

Prognosis of Total Occlusion of Culprit Artery in Acute Non-ST Elevation Myocardial Infarction for Different Follow-Ups: A Systematic Review and Meta-Analysis

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Abstract: This systematic review aims to analyze the clinical prognosis of NSTEMI patients with total occlusion of culprit artery (TOCA) and non-TOCA across different follow-up periods. The literature search up to March 26, 2024, identified 11 observational studies. TOCA patients had significantly higher in-hospital mortality (OR = 2.43, 95% CI [1.73–3.40]; $p < 0.00001$). TOCA also had higher MACE rates in all follow-up periods: in-hospital (OR = 1.58, 95% CI [1.11–2.24]; $p = 0.01$), short-term (OR = 1.86, 95% CI [1.57–2.20]; $I^2 = 0$; $P < 0.00001$), and long-term (OR = 1.55, 95% CI [1.05–2.28]; $I^2 = 74$; $p = 0.03$). Additionally, TOCA was linked to higher recurrent MI rates in short-term (OR = 1.53, 95% CI [1.13–2.09]; $I^2 = 25$; $p = 0.007$) and long-term follow-up (OR = 1.67, 95% CI [1.07–2.60]; $I^2 = 41$; $p = 0.02$). Despite worse prognosis for TOCA patients, further randomized controlled trials are needed for definitive conclusions.

1. Introduction

Non-ST-segment elevation myocardial infarction (NSTEMI) is one of the spectrums of acute coronary syndrome (ACS) and is a significant cause of mortality and morbidity in recent years[1, 2]. Despite the presence of a culprit artery total occlusion, these NSTEMI patients often undergo delayed revascularization due to atypical electrocardiographic findings[3, 4]. Therefore, in order to optimize the management of NSTEMI patients with TOCA, it is crucial to assess the clinical prognosis of such patients at different follow-up times.

In NSTEMI with TOCA, the myocardium in the ischemic area is actually at extreme risk, so a delayed intervention may have irreversible effects on the patient's prognosis[5]. Previous studies have demonstrated that NSTEMI patients with TOCA have a significantly increased risk of major cardiovascular events (MACE) in both the short- and long-term[3, 6-8]. Some researchers believe that NSTEMI patients with complete coronary occlusion should be treated according to the process for acute ST-segment elevation myocardial infarction (STEMI)[9, 10]. However, other researchers

believe that this is just a special type of NSTEMI patient, and their treatment process only needs to be supplemented based on existing guidelines[11]. In any case, the clinical prognosis of NSTEMI patients with TOCA is worthy of further exploration.

To our knowledge, no comprehensive data reports multiple follow-up periods for NSTEMI with TOCA. This study aims to evaluate clinical outcomes of NSTEMI with TOCA in in-hospital, short-term, and long-term periods via meta-analysis. We present this article in accordance with the PRISMA 2020 statement[12]. This study was registered with PROSPERO (CRD42024540575).

2. Methods

2.1 Eligibility criteria

Studies included in the analysis were prospective or retrospective cohorts. The inclusion criteria for this meta-analysis were (1) adults (≥ 18 years); (2) patients with NSTEMI and either totally or non-totally occluded culprit artery; (3) studies comparing clinical characteristics and outcomes during follow-up (in-hospital, short-term < 1 year, long-term ≥ 1 year).

The exclusion criteria were (1) meta-analyses; (2) reviews; (3) case reports; (4) animal studies; (5) meeting abstracts; (6) letters; (7) dissertations; (8) non-journal articles; (9) editorial material; (10) cross-sectional studies; (11) RCTs; (12) off-topic studies; (13) duplicate reports; (14) studies on patients with STEMI or NSTEMI-ACS; (15) studies lacking specified clinical characteristics, outcomes, or follow-up lengths.

2.2 Literature search and study selection

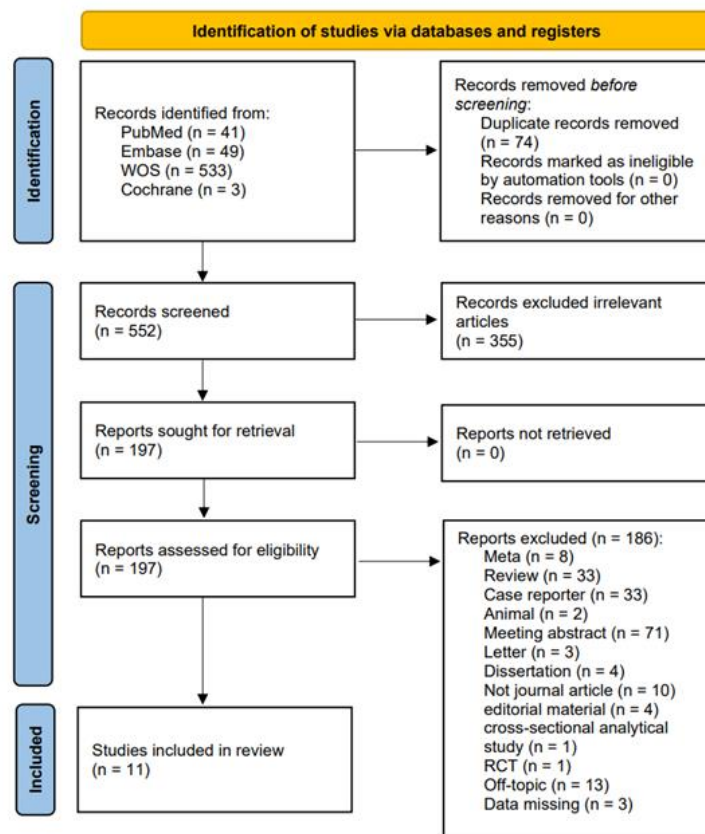


Figure 1 PRISMA flow diagram for article selection for meta-analysis

We conducted a comprehensive literature search across PubMed, EMBASE, Web of Science, and Cochrane Library until March 26, 2024, using terms including "non-ST elevated myocardial infarction," "coronary occlusion," and "prognosis," supplemented by manual reference list screening. Two reviewers (T.T.C. and H.Y.) independently performed the data collection included population of interest, study and patient characteristics, and relevant outcomes. The patient characteristics of studies embraced number of patients, whether coronary arteries are occluded (TOCA vs. non-TOCA) and follow-up periods, with disagreements resolved by a third reviewer (Y.S.). Outcomes assessed included death, major adverse cardiovascular events (MACE), target vessel revascularization (TVR) and recurrent myocardial infarction (MI) for different follow-ups. Subgroups were made for different follow-up lengths including in-hospital follow-up, short-term (<1 year) follow-up, and long-term (≥ 1 years) follow-up. The selection process is detailed in Figure 1.

2.3 Study risk of bias assessment

The quality of included studies was assessed by two authors (Y.S and T.W) using the Newcastle-Ottawa Scale tool [13]. The scale evaluates studies based on three areas: selection of study groups, comparability among groups, and outcome assessment between groups. Studies with ≥ 30 days follow-up were considered sufficient for outcome assessment. Quality was graded as low risk, high risk, or unclear risk if information was unavailable. Studies with an NOS scale ≥ 7 were high quality, while those with < 5 points were low quality.

2.4 Statistical analysis and synthesis methods

Forest plots were constructed to visually assess the pooled results, presented as odds ratios (OR) with 95% confidence intervals. The random-effects method was used for its conservative summary estimate. Heterogeneity was qualitatively analyzed using the chi-squared test and quantified by I^2 . If significant heterogeneity was present ($I^2 > 50$), sensitivity analysis by sequentially excluding studies was conducted to identify the source. Publication bias was assessed using a funnel plot combined with Egger regression, and if bias was detected, the trim and fill method was applied to evaluate result reliability. All analyses were performed using Review Manager (v5.4.1), with two-sided p values below 0.05 considered statistically significant.

3. Results

3.1 Study selection

From the 626 studies identified in our retrieval, 74 duplicates were removed and 197 titles and abstracts were screened for eligibility. Finally, 11 articles were included in the data quality assessment and data analysis [4, 6, 10, 14-21].

3.2 Study characteristics

All 11 studies included a total of 51,638 patients, of which 11,800 (22.9%) had TOCA, while 39,838 (77.1%) had non-TOCA. Most patients were male, with an average age of 64 years. In the TOCA group, 50%-79.41% of patients had hypertension, 20.33%-41.0% had diabetes, 7.2%-63% had hyperlipidemia, and 23.52%-56.4% were current smokers. Except for the study by Dixon and Soon et al., all studies had comparable research populations in terms of age, gender, and other comorbidities, and the study characteristics are summarized in Table 1.

Table 1: Baseline characteristics of patients in the included studies

Author	Mean Age, n (%)		Male, n (%)		Hypertension, n (%)		Diabetes mellitus, n (%)		Dyslipidemia, n (%)		Current smoking, n (%)	
	TOCA	non-TOCA	TOCA	non-TOCA	TOCA	non-TOCA	TOCA	non-TOCA	TOCA	non-TOCA	TOCA	non-TOCA
Soon, 2014	NA	NA	NA	NA	27 (79.41)	67 (61.47)	13 (38.24)	27 (24.77)	NA	NA	8 (23.52)	37 (33.94)
Shin, 2014	63.00±12.90	66.10±11.70	767 (71.7)	1,186 (65.6)	543 (50.7)	1,040 (57.5)	329 (30.7)	660 (36.5)	161 (15.0)	268 (14.8)	406 (37.9)	544 (30.1)
Dixon, 2008	58.00	73.00	NA	NA	60	69	22	28	NA	NA	NA	NA
Bahrman, 2011	67.00±12.00	67.00±12.00	90 (69)	211 (66)	105 (81)	263 (83)	53 (41)	116 (37)	58 (45)	120 (38)	41 (32)	84 (26)
Kim, 2012	62.39±12.20	62.84±12.10	462 (69.5)	1005 (70.4)	321 (48.5)	757 (53.0)	167 (25.2)	427 (29.9)	100 (15.1)	172 (12.1)	395 (59.5)	805 (56.5)
Karwowski, 2016	62.60±11.80	65.20±11.10	485 (66.62)	1302 (64.35)	477 (65.52)	1500 (73.57)	148 (20.33)	538 (26.39)	277 (38.05)	856 (41.98)	222 (30.49)	521 (25.55)
Jung, 2008	61.10±13.30	64.20±11.30	42 (67.74)	81 (56.64)	31 (50.0)	91 (63.6)	17 (27.4)	55 (38.5)	18 (29.0)	43 (30.1)	34 (54.8)	74 (51.7)
Wang, 2022	64.40±10.40	61.40±11.40	NA	NA	196 (64.5)	1098 (55.8)	80 (26.3)	432 (22.0)	22 (7.2)	183 (9.3)	119 (39.5)	873 (44.7)
Guner, 2023	55.62±11.34	57.25±11.66	398 (81.6)	1758 (63.1)	286 (58.6)	1510 (54.2)	126 (25.8)	654 (23.5)	172 (35.2)	982 (35.3)	188 (38.7)	1226 (44.1)
Fernando, 2021	61.00±12.00	65.00±12.00	755 (79)	4357 (74)	565 (59)	3921 (67)	206 (22)	1550 (26)	604 (63)	3930 (67)	319 (34)	1663 (29)
Hwang, 2018	62.10±13.20	65.20±12.60	51 (65.3)	185 (69.2)	41 (52.5)	168 (62.9)	22 (28.2)	95 (35.5)	14 (17.9)	43 (16.1)	44 (56.4)	159 (59.5)

3.3 Risk of bias and subgroup analysis

The methodological quality for each included study and the overall summary of the analysis are shown in Figure 2. The study by Doxin and colleagues[15] was defined as high risk due to the lack of specific numeric values for reported outcome events. Subgroup analysis was performed based on different follow-up times (in-hospital, short-term, and long-term), with TVR lacking in-hospital follow-up events. After conducting sensitivity analysis on studies with $I^2 > 50$, funnel plots in combination with Egger's regression were used to evaluate publication bias. No evidence of publication bias was found ($p = 0.998$ for Egger's regression test).

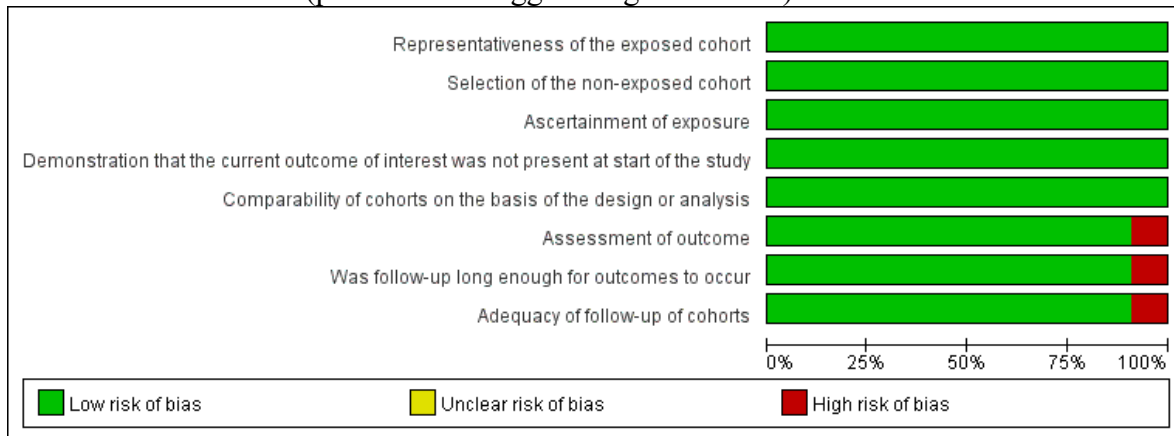


Figure 2 Risk of bias graph: Quality Assessment using NewCastle-Ottawa Scale Tool

4. Results of meta-analysis

4.1 Death

Among the 11 selected studies, 9 studies with data from 20,764 patients reported death rate outcomes. Our pooled analysis in Figure 3 shows no significant difference in death rates between

NSTEMI patients with TOCA and those with non-TOCA during short-term (OR = 1.44, 95% CI [0.86–2.39]; $I^2 = 76$; $p = 0.16$) and long-term follow-up (OR = 1.24, 95% CI [0.81–1.89]; $I^2 = 87$; $p = 0.33$). However, significantly higher death rates were observed in the in-hospital period for TOCA compared to non-TOCA (OR = 2.43, 95% CI [1.73–3.40]; $I^2 = 0$; $p < 0.00001$).

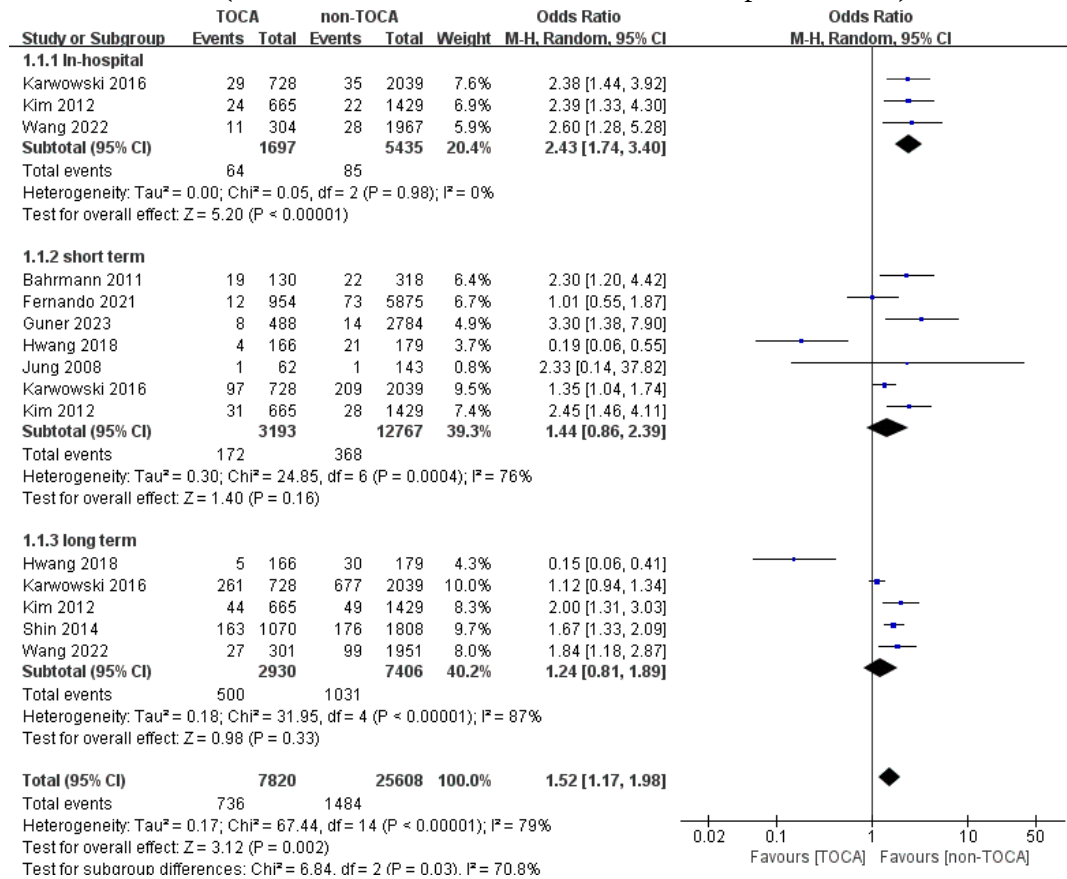


Figure 3 Forest plot of Death outcome in TOCA versus non-TOCA for NSTEMI for varying follow-up lengths

4.2 MACE

Among the studies, MACE was defined as death, target vessel revascularization, and recurrent myocardial infarction. Our meta-analysis in Figure 4 shows TOCA had significantly higher MACE rates than non-TOCA in all follow-up periods: in-hospital (OR = 1.58, 95% CI [1.11–2.24], $p = 0.01$), short-term (OR = 1.86, 95% CI [1.57–2.20], $I^2 = 0$, $p < 0.00001$), and long-term (OR = 1.55, 95% CI [1.05–2.28], $I^2 = 74$, $p = 0.03$).

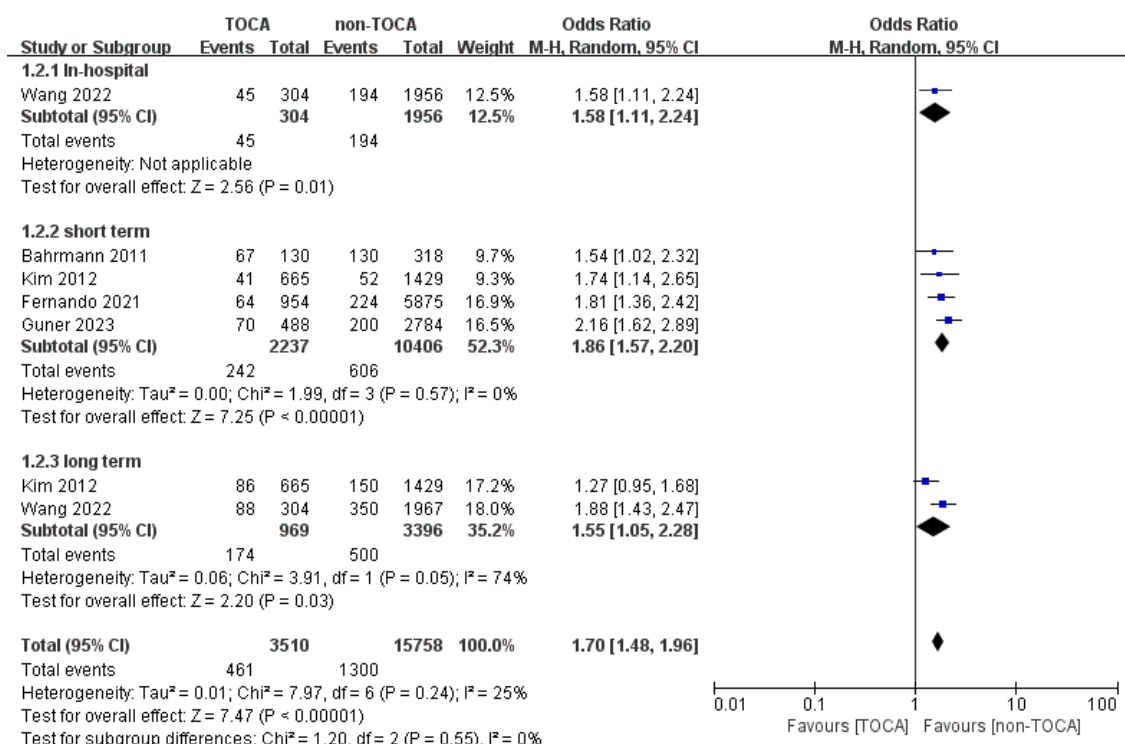


Figure 4 Forest plot of MACE outcome in TOCA versus non-TOCA for NSTEMI for varying follow-up lengths

4.3 TVR

Among the 11 studies, 5 studies with data from 17,310 patients reported TVR outcomes. Our pooled analysis in Figure 5 shows no significant difference in TVR rates between TOCA and non-TOCA during short-term (OR = 2.06, 95% CI [0.97–4.38], I² = 86, p = 0.06) and long-term follow-up (OR = 1.30, 95% CI [0.63–2.71], I² = 90, p = 0.48).

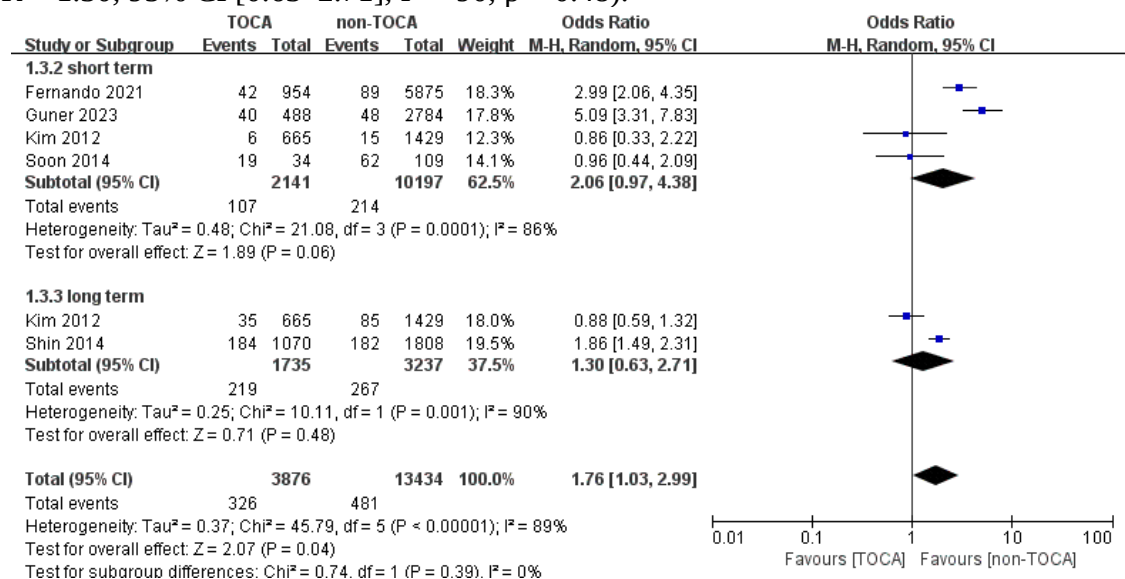


Figure 5 Forest plot of TVR outcome in TOCA versus non-TOCA for NSTEMI for varying follow-up lengths

4.4 Recurrent MI

Among the 11 studies, 8 studies with data from 17,337 patients reported recurrent MI outcomes. Sensitivity analysis identified Hwang's study [20] as the source of heterogeneity, reducing I^2 from 81% to 41% upon exclusion. Our pooled analysis (Figure 6) shows no significant difference in recurrent MI rates between TOCA and non-TOCA during the in-hospital period (OR = 0.58, 95% CI [0.08–4.55], $p = 0.61$). However, TOCA had significantly higher recurrent MI rates in short-term (OR = 1.53, 95% CI [1.13–2.09], $I^2 = 25$, $p = 0.007$) and long-term follow-up (OR = 1.67, 95% CI [1.07–2.60], $I^2 = 41$, $p = 0.02$).

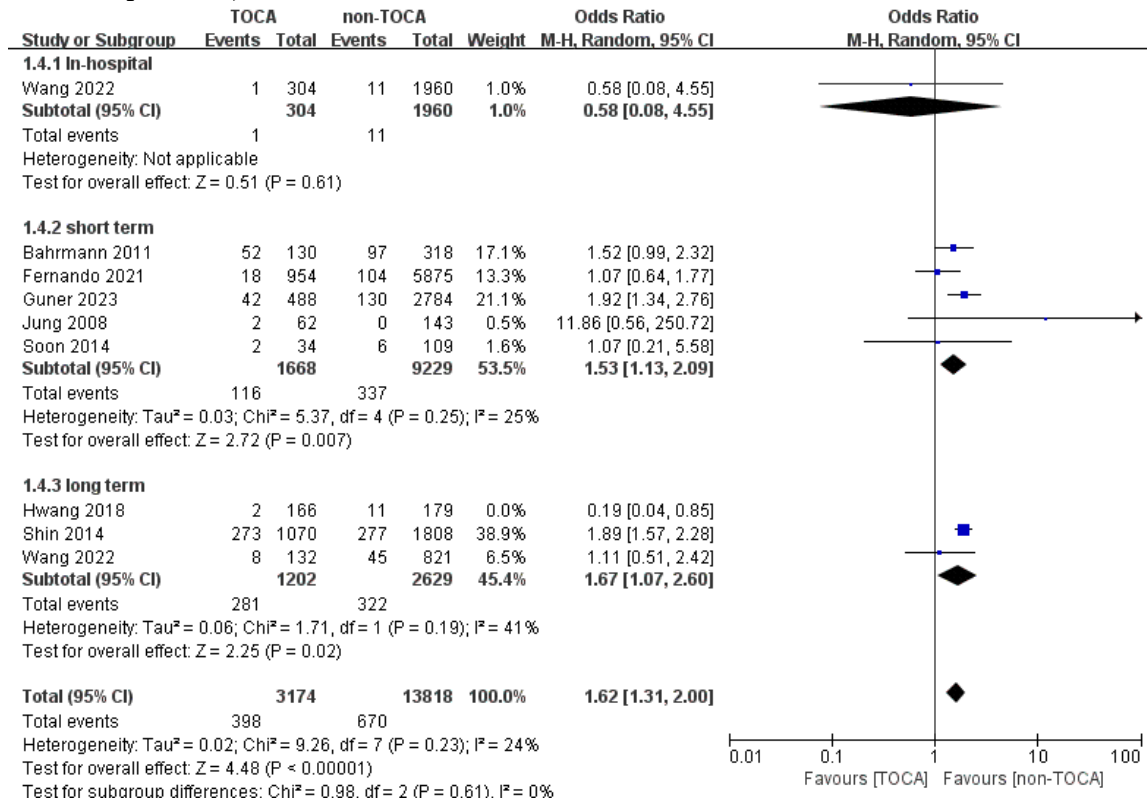


Figure 6 Forest plot of recurrent MI outcome in TOCA versus non-TOCA for NSTEMI for varying follow-up lengths

5. Discussion

Our systematic review and meta-analysis results provide strong evidence demonstrating that NSTEMI patients with TOCA may represent a higher risk group, as their risk of MACE during in-hospital, short-term, and long-term periods is increased, consistent with previous research findings[3, 7, 22, 23]. We included many observational studies with longer follow-up times in our study to address any discrepancies and overcome limitations in the literature, enhancing the generalizability and reliability of our results. To our knowledge, our meta-analysis included 11 observational studies with 51,638 patients, marking the first meta-analysis on different follow-up times for this disease, providing data on adverse outcomes during in-hospital, short-term, and long-term follow-up. Most previous meta-analyses on this topic only included prognostic studies, but our study, utilizing different follow-up times, offers a more accurate representation of clinical outcomes.

Our subgroup analysis revealed that compared to NSTEMI with non-TOCA patients, TOCA groups were associated with a higher in-hospital death rate and MACE events. However, there was

no significant difference in death rates during short-term or long-term follow-up (≥ 1 year). The results indicated that in short-term and long-term follow-up, non-TOCA groups had better outcomes in terms of MACE events and recurrent myocardial infarction compared to TOCA groups. However, there was no significant difference in in-hospital recurrent MI rates between TOCA groups and non-TOCA groups. There were no significant differences in TVR during the follow-up period for patients with either TOCA or non-TOCA groups.

Previous studies have confirmed that NSTEMI patients with TOCA have a significantly increased risk of MACE, death, recurrent MI, and cardiogenic shock compared to NSTEMI patients without complete occlusion of coronary vessels[3, 6-9, 11]. This may be related to the limitations in NSTEMI patients with MVD, including poorer electrocardiogram sensitivity[24-27], spontaneous thrombolysis[3, 28], collateral circulation formation[3, 11, 16, 29], delayed presentation[9], and smaller infarction area[9, 16], which result in patients with TOCA not receiving timely and necessary treatment. The findings of this study are highly consistent with two recent meta-analyses in assessing the prognosis of NSTEMI patients with TOCA[3, 9]. However, prior to angiography, there remains a lack of superior risk stratification tools to identify such high-risk ACS patients, thus hindering the implementation of more targeted therapies to improve the clinical outcomes of such patients. Considering the large number of NSTEMI patients worldwide[30], it is imperative to explore methods for identifying NSTEMI patients with TOCA.

This systematic review used rigorous methodology but has limitations. The included studies were observational cohorts, which may introduce bias and limit causal inference strength. The observational design doesn't establish causation, making our analysis hypothesis-generating. Additionally, we didn't summarize differences in biological indicators, number of occluded vessels, procedure types, or PCI timing, affecting result generalizability. It has been shown that high levels of creatine kinase isoenzyme (CK-MB), generally considered to be more than five times the upper limit, are a risk factor for complete coronary artery occlusion[5]. Finally, We didn't consider concurrent medical therapies, like antithrombotic drugs, that could affect the results, adding to result variability.

In conclusion, our analysis showed that TOCA in NSTEMI is linked to higher MACE rates and poorer in-hospital, short-term, and long-term outcomes. These patients also have increased recurrent MI rates in short-term and long-term follow-ups, as well as higher in-hospital death rates. However, there's no significant difference in TVR during follow-up, regardless of TOCA or non-TOCA status. A well-designed RCT is needed before definitive conclusions and management plans for TOCA in NSTEMI can be made.

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