Relation between lymphocyte to monocyte ratio and survival in patients with hypertrophic cardiomyopathy: a retrospective cohort study

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Background: Lymphocyte-to-monocyte ratio (LMR) has been proposed as a novel prognostic factor in malignancies and cardiovascular diseases. Our study aimed to ascertain whether LMR is a useful biomarker in discriminating the hypertrophic cardiomyopathy (HCM) patients at higher risk of all-cause mortality. **Methods:** This retrospective study consisted of 354 adult HCM patients. Cox's proportional hazards regression models were used to analyze the association between LMR and all-cause mortality. Smooth curve fitting was conducted to explore the linear relationship between LMR and all-cause mortality. **Results**: During the follow-up, 44 patients reached the study endpoint. The all-cause mortality rate was 7.3 per 100 person-years in the first tertile and decreased across the three tertiles of LMR. With the first tertile as reference, adjusted hazard ratios (HR) for all-cause mortality were 0.43 for the second tertile (95% CI: 0.20-0.91, p = 0.027) and 0.39 for the third tertile (95% CI: 0.17-0.90, p = 0.028), respectively. Smooth curve fitting exhibited a nonlinear relationship between LMR values and all-cause mortality. For LMR < 6.5, per SD increase resulted in a significantly decreased risk of all-cause mortality by 62% (HR: 0.38, 95% CI: 0.21-0.68). For LMR ≥ 6.5, the all-cause mortality risk did not progressively increase. Stratified and subgroup analyses revealed similar results to the main analyses, and E-value analysis suggested robustness to unmeasured confounding. **Conclusions:** The study demonstrated that LMR was an independent predictor of all-cause mortality in HCM patients, and LMR may be useful for identifying HCM patients at high mortality risk.

1 **Relation between lymphocyte to monocyte ratio and survival in patients with hypertrophic**

2 **cardiomyopathy:a retrospective cohort study**

3 **Running title: LMR and mortality in HCM**

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18 **Abstract:**

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22 risk of all-cause mortality.

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24 hazards regression models were used to analyze the association between LMR and all-cause

25 mortality. Smooth curve fitting was conducted to explore the linear relationship between LMR

26 and all-cause mortality.

27 **Results**: During the follow-up, 44 patients reached the study endpoint. The all-cause mortality

28 rate was 7.3 per 100 person-years in the first tertile and decreased across the three tertiles of

29 LMR. With the first tertile as reference, adjusted hazard ratios (HR) for all-cause mortality were

30 0.43 for the second tertile (95% CI: 0.20-0.91, p = 0.027) and 0.39 for the third tertile (95% CI:

31 0.17-0.90, p = 0.028), respectively. Smooth curve fitting exhibited a nonlinear relationship

32 between LMR values and all-cause mortality. For LMR < 6.5, per SD increase resulted in a

33 significantly decreased risk of all-cause mortality by 62% (HR: 0.38, 95% CI: 0.21-0.68). For

34 LMR ≥ 6.5, the all-cause mortality risk did not progressively increase. Stratified and subgroup

35 analyses revealed similar results to the main analyses, and E-value analysis suggested robustness

36 to unmeasured confounding.

37 **Conclusions:** The study demonstrated that LMR was an independent predictor of all-cause

38 mortality in HCM patients, and LMR may be useful for identifying HCM patients at high

39 mortality risk.

40 **Key words:** lymphocyte to monocyte ratio, cardiac inflammation, all-cause mortality,

41 hypertrophic cardiomyopathy

Introduction

Hypertrophic cardiomyopathy (HCM) is viewed as the most common inherited heart disease with an estimated prevalence of 0.2% of the general population [1]. The disease exhibits remarkable heterogeneity in clinical manifestations and natural history. Patients with HCM can be asymptomatic or oligosymptomatic or suffered from progressive heart failure, thromboembolic events, malignant arrhythmic events and unpredicted cardiac death [2]. Therefore, the discovery of novel inflammatory biomarkers has become meaningful so as to provide information of prognosis and guide clinical management in the disease.

Historical studies have suggested the existence of low grade systemic and local inflammation in patients with HCM [3,4]. Tissue-level inflammation is documented by immunohistological evidence of invading inflammatory lymphocytes and monocytes in the cardiac tissue [5,6]. Importantly, there was a significant correlation between the degree of inflammatory cell infiltration and myocardial fibrosis in these diseased hearts [7]. Besides, a series of systemic inflammatory biomarkers, including neutrophil to lymphocyte ratio, monocyte to high-density lipoprotein cholesterol ratio and high-sensitivity C reactive protein, all showed promising results in risk stratification in HCM [8-10]. Patients with increased levels of those biomarkers tend to be endangered by poor prognosis. Lymphocytes and monocytes are important immune cells in the inflammatory process.

The ratio of lymphocyte to monocyte, namely, LMR, has been reported to be significantly associated with the prognosis of various malignancies [11] and cardiovascular disorders [12-15]. In patients with ST-elevated myocardial infarction after primary percutaneous coronary intervention, both in hospital and long-term adverse cardiac and cerebrovascular events, such as nonfatal myocardial infarction, stroke, as well as cardiovascular mortality decreased with increasing LMR [12-13]. In patients with acute heat failure, a lower value of LMR was associated with a higher mortality risk within 6 months [14]. However, up to now, there is no data in HCM regarding LMR as a prognostic marker. As both lymphocytes and monocytes played important role in myocardial inflammation and fibrosis in HCM, we aimed to investigate whether LMR is a useful biomarker in discriminating the HCM patients at higher risk of all-cause mortality.

Methods

Study population

74   This is a retrospective study where all HCM patients greater than 18 years of age who have

75   been treated at Sichuan University West China Hospital, which is a tertiary referral center in

76   Southwest of China were consecutively enrolled, forming the inception cohort of 508 patients.

77   The enrollment started at Dec 2008 and ended at May 2016. The diagnosis of HCM was based

78   on the presence of increased left ventricular wall thickness ($\geq$ 15 mm), identified by

79   echocardiography, cardiac magnetic resonance or computed tomography, that was not solely

80   explained by abnormal loading conditions [16]. Patients with other inherited metabolic diseases

81   or syndromic causes of HCM (5 cardiac amyloidosis, 2 restrictive cardiomyopathy, 1 dilated

82   cardiomyopathy and 1 myocarditis) were excluded from the study. For the present study, other

83   exclusion criteria were as follows: (1) patients with comorbidities which would affect the white

84   blood cell count (WBCC) were excluded (n =91), such as infections, hematological system

85   diseases and taking corticosteroids; (2) patients with age under 18 (n = 5) and patients with

86   incomplete data (n = 26) were further excluded from the study; (3)We also excluded patients

87   who were lost to follow-up after the first evaluation (n = 23). Finally, the present study included

88   354 adult HCM patients for the final analysis.

89   This study was approved by the Biomedical Research Ethics Committee, West China Hospital

90   of Sichuan University (approval number: 2019-1147). This study was performed in keeping with

91   the criteria set by Declaration of Helsinki. Due to the retrospective nature of the study, informed

92   consent was waived. Other detailed information has been reported in the recently published

93   studies [17].

94   ***Baseline clinical evaluation***

95   Complete blood count (CBC) was measured by a Sysmex XN-9000 analyzer (Sysmex

96   Corporation, Kobe, Japan) at the time of hospital admission, and the laboratory parameters of

97   CBC included number of WBCC and percentage of lymphocyte and monocyte, and so on. The

98   normal range for WBCC was 4-10*10^9/L in this system. The LMR was calculated based on the

99   results of CBC. All patients underwent 2D transthoracic echocardiography examinations by

100   standard techniques at baseline, and the data and other detailed information of baseline

101   characteristics were collected from electronic medical records.

102   ***Study endpoint***

103   The endpoint of the study was all-cause mortality. Follow-up was carried out by medical

104   records review or telephone contacting with patients or their family members. All patients were

105 followed until the date of death or the end of follow-up at Feb 2020, whichever came first.

106 ***Statistical analysis***

107 To quantify in a simple form the association between LMR and all-cause mortality, the

108 patients were divided into three groups according to baseline LMR: tertile 1 (< 3.8), tertile 2

109 (3.8-5.4) and tertile 3 (≥ 5.5) [12,13, 18]. For each group, continuous variables were presented as

110 mean $\pm$ standard deviation (SD) and median with interquartile range (IQR) where appropriate,

111 and categorical variables as number (percentage). The baseline characteristics among the three

112 groups were analyzed by using the analysis of variance or Kruskal-Wallis tests for continuous

113 variables, and the chi-square or Fisher exact tests for categorical variables.

114 The cumulative mortality in each group was calculated by Kaplan-Meier method, and the log-

115 rank test was used for comparison. Cox proportional hazard regression analysis was used to

116 assess the role of LMR as an independent predictor of mortality. Variables for inclusion were

117 carefully chosen to ensure parsimony of the multivariate models. Age and gender were forced

118 into the multivariate models, and baseline variables that showed a univariate relationship with

119 mortality ($p < 0.05$) or that were considered clinically relevant [19] were included for adjustment

120 in multivariate models. Additionally, we explored the association between LMR and all-cause

121 mortality by smooth curve fitting after adjustment for potential confounders, and a two-

122 piecewise Cox model was also applied to examine the threshold effect of LMR on mortality.

123 Additionally, a time-dependent receiver operating characteristic (ROC) curve was generated to

124 evaluate the accuracy of LMR in the discrimination of mortality at different prediction times [20].

125 A generally accepted approach suggests that the area under curves (AUCs) of less than 0.60

126 reflects poor discrimination; 0.60 to 0.75, possibly helpful discrimination; and more than 0.75,

127 clearly useful discrimination.

128 The robustness of these findings was assessed in multiple sensitivity analyses. First, stratified

129 analysis assessed the consistency of association between LMR and mortality in different groups.

130 Second, we explored the potential for unmeasured confounding between LMR and all-cause

131 mortality by calculating E-values [21]. The E-value quantifies the required magnitude of an

132 unmeasured confounder that could negate the observed association between LMR and all-cause

133 mortality, and the E-value was calculated on the web calculator (https://www.evalue-

134 calculator.com/). Third, we also assessed the relation between LMR and mortality in the

135 subgroup with a normal WBCC range as another sensitivity analysis.

136   All analyses were performed with R version 3.6.3 including the "compareGroups", "rms",

137   "survminer", "tidyverse", "survival" "timeROC" and "base" packages (http://www.R-

138   project.org). All tests were two sided, and p values < 0.05 were considered statistically

139   significant.

140   **Results**

141   *Baseline characteristics*

142   Table 1 shows the baseline characteristics of the study cohort. The average age was 56 (IQR:

143   44.0-66.0) and male patients accounted for 55.1%. The LMR distribution ranged from 0.2-17.4.

144   There were 115 patients in title 1, 116 patients in tertile 2 and 123 patients in tertile 3. The

145   lymphocytes increased significantly across the LMR tertiles. On the contrary, WBCC,

146   neutrophils and monocytes decreased significantly across the LMR tertiles. Besides, patients

147   with higher LMR values tended to be younger and have significantly lower left atria diameter, as

148   well as significantly higher hemoglobin concentration and left ventricular ejection fraction. Other

149   clinical features did not show significant difference among the three groups.

150   *Survival analysis*

151   During the follow-up, 44 patients reached the endpoint of all-cause mortality. The specific

152   causes of deaths were as follows: 7 sudden cardiac deaths, 12 heart failure-related deaths, 9

153   stroke-related deaths, 2 HCM-related postoperative deaths, 1 other cardiac death and 9 non-

154   cardiac deaths. The cause of death could not be confirmed in 4 patients. The cumulative

155   incidence of all-cause mortality was 24.8% for the whole cohort.

156   Based on the baseline LMR, there were 23 all-cause mortality in the first terile, 12 in the

157   second tertile and 9 in the third tertile. The corresponding mortality rates were 7.3 (95% CI: 4.4-

158   10.1), 2.2 (95% CI: 1.0-3.5) and 1.0 (95% CI: 0.3-1.6) per 100 person years, respectively.

159   Kaplan–Meier analysis also demonstrated gradually decreased cumulative incidence of all-cause

160   mortality across the three tertiles with log-rank p = 0.004 (Figure 1).

161   *Relation of LMR to all-cause mortality*

162   Univariate Cox regression analysis revealed that dyspnea, atrial fibrillation, age and left atria

163   diameter were significant risk factors of all-cause mortality, while hemoglobin, lymphocyte,

164   triglycerides, low-density lipoprotein cholesterol were significant protective factors (Table 2). In

165   comparison of the top tertile versus the bottom tertile of LMR, the crude hazard ratio (HR) of all-

166   cause mortality was 0.32 (95% CI: 0.15-0.69; p = 0.004). Two models were constructed to

167   examine the effect of comorbidities, laboratory parameters, echocardiographic parameters and

168   clinically relevant prognostic factors on the association between LMR and all-cause mortality

169   risk. The association did not change materially after adjusting potential confounding factors. The

170   fully adjusted HRs of all-cause mortality were 0.43 (95% CI: 0.20-0.91, p = 0.027) for patients in

171   tertile 2 versus tertile 1 and 0.39 (95% CI: 0.17-0.90, p = 0.028) for patients in tertile 3 versus

172   tertile 1, respectively (Table 3).

173   ***Two-piecewise analysis and time-dependent AUCs***

174   Due to the similar all-cause mortality rate in tertile 2 and tertile 3, we speculated that there

175   might be a nonlinear association between LMR and all-cause mortality. Therefore, we further

176   assessed the association between LMR and all-cause mortality by smooth curve fitting after

177   adjustment for potential confounders, and a threshold effect was observed with a two-stage

178   change and an inflection point. For LMR < 6.5, per SD increase resulted in a significantly

179   decreased risk of all-cause mortality by 62% (adjusted HR: 0.38, 95% CI: 0.21-0.68), and the all-

180   cause mortality risk did not progressively increase for the patients with a LMR ≥ 6.5 (Figure 2A).

181

182   The time-dependent AUCs shown in Figure 3A were developed on the basis of time-

183   dependent ROC curves, which were calculated every four months. The AUCs indicated that

184   LMR had a helpful discrimination for all-cause mortality in the whole cohort, with AUC ranged

185   from 0.594 to 0.703 (Figure 3A).

186   ***Sensitivity analysis***

187   Stratified analysis suggested the consistency of association between LMR and all-cause

188   mortality remained in all subgroups, including age (< 60 and ≥ 60 years), gender (male and

189   female), AF (yes and no), beta-blocker (yes and no), hemoglobin (< 139 and ≥ 139 g/L), WBCC

190   (< 6.3 and ≥ 6.3 *10^9/L), left atria diameter (< 40 and ≥ 40 mm), left ventricular ejection faction

191   (< 50 and ≥ 50 %) and left ventricular outflow tract gradient (yes and no), and there were no

192   interactions between LMR and the above-mentioned variables.

193   Furthermore, we generated an E-value to assess the sensitivity to unmeasured confounding in

194   the whole cohort. Based on the model 4 in the table 3, the E-value was 2.97 for the tertile 2 of

195   LMR, and the upper limit of the confidence interval was 1.34. For the tertile 3, the E-Value was

196   HR = 3.22 (upper limit 1.36). For per SD increase of LMR (< 6.5), the E-values for the point

197   estimate and upper confidence bound for all-cause mortality were 3.29 and 1.94, respectively.

198   Combined with the present multivariate results (supplementary table 1) and the published data

199   [15], it is not likely that an unmeasured or unknown confounder would have a substantially

200   greater effect on all-cause mortality than these known risk factors by having a HR exceeding

201   about 3.0.

202   Finally, another sensitivity analysis including patients with normal WBCC (4-10*10^9/L)

203   revealed similar results with the main analyses. Kaplan-Meier curve showed a gradually higher

204   mortality risk with lower LMR (log-rank = 0.002). The adjusted HRs were significantly higher in

205   the tertile 2 (HR = 0.39, 95% CI: 0.18-0.86, p = 0.019), and in the tertile 3 (HR = 0.31, 95% CI:

206   0.12-0.77, p = 0.012) compared with the tertile 1. In addition, adjusted HR of all-cause mortality

207   was 0.35 (95% CI: 0.18-0.67) for per SD increase in the patients with a LMR < 6.5, and the all-

208   cause mortality risk did not significantly increase when LMR ≥ 6.5 (Figure 2B). Figure 3B

209   shows that LMR had a helpful discrimination for mortality, with AUC ranged from 0.617 to

210   0.720.

211   **Discussion**

212   In this study, we evaluated the value of LMR on admission in predicting the all-cause

213   mortality in patients with HCM. To the best of our knowledge, this study appears to be the first

214   to assess the predictive value of LMR for all-cause mortality in HCM patients. The results of the

215   present study revealed that LMR was a novel prognostic indicator for all-cause mortality and that

216   a higher LMR was significantly associated with better clinical outcomes. What's more, a non-

217   linear relationship and a threshold effect with the inflection point at 6.5 was observed.

218   During the past decades, the mortality rate in HCM patients has been largely reduced with

219   contemporary therapeutic strategies, which included implantable defibrillators to prevent sudden

220   death, surgical myectomy or alcohol septal ablation to reverse obstructive heart failure,

221   anticoagulation to reduce embolic stroke caused by atrial fibrillation and even heart

222   transplantation to treat nonobstructive end-stage disease [22]. With the use of such treatment

223   interventions, the HCM related mortality rate can be as low as 0.5% per year [23,24]. However,

224   the situation is not satisfactory in developing country [10,17]. For example, in an observation

225   study cohort consisted of 490 patients from Fuwai Hospital, China, Zhu et al reported that the

226   all-cause mortality rate and cardiovascular death rate were 2.12% and 1.67% per year,

227   respectively [10]. In this context, stratifying HCM patients for higher risk of adverse outcomes

228   and the following close monitoring in clinical practice could potentially improve the disparities

229   in the care of HCM patients across the world. According to the results of the present study, LMR,

230   as an inexpensive and easily accessible marker, might afford a useful screening tool in HCM

231   patients.

232   HCM has been ascribed to single sarcomere gene mutations. However, the heterogeneity of

233   HCM clinical and pathobiological features could not solely be explained by a single molecular

234   event [25]. Other alternative and complementary mechanisms might be involved. Myocardial

235   inflammation has recently been indicated as a contributor of cardiac hypertrophy, fibrosis and

236   dysfunction among heart diseases [26], which are all recognized features of HCM. During the

237   inflammatory process, immune cells played an important role. Neutrophils and monocytes would

238   infiltrate in the injury site and release a bunch of harmful mediators to initiate the inflammatory

239   response. Furthermore, lymphocytes take part in the sustention of inflammation via several

240   effectors [27]. However, the trigger for early inflammation in HCM has not been clearly defined

241   yet. The intrinsic cardiomyocyte disarray, sarcomere injury and microvascular dysfunction seem

242   to be related [26].

243   Cardiac inflammation leads to myocardial fibrosis [28,29], which is a hallmark of HCM and

244   regarded as a substrate for arrhythmias and heart failure [30]. The worst complications of HCM

245   mainly consisted of sudden cardiac death, heart failure related death and stroke related death.

246   Both the life-threatening arrhythmias and progressively decompensated heart failure in HCM are

247   significantly determined by myocardial fibrosis [31, 32]. Therefore, the presence of cardiac

248   inflammation and fibrosis might be the underlying mechanism of LMR as a prognostic factor in

249   HCM patients. Unfortunately, there is a knowledge gap in terms of the relationship between the

250   level of LMR and myocardial fibrosis in HCM patients and further prospective studies

251   concerning this issue are warranted.

252   The greatest strength of our study is that this is the first study to illustrate the prognostic value

253   of LMR in HCM patients. LMR act as a strong and independent predictor of all-cause mortality

254   in patients with HCM. Since LMR is a cost-effective and widely accessible marker, it may help

255   clinicians to identify high risk patients who require closer care and distribute the medical

256   resource more efficiently. Besides, we have used the E-value sensitivity analysis to quantify the

257   potential implications of unmeasured confounders and found that an unmeasured confounder was

258   unlikely to negate the prognostic value of LMR. Several limitations also existed in the present

259   study. First, those patients were from a single tertiary referral center, lack of region

260 diversification and race comparison; thus, the generalization of our conclusion into other

261 populations should be cautious. Second, this is a retrospective study, and data collection biases

262 might potentially exist. Third, we only assessed the baseline LMR values in the prediction of all-

263 cause mortality. The absence of serial LMR measurements during the follow-up time is one of

264 the most handicaps. Fourth, the study failed to measure inflammatory cytokines, including C

265 reactive protein, interleukin-6 and tumor necrosis factor, and these indicators may better help to

266 explain the relation between LMR and poor outcomes. Fifth, Since the study endpoint were

267 defined as all-cause mortality, the non-cardiac death and unknown death were also included for

268 analysis. It might provide more useful information if only HCM-related mortality was analyzed.

269 Due to the limited number of study endpoint, other large-scale studies based on multiple medical

270 centers are encouraged.

271 **Conclusion**

272 Our study denoted that LMR on admission was a novel and independent predictor for all-cause

273 mortality in patients with HCM. This marker could be useful when applied for risk stratification

274 of adverse clinical outcomes in HCM patients.

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278 **Conflicts of Interest**

279 None declared.

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402

404   Figure legends

405   Figure 1. Kaplan−Meier analysis showing cumulative all-cause mortality by baseline lymphocyte

406   to monocyte ratio tertiles. ACM = all-cause mortality.

407   Figure 2. Association between LMR and all-cause mortality by smooth curve fitting.

408   HR was adjusted for the covariates, which were the same as those in the model 2, and the red

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Table 1. Baseline characteristics of study cohort.

Values are mean ± SD or median (IQR) or n (%). LMR tertiles 1 to 3 were defined by < 3.8, 3.8 to 5.4, and ≥ 5.5, respectively. HCM = hypertrophic cardiomyopathy, SCD = sudden cardiac death, TE = thrombo-embolic event, ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, ICD = implantable cardioverter defibrillator, WBCC = white blood cell count, LMR = lymphocyte to monocyte ratio, LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, TG = triglyceride, LVEDD = left ventricular end-diastolic dimension, LA = left atrial, MWT = maximal LV wall thickness, LVEF= left ventricular ejection fraction, LVOTG = left ventricular outflow tract gradient. *: significant p values.

1   Table 1. Baseline characteristics of study cohort.

Variable	All patients (n = 354)	LMR, tertile 1 (n = 115)	LMR, tertile 2 (n = 116)	LMR, tertile 3 (n = 123)	p value
Age (years)	56.0 (44.0-66.0)	58.0 (44.5-67.0)	58.5 (47.8-67.0)	51.0 (39.5-63.5)	0.012*
Gender, male	195 (55.1%)	64 (55.7%)	66 (56.9%)	65 (52.8%)	0.811
Family history of HCM	35 (9.89%)	9 (7.83%)	10 (8.62%)	16 (13.0%)	0.350
Family history of SCD	16 (4.52%)	8 (6.96%)	6 (5.17%)	2 (1.63%)	0.130
Symptoms					
Chest pain	201 (56.8%)	61 (53.0%)	72 (62.1%)	68 (55.3%)	0.352
Palpitation	149 (42.1%)	45 (39.1%)	46 (39.7%)	58 (47.2%)	0.370
Syncope/pre-syncope	119 (33.6%)	35 (30.4%)	47 (40.5%)	37 (30.1%)	0.158
Dyspnea	201 (56.8%)	74 (64.3%)	63 (54.3%)	64 (52.0%)	0.129
Medical history					
Atrial fibrillation	60 (16.9%)	21 (18.3%)	19 (16.4%)	20 (16.3%)	0.901
Hypertension	112 (31.6%)	42 (36.5%)	38 (32.8%)	32 (26.0%)	0.209
Diabetes	30 (8.47%)	13 (11.3%)	8 (6.90%)	9 (7.32%)	0.412
Vascular disease	25 (7.06%)	10 (8.70%)	8 (6.90%)	7 (5.69%)	0.662
Prior TE	15 (4.24%)	7 (6.09%)	6 (5.17%)	2 (1.63%)	0.159
Therapy					

Aspirin	66 (18.6%)	19 (16.5%)	28 (24.1%)	19 (15.4%)	0.176
Clopidogrel	17 (4.80%)	9 (7.83%)	4 (3.45%)	4 (3.25%)	0.182
β-blocker	273 (77.1%)	85 (73.9%)	89 (76.7%)	99 (80.5%)	0.479
ACE inhibitor or ARB	65 (18.4%)	20 (17.4%)	21 (18.1%)	24 (19.5%)	0.911
Pacemaker	16 (4.52%)	8 (6.96%)	4 (3.45%)	4 (3.25%)	0.628
ICD	28 (7.91%)	10 (8.70%)	9 (7.76%)	9 (7.32%)	
Alcohol septal ablation	33 (9.32%)	8 (6.96%)	12 (10.3%)	13 (10.6%)	0.694
Septal myectomy	6 (1.69%)	1 (0.87%)	3 (2.59%)	2 (1.63%)	
Hematological					
Hemoglobin (g/L)	139 (126-151)	137 (120-150)	136 (124-150)	142 (132-154)	0.022*
WBCC (10^9/L)	6.25 (5.15-7.49)	7.00 (5.50-9.02)	6.19 (5.15-7.09)	5.87 (5.05-6.86)	<0.001*
Neutrophil (10^9/L)	3.79 (3.00-4.92)	4.87 (3.45-6.58)	3.78 (3.04-4.68)	3.44 (2.64-3.93)	<0.001*
Lymphocyte (10^9/L)	1.65 (1.32-2.02)	1.35 (0.98-1.61)	1.63 (1.38-1.94)	1.97 (1.73-2.34)	<0.001*
Monocyte (10^9/L)	0.35 (0.27-0.46)	0.47 (0.39-0.60)	0.35 (0.30-0.44)	0.28 (0.23-0.33)	<0.001*
LMR	5.02 ± 2.32	2.76 ± 0.82	4.61 ± 0.48	7.53 ± 1.85	<0.001*
Lipid profiles					
LDL-C (mmol/L)	2.42 (1.84-2.90)	2.38 (1.84-2.92)	2.33 (1.81-2.84)	2.55 (1.96-2.95)	0.489
HDL-C (mmol/L)	1.27 (1.02-1.53)	1.30 (1.02-1.54)	1.21 (1.00-1.48)	1.28 (1.04-1.52)	0.325
TG (mmol/L)	1.25 (0.94-1.92)	1.25 (0.96-1.68)	1.27 (0.96-2.10)	1.20 (0.90-1.99)	0.617
Echocardiographic					

LVEDD (mm)	43.0 (40.0-47.0)	43.0 (40.0-47.0)	44.0 (40.0-47.0)	42.0 (39.0-45.0)	0.120
LA diameter (mm)	40.0 (36.0-45.0)	40.0 (35.0-45.0)	41.5 (37.0-46.0)	39.0 (35.0-44.0)	0.023*
MWT (mm)	19.0 (17.0-22.0)	19.0 (17.0-21.0)	19.0 (17.0-22.0)	19.0 (17.0-22.0)	0.626
LVEF (%)	69.0 (63.0-73.0)	69.0 (63.0-73.0)	68.0 (63.0-71.0)	70.0 (64.0-73.0)	0.044*
Resting LVOTG $\geq$ 30 mm Hg	147 (41.5%)	47 (40.9%)	51 (44.0%)	49 (39.8%)	0.799

2 Values are mean ± SD or median (IQR) or n (%). LMR tertiles 1 to 3 were defined by < 3.8, 3.8 to 5.4, and $\geq$ 5.5, respectively.

3 HCM = hypertrophic cardiomyopathy, SCD = sudden cardiac death, TE = thrombo-embolic event, ACE = angiotensin-converting

4 enzyme, ARB = angiotensin receptor blocker, ICD = implantable cardioverter defibrillator, WBCC = white blood cell count, LMR =

5 lymphocyte to monocyte ratio, LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, TG =

6 triglyceride, LVEDD = left ventricular end-diastolic dimension, LA = left atrial, MWT = maximal LV wall thickness, LVEF= left

7 ventricular ejection fraction, LVOTG = left ventricular outflow tract gradient.

8 *: significant p values.

Table 2. Univariate Cox regression analysis of all-cause mortality.

HR = hazard ratio; CI = confidence interval. other abbreviations as in table 1. *: significant p values

1   Table 2. Univariate Cox regression analysis of all-cause mortality.

Variable	Change	HR (95% CI)	p value
Gender	female vs. male	1.30 (0.72-2.35)	0.388
Family history of HCM	yes vs. no	0.82 (0.30-2.31)	0.713
Family history of SCD	yes vs. no	2.00 (0.72-5.61)	0.186
Chest pain	yes vs. no	0.73 (0.40-1.32)	0.300
Palpitation	yes vs. no	0.74 (0.40-1.37)	0.334
Syncope/pre-syncope	yes vs. no	0.69 (0.36-1.34)	0.277
Dyspnea	yes vs. no	2.51 (1.27-4.97)	0.008*
Hypertension	yes vs. no	1.02 (0.54-1.93)	0.943
Diabetes	yes vs. no	1.36 (0.54-3.46)	0.515
Prior TE	yes vs. no	2.19 (0.78-6.14)	0.134
Vascular disease	yes vs. no	1.38 (0.49-3.87)	0.544
Atrial fibrillation	yes vs. no	2.57 (1.38-4.79)	0.003*
Aspirin	yes vs. no	1.15 (0.55-2.39)	0.714
Clopidogrel	yes vs. no	0.45 (0.06-3.29)	0.434
β-blocker	yes vs. no	0.62 (0.33-1.16)	0.138
ACE inhibitor or ARB	yes vs. no	0.57 (0.23-1.45)	0.240

Procedures

Alcohol septal ablation	alcohol septal ablation vs. none	0.50 (0.12-2.06)	0.335
Septal myectomy	septal myectomy vs. none	1.63 (0.22-11.9)	0.631
Devices			
Pacemaker	Pacemaker vs. none	1.60 (0.49-5.19)	0.431
ICD	ICD vs. none	0.50 (0.12-2.09)	0.345
Resting LVOTG $\geq$ 30 mm Hg	yes vs. no	1.38 (0.76-2.50)	0.283
Age (years)	per 1-SD increase	1.51 (1.09-2.11)	0.015*
Hemoglobin (g/L)	per 1-SD increase	0.67 (0.51-0.88)	0.005*
WBCC (10^9/L)	per 1-SD increase	0.87 (0.62-1.23)	0.439
Neutrophil (10^9/L)	per 1-SD increase	1.04 (0.77-1.39)	0.815
Lymphocyte (10^9/L)	per 1-SD increase	0.61 (0.43-0.84)	0.003*
Monocyte (10^9/L)	per 1-SD increase	1.12 (0.83-1.50)	0.470
TG (mmol/L)	per 1-SD increase	0.53 (0.32-0.89)	0.016*
HDL-C (mmol/L)	per 1-SD increase	0.96 (0.71-1.30)	0.803
LDL-C (mmol/L)	per 1-SD increase	0.64 (0.47-0.88)	0.006*
LVEDD (mm)	per 1-SD increase	0.85 (0.61-1.19)	0.350
LA diameter (mm)	per 1-SD increase	1.42 (1.08-1.86)	0.012*
MWT (mm)	per 1-SD increase	1.03 (0.77-1.38)	0.858
LVEF (%)	per 1-SD increase	0.77 (0.60-0.99)	0.044*

2   HR = hazard ratio; CI = confidence interval. other abbreviations as in table 1.

3   *: significant p values

Table 3. Associations of LMR with all-cause mortality.

Per 100 PYs. PYs = person-years, CI = confidence interval; other abbreviations as in tables 1 and 2. *: significant p values Model 1 with adjustment for age and sex. Model 4 with adjustment for model 1 plus dyspnea, syncope/pre-syncope, family history of SCD, atrial fibrillation, hemoglobin, TG, LDL-C, LA diameter, LVEF, MWT and Resting LVOTG ≥30 mm Hg.

1   Table 3. Associations of LMR with all-cause mortality.

	LMR		
☐	Tertile 1	Tertile 2	Tertile 3
No. of patients (n)	115	116	123
Follow-up (PYs)	317.2	534.7	926.5
Deaths (n)	23	12	9
Mortality rates# (95% CI)	7.3 (4.4-10.1)	2.2 (1.0-3.5)	1.0 (0.3-1.6)
Unadjusted HR (95% CI), p	ref	0.46 (0.23-0.93), 0.030*	0.32 (0.15-0.69), 0.004*
Adjusted HR (95% CI), p			
Model 1	ref	0.45 (0.22-0.90), 0.024*	0.33 (0.15-0.72), 0.006*
Model 2	ref	0.43 (0.20-0.91), 0.027*	0.39 (0.17-0.90), 0.028*

2   #Per 100 PYs. PYs = person-years, CI = confidence interval; other abbreviations as in tables 1 and 2.

3   *: significant p values

4   Model 1 with adjustment for age and sex.

5   Model 4 with adjustment for model 1 plus dyspnea, syncope/pre-syncope, family history of SCD, atrial fibrillation, hemoglobin, TG,

6   LDL-C, LA diameter, LVEF, MWT and Resting LVOTG ≥30 mm Hg.

Figure 1

Figure 1. Kaplan−Meier analysis showing cumulative all-cause mortality by baseline lymphocyte to monocyte ratio tertiles. ACM = all-cause mortality.
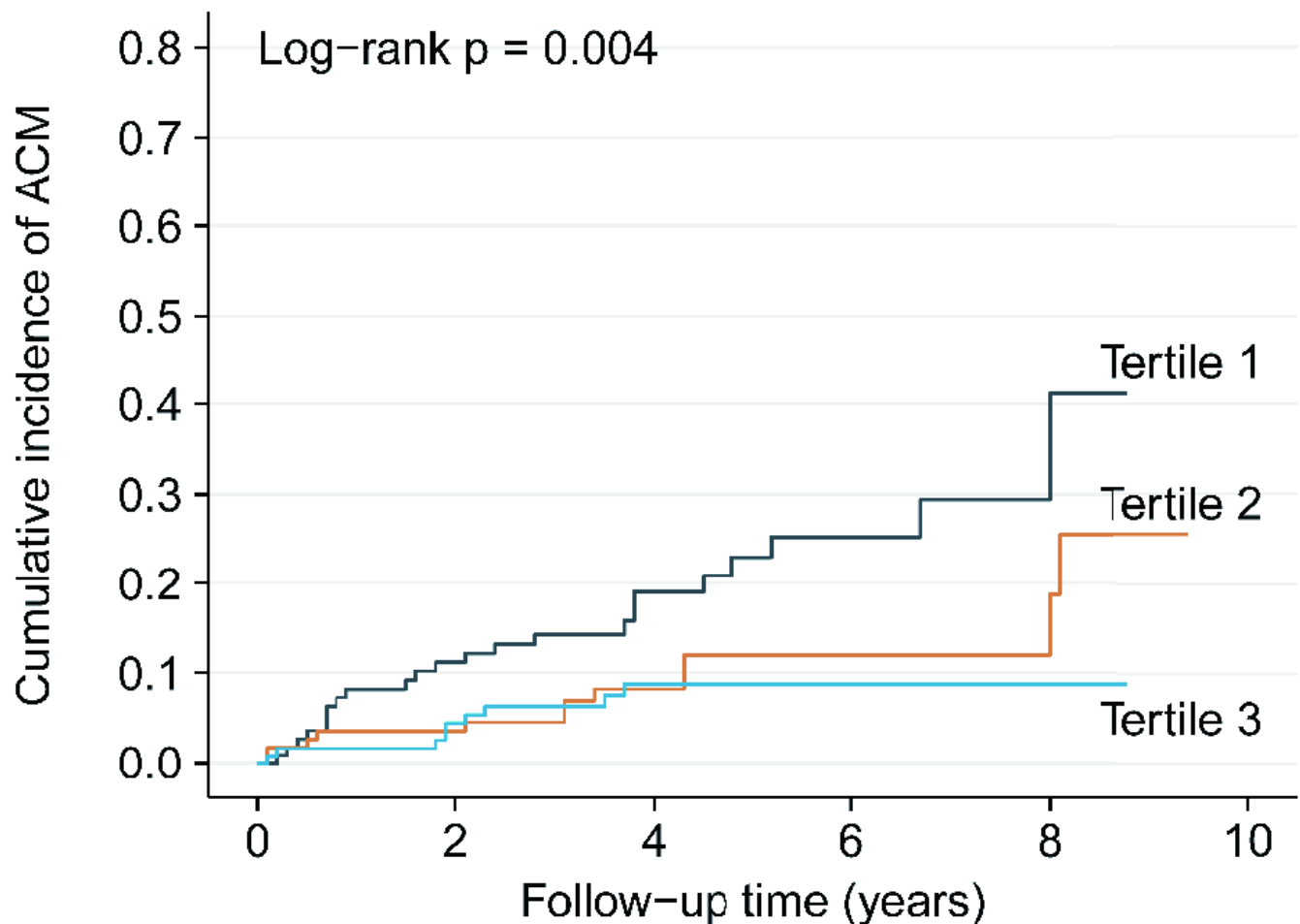
Figure 2

Figure 2. Association between LMR and all-cause mortality by smooth curve fitting.

HR was adjusted for the covariates, which were the same as those in the model 2, and the red lines and blue ribbons depict the adjusted HRs and 95%CI. Abbreviations as in table 1 and table 2.
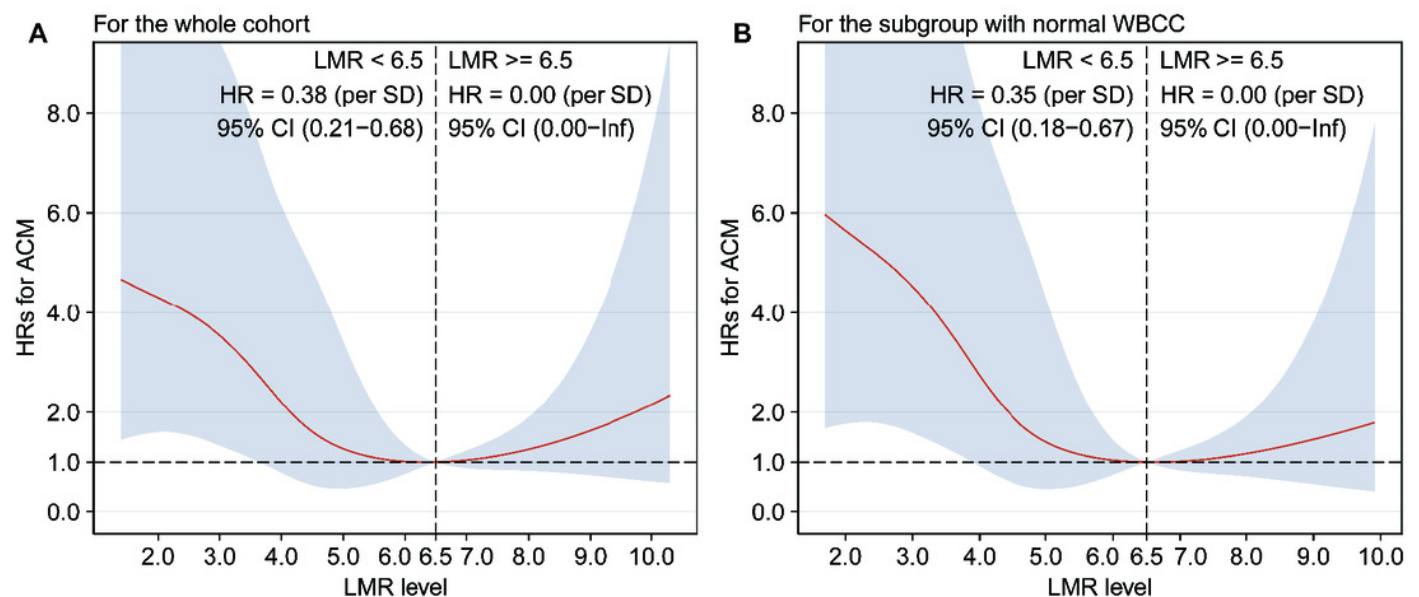
Figure 3

Figure 3. Time-dependent AUCs.

The red lines and grey ribbons depict the AUCs and 95%CI. Abbreviations as in table 1 and table 2.