High Killips Class as a Predictor of New-onset Atrial Fibrillation Following Acute Myocardial Infarction: Systematic Review and Meta-analysis

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Abstract

Background: Recent observational studies have shown that patients with higher Killips score (>I) have higher risk of new-onset atrial fibrillation (NOAF) following acute myocardial infarction (AMI), while others drew a neutral conclusion. The ultimate predictive value of high Killips class on NOAF remained obscure.

Methods: PubMed, Web of Science, China National Knowledge Infrastructure, and the Cochrane Controlled Trials Register Databases were searched until February 2015. Of the 3732 initially identified studies, 5 observational studies with 10,053 patients were analyzed.

Results: The meta-analysis of these studies showed that higher Killips score on admission was associated with higher incidence of NOAF following AMI (odds ratio = 2.29, 95% confidence interval 1.96–2.67, $P < 0.00001$), while no significant differences exist among individual trials ($P = 0.14$ and $I^2 = 43\%$).

Conclusions: Killips class >I was associated with the higher opportunity of developing NOAF following AMI.

Key words: Acute Myocardial Infarction; Killips, New-onset Atrial Fibrillation

INTRODUCTION

New-onset atrial fibrillation (NOAF) in the context of acute myocardial infarction (AMI) is common and usually induces severe hemodynamic dysfunction and has been shown to be an independent predictor of mortality among AMI patients. In addition, among the patients complicated with NOAF, the incidence of stroke, bleeding, and reinfarction are all higher than those without NOAF.[1,2] The secondary decrease in cardiac output aroused by impairment of atrial contraction, atrioventricular synchrony, and irregular RR interval may be partly responsible for the poor prognosis.[3] However, the potential mechanisms may be complex and have not been well-characterized. Whether higher Killips class is an independent predictor of NOAF remains controversial, so we performed this comprehensive meta-analysis to explore the potential relationship between higher Killips class and NOAF.

METHODS

We conducted this analysis according to the guidelines of the Meta-analysis of Observational Studies in Epidemiology Group.[4]

Inclusion criteria

We included prospective or retrospective observational studies with a primary objective to analyze the association between high Killips class (>I) and NOAF after AMI. Titles and abstracts of all articles were evaluated and rejected following inclusion criteria: (1) Human subjects with AMI; (2) Killips class at admission evaluated; (3) retrospective/prospective cohort studies; (4) baseline data available; (5) enough follow-up period for detect NOAF; (6) NOAF following AMI for patients with different Killips class mentioned; (7) AMI type mentioned; (8) enough sample size ($n > 100$) of patients from individual study.

Search strategies

We carefully searched on-line database of PubMed, Web of Science, China National Knowledge Infrastructure, and the Cochrane Controlled Trials Register Databases until February 2015 to identify relevant studies. We used the following keywords: "Atrial fibrillation (AF)," "new-onset" and "Killips," "heart failure" and "myocardial infarction." Titles and abstracts, as well as the reference lists of all

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the identified reports, were examined independently by two reviewers (Zhang EY and Cui L) in order to include potentially relevant studies. The two reviewers agreed on the inclusion/exclusion status in 90% of the reviewed studies. Disagreements were resolved by discussion or consensus of a third reviewer (Li ZY). There was no language restriction when we included the studies. In addition, a manual search was conducted using review articles on this topic, bibliographies of original papers, and abstracts of the scientific sessions of the, the American Heart Association, the European Society of Cardiology, Heart Rhythm Society, and American College of Cardiology during the past 2 years.

Quality assessment

To limit heterogeneity secondary to differences between study designs, the quality of each study was evaluated according to the guidelines developed by the Evidence-based Medicine Working Group[5] and the United States Preventive Task Force.[6] We applied the point score system assessed by the following characteristics: (1) Clear description of inclusion and exclusion criteria; (2) study sample representative for mentioned population; (3) clear description of sample selection; (4) full specification of clinical and demographic variables; (5) follow-up during hospitalization; (6) no loss of follow-up; (7) clear definition of Killips class; (8) clear definition of outcomes and outcome assessment; (9) temporality (assessment of Killips class once at presentation); (10) adjustment of possible confounders in multivariate analysis. If one of these key points was not mentioned clearly in a study, we considered it not performed. Therefore, the possibility of underestimation of the reported characteristics may be present.

Data extraction

Data extraction was performed by two blind investigators (Zhang EY and Cui L) independently with a standard data extraction form to determine eligibility for inclusion. The following information collected was tabulated: (1) Publication details: First author's last name, publication year; (2) characteristics of included studies: Study population, definition of NOAF, detection method, quality score, risk estimate and nation; (3) baseline data of the studied population: Sample size, age, gender, Killips >I (%), NOAF (%), current smoker (%), left atrium diameter, left ventricle ejection fraction (LVEF), ST-elevation myocardial infarction (%), anterior myocardial infarction (%), diabetes mellitus (%), hypertension (%), previous infarction (%), coronary revascularization (%).

Definition of important parameters

Cardiac function on admission was scored according to the Killips classification scheme class I–IV, I as absence of heart failure, II as presence of rales and/or jugular venous distention, III as presence of pulmonary edema and IV as cardiogenic shock. Killips class ≥I at presentation was defined as severe cardiac dysfunction in our meta-analysis.[7]

Statistical analysis

The magnitude of association between high Killips and NOAF following AMI was measured by adjusted odds ratio (*OR*) or *OR* with 95% confidence intervals (*CI*s). Two studies[8,9] gave a value of *OR* by calculation or univariate analysis. We used the inverse variance method to weight studies for the combined overall statistic. Finally, we examined the heterogeneity with the standard Chi-square test of heterogeneity. An $I^2 > 50\%$ indicates at least moderate statistical heterogeneity.[10] A pooled effect was calculated with a random-effects model when the Chi-square test for heterogeneity was found significant, through which we could take within-study and between-study variance into account, while not significant, a fixed-effects model was still used. Sensitivity analysis was done by dropping studies and checking the consistency of the overall effect estimate. Statistical significance for treatment effect was defined at $P < 0.05$. Publication bias was evaluated using funnel plot. All the jobs above were performed with Review Manager Version 5.2 (RevMan; The Cochrane Collaboration, Oxford, UK).

RESULTS

We found a total of 3732 records via the primary articles search. Among them, 1512 duplicates were discarded. However, after screening the titles and abstracts, 2194 studies were excluded because they were either review articles, laboratory studies, irrelevant to the current analysis, impertinent type of statistics, noncohort studies or retrospective studies. After the detailed evaluation, 5 prospective observational studies[8,9,11-13] finally met the inclusion criteria [Figure 1]. There were overall 10,053 patients involved in our analysis. The proportion of higher Killips classification ranged from 11.7%[11] to 25.0%,[9] while incidence of NOAF from 5.2%[9] to 13.6%.[12] Among the 10,053 patients included in our meta-analysis, 8.2% of the patients developed NOAF during their observational period. Patients with Killips class >I on admission occupy 19.8% of the total patients. The characteristics of each included studies and baseline data of the patients from corresponding study are
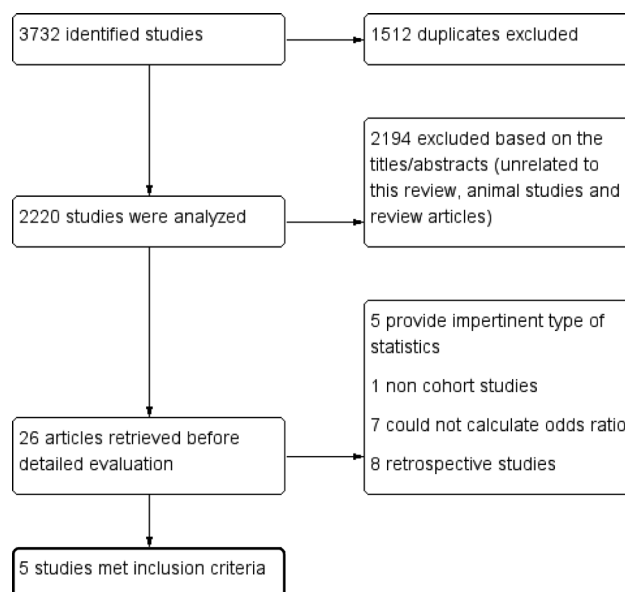

Figure 1: Flow diagram of study selection process.

depicted in Tables 1 and 2, respectively. The meta-analysis of these studies demonstrated that Killips score >I was associated with higher incidence rate of NOAF after AMI [OR = 2.29, 95% CI 1.96–2.67, $P < 0.00001$, Figure 2], no significant differences were found between individual trials ($P = 0.14$ and $I^2 = 43\%$). The funnel plot as the symbol of publication bias is presented in Figure 3.

DISCUSSION

Our results indicated the strong predictive value of higher Killips score for NOAF after AMI. Late recent research showed only NOAF perform independent predictive value for in-hospital mortality since different clinical characteristic and therapeutic implications, we should differ NOAF from existing AF. Data from the randomized Assessment of Pexelizumab in AMI trial showed the patients who developed NOAF (6.3%)

even exceeded those with AF at baseline (4.8%).[14] The risk of NOAF in the setting of AMI was 8.2% in our meta-analysis. Patients with NOAF following AMI were found to develop complications more easily, which includes cardiogenic shock, reinfarction, ventricular arrhythmias, and with worse laboratory or echocardiographic features.[15] With the increase of the Killips class, the accuracy for predicting overall mortality became higher. Maximum Killips class III and IV appeared an independent predictor of overall mortality, new-onset AF during acute coronary syndromes also carried a higher risk of death.[16]

Greater incidence of Killips class on admission usually indicates larger infarction size and correlates with a higher possibility of developing NOAF in our result, which in turn aggravates the cardiac dysfunction.[17] Abundant evidence has suggested that NOAF indicates higher rate of heart

### Table 1: Characteristics of studies included in meta-analysis

Investigator	Publication year	Patients (n)	Definition of NOAF	Detection method	Quality Score	Risk estimate	Nation
Bahouth et al.[13]	2010	1920	Newly episode of AF >30 s at admission or later during the hospital stay	ECG	9	aOR	Israel
Consuegra-Sanchez et al.[8]	2015	4284	Occur during hospitalization	ECG	8	OR	Spain
Gal et al.[11]	2015	830	Newly episode of AF >30 s within 30 days after admission	Telemetry strip/ ECG	9	aOR	Netherlands
Lau et al.[9]	2009	2843	Occur during hospitalization without AF history	ECG/monitoring evidence	8	OR	Australia
Yoshizaki et al.[12]	2012	176	Newly episode of AF >5 min within 7 days from admission	Continuous ECG	9	aOR	Japan

AF: Atrial fibrillation; NOAF: New-onset AF; ECG: Electrocardiogram; aOR: Adjusted odd ratio; OR: Odd ratio.

Table 2: Baseline clinical characteristics of included studies

Investigator	Publication year	Killip >I (%)	New-onset AF (%)	Age (years)	Current smoker (%)	Male (%)	LAD (mm)	LVEF (%)	STEMI (%)	Anterior MI (%)	DM (%)	HTN (%)	Previous infarction (%)	Coronary revascularization (%)
Bahouth et al.[13]	2010	22.5	8.4	60.8	16.5	78.4	40.2	44.7	82.0	43.8	28.4	50.8	21.6	49.5
Consuegra-Sanchez et al.[8]	2015	22.1	9.8	64.0	38.9	75.6	N/A	49.0	100	N/A	32.7	51.5	7.4	73.9
Gal et al.[11]	2015	11.7	8.8	62.1	48.6	76.0	N/A	N/A	100	N/A	10.2	33.3	8.2	N/A
Lau et al.[9]	2009	16.6	5.2	63.7	26.6	65.3	N/A	N/A	22.3	70.1	25.5	62.1	N/A	89.8
Yoshizaki et al.[12]	2012	25.0	13.6	67.1	54.5	76.7	35.4	56.6	100	60.2	30.7	59.7	11.9	N/A

AF: Atrial fibrillation; LAD: Left atrium diameter; LVEF: Left ventricle ejection fraction; STEMI: ST-elevated myocardial infarction; DM: Diabetes mellitus; HTN: Hypertension; N/A: Not applicable.
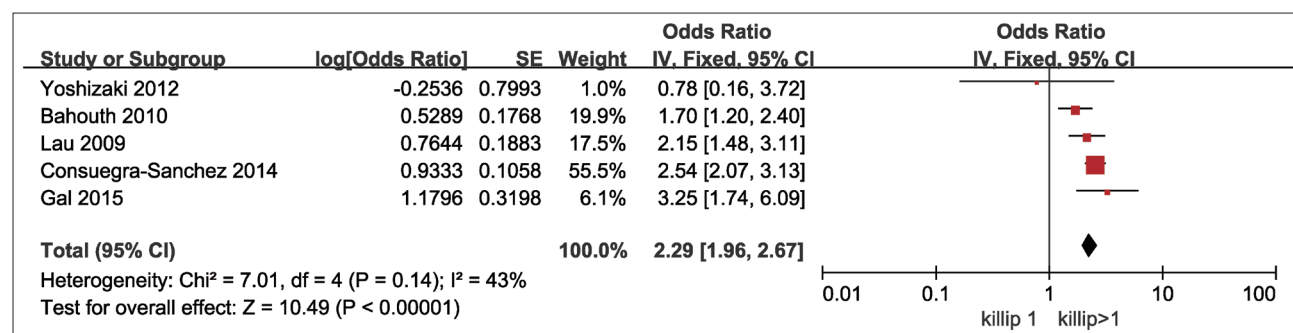
Figure 2: The risk of NOAF following AMI by higher Killips class. NOAF: New-onset atrial fibrillation; AMI: Acute myocardial infarction.
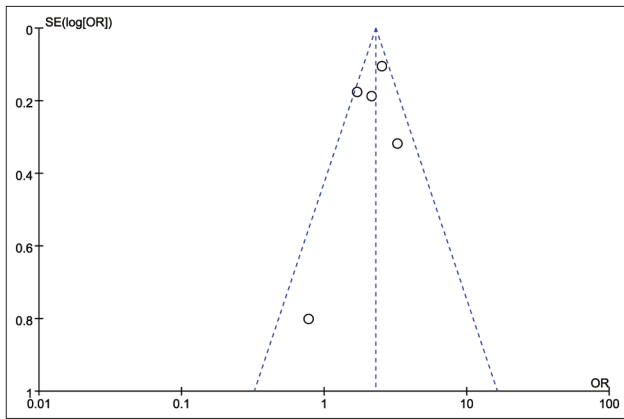
Figure 3: Funnel plot of the enrolled studies.

failure potentially,[18] while in turn more serious heart failure could prompt greater likelihood of developing NOAF, some studies have pointed out that NOAF may be considered a symbol of the current cardiac insufficiency.[19,20]

Prior studies have reported consistently that NOAF is mainly associated with the increase in left ventricular end-diastolic volume and pressure, which indirectly increase left atrial wall tension and induces AF occurrence.[21,22] NOAF among AMI patients had been proved associated with the presence of left ventricular function impairment[23] and atrial ischemia.[24] Rapid elevation of intra-atrial pressure with passive stretching of the left atrium was proved to facilitate AF via activation of some ion channels in animal experiment, complicated with increased AF vulnerability and shortening of the atrial effective refractory period.[25] In a study paying attention of gender and weight, Guenancia et al.[26] found LVEF impairment and higher Killips class after AMI usually reflect an acute increase in cardiac filling pressure and trigger NOAF. Therefore, severe left ventricular dysfunction and increased left atrial pressure may trigger NOAF in AMI patients.

Moreover, Dorje et al.[27] have indicated the predictive value of BNP for NOAF in AMI patients treated with primary PCI, which to some extent supported the relationship between Killips class and NOAF. Olgin et al.[28] have reported for long time that the alterations of autonomic tone may also contribute to the NOAF. Jons et al.[29] have also certified the key role of sympathetic cardiac autonomic activity dysfunction in NOAF during AMI. All above supported the potential relationship between NOAF following AMI and cardiac function reflected by Killips score. Considering our result, the Killips class at admission could predict NOAF within very period after AMI, and as an easily obtainable parameter, may help to stratify risk for NOAF in the setting of AMI.

Limitations

Although the total number of observational patients was large, there were still several limitations in our meta-analysis. First, the method for defining NOAF was not accordant between various trials in our study. Second, the type of NOAF was not precisely classified, which may bring bias

while confounding paroxysmal NOAF into persistent or even permanent NOAF. Moreover, some included studies in our meta-analysis did not provide adjusted *OR* of higher Killips class for predicting NOAF due to nonsignificant *P* value in univariate regression analysis. Future investigations are warranted to clarify the mechanisms of NOAF further.

In conclusion, patients with NOAF in the context of AMI could be independently predicted by Killips class >I on admission.

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