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Prognostic value of the monocyte-to-high-density lipoprotein-cholesterol ratio in acute coronary syndrome patients: A systematic review and meta-analysis

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WHAT'S NEW?

Recent studies suggest the monocyte-to-high-density lipoprotein-cholesterol ratio as an effective predictor of major adverse cardiovascular events following acute coronary syndrome. Our study revealed that the higher monocyte-to-high-density lipoprotein-cholesterol values are associated with increased risks of in-hospital and long-term mortality and major adverse cardiovascular events, offering a potential tool for improved cardiovascular risk assessment and patient management.

ABSTRACT

Background: Globally, diseases of the cardiovascular system stand as the principal contributors to mortality and are anticipated to show an upward trajectory. The occurrence of acute coronary syndrome (ACS) has been linked to underlying inflammatory processes. The monocyte-to-high-density lipoprotein-cholesterol ratio (MHR) has garnered significant attention as a prognostic biomarker, encapsulating the synergistic roles of inflammation and lipid metabolism in the pathophysiology of cardiovascular diseases, including ACS.

Aims: This meta-analysis examines the prognostic MHR ratio in ACS patients.

Methods: We systematically searched PubMed, Embase, Scopus, Web of Science, and the Cochrane Library databases to identify the relevant meta-analyses up to February 26, 2024. The findings were aggregated into risk ratios with 95% confidence intervals.

Results: Eleven studies, with 7421 patients, were included. Low MHR levels compared to high MHR levels were associated with statistically significantly lower in-hospital mortality (0.9% vs. 5.5%; respectively; P <0.001), 3-month mortality (4.4% vs. 11.2%; P = 0.02), 6-month follow-up mortality (4.0% vs. 10.2%; P = 0.03), 1-year mortality (4.2% vs. 10.2%; P <0.001), as well as long-term follow-up mortality (7.5% vs. 13.7%; P <0.001).

Conclusions: MHR has both good predictive properties for mortality and major adverse cardiovascular events (short- and long-term). Data indicate that MHR may improve in-hospital

and long-term cardiovascular risk prediction. It may, therefore, be an effective tool for risk re-estimation and the selection of patients for whom intensive lipid-lowering treatment may be particularly useful.

Key words: acute coronary syndrome, biomarker, diagnostic techniques, monocyte-to-high-density lipoprotein ratio

INTRODUCTION

Monocyte-to-high-density lipoprotein cholesterol ratio (monocyte-to-HDL-C ratio/MHR) appears to be a useful predictor of the risk of major adverse cardiovascular events (MACEs) in both the long- and short-term perspective [1]. MHR reflects the predictive properties of both monocytes and HDL involved in the pathogenesis of atherosclerosis. The role of inflammation in the development of atherosclerosis is well established. Monocytes have an undoubted pro-inflammatory effect, while HDL has an anti-inflammatory effect [2].

Kanbay et al. [3] demonstrated that MHR, among patients diagnosed with chronic kidney disease, is a useful predictor in assessing the risk of death and composite cardiovascular events [3]. MHR also proved to be a good predictor of cardiovascular disease risk in patients diagnosed with obstructive sleep apnoea syndrome. The MHR value was higher among those with more advanced obstructive sleep apnoea syndrome and cardiovascular disease compared to controls) [4]. Thus, in addition to indicators such as the time between coronary angiography and stent diameter, MHR has emerged as an independent predictor of in-stent restenosis among patients undergoing bare-metal stent implantation [5]. In addition, the same study found a close correlation between the MHR value and the Systematic Coronary Risk Evaluation-2 (SCORE2) and insulin resistance [6]. Moreover, Avci et al. [7], showed that a higher MHR was a predictor of intra-hospital mortality among patients admitted to an emergency clinic with a diagnosis of pulmonary embolism. Patients diagnosed with hypertension [8], primary biliary cholangitis [9], acute ischemic stroke after intravenous thrombolysis therapy [10], osteoporosis [11], Kawasaki disease [12], and colorectal cancer [13] may potentially use MHR as a predictor of disease progression or exacerbation. Despite its wide spectrum of potential use as an indicator of adverse events, MHR is not a universal biomarker. A study by Romo-Cordero [6] showed that the MHR value did not differ between patients with rheumatoid arthritis when compared to a control group without a rheumatoid arthritis diagnosis.

In the context of acute coronary syndrome (ACS), it is worth mentioning a recently published study (August 2023) in which the MHR was significantly higher in patients with ACS compared to two control groups of those with and without coronary artery disease but no ACS. Furthermore, as the severity of coronary lesions increases, the MHR also increases, as patients with single-vessel disease have lower MHRs compared to those with multi-vessel disease, suggesting that the MHR may also be a potential predictor of ACS severity [14]. The immune system's response to myocardial hypoxia can explain the increased MHR value in ACS. Monocytes activate during oxygen deprivation, releasing cytokines, other pro-inflammatory factors, and tissue modifiers that aid in compensatory and repair processes [15–17].

Finally, a 2022 meta-analysis showed that, compared to patients with a low MHR, those with high MHR and coronary heart disease are at increased risk of long term MACE. However, the meta-analysis only included nine cohort studies [18], indicating the need for further investigation to determine the most appropriate application of the MHR. Ultimately, the single-center nature of many studies describing the predictive properties of the MHR as a biomarker leaves many questions unanswered. Meta-analyses make it possible to consolidate results obtained in several individual studies, allowing consideration of a larger combined number of patients in the meta-analysis. Thus, the aim of this meta-analysis is to examine the predictive properties of MHR in the context of short- and long-term MACE after ACS.

MATERIAL AND METHODS

We conducted this systematic review and meta-analysis following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [19]. We prospectively registered our study protocol on PROSPERO (registration no. CRD42023480204).

Search strategy and study selection

Two investigators (MP and DS) independently conducted an electronic literature search using bibliographic databases (PubMed, Embase, Scopus, Web of Science, and the Cochrane Library) for articles published in English before February 26, 2024. The search question included the following keywords, along with their synonyms or relevant terms: “monocyte to high-density lipoprotein ratio” OR “monocyte count/HDL cholesterol ratio” OR “monocyte to high density lipoprotein“ OR “monocyte/high-density lipoprotein ratio” OR “monocyte/HDL ratio” OR “monocyte to HDL ratio” OR “MHR” AND "acute coronary syndrome" OR "ACS" or "ST Segment Elevation Myocardial Infarction" OR "ST Elevated Myocardial Infarction" OR “ST-

elevation MI” OR "STEMI" OR "non-ST elevation myocardial infraction" OR "NSTEMI" OR "myocardial Infarction" OR "unstable angina". We also included articles written in English. We exported the search results to EndNote X6 (Clarivate, London, United Kingdom) for organization and removal of duplicate publications. All search processes followed the PRISMA guidelines (Figure 1).

Two review authors (MP and DS) first independently read the titles and abstracts of the identified studies to select those of potential relevance. Any original publications that were cited in the systematic reviews or meta-analyses but missed by the initial search were added if they met our inclusion/exclusion criteria. We removed all duplicate articles. A thorough evaluation of the full-text articles was then performed to determine if they met all the inclusion criteria. We resolved disputes between reviewers about eligibility or inclusion by discussing with the senior author and reaching a consensus.

Eligibility criteria

The inclusion criteria for selecting articles were as follows: 1) The study must evaluate the MHR values in acute coronary syndrome patients; 2) they must evaluate the diagnostic value of MHR among ACS types; 3) in the context of the prognostic value of MHR, they must report any measure of the patient’s survival; 4) they must provide sufficient data to estimate risk ratios (RR) for mortality and adverse events, or standardized mean differences for MHR values among study groups; and 5) articles must be written in English.

We excluded papers that were: (A) review articles, letters, editorials, case reports/series, or conference abstracts; and (B) nonhuman animal studies. In cases where studies reported similar patients from the same institution in more than one publication, we only included the paper with the largest sample to avoid spurious precision due to duplication.

Data extraction

Two authors (MP and DS) independently extracted data from the selected studies into a standardized Microsoft Excel spreadsheet. Discussion with the third reviewer (LS) helped to resolve any disagreements. The characteristics that were extracted from each article were as follows: data on study characteristics (first author name, country, study design, study groups, sample sizes), patient demographics (baseline characteristics), MACE types (Supplementary material, *Table S1*), mortality outcomes among different follow-up periods, and MHR values. We obtained the mean and standard deviation or median and interquartile range for continuous data and the count of patients in each category for dichotomous variables. When the

corresponding authors didn't respond to the initial email request for more information, they sent two more.

Quality assessment

The risk of bias in each included study was independently assessed by two investigators (MP and DS) and confirmed by all other authors using the Newcastle–Ottawa Scale (NOS) to independently assess the likelihood of bias in each study [20]. We discussed the scoring of inconsistencies until we reached a consensus. Three broad perspectives were examined and scored in each study. (1) For the selection of the study groups, each study could be awarded a maximum of 4 points. (2) For comparability between the groups, a maximum of 2 points could be awarded for each study. (3) For ascertainment of the exposure of interest, a maximum of 3 points was awarded for each study. We used the conventional cut-off values to code a NOS ≥7 as high, 5–6 as moderate, and ≤4 as low-quality studies. Quality rating disputes were settled through author discussion.

Statistical analysis

A priori, we set a minimum requirement of ≥2 studies reporting the same outcomes to perform a meta-analysis, in line with Cochrane Handbook guidance [21]. All analyses were conducted with the Review Manager software (version 5.4, Nordic Cochrane Centre, Cochrane Collaboration, Denmark) and STATA version 18 (Stata Corp., College Station, TX, US). Statistical tests were 2-sided, with a significance level of 5%. To compare the outcomes reported by the studies, we calculated the RRs with 95% confidence intervals (CIs) for dichotomous data. RRs were analyzed separately using random-effects models. When the continuous outcome was reported as median, range, and interquartile range, we estimated means and standard deviations using the formula described by Hozo et al. [22]. The presence of statistical heterogeneity was assessed using the Cochran Q test. The quantification of heterogeneity was performed using the I^2 statistic. Values of 0% to 24.9%, 25% to 49.9%, 50% to 74.9%, and >75% were considered none, low, moderate, and high heterogeneity, respectively. Publication bias was assessed by visually inspecting funnel plots and using Egger’s test for meta-analyses with >10 included studies. Additionally, the single removal method was applied in the sensitivity analysis to test the stability of the results.

RESULTS

Results of study selection

We identified 2695 publications (after the removal of duplicates), of which 2474 were excluded after screening titles and abstracts, leaving 221 studies for the full review. No additional publications were identified through manual searches of the reference lists. After reading the full text, another 210 studies were excluded for the reasons listed in Figure 1. Finally, we included 11 studies with a total of 7421 participants in this review [23–33]. Figure 1 shows the PRISMA diagram for the study selection.

Description of the included trials

The main characteristics of the included trials are presented in Table 1 and Supplementary material, *Table S2*. The 33 included trials were published between 1992 and 2023. Seven studies were retrospective, and 4 were prospective trials. The trials included in this study were conducted in the following countries: 3 in China, 2 in Egypt, and 6 in Turkey. The reviewed studies reported results from 7421 participants, with 3858 participants in the low MHR group and 3563 participants in the high MHR group. According to the NOS, the assessment of quality studies is shown in Table 1, and all studies were rated as high quality.

Association between MHR level and mortality outcomes

In hospital mortality among low vs. high MHR levels varied and amounted to 0.9% vs. 5.5%, respectively (RR, 0.20; 95% CI, 0.12–0.33; P <0.001; Figure 2). In the case of mortality due to cardiovascular causes, the pooled results were 1.2% vs. 3.7%, respectively (RR, 0.35; 95% CI, 0.18–0.68; P = 0.002). The pooled analysis of all-cause mortality among the low MHR group was significantly lower than that in the high MHR level group in the context of 3-month mortality (4.4% vs. 11.2%; RR, 0.04 to 0.75; P = 0.02) as well as in the 6-month mortality follow-up (4.0% vs. 10.2%; RR, 0.08 to 0.90; P = 0.03).

Five studies reported 1-year mortality among study groups, and pooled analysis revealed that a low MHR was associated with a significantly lower mortality of 4.2%, vs. 10.2% for patients in the high MHR groups (RR, 0.34; 95% CI, 0.21–0.54; P <0.001; Figure 3). Only one study reported 1-year cardiovascular mortality, which was 2.7% vs. 6.0%, for low and high MHR, respectively (RR, 0.45; 95% CI, 0.28–0.73; P = 0.001).

Long-term follow-up mortality from any cause among low and high MHR groups varied and amounted to 7.5% and 13.7%, respectively, (RR, 0.49; 95% CI, 0.40–0.60; P <0.001; Figure 4). In the context of late follow-up mortality due to cardiovascular causes, mortality rates were 2.6% vs. 16.7%, respectively, (RR, 0.16; 95% CI, –0.8 to 0.31; P <0.001) among low and high MHR cohorts.

Association between MHR level and adverse events

Table 2 summarizes the adverse events. We selected 4 time frames to compare adverse events: in-hospital, 3-month, 1-year, and late-term outcomes. In the context of in-hospital adverse events, in five studies, the number of MACE incidents was statistically lower in the low MHR group vs. the high MHR group (3.6% vs. 8.9%; RR, 0.41; 95% CI, 0.32–0.53; *P* <0.001). Pooled analysis showed a statistically lower incidence of stent thrombosis in the low MHR group vs. the high MHR group (1.9% vs. 4.5%; RR, 0.42; 95% CI, 0.26–0.68; *P* <0.001). The low MHR group showed a statistically lower incidence of reinfarction compared to the high MHR group (2.3% vs. 6.1%; RR, 0.26; 95% CI, 0.12–0.59; *P* = 0.001). Only one study reported a statistically lower incidence of congestive heart failure in the low MHR group vs. the high MHR group (2.4% vs. 21.7%; RR, 0.11; 95% CI, 0.01–0.90; *P* = 0.04). The low MHR group experienced a lower incidence of target vessel revascularization compared to the high MHR group (1.0% vs. 4.1%, RR, 0.27; 95% CI, 0.27–0.80; *P* = 0.04).

After three months, one study found that the low MHR group had statistically fewer MACE events than the high MHR group (9.8% vs. 73.9%, RR, 0.13; 95% CI, 0.05–0.35; *P* <0.001). Moreover, two studies reported a lower reinfarction rate in the low MHR group vs. the high MHR group (19.6% vs. 37.1%, RR, 0.47; 95% CI, 0.31–0.71; *P* <0.001).

In a pooled analysis that looked at adverse events over a year, the low MHR group had statistically fewer MACE events than the high MHR group (7.1% vs. 14.0%, RR, 0.51; 95% CI, 0.38–0.68; *P* <0.001). Moreover, there was a statistically lower incidence of stent thrombosis in the low MHR group vs. the high MHR group (2.5% vs. 5.9%, RR, 0.42; 95% CI, 0.26–0.69; *P* <0.001).

DISCUSSION

Compared to the previously published meta-analyses, the current study includes patients diagnosed with ACS and includes more studies (Figure 5), especially those published after 2020 [34]. Nevertheless, the majority of studies included in this meta-analysis were aimed at understanding the predictive properties of ST-segment elevation myocardial infarction (STEMI). This seems to be justified, as myocardial damage is usually greater in STEMI and microvascular obstruction is greater among patients with STEMI. This may translate into increased activation of pro-inflammatory mechanisms and a higher MHR value, which would then be easier to observe in clinical practice and research [2, 35, 36]. The MHR biomarker is sometimes compared to other biomarkers derived from leukocytes, in particular neutrophil to

lymphocyte ratio (NLR). Interestingly, compared to other biomarkers, e.g., NLR [37], MHR seems to have worse predictive properties. Chen et al. [38] showed that an increased NLR is associated with shorter overall survival in patients with idiopathic pulmonary fibrosis, while PLR and MHR did not show significance in this group. Also, in patients with central retinal artery occlusions, NLR indicates a higher value than MHR or PLR [39]. Significant observational studies, including a nationwide cohort, show that MHR may also be a predictor of all-cause and cardiovascular mortality in the general population, regardless of established cardiovascular risk factors [40].

The results of our meta-analysis are similar to those published by Liu et al. [18], which showed that an increased MHR is associated with long-term mortality and the occurrence of long-term MACEs in patients with coronary heart disease [16]. Sun et al. [1] did a meta-analysis on ACS and found that a higher MHR value was linked to a higher risk of MACEs and all-cause mortality. This finding was maintained even when the most common confounding factors were taken into account, especially in patients with STEMI [1]. In the context of the prognostic properties of severe coronary artery stenosis in patients with STEMI, in addition to MHR, the neutrophil-to-high-density lipoprotein cholesterol ratio also showed good predictive properties, including for MACEs. This opens potential directions for further research into the development of new biomarkers, in which one of the components is based on leukocytes (in this case, monocytes) and the other on HDL [41]. MHR may also be a predictor of increased cardiovascular risk and allow the identification of patients at risk of cardiovascular complications, which is particularly important in groups of patients with other identifiable risk factors, e.g., type 2 diabetes. At this point, Chen et al. [42] showed that MHR can be a predictive indicator of the presence and/or progression of asymptomatic carotid atherosclerosis among patients with type 2 diabetes.

The directions for further research mentioned by Villanueva (in the meta-analysis published in 2020) remain relevant [34]. Prospective studies should be conducted to evaluate the relationship between MHR and the occurrence of ACS. Also, designing prospective randomized trials to determine if commonly accepted interventions for reducing cardiovascular risk will lead to a reduction in the MHR (and a reduction in the number of MACEs). The direction of such research seems important considering the study published by Tani et al. [43], which showed that an increase in fish consumption is associated with a reduced MHR value, as are health-promoting behaviours (such as sleep duration or smoking of tobacco products).

Limitations of the study

The first major limitation of our work was that “high” and “low” MHR were defined differently in the studies included in this meta-analysis (see Supplementary material, *Table S3*). Unfortunately, based on the data we have, it is not possible to determine the cut-off point, i.e., above what MHR value the risk of MACE or cardiovascular mortality increases. Prospective validation studies are necessary to definitively determine the prognostic utility of a specific cut-off in clinical practice.

Another limitation may be the unequal geographical representation of studies included in the meta-analysis; a large number of studies were performed in China. The heterogeneity of the included studies and the follow-up duration also require a careful approach to the results of our meta-analysis. Moreover, when assessing the usefulness of the data, it should be noted that the number of cardiovascular events was relatively low compared to the expected number resulting from the epidemiological estimation, and other clinically significant information is missing, e.g., cardiovascular disease mortality after 3 and 6 months.

CONCLUSIONS

This meta-analysis remains relevant to clinical practice. MHR has both good predictive properties for mortality and MACE (short- and long-term). Data indicate that MHR may improve in-hospital and long-term cardiovascular risk prediction. It may, therefore, be an effective tool for risk re-estimation and the selection of patients for whom intensive lipid-lowering treatment may be particularly useful.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

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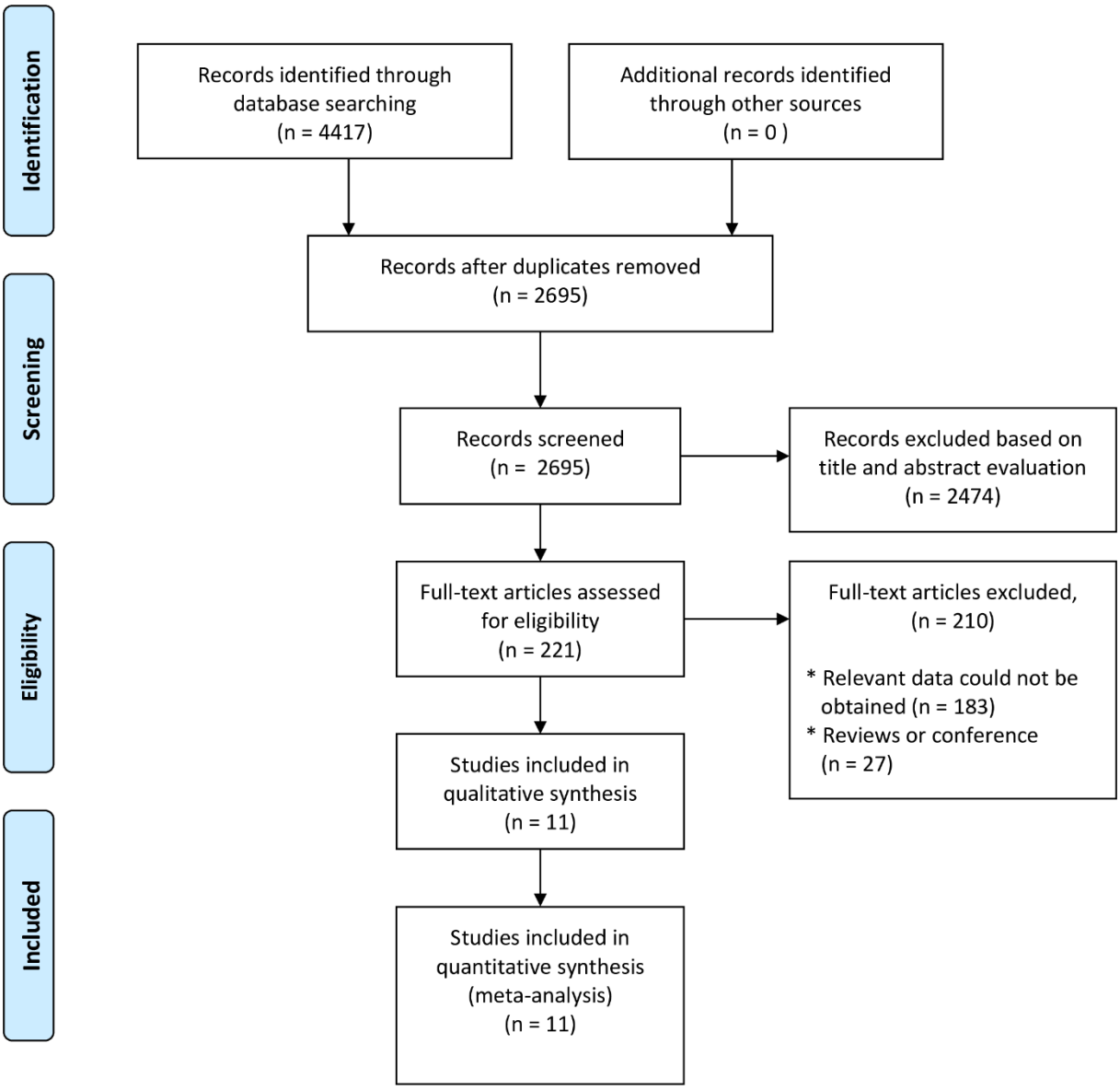

Figure 1. Flow-diagram of study selection

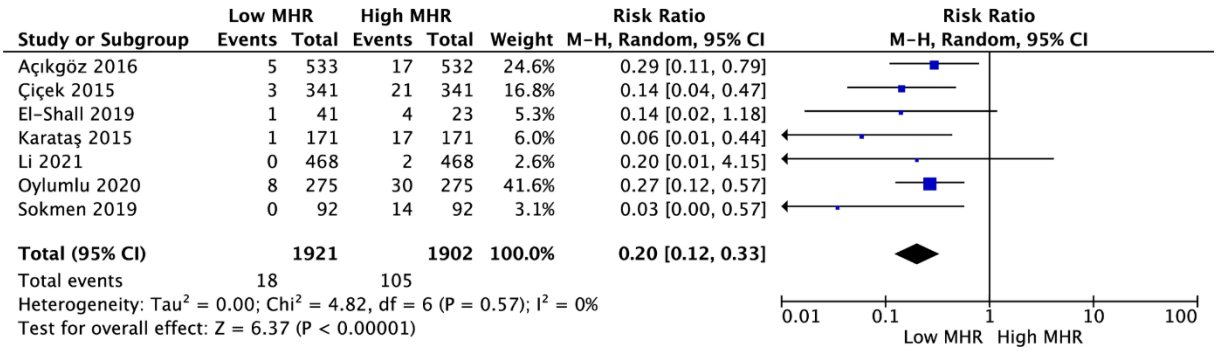

Figure 2. Forest plot of in hospital mortality among low and high monocyte-to-high-density lipoprotein-cholesterol ratio (MHR) patients. The center of each square represents the risk ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results

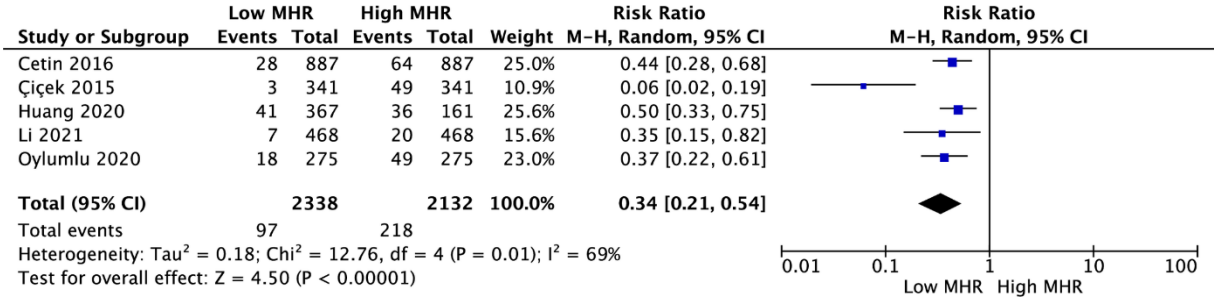

Figure 3. Forest plot of 1-year mortality among low and high monocyte-to-high-density lipoprotein-cholesterol ratio (MHR) patients. The center of each square represents the risk ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results

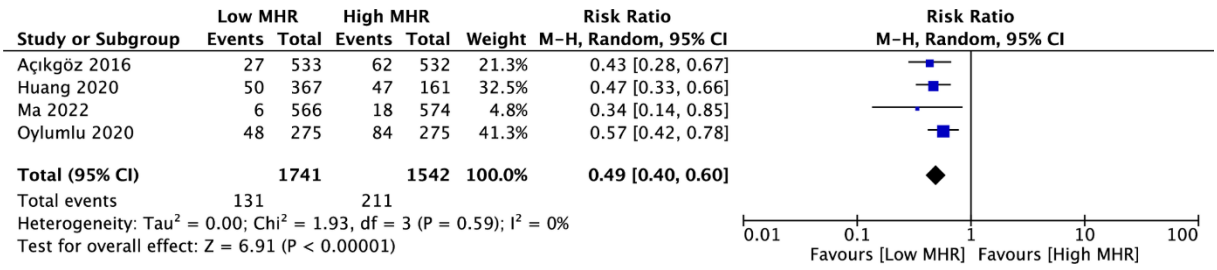

Figure 4. Forest plot of in long term mortality among low and high monocyte-to-high-density lipoprotein-cholesterol ratio (MHR) patients. The center of each square represents the risk ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results

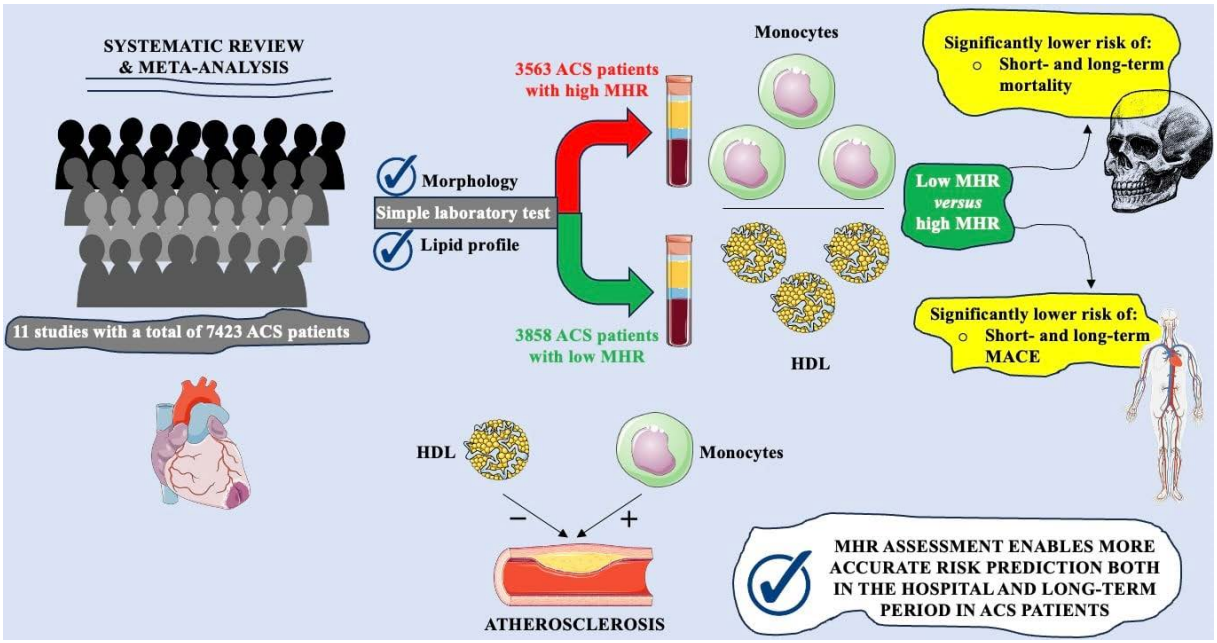

Figure 5. Central illustration presenting a graphical representation of the results obtained

Abbreviations: ACS, acute coronary syndrome; HDL, high-density lipoprotein; MACE, major adverse cardiovascular events; MHR, monocyte-to-high-density lipoprotein-cholesterol ratio

Table 1. Baseline characteristic of included trials

Study	Country	Study design	Study group	No of patricipants	Age, years	Gender (male)	Comorbidities				Ejection fraction [%]	NOS score
							DM	HT	Smoking	Hyp. lip.		
Açıkgöz et al., 2016	Turkey	RS	LMHR	533	58.2 (12.2)	423 (79.4%)	130 (24.5%)	210 (41.5%)	267 (54.9%)	NS	48.9 (10.7)	8
			HMHR	532	54.4 (11.5)	463 (87.0%)	138 (26.1%)	200 (39.6%)	332 (67.5%)	NS	46.9 (11.7)	
Cetin et al., 2016	Turkey	PS	LMHR	887	59.6 (18.4)	578 (65.2%)	229 (25.8%)	307 (34.6%)	298 (33.6%)	408 (46.0%)	42.0 (7.7)	9
			HMHR	887	60.0 (18.2)	601 (67.8%)	241 (27.2%)	281 (31.7%)	315 (35.5%)	395 (44.5%)	41.9 (7.2)	
Çiçek et al., 2015	Turkey	PS	LMHR	341	60.0 (11.5)	275 (80.6%)	68 (19.9%)	145 (42.5%)	226 (66.3%)	88 (25.8%)	45.5 (8.5)	8
			HMHR	341	52.9 (12.9)	303 (88.9%)	62 (18.2%)	138 (40.5%)	274 (80.4%)	72 (21.1%)	44.7 (8.9)	
El-Shall et al., 2019	Egypt	PS	LMHR	41	NS	NS	12 (29.3%)	14 (34.1%)	19 (46.3%)	NS	33.2 (11.0)	7
			HMHR	23	NS	NS	11 (47.8%)	10 (43.5%)	15 (65.2%)	NS	51.5 (10.4)	
	Egypt	RS	LMHR	117	NS	NS	NS	NS	NS	NS	NS	7

Ghanem et al., 2023			HMHR	39	NS	NS	NS	NS	NS	NS	NS	
Huang et al., 2020	China	RS	LMHR	367	72.4 (0.3)	206 (56.1%)	94 (25.6%)	215 (58.6%)	134 (36.5%)	NS	52.9 (0.6)	8
			HMHR	161	73.4 (0.4)	127 (78.9%)	43 (26.7%)	98 (60.9%)	76 (47.2%)	NS	50.0 (1.1)	
Karataş et al., 2015	Turkey	RS	LMHR	171	56.9 (12.5)	115 (67.3%)	32 (18.7%)	74 (43.3%)	82 (47.9%)	NS	45.4 (11.1)	8
			HMHR	171	56.7 (12.9)	114 (66.7%)	36 (21.1%)	71 (41.5%)	86 (50.3%)	NS	41.7 (13.6)	
Li et al., 2021	China	RS	LMHR	468	66.2 (9.4)	258 (55.1%)	468 (100.0%)	361 (77.1%)	59 (12.6%)	67 (14.3%)	62.1 (11.1)	8
			HMHR	468	64.5 (9.7)	369 (78.8%)	468 (100.0%)	354 (75.6%)	130 (27.8%)	40 (8.5%)	59.0 (12.4)	
Ma et al., 2022	China	RS	LMHR	566	61 (9)	355 (62.7%)	246 (43.5%)	373 (65.9%)	156 (27.6%)	379 (67.0%)	64.8 (1.2)	8
			HMHR	574	58 (11)	515 (89.7%)	241 (42.0%)	358 (62.4%)	354 (61.7%)	528 (92.0%)	62.8 (1.5)	
	Turkey	RS	LMHR	275	65.2 (11.5)	185 (67.3%)	80 (29.1%)	126 (45.8%)	87 (31.6%)	NS	48.0 (10.3)	8

Oylumlu et al., 2020			HMHR	275	60.1 (13.8)	201 (73.1%)	82 (29.8%)	119 (43.3%)	138 (50.2%)	NS	45.7 (10.3)	
Sokmen et al., 2019	Turkey	RS	LMHR	92	61.8 (2.5)	62 (67.4%)	38 (41.3%)	54 (58.6%)	42 (45.6%)	22 (23.9%)	42.4 (3.5)	8
			HMHR	92	59.3 (3.0)	76 (82.7%)	21 (22.8%)	32 (34.7%)	60 (65.2%)	26 (28.2%)	39.8 (3.2)	

Abbreviations: DM, diabetes mellitus; HMHR, high monocyte-to-high-density lipoprotein-cholesterol ratio; HT, hypertension; LMHR, low monocyte-to-high-density lipoprotein-cholesterol ratio; NOS, Newcastle–Ottawa Scale; NS, not specified; PS, prospective study; RS, retrospective study; TIMI, Thrombolysis in Myocardial Infarction; NS, not specified

Table 2. Full characterization of adverse events

Outcome	No. of studies	Event/ Participants		Events		Heterogeneity between Trials		*P*-value for differences across groups
		Low MHR	High MHR	RR	95% CI	*P*-value	I^2 statistics	
In hospital adverse events								
MACE	5	87/2400 (3.6%)	213/ 2399 (8.9%)	0.41	0.32 to 0.53	0.35	0%	<0.001
Stent thrombosis	2	23/1228 (1.9%)	55/1228 (4.5%)	0.42	0.26 to 0.68	0.66	0%	<0.001
Reinfarction	4	32/1386 (2.3%)	79/1290 (6.1%)	0.26	0.12 to 0.59	0.07	63%	0.001
Congestve heart failure	1	1/41 (2.4%)	5/23 (21.7%)	0.11	0.01 to 0.90	NA	NA	0.04
TVR	2	4/382 (1.0%)	15/364 (4.1%)	0.27	0.27 to 0.80	NA	NA	0.02
Stroke	1	0/341 (0.0%)	2/341 (0.6%)	0.20	0.01 to 4.15	NA	NA	0.30
Any bleeding	2	63/809 (7.8%)	85/809 (10.5%)	0.74	0.55 to 1.00	0.62	0%	0.05
Major bleeding	1	5/468 (1.1%)	7/468 (1.5%)	0.71	0.23 to 2.23	NA	NA	0.56
3-month averse events								
MACE	1	4/41 (9.8%)	17/23 (73.9%)	0.13	0.05 to 0.35	NA	NA	<0.001

Reinfrarction	2	31/158 (19.6%)	23/62 (37.1%)	0.47	0.31 to 0.71	0.66	0%	<0.001
Congestve heart failure	1	1/41 (2.4%)	3/23 (13.0%)	0.19	0.02 to 1.70	NA	NA	0.14
TVR	1	0/41 (0.0%)	1/23 (4.3%)	0.19	0.01 to 4.49	NA	NA	0.30
1-year adverse events								
MACE	1	63/887 (7.1%)	124/887 (14.0%)	0.51	0.38 to 0.68	NA	NA	<0.001
Stent thrombosis	1	22/887 (2.5%)	52/887 (5.9%)	0.42	0.26 to 0.69	NA	NA	<0.001
Reinfarction	1	40/887 (4.5%)	69/887 (7.8%)	0.58	0.40 to 0.85	NA	NA	0.005
Any bleeding	1	70/468 (15.0%)	104/468 (22.2%)	0.67	0..51 to 0.89	NA	NA	0.005
Major bleeding	1	7/468 (1.5%)	11/468 (2.4%)	0.64	0.25 to 1.63	NA	NA	0.35
Late term adverse events								
MACE	3	259/1440 (18.0%)	419/1447 (29.0%)	0.62	0.54 to 0.72	0.32	13%	<0.001
Reinfarction	3	55/1724 (3.2%)	145/1076 (13.5%)	0.38	0.29 to 0.50	0.54	0%	<0.001

Congestve heart failure	2	64/2264 (2.8%)	88/2217 (4.0%)	0.71	0.49 to 1.01	0.28	16%	0.06
TVR	2	121/907 (13.3%)	190/915 (20.8%)	0.66	0.45 to 0.98	0.07	71%	0.04
Stroke	2	64/2264 (2.8%)	88/2217 (4.0%)	0.71	0.49 to 1.01	0.28	16%	0.06

Abbreviations: CI, confidence interval; MACE, major adverse cardiovascular events; MHR, monocyte-to-high-density lipoprotein-cholesterol; NA, not applicable; RR, risk ratio; TVR, target vessel revascularization