Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

The predictors of no reflow phenomenon after percutaneous coronary intervention in patients with ST elevation myocardial infarction: A meta-analysis



IHJ

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ARTICLE INFO	A B S T R A C T
Article history: Received 20 October 2017 Accepted 16 January 2018 Available online 31 January 2018	<i>Objective:</i> To investigate the no reflow risk factors after percutaneous coronary intervention in SI elevation myocardial infarction patients. <i>Method:</i> Sample size, mean \pm standard deviation (SD) or frequencies (percent) of normal and no reflow groups were extracted from each study.
<i>Keywords:</i> No reflow phenomenon Myocardial infarction Percutaneous coronary intervention Risk factors	<i>Results:</i> Of 27 retrospective and prospective studies, we found that increasing risks of no reflow were associated with advanced age, male, family history of coronary artery disease, smoking, diabetes mellitus hypertension, delayed reperfusion, killip class ≥ 2 , elevated blood glucose, increased creatinine, elevated creatine kinase (CK), higher heart rate, decreased left ventricular ejection fraction (LVEF), collateral flow ≤ 1 , longer lesion length, multivessel disease, reference luminal diameter, initial thrombolysis in myocardial infarction (TIMI) flow, and high thrombus burden. Moreover, initial TIMI flow ≤ 1 and high thrombus burden had the greater impact on no reflow (OR95%CI = 3.83 [2.77–5.29], p < 0.0001 and 3.69 [2.39–5.68], p < 0.0001, respectively). <i>Conclusion:</i> Our meta-analysis reveals that initial TIMI flow ≤ 1 and high thrombus burden are the most
	impacted no reflow risk factors. © 2018 Published by Elsevier B.V. on behalf of Cardiological Society of India. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

1. Introduction

Percutaneous coronary intervention (PCI), first introduced by Grüntzig et al.¹ in Switzerland, has now become the gold standard and the preferred treatment for ST elevation myocardial infarction (STEMI)²⁻⁴ and its use has increased substantially in the last 12–15 years because of its clinical effectiveness.⁵ The benefits of PCI had been described by Rott et al.⁶ and Goff et al.⁷ revealed that compared to thrombolytic, PCI is considered more effective in restoring thrombolysis in myocardial infarction (TIMI) 3 flow and thus decreases mortality. Moreover, Singh⁸ suggested that PCI was preferable than coronary artery bypass grafting (CABG), although both of them had the same outcome related to quality of life.

* Corresponding author at: Department of Cardiology and Vascular Medicine, School of Medicine, Syiah Kuala University, Banda Aceh, 23111, Indonesia. *E-mail address:* teuku_hery@unsyiah.ac.id (T. Heriansyah). However, PCI does not always provide good outcome. One of PCI complications often reported is no reflow phenomenon.^{9,10}

No reflow phenomenon is defined as a complex condition associated with inadequate myocardial perfusion of the coronary artery without evidence of angiographic epicardial vessel obstruction, spasm, or dissection.^{9,11–15} No reflow phenomenon is diagnosed based on angiography, myocardial contrast echocardiography (MCE), and cardiac magnetic resonance imaging (CMRI).⁴ MCE is the gold standard for the diagnosis of no reflow¹⁶ and CMRI is the most sensitive and specific method to assess the extent of no reflow.⁴ According to several reports, the incidence of no reflow is vary, ranging from 2 to 44% of all patients undergoing both primary and elective PCI,^{4,11–13,17–20} and the mortality is ranging from 7.4– 30.3% of all no reflow patients.^{10,21-23} The pathogenesis of no reflow phenomenon is complex and dynamic which involves distal atherothrombotic embolisation, ischaemic injury, reperfusion injury, and heightened susceptibility of coronary microcirculation to injury.²⁴

https://doi.org/10.1016/j.ihj.2018.01.032

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The development of no reflow markedly increases the risk of poor clinical outcomes including death, re-myocardial infarction (MI), reduced left ventricular ejection fraction (LVEF), left ventricular remodelling, malignant ventricular arrhythmia, heart failure (HF), and cardiac rupture.¹⁶ Because of its adverse effects, accurate detection of no reflow including identification of the predictors is crucial. Until now, the predictors of the no reflow phenomenon remain unclear. Although some studies^{14,25–50} have reported no reflow risk factors, however they showed differences. Therefore, we aimed to perform a meta-analysis concerning the correlation between several factors and the risk of no reflow. Some of these factors are demographic data, clinical characteristics, laboratory parameters, electrocardiogram, echocardiography, and angiographic findings.

2. Method

2.1. Study design

During August 1st to October 10th, 2017, we conducted a metaanalysis to assess several factors (demographic and clinical characteristics, laboratory parameters, electrocardiogram, echocardiography, and angiographic findings) that might have the impact on no reflow phenomenon after PCI in patients with STEMI. In effort to reach this goal, we collected several studies from PubMed and Embase concerning this association to calculate a poolled odd ratio (OR) and 95% confidence interval (CI) using fixed or random effect model. This design of the study was adapted from our previous meta-analysis.^{51–55}

2.2. Eligibility criteria

The selection criteria for inclusion in this study were as follows: (1) retrospective studies; (2) prospective studies; (3) cross-sectional studies; (4) randomized-controlled trials (RCTs); (5) controlled before and-after studies; (6) cross-over studies; (7) evaluating several factors that might have the association between normal reflow and no reflow after PCI in patients with STEMI; and (8) sufficient data for calculation of OR95%CI. Articles were excluded because of: (1) obvious irrelevance title and or abstract, (2) family-based study, review and or commentary, (3) incomplete and or ungeneralized data, and (4) article with low quality (score <6).⁵⁶

2.3. Search strategy

We conducted a systematic literature search in PubMed and Embase with no language restrictions, using specified search terms to identify studies published up to July 20th, 2017. The search strategy involved the use of combination of the following key words: (percutaneous coronary intervention or PCI) and (no reflow or no reflow phenomenon or NRP) and (risk factors or predictors). The publication languages were restricted to English. The reference lists of retrieved articles were handsearched. If more than one article was published using the same study data; only the study with the largest sample size was included.

2.4. Data extraction

The following information was extracted from each study: (1) name of first author; (2) year of publication; (3) study design, (4) sample size of no reflow and normal reflow groups, (5) mean \pm standard deviation (SD) or frequencies and percent of no reflow and normal reflow groups. Demographic data, clinical characteristics, laboratory parameters, electrocardiogram,

echocardiography, and angiographic findings were analyzed in both no reflow and normal reflow groups.

2.5. Variables

2.5.1. The predictors of no reflow phenomenon

Several factors that might have the association with the risk of no reflow phenomenon including demographic data, clinical characteristics, laboratory parameters, electrocardiogram, echocardiography, and angiographic findings. Data were presented in mean \pm SD or frequencies and percents.

2.5.2. No reflow phenomenon

A dynamic and complex phenomenon that associated with the lack of myocardial perfusion without evidence of angiographic epicardial vessel obstruction, spasm, or dissection.^{9,11-15} No reflow is diagnosed according TIMI flow grade $\leq 1.5^{77}$ We compared the predictor data in subjects with normal reflow and no reflow after PCI.

2.6. Stastical analysis

We estimated the impact of several predictors between no reflow and normal reflow groups by calculating pooled ORs95%CI. A Z test was used to determine the significance of pooled ORs (p < 0.05 was considered statistically significant). A Q test was performed to evaluate whether the heterogeneity existed. Random effect model was used to calculate OR 95% CI if heterogeneity existed (p < 0.10). Otherwise, a fixed effect model was used. Publication bias was assessed using Egger's test (p < 0.05 was considered statistically significant). We used Comprehensive Meta-Analysis (CMA) version 2.1 to analyzed the data.

3. Results

3.1. Characteristics of the studies

A total of 6657 potentially relevant papers were identified based on the search strategy. Of these, 6611 papers were excluded because of obvious irrelevance by reading their titles and abstracts. After the full texts were read, nine papers were excluded because they did not provide sufficient data for calculation of OR with 95% CI; five papers were excluded because they were reviews or comments; and five papers were excluded because of same study data. A flow chart demonstrating the inclusion or exclusion of studies is displayed as Fig. 1. Finally, a total of 27 retrospective and prospective studies were included in the meta-analysis.

3.2. Quantitative data synthesis

Based on search strategy, covariates on demographic and clinical characteristics that meet the inclusion criteria for meta analysis were age, male, family history of coronary artery disease (CAD), smoking, previous CAD, diabetes mellitus, hypertension, hyperlipidemia, symptom to reflow time, and killip class.⁵⁸ Of 24 studies^{14,25–34,38–50} concerning the association between age, smoking, diabetes mellitus, and hypertension with the risk of no reflow, 23 studies^{14,25–34,38–44,46–50} regarding the association between male and the risk of no reflow, nine studies^{14,28,31,34,39,43–45,50} regarding the association between family history of CAD and the risk of no reflow, 16 studies^{26–30,33–35,38,39,41,42,45–48} regarding the association between symptom to reflow time and the risk of no reflow, and 12 studies^{26,27,29–31,33,34,39,41,44,45,50} concerning the



Fig. 1. Selection of articles for inclusion in meta-analysis.

association between killip class ≥ 2 and the risk of no reflow; we found that advanced age (OR95%CI = 1.89 [1.52–2.36], p < 0.0001), male (OR95%CI = 1.27 [1.05–1.55], p = 0.0160), family history of CAD (OR95%CI = 0.84 [0.72–0.99], p = 0.0330), smoking (OR95%CI = 0.78 [0.65–0.94], p = 0.0090), diabetes mellitus (OR95%CI = 1.45 [1.16–1.81], p = 0.0010), hypertension (OR95%CI = 0.84 [0.76–0.93], p = 0.0010), symptom to reflow time (OR95%CI = 1.92 [1.05–3.49], p = 0.0330), and killip class ≥ 2 (OR95%CI = 2.82 [1.90–4.18], p < 0.0001) were associated with the risk of no reflow. While, other covariates showed no significant association. Data regarding the association between demographic and clinical characteristics with the risk of no reflow are described in Table 1.

In laboratory parameters; blood glucose, white blood cell (WBC) count, creatinine, total cholesterol, tryglicerides, highdensity lipoprotein (HDL), low-density lipoprotein (LDL), and peak creatine kinase (CK) were met our inclusion criteria for meta analysis. For blood glucose, creatinine, and peak CK; we found nine,^{25,27,35,38,45-48,50} six,^{25,30,31,35,44,50} and 13 studies^{26–}

^{29,31,33,34,38,39,45–48} ; respectively. Our results found that elevated
blood glucose (OR95%CI = 1.90 [1.22-2.95], p = 0.0050), creatinine
(OR95%CI = 2.23 [1.08-4.60], p = 0.0300), and peak CK (OR95%)
CI = 3.13 [2.22–4.41], $p < 0.0001$) were correlated with the risk of
no reflow. Others, we did not find any correlation. Table 2 describes
the association between laboratory parameters and the risk of no
reflow.
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Concerning electrocardiogram and echocardiography, we included covariates such as anterior MI, inferior MI, lateral MI, heart rate, and LVEF for meta analysis. Our results found no association between infarct location and the risk of no reflow. While, higher heart rate (OR95%CI = 1.30 [1.07–1.57], p = 0.0080) of five studies^{25,27,30,44,45} and lower LVEF (OR95%CI = 3.10 [2.02–4.80], p < 0.0001) of 11 studies^{29,30,35,36,38,41,43,46–48,50} were associated with the risk of no reflow. Table 3 summarizes the association between electrocardiogram and echocardiography with the risk of no reflow.

Demographic and clinical characteristics of the study.

Baseline characteristics	Number of studies	Model	Normal reflow		No ref	low	OR	95%CI	pН	pЕ	р
			n	Values	n	Values					
Age (years)	24	Random	12922	59.6 ± 10.6	2163	$\textbf{63.3} \pm \textbf{11.4}$	1.89	1.52-2.36	< 0.0001	0.4750	< 0.0001
Male	23	Random	12683	9340 (73.6)	2082	1496 (71.9)	1.27	1.05-1.55	< 0.0001	0.3430	0.0160
Family history of CAD	9	Fixed	9390	2458 (26.2)	1103	251 (22.8)	0.84	0.72-0.99	0.7220	< 0.0001	0.0330
Smoking	24	Random	12892	5787 (44.9)	2163	957 (44.2)	0.78	0.65-0.94	< 0.0001	0.3400	0.0090
Previous CAD	16	Random	10616	1697 (16.0)	1588	361 (22.7)	0.86	0.58-1.23	< 0.0001	0.7040	0.4850
Diabetes mellitus	24	Random	12892	2963 (23.0)	2163	643 (29.7)	1.45	1.16-1.81	< 0.0001	0.4400	0.0010
Hypertension	24	Fixed	12883	7161 (55.6)	2163	1041 (48.1)	0.84	0.76-0.93	0.3710	0.0670	0.0010
Hyperlipidemia	18	Random	11486	4491 (39.1)	1421	569 (40.0)	1.09	0.93-1.28	0.0950	0.1860	0.2990
Symptom to reflow time (hour)	16	Random	4920	$\textbf{4.9} \pm \textbf{2.9}$	1385	$\textbf{5.6} \pm \textbf{3.0}$	1.92	1.05-3.49	< 0.0001	1.1900	0.0330
Killip class ^a ≥ 2	12	Random	9705	972 (10.0)	930	323 (34.7)	2.82	1.90-4.18	< 0.0001	0.5730	< 0.0001

Notes, Values are mean \pm SD or frequencies and percent n(%); OR, odds ratio; CI, confidence interval; *p*H, *p* heterogeniety; *p*E, *p* egger; CAD, coronary artery disease; No reflow is diagnosed according TIMI flow grade $\leq 1.5^{77}$

^a Killip class, (I) no evidence of heart failure. (II) mild heart failure, crackles over lower third or less of the lung, systolic BP >90 mmHg. (III) pulmonary oedema, crackles more than one-third of chest, systolic BP >90 mmHg. (IV) Cardiogenic shock, pulmonary oedema, crackles more that one-third of chest, systolic BP <90 mmHg.⁵⁸.

Table 2 Laboratory parameters on admission.

Laboratory parameter	Number of studies	Model	Norma	Normal reflow		low	OR	95%CI	pН	pЕ	р
			n	Values	n	Values					
Blood glucose (mg/dl)	9	Random	2743	152.7 ± 66.4	1143	$\textbf{183.3} \pm \textbf{89.7}$	1.90	1.22-2.95	< 0.0001	0.6380	0.0050
WBC count (/mm ³)	7	Random	2469	9977.9 ± 3509.1	852	12206.6 ± 4405.6	3.09	0.53-18.22	< 0.0001	2.3830	0.2120
Creatinine (mg/dl)	6	Random	8514	$\textbf{1.12}\pm\textbf{0.32}$	621	$\textbf{1.22}\pm\textbf{0.45}$	2.23	1.08-4.60	< 0.0001	0.8770	0.0300
Total cholesterol (mg/dl)	9	Fixed	2328	$\textbf{192.8} \pm \textbf{44.3}$	863	187.0 ± 45.9	0.88	0.76-1.02	0.4170	0.0340	0.0910
Triglycerides (mg/dl)	9	Fixed	1531	125.6 ± 76.0	758	121.7 ± 63.1	1.10	0.93-1.29	0.1260	0.1910	0.2570
HDL (mg/dl)	9	Random	2446	40.3 ± 10.1	904	$\textbf{39.9} \pm \textbf{9.8}$	1.01	0.80-1.27	0.0190	0.2560	0.9500
LDL (mg/dl)	9	Random	2854	108.6 ± 33.3	1026	107.0 ± 33.4	1.01	0.80-1.27	0.0190	0.2560	0.9500
Peak CK (IU/l)	13	Random	2855	2675.1 ± 1695.0	1076	3964.8 ± 2650.5	3.13	2.22-4.41	< 0.0001	0.5630	< 0.0001

Notes, Values are mean \pm SD or frequencies and percent n(%); OR, odds ratio; CI, confidence interval; *p*H, *p* heterogeniety; *p*E, *p* egger; WBC, white blood cells; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CK, creatine kinase; No reflow is diagnosed according TIMI flow grade $\leq 1.5^{77}$

Table 3 Electrocardiogram and echocardiography findings.

ECG & Echocardiography findings	Number of studies	Model	Norma	Normal reflow		flow	OR	95%CI	рН	pЕ	р
			n	Values	n	Values					
Anterior MI	11	Random	3893	1905 (48.9)	844	461 (54.6)	1.46	0.98-2.17	< 0.0001	0.6020	0.0640
Inferior MI	9	Random	3706	1245 (33.6)	765	260 (34.0)	1.12	0.83-1.51	0.0060	0.3540	0.4430
Lateral MI	8	Fixed	3467	310 (8.9)	684	44 (6.4)	0.95	0.67-1.34	0.5630	< 0.0001	0.7720
Heart rate (beats/min)	5	Fixed	7365	$\textbf{77.8} \pm \textbf{17.6}$	411	81.6 ± 21.4	1.30	1.07-1.57	0.2120	0.1530	0.0080
LVEF (%)	11	Random	4038	$\textbf{50.2} \pm \textbf{9.5}$	1193	$\textbf{44.0} \pm \textbf{9.8}$	3.10	2.02-4.80	< 0.0001	0.6750	< 0.0001

Notes, Values are mean \pm SD or frequencies and percent n(%); OR, odds ratio; CI, confidence interval; *p*H, *p* heterogeniety; *p*E, *p* egger; MI, myocardial infarction; LVEF, left ventricular ejection fraction; No reflow is diagnosed according TIMI flow grade $\leq 1.5^{77}$

For angiographic findings, we included collateral flow grade as described by Rosendorff [59], lesion length, multivessel disease, reference luminal diameter, initial TIMI flow as described by Gelfand & Cannon⁶⁰, and thrombus score as described by Topol & Teirstein⁶¹ for meta analysis. For collateral flow, lesion length, multivessel disease, reference lumen diameter, initial TIMI flow, and thrombus score; we found eight [26–29,33,34,39,45], nine, ^{31,32,34,35,39,40,42,44,45} seventeen, ^{14,28–32,34,38,39,43–50} sev-en, ^{31,32,33,34,39,40,42} fifteen, ^{14,26–34,38,39,42,44,45} and seven studies^{14,31,32,34,38,43,45}; respectively. We found that collateral flow (OR95%CI = 1.44 [1.06–1.97], p = 0.0210), lesion length (OR95% CI = 1.90 [1.35–2.70], p < 0.0001), multivessel disease (OR95%

CI = 1.56 [1.14–2.12], p = 0.0050), reference luminal diameter (OR95%CI = 1.97 [1.08–3.59], p = 0.0270), initial TIMI flow (OR95%CI = 3.83 [2.77–5.29], p < 0.0001), and thrombus score (OR95%CI = 3.69 [2.39–5.68], p < 0.0001) were associated with the risk of no reflow. Data regarding the association between angiographic findings and the risk of no reflow are summarized in Table 4.

3.3. Source of heterogeneity

Evidence of heterogeneity between studies was found in age (pH < 0.0001), male (p < 0.0001), smoking (p < 0.0001), previous

Table 4

Angiographic characteristics of the study.

Angiographic findings	Number of studies	Model	Normal reflow		No reflow		OR	95%CI	рН	pЕ	р
			n	Values	n	Values					
Collateral flow ^a ≤ 1	8	Fixed	1793	391 (21.8)	517	154 (29.8)	1.44	1.06-1.97	0.5790	< 0.0001	0.0210
Lesion length	9	Random	8200	18.3 ± 7.4	695	21.1 ± 9.3	1.90	1.35-2.70	< 0.0001	0.4540	< 0.0001
Multivessel disease	17	Random	11602	5898 (50.8)	1808	1044 (57.7)	1.56	1.14-2.12	< 0.0001	0.5850	0.0050
Reference luminal diameter	7	Random	1840	29.0 ± 6.1	400	$\textbf{30.6} \pm \textbf{7.9}$	1.97	1.08-3.59	< 0.0001	0.7270	0.0270
Initial TIMI flow ^b 0–1	15	Random	10290	6316 (61.4)	1178	1026 (87.1)	3.83	2.77-5.29	0.0010	0.4780	< 0.0001
Thrombus score ^c ≥ 4	7	Random	1818	955 (52.5)	639	490 (76.7)	3.69	2.39-5.68	0.0050	0.4500	<0.0001

Notes, Values are mean \pm SD or frequencies and percent n(%); OR, odds ratio; CI, confidence interval; *p*H, *p* heterogeniety; *p*E, *p* egger; TIMI, thrombolysis in myocardial infarction; No reflow is diagnosed according TIMI flow grade $\leq 1.5^{77}$

^a Collateral flow grade, (0) no collaterals presents. (1) Barely detectable collateral flow; contrast medium passes through the collaterals, but fails to opacify the resepient epicardial vessel. (2) Partial collateral flow; contrast medium enters, but fails to completely opacify the target epicardial vessel. (3) Complete collateral flow; contrast enters and completely opacifies the target epicardial vessel.⁵⁹.

^b TIMI flow grade, (0) No perfusion; no antegrade flow beyond the point of occlusion, (1) Penetration without perfusion; faint antegrade coronary flow beyond the occlusion, although filling of the distal coronary bed is incomplete. (2) Delayed flow; sluggisg antegrade flow with complete filling of the distal territory. (3) Complete perfusion; flow fills the distal territory completely.⁶⁰.

^c Thrombus grading score, (0) no angiographic characteristics of thrombus. (1) possible thrombus; angiographic features include decreased density of contrast; haziness; irregular lesion contour; or a smooth, convex meniscus at the site of total occlusion suggestive, but not diagnostic, of thrombus. (2) definite thrombus; present in multiple angiographic views; marked irregular lesion contour with a significant filling defect; greatest dimension less than half the vessel diameter. (3) definite thrombus in multiple views with greatest dimension more than half, but less than twice the vessel diameter. (4) definite large thrombus with greatest dimension more than twice the vessel diameter. (5) complete thrombotic occlusion of the vessel; a convex margin that stains with contrast and persists for several cardiac cycles.⁶¹.

Model	Study name		tics for each s	ludy		Odds ratio and 95% Cl						
A).		Odds ratio	Lower limit	Upper limit	Z-Value	p·Value	0,01	0,10	1,00	10,00	100,00	Relative weight
	Morishima et al 2000 Iwakura et al 2001 Yip et al 2002 Tanaka et al 2002 Iwakura et al 2003	2,063 1,437 1,574 0,712 2,689	0,970 0,858 1,106 0,247 1,428	4,390 2,409 2,240 2,051 5,067	1,880 1,377 2,518 -0,629 3,062	0,060 0,168 0,012 0,529 0,002						3,36 4,26 4,86 2,43 3,80
	Park et al 2004 Kirma et al 2008	0,660 1,934	0,321 1,263	1,358 2,962	-1,129 3,032	0,259 0,002			-++			3,48 4,60
	Dong - Bao et al 2010 Ndrepena et al 2010	2,367	1,268	4,419	2,704	0,007				-		3,84
	Chen et al 2012	1,450	0,917	2,293	1,591	0,112						4,48
	Celik et al 2014	1,538	1,038	2,255	2,640	0,008			+			4,04
	Celik et al 2015 Zhou et al 2014	1,538 2,377	1,011 1,390	2,342 4,066	2,009 3,162	0,045 0,002						4,62 4,18
	Dogan et al 2015 Celik et al 2016	1,904 0,635	1,024 0,297	3,539 1,359	2,036 -1,169	0,042 0,242						3,86 3,34
	Mazhar et al 2016 Matsumoto et al 2016	1,520 1,000	1,127	2,049	2,746	0,006			-+			5,04 2,51
	Balta et al 2016	1,831	1,342	2,496	3,821	0,000			+			5,01
	Kurtul et al 2017	4,441	3,340	5,905	10,256	0,002			-	+		4,98
	Padmajan et al 2017 Soeda et al 2017	3,971 2,815	2,138 1,172	7,376 6,759	4,365 2,316	0,000 0,021				-		3,86 2,95
Random	Liang et al 2017	7,564 1,894	5,215 1,520	10,973 2,359	10,661 5,697	0,000 0,000			+	-+	_	4,80
Model	Study name		Stati	stics for each :	study			0	dds ratio and 955	K CI		Weight (Random)
B).		Odds ratio	Lower limit	Upper limit	Z-Value	p•Value	0,01	0,10	1,00	10,00	100,00	Relative weight
	Morishima et al 2000 Iwakura et al 2001	0,952 1,598	0,397	2,282	0,111	0,912			-			3,15 4 12
	Yip et al 2002	0,990	0,575	1.704	-0.038	0,970						5,13
	Iwakura et al 2003	0,814	0,252	1,943	-0,463	0,643			-+			3,17
	Park et al 2004 Kirma et al 2008	0,705 1,460	0,293 0,769	1,699 2,774	-0,778 1,156	0,437 0,248						3,13 4,44
	Dong - Bao et al 2010 Ndrepepa et al 2010	0,646 1,208	0,308 0,778	1,354 1,875	-1,158 0.841	0,247 0,400			-++			3,83 5,94
	Akpek et al 2012	1,559	0,974	2,495	1,851	0,064			+			5,69
	Zhou et al 2014	0,702	0,371	1,326	-1,090	0,275			-++			4,47
	Leik et al 2015 Dogan et al 2015	3,602	1,626	7,983	3,157	0,332			T-			5,14 3,53
	Celik et al 2016 Mazhar et al 2016	3,929 1,735	1,235 1,212	12,492 2,484	2,318 3,011	0,020 0,003				·		2,14 6,60
	Matsumoto et al 2016 Balta et al 2016	0,778 1,593	0,217 1,068	2,793 2,376	-0,385 2,280	0,700 0,023						1,84 6,26
	Cenko et al 2016 Kurtul et al 2017	1,115	0,766	1,623	0,567	0,571			+	.		6,47
	Padmajan et al 2017	0,469	0,131	1,680	-1,163	0,245			-+			1,84
	Liang et al 2017	0,754	0,335	2,987	-1,339	0,181			-+-			6,15
Random Model	Study name	1,273	1,047 Statisl	1,549 ics for each sl	2,420 tudv	0,016	I,	1	+ ds ratio and 95%	1	I,	Weight
C)		Odda ratio	Lower limit	Unnerlimit	7)/shia	o.) (alua	0.01	0.10	1.00	10.00	100.00	(Handom) Relative
C).	Morishima et al 2000	0,365	0,154	0,869	-2,277	0,023				10,00		weight 2,78
	Iwakura et al 2001 Tanaka et al 2002	0,791	0,417	1,500 21,368	-0,718 1,875	0,473				_		3,88
	Yip et al 2002	0,685	0,464	1,012	-1,902	0,057						5,56
	park et al 2004	0,723	0,324	1,612	-0,792	0,428						3,46
	Kirma et al 2008 Ndrepepa et al 2010	0,546 0,646	0,327 0,421	0,914 0,991	-2,303 -1,999	0,021 0,046						4,68 5,28
	Dong - Bao et al 2010 Aknek et al 2012	1,217 1,140	0,606 0,765	2,444	0,552	0,581						3,56 5,49
	Chen et al 2012	1,658	0,867	3,173	1,527	0,127			+			3,83
	Zhou et al 2014	1,085	0,775	1,995	0,548	0,584			-			5,83
	Celik et al 2015 Dogan et al 2015	0,682 0,486	0,415 0,244	1,120 0,972	-1,512 -2,041	0,131 0,041						4,80 3,59
	Celik et al 2016 Mazhar et al 2016	0,717 0,686	0,299	1,720 1,011	-0,745	0,456						2,74
	Matsumoto et al 2016	0,848	0,242	2,970	-0,257	0,797						1,65
	Cenko et al 2016	1,175	0,853	1,672	0,898	0,828			+-			5,91
	Kurtul et al 2017 Padmajan et al 2017	0,390 0,458	0,283 0,222	0,539 0,944	-5,726 -2,117	0,000 0,034						6.05 3,43
	Soeda et al 2017 Liang et al 2017	0,539 1,305	0,206 0,862	1,412 1,975	-1,257 1,257	0,209 0,209		-				2,42 5,38
Random	-	0,785	0,654	0,942	-2,607	0,009			+			

Fig. 2. Forest plot regarding the association between age (A), gender (B), and smoking (C) with the risk of no reflow.

Model	Study name		Statis	tics for each s	tudy		Odds ratio and 95% Cl					
A).		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,01	0,10	1,00	10,00	100,00	Relative weight
	Morishima et al 2000	0,945	0,373	2,400	-0,118	0,906	1	1		1		3,05
	Iwakura et al 2001	0,834	0,417	1,668	-0,512	0,609						4,02
	Tip et al 2002 Tanaka et al 2002	0,739	0,461	6 170	-1,254	0,210				_		5,08 2,05
	Iwakura et al 2003	1,868	0,886	3,938	1,642	0,101			+ + -	-		3,78
	Park et al 2004	1,588	0,663	3,806	1,037	0,300						3,26
	Kirma et al 2008	1,214	0,688	2,139	0,669	0,503			-+			4,62
	Ndrepepa et al 2010	0,681	0,392	1,182	-1,365	0,172						4,69
	Aknek et al 2012	4 024	2,551	6,349	5,985	0,521						5,25
	Chen et al 2012	0,755	0,432	1,321	-0,985	0,325			-+-			4,66
	Celik et al 2014	2,909	1,927	4,392	5,080	0,000			-+	-		5,38
	Zhou et al 2014	1,192	0,555	2,557	0,450	0,652			- -			3,71
	Dogan et al 2015	2 844	1,784	6,526	2 466	0,000				_		4,69
	Celik et al 2016	3,401	1,242	9,311	2,382	0,017						2,80
	Mazhar et al 2016	1,240	0,817	1,882	1,011	0,312			+			5,36
	Cenko et al 2016 Balta et al 2016	1,153	0,778	1,709	0,711	0,477						5,48
	Matsumoto et al 2016	1,546	0.512	5,235	0.830	0,000				_		2.35
	Kurtul et al 2017	1,689	1,226	2,327	3,206	0,001						5,81
	Padmajan et al 2017	1,005	0,511	1,979	0,015	0,988						4,09
	Soeda et al 2017	1,140	0,440	2,956	0,270	0,787						2,98
Bandom	Liang et al 2017	1 447	0,525	1,361	-0,358 3,267	0,720						4,73
Model	Study name		St	atistics for eac	h study	-,		, 0	dds ratio and 9	5% CI		Weight (Fixed)
B).		Odds ra	tio Lowerlin	it Unnerlimi	7.Value	n.Value	0.01	0.10	1.00	10.00	100.00	Relative
	Mariahima at al 2000	000310		04 175	2 0 CO	0 0 507	1	1		10,00	100,00	weight
	Iwakura et al 2000	0,0	180 0,3	54 1,75 52 211	3 ·0,634 4 0.225	2 0,527 5 0,822						2.24
	Yip et al 2002	1.2	369 0,9	25 2,02	7 1,570	0,116			++			6,56
	Tanaka et al 2002	0,3	764 0,2	37 2,45	9 -0,45	0,652						0,74
	Iwakura et al 2003 Park et al 2004	1,2	203 0,6	04 2,39 42 1.70	3 0,526	5 0,599 0 511						2,13
	Kirma et al 2004	0,1	724 0,3	43 1,70 50 1,16	3 -1,336	5 0,511 5 0,182						4,49
	Ndrepepa et al 2010	1,0	0,6	77 1,57	0 0,143	3 0,886			-			5,70
	Dong - Bao et al 2010	0,0	524 0,3	10 1,25	7 -1,320	0,187			-++			2,06
	Akpek et al 2012 Chen et al 2012	U,. 1 -	/5/ U,5 151 0.6	UB 1,12 78 1,95	8 -1,365 3 0.525	9 U,171 2 0,602			-++			6,34 3,61
	Celik et al 2014	0,8	340 0,5	89 1,19	8 .0,962	2 0,336			-+-			8,02
	Zhou et al 2014	0,3	782 0,4	31 1,42	0.808	3 0,419			-+			2,84
	Celik et al 2015	0.9	979 0,6	06 1,58	0 0.08	B 0,929			-			4,40
	Celik et al 2015	0,0	54 0,3 256 0.1	31 1,29 07 0,61	5 ·1,217	7 0,224 7 0,002						2,17
	Mazhar et al 2016	0,9	969 0,6	95 1,35	3 -0,183	3 0,855			+			9,08
	Matsumoto et al 2016	0,0	321 0,2	06 3,27	9 -0,279	9 0,781				-		0,53
	Balta et al 2016	0,3	756 0,5	37 1,06	6 -1,596 7 0,496	5 0,111						8,57
	Kurtul et al 2017	0,0	505 0,6 557 0.4	10 1,33 80 0.89	7 ·0,463	7 0.008						10.33
	Padmajan et al 2017	0,9	947 0,4	69 1,91	3 -0,15	0,880						2,04
	Soeda et al 2017	0,9	954 0,3	36 2,71	2 .0,08	9 0,929						0,92
Fived	Liang et al 2017	U,U 0.1	558 0,4 341 0.7	37 0,99 61 0,93	0 -2,005	B 0,045			+			6,05
Model	Study name	0,0	Statis	tics for each st	udy	0,001	1	ı Odo	ls ratio and 95%	s CI	1	Weight (Bandom)
C).		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01	0.10	1.00	10.00	100.00	Relative
	Morishima et al 2000	1.000	0.473	2.116	0.000	1,000	1	1	_	1	1	weight 5.98
	Iwakura et al 2001	1,000	0,597	1,674	0,000	1,000						6,29
	Tanaka et al 2002	0,546	0,189	1,577	-1,118	0,264		_				5,47
	Yip et al 2002	5,282	3,679	7,583	9,020	0,000						6,44
	Park et al 2004	1.000	0,383	2.054	0,000	1,000						6,02
	Kirma et al 2008	2,477	1,613	3,802	4,147	0,000			-+-	-		6,38
	Ndrepepa et al 2010	10,325	7,117	14,979	12,297	0,000				+		6,43
	Dong - Bao et al 2010 Akoak et al 2012	3,351	1,785	6,289	3,764	0,000				_		6,15
	Chen et al 2012	1.336	4,158	2,111	3,378 1,240	0,000			+	-		6,4 <i>3</i> 6,35
	Celik et al 2014	6,134	4,381	8,587	10,565	0,000				-+-		6,46
	Zhou et al 2014	3,351	1,951	5,755	4,382	0,000				-		6,26
	Celik et al 2015	6,134	3,875	9,708	7,742	0,000						6,35
	Abdi et al 2015 Liang et al 2017	1 000	0,089	1 429	-9,132 0.000	1,000			+			6,38 6,45
Random	2.519 01 01 2011	1,919	1,054	3,495	2,132	0,033						0,40

Fig. 3. Forest plot regarding the association between diabetes mellitus (A), hypentension (B), and symptom to reflow time (C) with the risk of no reflow.

CAD (p < 0.0001), diabetes mellitus (p < 0.0001), hyperlipidemia (p = 0.0950), symptom to reflow time (p < 0.0001), killips class (p < 0.0001), blood glucose (p < 0.0001), WBC (p < 0.0001), creatinine (p < 0.0001), HDL (p = 0.0190), LDL (p = 0.0190), peak

CK (p < 0.0001), anterior MI (p < 0.0001), inferior MI (p = 0.0060), LVEF (p < 0.0001), lesion length (p < 0.0001), multivessel disease (p < 0.0001), reference luminal diameter (p < 0.0001), TIMI flow (p = 0.0010), and thrombus score (p = 0.0050). Therefore, these

data were assessed using random effect model. While, other variables including family history of CAD (p = 0.7220), hypertension (p = 0.3710), total cholesterol (p = 0.4170), tryglicerides (p = 0.1260), lateral MI (p = 0.5630), heart rate (p = 0.2120), and collateral flow (p = 0.5790) were assessed using fixed effect model because we found no heterogeneity between studies. The summary of heterogeneity evidence is described in Tables 1–4.

3.4. Potential publication bias

Using Egger's test, we found publication bias in family history of CAD (p < 0.0001), total cholesterol (p = 0.0340), lateral MI (p < 0.0001), and collateral flow (p < 0.0001). In other variables, we found no publication bias. We described the results of Egger's test in Tables 1–4.

4. Discussion

The pathogenesis and risk factors of no reflow are still incompletely understood. However, some literatures have proposed several mechanisms: (1) pre-existing microvascular dysfunction, (2) distal micro-thrombo-embolization due to high platelet activity and much thrombus burden, (3) ischemic injury, (4) reperfusion injury, (5) swelling of myocardial cells compressing microvascular vessels, and (6) individual susceptibility.^{4,24,34,62} Although some studies had reported possible risk factors, however these reports were accompanied by inconsistency. This is the first meta-analysis reporting the comparison of the possible risk factors between normal reflow and no reflow groups.

Our demographic and clinical characteristics found that age, male, family history of CAD, smoking, diabetes mellitus, hypertension, and killip class were proven to be associated with the risk of no reflow. We displayed forest plot concerning this association in Figs. 2–4. Age is widely known as one of risk factors for coronary heart disease (CHD).⁶³ However, the understanding regarding agerelated to no reflow is limited. This mechanism is probably through pre-existing microvascular dysfunction.⁴ Advancing age is one of the major risk factors for cardiovascular disease because aging has the significant role in the development of vascular endothelial dysfunction and stiffening of large elastic arteries.⁶⁴ Moreover, endothelial dysfunction has been known to impairs coronary flow reserve (CFR) and increases the vulnerability of affected myocardium to the PCI induced injury.⁴ In addition, diabetes mellitus; hypertension; and male have also been shown to have a correlation with endothelial dysfunction.^{65–67}

Our results found that delayed reperfusion (a long duration from symptom to reperfusion) increased the risk of no reflow. The possible mechanism underlying this outcome is microembolization. As has been disclosed that prolonged ischemia triggers distal capillary beds edema, myocardial cells swelling, neutrophil plugging, alterations of capillary integrity, and microvascular bed disruption.⁶⁸ This leads to the thrombus takes on more erythrocytes and becomes more rigid, which may lead to distal coronary embolization.⁶⁹

Model	Study name		Stati	stics for each s	study		Odds ratio and 95% Cl					
A).		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,01	0,10	1,00	10,00	100,00	Relative weight
	Morishima et al 2000	4,636	1,934	11,116	3,438	0,001	1	1	-		1	7,69
	Iwakura et al 2001	2,922	1,390	6,146	2,827	0,005				<u> </u>		8,59
	Tanaka et al 2002	0,873	0,175	4,349	-0,166	0,868				_		4,06
	Iwakura et al 2003	15,405	3,288	72,175	3,471	0,001						4,28
	Park et al 2004	0,788	0,253	2,454	.0,412	0,681						6,11
	Ndrepepa et al 2010	1,435	0,950	2,169	1,715	0,086			<u> </u>			10,88
	Chen et al 2012	2,408	1,441	4,025	3,355	0,001			-+	_		10,22
	Zhou et al 2014	2,652	1,459	4,821	3,200	0,001				_		9,63
	Cenko et al 2016	2,574	1,178	5,625	2,371	0,018						8,32
	Kurtul et al 2017	7,593	4,845	11,898	8,846	0.000				-++		10,65
	Padmajan et al 2017	4,599	2,190	9,659	4,031	0,000				-+		8,60
	Liang et al 2017	2,079	1,397	3,094	3,606	0,000						10,98
Random	5	2,818	1,899	4,183	5,143	0,000						
Model	Study name		Statisti	cs for each st	udy			Odd	s ratio and 95	% CI		Weight (Fixed)
B).		Odds ratio L	ower limit	Upper limit	Z-Value	p-Value	0,01	0,10	1,00	10,00	100,00	Relative weight
	lwakura et al 2003	2.234	1,190	4,193	2,501	0.012	1	1	1-+	- 1	1	9.15
	Ndrepepa et al 2010	1.000	0.698	1,433	0.000	1.000			-			28.08
	Chen et al 2012	1,484	0.938	2,346	1.688	0.091						17.30
	Dogan et al 2015	1.619	0.873	3.005	1.528	0.127						9.50
	Cenko et al 2016	1,222	0.889	1.679	1,237	0.216			+-			35.97
Fixed		1,297	1.072	1,569	2.672	0.008			+			
Model	Study name	.,	Stati	stics for each	study	.,		Odd	s ratio and 95	% CI	·	Weight (Random)
C).		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,01	0,10	1,00	10,00	100,00	Relative weight
	Morishima et al 2000	6,711	3.054	14,745	4,740	0.000	1	1	T a		1	7,79
	Park et al 2004	4,362	2.091	9,099	3,926	0.000						8.06
	Dong - Bao et al 2010	16,186	8,252	31,750	8.099	0.000					e	8.38
	Ndrepepa et al 2010	1.353	0,944	1,939	1.647	0,100			+-			9,83
	Akpek et al 2012	1,437	1.003	2.059	1,978	0.048						9.83
	Celik et al 2014	1,437	1.044	1,978	2,227	0.026						9,98
	Celik et al 2015	1,460	0,945	2,254	1,705	0,088						9.53
	Abdi et al 2015	2,601	1,725	3,924	4,559	0,000			-+	-		9.63
	Balta et al 2016	1,545	1,134	2,104	2,755	0,006			+			10.01
	Al - Jabari et al 2017	29,791	11,291	78,604	6,857	0.000				<u></u>		6.86
	Kurtul et al 2017	3,486	2,627	4,627	8,647	0,000				+		10.10
Random		3,104	2,020	4,769	5,168	0,000			-			

Fig. 4. Forest plot regarding the association between killip class (A), heart rate (B), and LVEF (C) with the risk of no reflow.

Model	Study name		Statis	tics for each s	tudy		Odds ratio and 95% Cl						
A).		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,01	0,10	1,00	10,00	100,00	Relative weight	
	Iwakura et al 2003	4,072	2,140	7,751	4,277	0,000	1	1	-	+	1	9,91	
	Dong - Bao et al 2010	3,836	2,039	7,218	4,169	0,000			_	+		9,98	
	Akpek et al 2012	2,948	2,044	4,250	5,789	0,000				-		11,55	
	Chen et al 2012	1,492	0,944	2,359	1,712	0,087			++-			11,05	
	Celik et al 2014	2,662	1,926	3,680	5,925	0,000			-+	-		11,75	
	Celik et al 2015	2,992	1,921	4,660	4,848	0,000				-		11,14	
	Dogan et al 2015	0,481	0,322	0,720	-3,555	0,000						11,35	
	Abdi et al 2015	0,847	0,564	1,271	-0,803	0,422			-+-			11,34	
	Kurtul et al 2017	1,682	1,272	2,224	3,648	0,000			-+-			11,94	
Random		1,896	1,218	2,952	2,832	0,005	I	1			I		
Model	Study name		Stati	istics for each s	study			Odds ratio and 95% Cl					
B).		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,01	0,10	1,00	10,00	100,00	Relative	
	Networks at al 2010	1 221	0.052	1 740	1 000	0 277	1	1	1.	1	1	17.00	
	Norepepa et al 2010	2,221	0,652	5 C/F	2,450	0,277						17,00	
	Abdi at al 2015	5,010	/ 1,011	9,040	0,400	0,001						15,72	
	Centre et al 2015	5 251	2 999	7 362	10 204	0,000						17.22	
	Kurtul et al 2017	1 000	0 757	1 321	0,004	1 000			_			17.22	
	Padmaian et al 2017	1,000	0,737	1,921	0,000	1,000						15.86	
Bandom	r daniajan et al 2011	2 227	1 079	4 599	2 165	0.030				_		10,00	
		-,	1,010	1,000	2,.00	0,000	1		1	1	1		
Model	Study name		Statis	tics for each s	tudy			Ode	ds ratio and 95	% CI		Weight (Random)	
\sim												Belative	
C).		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,01	0,10	1,00	10,00	100,00	weight	
	Morishima et al 2000	5,314	2,439	11,576	4,204	0,000	1		1 -		1	6,46	
	Iwakura et al 2001	8,558	4,905	14,931	7,560	0,000				-+		7,72	
	Tanaka et al 2002	12,441	4,086	37,875	4,438	0,000					-	4,80	
	lwakura et al 2003	5,697	2,962	10,960	5,213	0,000						7,16	
	Kirma et al 2008	1,931	1,261	2,958	3,025	0,002						8,42	
	Dong - Bao et al 2010	1,908	1,025	3,555	2,037	0,042				-		7,35	
	Akpek et al 2012	1,351	0,943	1,934	1,640	0,101			+			8,75	
	Chen et al 2012	2,251	1,419	3,570	3,446	0,001			-+-	-		8,24	
	Celik et al 2014	2,965	2,142	4,104	6,554	0,000			-	-		8,91	
	Zhou et al 2014	2,286	1,337	3,908	3,021	0,003			-+-	-		7,83	
	Celik et al 2015	1,342	0,869	2,071	1,327	0,185			++-			8,38	
	Padmajan et al 2017	9,095	4,776	17,319	6,717	0,000						7,22	
	Liang et al 2017	2,492	1,738	3,573	4,967	0,000			-+	-		8,75	
Random		3,130	2,220	4,413	6,509	0,000			-				

Fig. 5. Forest plot regarding the association between blood glucose (A), creatinine (B), and peak CK (C) with the risk of no reflow.

Interestingly, our findings revealed that smoking was 0.78 fold associated with the risk of no reflow. It means that non smoker subjects had 1.25 fold the risk of no reflow compared with smoker subjects. See forest plot in Fig. 2C. This finding is a controversy. Theoretically, smoking is associated with the risk of CAD⁷⁰ and endothelial dysfunction.⁷¹ We could not explain our result theoretically. We had tried to search and correlate with several possible no reflow mechanisms. However, we did not find the answer. Nevertheless, it has been described that the causes of no reflow are multifactoral. Therefore, it cannot be judged that smoking is the only factor influencing no reflow.

Killip class \geq 2 suggests that evidence of HF has been found.⁵⁸ Our results showed that subjects with killip class \geq 2 had 2.82 fold the risk for no reflow as described in Fig. 4A. The correlation between HF and no reflow is a complex involving neurohumoral activation that leads to imbalance between nitric oxide (NO) and reactive oxygen species (ROS). Reduced bioavailability of NO and abundant formation of ROS within vascular wall play an important role in endothelial dysfunction⁷² which is the basic of pre-existing microvascular dysfunction mechanism.⁴

Our laboratory findings found that elevated creatinine was associated with the risk of no reflow. We summarized this association in Fig. 5B. The correlation between creatinine level and no reflow is complicated. Of the five possible no reflow mechanisms, the closest possible mechanism is through

endothelial dysfunction. Although the association between renal function and endothelial dysfunction is unclearly elucidated. However, the basic correlation has been proposed. Creatinine level indicates renal function and elevated its level is associated with renal impairment.⁷³ On the other, reduction of renal function has been proven to cause retention of vasotoxic substances and cause metabolic changes that lead to increase ROS. These changes are believed to have an important role to create an atherogenic milieu.⁷⁴ As the result, plasma concentration of endothelium-derived protein will be increased and endothelium-dependent vasodilatation will be decreased. The changes of this level are responsible to increase soluble vascular cell adhesion molecule-1 (sVCAM-1) expression, the earlier step of endothelial dysfunction.⁷⁵ Not only sVCAM-1, Stam et al.⁷⁶ showed that elevated level of von willebrand factor (vWf), soluble intercellular adhesion molecule-1 (sICAM-1), serum secretory phospholipase A2 (sPLA2), and C-reactive protein (CRP) also played an important role that bridge between renal function and endothelial dysfunction. Moreover, endothelial dysfunction also has a correlation with elevated blood glucose levels⁷⁷ as reported in our study.

In adition, our laboratory findings also found that elevated CK was associated with the risk of no reflow. See Fig. 5C. The correlation between CK level and the risk of no reflow is possible through vascular contractility.⁷⁸ CK, known as cardiac biomarker

Model	Study name		Stati	stics for each s	study			Odds ratio and 95% CI					
A).		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,01	0,10	1,00	10,00	100,00	Relative weight	
	Morishima et al 2000	1,888	0,807	4,417	1,465	0,143			++	-	1	13,40	
	Iwakura et al 2001	1,314	0,653	2,647	0,765	0,444			-+			19,75	
	Tanaka et al 2002	1,806	0,555	5,875	0,982	0,326						6,96	
	Iwakura et al 2003	1,257	0,597	2,645	0,603	0,547			-+			17,49	
	Kirma et al 2008	1,038	0,400	2,698	0,077	0,938						10,62	
	Chen et al 2012	4,104	1,423	11,833	2,614	0,009						8,63	
	Zhou et al 2014	1,200	0,385	3,742	0,314	0,753				-		7,49	
	Liang et al 2017	1,045	0,476	2,294	0,111	0,912						15,67	
Fixed		1.443	1.057	1.970	2.311	0.021			⊢ ⊷				
Model	Study name		Statis	tics for each s	tudy			Odd	ls ratio and 95	% CI		(Bandom)	
												Deletion	
В).		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,01	0,10	1,00	10,00	100,00	weight	
	Yip et al 2002	1,679	1,179	2,390	2,876	0,004	1				1	13,14	
	Chen et al 2012	2,613	1,645	4,152	4,066	0,000			-+	-		11,97	
	Zhou et al 2014	2,995	1,747	5,136	3,987	0,000				<u> </u>		11,13	
	Abdi et al 2015	1,000	0,666	1,501	0,000	1,000			+			12,59	
	Matsumoto et al 2016	1,846	0,657	5,188	1,163	0,245				-		6,48	
	Cenko et al 2016	1,000	0,728	1,374	0,000	1,000			+			13,49	
	Padmajan et al 2017	3,118	1,687	5,761	3,630	0,000				-		10,31	
	Soeda et al 2017	1,632	0,689	3,870	1,113	0,266			++-	-21		7,84	
	Liang et al 2017	3,016	2,100	4,330	5,981	0,000				-		13,05	
Random		1,905	1,346	2,696	3,638	0,000	1	I.		1			
Model	Study name		Stati	stics for each s	study			Odd	s ratio and 95%	K CI		Weight (Random)	
C).												Relative	
-,.		Udds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,01	0,10	1,00	10,00	100,00	weight	
	Morishima et al 2000	1,167	0,483	2,821	0,342	0,732		1		1		4,57	
	Kirma et al 2008	1,269	0,790	2,037	0,985	0,325			+			6,22	
	Dong - Bao et al 2010	0,726	0,331	1,590	-0,801	0,423			-+-			4,96	
	Ndrepepa et al 2010	0,964	0,638	1,457	-0,174	0,862						6,45	
	Akpek et al 2012	4,233	2,779	6,447	6,722	0,000			-	+		6,42	
	Chen et al 2012	0,489	0,262	0,912	-2,248	0,025						5,62	
	Celik et al 2014	4,681	3,207	6,833	8,001	0,000			-			6,57	
	Zhou et al 2014	1,244	0,685	2,257	0,717	0,473			-+			5,74	
	Celik et al 2015	3,012	1,834	4,946	4,358	0,000				-		6,14	
	Celik et al 2016	2,267	0,971	5,294	1,892	0,058			+			4,71	
	Mazhar et al 2016	1,075	0,715	1,617	0,346	0,729						6,46	
	Cenko et al 2016	2,283	1,542	3,378	4,126	0,000				0		6,52	
	Balta et al 2016	2,855	1,988	4,102	5,677	0,000			-+			6,62	
	Kurtul et al 2017	1,929	1,394	2,669	3,964	0,000						6,74	
	Padmajan et al 2017	1,1/1	0,602	2,278	0,464	0,642						5,45	
	Soeda et al 2017	0,726	0,278	1,896	-0,653	0,514		87				4,29	
Daudau	Liang et al 2017	0,971	0,654	1,442	-0,144	0,885			—			6,51	
Handom		1,000	1,141	2,115	2,795	0,005	1	1	1	1	1	Weight	
Model	Study name		Statis	ics for each st	udy			Odd	s ratio and 95%	% CI		(Random)	
D).		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,01	0,10	1,00	10,00	100,00	Relative weight	
	Tanaka et al 2002	0.878	0.305	2.529	-0.240	0.810	L	1 -		1	1	11.45	
	Yip et al 2002	5.564	3.873	7.992	9.287	0.000						16.68	
	Zhou et al 2014	3,113	1.814	5.341	4.123	0.000				_		15.53	
	Matsumoto et al 2016	1.398	0.500	3.908	0.638	0.523				-		11.67	
	Padmajan et al 2017	0.621	0.339	1.136	-1.546	0.122						15.05	
	Soeda et al 2017	2.363	0.989	5.645	1.935	0.053				_		12.93	
	Liang et al 2017	2,477	1,727	3,551	4.934	0.000			-+-			16.69	
Random		1,969	1,081	3,589	2,213	0,027				-			

Fig. 6. Forest plot regarding the association between collateral flow (A), lesion length (B), multivessel disease (C), and reference luminal diameter (D) with the risk of no reflow.

since 1975,⁷⁹ is an enzyme found primarily in the cardiac muscle and skeletal muscle⁸⁰ and its elevation in serum is highly specific and sensitive for myocardial cell wall injury especially MI.⁸¹ However, the report concerning its role in vascular contractility is limited. CK enzyme is involved as an energy transducer in energy production and consumption.⁸² CK functionates as a channel for high-energy phosphoryl groups and lead to occur sequential phosphotransfers that responsible for transmission of adenosine triphosphate (ATP) from mitochondria to ATP-consuming sites. In ATP-consuming site, CK rapidly regenerates ATP from creatinephosphate. Therefore, CK may facilitate highly energy-demanding functions for vascular contractility⁸³ that may contribute for the development of no reflow.⁷⁸

We found that elevated heart rate was associated with the risk of no reflow. The data of this association is displayed in Fig. 4B. No study explains the direct correlation between heart rate and no reflow. We proposed that HF may bridge the association between heart rate and no reflow. Although decreased HR variability was correlated with increased sympathetic or decreased vagal tone, which might predispose to ventricular fibrillation.^{84,85} Recently, it has been known that higher heart rate above 70 beats per minute is known as an independent risk factor for the development of HF.⁸⁶⁻⁸⁹ Moreover, reducing heart rate is beneficial for clinical outcomes⁹⁰ and better survival of the patients with HF,⁹¹ and therefore Tavazzi⁹² suggested that heart rate can be considered as the target for medical intervention in HF patients. Based on forest plot in Fig. 4C, our findings suggested that low LVEF was proven to be associated with no reflow. The association between no reflow and LVEF has not been discussed previously. However, this mechanism is probably associated with HF. LVEF, a predictor of the outcome in patients with chronic HF,⁹³ is the percent decrease of left ventricle volume in end-systole compared with end-diastole.⁹⁴ The normal range of LVEF is more than 50%⁹⁵ or about 50–70%⁹⁶ and 50%–55% is commonly defined as having low-normal LVEF.⁹⁷ Low LVEF had been associated with survival of HF.⁹⁹ Therefore, low LVEF as the result of our findings reflected poor prognosis of HF that migh contribute to the development of no reflow.

In angiographic parameters as summarized in Figs. 6 and 7, our study demonstrated that lesion length and reference lumen diameter were associated with no reflow. There are several aspects that may explain these results. First, large vessels are able to accommodate large amounts of plaque lipid or thrombus. The larger the lesioned vessels are directly proportional to the slower the flow velocity, and the longer the target lesion reflects the larger amount of thrombus and plaque burden¹⁰⁰ This was supported by Goldstein et al.¹⁰¹ reported that the presence of multiple complex plaques was associated with a poor prognosis in MI patients. Second, longer lesion indicates the use of longer stent length. Hong et al.¹⁰² found that longer stent length was associated with plaque prolapse, and plaque prolapse had been proven to be associated with myonecrosis after stenting and no reflow.¹⁰³ This would explain the high risk for no reflow observed in our study.

Our angiographic findings also revealed that initial TIMI flow \leq 1, collateral flow, multivessel disease, and high thrombus burden had significant correlation with the risk of no reflow. Moreover, compared to other covariates, TIMI flow and thrombus burden were the most correlated coaviates for no reflow. It has been reported that no reflow with large infarct size was more frequent in

patients with high thrombus burden,¹⁰⁴ reduced TIMI flow and collateral flow.¹⁰⁵ Thrombus burden, collateral flow, and TIMI flow are interrelated, with the higher thrombus burden reflects the lower TIMI flow and collateral flow.¹⁰⁶ The basic mechanism of no reflow correlated with TIMI flow and thrombus burden is microvascular obstruction caused by the embolization of thrombus originating from unstable plaque during PCI.¹⁰⁵ A high thrombus burden was shown to be an independent predictor of distal embolization^{107,108} and had been associated with worse TIMI flow and collateral flow.¹⁰⁷ This was supported by Okamura et al.¹⁰⁹ who found multiple embolic particles using doppler guidewires in patients who underwent PCI. Embolization was reported causing about 50% obstruction of coronary capillaries results in an irreversible reduction of myocardial blood flow.¹¹⁰ Moreover, Skyschally et al.¹¹¹ also reported that distal coronary embolization was associated with severe regional contractile dysfunction in animal models.

Our results reported evidence-based data regarding no reflow risk factors. Based on these results, we recommend that every patient with STEMI should be evaluated for these factors. Therefore, the possibility of the no reflow occurrence may be anticipated. In addition, Cardiology Organizations are expected to review no reflow risk factors. Therefore, a standard recommendation to prevent no reflow may be enforced.

There were several limitations in the study. First, most studies included in this meta analysis were retrospective. Therefore, further studies included only RCT are needed to get the conclusion with the higher evidence level. Second, there was the possibility of a false negative finding due to the small samples size even combined. Thus, further studies with a larger sample size are required to investigate the better associations. Third, meta analysis is about testing the covariates that have been reported. Thus, we can not test other covariates that we consider to have the correlation with the risk of no reflow.

Model	Study name	Statistics for each study					Odds ratio and 95% Cl					Weight (Random)
A).		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,01	0,10	1,00	10,00	100,00	Relative weight
	Morishima et al 2000	1,923	0,663	5,580	1,203	0,229	1		-++-	- 1		5,21
	lwakura et al 2001	4,289	2,009	9,157	3,763	0,000			-			7,22
	Tanaka et al 2002	3,258	0,839	12,653	1,706	0,088				++		3,86
	Yip et al 2002	5,705	2,609	12,477	4,362	0,000			-			7,04
	lwakura et al 2003	3,753	1,351	10,429	2,536	0,011				+		5,46
	Kirma et al 2008	6,245	2,630	14,826	4,152	0,000			-			6,45
	Ndrepepa et al 2010	3,898	2,153	7,057	4,492	0,000						8,52
	Dong • Bao et al 2010	1,496	0,684	3,269	1,009	0,313				•		7,04
	Chen et al 2012	3,332	1,743	6,368	3,642	0,000			_	·		8,08
	Zhou et al 2014	5,278	1,841	15,129	3,096	0,002						5,28
	Mazhar et al 2016	1,896	1,296	2,773	3,295	0,001						10,25
	Cenko et al 2016	11,139	5,435	22,828	6,584	0,000						7,53
	Padmajan et al 2017	12,115	4,117	35,648	4,530	0,000						5,13
	Soeda et al 2017	4,310	1,117	16,628	2,121	0,034						3,88
	Liang et al 2017	2,522	1,484	4,284	3,420	0,001			-+	-		9,05
Random		3,829	2,769	5,294	8,122	0,000		I.		+		
Model	Study name	Statistics for each study						Odds ratio and 95% Cl				Weight (Random)
B).		Odds ratio	Lower limit	Upper limit	Z-Value	p·Value	0,01	0,10	1,00	10,00	100,00	Relative weight
	Dong - Bao et al 2010	5,085	2,378	10,870	4,195	0,000	1	1	- 1		1	13,84
	Chen et al 2012	5,037	2,317	10,949	4,081	0,000			-			13,58
	Zhou et al 2014	1,989	1,091	3,624	2,245	0,025				-		16,48
	Mazhar et al 2016	2,225	1,470	3,367	3,782	0,000			-+	-		19,74
	Balta et al 2016	2,873	2,002	4,123	5,728	0,000			-	-		20,64
	Padmajan et al 2017	11,044	5,124	23,804	6,130	0,000						13,71
	Soeda et al 2017	7,937	0,422	149,360	1,383	0,167				+		2,00
Random		3,686	2,390	5,684	5,901	0,000			-			

Fig. 7. Forest plot regarding the association between initial TIMI flow (A) and thrombus score (B) with the risk of no reflow.

5. Conclusion

In conclusion, of the 29 covariates, our meta analysis suggested that advanced age, male, family history of CAD, smoking, diabetes mellitus, hypertension, delayed reperfusion, killip class ≥ 2 , elevated blood gulcose, elevated creatinine, elevated peak CK, increased heart rate, decreased LVEF, collateral flow, lesion length, multivessel disease, reference luminal diameter, initial TIMI flow, and thrombus score were proven to be associated with the risk of no reflow. Our results may contribute to develop better understanding regarding the risk factors of no reflow.

Conflicts of interest

The author declared that there is no conflict of interest.

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