The Impact of SYNTAX Score on Long term All-Cause Mortality and Late MACCE of Coronary Artery Bypass Grafting and Percutaneous Coronary Intervention for Left Main Coronary Artery Disease: A Systematic Review and Meta Analysis of Cohort Studies

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ABSTRACT

Background: Coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) are the best revascularization methods for patients with left main coronary artery disease (LMCAD). The SYNTAX score has been recommended for selecting revascularization methods. However, CABG is the standard for complex lesions measured by SYNTAX score at baseline.

Methods: This systematic review and meta-analysis used all studies on the different impacts of SYNTAX score with long-term all-cause mortality and late MACCE on patients with PCI and CABG for LMCAD. This search yielded 1,675 studies, of which 4 studies were included for the final analysis. In these studies, 4,490 patients were treated with PCI and CABG.

Results: A total of four studies were included and analyzed. The results shown that, there was a significantly higher difference in the long term all-cause mortality with high SYNTAX score of PCI compared to CABG (HR: 1.44; 95% CI: 1.16-1.79; p=0.0010) and not significant in low to intermediate SYNTAX (HR:0.94; 95% CI: 0.73-1.21, p=0.63). The pooled analysis showed that there was no significant difference in long term late MACCE in high and low to intermediate SYNTAX score (HR: 1.37; 95% CI: 0.94-1.98; p=0.10 and HR: 1.04; 95% CI: 0.85-1.28; p=0.69, respectively).

Conclusion: Among LMCAD patients, CABG is associated with a lower risk of causing long-term all-cause mortality than PCI with a high SYNTAX score. Meanwhile, the outcomes of MACCE in any SYNTAX score are not significantly different between CABG and PCI.

Keywords : Syntax Score, CABG, PCI, LMCAD, Mortality, and MACCE

BACKGROUND

Coronary artery disease (CAD) is a term for a prevalent cardiovascular disorder characterized by decreasing blood flow to the heart caused by the narrowing or blockage of coronary arteries [1]. Left main coronary artery disease (LMCAD) refers to the involvement of the left main coronary artery, which is a critical artery supplying a significant portion of the heart [2]. LMCAD can be treated by either one of these two primary revascularization procedures which are coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). The SYNTAX Score, developed by the SYNTAX Study Group, is a tool that quantifies the complexity and extent of CAD, providing a comprehensive evaluation of the CAD severity [3] The choice between CABG and PCI for patients with LMCAD remains a challenging decision for clinicians [3]. Although both procedures have shown efficacy in improving clinical outcomes, it is essential to identify factors that can guide treatment decisions and predict long-term outcomes. The SYNTAX score helps practitioner in making a decision by considering the complexity and anatomical

extent of coronary lesions, therefore it is considered as a promising prognostic tool. However, a comprehensive review of existing cohort studies is required to assess the correlation between SYNTAX Score and long-term all-cause mortality, as well as major adverse cardiovascular and cerebrovascular events (MACCE), in the context of CABG and PCI for treating LMCAD. This meta-analysis aims to synthesize the results of cohort studies investigating the impact of SYNTAX Score on long-term all-cause mortality and late MACCE in LMCAD patients undergoing CABG and PCI. The results found in this meta-analysis will present valuable insights into the prognostic value of SYNTAX Score in LMCAD patients receiving revascularization procedures.

METHODS
The current investigation followed the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020[4]. No ethical approval was conducted as the used data had been published in the former studies and no patients were directly participated.The review protocol had been registered in Prospero (CRD42023434626).

Eligibility
A systematic searching on cohort studies was performed. Studies reporting patient managed without considering the SYNTAX scorewere excluded. There were no restrictions on the publication year. Furthermore, studies conducted in languages other than English, studies without full text availability, and studies involving nonhuman subjects were also omitted.The duplication of articles was addressed prior to the commencement of the title and abstract screening process.

Search Strategy and Selection of Studies
Comprehensive systematic database search was conducted in PubMed and ScienceDirect independentlyby two authors on June 05, 2023. The keywords were derived from "SYNTAX Score" AND "PCI" AND "CABG" AND "mortality" AND "MACCE", in addition to their corresponding MeSH terms, synonyms, and further explanation. Review articles were excluded,though the references would be screened for potentially missed relevant studies.A preliminary assessment was conducted on the titles and abstracts of the articles to identify any that might qualify as eligible prior to the full-text review.

Article Extraction
The pertinent scholarly articles were extracted autonomously utilizing a methodical and standardized format. Author, publication year, country, sample size, age, gender, medical history, duration of follow-up, study design, revascularization method, syntax score, all-cause mortality, and late MACCE were extracted as data. General consensus was reached by all authors regarding any inconsistencies that arose during the data extraction procedure.

Quality Assessment
A minimum of two authors working independently would carry out the assessment of risk of bias.Disputes would be resolved through dialogue involving the senior author. The Newcastle Ottawa Scale would be employed as the assessment instrument for the cohort study.

Statistical Analysis
All data were analyzed utilizing version 5.4 of the Statistical Analysis Review-Manager (RevMan) software developed by the Cochrane Collaboration. The synthesised HRs with 95% CIs were employed to assess the late MACCE and long-term all-cause mortality of LMCAD patients.Pooled HRs were calculated by log hazard ratio (ln(HR)) and standard error (SE) for each study using reported HRs and CIs.For studies with low, intermediate, and high syntax score classifications, we combined the HRs of the low (as HR1) and intermediate (as HR2) classifications using the Mantel-Haenzsel method. We calculated the natural logarithm (ln) of each HR and its confidence interval.HR weights were determined based on the inverse variance method. Then the weighted sum of ln(HR) was calculated using the formula: Weighted sum = (HR1 * ln(HR1)) + (HR2 * ln(HR2)). And the calculation of the weighted sum of ln(Lower CI) and ln(Upper CI) used the formula: Weighted sum Lower CI = (HR1 * ln(Lower CI1) weights) + (HR2 * ln(Lower CI2) weights); Weighted sum Upper CI = (Weight HR1 * ln(Upper CI1)) + (Weight HR2 * ln(Upper CI2)). Combined HR and CI were obtained by using the exponential of the previously calculated weighted sum.The heterogeneity within the included literature was evaluated using Higgins I2 statistics and Cochran's Q. In cases where the heterogeneity was not statistically significant (I2<50% and P>0.1), a fixed-effects model was employed. However, if the heterogeneity was found to be significant, a random-

effects model was utilized.In addition to visible plots, Begg's test was utilized to determine the likelihood of publication bias.

RESULTS

Search Findings and Characteristics of the Study

An initial 1675 articles were found according to the used keywords. Complete eligibility assessment yielded four matched articles for further qualitative and quantitative analysis (Figure 1). The included studies were performed with a cohort design. Table 1 presents a comprehensive overview of the characteristics of the studies that were included in the analysis. A total of 4490 patients, all of whom were above the age of 18, were selected from various articles without any restrictions on the publication year. All studies were published within the last 10 years. All of these patients were measured for syntax score preoperatively and followed up after 5 – 10 years. Only Morice et al did not mention any details about participants risk factors. Meanwhile, in other studies, risk factors were included, such as hypertension, type 2 diabetes mellitus, dyslipidemia, and smoking history.
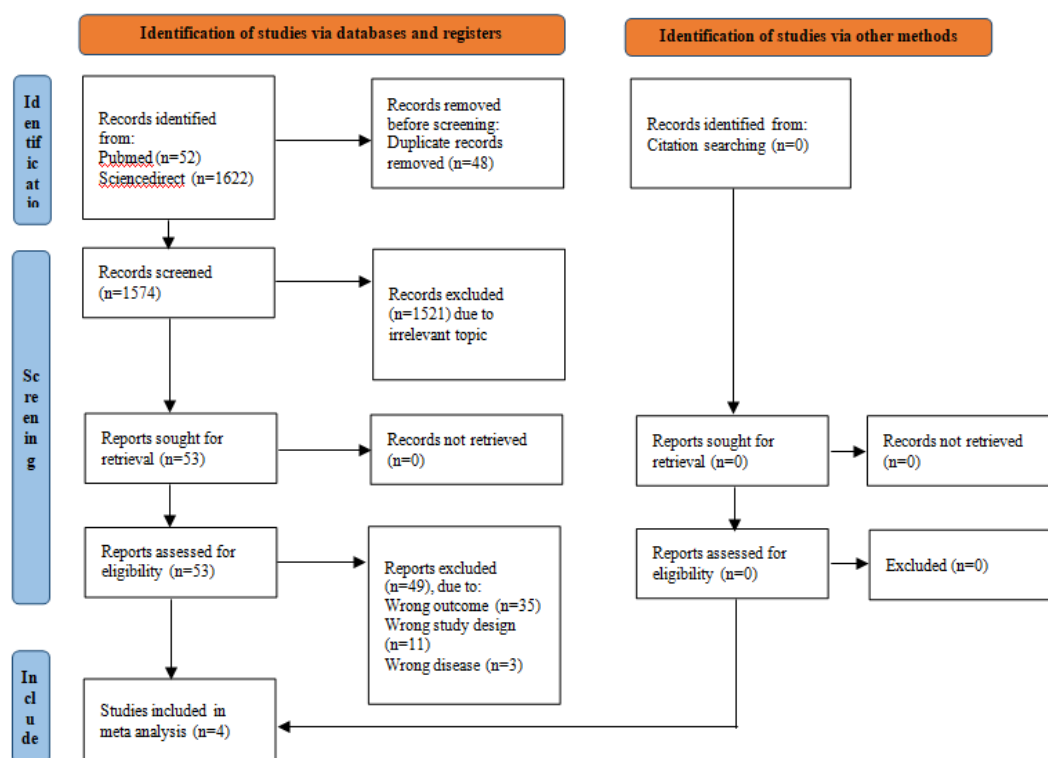

Table 1. Study characteristics of included studies

Authors/Year of Publication	Country	Population (n)		Age (years)	Males (%)	HT (%)	Ds (%)	Cs (%)	DM (%)	Follow up periods
		PCI	CABG							
Morice et al, 2014	17 countries (MCS)	346	322	NA	NA	NA	NA	NA	NA	5 years
Yoon et al, 2019	Korea	819	761	60.3±16.3	71.51	50.44	34.24	37.61	32.27	10 years
Lee et al, 2021	Korea	291	275	59.8±16	76.5	51.7	41.5	28.9	NA	10 years
Mohr et al, 2023	USA and Europe	871	805	65.1	83.41	NA	NA	NA	26.96	5 years

MCS: multi center study, NA: Not Avalaible, HT: hypertension, Ds: dyslipidemia, Cs: current smoker, DM: diabetes mellitus

Risk of Bias Among the Included Studies

The Newcastle-Ottawa Scale (NOS) criteria were used to evaluate the quality of the study. In terms of selection, all included studies indicated a valid selection process, as the populations of the studies were sufficientlyrepresentative of the impact of SYNTAX Score on long-term all-cause mortality and late MACCE in patients undergoing CABG and PCI for LMCAD. In addition, good comparative and exposure aspects were observed, with adequate follow-up duration and fairly low dropout rates. Based on the final assessment, all included studies had a mean NOS score above7,indicating exceptional quality.

Long Term All-Cause Mortality

Four studies consisted of 4490 populations were examined for long-term all-cause mortality in high and low to moderate SYNTAX scores. There was a significantly higher difference in the long term all-cause mortality with high SYNTAX score of PCI compared to CABG (HR: 1.44; 95% CI: 1.16-1.79; p=0.0010) as depicted in Figure 2.Fixed effects models were used for meta-analysis, as a result of low heterogeneity between studies (p=0.60).Meanwhile, the pooled analysis found that long term all-cause mortality in patients with low to intermediate SYNTAX of PCI compared to CABG were not significant (HR:0.94; 95% CI: 0.73-1.21, p=0.63) as depicted in Figure 3.Fixed effects models were used for meta-analysis, as a result of low heterogeneity between studies (p=0.53).
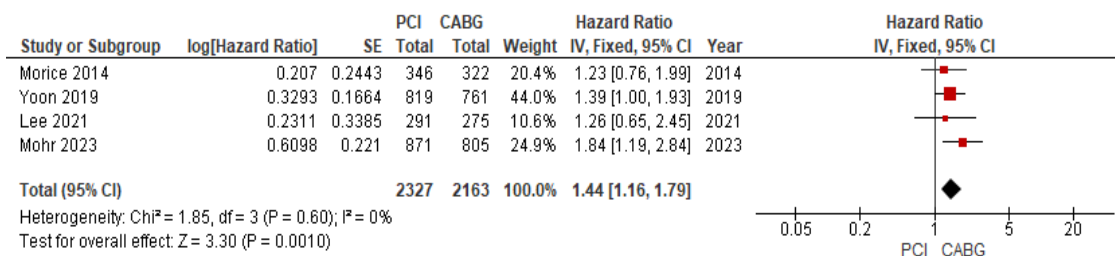

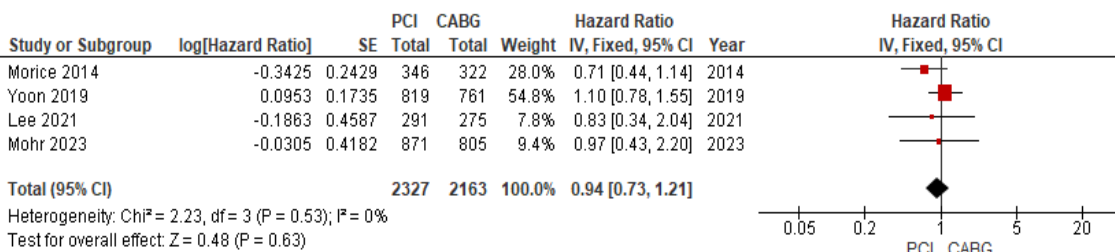**Figure 2.** Forest plot pooled for long term all-cause mortality in high SYNTAX Score

Figure 3. Forest plot pooled for long term all-cause mortality in low to intermediate SYNTAX Score

Long Term Late MACCE

Meta analysis of hazard ratios in long term late MACCE between the PCI and CABG groups was performed in four included studies. The pooled analysis showed that there was no significant difference in long term late MACCE in high SYNTAX (HR: 1.37; 95% CI: 0.94-1.98; p=0.10) as depicted in Figure 4. A random-effect model was used for this outcome, as the heterogeneity between studies was found to be high (p = 0.006). Meanwhile, the pooled analysis found that long term late MACCE in patients with low to intermediate SYNTAX score were not significant (HR: 1.04; 95% CI: 0.85-1.28; p=0.69) as depicted in Figure 5.Fixed effects models were used for meta-analysis, as a result of low heterogeneity between studies (p=0.10).
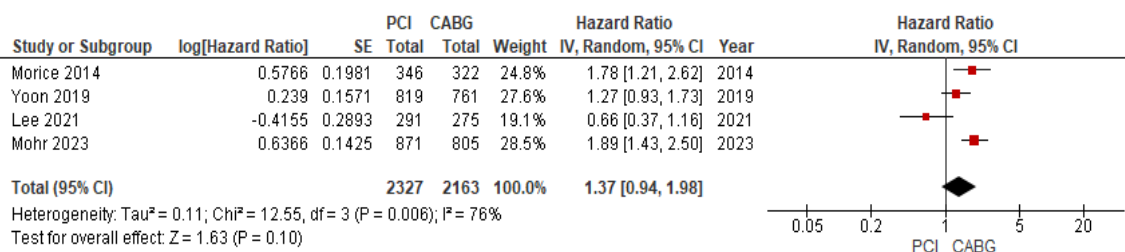

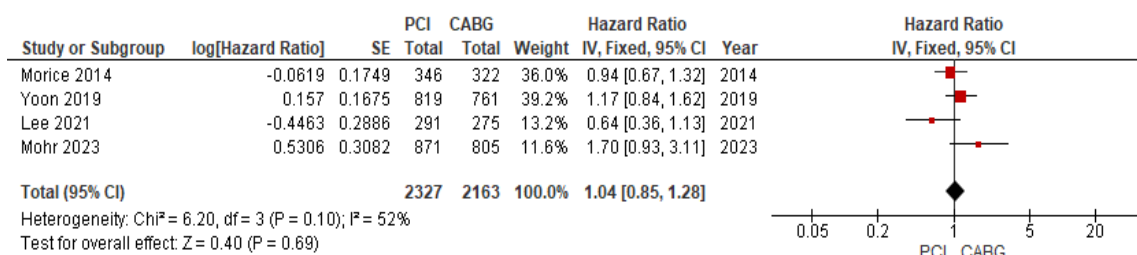**Figure 4.** Forest plot pooled for late MACCE in high SYNTAX Score

Figure 5. Forest plot pooled for late MACCE in low to intermediate SYNTAX Score

DISCUSSION

Due to the wide territory of the left main coronary artery which supplies 75-100% of the myocardium, LMCAD poses a poor prognostic value. The decision on revascularization methods has always been an issue of concern among physicians[5]. Current ESC/EACTS guidelines make the use of SYNTAX score in the decision-making process of revascularization therapy[6]. This meta-analysis aims to further compare the long-term all-cause mortality and MACCE outcomes of LMCAD with low to intermediate, or high SYNTAX scores following CABG versus PCI.

Pooled analysis from this study showed that the long-term all-cause mortality in high SYNTAX score is significantly higher following PCI than CABG (HR: 1.44; 95% CI: 1.16-1.79; p=0.0010), although no significant difference is found between low to intermediate SYNTAX score following PCI and CABG. One systematic review and meta-analysis showed similar results. Mortality is said to be significantly lower in patients with low SYNTAX scores following PCI compared to high SYNTAX scores (20% versus 49.2% for mortality), as well as following CABG with low SYNTAX scores (10.0% versus 15.9%). The study, also states that the all-cause mortality from a low SYNTAX score following PCI is comparable to that of a high SYNTAX score following CABG[7].

The SYNTAX trial supports these findings due to its results which concluded that CABG should be the chosen standard of care because of its lower rates of complications, and also because PCI has a higher rate of repeated revascularization in 1 year[8]. From past studies, CABG is acknowledged to be generally safer than PCI, especially in a geriatric population where more comorbidities may affect the effectiveness of stenting[9]. However, more recent studies show that PCI has a comparable mortality outcome to CABG. However these differences could be due to different complexity of lesions in the CABG population, some research not considering patient's SYNTAX score, and further advances in PCI[10].

Long-term late MACCE outcomes from this study were not significantly different between high SYNTAX score following PCI versus CABG (HR: 1.37; 95% CI: 0.94-1.98; p=0.10), so is in low to intermediate SYNTAX score following PCI versus CABG (HR: 1.04; 95% CI: 0.85-1.28; p=0.69). Other studies showed contrasting results, in which patients with LMCAD and three-vessel disease with low to high and intermediate to high SYNTAX scores, respectively, had significantly lower MACCE rates following CABG than PCI[11,12]. One study also found that the outcome of a major adverse coronary event (MACE) is significantly higher in LMCAD with a high SYNTAX subgroup following PCI[13].

The difference in outcomes between this study and previous research may be due to the incomplete information on baseline comorbidities provided by some of the included cohort studies. It has been suggested that diabetes increases the risk of MACCE in patients post-PCI, and better outcomes are associated with CABG rather than PCI[14,15]. So those without clear findings of diabetes comorbidity or other types of comorbidities might affect the result.

CONCLUSIONS

This meta-analysis of existing cohort studies on the impact of SYNTAX score on long-term all-cause mortality and long-term MACCE in patients with LMCAD following PCI or CABG shows that CABG has a lower risk in causing long-term all-cause mortality than PCI in those with high SYNTAX score, but the outcomes of MACCE in any syntax scoreare not significantly different between CABG and PCI.

It is worth noting that most of the study participants are male, so this study might not be too representative of the female population, therefore it is ideal if future research analyze the outcomes in women. Furthermore, additional meta-analysis of cohort studies is needed to compare the outcomes of PCI and CABG on other short-term and long-term end results.

List of Abbreviations

CABG	Coronary Artery Bypass Grafting
PCI	Percutaneous Coronary Intervention
LMCAD	Left Main Coronary Artery Disease

MACCE	Major Adverse Cardiovascular and Cerebrovascular Events
CAD	Coronary Artery Disease
REVMAN	Review Manager
NOS	The Newcastle-Ottawa Scale

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Conflict of Interest

None

Author Contributions

FM, CFA, VLP, ATH, AFM conceptualized and wrote thedraft. FM, CFA analyzed the data and validated the results. SF, KAS were responsible for reviewing the final draft. FM, CFA submitted the manuscript All authors read and approved the final manuscript.

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Availability of Data and Materials

Authors declare availability of data used in the study

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