Associations of myocardial bridging with adverse cardiac events: a meta-analysis of published observational cohort studies involving 4,556 individuals

Changsheng Zhu, Shuiyun Wang, Hao Cui, Bing Tang, Shengwei Wang

Department of Cardiovascular Surgery, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China

Contributions: (I) Conception and design: C Zhu, S Wang; (II) Administrative support: S Wang; (III) Provision of study materials or patients: C Zhu, S Wang, B Tang; (IV) Collection and assembly of data: C Zhu, S Wang, H Cui, B Tang; (V) Data analysis and interpretation: C Zhu, S Wang, H Cui; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Shuiyun Wang, MD. Department of Cardiovascular Surgery, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beilishi Road 167, Xicheng District, Beijing 100037, China. Email: wsymd@sina.com.

Background: Data derived from small series have demonstrated an association of myocardial bridge (MB) with adverse cardiac events, while MB has been traditionally considered as a benign condition. Hence, the precise clinical implications of MB on prognosis remains inconsistent. Our purpose is to perform a meta-analysis to assess the clinical implications of MB on prognosis.

Methods: We performed an extensive search of PubMed and reference lists of relevant articles. Studies which compared prognosis between subjects with and without MB were identified from 1960 to 31 March 2018. Studies selection was limited to human data and restricted to English language.

Results: Six eligible studies were included in current meta-analysis. Of 4,556 subjects, 1,389 (30.5%) presented MB. MB was associated with an increased risk of adverse cardiac events [odds ratio (OR), 1.71; 95% confidence interval (CI): 1.29 to 2.26; P=0.0002], non-fatal myocardial infarction (OR: 3.17; 95% CI: 1.21 to 8.31; P=0.02), and angina requiring hospitalization (OR: 2.31; 95% CI: 1.55 to 3.45; P<0.0001), respectively, compared with subjects without MB.

Conclusions: This meta-analysis of currently available observational cohort studies suggests that MB has an association with adverse cardiac events. Further prospective multicenter studies with large sample size are needed to confirm current findings. Moreover, studies refining the impact of different types of MB on cardiac events, myocardial ischemia, and symptoms requiring therapy, may provide more insights to this issue.

Keywords: Myocardial bridging (MB); adverse cardiac events (ACEs); prognosis; meta-analysis

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Introduction

Myocardial bridging (MB) is a congenital variant of coronary artery anatomy which indicates the myocardium overlying an intramural segment of an epicardial coronary artery. MB mostly involves the middle segment of the left anterior descending artery (LAD), though its prevalence varies according to different imaging modalities and methods used (1-3). The data derived from small sample studies indicate MB may cause a variety of adverse cardiac events (ACEs) including myocardial infarction (MI), life-threatening arrhythmias, and sudden cardiac death (3-6). In this regard, the clinical relevance of MB is of crucial

importance. Actually, MB has long been considered as a benign condition given that the prevalence of MB is usually high in autopsy and blood flow runs through normal coronary artery mainly during diastolic phase, while MB compression occurs during systolic phase and only approximately in one third of subjects with MB (3,7-10). Therefore, the precise clinical implication of MB on prognosis remains controversial. We aimed to conduct a meta-analysis of currently available evidence to examine the clinical implication of MB on prognosis among general population.

Methods

The present meta-analysis was performed with a predefined protocol and complied with PRISMA and MOOSE guidelines (*Table S1*,*S4*).

Search strategy

An extensive search of PubMed with English language restriction was performed using the terms like "myocardial bridging", "myocardial bridge", "intramural coronary artery", "mural coronary artery", "coronary artery overbridging", "tunneled artery" and "myocardial loop". Additional reference lists of relevant articles were reviewed. Studies published between 1960 in which year MB was first reported angiographically and 31 March 2018 were identified (3,4,11). The detailed search strategy was presented in *Table S2*.

Study selection

We only included observational cohort studies either prospective or retrospective comparing the outcome of subjects with and without MB, which represent the best level of clinical evidence to date. Inclusion criteria were the followings: (I) population referred consecutively to hospital for imaging examination of coronary artery; (II) explicit description of inclusion or exclusion criteria; and (III) comparison of outcome during follow-up between subjects with and without MB. Exclusion criteria were the followings: (I) studies incapable of extracting specific data; (II) studies dealing with patient population with specific disease like hypertrophic cardiomyopathy. Potentially eligible studies were evaluated by two independent reviewers (C Zhu and S Wang) as well as data extraction and quality evaluation of the final included studies. Any discrepancies were resolved by consensus meeting of all authors of this meta-analysis subsequently.

Quality evaluation of included studies

The Newcastle-Ottawa Scale for cohort studies, which is a "star system" providing an easy and convenient quality assessment of nonrandomized studies in a systematic review, was used to evaluate the quality of included studies on three perspectives: selection of cohorts, comparability of cohorts, and ascertainment of outcome for cohorts (12,13). Nine stars represent the highest study quality. At least 5 stars were defined to be adequate quality for inclusion in the present meta-analysis. With regard to evaluation for publication bias of included studies, the visualized funnel plot was used if applicable.

Outcomes

The primary outcome was defined as ACEs including cardiovascular death and non-fatal MI. Secondary outcomes were non-fatal MI, angina requiring hospitalization, and all-cause mortality. Furthermore, a composite endpoint was defined as a combination of ACEs, non-cardiac death and angina requiring hospitalization.

Statistical analysis

Analysis was conducted using Review Manager Version 5.3 (The Cochrane Collaboration, Update Software, Copenhagen, The Nordic Cochrane Centre). Heterogeneity test was measured utilizing the v^2 test (Cochrane's Q) and I^2 value. I^2 values less than 50%, 50% to 75%, and more than 75% represent a low, moderate, high degree of heterogeneity, respectively. If homogenous, fixed-effect model was used. Otherwise, a random-effects model was used. Odds ratio (OR) was calculated for dichotomous variables with 95% confidence interval (CI). An OR represents the ratio between odds of outcomes in the context of a particular exposure and odds of outcomes in absence of the exposure. A P value of less than 0.05 was considered statistically significant.

Results

Selection of studies

Six observational cohort studies were included in the

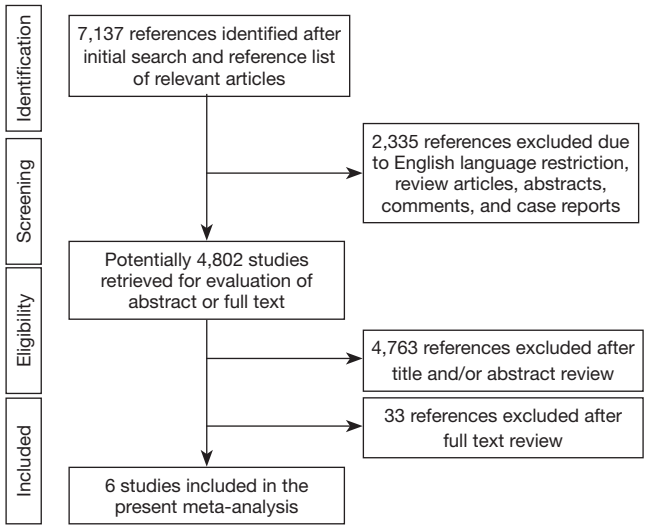

Figure 1 Flow diagram of search strategy and study selection in the present meta-analysis.

present meta-analysis for data extraction which yielded a total of 4,556 selected subjects (*Figure 1*) (11,14-18). Of these six included studies, only the study by Rubinshtein *et al.* was prospective, whereas the remaining 5 studies were retrospective. The study by Rubinshtein *et al.* included subjects with compromised left ventricular function or valvular heart disease who were referred to rule out obstructive coronary artery disease (11). In contrast, the study by Kim *et al.* excluded subjects with any risk factors of chest pain including valvular heart disease (18). The detailed inclusion and exclusion criteria and outcome measurements of selected studies were presented in *Table 1*. Besides, the study by Kim *et al.* assessed MB with coronary angiography. *Table 2* demonstrates data extracted from all included studies in the present meta-analysis. All subjects were in absence of prior coronary heart disease or obstructive coronary artery disease which was defined as equal to or more than 50% coronary luminal stenosis of any coronary artery.

The quality evaluation of selected studies was demonstrated in *Table S3*. None of these six included studies provided information on losses to follow-up.

Pooled prevalence and characteristics of MB

Of the 4,556 selected subjects included, 1,389 had MB. Thus, the pooled prevalence of MB in the present study is 30.5%. Most MB involved the LAD, which was consistent among included studies. Three studies reported MB with

Table 1 Characteristics of included studies in the present meta-analysis

First author, year	Location	Source of participants	Total number of participants	Inclusion criteria	Exclusion criteria	Study endpoints	Risk of bias*
Liu *et al.*, 2017 (14)	China	Zhongnan Hospital of Wuhan University	2,092	Subjects undergoing coronary computed tomographic angiography for suspected coronary artery disease or for physical health check	Previous coronary artery bypass grafting or stent placement; lesions in the mediastinum, esophagus, lungs, or thorax; history of coronary artery disease or myocardial infarction or obstructive coronary artery disease (≥50% stenosis); poor image quality due to arrhythmia, poor breath holding, and motion artifacts	Adverse cardiac events (cardiac death, nonfatal myocardial infarction)	Low
Dimitriu-Leen *et al.*, 2017 (15)	The Netherlands, Finland	Leiden University Medical Centre in the Netherlands, Turku University Hospital in Finland	947	Subjects with cardiac complaints and/or an increased cardiovascular risk profile and low-to-intermediate pre-test probability referred for coronary computed tomographic angiography	A history of coronary artery disease (previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery), heart failure, valvular heart disease, arrhythmia, or congenital heart disease; obstructive coronary artery disease (≥50% stenosis); patients lost to follow-up	All-cause death Nonfatal myocardial infarction Unstable angina pectoris requiring hospitalization	Low

Table 1 (*Continued*)

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First author, year	Location	Source of participants	Total number of participants	Inclusion criteria	Exclusion criteria	Study endpoints	Risk of bias*
Rubinshtein *et al.*, 2013 (11)	Israel	Lady Davis Carmel Medical Center and the Ruth and Bruce Rappaport School of Medicine	334	Subjects with chest pain syndromes referred for coronary computed tomographic angiography	Prior history of obstructive coronary artery disease or coronary revascularization; obstructive coronary artery disease (≥50% stenosis); obstructive disease	Adverse cardiac events (cardiac death, nonfatal myocardial infarction) Non-cardiac death	Low
Sheu *et al.*, 2011 (16)	China	Taipei Veterans General Hospital	425	Subjects undergoing coronary computed tomographic angiography for known or suspected coronary artery disease or for physical health check	A history of coronary artery disease; previous percutaneous coronary intervention/stenting, and coronary artery bypass graft; Inadequate clinical information of cardiovascular illness; loss to follow-up	Cardiac death Nonfatal myocardial infarction Revascularization (CABG, PCI) Ventricular arrhythmia	Low
Marcos-Alberca *et al.*, 2011 (17)	Spain	Hospital Clínico San Carlos	74	Subjects with stable chest pain and intermediate risk of coronary artery disease (30–70% stenosis) referred for coronary computed tomographic angiography	NR	Cardiac death Nonfatal myocardial infarction Revascularization (CABG, PCI) Recurrent ischemic symptoms requiring hospitalization	Low
Kim *et al.*, 2010 (18)	Korea	Chonnam National University Hospital	684	Subjects with chest pain and without significant coronary artery disease (<50% stenosis) referred for coronary angiography	Obstructive coronary artery disease (≥50% stenosis)	Readmission during follow-up† Cardiac death Nonfatal myocardial infarction Non-cardiac death Recurrent angina refractory to medical therapy	Moderate

†, including death (cardiac death, non-cardiac death), nonfatal myocardial infarction, and recurrent angina refractory to medical therapy; *, the risk of bias was evaluated by two reviewers independently. Based on the comprehensive analysis of selection bias, multiple publication biases, measurement bias, statistical reporting bias, studies were classified into three levels: high, moderate and low. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; NR, not reported.

Table 2 Extracted data of included studies in the present meta-analysis

Variable	Liu *et al.*, 2017 (14)			Dimitriu-Leen *et al.*, 2017 (15)			Rubinshtein *et al.*, 2013 (11)			Sheu *et al.*, 2011 (16)			Marcos-Alberca *et al.*, 2011 (17)			Kim *et al.*, 2010 (18)		
	Total	MB	MB−	Total	MB	MB−	Total	MB	MB−	Total	MB	MB−	Total	MB	MB−	Total	MB	MB−
Study design	Retrospective cohort study			Retrospective cohort study			Prospective cohort study			Retrospective cohort study			Retrospective cohort study			Retrospective cohort study		
N	2,092	634	1,458	947	210	737	334	117	217	425	89	336	74	31	43	684	308	376
Modality	CTG			CTG			CTG			CTG			CTG			CAG		
Definition of MB	At least half encasement			>1 mm of myocardium surrounding			Covered by a bridge of myocardium			Full encasement			Myocardium surrounding			Systolic compression		
Age, years	58.9±8.9	59.3±9.2	58.7±9.2	53.0±12.0	54.0±11.0	53.0±12.0	57±13	57±13	57±12	NR	57.4±16.1	NR	NR	62±13	59±12	60.59±11.02	57.65±10.67	62.99±10.72
Female, %	43.1	44.6	42.4	56	60	55	43	34	48	NR	23.7	NR	NR	61	74	49.9	53.9	47.1
BMI, kg/m^2	24.7±3.7	24.6±3.7	24.7±3.7	NR	NR	NR	NR	NR	NR	NR	25.3±3.6	NR	NR	NR	NR	NR	NR	NR
Hypertension, %	75.8	78.2	74.8	40	40	39	36	31	39	NR	59.5	NR	NR	48	33	NR	37.7	43.9
Hyperlipidemia, %	69.7	72.2	68.6	NR	NR	NR	38	42	36	NR	44.9	NR	NR	NR	NR	NR	4.2	6.9
Hypercholesterolemia, %	NR	NR	NR	35	35	35	NR	NR	NR	NR	NR	NR	25.9	16	33	NR	NR	NR
Diabetes mellitus, %	21.7	19.2	22.8	27	29	26	12	14	11	NR	17.9	NR	NR	26	12	NR	16.2	16.0
Smoking, %	42.3	39.7	43.4	15	16	15	20	22	19	NR	13.4	NR	NR	3	11	NR	26.9	21.5
Clinical symptom, %	53.8	59.6	51.3	57	53	58	100	100	100	NR	66.2	NR	100	100	100	100	100	100
Non-obstructive CAD, %	47.8	56.6	43.9	58	62	57	52	63	45	NR	NR	NR	NR	NR	NR	22.7	23.7	21.8
Prevalence of MB, %		30.3			22			35			20.9			41.9			45	
MB of LAD, %		79.4			39			71			49.9			87			98.7	
Complete MB, %		NR			NR			73			100			NR			NR	
Deep MB, %		70.6			40			NR			10.7			NR			NR	
MB length, mm		20.5±7.5			NR			27±14			21.4±9.6			NR			NR	
MB depth, mm		2.6±0.9			1.9			2.6±1.4			2.55±9.6			NR			NR	
Follow-up time, years		4.3±0.7			4.9			6.1±1			1.8±0.3			0.5			3.1±1.2	
Angina requiring hospitalization	NR	NR	NR	13	2	11	NR	NR	NR	3	0	3	33	19	14	79	52	27
Revascularization	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	9	NR	2	2	0	NR	NR	NR
Adverse heart events	202	81	121	NR	NR	NR	13	6	7	0	0	0	2	1	1	8	7	1
Cardiac death	NR	NR	NR	NR	NR	NR	10	4	6	0	0	0	0	0	0	0	0	0
Non-fatal MI	NR	NR	NR	7	2	5	3	2	1	0	0	0	2	1	1	8	7	1
All-cause mortality	NR	NR	NR	23	4	19	19	7	12	NR	NR	NR	NR	NR	NR	4	0	4

MB, myocardial bridging; CTG, coronary computed tomographic angiography; CAG, coronary angiography; BMI, body mass index; CAD, coronary artery disease; LAD, left ascending artery; MI, myocardial infarction; NR, not reported.

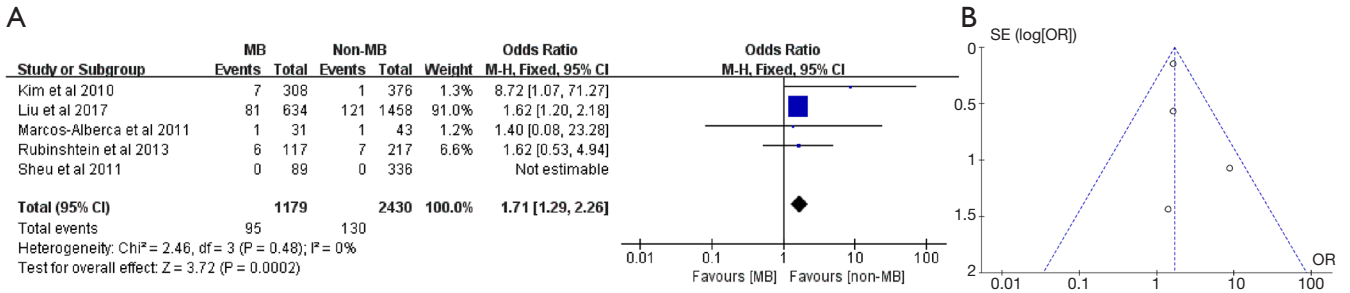

Figure 2 Pooled risk of adverse cardiac events. (A) Forest plot of included studies describing adverse cardiac events during follow-up. Subjects with myocardial bridging had higher risk of experiencing adverse cardiac events; (B) corresponding funnel plot of included studies. MB, myocardial bridge; CI, confidence interval; OR, odds ratio; SE, standard error.

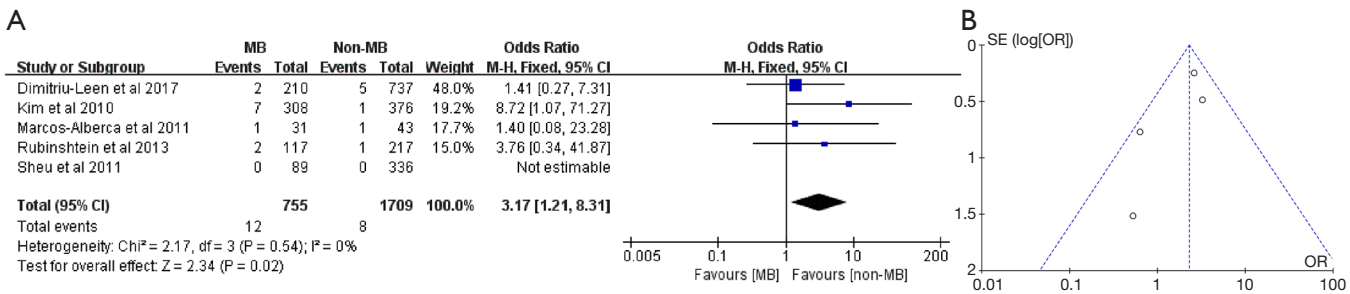

Figure 3 Pooled risk of non-fatal myocardial infarction. (A) Forest plot of included studies describing non-fatal myocardial infarction during follow-up. Subjects with myocardial bridging had higher risk of experiencing non-fatal myocardial infarction; (B) corresponding funnel plot of included studies. MB, myocardial bridge; CI, confidence interval; OR, odds ratio; SE, standard error.

mean length of 2 to 3 mm and mean depth of 2.6 mm (11,14,16).

Primary outcome

ACEs were reported in five included studies comprising a total of 225 events among 3,609 subjects (11,14,16-18). The pooled incidences of ACEs were 8.1% and 5.3% in subjects with MB and without MB, respectively. On pooled analysis, subjects with MB had an increased risk of ACEs compared with subjects without MB (OR: 1.71; 95% CI: 1.29 to 2.26, P=0.0002) (*Figure 2A*). There was no statistical significance of heterogeneity test between included studies (Cochrane Q =2.46, P=0.48, I^2 =0%). Besides, the corresponding funnel plot indicated that no publication bias existed (*Figure 2B*).

Sensitivity analysis was performed by only including five studies which used coronary computed tomographic angiography for detection of MB. Results were unchanged for ACEs in subjects with MB compared to that in subjects without MB (OR: 1.62; 95% CI: 1.21 to 2.15, P=0.001) (*Figure S1*).

Secondary outcomes

Non-fatal MI was reported in five studies comprising a total of 20 events among 2,464 subjects (11,15-18). The pooled incidences of non-fatal MI were 1.6% and 0.5% in subjects with MB and without MB, respectively. Subjects with MB had an increased risk of experiencing non-fatal MI compared with subjects without MB (OR: 3.17; 95% CI: 1.21 to 8.31, P=0.02) (*Figure 3*). There was no statistical heterogeneity for the outcome of non-fatal MI between included studies (Cochrane Q =2.17, P=0.54, I^2 =0%).

Angina requiring hospitalization was reported in 4 studies comprising a total of 128 events among 2,130 subjects (15-18). The pooled incidences of angina requiring hospitalization were 11.4% and 3.7% in subjects with MB and without MB, respectively. Subjects with MB had an increased risk of angina requiring hospitalization compared with subjects without MB (OR: 2.31; 95% CI: 1.55 to 3.45,

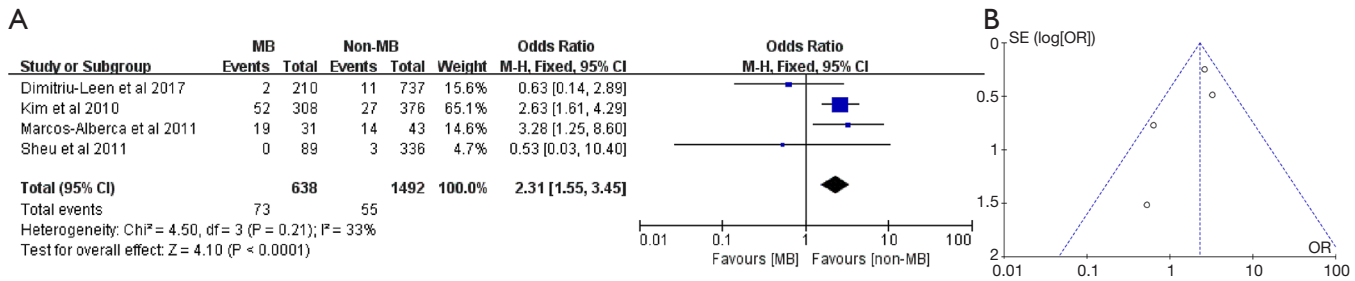

Figure 4 Pooled risk of angina requiring hospitalization. (A) Forest plot of included studies describing angina requiring hospitalization during follow-up. Subjects with myocardial bridging had higher risk of experiencing angina requiring hospitalization; (B) corresponding funnel plot of included studies. MB, myocardial bridge; CI, confidence interval; OR, odds ratio; SE, standard error.

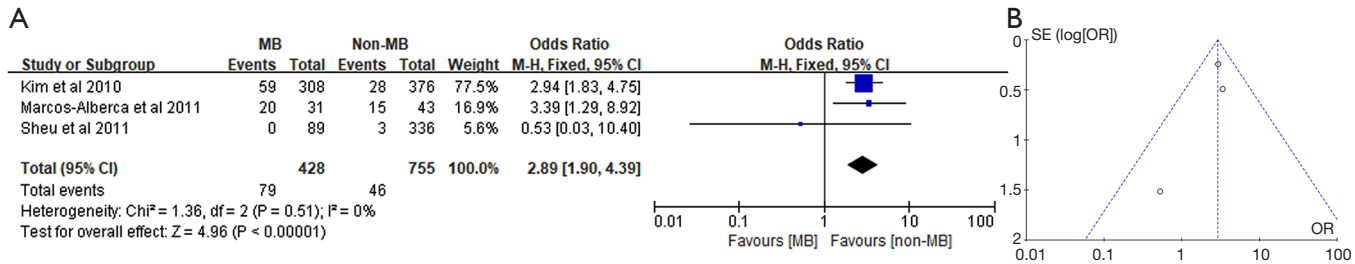

Figure 5 Pooled risk of the composite endpoint. (A) Forest plot of included studies describing the composite endpoint during follow-up. Subjects with myocardial bridging had higher risk of experiencing the composite endpoint. (B) Corresponding funnel plot of included studies. MB, myocardial bridge; CI, confidence interval; OR, odds ratio; SE, standard error.

P<0.0001) (*Figure 4*). There was no statistical heterogeneity between included studies (Cochrane Q =4.50, P=0.21, I^2 =33%).

All-cause mortality was reported in three studies comprising a total of 46 events among 1,965 subjects (11,15,18). The pooled incidences of all-cause mortality were 1.7% and 2.6% in subjects with MB and without MB, respectively. Subjects with MB had no significant increase in the risk of all-cause mortality compared with subjects without MB (OR: 0.75; 95% CI: 0.38 to 1.49, P=0.41) (*Figure S2*). There was no statistical heterogeneity between included studies (Cochrane Q =1.90, P=0.39, I^2 =0%).

Composite endpoint

Of six included studies, three studies involving 1,183 subjects, reported composite endpoint comprising of ACEs, non-cardiac death and angina requiring hospitalization (16-18). The pooled incidences of the composite endpoint were 18.5% and 6.1% in subjects with MB and without MB, respectively. Subjects with MB had an increased risk of experiencing the composite endpoint compared with subjects without MB (OR: 2.89; 95% CI: 1.90 to 4.39, P<0.00001) (*Figure 5*). There was no statistical heterogeneity between included studies (Cochrane Q =1.36, P=0.51, I^2 =0%).

Discussion

The present meta-analysis aims to examine the impact of MB on clinical prognosis in the general population which includes the latest cohort studies to date as far as we know. Our results indicate that MB is associated with an increased risk of ACEs and non-fatal MI in the present study. Thus, our findings may have important implications with regard to clinical practice and may alter our previous conceptions and strategies to provide more attention and optimal management of MB.

The pooled prevalence of MB with 30.5% in the present study is similar to that in the prospective study by Rubinshtein *et al.* and the average prevalence of 25% detected in autopsy which is usually regarded as a reference

standard (7,11,16). Generally, according to previous studies, depiction rate of MB in coronary angiography, coronary computed tomographic angiography and autopsy is increased in ascending order (4,5,7,11). The prevalence of MB on coronary computed tomographic angiography in more recent studies is in accordance with autopsy series, which may be attributed to the increasingly high spatial resolution of newer generation computed tomography capable of refining MB (4,19).

Our key findings suggest that MB confers an increased risk of ACEs (OR: 1.71; 95% CI: 1.29 to 2.26, P=0.0002) and non-fatal MI (OR: 3.17; 95% CI: 1.21 to 8.31, P=0.02) in subjects with MB compared with subjects without MB, respectively. Thus, our findings are contrary to previous studies and traditional consideration that MB is a normal variant or a benign coronary anomaly (11,15). Regarding clinical symptom, subjects with MB had an increased risk of angina requiring hospitalization (OR: 2.31; 95% CI: 1.55 to 3.45, P<0.0001) compared with subjects without MB.

There are several potential mechanisms that may attribute to the association of MB with ACEs or myocardial ischemia. First, MB itself mostly involves the LAD which is one of the most important coronary arteries and whose lesion commonly contributes to most MI or myocardial ischemia in obstructive coronary artery disease. Hemodynamic relevance of MB differs significantly with regard to its anatomy especially depth (1,20). Second, multiple studies on MB using intracoronary ultrasound, Doppler and quantitative coronary angiography have revealed that systolic compression of MB persists into diastolic phase of cardiac cycle rather than that MB is just a systolic event (21-25). This finding is deemed highly unique as it can only be detected in the segment of MB with systolic compression (1,26). Moreover, findings by intracoronary Doppler demonstrate that MB compression delays luminal recovery in early diastole which may impair diastolic hemodynamics, which is left unidentified before (21). Additionally, the degree of the systolic compression of MB is positively associated with reduction of luminal diameter and corresponding decrease in flow and flow reserve during diastole (27). Third, previous studies reveal endothelial dysfunction of the tunneled coronary artery beneath MB (28,29). Furthermore, reduced expression of some vasoactive agents like endothelial nitric oxide synthase, endothelin-1, and angiotensin-converting enzyme at the MB site were ascertained to attribute to endothelial dysfunction of the tunneled coronary artery, which may predispose tunneled coronary artery to spasm at the same time (4,28,29). Fourth, several studies demonstrated a higher incidence of cardiac death and nonfatal MI in subsets of patients with coronary artery spasm and without obstructive coronary artery disease (30,31). Fifth, it has been found that vessel segment proximal to MB predisposes to development of atherosclerosis or formation of plaques, though vessel segment within MB is protected from development of atherosclerotic lesions (6,10,32). Disturbed retrograde flow produced by systolic compression of MB alters significantly shear stress on the coronary artery wall proximal to MB leading to atherosclerosis of corresponding part of the coronary artery (6,32). This finding has been thought to increase the risk of ACEs or myocardial ischemia.

Limitations

This meta-analysis has some limitations. First, our study itself is prone to inherent limitations of this kind of analysis like publication bias. Our data are confined to rely on published studies. Second, most included studies are retrospective except the study by Rubinshtein and colleagues (11). Therefore, our study may have limitations, potential confounding and biases of all retrospective studies. However, prospectively observational study examining the impact of MB on prognosis is relatively lacking, especially with a comparison group of subjects without MB, and has relatively small sample size. Third, of six included studies, the study by Kim *et al.* uses coronary angiography to detect MB, which differs from the other five included studies with coronary computed tomographic angiography used and is usually thought to has a lower detection rate of MB. However, Kim *et al.* administered intracoronary nitroglycerin in order to well define MB once suspecting MB during coronary angiography (18). Besides, six included studies only provided limited information about functional effects of MB or clinical symptoms in participants. Fourth, tools employed for diagnosis of MB may be different among included studies in different periods. However, the time span is relatively short, so differences in terms of anatomical definition and functional relapse are slight. Fifth, follow-up duration in two included studies was relatively short and none of included studies provided information on loss to follow-up, which may add some bias to our study (16,17). Sixth, our study could not respectively refine association of different MB types with presence/magnitude of coronary mal-perfusion and prognosis basing on current evidences due to a lack of source data.

Conclusions

MB is not uncommon especially assessed on coronary computed tomographic angiography. Subjects with MB and without obstructive coronary artery disease have increased risk of experiencing ACEs including cardiac death and non-fatal MI, as well as angina requiring hospitalization. These findings may have substantially important implication which may alter our traditional conception of MB as well as clinical practice. However, the present finding needs further prospectively longitudinal multicenter study with large sample size to validate.

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Footnote

Conflicts of Interest: 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.

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Table S1 PRISMA checklist*

Section/topic	#	Checklist item	Reported on page#
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	1–2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	1–2
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	*Table S2*
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Methods
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Methods
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	Methods
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	None
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	*Figure 1*
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	*Tables 1,2*
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12)	*Table S3*
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (I) simple summary data for each intervention group and (II) effect estimates and confidence intervals, ideally with a forest plot	Results and *Figures 2,5*
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Results and *Figures 2-5*
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	Results, *Figure 3*, and *Table S3*
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression) (see Item 16)	None
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers)	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias)	Limitations
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Conclusions
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	Funding

*, Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

Table S2 Search strategy used in the PubMed database from 1960 to 31 March 2018

Number	Search items
1	Myocardial bridging
2	Myocardial bridge
3	Intramural coronary artery
4	Mural coronary artery
5	Coronary artery overbridging
6	Myocardial loop
7	Intramural course of coronary artery
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	Limit 8 to ("1960/01/01"[PDAT] : "2018/03/31"[PDAT])
10	Limit 9 to English [LA]
11	10 not Review [PT]
12	11 not "Case reports" [PT]
13	12 not Editorial [PT]
14	13 not Comment [PT]

Table S3 Quality evaluation of included studies

	Selection				Comparability		Outcome		
Study (published year)	1	2	3	4	5	6	7	8	9
Liu *et al.*, 2017 (14)	★	★	★	★	★		★	★	
Dimitriu-Leen *et al.*, 2017 (15)	★	★	★	★	★		★	★	
Rubinshtein *et al.*, 2013 (11)	★	★	★	★	★		★	★	
Sheu *et al.*, 2011 (16)	★	★	★	★			★		
Marcos-Alberca *et al.*, 2011 (17)	★	★	★	★	★		★		
Kim *et al.*, 2010 (18)	★	★	★	★	★		★	★	

Table S4 MOOSE checklist*

Checklist item	Brief description
Reporting of background	
Problem definition	Data derived from small series have demonstrated an association of myocardial bridge (MB) with adverse cardiac events, while MB has been traditionally considered as a benign condition. Hence, the precise clinical implications of MB on prognosis remains inconsistent
Hypothesis statement	MB may have an association with adverse cardiac events (ACEs)
Description of study outcomes	ACEs including cardiovascular death and non-fatal myocardial infarction (MI); secondary outcomes like non-fatal MI, angina requiring hospitalization, and all-cause mortality; composite endpoint defined as a combination of ACEs, non-cardiac death and angina requiring hospitalization
Type of exposure	With MB
Type of study designs used	Population-based cohort studies
Study population	Populations referred for computed tomographic coronary angiography or coronary angiography in hospital
Reporting of search strategy should include	
Qualifications of searchers	Changsheng Zhu, MD; Shuiyun Wang, MD
Search strategy, including time period included in the synthesis and keywords	Time period: from inception of PubMed to March 31, 2018 Search strategy: *Table S2*
Databases and registries searched	PubMed
Search software used, name and version, including special features	Endnote X 8.2 was used to manage references
Use of hand searching	Additional reference lists of relevant articles were searched
List of citations located and those excluded, including justifications	Details of the literature search process are presented in the flow chart (*Figure 1*). List of excluded citations is available on request
Method of addressing articles published in languages other than English	The search was restricted to the English language
Method of handling abstracts and unpublished studies	None
Description of any contact with authors	Not applicable
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Methods section
Rationale for the selection and coding of data	Extracted data from included studies were related to population characteristics, study design, exposure and outcome measurements
Assessment of confounding	Not applicable
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed with the nine-star Newcastle-Ottawa Scale (NOS) which is pre-defined criteria including population representativeness, comparability, ascertainment of outcome (*Table S3*)
Assessment of heterogeneity	Heterogeneity of the studies was evaluated with I^2 statistic
Description of statistical methods in sufficient detail to be replicated	Details of statistical methods were described in the Methods section
Provision of appropriate tables and graphics	*Tables 1,2, Figures 1-5*
Reporting of results should include	
Graph summarizing individual study estimates and overall estimate	*Figures 2-5*
Table giving descriptive information for each study included	*Tables 1,2*
Results of sensitivity testing	Not applicable
Indication of statistical uncertainty of findings	95% confidence intervals were calculated for all summary estimates
Reporting of discussion should include	
Quantitative assessment of bias	Publication bias was assessed with funnel plot
Justification for exclusion	All studies were excluded based on the pre-defined inclusion and exclusion criteria in the Methods section
Assessment of quality of included studies	Quality assessment of included studies was described in Methods section
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	Discussion section
Generalization of the conclusions	Results section
Guidelines for future research	Further prospective multicentre studies with large sample size are needed to confirm current findings
Disclosure of funding source	Dr. Shuiyun Wang has received grants from National Natural Science Foundation of China

*, Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.

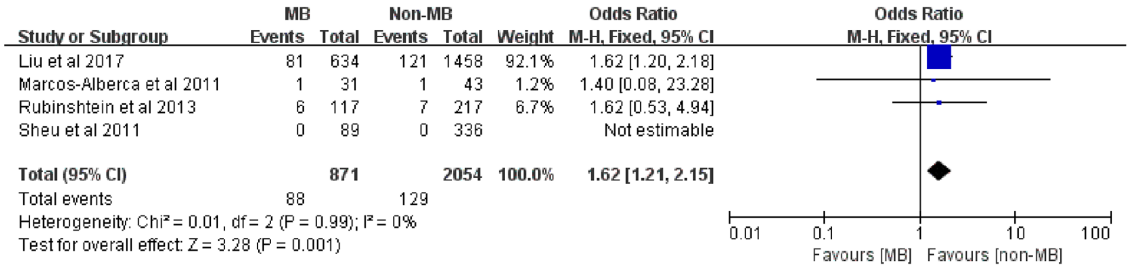

Figure S1 Sensitivity analysis only including five studies which used coronary computed tomographic angiography for detection of myocardial bridging. Subjects with myocardial bridging had higher risk of experiencing adverse cardiac events. MB, myocardial bridge; CI, confidence interval.

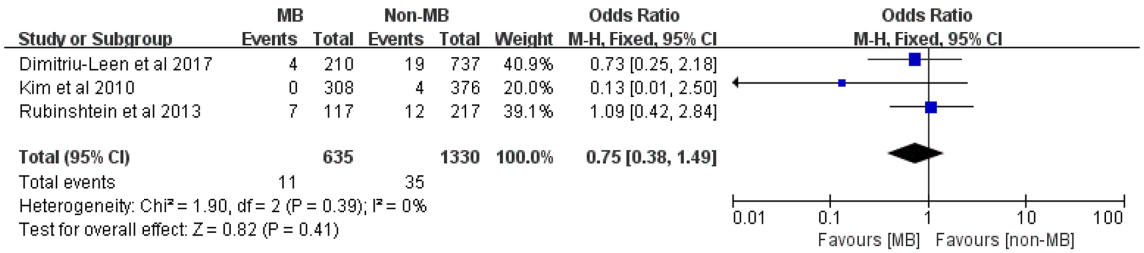

Figure S2 Forest plot of included studies describing all-cause mortality during follow-up. Subjects with myocardial bridging had higher risk of experiencing all-cause mortality. MB, myocardial bridge; CI, confidence interval.