chosen from a database described elsewhere [21]. Briefly, the database consisted of hospitalization information of 1,204 adult patients admitted to three hospitals (Beijing Tongren Hospital, Capital Medical University, from September 2008 to December 2018; Beijing Friendship Hospital, Capital Medical University, from January 2013 to March 2018; China-Japan Friendship Hospital, from April 2011 to May 2018) in Beijing, China, who diagnosed with both AF and AMI at discharge or on death.

The diagnosis of AMI was made in accordance with the recent guideline, which required cardiac biomarkers elevation plus at least one of the following items: (i) Cardiac ischemic symptoms; (ii) Suggestive changes in the electrocardiograms (e.g. ST segment elevation or depression or pseudonormalization, newly appeared left or right bundle branch block or Q waves); (iii) Ventricular wall motion abnormalities detected by images with the exclusion of a previous MI of the same ventricular segment; (iv) Thrombi demonstrated by Coronary Angiography (CAG). Patients with either acute ST-segment Elevation MI (STEMI) or acute Non-STEMI (NSTEMI) were included [22].

AF was defined as the discharge/death diagnoses including at least one of the following diagnosis codes: I48xx01, I48xx02, I48xx03, I48xx04, I48xx05, I48xx06, I48xx07, I48xx08, I48xx09, I48xx10, I48xx11, I48xx12, I48xx13 and I48xx14 according to the International Classification of Disease - 10th edition (ICD-10) [23]. With these criteria, patients with different types of AF could be enrolled. They were further classified as Paroxysmal AF (PAF) and non-PAF, of which the latter including both persistent AF and permanent AF.

Among patients with re-admissions, only the first was studied. Patients' demographics (e.g. age, sex, smoking status), comorbidities (e.g. history of hypertension, DM, Heart Failure (HF), stroke, previous MI), results of laboratory biochemical tests (e.g. Serum Uric Acid (SUA), Creatinine (Cr), low Density Lipoprotein-Cholesterol (LDL-C)) and discharge status (alive/dead) were collected from medical records. Only laboratory tests within one day before or after the admission were studied. UA was used both as a continuous variable (SUA, mg/dl) and a categorical variable (Hyperuricemia (HUA)) during analyses. HUA was defined as SUA ≥ 6.8 mg/dl according to the recent guideline [24]. Furthermore, data on ventricular arrhythmia, Killip classification and undergoing CAG or not were also collected. Ventricular arrhythmia was defined as sustained ventricular tachycardia required medical or electrical cardioversion, ventricular flutter or ventricular fibrillation occurring during hospitalization or emergency care prior to the admission. Device support referred to the use of circulation supporting devices, such as Intra-Aortic Balloon Pump (IABP) and Extra Corporeal Membrane Oxygenation (ECMO). Invasive or non-invasive treatment strategies were chosen according to the physicians' opinions for each individual.

Endpoint of the study

The endpoint of the study was in-hospital all-cause mortality, which was defined as death due to any cause during hospitalization. The direct cause of death for each patient was extracted from the medical record.

Subgroup analyses

Subgroup analyses were done categorized by sex and in those who underwent CAG. As for the latter, further information of CAG and revascularization results were collected. Left Main (LM) coronary artery disease referred to ≥ 50% stenosis or less than grade 3 of the Thrombolysis In Myocardial Infarction (TIMI) blood flow of the vessel. Multivessel disease was defined as ≥ 50% stenosis or TIMI blood flow less than 3 in more than one coronary artery branch except LM (left anterior descending branch, left circumflex branch or right coronary artery). Those who accepted Percutaneous Coronary Intervention (PCI) treatment with all target vessels reaching TIMI 3 blood flow and with residual stenosis <20% with stent implanting or <50% with balloon dilation, or those who received Coronary Artery Bypass Grafting (CABG) were considered as with successful revascularizations.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by clinical research ethics committee of our centers (NO.:TRECKY2020-097) and individual consent for this retrospective analysis was waived.

Statistical analysis

SPSS version 24.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Whether continuous data was conformed to normal distribution was tested by one-sample Kolmogorov-Smirnov test. Continuous data were reported as median with interquartile (median (25th percentile-75th percentile)). Comparisons between groups were performed with student's t tests for variables with normal distribution or Wilcoxon rank sum tests for variables not normally distributed. Categorical data were expressed as counts with percentages and comparisons between groups were performed with Pearson's Chi-square test or Chi-square test with continuity correction when appropriate.

Univariate logistic regression was done for every variable including SUA/HUA to explore whether it was a risk factor of the endpoint and a backward stepwise multivariate logistic regression with HUA was done to adjust for the confounding factors.

The input cut-off p value was 0.05 and the output cut-off p value was 0.1 for multivariate logistic regressions. Other results were considered statistically significant with two-tailed p values <0.05.

RESULTS

Patients' characteristics

After excluding 444 patients without SUA results during the required period and another 109 for missing data of other studied variables, 651 patients were included in the study Figure 1, with the median age of 76 years old and 40.25% were women. According to the cut-off value described previously, 263 (40.40%) belonged to the HUA group. Patients' characteristics at baseline were listed in Table 1. Patients with HUA were elder, more likely to have DM and

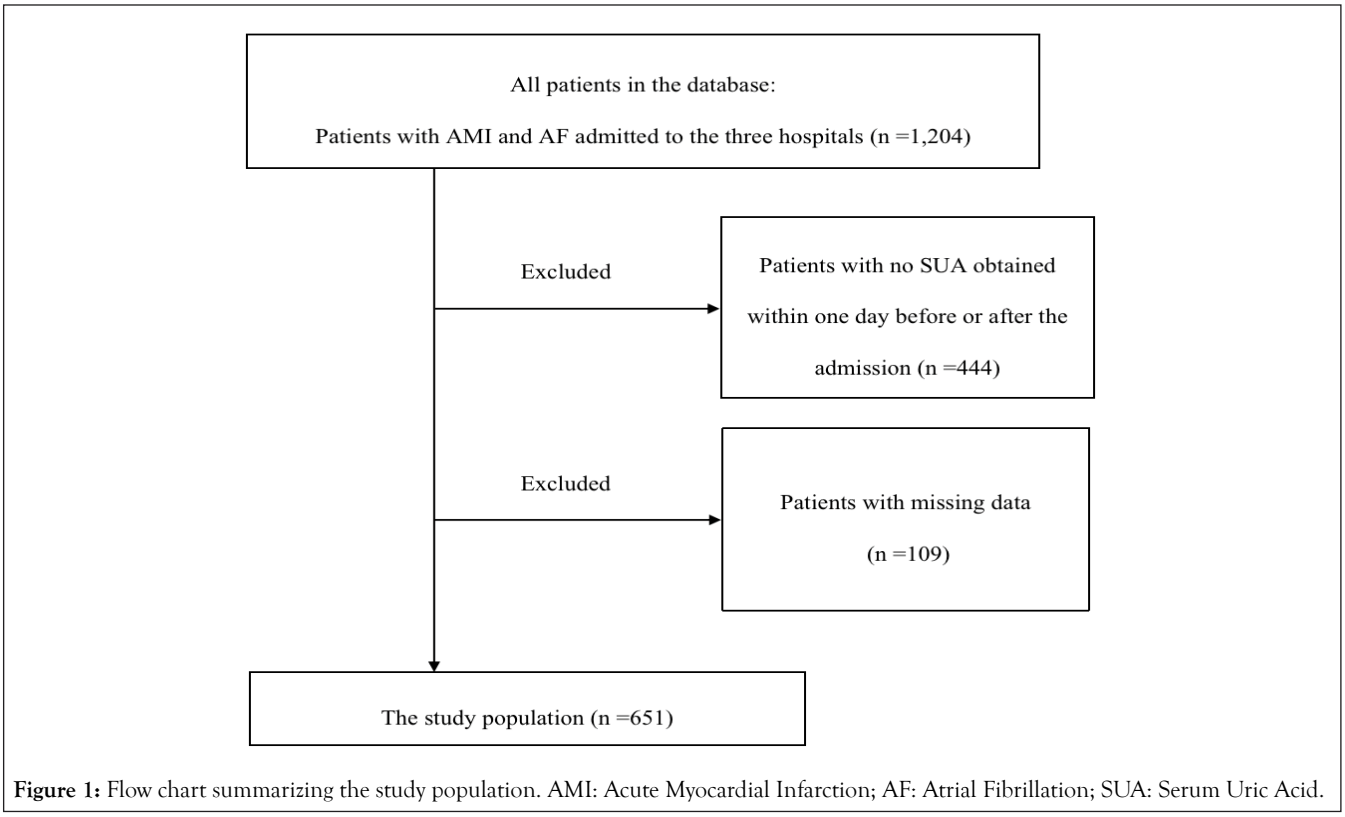

Figure 1: Flow chart summarizing the study population. AMI: Acute Myocardial Infarction; AF: Atrial Fibrillation; SUA: Serum Uric Acid.

Table 1: Baseline characteristics of patients with/without HUA.

	Total patients	With HUA†	Without HUA	p
	(n=651)	(n=263)	(n=388)	
Age (years)*	76 (66-82)	77 (68-82)	75 (64-81)	0
Sex (female)	262 (40.25%)	95 (36.12%)	167 (43.04%)	0
HBP history	480 (73.73%)	199 (75.67%)	281 (72.42%)	0
DM history*	271 (41.63%)	122 (46.39%)	149 (38.40%)	0
HF history	257 (39.48%)	113 (42.97%)	144 (37.11%)	0
Previous MI*	101 (15.51%)	58 (22.05%)	43 (11.08%)	<0.001
Stroke history	126 (19.35%)	54 (20.53%)	72 (18.56%)	1
Current smoker	176 (27.04%)	69 (26.24%)	107 (27.58%)	1
SUA (mg/dl)*	6.27 (4.88-7.69)	8.25 (7.39-9.76)	5.13 (4.24-5.85)	<0.001
LDL-C (mmol/L)*	2.48 (1.88-3.09)	2.56 (2.00-3.14)	2.40 (1.80-3.03)	0
Cr (mg/dl)*	1.04 (0.83-1.43)	1.30 (1.00-1.90)	0.92 (0.77-1.14)	<0.001
AF type (PAF)	460 (70.66%)	175 (66.54%)	285 (73.45%)	0
Ventricular arrhythmia	67 (10.29%)	28 (10.65%)	39 (10.05%)	1
Killip class ≥ 2*	417 (64.06%)	191 (72.62%)	226 (58.25%)	<0.001
CAG*	394 (60.52%)	140 (53.23%)	254 (65.46%)	0
Device support*	57 (8.76%)	30 (11.41%)	27 (6.96%)	0
Died during hospitalization*	101 (15.51%)	62 (23.57%)	39 (10.05%)	<0.001

*p<0.05.

Abbreviations: HUA: Hyperuricemia; HBP: Hypertension; DM: Diabetes Mellitus; HF: Heart Failure; MI: Myocardial Infarction; SUA: Serum Uric Acid; LDL-C: Low Density Lipoprotein-Cholesterol; Cr: Creatinine; AF: Atrial Fibrillation; PAF: Paroxysmal Atrial Fibrillation; CAG: Coronary Angiography

†HUA referred to patients with SUA ≥ 6.8 mg/dl.

previous MI, with higher Cr and LDL-C levels, more Killip class ≥ 2 and circulation supporting devices using but fewer receiving CAG. There also appeared to be more patients died in the HUA group (62 (23.57%) vs. 39 (10.05%), p<0.001).

In-hospital mortality

One hundred and one (15.51%) patients died during hospitalization. Among these patients, 68 died of cardiac causes, including lethal ventricular arrhythmia, heart failure, cardiac shock

and heart rupture while 19 died of other causes, such as pneumonia and respiratory failure, and there were no clear records of the direct cause of death for the rest 14 patients.

The SUA level of survived patients was significantly lower than that of patients who died (6.03 (4.75-7.49) mg/dl vs. 7.18 (5.41-9.98) mg/dl, p<0.001). Univariate logistic regressions showed that SUA level (Odds Ratio (OR) 1.24, 95% Confidence Interval (CI) 1.15-1.34, p<0.001) and HUA (OR 2.76, 95%CI 1.78-4.27, p<0.001) were both predictors of in-hospital all-cause mortality (Table 2). The crude ORs of other variates were also shown in Table 2.

HUA remained as an independent predictor of in-hospital all-cause mortality in the final model of the multivariate logistic regression after adjusting for age, sex, hypertension history, DM history, HF history, previous MI, stroke history, smoking status, LDL-C, Cr, AF type, ventricular arrhythmia, Killip classification, CAG and device support (Adjusted OR 2.09, 95% CI 1.29-3.40, p=0.003). Other independent predictors were elder age, history of DM, ventricular arrhythmia occurrence, Killip class ≥ 2, without CAG, and with IABP or ECMO support (Table 2).

Subgroup analysis

Subgroup analysis by sex: Subgroup analyses in male and female patients were performed. SUA level of male patients was significantly higher than that of female patients (6.48 (5.02-8.04) mg/dl vs. 5.95 (4.65-7.40) mg/dl, p=0.014). Baseline characteristics of male and female patients were shown in Table S1.

The result of the univariate logistic regression with HUA was similar to the whole population for both male and female patients (Male: OR 3.21, 95% CI 1.78-5.81, p<0.001; Female: OR 2.35, 95% CI 1.21-4.55, p=0.012) (Table S2 and Table S3). However, multivariate logistic regression results were different. When the same variates were adjusted as the whole population except for sex, HUA was still an independent predictor of in-hospital all-cause mortality in the final model for male patients (Adjusted OR 2.02, 95% CI 1.04-3.95, p=0.039) Table S2, but not for female patients (Table S3).

Subgroup analysis in patients underwent CAG

As approximately only 60% patients received CAG, we performed the subgroup analysis in this population. The SUA level (6.08 (4.95-7.36) mg/dl vs. 6.66 (4.76-8.82) mg/dl, p=0.002) and HUA prevalence (35.53% vs. 47.86%, p=0.002) were lower in patients who underwent CAG compared to those who did not.

With univariate logistic regressions, significant associations were found between the in-hospital mortality and SUA (OR 1.45, 95% CI 1.23-1.72, p<0.001) or HUA (OR 2.39, 95% CI 1.12-5.13, p=0.025) (Table S4). As for the multivariate logistic regression, besides HUA and the covariates used for the whole population, LM disease, multivessel disease and successful or no need for revascularization were also added to the analysis. However, HUA was excluded from the final model which included age, DM history, ventricular arrhythmia, Killip classification and the use of circulation supporting devices (Table S4).

Table 2: Results of univariate and multivariate logistic regressions for in-hospital all-cause mortality.

	Univariate			Multivariate		
	OR	95% CI	p	Adjusted OR	95% CI	p
Age (years)*†	1	1.03-1.08	<0.001	1	1.01-1.06	0
Sex (female)	1	0.73-1.72	1			
HBP history	1	0.67-1.79	1			
DM history*†	2	1.32-3.12	0	2	1.21-3.35	0
HF history	1	0.80-1.88	0			
Previous MI	1	0.76-2.30	0			
Stroke history	1	0.83-2.27	0			
Current smoker	1	0.46-1.26	0			
SUA (mg/dl)*	1	1.15-1.34	<0.001	NA	NA	NA
HUA*†‡	3	1.78-4.27	<0.001	2	1.29-3.40	0
LDL-C (mmol/L)	1	0.78-1.25	1			
Cr (mg/dl)	1	0.98-1.08	0			
AF type (PAF)	1	0.53-1.31	0			
Ventricular arrhythmia*†	3	1.78-5.48	<0.001	5	2.24-9.49	<0.001
Killip class ≥ 2*†	17	6.32-48.06	<0.001	7	2.28-18.85	<0.001
CAG*†	0	0.13-0.33	<0.001	0	0.12-0.43	<0.001
Device support*†	3	1.55-5.20	0	3	1.47-7.40	0

*p<0.05 for univariate logistic regression; †Variates remained in the final multivariate logistic regression model

Abbreviations: OR: Odds Ratio; CI: Confidence Interval; HBP: Hypertension; DM: Diabetes Mellitus; HF: Heart Failure; MI: Myocardial Infarction; HUA: Hyperuricemia; LDL-C: Low Density Lipoprotein-Cholesterol; Cr: Creatinine; AF: Atrial Fibrillation; PAF: Paroxysmal Atrial Fibrillation; CAG: Coronary Angiography

‡HUA referred to patients with SUA ≥ 6.8 mg/dl.

DISCUSSION

The present study showed that HUA (SUA ≥ 6.8 mg/dl) was an independent predictor of in-hospital all-cause mortality in patients with AMI and AF. The results in male patients were mostly consistent with the whole population, but different in the female patients or those who underwent CAG. To our knowledge, this might be the first study specifically concerning the impact of UA on in-hospital mortality of such population.

The relationship between UA and AMI has long been investigated, but the role of UA in the prognosis is still controversial. In 2005, Japanese investigators found that the all-cause mortality of patients with AMI in the highest UA quartile was 3.7 fold of that in the lowest quartile [25,26]. Similar results were seen in some later studies involving patients with different MI types (STEMI only or STEMI and NSTEMI), using SUA or "HUA" defined by different cut-off values and with either short- or long-term follow-ups [4-6,10,27-30]. A retrospective study involving 621 AMI patients demonstrated that higher SUA (every 10 μmol/L increase) was an independent predictor of in-hospital mortality after adjusting for con-founders (OR 1.016, 95% CI 1.001-1.031, p=0.043), which was similar to our study, but the population was younger and the death rate appeared lower [31]. Moreover, the association between UA and AMI outcomes was also supported by some meta-analyses [32-35]. A recent meta-analysis which involved 29 studies and more than 950,000 participants showed that, for every 1 mg/dl increment in UA, the mortality of Coronary Heart Disease (CHD) would increase by 13% [36].

However, some studies showed different results [7,8,37]. In a cohort study of AMI patients with mild renal dysfunction, no significant difference was found in in-hospital and one-year mortality among patients in different SUA tertiles [38]. Besides, a recent study of elder AMI patients showed similar short-term death rate between those with lower and higher SUA levels [39]. The divergence of the results probably came from the difference of the study populations and "HUA" stratification values. The heterology in con-founders chosen might also contribute to the difference of the results.

It was still not clearly explained on the mechanism of the impact caused by UA on the prognosis of AMI patients. Impaired myocardial reperfusion was supposed to be one of the possible explanations [40]. However, conflicting results were seen in the protective effect of allopurinol on reperfusion injury [41]. Besides, UA was found to be an independent risk factor for new-onset AF in the setting of AMI, which was associated with worse outcomes [18-20,42]. Furthermore, UA was associated with many other well-established risk factors for adverse outcomes in AMI patients, such as age, obesity, serum Cr and cholesterol [43]. It was hard to confirm whether UA had direct impact on AMI outcomes or was just a marker for adverse prognosis by observational studies. However, as an easily obtained and widely tested biomarker, UA was still of importance in clinical practice.

Substantial data were available for the relationship between UA and AF. A recent meta-analysis found higher SUA levels in patients with AF than those without AF [44]. Several large scale cohort studies with long-term follow-ups consistently demonstrated the association between UA and AF incidence [45-48]. Their causal relationship was also supported by a recent Mendelian randomization study [49]. However, studies concerning the effect of UA on AF patients' prognosis were rare. Some studies showed the association between higher UA levels and atria thrombosis [16,17]. As atrial thrombi were the major causes of stroke and other thromboembolism complications, it might be reasonable to assume an adverse impact of HUA on the outcomes of AF patients.

Subgroup analyses categorized by sex were performed because some previous researches reported different results between males and females in the effect of UA on the prognosis of AMI. In the multivariate logistic regression of 184 patients with STEMI, HUA was an independent predictor of in-hospital and 30-day mortality in men but not in women [50]. On the contrary, a recent study only showed significant association between UA and fatal MI in women yet not in men [51]. Results from a meta-analysis showed stronger association between HUA and CHD and all-cause mortality in women [52]. However, the definition of HUA varied among studies. Some took different cut-off values for males and females [5,6,27,50]. While others used the same standard for both sexes [7,26,28,39]. We chose the uniform cut-off value of 6.8 mg/dl based on the recent guideline [24]. With this cut-off value, results were similar for male patients and the whole population, but different for females. A higher SUA level was seen in the present study in male than in female patients, which was consistent with some epidemiological studies [53,54]. Although the effect of estrogen on UA metabolism was proven to be a cause of this phenomenon, it might be of less importance in the present population as most of the female patients might be menopause due to their age shown in the baseline characteristics [55]. Better renal function and more complications with DM might be some potential reasons [56]. The mechanism of sex difference in the prognostic role of HUA was unclear. In the study population, a possible explanation could be the higher prevalence of DM in female patients, which was a stronger risk factor for fatal ischemic heart disease especially for women, but further investigations were needed [57].

Some previous studies have shown the association of higher UA levels and poor prognosis in patients undergoing PCI [4,26,27,29]. However, in our study, HUA was not remained in the final adjusted multivariate model. The level of SUA and the proportion of HUA were significantly lower in patients who received CAG, but the prevalence of stronger risk factors for mortality were much higher, such as ventricular arrhythmia, Killip class and device support, which could weaken the value of HUA to some extent. However, further studies are required to confirm the hypothesis.

CONCLUSION AND LIMITATIONS

In conclusion, Hyperuricemia (HUA) defined as Serum Uric Acid (SUA) ≥ 6.8 mg/dl was an independent predictor of in-hospital all-cause mortality in patients with Acute Myocardial Infarction (AMI) and coexisting Atrial Fibrillation (AF), who were at high risk of death. Similar impacts were found in male patients, but not in the female patients or those who underwent Coronary Angio Graphy (CAG).

At last, some limitations of our study should be noticed. Firstly, as the study was retrospective, bias could not be avoided and the insufficiency in confounding factors adjusting might exist. Secondly, the number of patients was relatively small and long-term follow-up data was not available. The results, therefore, should be restricted in specific population and with conditions. Thirdly, due

to the data deficit, we were unable to precisely identify whether the AF was new-onset or previously existed.

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CONFLICTS OF INTEREST

None.

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