Inflammation in coronary artery disease-clinical implications of novel HDL-cholesterol–related inflammatory parameters as predictors

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Coronary artery disease (CAD) is the leading cause of death worldwide. Inflammation and atherosclerotic plaques are the primary pathological mechanisms of CAD. Upon stimulation by deposited lipids and damaged endothelium, innate and adaptive immune cells are activated and recruited to initiate plaque development. Therefore, inflammatory cells and mediators are used to identify inflammatory risk in CAD patients. HDL-cholesterol (HDL-C) is demonstrated to have anti-inflammatory roles in atherosclerosis by interfering with plasma membrane lipid rafts of immune cells. Based on this, novel inflammatory parameters such as monocyte to HDL-C ratio are explored to improve the risk estimation of CAD prognosis. Moreover, with the advance in treatment strategies targeting the inflammatory process in atherosclerosis, identifying CAD patients with increased inflammatory risk by novel inflammatory parameters is of great importance in guiding CAD management. Therefore, this review aims to summarize the current information regarding inflammatory activation and HDL-C in atherosclerosis with a particular focus on the clinical implication of the novel HDL-C–related inflammatory parameters in CAD. *Coron Artery Dis* **34: 66–77** **Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Keywords: atherosclerosis, coronary artery disease, HDL-cholesterol, inflammation, novel biomarkers

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Introduction

Coronary artery disease (CAD) is a cardiovascular (CV) disorder due to atherosclerosis or atherosclerotic occlusion of coronary arteries. Hypercholesterolemia, hyperglycemia, and hypertension are prominent CV risk factors that contribute to the development of atherosclerosis [1]. During the past few decades, though advances in the prevention and management of these disease-modifying factors have led to a decrease in mortality from CAD causes, CAD remains the leading cause of death across the globe and accounts for approximately 17.9 million deaths annually [2]. Given that inflammation plays a pivotal role in the pathophysiology of atherosclerosis and CAD progression, a renewed focus has been put on this topic, which might provide clinical benefits by identifying residual risk [3]. HDL-cholesterol (HDL-C) is a class of lipoprotein responsible for reverse cholesterol transport (RCT) [4]. Decreased HDL-C is frequent in CAD and has acted as an indicator in evaluating CV risk in CAD patients [5,6]. Evidence has recently demonstrated that HDL-C was directly involved in the inflammatory process of atherosclerosis, and the predictive value of HDL-C could be improved by integrating it with inflammatory parameters [7–9]. Therefore, our review will elaborate on the association between inflammation and HDL-C in atherosclerosis, summarize novel HDL-C–related inflammatory parameters in CAD, and thus provide an up-to-date perspective on this issue.

Inflammation in coronary artery disease

Concept of inflammation in atherosclerosis

Atherosclerosis is a chronic inflammatory disease. Genetic studies have discovered that genetic variants in the inflammatory signaling pathways could lead to atherosclerosis among the general population [10]. Patients with atherosclerosis, compared with control individuals, have a higher level of inflammatory biomarkers such as C-reactive protein (CRP) and interleukin-1β (IL-1β) [11,12]. Through analyzing atherosclerotic plaques, abundant infiltrated immune cells and increased expression of inflammatory mediators are identified [13]. Besides, imaging techniques have enabled the characterization of arterial inflammation in CAD patients and atherosclerotic animal models [14,15]. Moreover, it is reported that patients with inflammatory diseases, such as chronic kidney disease (CKD), are associated with elevated atherosclerosis risk, and nearly 50% of deaths in end-stage CKD patients attribute to CV causes [16].

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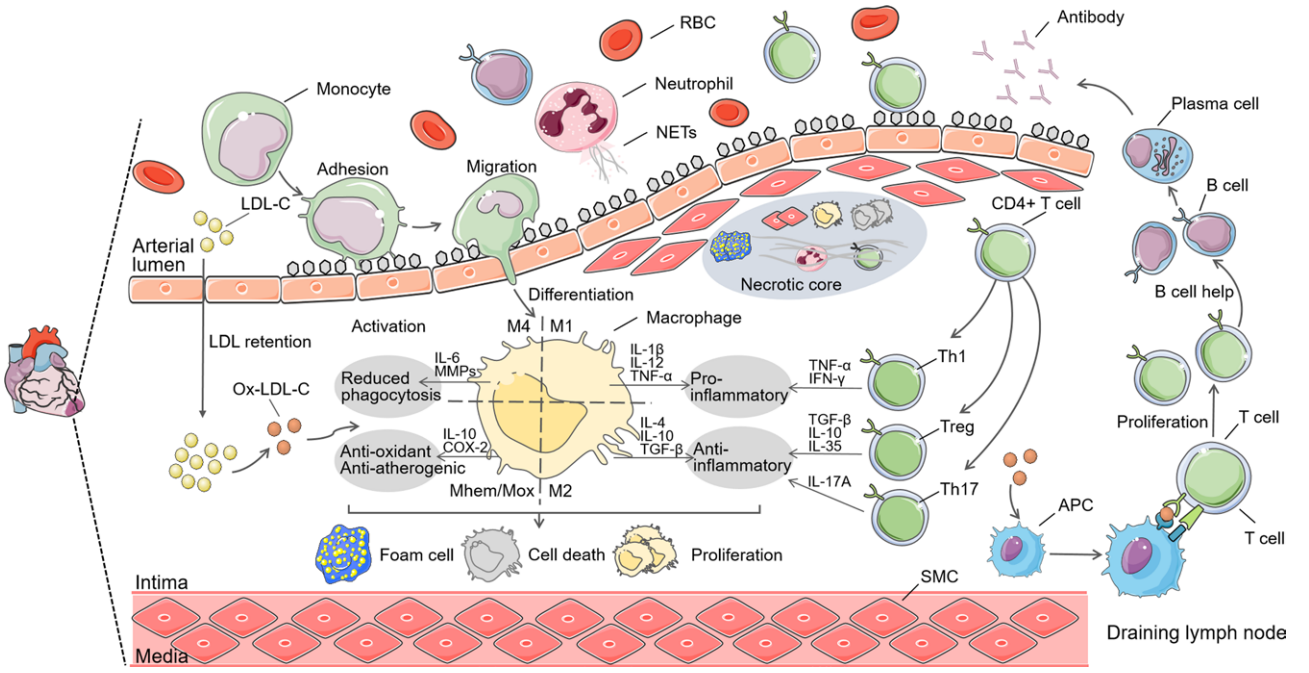
Fig. 1



Innate and adaptive immune responses in atherosclerosis. Lipid retention and oxidation initiate atherosclerosis development. Subsets of macrophage and CD4+ T cell exert distinctive roles in atherosclerosis progression. APC, antigen-presenting cell; COX-2, cyclooxygenase-2; IL, interleukin; LDL-C, LDL-cholesterol; MMPs, matrix metalloproteinases; NETs, neutrophil extracellular traps; Ox-LDL-C, oxidized LDL-C; RBC, red blood cell; SMC, smooth muscle cell; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α.

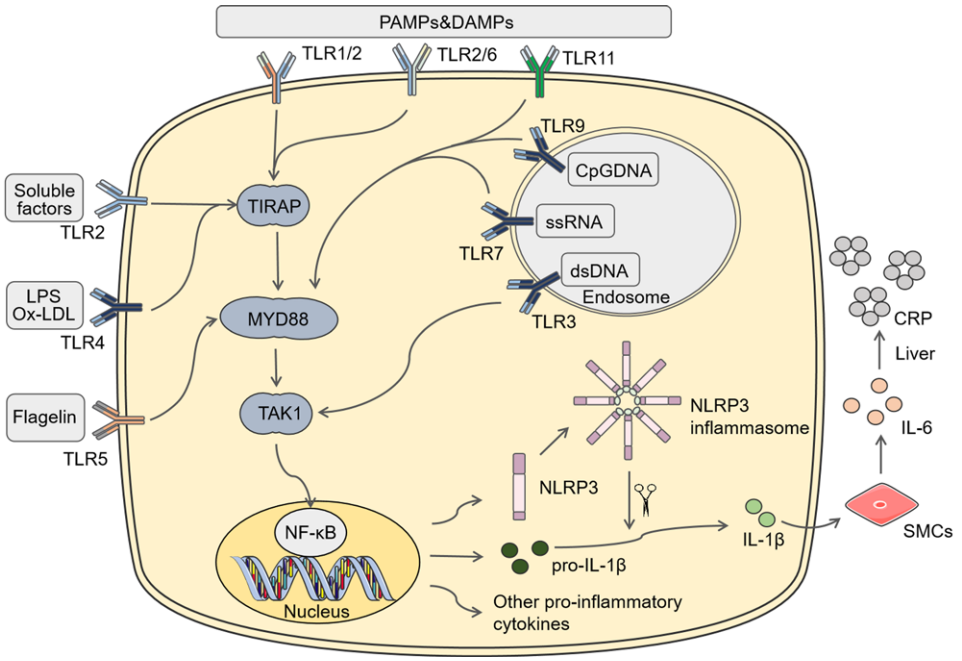
Therefore, it is essential to discuss the inflammatory activation in atherosclerosis involving innate and adaptive immunity.

Basic mechanisms of innate immunity in atherogenesis

Innate immunity is intimately connected with atherogenesis (Figs. 1 and 2). During early stages, exposure to CV risk factors renders arterial intima susceptible to lipid deposition and stimulates the endothelium to express adhesion molecules and cytokines such as vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemoattractant protein-1 [17]. In response to the retained lipids and activated endothelium, circulating monocytes are recruited to the lesion and differentiate into macrophages, which in turn scavenge lipids to form foam cells [18]. Oxidation of the deposited atherogenic lipids, primarily the LDL-cholesterol (LDL-C), could prompt the differentiation of monocyte into macrophages and foam cells by inducing reactive oxygen species and inflammatory cytokines in these leukocytes [19]. Moreover, oxidized LDL-C could activate endothelium to attract more leukocytes, resulting in inflammation propagation. Debris of apoptotic foam cells and macrophages would form a necrotic core, which then develops into atherosclerotic plaque through accumulating large amounts of extracellular matrix. Consequently, the progressive growth of atherosclerotic plaques would obstruct coronary blood flow, and CAD would arise when the flow-limiting obstructions are greater than 50%. Additionally, as the ongoing inflammatory macrophages and vascular smooth muscle cells (VSMC) could produce matrix metalloproteinases (MMPs) capable of degrading collagen and other extracellular matrices, the plaques could become vulnerable to rupture [20]. Acute coronary events such as myocardial infarction (MI) might occur under plaque rupture and subsequent thrombosis, leading to ischemic myocardial damage.

Histological examinations have found that monocyte-derived macrophages account for the primary cell population in plaques and exhibit high heterogeneity through the entire process of atherosclerosis [21]. The ability of macrophages displaying different phenotypes to mediate inflammatory response is called polarization, which involves diverse gene expression patterns and depends on microenvironment stimuli [22]. The M1 macrophage is a proinflammatory subset stimulated by interferon γ (IFN-γ) and lipopolysaccharide. It is found to promote plaque growth and instability by secreting ILs such as IL-1β and IL-18. Markers of M1 are identified across all stages of atherosclerotic lesions, and M1 is vastly enriched in the rupture-prone shoulder region of vulnerable plaques. Moreover, M1 is generally lipid-filled and could promote microcalcification within the necrotic core, which indicates potential for foam cell transition and plaque modification [23]. M2 macrophages are alternatively activated by IL-4 or IL-13. It is found to induce plaque regression and improve plaque stability

Fig. 2



Toll-like receptor signaling pathway in macrophages. Activation of TLR signaling leads to increased proinflammatory gene transcription, including pro-IL-1β and NLRP3. The NLRP3 inflammasome is responsible for processing pro-IL-1β into the active form IL-1β. The IL-1β could act on smooth muscle cells to induce IL-6 which would then promote CRP production in the liver. CRP, C-reactive protein; DAMPs, damage-associated molecular patterns; IL, interleukin; LPS, lipopolysaccharide; MyD88, myeloid differentiation protein 88; NF-κB, nuclear factor κB; NLRP3, nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3; PAMPs, pathogen-associated molecular patterns; SMC, smooth muscle cell; TAK1, transforming growth factor β-activated kinase 1; TIRAP, TIR domain-containing adaptor protein; TLR, Toll-like receptor.

by enhancing efferocytosis and generating anti-inflammatory mediators, including IL-10 and transforming growth factor β (TGF-β) [24]. Compared with M1, M2 is localized away from the necrotic core and possesses a relatively higher proportion in stable plaques. Besides, M2 is less lipid-filled due to reduced expression of scavenge receptors and is correlated with plaque stability by promoting macrocalcification. Distinct from M1 and M2, M4 macrophages have reduced phagocytosis and are associated with plaque instability [25]. Mhem, a group of newly discovered macrophages stimulated upon intraplaque hemorrhage, is found to prevent atherogenesis via reducing oxidative injuries [26]. Results from the LDL receptor-deficient mice model have found that Mox macrophages were responsive to oxidized phospholipid and could regulate intraplaque redox status by generating antioxidant enzymes, thus exacerbating atherosclerosis [27]. Interestingly, VSMCs have been observed to be able to transdifferentiate into macrophage-like cells, and there are about 30% of VSMCs expressing macrophage markers in plaques. Further investigation is needed to establish whether the VSMC-derived macrophages contribute to plaque formation [28].

Toll-like receptor (TLR) signaling plays critical roles in the chronic innate immune activation in atherosclerotic lesions [29]. Upon activation by oxidized lipids and damage-associated molecule patterns, downstream signaling molecules of TLRs would transmit the proatherosclerotic signal to the IL-1 gene class family. Increased levels of IL-1β could aggravate the inflammation by facilitating adhesion molecules expression on the endothelium. Moreover, IL-1β acts on VSMC to elicit IL-6 production, which could promote acute phase protein production such as CRP in the liver, further inciting inflammatory responses [30]. Studies focused on the association between IL-1β and atherosclerosis have revealed that patients with atherosclerotic lesions had significantly elevated IL-1β and reduced IL-1β was atheroprotective in mice [31]. Furthermore, the nucleotide-binding leucine-rich repeat-containing pyrin receptor3 (NLRP3) inflammasome, an intracellular protein complex widely expressed in macrophages and foam cells, could activate the IL-1β meanwhile increase the IL-1β expression under the activation of cholesterol crystals [32].

Other innate immune cells, such as neutrophils and mast cells, are also important in atherogenesis. Mice models of hypercholesterolemia have found that circulating neutrophils proliferated, and the degree of neutrophilia was positively correlated with the extent of atherosclerotic lesions. Besides, neutrophils are further found to promote plaque formation and atherothrombosis by releasing the neutrophil extracellular traps [33].

Experimental studies have discovered that mast cells could directly participate in plaque progression and destabilization via secreting MMPs, IL-6, and IFNγ [34].

Adaptive immunity in atherogenesis

$CD4^+$ T_H cells are the main effector adaptive cells in atherogenesis [35]. Immunodeficient $Apoe^{-/-}$ mice display reduced development of atherosclerotic plaque, whereas transfer of $CD4^+$ T_H cells could significantly promote the atherogenic process [36]. Based on this, distinctive roles of $CD4^+$ T_H subsets are investigated. Single-cell data from human atherosclerotic lesions has revealed that T_H1 cells were the most abundant $CD4^+$ T_H cells [37]. The immune activity of T_H1 cells is primarily mediated by IFNγ. IFNγ-deficient mice have shown inhibited atherosclerosis, whereas IFNγ administration could aggravate atherosclerosis in $Apoe^{-/-}$mice [38]. T_H17 cells and their signature cytokine IL-17A have been found to be elevated in patients with acute coronary syndrome (ACS), and low serum IL-17A levels are considered an indicator of increased risk of recurrent CV events [39]. IL-17A is further discovered to have plaque stabilizing effects by stimulating collagen synthesis in VSMC [40]. T_{reg} cells have been demonstrated to promote plaque stability and induce plaque regression. Moreover, T_{reg} cell-related anti-inflammatory cytokines IL-10 and TGF-β are found effective in preventing CAD progression and plaque vulnerability [41].

B cell is much less frequent in atherosclerotic plaques than $CD4^+$ T_H cell, but it is found to protect against atherosclerosis [42]. Mice who underwent splenectomy have aggravated atherosclerosis, and splenectomized patients have a higher risk for MI [43,44]. The atheroprotective effect of humoral immunity is supported by findings that antibodies against auto-antigens derived from plaques could reduce lipids uptake in macrophages by neutralizing the oxidized lipids and inhibiting the proinflammatory epitopes through immune complex formation [45].

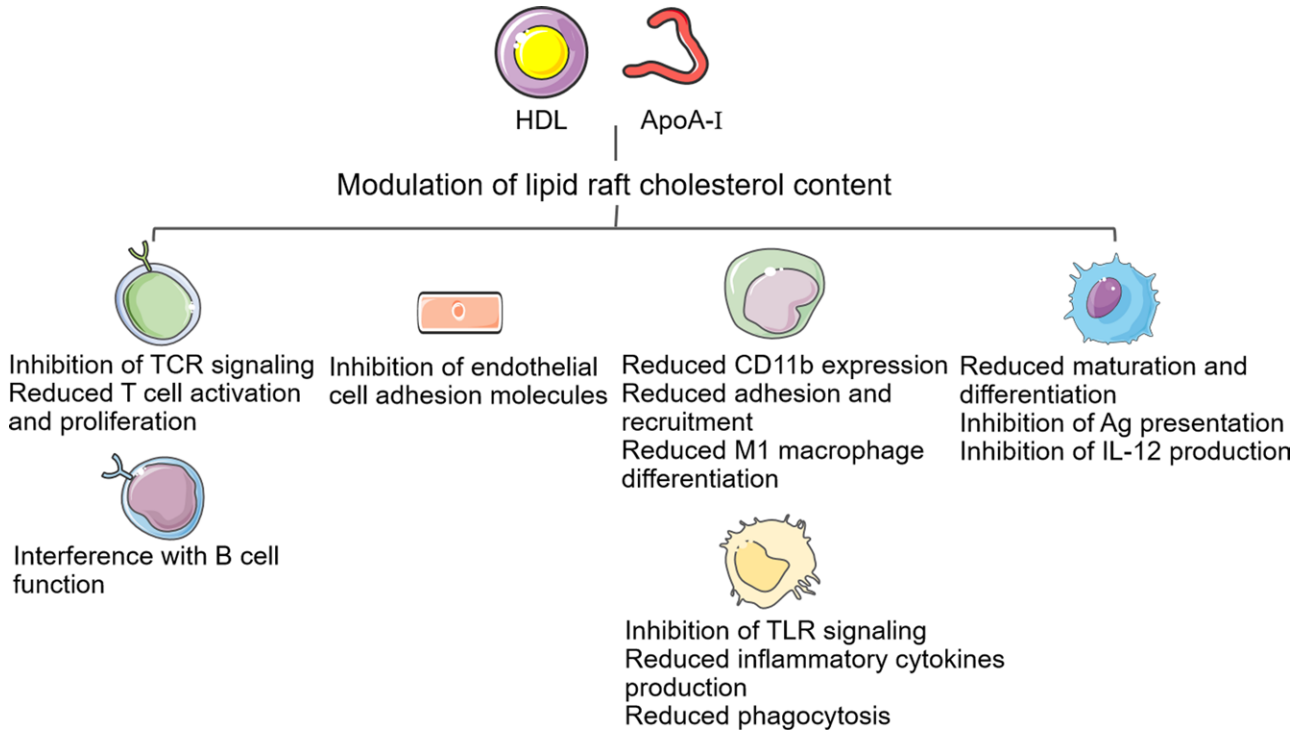
HDL-cholesterol

Dyslipidemia characterized by low HDL-C has been shown relevant to CAD manifestation [46] (Fig. 3). HDL-C is generally considered antiatherogenic as it is the critical mediator of RCT, which promotes cholesterol efflux from macrophages and foam cells [4]. Decreased HDL-C has been inversely correlated with CV events among atherosclerotic patients. However, despite the strong association between HDL-C and atherosclerosis, genetic studies of rare variants that have elevated serum HDL-C but increased CV risk and failure of clinical trials aiming to boost HDL-C via medications have led to the atheroprotective effects of HDL-C being challenged [47]. Actually, emerging data from large cohorts have demonstrated that HDL-C was linked to CV diseases and all-cause/cause-specific mortality in a U-shape relationship [48]. Therefore, HDL-C might not be a causal factor in atherosclerosis.

Interestingly, the protective roles of HDL-C are found independently in persons without CAD, and administration of HDL in animal models shows significant protection from atherosclerosis [49]. Investigations of HDL-C particles reveal that inflammatory mediators during atherogenesis could alter the composition thereby the function of HDL-C [50]. Moreover, several lines of evidence have suggested that instead of serum levels, the cholesterol efflux capacity of HDL-C, a rate-limiting step in RCT, was directly correlated with CV outcomes in CAD patients and could be impaired under inflammatory remodeling [51]. Meanwhile, HDL-C is found directly interfere with the immune response in atherosclerosis. Among patients with CAD, serum levels of HDL-C are significantly but negatively associated with circulating monocyte and CRP and the association remains consistent during statin treatment [52]. Similarly, an increase in apolipoprotein A-I (apoA-I), a major protein component of HDL, is accompanied by CRP reduction in hypercholesterolemic patients [53]. Infusion of reconstituted HDL in patients at significant risk for CV events has shown notable anti-inflammatory effects and reduced adhesion ability of leukocytes [54]. Furthermore, HDL remodeling by CSL112, a reconstituted apoA-I, could enhance the anti-inflammatory activity of peripheral blood by reducing proinflammatory cytokines production [55]. Determined as the ability to suppress tumor necrosis factor-α (TNF-α)–induced VCAM-1 expression, the anti-inflammatory capacity of HDL is found to be independently associated with CV incidence among the general population [56].

Based on the observations between HDL-C and inflammation, HDL and its components are demonstrated to be anti-inflammatory by affecting cholesterol content in plasma membrane lipid rafts of immune cells. It is shown that HDL-C could prevent monocyte from recruiting to vascular endothelium by inhibiting the expression of monocyte adhesion molecules such as CD11b. Moreover, HDL-C could promote monocyte-derived M2 macrophage transition by modulating the expression pattern, leading to anti-inflammatory cytokines production and atherosclerotic plaque regression [57]. Besides, HDL-C could limit TLR-induced proinflammatory signaling in macrophages via increasing the expression of negative transcriptional regulator ATF3 [58]. As receptors of B lymphocytes and T lymphocytes are closely correlated with membrane lipid rafts, HDL and its molecules could cause dysfunctional adaptive immunity that the HDL-deficient mice models are discovered to have abnormal expansions of progenitor lymphocytes and imbalanced production of cytokines and antibodies [59]. In addition, apoA-I injection is able to regulate

Fig. 3



Anti-inflammatory roles of HDL and its components. HDL and ApoA-I could directly interfere with the inflammatory process in atherosclerosis by modulating the cholesterol content of the plasma membrane lipid raft. Ag, antigen; ApoA-I, apolipoprotein A-I; IL, interleukin; TCR, T cell receptor; TLR, toll-like receptor.

inflammation by inducing Treg cells [60]. Furthermore, HDL and its components could influence the differentiation and maturation of antigen-presenting cells such as dendritic cells (DC), thus affecting lymphocyte activation [61].

Therefore, by considering the modification between inflammation and HDL-C in atherosclerosis, integrating HDL-C with related inflammatory parameters might provide a more precise risk evaluation of CAD.

HDL-cholesterol–related inflammatory parameters in coronary artery disease

Monocyte to HDL-cholesterol ratio

Monocytes account for up to 10% of peripheral white blood cells (WBCs) and play fundamental roles in inflammation (Table 1). Activation of monocytes is the crucial initial step in the development of CAD. Studies have shown that circulating monocytes would undergo proliferation and activation under the stimulation of soluble proinflammatory mediators. Thus, the circulating monocytes have been used as an independent predictor of coronary events and plaque severity [62]. As HDL-C could prevent inflammation by directly acting on monocytes, the monocyte to HDL-C ratio (MHR) is proposed as a novel parameter enabling a better assessment of inflammation in atherosclerosis.

In patients with ACS who have undergone PCI, MHR greater than 17.1 is found to be closely related to inhospital mortality [odds ratio (OR), 1.03; 95% confidence interval (CI), 1.01–1.05; $P < 0.01$], which has a sensitivity of 88.5% and a specificity of 49.5% [area under the curve (AUC), 0.756; $P < 0.01$] [63]. Increased MHR is also found to correlate with major adverse cardiac events (MACE) (OR, 1.02; 95% CI, 1.01–1.04; $P < 0.01$). Studies focused on the long-term prognosis of ACS have discovered that MHR could act as a powerful independent predictor of all-cause mortality (risk ratio [RR], 2.61; 95% CI, 1.29–4.89) and MACE (RR, 1.65; 95% CI, 1.36–2.02) [92]. For diabetes complications with ACS, MHR is significantly correlated with inhospital MACE (adjusted hazard ratio [HR], 8.36; 95% CI, 1.57–44.47; $P = 0.013$) and long-term bleeding (adjusted HR, 1.21; 95% CI, 1.07–1.37; $P = 0.002$) [86]. Moreover, MHR independently contributes to bare-metal stent restenosis (SR) in population with stable or unstable angina pectoris (OR, 3.64; 95% CI, 2.45–4.84; $P < 0.001$) and ACS (HR, 1.03; 95% CI, 1.02–1.06; $P < 0.01$) [69,93]. Similarly, a high relation between SR and MHR is demonstrated in ACS patients who have received drug-eluting stent implantation after a mean follow-up duration of 12 months [83]. As contrast-induced nephropathy (CIN) is an acute complication of PCI and inflammation is the main pathophysiological mechanism, MHR is explored

Table 1 Characteristics of clinical studies on the association between HDL-C–related inflammatory parameters and atherosclerosis

Study	Year	Study population	Sample size	Outcomes	Adjusted, OR/HR (95% CI)	*P*	Cutoff value	AUC (95% CI)	Sen (%)	Spe (%)
Karataş *et al.* [63]	2016	STEMI patients undergoing primary PCI	513	Inhospital MACE MHR < 13.90	–	–	20.400	0.639 *P* < 0.01	60.5	65.6
				13.9 ≤ MHR ≤ 22.90	1.320 (0.660–2.660)	0.430				
				MHR>22.90	2.810 (1.480–5.320)	<0.010				
				MHR*	1.020 (1.010–1.040)	<0.010				
Çiçek *et al.* [64]	2016	STEMI patients undergoing successful primary PCI	682	Short-term mortality MHR* Long-term mortality	2.046 (1.701–2.462)	<0.001	2.170	0.840 (0.812–0.868)	81.8	78.1
				MHR < 1.16	–	–				
				1.16 ≤ MHR ≤ 1.59	7.854 (0.977–63.112)	0.053				
				1.60 ≤ MHR ≤ 2.21	5.224 (0.582–46.911)	0.140				
				MHR>2.21	43.559 (5.986–316.994)	<0.001				
Balta *et al.* [65]	2016	STEMI patients undergoing primary PCI	600	No-reflow phenomenon MHR	1.090 (1.070–1.120)	<0.001	22.500	0.768 (0.725–0.811)	70.2	73.3
Arısoy *et al.* [66]	2017	STEMI patients undergoing primary PCI	414	High thrombus burden MHR	1.067 (1.031–1.105)	<0.001	19.700	0.688 (0.641–0.733)	60.5	69.6
Sağ *et al.* [67]	2017	STEMI patients undergoing primary PCI	209	Contrast-induced nephropathy MHR	4.480 (1.380–14.500)	<0.010	0.950	0.780 *P* < 0.01	75.1	74.9
Çağdaş *et al.* [68]	2018	STEMI patients undergoing primary PCI	264	SYNTAX Score II > 34.20 MHR	1.027 (1.013–1.041)	<0.001	13.900	0.786 *P* < 0 0.01	76.0	74.0
Avci *et al.* [69]	2018	STEMI patients undergoing primary PCI	448	Bare stent restenosis MHR ≤ 1.33	–	–	–	–	–	–
				1.33 < MHR < 2.07	1.210 (1.050–1.590)	0.040				
				MHR ≥ 2.07	1.650 (1.190–2.300)	<0.010				
				MHR*	1.030 (1.020–1.060)	<0.010				
Ulus *et al.* [70]	2018	ACS patients undergoing primary/urgent PCI	647	Contrast-induced nephropathy MHR	1.085 (1.051–1.121)	<0.001	17.420	0.700 (.664–.736)	65.7	64.0
Ma *et al.* [71]	2022	ACS patients undergoing PCI	1720	MACE MHR < 7.70	–	–	9.900	0.594(0.562-0.627)	57.5	59.2
				7.7 ≤ MHR ≤ 11.30	1.450 (1.080–1.950)	0.013				
				MHR ≥ 11.30	1.760 (1.300–2.400)	<0.001				
				MHR*	1.030 (1.010–1.050)	0.004				
Yilmaz *et al.* [72]	2016	CAD patients undergoing successful bare-mental stenting	705	Bare-mental stent restenosis MHR	1.290 (1.150–1.490)	<0.001	143.100	0.790 (0.710–0.900)	79	71
Wu *et al.* [73]	2019	CAD patients undergoing PCI	673	All-cause mortality MHR* MACE	3.655 (1.170–11.419)	0.026	Not reported	0.714 p =.006	78.6	61.5
				MHR ≤ 0.19	–	–				
				0.19 < MHR ≤ 0.33	1.652 (0.844–3.233)	0.143				
				0.33 < MHR ≤ 0.53	2.831 (1.433–5.596)	0.003				
				MHR>0.53	3.258 (1.604–6.619)	0.001				
				MHR*	2.390 (1.379–4.143)	0.002				
Zhang *et al.* [74]	2020	CAD patients undergoing PCI	5679	Long-term mortality MHR < 0.40	0.658 (0.480–0.903)	0.009	–	0.600 (0.529–0.670)	–	–
				0.40 ≤ MHR < 0.61	0.712 (0.538–0.941)	0.017				
Açıkgöz *et al.* [75]	2016	STEMI patients	1598	Inhospital MACE MHR	1.501 (1.015–1.993)	0.022	–	–	–	–
				Five-year MACE MHR	1.285 (1.064–1.552)	0.009				
Sercelik *et al.* [76]	2018	STEMI patients	161	TIMI score ≥ 2 MHR	2.340(1.275–4.297)	0.006	2.409	0.669 (0.569–0.8769)	43.1	87.2
Eyyupkoca *et al.* [77]	2022	STEMI patients	231	Adverse cardiac remodeling MHR	3.210 (1.510–840)	0.002	1.600	0.840 (0.780–0.880)	92.7	70.1
Cetin *et al.* [78]	2016	ACS patients	2661	Long-term MACE MHR	1.440 (1.234–1.681)	<0.001	142.900	0.806 (0.785–0.827)	81.5	71.2
Oylumlu *et al.* [79]	2021	ACS patients	825	Long-term mortality MHR	1.027 (1.012–1.043)	<0.001	–	–	–	–
Akboga *et al.* [80]	2016	CAD patients	1229	SYNTAX score ≥ 23 MHR	1.083(1.060–1.108)	<0.001	–	–	–	–
Kundi *et al.* [81]	2016	CAD patients	428	SYNTAX score ≥ 23 MHR	0.474 (0.009–0.019)	<0.001	24.000	0.750 (0.700–0.769)	66.0	65.1
Kalyoncuoglu *et al.* [82]	2020	NSTEMI patients undergoing PCI	426	Slow flow/no-reflow MHR	1.174 (1.006–1.371)	0.040	1.900	0.741 (0.697–0.782)	73.0	65.0
Nan *et al.* [83]	2020	NSTEMI patients undergoing drug-eluting stenting	214	Drug-eluting stent restenosis MHR	1.020 (1.010–1.030)	0.041	402.500	0.650 (0.540–0.750)	62.5	63.7

(Continued)

Study	Year	Study population	Sample size	Outcomes	Adjusted, OR/HR (95% CI)	*P*	Cutoff value	AUC (95% CI)	Sen (%)	Spe (%)
Zhang *et al.* [84]	2016	Suspected patients undergoing coronary angiography	3798	Long-term MACE MHR	2.031(1.268–3.254)	0.003	–	0.562 (0.530–0.594)	–	–
Tok *et al.* [85]	2016	Angina pectoris patients undergoing successful bare-mental stenting	831	Bare stent restenosis 7 ≤ MHR ≤ 10	–	–	14.000	0.746 <.001	71.0	69.0
				12 ≤ MHR ≤ 15	1.020 (0.750–1.320)	0.740				
				18 ≤ MHR ≤ 24	1.450 (1.060–1.880)	0.001				
Li *et al.* [86]	2021	T2DM patients with NSTEMI undergoing PCI	1405	Inhospital MACE MHR	8.360(1.570–44.470)	0.013	0.022	0.722 (0.510–0.933)	75.0	72.7
Kou *et al.* [87]	2021	Suspected patients undergoing coronary angiography	404	CAD presence NHR	1.163 (1.034–1.308)	0.012	1.510	0.617 (0.560–0.675)	94.8	7.6
Başyiğit *et al.* [88]	2022	Patients with documented ischemia	306	Significant coronary stenosis NHR	2.084 (1.147–3.786)	0.016	103.200	0.607 (0.535–0.678)	61.2	58.1
Huang *et al.* [89]	2020	Elderly AMI patients	528	Long-term mortality NHR	1.960 (1.020–3.750)	0.044	5.740	0.690 (0.630–0.760)	77.6	50.8
				Long-term recurrent MI NHR	2.230 (1.040–4.790)	0.040				
Wu *et al.* [90]	2021	CAD patients undergoing PCI	5679	All-cause mortality ACS-WHR	2.036 (1.258–3.296)	00.004	–	–	–	–
				HR stable CAD-WHR	1.586 (1.178–2.136)	0.002				
Luo *et al.* [91]	2021	Subjects undergoing coronary angiography	420	Presence of CAD CHR	1.178 (1.016–1.366)	0.030	1.170	0.662 (0.606–0.719)	39.7	86.7

ACS, acute coronary syndrome; AUC, area under the curve; CAD, coronary artery disease; CHR, C-reactive protein to HDL-C ratio; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events; MHR, monocyte to HDL-C ratio; NHR, neutrophil to HDL-C ratio; NSTEMI, non-ST segment elevated myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; Sen, sensitivity; Spe, specificity; STEMI, ST segment elevated myocardial infarction; M, diabetes mellitus type 2; WHR, white blood cell to HDL-C ratio.

to reveal the association with CIN (adjusted OR, 4.48; 95% CI, 1.38–14.5; $P < 0.01$) [67]. To further explore the relevance between MHR and CAD, MHR is shown to be an independent indicator of high thrombus burden in patients after PCI (OR, 1.067; 95% CI, 1.031–1.105; $P < 0.001$) [66]. Additionally, studies using SYNTAX score to evaluate the severity of CAD have found that MHR was positively correlated with SYNTAX score in ST-elevation MI (STEMI) patients ($r = 0.580$; $P < 0.001$) and stable CAD patients ($r = 0.371$; $P < 0.001$) [68,72]. Furthermore, MHR is significantly associated with Gensini score and TIMI grade in ACS and CAD patients, indicating a prognostic role of MHR in predicting the complexity and plaque burden of CAD [76,94]. Based on angiographic results, MHR is found to be highly associated with the no-flow phenomenon [82]. In sum, robust evidence has demonstrated the prognostic value of MHR in predicting the prognosis of CAD.

Neutrophil to HDL-cholesterol ratio

Neutrophils comprise the largest fraction of WBC and are the main effector cells in acute Inflammation. It is found that neutrophils could secrete an array of immunomodulatory cytokines to enhance the recruitment and function of immune cells in atherosclerosis. Therefore, the neutrophil count has been used to predict the presence of CAD and long-term mortality in patients with stable CAD [95]. Besides, neutrophils are significantly increased among patients experiencing MI, and plaque injury could induce myeloperoxidase production in neutrophils [96]. To improve the risk prediction value of neutrophils, the neutrophil to HDL-C ratio (NHR) is investigated. A cross-sectional study has shown that NHR with a cutoff value of 1.51 could independently predict CAD and has a sensitivity of 94.8%, Yoden index of 0.024, and AUC of 0.617 (95% CI, 0.560–0.675; $P < 0.001$) [87]. Besides, NHR displays a superiority over MHR in predicting long-term mortality (HR, 1.96; 95% CI, 1.02–3.75; $P = 0.044$) and long-term recurrent MI (HR, 2.23; 95% CI, 1.04–4.79; $P = 0.040$) in elderly ACS patients [89]. Furthermore, NHR is positively correlated with the Gensini score and the extent of stenosis in CAD patients, which suggests a relevance between NHR and CAD severity [88].

White blood cell to HDL-cholesterol ratio

WBC is an important marker of systemic inflammation and has been reported to be a risk factor for CV events in patients with inflammatory bowel disease [97]. Based on this, WBC is further found to be positively associated with the incidence of CAD among young adults and is an independent risk factor for multivessel diseases in the general population [98,99]. Previous studies have proposed that WBC count was linked to the severity of atherosclerosis in CAD patients and correlated with the adverse CV outcomes in patients who had PCI and diabetic patients who manifested CAD [100]. Besides,

a higher level of WBC is shown to indicate the development of heart failure in patients with stable CAD [101]. Interestingly, the association between WBC and CAD could be improved and serve as an independent predictor by associating with apoA-I [102]. Therefore, the WBC to HDL-C ratio (WHR) is utilized to measure the inflammatory status. A large retrospective study with a sample size of 5679 has discovered that WHR could predict the prognosis of CAD patients who have undergone PCI. Moreover, a cutoff value of 8.25 enables WHR independently associated with all-cause death in ACS patients (adjusted HR, 2.036; 95% CI, 1.258–3.296; $P = 0.004$) and CAD patients (adjusted HR, 1.586; 95% CI, 1.178–2.136; $P = 0.002$) [90].

High-sensitive C-reactive protein to HDL-cholesterol ratio

CRP is a well-established inflammatory biomarker induced in the early stages of atherosclerosis. High-sensitive CRP (hs-CRP) test is a highly sensitive assay that could detect extremely low serum levels of CRP. A wealth of data has discovered that hs-CRP was valuable in short-term prognosis and long-term risk assessment of CAD [103]. Notably, elevated hs-CRP with low HDL-C level is significantly linked to an increased incidence of all-cause death in patients who received PCI. Moreover, hs-CRP is found to be inversely associated with the RCT of HDL and the association between hs-CRP and coronary artery calcification score could be modified by HDL-C [7,104]. Therefore, hs-CRP to HDL-C ratio (CHR) is explored and has been discovered to be an independent predictor of CAD presence (adjusted OR, 1.178; 95% CI, 1.016–1.366; $P = 0.03$) with a specificity of 86.7%, Yoden index of 0.264 and AUC of 0.662 (95% CI, 0.606–0.719; $P < 0.001$) [91]. Additionally, CHR is shown closely related to Gensini score in coronary angiography ($r = 0.389$; $P < 0.001$). Moreover, in a population with subclinical CAD, CHR is correlated with left ventricular diastolic dysfunction (OR = 0.649; 95% CI, 0.444–0.948; $P = 0.025$) [105].

Discussion

As stated above, HDL-C–related inflammatory parameters are strongly associated with CV events in CAD populations, which might benefit the management of CAD by identifying patients with elevated residual risk. However, most of these studies are based on single-center cross-sectional retrospective cohorts, which might result in bias as potential confounding factors could not be included in the analysis. Besides, given that HDL-C–related inflammatory parameters are measured at different time points across studies and mostly only once, the interpretation and consistency of results are largely limited. Moreover, the practical use of these parameters would be restricted as the cutoff value and reference range vary from study to study. Because the association between inflammation and atherosclerosis is complex and vast, the additive clinical value of HDL-C–related inflammatory parameters in current risk scoring models needs further investigation to avoid underestimation. Therefore, more data is needed to assess the clinical implication of the HDL-C–related inflammatory parameters in CAD.

Evidence-based guidelines on CV disease prevention have established the critical role of persistent inflammation in driving atherosclerosis [106]. Chronic inflammatory conditions and biomarkers such as rheumatoid arthritis and hs-CRP are listed as risk-enhancing factors in CAD, which could contribute to the revision of risk estimation. However, adding inflammatory biomarkers such as hs-CRP has shown minor improvements in risk assessment of conventional models, and the cumulative effects of hs-CRP in discrimination and reclassification are inconsistent across studies [107]. In this regard, as most of these results come from synthesized literature, the practical value of inflammation in predicting CAD might be underestimated due to the limits of these models. Moreover, it remains discussed whether the introduction of hs-CRP could explain the overall inflammatory risk. Because there are differences in the prevalence of autoimmune diseases and inflammatory conditions concerning sex, ethnic groups, ages, cigarette consumption, obesity, etc. [108], adding these factors might help to modify the inflammatory assessment. Therefore, a risk calculator that incorporates comprehensive inflammatory parameters calls for need, and in this sense, the HDL-C–related inflammatory parameters might contribute to improvements in the model.

Identification of elevated inflammatory risk in CAD patients calls for intensity-matched treatment. Therapy with statin in ACS patients has been observed to reduce recurrent coronary events and mortality through its anti-inflammatory effects [109]. The target level of hs-CRP less than 2 mg/l achieved by statin is significantly associated with event-free survival, and the achieved hs-CRP levels are independently associated with long-term survival among ACS patients [110]. With the aid of intravascular ultrasonography, the change of hs-CRP is further identified as an independent predictor of plaque regression after statin therapy. Besides, guided by high hs-CRP level but normal LDL-C level, statin has effectively reduced coronary risk in healthy individuals [111]. Moreover, anti-inflammatory drugs such as steroids could further reduce CV events in CAD patients [112]. Disease-modifying antirheumatic drugs and TNF-α inhibitors are found to prevent CAD risk by reducing systemic inflammatory burden while improving lipid profiles and insulin resistance [113]. Nevertheless, in addition to myopathy and hepatic injury, statin administration among the healthy population has reported significant diabetes, and concurrent

anti-inflammatory treatment might increase the risk of bleeding and life-threatening infection in CAD patients [114]. Therefore, exploring novel therapeutic agents with good safety profiles to ameliorate inflammation in CAD is of great clinical relevance. In this regard, efforts have been made to target innate immunity in atherosclerosis, such as the anti-IL-1β antibody canakinumab, which could reduce recurrent major adverse CV events over guideline-recommended standard therapies in MI patients with hs-CRP greater than 2 mg/l [115]. Moreover, the success of canakinumab has spurred the development of NLRP3 inflammasome inhibitors, which have yielded convincing results in preventing the initiation and progression of atherosclerosis [116]. Although much accomplishment has been achieved, translation from research to clinical use requires more investigation and consideration.

Conclusion

In terms of the association between inflammation and HDL-C in atherosclerosis, our review summarizes clinical trials about HDL-C–related inflammatory parameters in CAD for the first time. We have found that HDL-C is closely interconnected with the inflammatory process, and the HDL-C–related inflammatory parameters are positively correlated with the adverse outcomes in CAD patients. Besides, experimental and clinical studies have suggested that modulating the inflammatory process provides promising targets for mitigating the CAD burden. Moreover, evidence is absent on whether these novel inflammatory parameters could serve as indicators in measuring the efficacy of anti-inflammatory treatment. Therefore, further studies are needed to reveal the clinical implications of the HDL-C–related inflammatory parameters.

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Conflicts of interest

There are no conflicts of interest.

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