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Review Article

Association of follow-up time and all-cause mortality in type 2 myocardial infarction: a systematic review and meta-analysis

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Abstract: Currently, the classification of type 2 myocardial infarction (T2MI) is contentious, with no consensual management or treatment strategy available. Therefore, patients with T2MI have poorer clinical outcomes, especially higher all-cause mortality, compared with type 1 myocardial infarction (T1MI) patients. Online databases, such as PubMed, Web of Science, Medline, EmBase, and Cochrane Library, were systematically searched. The search strategy included the terms "type 2 myocardial infarction", "follow-up time", and "mortality". All studies were reviewed from January 1, 2007 to December 31, 2016. Nine eligible retrospective cohort studies involving 23914 patients with T1MI or T2MI were included. The total pooled risk ratios for in-hospital, 30-day, and 1-year all-cause mortality, respectively, were 2.80 (95% CI 1.93-4.04; P<0.01), 2.44 (95% CI 1.82-3.27; P<0.01), 2.21 (95% CI 1.92-2.54; P<0.01) in the fixed-effects model, with no significant heterogeneity. In subgroup analysis, the pooled risk ratio (RR) for 150 to 180 day all-cause mortality showed no significant difference between the T2MI and T1MI groups (RR 1.25; 95% CI 0.80-1.94; P=0.33) in the fixed-effects model, with no significant heterogeneity. The pooled RR for 1-year all-cause mortality extracted from two studies was 1.81 (95% CI 1.64-2.00; P<0.01) in the fixed-effects model, with no significant heterogeneity. After multivariable adjustment, no significant difference was found between T2MI and T1MI. Follow-up time is negatively correlated with all-cause mortality in T2MI. The risk of mortality in T2MI was twice the value obtained for T1MI. More studies are required to confirm the association of follow-up time and all-cause mortality in T2MI.

Keywords: Type 2 myocardial infarction, meta-analysis, follow-up time, all-cause mortality, retrospective cohort study

Introduction

Myocardial infarction (MI) remains the leading cause of major adverse cardiovascular events around the globe. In 2012, a redefinition of MI with as many as five different types was introduced for the very first time [1]. Among these, type 2 myocardial infarction is concerning to physicians. T2MI is secondary to an imbalance between myocardial oxygen supply and demand due to conditions other than coronary atherosclerosis [2-4]. However, this classification has not been widely adopted in practice, because the current diagnostic criteria for T2MI are controversial, with diagnosis implications uncertain [5-9]. T2MI is frequently found in clinical practice, and associated with poor outcomes, both short- and long term [10]. A study showed that absolute mortality and adjusted risk ratio for all-cause mortality in patients with T2MI and non-ischemic myocardial injury are significantly higher than the values obtained for patients with T1MI at 2 years [11]. Chapman AR et al. demonstrated that 60% of patients with T2MI do not survive at 5 years of disease onset [12]. Therefore, we carried out a systematic review and meta-analysis of relevant studies assessing follow-up time and all-cause mortality in patients with type 1 myocardial infarction (T1MI) due to atherosclerotic plaque rupture, ulceration, fissuring, erosion or dissection with resulting intraluminal thrombus [1], and T2MI due to myocardial oxygen supply-demand imbalance, to assess whether the risk of mortality may

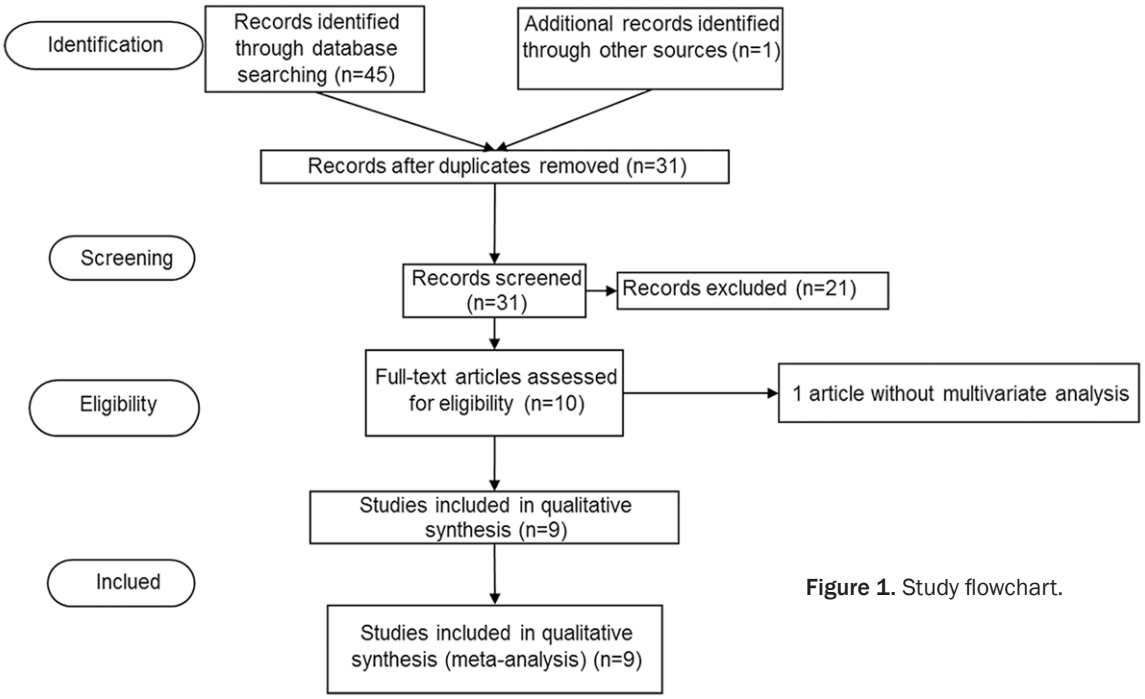

Figure 1. Study flowchart.

Table 1. Quality assessment of individual study

Study	Study-type	Selection	Comparability	Outcome	Newcastle-Ottawa Scale	Level of quality
Bonaca MP 2012	RC	3	2	2	7	A
Stein GY 2014	RC	4	2	3	9	A
Sandoval Y 2014	RC	4	2	2	8	A
Saaby L 2014	RC	4	2	2	8	A
Baron T 2014	RC	4	2	3	9	A
Shah Anoop SV 2015	RC	4	2	2	8	A
Sandoval Y 2015	RC	4	2	2	8	A
Lopez-Cuenca A 2016	RC	4	2	3	9	A
Landes U 2016	RC	4	2	2	8	A

RC-retrospective cohort study; A-high quality: ≥7.

be associated with the MI type [6], and follow-up time. Identifying the risk of mortality in patients with T2MI may provide an opportunity for clinicians to take preventative therapies that could reduce the mortality risk.

Materials and methods (Supplementary Data)

Search strategy

The present study aimed to assess overall mortality in T2MI using studies in online databases such as PubMed, Web of Science, Medline, EmBase, and Cochrane Library. In addition, a report was obtained by contacting the authors [12]. The search strategy included the terms "type 2 myocardial infarction", "follow-up time", and "mortality" and the recommended, highly sensitive Cochrane Collaboration strategy for RCT systematic reviews was utilized. All potentially eligible studies were considered for review, limiting the dates to January 1, 2007-December 31, 2016.

Eligibility criteria

The inclusion criteria were: (1) study population consisting of patients with T2MI and T1MI; (2) comparison of all-cause mortality between T2MI and T1MI; (3) observational design with follow-up time ranging from 0 to 1 year; and (4) study including an available clinical database.

Table 2. Characteristics of the included studies

Study	Follow-up time	T2MI		T1MI		Multivariable adjustment	T2MI Study Definition
		Death	Total	Death	Total		
Bonaca MP 2012	180 days	3	42	30	359	1	Adjudicated diagnoses according to the universal definition of MI classification system defining T2MI as secondary to increased oxygen demand or decreased supply.
Stein GY 2014	1 year	30	127	231	2691	1	Diagnosis of T1MI and T2MI were at the discretion of the treating physician. To ensure compliance with the definition, a retrospective validation of the diagnosis of all T2MI was performed independently by two expert physicians. Patients for whom a specific valid cause for T2MI was not established were reclassified as T1MI.
Sandoval Y 2014	180 days	51	147	15	57	1	T2MI was defined according to the universal definition. Two clinicians adjudicated all cases with at least one cTnI value (≥34 ng/L) above the 99th percentile.
Saaby L 2014	1 year	52	119	60	360	1	The cardiac troponin I value >0.03 ug/L was considered the decision limit for the diagnosis of MI. Specified criteria were used for the classification of T2MI. Three experienced cardiologists adjudicated the final diagnosis of T2MI.
Baron T 2014	1 year	315	1278	2169	16067	0	The classification of T2MI was done by the treating physician according to the universal definition.
Shah Anoop SV 2015	1 year	133	429	187	1171	1	T2MI with plasma cardiac troponin I concentrations ≥50 ng/L was defined as myocardial ischemia due to increased oxygen demand or decreased supply. Two cardiologists reviewed and classified each case independently. Any discrepancies were resolved by consensus through in-depth review of source data.
Sandoval Y 2015	150 days	2	20	0	10	1	MI was defined and adjudicated according to the Third Universal Definition of MI. Sex-specific 99th percentile cutoffs for the hs-cTnI assay were 16 ng/L for females and 34 ng/L for males.T2MI was defined as MI secondary to a supply/demand imbalance in the absence of plaque rupture.
Lopez-Cuenca A 2016	1 year	27	117	102	707	0	The patients with T2MI were classified according the third universal MI definition, and three cardiologists reached a consensus for each case.
Landes U 2016	1 year	51	106	22	107	1	MI was diagnosed when there was a rise/fall in cardiac troponin T above the 99th percentile, with symptoms or electrocardiography patterns specific for ischemia. T2MI was diagnosed when there was one of the following conditions (sepsis-systemic inflammatory response syndrome, shock, anemia, active bleeding, tachyarrhythmia, bradyarrhythmia, respiratory failure, hypertensive crisis) triggered a supply-demand imbalance.

1-The difference reached statistical significance; 0-The difference did not reach statistical significance.

Table 3. Baseline characteristics of included studies

Baseline characteristics	MI Type	Bonaca MP 2012	Stein GY 2014	Sandoval Y 2014	Saaby L 2014	Baron T 2014	Shah Anoop SV 2015	Sandoval Y 2015	Lopez-cuenca A 2016	Landes U 2016
Age (mean ± SD)	I	N/A	63.8±13	60±12	73	71.1±12.5	68±14	67	68±13	72±12.5
	II	N/A	75±12	64±18	75	75.9±11.4	75±14	61	72±12	74±10.4
Male	I	N/A	2090	49	230	11508	709	5	539	69
	II	N/A	72	106	63	747	222	9	61	69
Female	I	N/A	601	17	130	5980	462	5	168	38
	II	N/A	55	84	56	656	207	13	56	38
BMI (mean ± SD)	I	N/A	27.6±4.7	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	II	N/A	25.8±4	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Current smoker	I	N/A	1095	N/A	284	10248	380	N/A	232	41
	II	N/A	20	N/A	91	764	62	N/A	23	44
Prior MI	I	N/A	756	20	71	5316	231	5	261	N/A
	II	N/A	56	27	26	562	109	3	59	N/A
Prior PCI	I	N/A	756	19	45	3077	153	5	196	38
	II	N/A	47	15	15	244	17	3	40	49
Prior CABG	I	N/A	223	N/A	28	1748	62	0	31	N/A
	II	N/A	18	N/A	9	206	30	1	12	N/A
Dyslipidemia	I	N/A	1924	36	137	N/A	539	10	530	N/A
	II	N/A	93	63	48	N/A	177	9	89	N/A
Diabetes	I	N/A	944	N/A	46	3882	185	3	336	54
	II	N/A	61	N/A	28	376	93	9	52	54
Hypertension	I	N/A	1630	49	193	8866	533	9	522	82
	II	N/A	107	125	66	760	254	14	103	87
CKD	I	N/A	328	9	N/A	N/A	N/A	2	N/A	17
	II	N/A	45	49	N/A	N/A	N/A	5	N/A	29
Past CVA	I	N/A	215	N/A	43	1608	92	1	81	N/A
	II	N/A	21	N/A	24	195	48	2	20	N/A
COPD	I	N/A	193	N/A	38	N/A	N/A	N/A	71	N/A
	II	N/A	18	N/A	31	N/A	N/A	N/A	17	N/A
Malignancy	I	N/A	N/A	N/A	N/A	N/A	N/A	N/A	48	4
	II	N/A	N/A	N/A	N/A	N/A	N/A	N/A	15	4
Arrhythmia	I	N/A	N/A	N/A	32	N/A	N/A	1	103	N/A
	II	N/A	N/A	N/A	25	N/A	N/A	1	51	N/A
CHF	I	N/A	247	7	32	1853	N/A	2	42	N/A
	II	N/A	32	46	26	287	N/A	4	21	N/A

MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure.

The exclusion criteria were: (1) study design was a review, case report, or non-English publication; or (2) duplicate reporting; or (3) lack of follow-up outcome data or multivariable analysis.

Study selection

No RCT reported all-cause mortality data in T2MI, although retrospective cohort studies were found in online databases. As most studies were not specifically designed to evaluate these outcomes, missing information was frequently encountered. In such cases, we attempted to contact the respective corresponding authors before excluding any study due to lack of data. Duplicate reports of retrospective cohort studies were not considered in the present analysis. We included studies comparing T2MI and T1MI, with multivariate analysis performed. **Figure 1** depicts a flow diagram of the selection process for relevant studies [13].

Quality assessment

Two investigators (G.Q.W. and N.Z.) reviewed the selected data. The methodological quality of the included studies was assessed based on the Newcastle-Ottawa Scale (NOS) for quality of case-control and cohort studies. A star system of the NOS (range, 0-9 stars), which consists of three quality parameters (selection, comparability and exposure/outcome assessment), was recently developed [14]. Based on

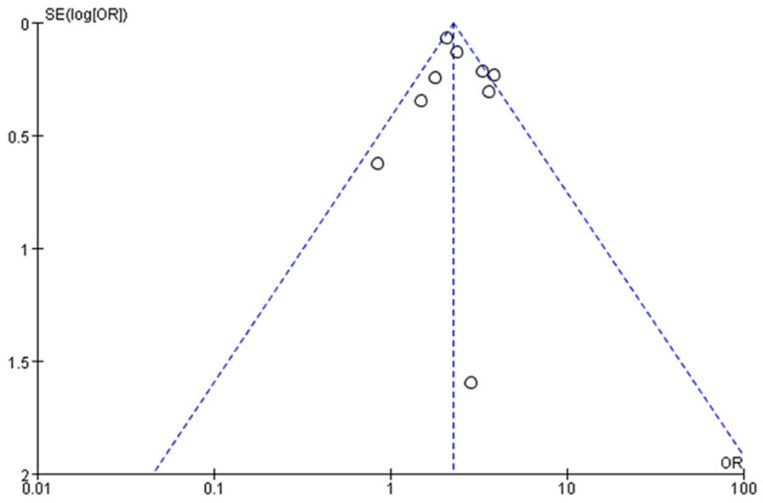

Figure 2. Funnel plot of relevant studies included in the current meta-analysis. OR, odds ratio; SE, standard error.

quality assessment criteria, each study was assigned to one of the following quality categories: A, high quality ≥7; B, low quality <7. The scores of the included studies were summarized in **Table 1**.

Data extraction

Two investigators (G.Q.W. and N.Z.) independently evaluated the titles and abstracts of the articles retrieved in the databases. Abstracts not meeting the eligibility criteria were discarded. The remaining studies were selected for full-text evaluation and data extraction. Any disagreements regarding the inclusion or exclusion of a study were resolved by consensus; in case of persistent doubt, a third reviewer evaluated the particular reference.

A standardized form was used to extract the following details from the retrieved studies: first author's name and publication year, study characteristics (study-type, multivariable adjustment), study methodology (follow-up time), comorbidities, number of patients included, and all-cause death rate in both groups (**Tables 2**, **3**).

Statistical analysis and meta-analysis

The analyses were mainly conducted using Stata version 14.0 (Stata Corp) and RevMan version 5.3 (Cochrane Collaboration). Heterogeneity was assessed by the Cochran Q test, with a threshold *p*-value of 0.1 and I^2 of 50%; 95% confidence intervals for I^2 values were calculated A fixed-effects model was selected for meta-analysis because of the homogeneity, accompanied by P≥0.1 and I^2≤50%, and a random-effects model was used due to the heterogeneity with P< 0.1 and I^2>50% [15]. Inconsistency was assessed with the I^2 statistics, and heterogeneity was analyzed by meta-regression analysis (recommended for small event meta-analyses). Publication bias was roughly evaluated by funnel plot.

Results

Characteristics of the included studies

A total of 45 reports were identified, and one full-text article was provided after author contact. Only nine retrospective cohort studies involving 23914 patients with T2MI or T1MI were included in the current meta-analysis. The detailed literature search strategy is shown in **Figure 1**. The characteristics of relevant studies are summarized in **Tables 2**, **3** [16-24]. The quality of all studies included in this meta-analysis was acceptable. As shown in **Table 1**, the mean value for the included studies was over eight stars, indicating relatively high quality. The funnel plot provided a qualitative estimation of publication bias for the studies, and no evidence of bias was found (**Figure 2**).

In-hospital all-cause mortality in patients with T2MI and T1MI

Two studies assessed in-hospital all-cause mortality in patients with T2MI and T1MI. As shown in **Figure 3**, the total pooled RR for in-hospital all-cause mortality was 2.80 (95% CI 1.93 to 4.04; P<0.00001) in the fixed-effects model, with no significant heterogeneity (I^2= 0%; P=0.98).

30-day all-cause mortality in patients with T2MI and T1MI

Three studies evaluated one month mortality in patients with T2MI and T1MI. As shown in **Figure 4**, the total pooled RR for 30-day all-cause mortality was 2.44 (95% CI 1.82 to 3.27;

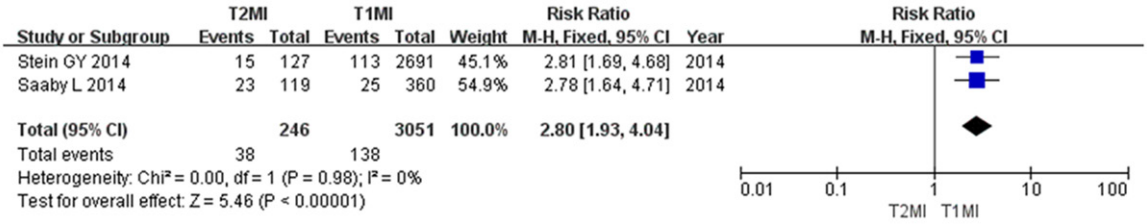

Figure 3. Forest plot for risk of in-hospital mortality in T2MI compared with T1MI. MH, Mantel Haenszel; CI, confidence interval.

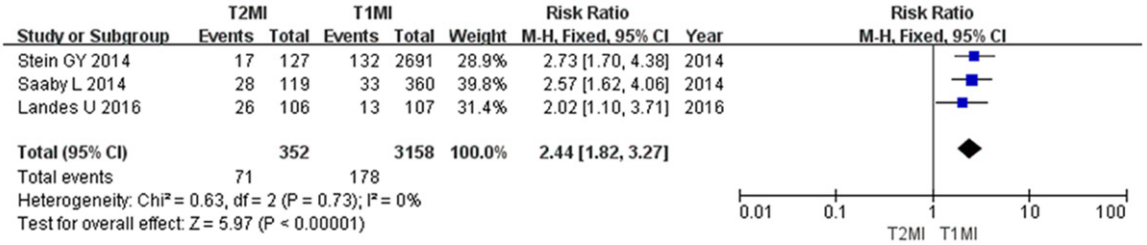

Figure 4. Forest plot for risk of 30-day mortality in T2MI compared with T1MI. MH, Mantel Haenszel; CI, confidence interval.

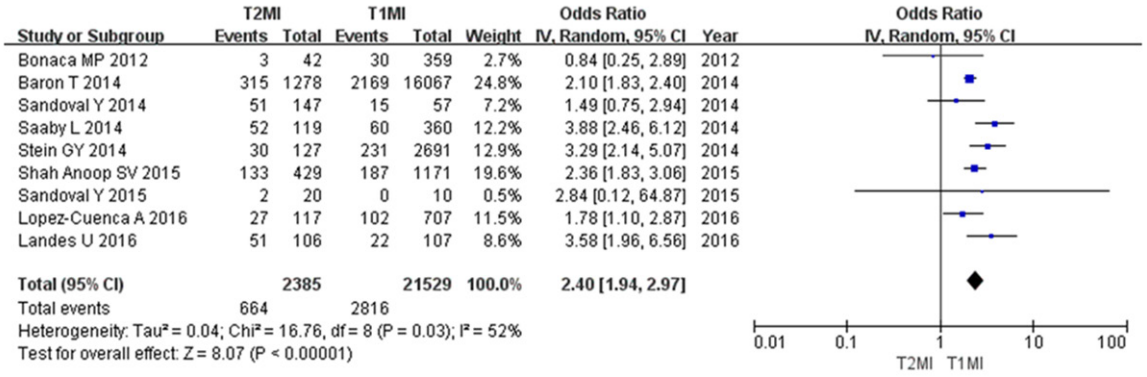

Figure 5. Forest plot for risk of 150 to 365 day mortality in T2MI compared with T1MI. IV, inverse variance; CI, confidence interval.

P<0.00001) in the fixed-effects model, with no significant heterogeneity (I^2=0%; P=0.73).

150 to 365 day all-cause mortality in patients with T2MI and T1MI

The current meta-analysis showed that 150 to 365 day all-cause mortality had a significant difference between T2MI and T1MI (OR=2.40; 95% CI 1.94 to 2.97; P<0.00001) (**Figure 5**). However, high heterogeneity was found (I^2= 52%; P=0.03). A subsequent analysis of 1-year mortality in T2MI also revealed significant heterogeneity (I^2=54%; P=0.05) as shown in **Figure 6**. These data were obtained by meta-regression analysis.

After accounting for multivariable adjustment and duration of follow-up, there was no significant heterogeneity among the studies (**Figure 7**). Therefore, multivariable adjustment and duration of follow-up were possibly responsible for the significant heterogeneity of pooled data regarding all-cause mortality in this meta-analysis. Interestingly, 150 to 180 day all-cause mortality showed no significant difference between the T2MI and T1MI groups (RR=1.25; 95% CI 0.80 to 1.94; P=0.33) in the fixed-effects model, with no significant heterogeneity (I^2=0%; P=0.70). The pooled RR for 1-year all-cause mortality from two studies was 1.81 (95% CI 1.64 to 2.00; P<0.00001) in the fixed-effects model, with no significant heterogeneity

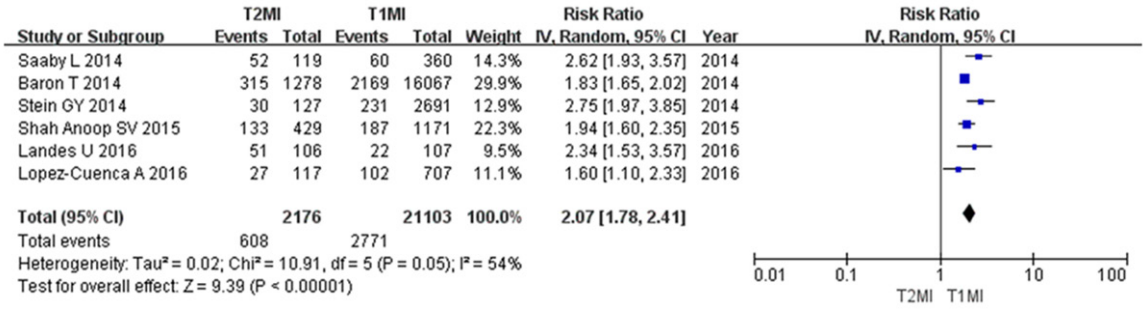

Figure 6. Forest plot for risk of 1-year mortality in T2MI compared with T1MI. IV, inverse variance; CI, confidence interval.

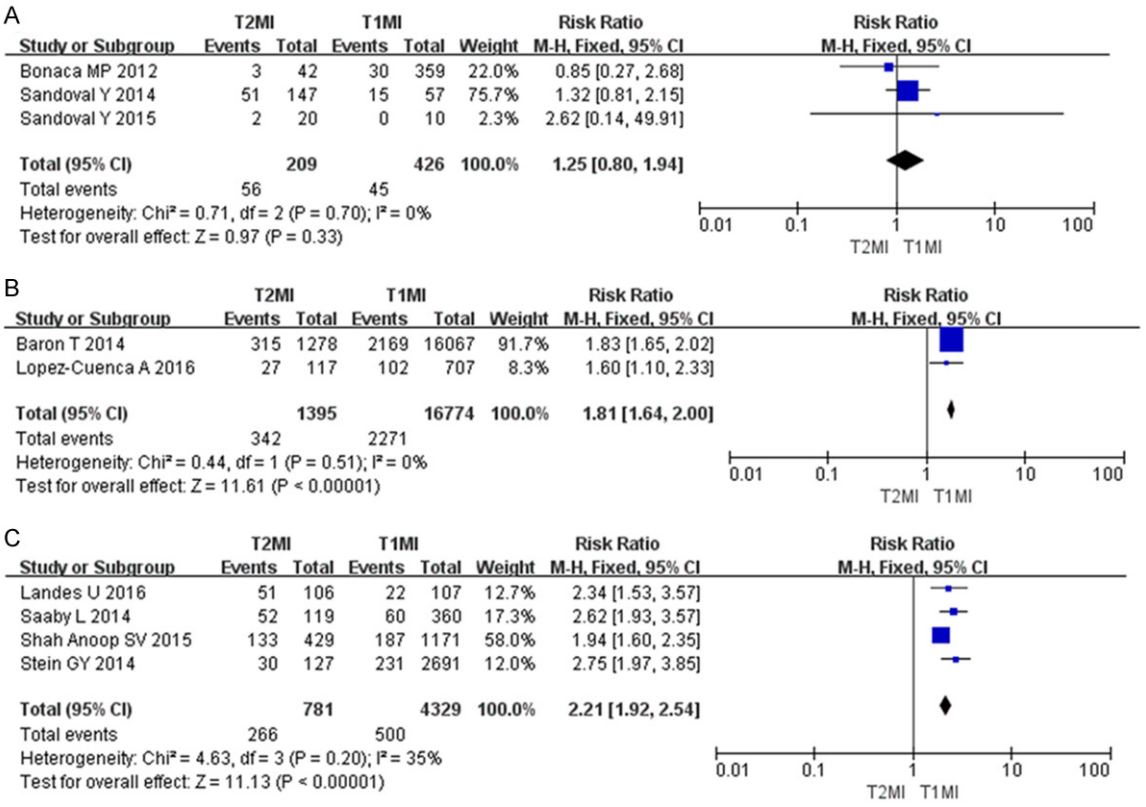

Figure 7. Forest plots showing changes in different subgroups: A. 150 to 180 days; B. 1-year without significant difference; C. 1-year with significant difference. MH, Mantel Haenszel; IV, inverse variance; CI, confidence interval.

(I^2=0%; P=0.51). However, after multivariable adjustment, there was no significant difference between T2MI and T1MI. The pooled RR for 1-year all-cause mortality from the remaining four studies was 2.21 (95% CI 1.92 to 2.54; P< 0.00001) in the fixed-effects model, with no significant heterogeneity (I^2=35%; P=0.20).

Discussion

The current systematic review and meta-analysis of nine studies demonstrated that follow-up time was negatively correlated with all-cause mortality in patients with T2MI. The pooled RR for all-cause mortality between T2MI and T1MI decreased with increasing follow-up time (**Figure 8**). However, compared to T1MI, T2MI had twice the risk of all-cause mortality.

No previous systematic review has evaluated the association of follow-up time with all-cause mortality in T2MI. Previous studies have reported inconsistent results for all-cause mortality in patients with T2MI. Lippi G et al. conducted a

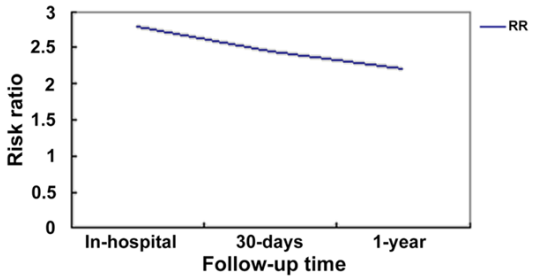

Figure 8. Association of follow-up time with risk ratio for T2MI mortality.

systematic review and found nearly three-fold higher mortality in T2MI compared with T1MI [6]. No other systematic review evaluated whether the latter data had enough power to support the conclusion. Meanwhile, Baron T et al. and Lopez-Cuenca A et al. reported that the difference in 1-year mortality does not reach statistical significance between the two groups [20, 23]. To date, Gupta S et al. showed a comparison of clinical characteristics and outcomes between T2MI and T1MI in a meta-analysis, and it demonstrated that T2MI tended to result in higher mortality [25]. In the current meta-analysis, the follow-up time was associated with decreased risk of mortality in patients with T2MI, and more than doubled that of T1MI in pooled data from relevant studies.

Nestelberger T et al. discovered that reclassified $T2MI_{2012}$ had a substantially lower event-related mortality rate compared with $T2MI_{2007}$ and T1MI [26]. It seemed to be in contradiction with our conclusion. In fact, $T2MI_{2012}$ was composed of $T2MI_{2012\ reclassified}$ and $T2MI_{2007}$, and had a higher mortality rate compared with T1MI. There was an important distinction on the definition of $T2MI_{2007}$ and $T2MI_{2012\ reclassified}$ related to whether should require the presence of coronary artery disease (CAD) or not. Chapman AR et al. also found that the all-cause mortality rate of T2MI was higher than that of T1MI at five years [27]. In addition, they confirmed that the presence of coronary artery disease was one of the strongest predictors of major adverse cardiovascular events in patients with T2MI. So that the risk of cardiovascular deaths may be increased in those patients with T2MI, which were less likely to receive secondary prevention therapies compared to those patients with T1MI. Thus the secondary prevention therapies were important in patients with T2MI, especially which required the presence of CAD.

The current study had some strengths. First, our meta-analysis demonstrated that the all-cause mortality risk of T2MI was higher than that of T1MI. Therefore, the prognosis of T2MI was poor and deserved our attention. Meanwhile, a large sample significantly increased the statistical power of the meta-analysis. Secondly, the meta-analysis explored the negative correlation between follow-up time and all-cause mortality in patients with T2MI, which was different from previous studies. And the included studies had relatively satisfactory quality, and met the predefined inclusion criteria. Thirdly, no publication bias was found, suggesting unbiased results. Fourthly, subgroup analyses were used to explore potential sources of heterogeneity.

Some limitations of this study must be acknowledged. First, the definition of T2MI remains subjective, representing an important inconvenience; in addition, objective diagnostic criteria for T2MI have not been clearly specified. Therefore, some studies may have been missed. And all selected studies are observational studies, which are a limitation. Secondly, patients with T2MI often have multiple co-morbidities at presentation, which could be responsible for their non-cardiovascular deaths. Chapman AR et al. found an excess in non-cardiovascular death was the majority of all-cause death in patients with T2MI [27]. Confounding factors with negative impact on the risk of mortality may represent potential sources of heterogeneity. However, the meta-regression is impossible due to only nine studies included. Thirdly, it is unclear whether restricting the analysis to long follow-up duration (at least 2 year) would change the results. The patients with T2MI receive different in-hospital medical treatments, which is triggered by many heterogeneous conditions. This may have led to treatment bias. Compared to those patients with T1MI, those with T2MI less likely receive secondary prevention therapies after discharge. It may have an impact on mortality during follow up. Therefore, the current findings should be interpreted with caution until confirmation by future large studies.

Overall, the present study suggested a negative correlation between follow-up time and the risk of all-cause mortality in patients with T2MI. The risk of mortality in T2MI was twice the value obtained for T1MI. However, more stringent evidence-based studies are required to confirm

the association of follow-up time with all-cause mortality in T2MI.

Disclosure of conflict of interest

None.

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