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Comparison of the Utility of New Putative Inflammatory Biomarkers for Predicting the Incidence of All-cause and Cause-Specific Mortality

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Abstract

Background: Inflammation and dyslipidemia have significant roles in the pathophysiology of cardiovascular disease (CVD). Recently, leukocyte subtypes to high-density lipoprotein cholesterol (HDL-C) ratios have been proposed as potential indicators of inflammation. However, their value for the mortality incidence remains unclear.

Objectives: We investigated and compared the association of neutrophil /HDL-C (NHR), lymphocyte /HDL-C (LHR), white blood cell (WBC) /HDL-C, and mixed cell /HDL-C(defined as the sum of monocyte, basophil, and eosinophil counts divided by HDL-C) with all-cause and cause-specific mortality.

Methods: Data from the Mashhad stroke and heart atherosclerotic disorder (MASHAD) study was analyzed. Cumulative hazard analysis and log-rank test were utilized to evaluate the differences in mortality within different indices tertiles. The associations of baseline indices with mortality were investigated using Cox proportional hazard regression among various models. Predictive performance was evaluated utilizing c-statistic, integrated discrimination improvement (IDI), and continuous net reclassification improvement (cNRI).

Results: 8702 subjects were recruited. During 10 years of follow-up, 343 deaths from all-cause, 140 from CVD, and 106 from coronary heart disease (CHD) were identified. Using multivariable models, mixed cell /HDL-C showed the strongest association, although non-significant, with total mortality compared to the other indices, with hazard ratios (HRs) and 95% confidence intervals (95%CI) of 1.264 (0.992-1.610). For CVD and CHD mortality, the HRs (95% CI) were 1.070 (0.683-1.676) and 1.221 (0.791-1.887), respectively. Based on the c-statistic and IDI, WBC/HDL-C showed a non-significant improvement in predictive performance for all-cause mortality (IDI 0.003, 95%CI 0-0.014) for all-cause mortality (IDI 0.003, 95%CI 0-0.014). Based on the c-statistic index and NRI, mixed cell/ HDL-C had better performance for CVD (cNRI 0.125, 95%CI 0.021-0.175) and CHD (cNRI 0.137, 95%CI 0.038-0.218) mortality.

Conclusion: Among the MASHAD study population, WBC/HDL-C had a greater predictive ability for all-cause mortality. However, the mixed cell/ HDL-C index was a promising predictive biomarker for the incidence of CVD and CHD mortality.

Keywords: leukocyte subtypes, high-density lipoprotein cholesterol, all-cause mortality, cardiovascular mortality, coronary heart disease mortality

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1. Background

Cardiovascular disease (CVD) remains at the forefront of global mortality causes, accounting for almost a third of all annual deaths (1). Age-standardized estimates show a global prevalence of around 6.2%, resulting in a mortality rate of 233 per 100,000 (1). Additionally, with the demographic shift being seen global landscape, the burden of CVD is expected to rise (2). There has been a growing interest in the significance of inflammatory biomarkers in chronic diseases and their ability to predict mortality. Inflammation is also increasingly recognized as a critical underlying mechanism influencing the pathogenesis of various chronic conditions, including CVD, diabetes, and cancer (3, 4). As such, various biomarkers have been studied to evaluate their efficacy as prognostic tools in this regard (5-8).

Recently, multiple biomarkers such as neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP), platelet to lymphocyte ratio (PLR), and systemic immune inflammation index (SII) have been extensively investigated in this regard (3-5, 7, 9, 10). These appear to serve as important markers for assessing the risk of all-cause and cause-specific mortality, with each providing unique insights into systemic inflammation and immune response dynamics (3-5, 7, 9, 10). However, interest is growing in the use of novel markers, chiefly among them the ratio between various white blood cell (WBC) and high-density lipoprotein cholesterol (HDL-C). This interest stems from an evolving understanding of HDL-C not only as a plasma cholesterol carrier but also as a modulator of anti-inflammatory responses, with reduced levels being associated with accelerated atherosclerosis and cardiovascular death (11). A previous study has shown that the ratios of both lymphocytes and neutrophils to HDL-C were valuable markers for predicting metabolic syndrome in women (12). Another study showed that elevation of all HDL-C–related inflammatory parameters correlated with increased severity and mortality among COVID-19 patients (13). In patients with CVD, elevated platelet to HDL-C ratio (PHR) (14), monocyte to HDL-C ratio (MHR) (6), neutrophil to HDL-C ratio (NHR) (15), and WBC to HDL-C ratios (16) were independent predictors of long-term mortality and disease severity. Interestingly, elevated levels of NHR were also seen to be significantly correlated with the risk of developing depression in adults (17). Despite the growing body of evidence in favor of these novel biomarkers, there is sparse evidence of their prognostic utility in predicting all-cause mortality. Thus, the present study aims to evaluate NHR, LHR, WBC /HDL-C, and mixed cell /HDL-C and assess their value as potential prognostic markers for predicting all-cause and cause-specific mortality. We hypothesized that WBC/HDL-C would demonstrate superior prognostic performance compared with the other indices, particularly for all-cause mortality.

2. Methods

2.1. Study Design and Participants

This study utilized data from the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) study, which began in 2010 (18). We selected participants from three regions in Mashhad, Iran, using stratified cluster random sampling. Each region included nine sites within Mashhad Healthcare Center divisions. Eligible individuals, aged 35-65 years, were identified, and local authorities distributed informative brochures to families. Community leaders also assisted in identifying and recruiting participants. After identifying eligible individuals, appointments were scheduled for physical exams. A nurse and two healthcare professionals gathered lifestyle, demographic, and anthropometric data using questionnaires. Questionnaires covered questions relating to: demographics, tobacco and alcohol use, physical activity,

food frequency, 24-hour food records, anxiety, and depression.

2.2. Study Phases

In the first phase of the MASHAD study, cross-sectional data were collected from participants with and without CVD. In the second phase, individuals with CHD, peripheral arterial disease, and stroke were excluded, and the remaining participants were followed for 10 years to assess the incidence of these disorders. Those identified as medium- or high-risk received counseling on physical activity, diet, and smoking cessation and were referred for cardiology consultations. Participants with elevated blood pressure, cholesterol, or other concerning findings were referred for medical follow-up. Urgent findings requiring immediate medical attention were promptly communicated to both the participant and their physician by telephone upon identification. In the present study, subjects with established CVD at baseline and missing mortality data were excluded. Also, to diminish the risk of acute infection that affects leucocyte subtypes, subjects with high sensitivity C-reactive protein (hs-CRP) ≥10 mg/L were excluded.

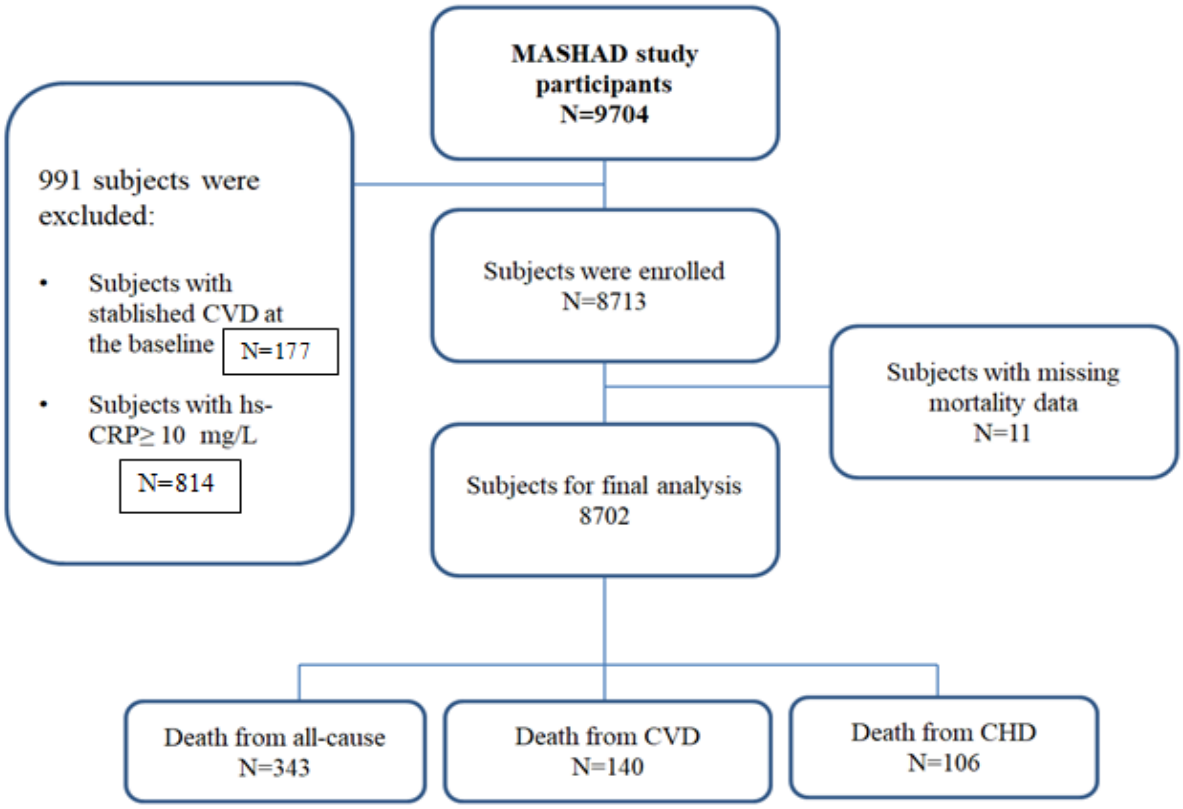

Figure 1. Flowchart of the present study

2.3. Biochemical and other measurements

Fasting blood samples were collected between 8 and 10 a.m. Blood was processed within 30-45 minutes, with plasma and serum divided into six aliquots, and dispatched to Bu Ali Research Institute of Mashhad. Serum aliquots were stored at -80°C for future analysis. Biochemical parameters were measured using a BT3000 auto-analyzer (Pars Azmoon kits, Iran). A standard 12-lead electrocardiogram with properties of 25 mm/s paper speed and 10 mm/mV was performed and scored using Minnesota codes (19). Stroke was defined according to WHO criteria as the sudden onset of focal or global cerebral dysfunction lasting more than 24 hours with no clear

cause other than a vascular origin (20). CHD was diagnosed based on angina, myocardial infarction (6), or ECG findings. Current smokers were defined as daily smokers, while ex-smokers were former daily smokers who no longer smoked.

2.4. Covariates

Body mass index (BMI) was calculated by dividing weight (kg) by height (m^2) (21). A BMI ≥25 kg/m^2 indicated overweight, while a BMI ≥30 kg/m^2 signified obesity (22). Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or current use of antihypertensive medications (23). Diabetes was diagnosed with fasting blood glucose ≥126 mg/dL or treatment with insulin or hypoglycemic agents, following the American Diabetes Association criteria (24). Dyslipidemia was identified as total cholesterol ≥200 mg/dL, LDL-C ≥130 mg/dL, triglycerides ≥150 mg/dL, or HDL-C <40 mg/dL in men and <50 mg/dL in women (25). The mixed cell consisted of monocytes, basophils, and eosinophils (26). The mixed cell count was defined as the sum of monocytes, eosinophils, and basophils, as reported in the complete blood count differential. The mixed cell-to-HDL-C ratio was subsequently calculated as mixed cell count divided by HDL-C. Because the mixed cell parameter is a composite measure rather than a conventional inflammatory biomarker, sensitivity analyses were performed by separately evaluating the monocyte-to-HDL-C ratio (MHR), eosinophil-to-HDL-C ratio (EHR), and basophil-to-HDL-C ratio (BHR). In addition, Spearman correlation coefficients were calculated to assess the internal correlation among monocyte, eosinophil, and basophil counts.

The following ratios were calculated: neutrophil to HDL-C ratio (NHR)= neutrophils/HDL, lymphocyte to HDL ratio (LHR)= lymphocytes /HDL-C (27), WBC to HDL-C= WBC /HDL-C (28), and mixed cell to HDL-C= mixed cell /HDL-C.

2.5. Mortality surveillance

Participants were monitored for mortality from baseline until 2020, with follow-ups every three years. Follow-up questionnaires assessed health and lifestyle changes and accompanied follow-up analysis. Death causes were confirmed through the Iranian Ministry of Health registry and the death cause questionnaire which was asked from their spouse or children. CVD death was defined as death from MI, chronic ischemic heart disease, heart failure, fatal arrhythmia, cerebrovascular, pulmonary thromboembolism, peripheral vascular disease, and sudden cardiac arrest. CHD death was defined as death because of MI and chronic ischemic heart disease.

2.6. Ethics statement

Participants received a 10-minute explanation and were provided with written informed consent. The Ethics Committee of Mashhad University of Medical Sciences approved the study (approval number: IR.MUMS.REC.1386.250).

2.7. Statistical analysis

Categorical variables are presented as frequencies and percentages, while continuous variables are reported as means ± standard deviations (SD). The chi-square test compared categorical variables, and one-way ANOVA was used for continuous variables. Kaplan-Meier method was used to estimate the mortality, and differences in curves were tested by log-rank test. The associations of the indices with the risk of mortalities were estimated using multivariate Cox proportional hazards models, and the result is presented as hazard ratios (HR) and 95% confidence intervals (CI). Predictive performance was evaluated utilizing informativeness, c-statistic, integrated discrimination improvement (IDI), and continuous net reclassification improvement (cNRI). A p-value of less than 0.05 was considered significant.

3. Results

3.1. Baseline Characteristics and Tertile Mortality

A total of 8702 individuals were included. Table 1 shows the baseline characteristics of participants categorized by all-cause, CVD, and CHD mortality. Significant differences were observed regarding the ages of each category. In all instances, the average age of those in the mortality subgroups was substantially higher than their counterparts (P < 0.001). In regards to the inflammatory biomarkers, the ratio of WBC /HDL-C was significantly higher in those with all-cause mortality (6.20 ± 2.86) compared to those without (5.73 ± 2.06, P = 0.003). A similar trend was observed for all the biomarkers assessed, with them being significantly higher in all-cause mortality. This was true for CHD mortality except for NHR, however, none of the baseline measurements were seen to significantly differ concerning CVD mortality. Table 2 summarizes mortality according to the tertiles of the studied markers. The results indicate that all-cause and cause-specific mortality was significantly associated with the higher tertiles of WBC and Mixed-cell ratios. In contrast, except for CHD mortality and LHR, none of the other observations were deemed statistically significant.

Table 1. Baseline characteristics stratified by all-cause and cause-specific mortality

Variable		All-cause mortality			CVD mortality			CHD mortality		
		YES (343, 3.90%)	**NO** (8359, 96.10%)	**P-value**	**YES** (140, 1.60%)	**NO** (8562, 98.40%)	**P-value**	**YES** (106, 1.20%)	**NO** (8596, 98.80%)	**P-value**
Age (year)		54.37±7.69	47.59±8.11	<0.001	54.65±7.64	47.75±8.17	<0.001	54.67±7.96	47.78±8.17	<0.001
Sex (female)		151 (44.00%)	5072 (60.70%)	<0.001	52 (37.10%)	5171 (60.40%)	<0.001	38 (35.80%)	5185 (60.30%)	<0.001
Smoking status	**Non-smoker**	205 (59.80%)	5802 (69.40%)	0.001	76 (54.30%)	5931 (69.30%)	0.001	58 (54.70%)	5940 (69.20%)	0.006
	Ex-smoker	788 (9.40%)	46 (13.40%)		21 (15.00%)	813 (9.50%)		15 (14.20%)	819 (9.50%)	
	Current smoker	92 (26.80%)	1769 (21.20%)		43 (30.70%)	1818 (21.20%)		33 (31.10%)	1828 (21.30%)	
Diabetes (YES)		108 (32.00%)	1036 (12.50%)	<0.001	54 (39.10%)	1090 (12.80%)	<0.001	39 (37.10%)	1105 (13.00%)	<0.001
Hypertension (YES)		164 (48.00%)	2453 (29.40%)	<0.001	80 (57.10%)	2537 (29.70%)	<0.001	58 (54.70%)	2559 (29.80%)	<0.001
BMI (kg/m2)		27.86±4.85	27.70±4.62	0.575	28.01±4.78	27.71±4.62	0.459	28.24±4.85	27.70±4.62	0.262
Glucose (mmol)		6.24±3.33	5.02±1.98	<0.001	6.66±3.70	5.04±2.01	<0.001	6.52±3.58	5.05±2.03	<0.001
LDL-C (mmol)		3.05±0.93	3.00±0.90	0.363	3.11±0.95	3.00±0.90	0.195	3.12±0.95	3.00±0.90	0.201
HDL-C (mmol)		1.08±0.27	1.11±0.26	0.075	1.05±0.24	1.11±0.25	0.012	1.05±0.23	1.10±0.26	0.022
TC (mmol)		5.08±1.12	4.92±0.99	0.004	5.14±1.15	4.92±0.99	0.012	5.16±1.10	4.92±0.99	0.029
Triglycerides (mmol)		1.86±1.41	1.59±1.02	<0.001	1.89±1.39	1.60±1.03	0.001	1.95±1.50	1.59±1.03	<0.001
Hs-CRP (mg/l)		2.52±2.04	2.22±1.92	0.005	2.37±1.87	2.23±1.92	0.367	2.39±1.97	2.22±1.92	0.380
RBC (10^6/ul)		4.92±0.49	4.84±0.49	0.007	4.98±0.48	4.85±0.49	0.002	5.02±0.48	4.85±0.49	<0.001
Hemoglobin (g/dL)		14.03±1.50	13.72±1.56	<0.001	14.18±1.47	13.72±1.56	0.001	14.25±1.50	13.72±1.56	0.001
Platelets (10^3/ul)		219.34±63.18	229.52±59.80	0.004	222.15±65.28	229.23±59.89	0.207	228.89±62.44	229.13±59.94	0.969
WBC (10^3/ul)		6.27±2.31	6.01±1.47	0.002	6.19±1.45	6.01±1.51	0.168	6.36±1.44	6.01±1.51	0.015
Neutrophil (10^3/ul)		3.31±1.16	3.25±1.10	0.310	3.24±1.10	3.27±1.12	0.803	3.35±1.16	3.24±1.16	0.401
Lymphocyte (10^3/ul)		2.29±1.70	2.16±0.66	0.002	2.21±0.64	2.16±0.72	0.399	2.25±0.66	2.16±0.72	0.157
Mixed cell (10^3/ul)		0.67±0.34	0.61±0.34	0.003	0.66±0.32	0.61±0.34	0.085	0.70±0.31	0.61±0.34	0.009
WBC /HDL-C		6.20±2.86	5.73±2.06	**0.003**	6.09±1.96	5.74±2.10	0.052	6.31±2.01	5.74±2.10	**0.006**
NHR		3.20±1.57	3.08±1.32	**0.046**	3.20±1.28	3.09±1.33	0.328	3.30±1.32	3.09±1.33	0.114
LHR		2.25±1.58	2.06±0.83	**0.032**	2.19±0.84	2.06±0.88	0.099	2.25±0.88	2.06±0.88	**0.029**
Mixed cell /HDL-C		0.66±0.41	0.58±0.38	**0.002**	0.64±0.33	0.58±0.38	0.096	0.68±0.31	0.58±0.38	**0.018**

Abbreviations: CVD: cardiovascular disease; CHD: coronary heart disease; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; Hs-CRP: high sensitivity C-reactive protein; RBC: red blood cell; WBC: white blood cell; NHR: neutrophil to HDL-C ratio; LHR: lymphocyte to HDL-C ratio.

Table 2. Mortality according to WBC/HDL, NHR, LHR, and Mixed-cell/HDL-C tertiles

Mortality	WBC /HDL Tertile			P-value	NHR Tertile			P-value	LHR Tertile			P-value	Mixed cell /HDL-C Tertile			P-value
	1	2	3		1	2	3		1	2	3		1	2	3	
All-cause	90	116	126	**0.002**	89	106	117	0.137	105	101	122	0.299	91	87	134	**0.001**
CVD	28	52	54	**0.004**	31	47	48	0.111	35	41	57	0.050	32	39	55	**0.035**
CHD	20	39	44	**0.004**	23	38	38	0.101	24	34	45	**0.038**	18	34	47	**0.002**

Abbreviations: CVD: cardiovascular disease; CHD: coronary heart disease; WBC: white blood cell; NHR: neutrophil to HDL-C ratio; LHR: lymphocyte to HDL-C ratio.

3.2. Multivariate Adjusted Model and Kaplan-Meier survival curves

Table 3 summarizes the multivariable-adjusted HRs for the association of various biomarkers with total and cause-specific mortality. Adjustment was made to age, sex, smoking status, physical activity level (PAL), diabetes mellitus, hypertension, cholesterol, triglycerides, and low-density lipoprotein cholesterol. In the crude model, all of the biomarkers were significantly associated with all-cause mortality, however, after adjustment, this only held for WBC and lymphocyte ratios (P-values of 0.013 and 0.008, respectively). Although some associations were observed in the crude model for CVD and CHD mortality, none remained statistically significant after adjustment. Notably, although the Kaplan–Meier analysis showed a significant difference in all-cause mortality according to NHR (log-rank P = 0.003), this association was no longer significant after multivariable adjustment (adjusted HR, P = 0.228), indicating that the unadjusted survival difference disappeared after adjustment for age, sex, and cardiovascular risk factors. Kaplan-Meier survival curves illustrated the relationship between various biomarkers and mortality outcomes, and in contrast to the adjusted model, more significant associations were seen in cause-specific mortality than with all-cause. The log-rank test results indicated significant differences in survival based on WBC /HDL-C (P = 0.007) and mixed cell /HDL-C (P < 0.001) for all-cause mortality. For both CVD and CHD mortality, all but NHR were deemed statistically significant (Figure 2).

Table 3. Univariable and multivariable hazard ratios for the association of variables with total and cause-specific mortality

Variable	All-cause mortality		CVD mortality		CHD mortality	
	Crude model HR (95%CI) P-value	**Adjusted model** HR (95%CI)* P-value	**Crude model** HR (95%CI) P-value	**Adjusted model** HR (95%CI) * P-value	**Crude model** HR (95%CI) P-value	**Adjusted model** HR (95%CI) * P-value
WBC /HDL-C (Continuous)	1.102 (1.055-1.152) **<0.001**	1.070 (1.014-1.129) **0.013**	1.082 (1.006-1.162) **0.033**	1.018 (0.932-1.112) 0.690	1.121 (1.039-1.210) **0.003**	1.055 (0.959-1.161) 0.275
NHR (Continuous)	1.100 (1.021-1.186) **0.012**	1.055 (0.967-1.150) 0.228	1.069 (0.946-1.208) 0.285	0.979 (0.847-1.131) 0.771	1.117 (0.981-1.272) 0.096	1.015 (0.867-1.188) 0.853
LHR (Continuous)	1.185 (1.098-1.278) **<0.001**	1.151 (1.037-1.278) **0.008**	1.145 (0.996-1.317) 0.057	1.032(0.839-1.268) 0.767	1.188 (1.038-1.360) **0.012**	1.086 (0.876-1.348) 0.451
Mixed cell/HDL-C	1.339 (1.162-1.543) **<0.001**	1.264 (0.992-1.610) 0.058	1.295 (1.004-1.670) **0.046**	1.070 (0.683-1.676) 0.767	1.372 (1.092-1.723) **0.007**	1.221 (0.791-1.887) 0.367

Abbreviations: CVD: cardiovascular disease; CHD: coronary heart disease; WBC: white blood cell; NHR: neutrophil to HDL-C ratio; LHR: lymphocyte to HDL-C ratio.

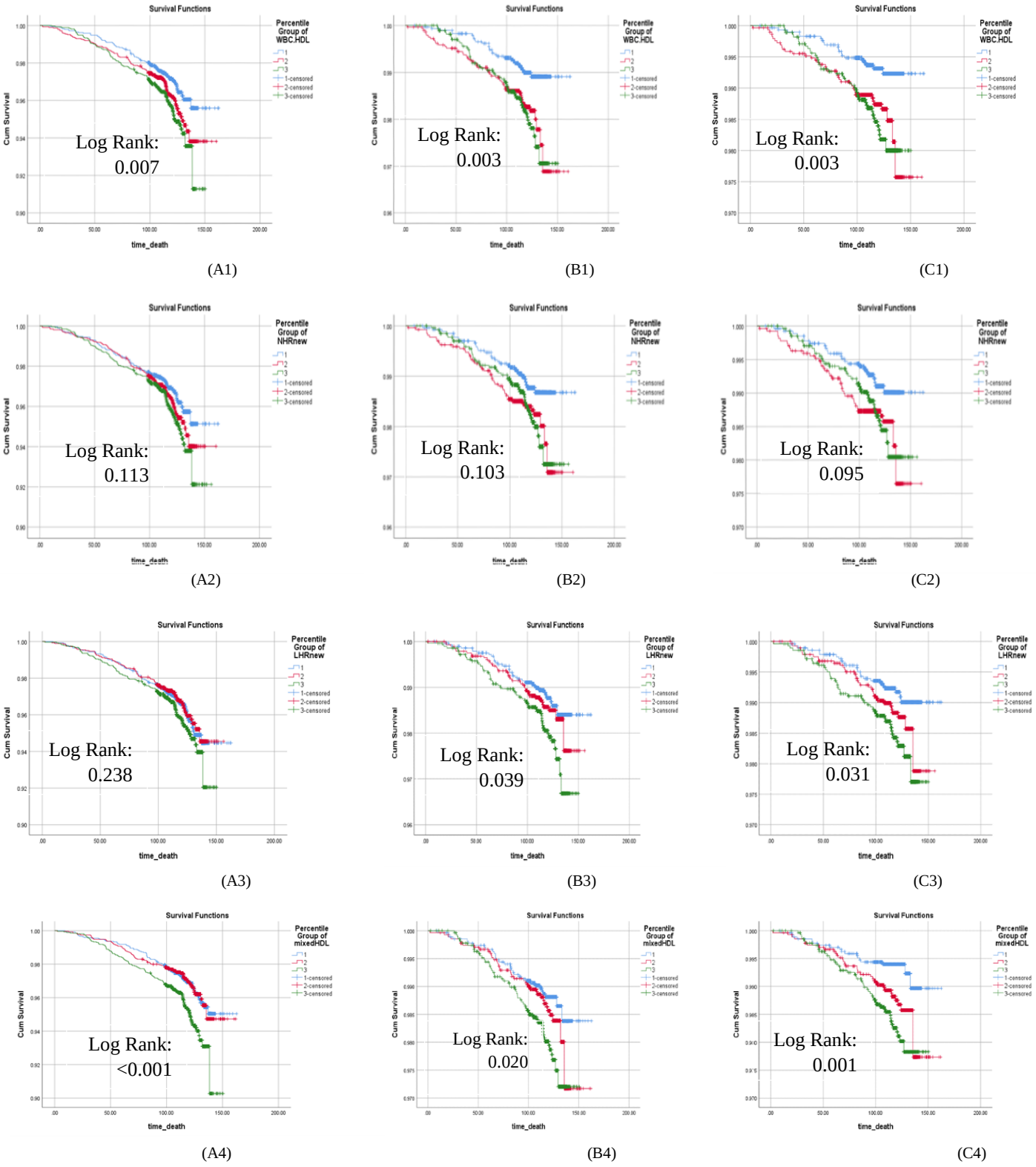

Figure 2. Kaplan-Meier survival curves for all-cause (A), cardiovascular (B), and CHD (C) mortality according to the WBC/HDL-C, NHR, and LHR.

A1 Kaplan-Meier survival curves of all-cause mortality according to WBC/HDL-C; B1 Kaplan-Meier survival curves of cardiovascular mortality according to WBC/HDL-C; C1 Kaplan-Meier survival curves of CHD mortality according to WBC/HDL-C; A2 Kaplan-Meier survival curves of all-cause mortality according to NHR; B2 Kaplan-Meier survival curves of cardiovascular mortality according to NHR; C2 Kaplan-Meier survival curves of CHD mortality according to NHR; A3 Kaplan-Meier survival curves of All-cause mortality according to LHR; B3 Kaplan-Meier survival curves of cardiovascular mortality according to LHR; C3 Kaplan-Meier survival curves of CHD mortality according to LHR. A4 Kaplan-Meier survival curves of all-cause mortality according to Mixed-cell/HDL-C; B4 Kaplan-Meier survival curves of cardiovascular mortality according to Mixed-cell/HDL-C; C4 Kaplan-Meier survival curves of CHD mortality according to Mixed-cell/HDL-C.

3.3. Risk Reclassification Improvement with Lipid Indices and C-Statistic

Tables 4 and 5 show the C-statistic for models incorporating the indices in predicting total and cause-specific mortality, also incorporating integrated discrimination improvement (IDI) and net reclassification improvement (NRI). The base model exhibited a C-statistic of 0.764 for all-cause mortality, which improved with the addition of lipid indices, reaching 0.77 with WBC /HDL-C. For CVD mortality, the base model C-statistic was 0.797, and the inclusion of NHR and mixed cell /HDL-C improved it to 0.805. Similarly, for CHD mortality, the C-statistic increased from 0.784 to 0.799 with the addition of mixed cell /HDL-C. Furthermore, risk reclassification improvement was assessed using IDI and NRI metrics. For all-cause mortality, the addition of WBC /HDL-C resulted in an IDI of 0.003 (0, 0.014), indicating a modest improvement in risk prediction. For CVD mortality, mixed cell /HDL-C achieved an NRI of 0.125, suggesting a significant enhancement in predictive accuracy. A similar improvement was seen with mixed cell /HDL-C in CHD mortality, resulting in an NRI of 0.137.

Table 4. C-statistic for the models includes indexes in the prediction of total and cause-specific mortality.

Parameter	C-statistic(95%CI) P-value		
	All-cause mortality	CVD mortality	CHD mortality
Base model[#]	0.764 (0.74,0.788)	0.797 (0.763,0.831)	0.784 (0.742,0.826)
LHR	0.766 (0.742,0.79) P-value=0.102	0.8 (0.766,0.834) P-value=0.163	0.792 (0.75,0.834) P-value=0.180
NHR	0.769 (0.745,0.793) P-value=0.126	0.805 (0.771,0.839) P-value=0.589	0.798 (0.756,0.84) P-value=0.612
Mixed cell /HDL-C	0.769 (0.745,0.793) P-value=0.021*	0.805 (0.771,0.839) P-value=0.176	0.799 (0.757,0.841) P-value=0.062
WBC /HDL-C	0.770 (0.746,0.794) P-value=0.023*	0.803 (0.769,0.837) P-value=0.106	0.796 (0.754,0.838) P-value=0.090

[#]Base model includes age, sex, smoking status, PAL, diabetes, hypertension, Cholesterol, TG, and LDL-C. Each lipid index was added to the base model (base model+LHR, base model+NHR, base model+ mixed/ HDL-C, and base model+ WBC/HDL-C).
P-value indicates the statistical significance of the difference between the C-statistics of the two Cox regression models, as assessed using the compareC test.
Abbreviations: CVD: cardiovascular disease; CHD: coronary heart disease; WBC: white blood cell; NHR: neutrophil to HDL-C ratio; LHR: lymphocyte to HDL-C ratio; CI: Confidence Interval.

Table 5. Risk reclassification improvement* for total and cause-specific mortality with the addition of covariates to the base model

Parameter	IDI	NRI
All-cause mortality		
LHR	0.001 (0,0.005)	0.030 (-0.094,0.091)
NHR	0.003 (0,0.011)	0.014 (-0.037,0.082)
Mixed cell /HDL-C	0.001 (0,0.003)	0.132 (-0.027,0.166)
WBC /HDL-C	0.003 (0,0.014)	0.047 (-0.001,0.108)
CVD mortality		
LHR	0 (0,0.001)	0.053 (-0.122,0.118)
NHR	0.002 (0,0.014)	0.031 (-0.020,0.094)
Mixed cell /HDL-C	0 (0,0.003)	0.125 (0.021,0.175)*
WBC /HDL-C	0.001 (0,0.004)	0.056 (0.004,0.112) *
CHD mortality		
LHR	0 (-0.001,0.002)	0.075 (-0.008,0.177)
NHR	0.004 (0.001,0.019)*	0.044 (-0.005,0.141)
Mixed cell /HDL-C	0 (0,0.002)	0.137 (0.038,0.218)*
WBC /HDL-C	0.004 (0,0.012)	0.131 (-0.011,0.247)

* IDI and NRI show the improvement of risk prediction between the base model: including age, sex, smoking status, PAL, DM, HTN, Cholesterol, TG, and LDL-C, and the extended model which additionally includes each lipid index.

4. Discussion

This study aimed to investigate the relationship between inflammatory biomarkers (WBC /HDL-C, NHR, LHR, mixed cell/HDL-C) and mortality outcomes, including all-cause, CVD, and CHD mortality. A population totaling 8713 patients was examined, and the results showed that higher levels of these biomarkers, in particular WBC /HDL-C and LHR, were associated with increased risk of all-cause mortality. Although there was a promising trend for these markers to predict cause-specific mortality, the adjusted model which took into consideration several key variables revealed an insignificant correlation within the population for all of them. However, Kaplan-Meier survival curves did show a significant correlation with cause-specific mortality in all but NHR. Moreover, C-statistic analysis indicated that models incorporating these biomarkers improved predictive accuracy for mortality outcomes, with WBC /HDL-C showing greater performance for all-cause mortality, while mixed cell /HDL-C and NHR excelled for CVD and CHD mortality.

4.1. WBC to HDL-C Ratio and its Predictive Value

Baseline WBC /HDL-C was shown to be significantly higher in those with CHD and all-cause mortality, and by examining the tertiles amongst the population, this finding was also extended to CVD-related mortality. This was also corroborated by the Kaplan-Meier survivable curve. However, when adjusted using several demographic and medical variables, elevations were only determined to significantly affect all-cause mortality rates, with an HR of 1.07 and p-value of 0.013. This marker also showed greater superiority in predicting all-cause mortality when using the C-statistic and IDI models. In previous research involving 61 thousand individuals, it was shown that consistent increases in white blood cell counts were associated with a higher risk of overall mortality, with a hazard ratio of 1.77, which was considerably higher compared to four other WBC patterns (29). Another study on a group of 436,000 people showed comparable findings, although with a decreased hazard ratio (30). Several previous studies have demonstrated that increased WBC levels are strongly associated with an elevated risk of overall mortality, even after accounting for potential confounding factors (31-34). The impact of high WBC levels can be observed early in the development of atherosclerosis, increasing the risk of coronary artery calcification within two decades (35). Additionally, decreased levels of HDL-C have also been observed to have a "U"-shaped relationship with overall mortality (36-39). Although it can potentially be extrapolated from these studies, in which elevated WBC and diminished HDL-C levels were associated with a higher risk of all-cause mortality (40), that an elevated ratio between these two markers also results in a higher risk of all-cause mortality in the general population, there has been limited research on this matter. Amongst COVID-19 patients, the ratio of WBC to HDL-C has been seen to be a significant and independent predictor of mortality (28). Moreover, research on 6 thousand CAD patients who underwent percutaneous intervention found that this proportion was linked with long-term mortality on its own, even after adjusting for confounders (16). In conclusion, this study highlights the significant relationship between elevated WBC /HDL-C ratios and all-cause mortality, reinforcing previous research that links high WBC and low HDL-C levels to increased mortality risk. To the best of our knowledge, evidence regarding the association between the WBC/HDL-C ratio and mortality in the general population remains limited. Our findings therefore provide additional evidence from a population-based cohort and warrant further investigation in other populations. If this correlation is indeed accurate and

generalizable to different populations, then mortality predictions and risk assessment can be made through a simple CBC without the need for differential counts. This, in turn, makes it a highly applicable test, even in settings with limited laboratory resources, thereby reducing unnecessary costs in patient care.

4.2. Neutrophil to HDL-C Ratio and its Predictive Value

In our study, baseline NHR was significantly higher among participants who experienced all-cause mortality; however, this association was not sustained in the tertile analysis, Kaplan–Meier survival curves, or multivariable-adjusted models. This finding contrasts with previous studies reporting prognostic value for NHR in specific clinical populations, including patients with hepatocellular carcinoma, acute coronary syndrome, and acute myocardial infarction (15, 41-46). Importantly, Jiang et al. reported that higher NHR was independently associated with increased all-cause and cardiovascular mortality in approximately 34,000 adults from the general population, with 29% and 44% higher risks, respectively(47). The discrepancy between their findings and ours may be related to differences in population characteristics, including ethnicity, age distribution, baseline cardiovascular risk, and follow-up duration, as well as differences in study design and covariate adjustment. Our findings therefore suggest that although NHR may have prognostic value in selected high-risk clinical populations, its independent predictive utility for mortality in the general population may be more limited and potentially population-dependent.

4.3. Lymphocyte to HDL-C Ratio and its Predictive Value

Similar to that of NHR, the baseline LHR was also significantly higher, although this wasn't seen in the analysis of tertiles. However, LHR was also significantly elevated in CHD mortality, remaining so in tertile analysis and survivable curves, although the adjusted model was only significant for all-cause mortality (HR of 1.151 and p-value of 0.008) (12). Chen et al.'s study also found that LHR is a reliable predictor of metabolic syndrome in women, with an OR of 3.6 in the general population. Nevertheless, like NHR, both markers became insignificant once adjusted for fasting blood sugar (FBS) (12). In our research involving a bigger group of people, LHR continued to be important even when taking diabetes into account, although FBS specifically was not assessed. Another study involving 852 individuals also demonstrated the importance of LHR in evaluating metabolic syndrome, even following adjustments, showing that this marker was useful in predicting its presence and severity (48). In our previous study of approximately 8,000 patients, we found that LHR was a reliable and independent indicator of metabolic syndrome in both males and females (49). Another study involving 440 patients with COVID-19 revealed that LHR was significantly elevated in those in critical condition (40). These few studies show that LHR may be a useful tool in evaluating mortality risk. In conclusion, while this study indicates a significant association between LHR and all-cause mortality, it is important to note that research on this topic remains limited. The findings suggest that LHR could serve as a valuable biomarker for evaluating mortality risk, particularly in the context of metabolic syndrome, however, the existing literature is sparse.

4.4. Mixed Cell to HDL-C Ratio and its Predictive Value

As was seen in all previous markers, baseline mixed-cells were also significantly elevated in all-cause mortality, with the addition of CHD mortality. Tertile analysis and Kaplan-Meier curves showed significant findings across the board, although the adjusted model showed it to be insignificant.

Interestingly, however, the C-statistic and NRI model showed that the mixed cell /HDL-C were superior in its predictive value for both CVD and CHD mortality. In our research, mixed cells were made up of basophils, eosinophils, and monocytes. There is limited research on the relationship between this combination of cells and the risk of mortality, but there are existing studies on each cell type separately. Eosinophils are primarily known for their role in allergic reactions and parasitic infections, however, elevated levels in CAD patients are significantly associated with mortality risk (50). A study involving 4 thousand adults revealed that elevated eosinophils were strongly associated with predicting CHD (51). In research involving 270 patients, it was found that eosinophils were linked to both angiographically confirmed CAD and the severity of the disease (52). Even sequence variations affecting eosinophil counts have been seen to affect MI incidence (53). Basophils have also been linked to lipid abnormalities according to a cohort of 3 thousand patients (54). Research involving 478 thousand individuals found that basophil levels were higher in instances of both cardiovascular and non-cardiovascular deaths (55). Increased levels of basophils in clinically stable CAD patients were linked to higher factor II plasma coagulant activity, and could effectively predict mortality rates (50). Monocytes have been observed to impact the likelihood of mortality. Research on 64 individuals demonstrated a significant relationship between MHR and CAD (56). In contrast, another study involving 5,000 participants with CAD reported that MHR was related to all-cause and CVD mortality risk, although only in patients with hypertension (57). Nevertheless, this research indicated that the ratio of monocytes to HDL-C was more effective in the ROC curve than the individual markers, and was associated with a higher risk of complications amongst the study population (57). In conclusion, our investigation highlights the significant association between baseline mixed cell /HDL-C and mortality, evaluating the combined role of eosinophils, basophils, and monocytes in cardiovascular health. Although individual studies have explored the contributions of eosinophils, basophils, and monocytes to mortality risk, our research indicates that their collective analysis may provide a new avenue for evaluating cardiovascular health and outcomes.

4.5. Study Limitations and Research Gaps

To our knowledge, this is the first study to evaluate the use of these novel biomarkers in predicting all-cause and cardiovascular mortality in the general population. Although the study population was large and the follow-up duration was long, several factors may limit the interpretation of our findings. First, the relatively small number of cause-specific mortality events, particularly 140 CVD deaths and 106 CHD deaths, resulted in limited statistical power to detect modest associations. For an HR of 1.3 at a two-sided $\alpha = 0.05$, the estimated power was approximately 34% for CVD mortality and 27% for CHD mortality, indicating a potential risk of type II error. Therefore, the null findings for CVD and CHD mortality should be interpreted with caution. Second, although the study adjusted for a comprehensive set of potential confounders, residual confounding by unmeasured variables cannot be entirely excluded. Third, monocytes were not evaluated independently; instead, they were incorporated into the composite mixed-cell measure, which may have influenced the observed associations. Finally, temporal changes in these inflammatory indices were not evaluated, and the use of baseline measurements may not fully capture their longitudinal relationship with mortality.

5. Conclusion

In conclusion, our study presents strong evidence of the predictive value of some novel inflammatory biomarkers in evaluating

mortality outcomes. The results show that high levels of WBC /HDL-C were strongly correlated to higher all-cause mortality, supporting previous research linking individual factors to elevated mortality risk. Although the Kaplan-Meier survival curves denoted notable correlations between most markers and cause-specific mortality, there were inconsistent results produced by adjusted models. When analyzed using C-statistics, the ratio of mixed cell /HDL-C was found to be a strong predictor of CVD and CHD mortality, a correlation previously seen with each of the individual cells; basophils, eosinophils, and in particular monocytes. Our results show that the combination of these cells can potentially provide a better prognostic result, than that of previous research on monocytes individually. Overall, this study adds to the increasing evidence backing the use of these inflammatory biomarkers in clinical practice to assess mortality risk in the general population. As such, further research in larger populations with a greater number of cause-specific mortality events is warranted to confirm these findings and exclude modest associations with CVD and CHD mortality, while further assessing the prognostic potential of these biomarkers.

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Ethics approval: The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The study protocol was given approval by the Ethics Committee of Mashhad University of Medical Sciences (MUMS) (ethics approval code: IR.MUMS.REC.1386.250). Written informed consent was obtained from participants before the inclusion.

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Availability of data and materials: The data that support the findings of this study are available from MUMS, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of MUMS.

Approval date of Registry and the Registration No: The study was given approval by the Ethics Committee of MUMS (Approval date: August 15, 2007 and registration No: 85134).

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