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ORIGINAL RESEARCH

Mediating Role of Lipid Accumulation Products (LAP) in the Association of WBC with MASLD: SWH 2021-2023

Junliang Zhou, Zhen Cheng, Li Sun*, Zongtao Chen*

Health Management Center, First Affiliated Hospital of Army Medical University, Chongqing, 400038, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zongtao Chen; Li Sun, Email zongtaochen@126.com; 51088031@qq.com

Background and Objectives: The association between various inflammatory markers and Metabolic dysfunction associated steatotic liver disease (MASLD) and the role of lipid accumulation products in this is unclear. The aim of this study was to explore the relationship between various inflammatory markers and MASLD, and to explore the potential mediating role of LAP in inflammatory markers (WBC).

Methods: The binary logistic regression model was used to evaluate the correlation between various inflammatory markers and MASLD. We used the Restricted Cubic Spline (RCS) to describe the measurement-response relationship between these factors and MASLD. In addition, we assessed whether lipid accumulation products have a mediating role in the association by intermediary analysis, which was verified by the Bootstrapping method.

Results: From 2021 to 2023, a total of 13,628 participants' testing data were collected and used from the Health Management Center of Southwest Hospital (SWH), including 10,988 non-MASLD and 2,640 MASLD. The results of independent sample *T*-test showed that inflammation-related markers such as PLT, WBC, SII, NLR, and PLR were significantly different between the control group (Non-MASLD) and the experimental group (MASLD), and WBC was particularly prominent. The results of binary logistic regression analysis showed that there was a close positive correlation between WBC and MASLD after adjusting for various confounding factors such as age, sex, BMI, and smoking status (OR = 1.255, 95% confidence interval: 1.135–1.388), $p < 0.001$. The RCS results once again demonstrated a linear dose-response relationship between WBC and MASLD risk. Finally, the results of mediation analysis and bootstrapping validation showed that LAP partially mediated the association between inflammatory marker (WBC) and MASLD, and its effect percentage was 13.58%.

Conclusion: The results of this study suggest that the inflammatory marker WBC is positively correlated with the risk of MASLD, and LAP plays a partial mediating role in this association.

Keywords: inflammatory markers, mediation analysis, RCS, LAP, MASLD

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a chronic liver disease with metabolic dysfunction at its core, and its diagnostic criteria were first systematically defined by an international expert consensus in 2020.[1] (It is important to note that the terminology for fatty liver disease has recently evolved. While this study was conducted using the 2020 MAFLD criteria,[1] the most recent multisociety Delphi consensus in 2023 has recommended the use of "metabolic dysfunction associated steatotic liver disease" (MASLD) as the preferred terminology.[2] We have adopted this updated terminology throughout the manuscript while maintaining the original diagnostic criteria for consistency with our study design). Unlike traditional nonalcoholic fatty liver disease (NAFLD), MASLD emphasizes the central role of metabolic abnormalities in the development of the disease without completely excluding the possibility of coexisting with other liver diseases.[3] Global epidemiological data show that the combined prevalence of MASLD is approximately

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39.22%,[4] especially in Asian populations, and is closely related to lifestyle changes. At present, it has been shown that the risk of all-cause mortality in patients with MASLD is significantly higher than that of patients with NAFLD, especially in patients with diabetes mellitus or cardiometabolic disorders, and the risk of adverse events such as myocardial infarction and stroke is increased by 2 to 3 times.[5] It is important to note that MASLD is not only a liver disease but also closely related to systemic diseases such as chronic kidney disease, polycystic ovary syndrome, and cognitive impairment.[6] At present, although the public health burden of MASLD is lower than that of malignant tumors and cardiovascular diseases, its rapidly increasing prevalence (32.9% in China in 2018)[7] and complex multisystem complications have urged us to strengthen early intervention, early detection, and early treatment. Current management strategies include lifestyle modification (eg, weight loss of 5 to 10% significantly improves hepatic steatosis),[8] regulation of metabolic abnormalities (eg, GLP-1 receptor agonist use),[9] and targeted therapies for liver fibrosis (eg, rmelterole).[10] However, the molecular mechanism of MASLD is still unclear and needs to be further explored, and this global health challenge maybe can be addressed by establishing a multi-indicator risk prediction model.[11]

In recent years, a number of studies have shown a strong association between systemic inflammation levels and MASLD.[12] Indicators of inflammation levels include inflammatory markers and indices such as white blood cell (WBC), platelet (PLT), systemic immune inflammation index (SII), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and others.[13,14] For example, SII can reflect systemic inflammatory status by integrating neutrophil, platelet, and lymphocyte counts, and its elevation is closely related to an increased risk of atherosclerosis in patients with MASLD.[12] Experiments have shown that The Kupffer-cell products interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha) have been shown to stimulate hepatic lipogenesis in vivo.[15] Therefore, Elevated WBC count may promote hepatic inflammation through releasing pro-inflammatory cytokines (eg, TNF-α, IL-6), which accelerate lipid accumulation in hepatocytes. MASLD is characterized by hepatic steatosis, inflammation, and fibrosis. Compared to NAFLD, MASLD highlights metabolic comorbidities (eg, obesity, diabetes) that drive systemic inflammation, whereas NAFLD focuses on exclusion of other liver diseases.[16] However, existing therapies for MASLD (eg, lifestyle modification) have limited efficacy in controlling chronic inflammation, leading to disease progression in 20–30% of patients.[17]

LAP play an important role in the association between inflammation and MASLD.[18] Systemic inflammatory response and LAP are often inseparable in the onset and progression of MASLD. In a cross-sectional study of 805 patients with MASLD, LAP was closely related to inflammatory markers such as MHR (monocyte/high-density lipoprotein ratio) and NLR (neutrophil/lymphocyte ratio), suggesting that LAP may affect the inflammatory microenvironment by regulating the proportion of immune cell subsets.[19] Therefore, there is an urgent need to elucidate the internal relationship between LAP and MASLD.

In this study, LAP were calculated based on indicators such as waist circumference and triglycerides, and are an indirect indicator of lipid accumulation in the body.[20] Compared with traditional evaluation methods, it has the advantages of more convenience and lower cost. Although traditional liver aspiration can more accurately reflect the accumulation of liver fat,[21] its invasiveness to the body is not accepted by the general public, and it is difficult to apply it to the usual health screening. In clinical practice, LAP has notable advantages. Calculated using waist circumference and triglycerides, it is simple to obtain, more accurately predicts risks of metabolic syndrome and MASLD than single indicators like BMI, suits diverse populations, and dynamically reflects intervention effects. However, it has limitations: relying on accurate measurements, failing to distinguish fat distribution, being less effective in predicting non-obese metabolic diseases, and lacking unified cutoff values.[22] LAP has been shown to be significantly associated with the risk of diabetes, especially in women.[23] In a prospective cohort study, cumulative LAP (a measure of long-term exposure) was significantly associated with the risk of hypertension, with a 2.339-fold higher risk in the high-cumulative LAP group than in the low-value group.[24] Due to its significant effects and advantages, we chose LAP to explore its association with inflammatory response and MASLD.

The aim of this study was to assess the overall burden of inflammation in individuals by using WBC, an inflammatory marker, in the physical examination population, and elucidate the intrinsic association between LAP in the risk of WBC and MASLD.

Methods

Data Sources and Filtering

The data of this study are from the collection of physical examination data from the Department of Health Management of Southwest Hospital from January 2021 to December 2023. The data system collected the demographic characteristics, lifestyle questionnaires, physical examination indicators and laboratory test data (blood routine, biochemical routine, etc.) of the subjects, covering core health indicators such as blood pressure, blood glucose, blood lipids, liver and kidney function. This study initially included the original physical examination data of 114,721 physical examiners. According to the research objectives and methods, we screened 13,768 samples for follow-up analysis through multi-level data screening quality control. Subsequently, a total of 2,640 patients with MASLD were screened according to the criteria of whether they were diagnosed with MASLD, including 660 female patients and 1980 male patients (Figure 1). The sample size estimation for this study was based on the primary endpoint. Referring to the effect size (OR = 1.3) of similar exposure factors associated with MASLD in previous studies, statistical power was calculated using SPSS 27 software. With a significance level of $\alpha = 0.05$ (two-tailed) and a required power $(1-\beta) \geq 0.9$, the minimum sample size was estimated to be 1800 cases. The actually included 2640 MASLD patients (660 females, 1980 males) met the sample size requirement. Post-hoc analysis showed that the statistical power of this study reached 0.93, which was sufficient to detect differences in the preset effect size, ensuring the statistical reliability of the results. The research protocol was reviewed and approved by the Ethics Committee (Grant No. [A]KY202227).

Diagnosis of MASLD

The diagnostic criteria for MASLD were based on the 2020 international expert consensus,[1] with reference to the updated 2023 nomenclature guidelines [Rinella et al, 2023]. It adopt a "definitive" diagnostic strategy without the need to rule out other liver disease or alcohol consumption factors, as follows: Measured by imaging (CT, MRI), ultrasound (controlled attenuation parameter (CAP) of transient elastography (FibroScan) ≥248 dB/m can be used as a quantitative standard).[20] The diagnosis of MASLD is made by liver biopsy testing that confirms hepatic steatosis and meets any of the following criteria: (1) Overweight/obesity: BMI ≥ 23 kg/m² (Asian population) or ≥25 kg/m² (non-Asian population). (2) Type 2 diabetes: patients with diagnosed diabetes. (3) Metabolic abnormalities (at least 2 of the following): ①Waist circumference: Asian male ≥ 90 cm, female ≥ 80 cm; ② Blood pressure ≥ 130/85 mmHg or receiving antihypertensive therapy. ③Triglycerides ≥ 1.70 mmol/L or receiving lipid-lowering therapy. ④HDL-C: 1.0 mmol/L < for males and 1.3 mmol/L < for females. ⑤Prediabetes: fasting blood glucose 5.6–6.9 mmol/L, or 2-hour postprandial blood glucose of 7.8–11.0 mmol/L, or HbA1c 5.7%–6.4%. ⑥Insulin resistance (HOMA-IR ≥ 2.5). ⑦Chronic inflammation: hypersensitive C-reactive protein (hs-CRP) > 2 mg/L.[1]

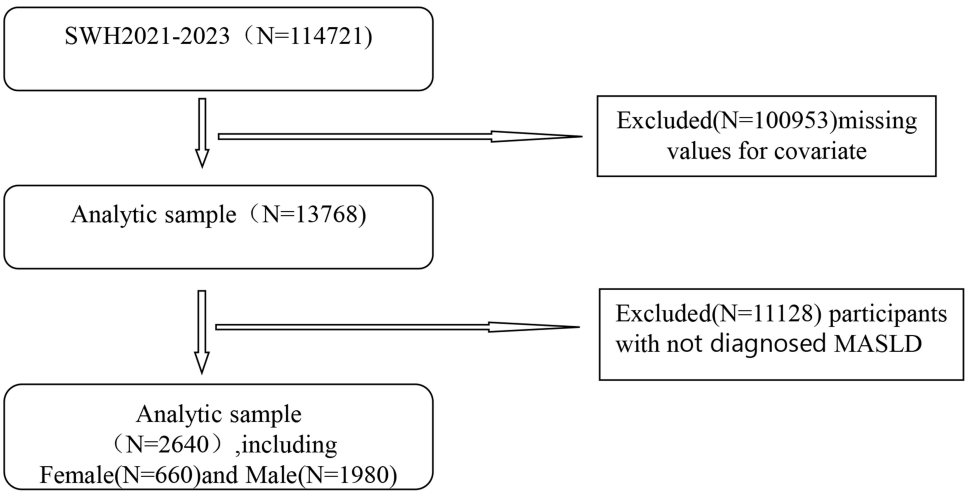

Figure 1 The flowchart of study and excluded participants, from Southwest Hospital (SWH) China.

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Calculation of Inflammatory Markers and LAP

For each participant, the inflammatory markers leukocyte (WBC) and platelet (PLT) were determined based on routine blood results. In addition, the following ratios are calculated: neutrophil-to-lymphocyte ratio (NLR), calculated by dividing neutrophil count by lymphocyte count; platelet-to-lymphocyte ratio (PLR), which is calculated by dividing the platelet count by the lymphocyte count; Systemic Immune Inflammatory Index (SII), which is the product of neutrophil count and platelet count divided by lymphocyte count; At the same time, the LAP is calculated according to the sex. Table S1 lists the formulas for all the calculated values involved in this document.

RCS and Mediating Effect Analysis

First, we downloaded the "rms" package via R. And then, prepared data and check distribution. Use rcs() from the rms package to set knots for the independent variable (usually 3–5, default Harrell's method).[23] Include RCS terms in regression models (eg, lm() or coxph()), extract effect estimates and 95% *CI*, plot nonlinear curves with ggplot2, check model fit (eg, AIC), and report knot positions, *P*-values, and trend.

Subsequently, to confirm whether LAP mediate the association between leukocyte levels and MASLD risk, we introduced a mediating effects analysis framework.[24] We input data and test normality, linearity, and multicollinearity by SPSS. Use Process plugin, select model 4, set independent variable (X), mediator (M), dependent variable (Y), set Bootstrap samples (eg, 5000) and 95% *CI*. Run to get total, direct, and mediation effects with 95% *CI*. Mediation is significant if *CI* excludes 0. Report effect values, *P*-values, and effect ratio.

Statistical Analysis

In this study, the basic characteristics of categorical variables were expressed in counts and percentages (%), while the basic characteristics of continuous variables were expressed in mean ± standard deviation (X ± S). The *T*-test, Chi-square test, and Mann–Whitney *U*-test were used to describe the differences between the control and MASLD groups for categorical variables and continuous variables. The following are the specific operation methods and parameters of the three statistical tests: Comparisons between two groups were performed using the independent samples *t*-test (significance level $\alpha = 0.05$, degrees of freedom df = n1+n2-2). Non-normally distributed data were expressed as median (interquartile range) [M (Q1, Q3)], and the Mann–Whitney *U*-test was used for between-group comparisons (test statistic U, $\alpha = 0.05$). Categorical data were presented as frequency (percentage) [n (%)]. Comparisons between groups were conducted using the Pearson's chi-square test (when all expected cell frequencies ≥5) or Fisher's exact test (when any expected cell frequency <5), with the test statistic χ^2 (degrees of freedom df = (rows-1) × (columns-1), $\alpha = 0.05$). The Z-test was used for comparing rates, with the test statistic $Z = (p1-p2)/\sqrt{[p(1-p)(1/n1+1/n2)]}$ (where p is the pooled rate, n1 and n2 are sample sizes of the two groups; $\alpha = 0.05$, two-tailed critical value $Z\alpha/2 = 1.96$). All statistical analyses were performed using SPSS 27.0 software.

Binary logistic regression analysis was used to assess the correlation between various inflammatory markers and MASLD. Three models were designed using logistic regression analysis: model 1 was a rough model; Model 2 adjusted for gender, age; Model 3 adjusted for age, sex, BMI, blood glucose, uric acid, AST, ALT, and whether or not to smoke. The Spearman test was used for correlation analysis for each indicator. The statistical software used in this study was SPSS version 27.0 for statistical analysis of all data. ($P < 0.05$, the difference was considered statistically significant; $P < 0.01$, the difference was significant. $P < 0.001$, there was a significant difference).

Results

Basic Characteristics of the Participants

A total of 13,628 participants were included in the study, including 10,988 in the control group (Non-MASLD) and 2,640 in the test group (MASLD). As can be seen from Table 1, WBC was significantly elevated in MASLD participants compared with control participants [6.34 ± 1.58 vs 5.62 ± 1.65] (Table 1). Other inflammatory markers PLT, SII, NLR, and PLR also showed higher levels in the MASLD group, and the differences were statistically significant. In addition, BMI, UA, and FBG also had large differences between the Non-MASLD group and the MASLD group ($P < 0.05$, considered statistically significant).

Table 1 Characteristic of Participants

Characteristics	Non-MASLD	MASLD	t/z/ χ^2	*P*-value
Sex (%)	10,988	2640	1247.581	<0.001
Female	6926 (63.0%)	660 (25.0%)		
Male	4062 (37.0%)	1980 (75.0%)		
Age (%)			14.897	<0.001
18–65	10,776 (98.1%)	2554 (96.7%)		
≥65	212 (1.9%)	86 (3.3%)		
BMI	22.6 ± 2.8	27.2 ± 3.0	−73.381	<0.001
WHtR	0.47 ± 0.06	0.55 ± 0.11	−45.614	<0.001
FBG (mmol/L)	5.42 ± 0.84	6.16 ± 1.74	−21.259	<0.001
UA (umol/L)	328.74 ± 85.09	417.65 ± 98.95	−42.531	0.000
AST (U/L)	22.32 ± 11.93	28.81 ± 14.51	−21.325	<0.001
ALT (U/L)	20.66 ± 16.94	39.81 ± 28.20	−33.46	<0.001
LAP	21.15 ± 23.44	67.49 ± 55.37	−42.105	<0.001
Inflammatory markers				
PLT (10^9/L)	220.04 ± 54.26	224.41 ± 56.28	−3.608	<0.001
WBC (10^9/L)	5.62 ± 1.65	6.34 ± 1.58	−20.614	<0.001
SII	430.61 ± 224.16	445.55 ± 218.36	−3.139	0.002
NLR	1.96 ± 0.85	1.99 ± 0.83	−1.89	0.059
PLR	131.04 ± 43.50	119.89 ± 38.96	12.892	0.002

Abbreviations: BMI, body mass index; WHtR, Waist-to-Height Ratio; FBG, fasting blood glucose; UA, Uric Acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LAP, Lipid Accumulation Product; PLT, platelet count; WBC, white blood cell; SII, systemic immune inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio;

Associations Between Various Inflammatory Markers and the Risk of MASLD

In order to explore the correlation between various inflammatory markers and metabolically associated fatty liver disease (MASLD), we constructed three inflammatory marker evaluation models by binary logistic regression analysis to evaluate the correlation between various inflammatory markers and MASLD. Through comparative analysis, we found that after adjusting for various confounding factors such as age, gender, BMI, FBG, uric acid, AST, ALT, and smoking or not, the WBC was still positively correlated with MASLD risk in Model 3, with an odds ratio (OR) of 1.255, 95% confidence interval (CI) of 1.135–1.388, $P < 0.001$. However, the inflammatory marker PLT (PLT, OR = 1.007, 95% CI 1.004–1.010) and systemic immune inflammatory index (SII, OR = 1.001, 95% CI 1.000–1.002) were statistically significant, but the risk value was low. The correlation between NLR and PLR and MASLD risk in Model 3 was no longer significant, both $P > 0.05$ (Table 2 for details).

There is a Linear Dose-Response Relationship Between WBC and the Risk of MASLD

Based on restriction cubic spline (RCS) analysis, this study presents the results of the dose-response relationship between white blood cell count level (WBC) and MASLD. As shown in Figure 2A, there was a significant nonlinear dose-response association between WBC and MASLD before adjusting for confounders (the nonlinearity test *p*-value < 0.05). However, when the potential confounders (consistent with Model 3 above) were fully corrected, the true

Table 2 Correlation of Various Inflammatory Markers with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

Variables	OR	95% *CI*	*p*- value
PLT			
Model 1	1.001	1.001–1.002	<0.001
Model 2	1.005	1.004–1.006	<0.001
Model 3	1.007	1.004–1.010	<0.001
WBC			
Model 1	1.333	1.296–1.37	<0.001
Model 2	1.322	1.283–1.363	<0.001
Model 3	1.255	1.135–1.388	<0.001
SII			
Model 1	1.000	1.000–1.000	0.002
Model 2	1.001	1.000–1.001	<0.001
Model 3	1.001	1.000–1.002	<0.001
NLR			
Model 1	1.047	0.998–1.099	0.063
Model 2	0.988	0.937–1.042	0.659
Model 3	1.156	0.963–1.387	0.119
PLR			
Model 1	0.993	0.992–0.994	<0.001
Model 2	0.996	0.995–0.997	<0.001
Model 3	1.001	0.997–1.005	0.710

Notes: Model 1 was the crude model; Model 2 adjusted for gender and age; Model 3 was adjusted for age, sex, BMI, FBG, uric acid, AST, ALT, smoking or not.
Abbreviations: BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; OR, odds ratio.

dose-response pattern between the two changed to a linear relationship (the nonlinearity test p-value > 0.05) (Figure 2B). In summary, with the gradual increase of WBC level, the risk of MASLD also showed a synchronous upward trend.

LAP Partially Mediate the Association Between WBC and MASLD

In the process of in-depth exploration of the pathogenesis of MASLD, it is important to clarify the intrinsic relationship between these related factors. In this mediation analysis, we focused on the key indicator of LAP, and set it as a mediating variable, with the core purpose of exploring whether LAP plays a bridging role between WBC and MASLD, and the specific extent of this mediating effect. The study found that in Model 1, there was a strong association between inflammatory markers and the risk of developing MASLD, and about 14.15% of the association may be mediated by LAP. In model 2, considering that factors such as gender and age may interfere with the results of the study. We further found that the mediating effect of LAP on the association of inflammatory markers with the risk of MASLD was still significant, with a mediating percentage of 13.58% (Figure 3). This robust result provides a key clue for an in-depth understanding of the pathogenesis of MASLD, and also provides a strong theoretical basis for the formulation of subsequent targeted prevention and treatment strategies.

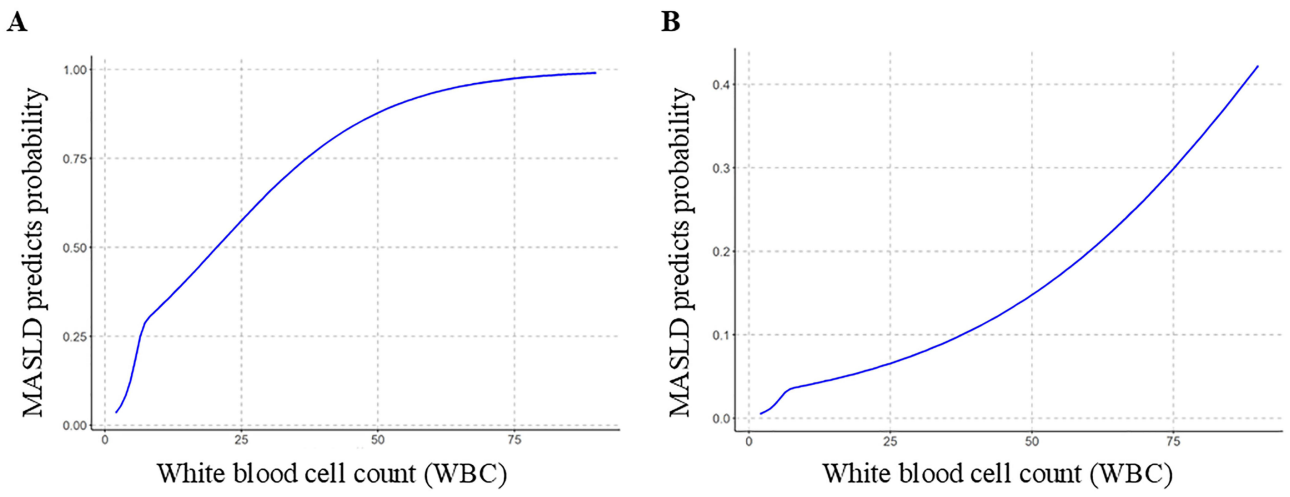
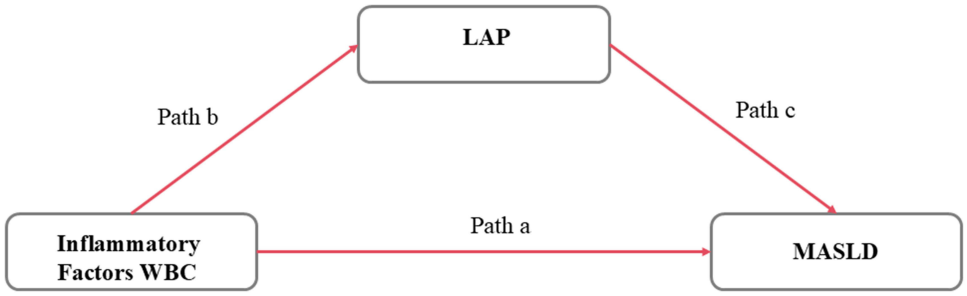


Figure 2 White blood cell count (WBC) versus dose-response relationship of MASLD.
Notes: (**A**) Dose-response relationship between the inflammatory marker WBC and MASLD without any factor adjustment; (**B**). Adjusted dose-response relationship between inflammatory marker WBC and MASLD in the case of adjustment for factors including age, gender, BMI, GLU, UA, AST, ALT, smoking or not (**A**) $P < 0.05$; (**B**) $P > 0.05$).



Variables	Model 1	Model 2
Total effect	0.325(0.292 - 0.361)	0.324(0.287 - 0.362)
Direct effect (Path a)	0.279(0.246 - 0.311)	0.278(0.243 - 0.313)
Indirect effect (Path bc)	0.046(0.044 - 0.048)	0.044(0.042 - 0.046)
Percent mediation (%)	14.15%	13.58%

Figure 3 Mediating analysis of the association between WBC and MASLD by LAP.
Notes: Model 1 is a rough model; Model 2 was adjusted for age and gender. Total effects: the overall effect of inflammatory markers (WBCs) on MASLD without considering the mediating role of LAP; Direct effect: direct effect of inflammatory marker (WBC) on MASLD after the effects of controlling LAP; Indirect effect: refers to the effect of inflammatory marker (WBC) on the risk of MASLD through the LAP pathway; Percent mediation: the proportion of indirect effects in the total effect.

Discussion

In this cross-sectional study based on data from 2020 to 2023, we focused on the association between WBC, a systemic inflammatory marker, and MASLD. It also explores the mediating role of LAP in the association between WBC and MASLD. Through binary logistic analysis and the construction of a mediating effect model, we found a significant positive association between WBC and MASLD, which is consistent with the conclusions of many studies that have revealed an association between systemic inflammation and MASLD.[25] As a key component of the body's immune defense system, the number of leukocytes increases significantly in the inflammatory state, reflecting that the body is under inflammatory stress.[26] When systemic inflammation levels increase, the release of inflammatory mediators

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increases, which interfere with the normal metabolic homeostasis of the liver, which in turn promotes excessive fat deposition in the liver and promotes the pathogenesis of MASLD.[27] LAP can better reflect the degree of visceral fat accumulation and are effective predictors of the risk of metabolic diseases such as diabetes and cardiovascular diseases,[28,29] which is helpful for early identification and intervention, which is its advantage over traditional indicators such as body mass index (BMI), because LAP can more accurately reflect the accumulation of visceral fat.[30] The innovation of this study is that it clearly reveals the mediating effect of LAP in the association between white blood cell count and MASLD. Using mediating effects analysis, we found that the effect of WBC on MASLD was mediated in part by LAP. From the perspective of physiological and pathological mechanisms, when WBC is elevated due to systemic inflammation, it will lead to the aggravation of adipose tissue metabolism disorders, resulting in visceral fat accumulation and a significant increase in LAP levels. A high level of LAP means a high level of fat accumulation, which leads to a double hazard: on the one hand, it can directly affect the expression of lipid metabolism-related genes in liver cells, and promote the further accumulation of lipids in the liver; On the other hand, it can further exacerbate the local inflammatory response of the liver, leading to increased hepatocellular damage and ultimately accelerating the development of MASLD.[27]

Previous studies have focused on the direct association between WBC and MASLD, but have not explored the underlying mediating mechanisms. Jung et al found in a retrospective study that baseline inflammation reflected in WBC levels influences future development of multiple sclerosis,[31] and our study provides a new and more comprehensive perspective for understanding the pathogenesis of MASLD by providing an in-depth and confirmed mediating role of LAP in this association for the first time. Of course, there are some differences in results between different studies. For example, some studies may have been found to differ due to the use of different measures of systemic inflammation, or the inclusion of participants who were significantly different from this study in terms of age, ethnicity, geography, and distribution of underlying diseases.

From a therapeutic perspective, our findings suggest that interventions targeting both systemic inflammation and lipid accumulation may be particularly effective for MASLD management. Recent clinical trials have demonstrated the efficacy of glucagon/GLP1 receptor dual agonists (eg, survodutide) in improving hepatic steatosis and fibrosis in MASLD patients.[32] Additionally, thyroid hormone receptorβ selective agonists like resmetirom have shown promise in Phase 3 trials for reducing liver fat content and improving fibrosis.[10] Our results support the potential value of such dual-target approaches given the interconnected roles of inflammation and lipid metabolism in MASLD pathogenesis. Recent studies suggest that targeting FABP5-positive macrophages may reduce the release of pro-inflammatory cytokines (eg, TNF-α, IL-6) while inhibiting their promotion of hepatic lipid uptake, a strategy that has shown efficacy in reducing hepatic steatosis in animal models.[33] Additionally, activating the peroxisome proliferator-activated receptor α (PPARα) pathway can enhance hepatic fatty acid β-oxidation and lower circulating triglyceride levels, thereby downregulating LAP; its agonists have demonstrated improvements in hepatic inflammation and fibrosis in preclinical studies.[34] Validation of these targets may guide the development of drugs with both anti-inflammatory and lipid-modulating properties. These pathways warrant exploration in future interventions.

Despite the innovative results of this study, there are inevitably some limitations. First, as a cross-sectional analysis, our study cannot establish causal relationships between WBC, LAP and MASLD. Second, while we adjusted for multiple confounders, residual confounding from unmeasured factors (eg, dietary patterns, physical activity levels) may persist. Third, our reliance on ultrasound rather than liver biopsy for steatosis assessment may have resulted in some misclassification, particularly for mild steatosis cases.[35] Fourth, WBC represents only one aspect of systemic inflammation, and future studies should incorporate additional inflammatory markers (eg, CRP, IL6) to provide a more comprehensive assessment. Finally, our study population was drawn from a single Chinese Medical Center, which may limit generalizability to other ethnic groups and geographic regions.

Based on this study's findings, future research could further explore MASLD mechanisms and interventions. Prospective cohorts combined with Mendelian randomization are needed to clarify causal relationships among WBC, LAP, and MASLD. Multi-omics technologies should be integrated to decipher how inflammatory signals affect hepatic lipid deposition via LAP, particularly crosstalk between inflammatory and lipid regulatory pathways. For clinical translation, dual-target intervention trials using precise assessment methods are warranted. Additionally, studies should expand samples to diverse populations and measure multiple inflammatory markers to enhance generalizability and comprehensiveness. Exploring the value of composite biomarkers like combined WBC and LAP for risk prediction and treatment response may provide new tools for personalized care.

Conclusion

The results of this study suggest that WBC, but not other inflammatory markers examined, is positively correlated with the risk of MASLD. LAP plays a partial mediating role in this specific association. WBC and LAP as potential biomarkers for MASLD risk stratification, suggesting that combined targeting of inflammation and lipid metabolism may enhance therapeutic efficacy.

This discovery opens up a new direction for in-depth exploration of the potential mechanism of fatty acid metabolism, inflammation and infection, and fatty liver, and is expected to provide a new strategy and method for early identification and reduction of MASLD risk. Future studies should explore whether modulating LAP or WBC-related inflammation (eg, via lifestyle interventions or targeted drugs) can reduce MASLD risk.

Ethics Approval

The study is in line with the principles of the Declaration of Helsinki. The Ethics Committee of the First Affiliated Hospital of Army Medical University approved the research protocol (Grant No.[A]KY202227). Informed consent was obtained from all participants.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflicts of interest in this work.

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