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Lymphocyte-to-Monocyte Ratio: A Simple and Effective Inflammation Marker in Predicting Mortality of Non-Institutionalized Americans with Cancers

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Abstract: *Cancer is a serious disease with a high mortality rate. In view of the urgent need of prognosis, the lymphocyte-to-monocyte ratio (LMR) may be a promising cancer marker, but the evidence is weak. Accordingly, we evaluated the clinical impact of LMR based on the Health and Nutrition Examination Survey (NHANES) data. An overall sample of 2363 cancer patients was studied. Based on the Cox proportional hazards model, we examined the relationship between LMR and all-cause mortality. The Kaplan-Meier (KM) analysis assessed the predictive power of LMR for cancer prognosis in comparison to Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR). In addition, extra subgroup analyses and sensitivity analyses were carried out to examine the robust of the outcomes. After accounting for multiple covariates, LMR was associated with mortality for all-causes among cancer patients. In Kaplan-Meier survival curves, mortality rate was significantly elevated among low-LMR group versus high-LMR group (Log rank test P < 0.001). Multiple regression analyses revealed the same result that LMR in continuous or categorical variables were respectively associated with the risk of all-cause mortality in participants with cancer (P <0.05). Further analyses were conducted on subgroups of age, gender, body mass index, baseline medical condition and extra sensitivity analyses, the results are still robust. In conclusion, an elevated LMR was associated with a lower mortality rate in patients with cancers. LMR may serve as a potential inflammatory predictor of cancer mortality prognosis, outperform NLR and PLR, as well as guide clinical treatment.*

Keywords: *LMR, Mortality, Cancer Prognosis, Inflammation, NHANES*

1. Introduction

There is no doubt that cancer is a serious public health issue worldwide and it is the second leading cause of death in the United States. By 2021, it is projected that in the United States, there will be 1,898,160 new cancer cases and 608,570 deaths caused by cancer1. Moreover, the Coronavirus disease 2019 (COVID-19) pandemic has further hampered the diagnosis and treatment of cancer and may even have increased the personal and social burden of the disease. Thus, applying an objective, accurate, affordable, and convenient method to observe the prognosis of cancer patients, such as the neutrophil to lymphocyte ratio (LMR), is of great importance.

The LMR is a prognostic biomarker for inflammation. The lymphocyte is the main part in it that invovles interaction between various inflammatory cells, immune cells and play a crucial rule in different stages of tumor development, including initiation, promotion, and metastasis2. In cancer, tumor cells evade lymphocytes' attacks. Lymphocytes are crucial components of the adaptive immunity system, which eliminates cancer cells. Lymphopenia indicates a weak immune response and a poor prognosis3. On the other hand, tumor-associated macrophage, derived from monocytes, is significantly associated with tumor invasiveness and outcomes. Monocytes also indicate a poor prognosis for cancer and treatments that inhibit monocytes could promote anti-tumor immunity4. Calculated from these two parameters, LMR could reflect systemic inflammation status efficiently, and inflammation is a major factor in cancer pathogenesis and outcome5. Based on the widely available and inexpensive full blood count (FBC), the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) have already been used as prognostic biomarkers6-8. Emerging consensus showed that LMR can even be used

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for determining clinical outcomes across a broader spectrum of tumors. It has shown prognostic value independent of the TNM staging system, rather than PLR or NLR. Low lymphocyte counts, with or without high baseline monocyte counts, resulting in a low LMR, are generally associated with a poorer cancer prognosis9, 10.

However, it remains unclear whether LMR has a consistent and measurable effect on prognosis. Research on the relationship between LMR and cancer mortality in the general population is rather scarce, and the results are inconclusive. Insufficient participants and a short follow-up period compromise the validity of the results. Consequently, our study aimed to examine the association of LMR levels with all-cause mortality and provide a reliable prognosis for cancer patients by accessing cancer patients from the NHANES 2005 to 2014[1-8].

2. Methods

2.1 Study population

The research data came from the NHANES available on https://www.cdc.gov/nchs/nhanes/. The NHANES was conducted by the Centers for Disease Control and Prevention (CDC) and approved by the institutional review board of the National Center of Health Statistics (NCHS). It is an ongoing program involving a series of independent, nationally representative cross-sectional surveys designed to assess the health and nutritional status of Americans. All participants signed the consent form and joined household interviews, physical examinations, laboratory tests, and nutritional status assessments. For our study, data were selected in five cycles of the NHANES survey (2005 - 2006, 2007 - 2008, 2009 - 2010, 2011 - 2012, 2013 - 2014) to assess the association between LMR and all-cause Mortality.

In our study, a total of 50965 individuals took part in the NHANES from 2005 to 2014. Firstly, we excluded 48320 people without history of cancer. Secondly, our analyses were limited to 276 participants who had missing data on LMR. Thirdly, 6 participants with incorrect depression scores and incomplete demography questionnaires. Ultimately, a total of 2363 participants were recruited (Figure 1).

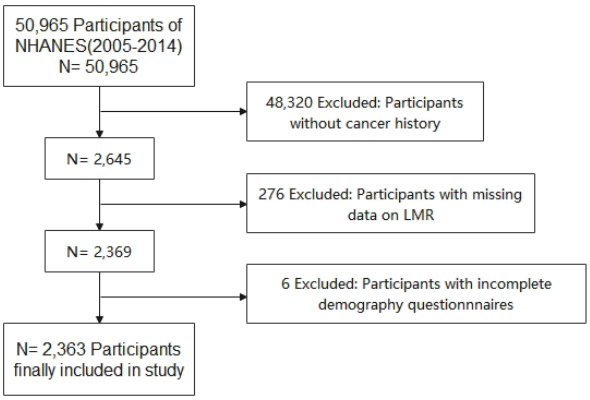

Figure 1: Flow diagram for exclusion or inclusion in the studied sample.

3. Data collection

3.1 LMR

The morning fasting venous blood of all participants was collected for routine clinical chemistry analysis. Lymphocyte and monocyte count in 1000 cells/μL were obtained from the whole blood using Coulter counter method. Lymphocyte-to-monocyte ratio (LMR) was then calculated as the lymphocyte count divided by the monocytes count. To determine the exact relationship between the inflammation marker in hematology and mortality of cancer patients, we treated LMR as continuous variables in four similar parts (< 2.5, < 3.5, < 4.5, ≥ 4.5).

3.2 Mortality data

Mortality data was obtained from the NHANES public use linked mortality file and linked to

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NHANES normal data using each unique respondent sequence number. In the file, the mortality status, leading cause of death, and follow-up time were included. Survival status was divided into two stages: survival or death. The leading cause of death was determined by the US National Death Index (NDI), and cancer mortality was derived from ICD-10 codes C00-C97. It was validated to have a discrepancy rate of approximately 5%. But it is not a problem for us to mainly focus on all-cause mortality. As for follow-up time, the duration was defined from interview date to the last follow-up or death date through December 31, 2015. During 131 months of follow-up (median, 62.94 months) with 2,363 participants. Totally 458 patients (19.38%; 272 male and 186 female) were determined for death, 137 of them died from cancer (86 male and 51 female)[9-16].

3.3 Covariates

Two sets of covariates at the time of survey were considered for multiple levels of analysis. For the first set, age, gender, race/ethnicity, education level and marital status of participants were collected with questionnaires at survey interviews. The mean age was 65.08 (± 14.73) years ranging from 20 to 85 years. Race/ethnicity was classified as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, or another race. Education level was categorized as less than high school, high school or above. Marital status was divided into Married/living with partners, Widowed/divorced/separated, or never married. Further investigations are required to exclude other confounding factors. Additionally, smoking, alcohol, coronary heart disease (CHD), hypertension, diabetes, BMI, depression, kidney injury, asthma, and use of aspirin were included to adjust for analysis. Smoking status was classified as former, current, or never. Alcohol status was grouped into 'yes or no', CHD, hypertension, diabetes, kidney injury and asthma were all the same. We calculated BMI as measured weight (kg) divided by square of height (m2), and the mean is (27.95 ± 6.03) kg/m2. Diagnosis of depressive disorders used the PHQ-9 instrument and a score of ≥10 has been valid for depression diagnosis. Prescription medication use was obtained during the interview and verified by interviewers through examination of medication containers, including aspirin taking or not.

3.4 Statistical Analysis

When it came to the statistical analysis, the complex survey design factors involved in NHANES, including weights, clustering, and stratification, were all considered as recommended. The statistical differences between groups of LMR levels with all the variables were tested by linear regression model and weighted chi-square test. In the next step, we estimated hazard ratios (HRs) and 95% confidence intervals (CIs) using univariate and multivariate Cox proportional hazards models. Together with the above results, Kaplan-Meier analysis was applied to determine the association between LMR levels and all-cause mortality, adjusting for potential confounding factors such as demographic variables, lifestyle behaviors, medical history, and prescription medication use. The multivariate models were adjusted for age, gender, race/ethnicity, education level, and marital status, except for model 2. We further adjusted model 3 to account for BMI, smoking and drinking status, diabetes, hypertension, coronary heart disease, asthma, depression, kidney injury, and aspirin consumption. Extra sensitivity analyses were carried out in the same way. In addition, we conducted subgroup analyses to examine the association between all-cause mortality and covariates. To determine the statistical significance of interactions, the likelihood ratio test was used by creating interaction terms between continuous LMR and the demographic and disease variables. For missing values in covariates, median interpolation was used for continuous variables, and third categories were added for classified variables to assess the effect of missingness on the outcome. In this study, SPSS 26.0 software, R software, and Empower Stats were used for data analysis.

4. Results

4.1 Baseline Participant Characteristics

Sociodemographic and clinical characteristics at baseline of 2363 participants in four groups of LMR are presented in Table 1 (LMR< 2.5, 2.5 ≤ LMR < 3.5, 3.5 ≤ LMR < 4.5, LMR ≥ 4.5). Data were presented as mean ± standard deviation (SD) for continuous variables and as numbers (%) for categorical variables. The weighted mean age at baseline was 61.86 ± 14.67 years, 1,264 (53.49%) were female and 1,690 (71.52%) were non-Hispanic white. The average LMR was 3.76 ± 2.17. As for sociodemographic characteristics, lower groups of LMR were more associated with older age, male, non-Hispanic white,

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widowed/divorced/separated, current smokers and more sleep. To mention clinical characteristics, the prevalence of CHD and hypertension decreases across groups. Moreover, patients with lower LMR take less aspirin. However, education, alcohol consumption, depression, kidney injury, asthma, diabetes was similar among groups.

4.2 Survival Analysis of LMR for Mortality Risk

During a follow-up of 478727 person years, 458 individuals died. LMRs were significantly lower in participants who died than in those who did not (3.19 vs. 3.90, $p < 0.001$). As shown in Kaplan-Meier survival curves (Figure 2), the outcome was significantly elevated among low-LMR group versus high-LMR group (Log rank test $P < 0.001$). The results remained unchanged when a quarter classification scheme was used (Supplementary Figure 1), and the LMR seems to be more effective than either the PLR or NLR (Supplementary Figure 2). After multiple regression analyses, the estimated HR and CIs showed, groups of LMR were significantly associated with all-cause mortality adjusted or not. In the multivariable model III, every 1 increase in LMR was linked with a 7% reduction in the risk of all-cause mortality (HR 0.93, 95% CI 0.88–0.99, P=0.0301). Comparing with the lowest group of LMR (G1), the HRs, 95% CIs and P values for all-cause mortality from G2 to G4 in the multivariable model III were respective 0.78 (0.62–0.99, P =0.0431), 0.67 (0.51–0.88, P =0.0039), and 0.59 (0.43–0.81 P =0.009). To sum up, LMR in continuous or categorical variables were respectively associated with the risk of all-cause mortality in participants with cancers (all $P < 0.05$).

Survival according to LMR levels was determined using Kaplan Meier curves. As the Red, green, dark blue, and light blue lines standing for, participants with lower LMR levels had unfavorable prognosis compared with those with higher.

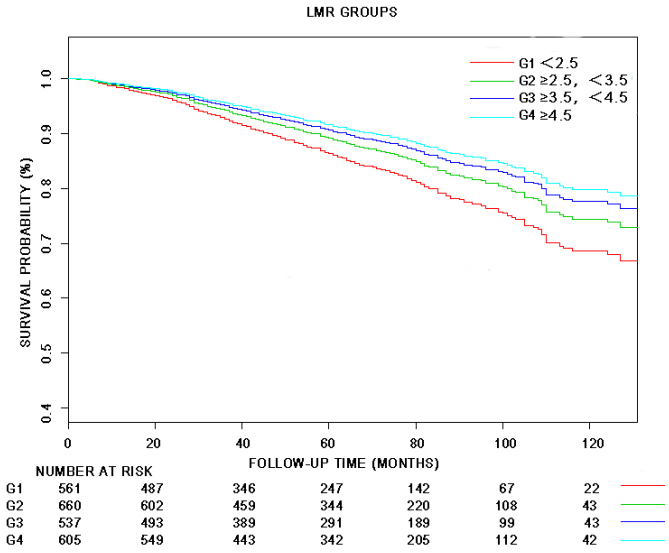

Figure 2: Kaplan–Meier estimated cumulative survival curves based on LMR Groups, 2005-2014.

4.3 Subgroup Analyses

Further analyses were conducted on subgroups of age, gender, body mass index, and baseline medical condition in order to determine whether LMR levels were associated with all-cause mortality. Across all of these subgrouping variables, the association between LMR levels and all-cause mortality was consistent (P for trend < 0.05). No significant interactions were detected between LMR levels and these stratifying variables (all P interactions > 0.05).

We conducted additional sensitivity analyses to test the robustness of the results. Excluding individuals whose LMR levels exceeded three standard deviations (Supplementary Table 1), or participants with major diseases of CHD at baseline, or participants whose follow-up time was adjusted to the month when blood was drawn. The results of these sensitivity analyses suggest that the relationships between LMR levels and mortality are robust to unmeasured confounders, except in the case of a strong unmeasured confounder[17-23].

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4.4 Discussion

Nowadays, cancer prognosis is mostly determined by the TNM stage11. However, the postoperative pathological stage of the tumor would differ significantly and many patients cannot undergo surgery for pathological identification. As we all know, inflammation and immune response play an instrumental role in cancer development which can be tested through blood components12. Thus, indicators such as CA125, BRCA1, EGFR are used in cancer prognosis13. Extra biopsy for molecular markers may causes patient discomfort, and measurement and quantification require complex and expensive assays. All the above defects can be corrected by accurate and convenient markers like neutrophils, lymphocytes, and monocyte counts. Mix scores like NLR, PLR, and LMR, which combine neutrophils, lymphocytes, and monocytes, may be more accurate. It is simple, rapid, and inexpensive to measure NLR, PLR, and LMR. Only peripheral blood samples are required, which almost cause no discomfort. Therefore, these new indexes have attracted a great deal of research interest, especially NLR and PLR. LMR can predict the prognosis of multiple diseases, acute diseases like coronary syndrome14, pulmonary embolism15, and influenza virus infection16, chronic diseases including rheumatoid arthritis17, depression18 and liver cirrhosis19. Recent studies also confirm that LMR is a strong prognostic factor for various malignancies20-23.

To the best of our knowledge, this is the first prospective study examining the relationship between LMR scores and all-cause mortality in cancer patients using NHANES. This study involved a cohort of US cancer patients recorded in NHANES between 2005 and 2014. After assessing multiple covariates, we found a robust correlation between levels of LMR and all-cause mortality in cancer. Based on the Cox model and Kaplan-Meier curve, our results demonstrate that participants with lower LMR levels had an unfavorable prognosis compared with participants with higher levels. The conclusion remained the same whenever the LMR was divided into four groups with cutoff points of 2.5, 3.5, 4.5, or quarters, and was more effective than either PLR or NLR. Similarly, Pan et al24 found that NLR and PLR were not independently associated with the prognosis of GC, while patients with LMR$<$5.43 had a shorter lifespan and a lower 5-year survival rate (HR: 1.49, 95% CI: 1.17-1.89). According to Lv et al.25, preoperative LMR $\geq$ 2.95 groups had higher overall survival ($p < 0.05$), and LMR is more accurate than NMR, RDW and PDW. However, several studies have demonstrated the disadvantage of LMR8, 26, 27., for example, Yapar et al. 28 found that LMR was weaker than NLR (AUC=0.603 and 0.681) in patients with osteosarcoma. It is possible that observational studies are subject to uncontrolled confounding factors, such as physical activity, diet, and chronic illness. The consistency and magnitude of the prognostic impact of LMR remain unclear so on29.

Furthermore, most studies were performed on the preoperative LMR, and very few studies were conducted on the postoperative or terminal period. Based on perioperative LMR, Yoshida et al30 reached a significant different OS and CSS ($p < 0.001$, each) in each three groups of LMR levels. In another study, Go et al31 reported that progression-free survival and overall survival were significantly shorter in the low LMR group ($p<0.005$, respectively). Moreover, we found no significant differences in the subgroup analyses like most studies32, 33. Pan et al24, for example, found similar trends only among patients with TNM II and III, which may be due to insufficient participation. On multivariate analysis, a low LMR with various cutoff point at diagnosis was an independent unfavorable prognostic factor for predicting OS, PFS, CCS and any other survival rate. We hope to provide solid evidence that LMR can be effective at most stages of most types of cancer, and the optimal cutoff point for LMR will vary from one situation to another. This will enable us to provide a reliable index for bringing the gospel to cancer patients.

Biomarker LMR can not only be used for prophylaxis, but also for therapeutic purposes. In the context of LMR, lymphocytes are essential to immunosurveillance and immunoediting. A low lymphocyte count indicates an insufficient immune response to the tumor, together or not with high monocyte counts, which promote tumor growth and metastasis10. The LMR indicates tumor diameter, grade, and whether infiltrated lymph nodes and distant metastases are present. Based on these results, the type of surgery and treatment will be selected34. Unveiling the LMR as a prognostic biomarker could also validate a causal association between white blood cells and cancer outcomes. The causal association LMR revealed could give further insight into therapy which involves lymphocytes and monocytes as a therapeutic target to improve outcomes in cancer. With the LMR levels, one can track treatment and outcomes in real time among the application of lymphocytes and monocytes related therapy[24-31].

Our study has some strengths. To begin with, we utilized the generalizability of NHANES data, which contained representative non-institutionalized Americans, which allowed our findings to be presented of generalizability. Second, we adjusted for covariates, such as demographic factors, lifestyle habits, chronic health conditions, and prescription medication use. In this way, potential sources of bias could be

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minimized. Then, with the prospective nature of mortality follow-up and spand a longer period (median, 62.94 months), we could eliminate the possibility of recall bias from our analysis. Last but not the least, our initial outcomes remained in extra subgroup analyses and sensitivity analyses, suggesting the robustness of the relation.

We also found limitations in our study. Firstly, due to the nature of the observational design, we could not exclude all the possible effects of unmeasured or unrecognized covariates. Even after adjusting for a variety of covariates. Secondly, the death data we obtained from the National Death Index might introduce some biases for the possible incomplete linking, and inaccurate death certificates. Thirdly, this database has a relatively small group of cancer patients, and whether these associations remain for patients who are hospitalized or willingly participate in the survey requires further investigation. Lastly, in this study, only baseline LMR was examined. Given that the LMR score level is subject to change over time, the use of a single LMR score may lead to bias in certain cancers and treatments. Longitudinal studies can compensate for this limitation.

There are still some issues to be clarified. Based on the variation of LMR measurements according to clinical condition, LMR's effect size and cut-off variables could differ according to the type of cancer and treatment. The optimal condition and cut-off value for LMR should be validated for future research needs and clinical applications. Thus, a larger sample size is required. In view of the epidemiology statement, a greater number of patients with lung and colon cancers should be studied, and not just the non-institutionalized United States. Furthermore, research should investigate the dose-response relationship between LMR and prognosis. In order to determine whether the association is linear or threshold-related. Additionally, few studies have evaluated the association between systemic inflammation markers and cancer risk prior to diagnosis. Whether these markers can be used as biomarkers of cancer risk and to assist in the early detection of the disease still needs further study.

5. Conclusion

Our findings suggest that elevated LMR is associated with a decreased risk of all-cause mortality among US cancer patients. Based on routine complete blood count testing, LMR may serve as a potential inflammatory predictor of cancer mortality prognosis, outperform NLR and PLR, as well as apply readily and guide treatment in clinical practice.

Table 1: Baseline Characteristics of Participants with Cancer according to LMR Groups in NHANES 2005-2014

LMR Level	All	G1 (<2.5)	G2 (<3.5)	G3 (<4.5)	G4 (≥4.5)	P value
Number	2363	561 (23.74%)	660 (27.93%)	537 (22.73%)	605 (25.60%)	
Age(years)	61.86 ± 14.67	68.84 ± 12.59	64.16 ± 13.12	59.96 ± 14.51	55.58 ± 14.98	<0.0001
BMI(kg/m2)	27.95 ± 6.03	27.16 ± 5.90	27.86 ± 5.94	27.85 ± 5.91	28.77 ± 6.25	<0.0001
Depression score(n)	3.28 ± 4.60	2.65 ± 3.73	3.04 ± 4.28	2.88 ± 4.31	3.79 ± 4.80	<0.0001
Gender(n,%)						<0.0001
Male	1099 (46.51%)	374 (61.62%)	325 (43.64%)	228 (39.83%)	172 (28.46%)	
Female	1264 (53.49%)	187 (38.38%)	335 (56.36%)	309 (60.17%)	433 (71.54%)	
RACE/ethnicity(n,%)						<0.0001
Mexican American	149 (6.31%)	15 (0.75%)	37 (1.71%)	38 (2.58%)	59 (4.25%)	
Other Hispanic	116 (4.91%)	18 (0.95%)	30 (1.78%)	30 (2.78%)	38 (2.57%)	
Non-Hispanic White	1690 (71.52%)	449 (91.66%)	501 (90.09%)	380 (87.63%)	360 (81.35%)	
Non-Hispanic Black	320 (13.54%)	61 (4.00%)	67 (3.29%)	76 (4.79%)	116 (7.90%)	
Other	88 (3.41%)	18 (2.63%)	25 (3.13%)	13 (2.21%)	32 (3.94%)	
Education(n,%)						0.3396
Less than high school	238 (10.07%)	59 (5.78%)	58 (4.39%)	56 (5.31%)	65 (5.39%)	
High school	303	77	68	73	85	

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	(12.82%)	(10.13%)	(7.48%)	(8.91%)	(10.92%)	
Above	1822 (77.11%)	425 (84.09%)	534 (88.13%)	408 (85.78%)	455 (83.68%)	
Marital status(n,%)						0.0411
Married/living with partner	1449 (61.32%)	340 (64.13%)	422 (68.40%)	324 (67.71%)	363 (66.55%)	
Widowed/divorced /separated	774 (32.75%)	200 (32.26%)	207 (26.57%)	175 (26.18%)	192 (26.16%)	
Never married	140 (5.92%)	21 (3.62%)	31 (5.03%)	38 (6.11%)	50 (7.29%)	
Smoking(n,%)						<0.0001
Never	1074 (45.45%)	236 (42.90%)	303(49.14%)	243(43.84%)	292(47.37%)	
Current	912 (38.60%)	273 (47.68%)	277 (37.61%)	191 (36.06%)	171 (28.61%)	
Former	376 (15.91%)	52 (9.24%)	80 (13.25%)	102 (20.03%)	142 (24.02%)	
Alcohol drinking (n,%)						0.5451
Yes	1538 (65.09%)	386 (73.77%)	435 (70.47%)	334 (69.23%)	383 (71.30%)	
No	667 (28.23%)	134 (20.19%)	182 (25.42%)	164(24.69%)	187 (23.52%)	
CHD (n,%)						0.0003
Yes	212 (8.97%)	75 (11.58%)	62 (7.34%)	37 (5.15%)	38 (4.54%)	
No	2137 (90.44%)	482 (87.93%)	593 (92.34%)	497 (94.56%)	565 (95.25%)	
Diabetes (n, %)						0.6201
Yes	449 (19.00%)	106 (17.23%)	124 (15.17%)	99 (14.62%)	120 (14.28%)	
No	1834 (77.61%)	439 (79.14%)	503 (80.66%)	424 (82.18%)	468 (82.97%)	
Hypertension (n,%)						<0.0001
Yes	1348 (57.05%)	378 (65.46%)	388 (53.78%)	283 (46.99%)	299 (44.39%)	
No	1009 (42.70%)	181 (34.20%)	271 (46.18%)	253 (52.99%)	304 (55.37%)	
Arsthma (n,%)						0.2455
Yes	380 (6.18%)	77 (14.97%)	99 (15.48%)	99 (18.80%)	105 (17.37%)	
No	2215 (93.74%)	484 (85.03%)	561 (84.52%)	438 (81.20%)	497(82.39%)	
Kidney injury (n,%)						0.0263
Yes	146 (6.18%)	51 (8.02%)	30 (3.78%)	34 (4.31%)	31 (4.14%)	
No	1980 (93.74%)	510 (91.98%)	628 (96.16%)	503 (95.69%)	574 (95.86%)	
Regular aspirin use(n,%)						0.0030
Yes	163 (6.90%)	42 (5.73%)	38 (6.69%)	39 (6.67%)	44 (7.74%)	
No	1875 (79.35%)	468 (82.96%)	549 (80.08%)	417(77.25%)	441 (72.88%)	

Notes: †·The complex survey design was accounted for when computing means, standard deviation and proportions. ‡·Values are standardized to four groups of LMR distribution of the study population except LMR itself. §·For continuous variables, datas were mean if the carriable distribution is normal and P value was calculated by weighted linear regression model. For categorical variables, datas were presented as n (%) and P value was calculated by weighted chi-square test.

Abbreviations: LMR, Lymphocyte-to-monocyte ratio; BMI, body mass index; CHD, coronary heart disease; G, groups.

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