

Association between White Blood Cell Count and Remnant Cholesterol Inflammatory Index in Middle-Aged and Older Adults: A Cross-National Database Study Using NHANES and CHARLS

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Abstract: *Objectives:* The remnant cholesterol inflammatory index (RCII) is a novel composite biomarker that integrates lipid residual risk and inflammatory status. White blood cell (WBC) count, one of the most routine clinical inflammatory indicators, has an undefined association with RCII and unknown joint prognostic significance. This study aimed to investigate the cross-sectional association and longitudinal prognostic implications of WBC and RCII in middle-aged and older populations, so as to deepen the understanding of the “lipid-inflammation” cycle. *Methods:* Cross-sectional analyses were performed in two cohorts of adults aged 45 years and older: NHANES (2015–2016, n = 2,839) and CHARLS (2011, n = 5,955). Multivariable logistic regression and restricted cubic spline (RCS) analyses were used to assess the association and its nonlinearity. Longitudinal analyses utilized CHARLS follow-up data (2011–2015), applying Kaplan-Meier curves and Cox proportional hazards models to examine differences in long-term survival across categories of RCII and WBC. *Results:* In fully adjusted models, WBC was significantly and positively associated with RCII in both cohorts (NHANES: OR = 1.097, 95% CI: 1.038–1.158; CHARLS: OR = 1.309, 95% CI: 1.266–1.354). RCS analyses further revealed a nonlinear relationship. Longitudinal analyses demonstrated a noteworthy interactive phenomenon: in the low RCII group, individuals with high WBC exhibited significantly lower 5-year survival than those with low WBC, whereas in the high RCII group, the survival curves for different WBC levels tended to overlap. *Conclusion:* WBC count is nonlinearly and positively associated with RCII in both U.S. and Chinese middle-aged and older adults, with elevated WBC independently predicting higher mortality specifically in low-RCII individuals. This supports WBC as a low-cost adjunctive marker for risk stratification and highlights its prognostic value beyond RCII alone.

Keywords: China health and retirement longitudinal study; White blood cell count; National health and nutrition examination survey; Remnant cholesterol inflammatory index; Middle-aged and older adults

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of global mortality, imposing substantial burdens on middle-aged and older populations ^[1]. Chronic inflammation is pivotal in CVD pathogenesis. The remnant cholesterol inflammatory index (RCII), a novel cardiovascular risk biomarker, integrates lipid residual risk and systemic inflammation. White blood cell (WBC) count, a routine clinical indicator, reflects inflammatory status. However, the quantitative relationship between WBC and RCII remains unexplored ^[2].

Remnant cholesterol (RC), calculated as total cholesterol minus HDL-C and LDL-C, is a key CVD risk factor. High-sensitivity C-reactive protein (hs-CRP) is used for both inflammation monitoring and CVD risk assessment ^[3]. Middle-aged and older adults have higher atherosclerotic burden and chronic inflammation ^[4]. Although RC and hs-CRP independently predict cardiovascular residual risk, they represent intertwined dimensions of the “lipid-inflammation” axis ^[5]. Evaluating either alone may underestimate high-risk individuals with acceptable lipid levels but chronic inflammation. RCII was thus proposed to capture the synergistic effects of dyslipidemia and inflammation ^[6]. Its computational simplicity makes it a potential tool for epidemiological research and primary care ^[7].

WBC count is a readily available peripheral blood indicator. Even within the normal range, subtle WBC fluctuations may reflect low-grade systemic inflammation ^[8], closely linked to atherosclerosis. WBC thus serves as both an “alarm” for infection and a “barometer” of cardiometabolic risk ^[9]. However, whether a quantitative association exists between WBC and RCII, and whether this association carries differentiated clinical significance, remains largely unexplored.

This association is rooted in a “lipid-inflammation” vicious cycle ^[10]. Oxidized remnant cholesterol particles activate endothelial cells and monocytes, releasing IL-6, TNF- α , and MCP-1 ^[11]. These cytokines stimulate hepatic CRP synthesis (elevating RCII) and activate bone marrow hematopoiesis (raising WBC). Conversely, inflammatory cells infiltrate the vessel wall, exacerbating plaque progression ^[12]. Thus, the WBC-RCII association is a population-level manifestation of this cycle.

2. Methods

2.1. Study design and participants

This study utilized data from two nationally representative cohorts: NHANES (2015–2016) and CHARLS (2011), including participants aged ≥ 45 years. After applying inclusion and exclusion criteria, 2,839 NHANES and 5,955 CHARLS participants were included.

2.2. Definition of white blood cell count

WBC count ($\times 10^9/L$) was obtained from laboratory data in both cohorts. RC was calculated as: $RC\ (mg/dL) = TC - (HDL-C + LDL-C)$. RCII was computed as: in NHANES, $RCII = RC\ (mg/dL) \times hs-CRP\ (mg/L)$; in CHARLS, $RCII = RC\ (mg/dL) \times CRP\ (mg/dL) / 10$ (unit conversion for consistency).

Covariates included sociodemographic characteristics (age, sex, race/ethnicity [NHANES only], education, marital status, income), health status (hypertension, diabetes, coronary heart disease, stroke, cancer, based on self-reported physician diagnosis or measured parameters), and physical/laboratory measurements (BMI, etc.).

2.3. Calculation of RC and RCII

Remnant cholesterol (RC) was calculated as: $RC \text{ (mg/dL)} = \text{total cholesterol (TC)} - [\text{high-density lipoprotein cholesterol (HDL-C)} + \text{low-density lipoprotein cholesterol (LDL-C)}]$. The remnant cholesterol inflammatory index (RCII) was computed as follows: in NHANES, $RCII = RC \text{ (mg/dL)} \times \text{hs-CRP (mg/L)}$; in CHARLS, because the measurement unit for C-reactive protein is mg/dL, these units were converted to maintain consistency of magnitude with NHANES, and the formula used was: $RCII = RC \text{ (mg/dL)} \times \text{CRP (mg/dL)} / 10$.

2.4. Covariate assessment

Covariates were collected through standardized questionnaires and physical examinations, covering three main categories of information:

- (1) sociodemographic characteristics, including age, sex, race/ethnicity (NHANES only), education level, marital status, and household income level;
- (2) health status and disease history, with hypertension defined as self-reported physician diagnosis, current use of antihypertensive medication, or measured systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg; other self-reported chronic disease histories including diabetes, coronary heart disease (encompassing heart failure, angina pectoris, and myocardial infarction), stroke, and cancer, all based on physician diagnosis reported by participants;
- (3) physical measurements and laboratory indicators, including body mass index (BMI), among others.

2.5. Statistical analysis

Analyses were performed using RevMan 5.4. Cross-sectionally, WBC and RCII were continuous variables. Logistic regression and RCS assessed the association. Longitudinally, Cox regression and Kaplan-Meier curves examined survival. Statistical significance was set at two-sided $P < 0.05$.

3. Results

3.1. Baseline characteristics

Table 1. Baseline characteristics of the CHARLS database stratified by RCII

Variable	Low RCII group	High RCII group	<i>p</i> value
Sex	0.5 ± 0.5	0.5 ± 0.5	0.0202
Age	60.20 ± 9.64	61.56 ± 9.63	0.0000
Hypertension	22%	35%	0.0000
Dyslipidemia	7%	13%	0.0000
Diabetes	4%	8%	0.0000
Region	0.0%	0.0%	0.3840
Education category	1.1 ± 0.3	0.7 ± 0.4	0.2700
BMI	22.80 ± 13.58	24.35 ± 10.33	0.0000
Body mass category	8.0%	7.5%	0.0002
MetS	59.0%	65.6%	0.0000
Platelet count	208.24 ± 75.39	214.51 ± 82.38	0.0022
Blood urea nitrogen	16.10 ± 4.79	15.74 ± 4.48	0.0028
Blood glucose	104.27 ± 25.42	117.93 ± 47.09	0.0000

Variable	Low RCII group	High RCII group	<i>p</i> value
Creatinine	0.77 ± 0.21	0.80 ± 0.23	0.0000
Total cholesterol	189.18 ± 35.45	197.99 ± 40.86	0.0000
Triglycerides	94.21 ± 41.59	168.39 ± 115.69	0.0000
HDL-C	56.84 ± 14.84	45.90 ± 13.94	0.0000
LDL-C	113.49 ± 34.94	119.27 ± 35.38	0.0000
C-reactive protein	0.78 ± 0.69	5.20 ± 11.55	0.0000
HbA1c	5.18 ± 0.68	5.40 ± 0.97	0.0000
Uric acid	4.21 ± 1.16	4.70 ± 1.30	0.0000
Serum creatinine	41.23 ± 6.25	41.91 ± 6.38	0.0000
Hemoglobin	14.18 ± 2.22	14.56 ± 2.32	0.0000
Cystatin C	1.02 ± 0.24	1.06 ± 0.32	0.0000
White blood cell count	5.87 ± 1.68	6.70 ± 2.76	0.0000

Table 2. Baseline characteristics of the NHANES database stratified by RCII

Variable	High RCII group	Low RCII group	<i>p</i> value
Sex (Male %)	51.9	65.4	0.0364
Sex (Female %)	48.1	34.6	0.0258
Age	62.4 ± 10.9	0.0066	<0.0001
Race/ethnicity	64 ± 10.3	47 ± 6.6	<0.0001
Education (College % or above)	86 ± 13.8	90 ± 12.7	<0.0001
Marital status (Married %)	58.5	53.2	<0.0001
White blood cell count (LBXWBCSI)	7.0 ± 2.7	6.2 ± 2.2	<0.0001
Red blood cell count (LBXRBCSI)	4.6 ± 0.5	6.5 ± 0.4	<0.0001
Dyslipidemia	14.1	13.7	<0.0001
Hematocrit (LBXHCT)	41.4 ± 4.0	40.4 ± 4.2	<0.0001
Mean corpuscular volume (LBXMCVSI)	90.5 ± 5.5	90.8 ± 6.3	0.3886
Platelet count (LBXPLTSI)	235.5 ± 60.1	223.7 ± 63.0	0.0005
Hypertension (%)	56.4	49.5	0.0229
Urine microalbumin (URXUMA)	374.1 ± 71.6	312.0 ± 53.3	0.0335
Urine creatinine (URXCRS)	10476.5 ± 5888.0	10352.7 ± 6089.8	0.0079
Diabetes	26.4	21.7	<0.0001
Aspartate aminotransferase (LBXSASSI)	26.7 ± 17.9	25.1 ± 12.8	0.0743
Alkaline phosphatase (LBXSAPSI)	74.0 ± 34.9	69.5 ± 24.0	0.0064
Calcium (LBXSACA)	9.4 ± 0.4	9.3 ± 0.3	0.0208
Creatine kinase (LBXSCK)	144.5 ± 121.6	127.2 ± 13.3	0.0079
Total cholesterol (LBXSCH)	200.8 ± 43.1	186.6 ± 40.0	<0.0001
Creatinine (LBXSCR)	1.0 ± 0.4	0.9 ± 0.6	0.8190
γ-glutamyl transferase (LBXSGTTSI)	34.6 ± 2.8	26.1 ± 3.3	0.0001
Blood glucose (LBXSGL)	114.1 ± 40.8	103.9 ± 29.5	<0.0001
Total cholesterol (LBXTC)	203.3 ± 42.4	188.7 ± 40.0	<0.0001
LDL-C (LBDLDL)	120.2 ± 38.9	112.5 ± 33.6	0.0001
HDL-C (LBDHDD)	48.2 ± 11.7	60.2 ± 16.9	<0.0001
RC	34.9 ± 11.7	16.0 ± 3.8	<0.0001

Table 1 and **Table 2** summarize the baseline characteristics of the CHARLS (n = 5,955) and NHANES (n = 2,588) cohorts stratified by RCII. In both populations, the high RCII group exhibited significantly higher WBC counts (CHARLS: 6.70 vs. 5.87 $\times 10^9/L$; NHANES: 7.0 vs. 6.2 $\times 10^9/L$, both $p < 0.001$) and a greater burden of cardiometabolic risk factors, including hypertension, diabetes, dyslipidemia, and elevated BMI, triglycerides, and blood glucose ($p < 0.05$).

3.2. Weighted univariate analysis

Table 3. Weighted univariate logistic regression analysis in the CHARLS database

Variable	OR	95% CI lower	95% CI upper	P value	Sample size
WBC	1.272	1.235	1.311	0.0000	5955
Age	1.015	1.009	1.020	0.0000	5955
Sex	0.945	0.854	1.047	0.2807	5955
Hypertension	1.887	1.683	2.117	0.0000	5955
Dyslipidemia	1.795	1.508	2.136	0.0000	5955
Diabetes	2.012	1.612	2.511	0.0000	5955
Income	1.000	1.000	1.000	0.1124	5955
Education	1.010	0.958	1.065	0.7074	5955
BMI	1.072	1.058	1.087	0.0000	5955
MetS	3.380	3.017	3.786	0.0000	5797
Total cholesterol	1.006	1.005	1.007	0.0000	5955
Marital status	0.973	0.848	1.116	0.6961	5955
Education level	0.935	0.785	1.114	0.4517	5955
Platelet count	1.001	1.000	1.002	0.0024	5954

Table 4. Weighted univariate logistic regression analysis in the NHANES database

Variable	OR	95% CI lower	95% CI upper	P value	Sample size
Sex (RIAGENDR)	0.830	0.565	1.219	0.3568	1332
Age (RIDAGEYR)	1.002	0.983	1.022	0.8075	1332
Race/ethnicity (RIDRETH3)	0.942	0.800	1.110	0.4877	1332
Education (DMDEDUC2)	0.836	0.738	0.947	0.0125	1332
Marital status (DMDMARTL)	0.994	0.901	1.096	0.9002	1332
Hypertension (BPQ020)	0.655	0.425	1.009	0.0728	1332
WBC (LBXWBCSI)	1.279	1.183	1.383	0.0000	1332
Platelet count (LBXPLTSI)	1.004	1.002	1.007	0.0076	1332
Total cholesterol (LBXTC)	1.008	1.005	1.011	0.0002	1332

Table 5. Weighted logistic regression analysis of the association between white blood cell count and remnant cholesterol inflammatory index in the CHARLS database (stepwise adjustment)

Model	Sample size	OR	95% CI lower	95% CI upper	P value
Model 2: +Age	5955	1.272	1.235	1.311	<0.001
Model 3: +Income	5955	1.273	1.235	1.312	<0.001
Model 4: +Education	5955	1.274	1.236	1.313	<0.001

Model	Sample size	OR	95% CI lower	95% CI upper	P value
Model 5: +Hypertension	5955	1.233	1.310	<0.001	<0.001
Model 6: +Sex	5955	1.275	1.237	1.315	<0.001
Model 7: +Urban residence	5955	1.309	1.266	<0.001	<0.001

Note: Model 1 (unadjusted) OR=1.272 (95% CI: 1.235–1.311, $P < 0.001$)

Table 6. Logistic regression analysis of the association between white blood cell count and remnant cholesterol inflammatory index in the NHANES database (stepwise adjustment)

Model	OR	95% CI lower	95% CI upper	P value
Model 1 (univariate)	1.075	1.028	1.124	0.0059
Model 2 (+demographics)	1.126	1.060	1.196	0.0032
Model 3 (+socioeconomic)	1.110	1.050	1.174	0.0217
Model 4 (+hypertension)	1.097	1.038	1.158	0.0458

Table 7. Association between white blood cell count quartiles and remnant cholesterol inflammatory index in the NHANES database

Group	OR	95% CI	P value
Q1	1.000	Reference	Reference
Q2 vs Q1	0.755	0.354 – 1.613	0.601
Q3 vs Q1	0.982	0.540 – 1.785	0.962
Q4 vs Q1	1.273	0.574 – 2.825	0.659
Test for trend	1.109	0.845 – 1.456	0.508

Weighted univariate logistic regression (**Tables 3–4**) identified WBC as a significant correlate of high RCII in both cohorts (CHARLS: OR=1.272, 95% CI: 1.235–1.311; NHANES: OR=1.279, 95% CI: 1.183–1.383). Metabolic syndrome and its components (hypertension, diabetes, dyslipidemia) were strongly associated with RCII in CHARLS; in NHANES, higher education emerged as a protective factor (OR=0.836, $p=0.0125$), while hypertension did not reach significance.

3.3. Multivariable logistic regression analysis of WBC and RCII

After stepwise adjustment (**Tables 5–6**), the WBC-RCII association remained significant in both cohorts. In CHARLS, the fully adjusted OR was 1.309 (95% CI: 1.266–1.354); in NHANES, it was 1.097 (95% CI: 1.038–1.158) (**Table 7**). Categorical analyses revealed a graded relationship: in NHANES (tertiles, **Table 8**), the ORs for T2 and T3 were 1.532 and 1.982, respectively; in CHARLS (quartiles, **Tables 9–10**), the adjusted OR for Q4 versus Q1 was 3.537 (95% CI: 2.997–4.174, $p < 0.001$).

Table 8. Association between white blood cell count tertiles and remnant cholesterol inflammatory index in the NHANES database

Group	OR	95% CI	P value
T1	1.000	Reference	Reference
T2 vs T1	1.532	1.086 – 2.160	0.015
T3 vs T1	1.982	1.389 – 2.828	<0.001

Group	OR	95% CI	P value
T1	1.000	Reference	Reference
Test for trend	1.402	1.176 – 1.672	<0.001

Table 9. Association between white blood cell count quartiles and remnant cholesterol inflammatory index in the CHARLS database (unadjusted)

Group	OR	95% CI	P value
Q1	1.000	Reference	Reference
Q2	1.383	1.198 – 1.598	<0.001
Q3	2.072	1.791 – 2.397	<0.001
Q4	3.072	2.649 – 3.561	<0.001

Table 10. Association between white blood cell count quartiles and remnant cholesterol inflammatory index in the CHARLS database (adjusted for all covariates)

Group	OR	95% CI	P value
Q1	1.000	Reference	Reference
Q2	1.464	1.255 – 1.708	<0.001
Q3	2.257	1.926 – 2.643	<0.001
Q4	3.537	2.997 – 4.174	<0.001

3.4. Nonlinear analysis

Table 11. Restricted cubic spline analysis: OR at specific percentiles of white blood cell count

Percentile	WBC	OR	95% CI
5%	3.80	0.571	0.409 – 0.797
25%	5.00	0.797	0.576 – 1.102
75%	7.30	1.457	1.062 – 1.999
95%	9.70	2.556	1.836 – 3.559

Restricted cubic spline analysis confirmed a nonlinear association between WBC and RCII in both cohorts (**Table 11, Figures 1–2**). The inflection points differed markedly: $\sim 3.79 \times 10^9/\text{L}$ in CHARLS versus $\sim 10.01 \times 10^9/\text{L}$ in NHANES, suggesting population-specific thresholds in the lipid-inflammation cycle.

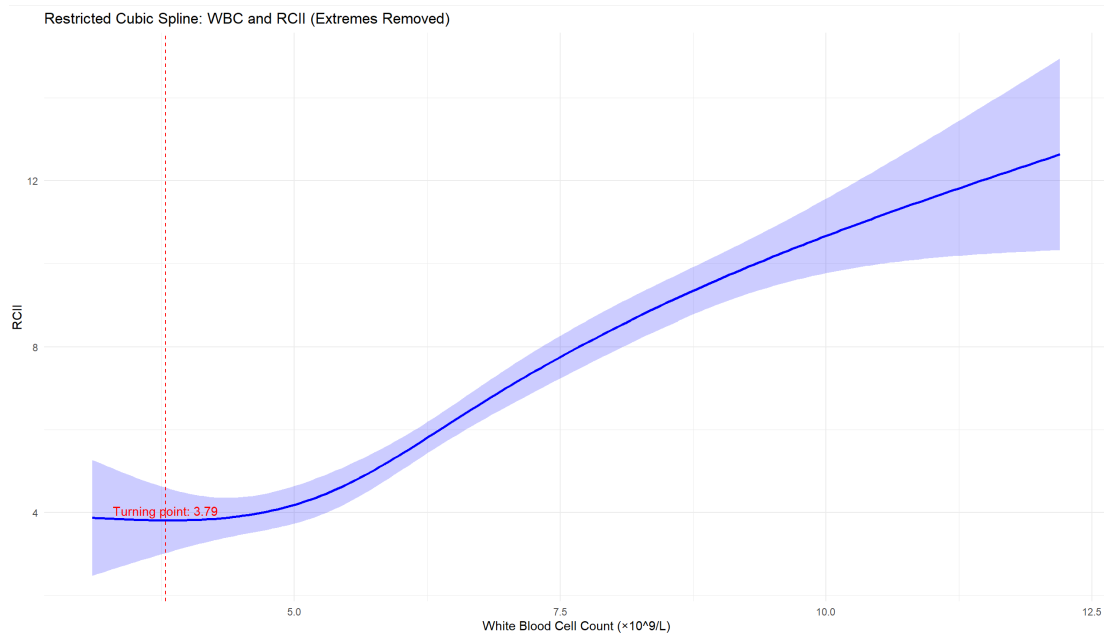


Figure 1. Restricted cubic spline analysis (RCS analysis) with extreme values excluded — CHARLS results.

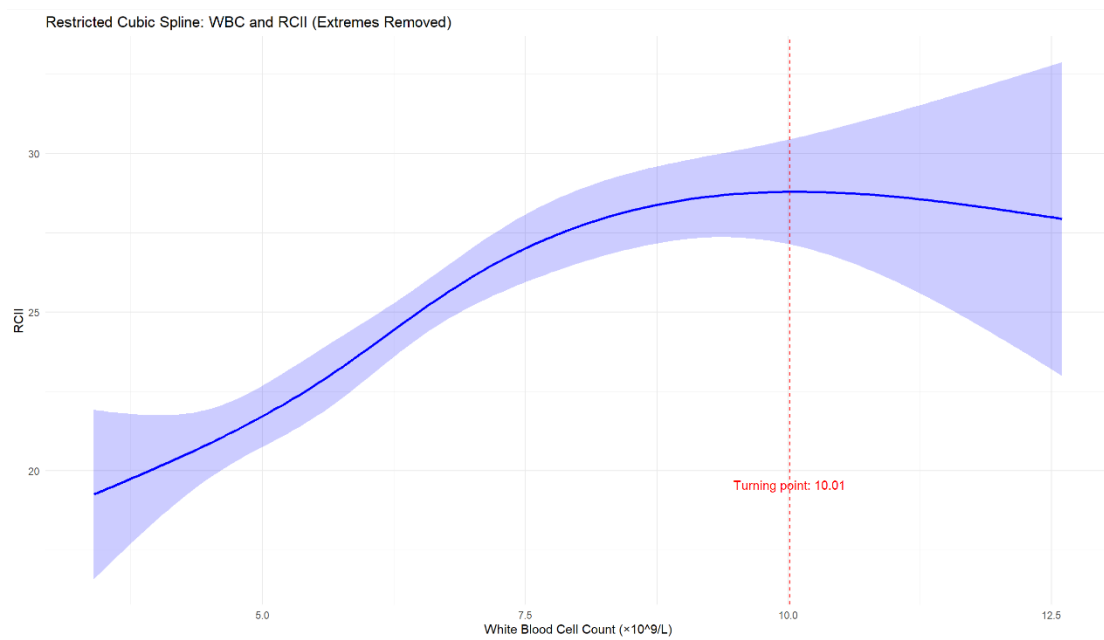


Figure 2. Restricted cubic spline analysis (RCS analysis) with extreme values excluded — NHANES results.

3.5. Subgroup analysis and interaction tests

Table 12. Description of white blood cell count in different subgroups of the CHARLS database

Subgroup	N	Mean $\pm$ SD	95% CI	<i>P</i> value
Overall	5955	6.29 $\pm$ 2.32	6.23 – 6.34	0.0000
Male	2780	6.43 $\pm$ 2.74	6.33 – 6.53	0.0000
Female	3175	6.17 $\pm$ 1.93	5.98 – 6.25	0.0000

Subgroup	N	Mean $\pm$ SD	95% CI	P value
Hypertension	1696	6.43 $\pm$ 3.16	6.28 – 6.58	0.0000
No hypertension	4259	6.23 $\pm$ 1.89	6.17 – 6.28	0.0000
Hyperlipidemia	598	6.32 $\pm$ 1.89	6.16 – 6.47	0.0000
No hyperlipidemia	5357	6.28 $\pm$ 2.37	6.22 – 6.35	0.0000
Diabetes	369	6.68 $\pm$ 1.93	6.48 – 6.87	0.0001
No diabetes	5586	6.26 $\pm$ 2.35	6.20 – 6.32	0.0000
Older age group	2928	6.29 $\pm$ 1.91	6.22 – 6.36	0.0000
Younger age group	3027	6.28 $\pm$ 2.66	6.19 – 6.38	0.0000
High BMI group	2977	6.38 $\pm$ 2.66	6.29 – 6.48	0.0000
Low BMI group	2978	6.19 $\pm$ 1.92	6.12 – 6.25	0.0000
Metabolic syndrome	3706	6.37 $\pm$ 1.89	6.31 – 6.43	0.0000
No metabolic syndrome	2091	6.11 $\pm$ 2.93	5.99 – 6.24	0.0000
High total cholesterol group	2968	6.45 $\pm$ 1.90	6.38 – 6.52	0.0000
Low total cholesterol group	2987	6.12 $\pm$ 2.67	6.02 – 6.21	0.0000
High-income group	2976	6.19 $\pm$ 1.83	6.13 – 6.26	0.0000
Low income group	2979	6.38 $\pm$ 2.73	6.28 – 6.47	0.0000
Married	4978	6.27 $\pm$ 2.39	6.20 – 6.34	0.0045
Unmarried	977	6.36 $\pm$ 1.96	6.24 – 6.48	0.0000
High education group	401	6.01 $\pm$ 1.67	5.84 – 6.17	0.0023
Low education group	5554	6.31 $\pm$ 2.36	6.24 – 6.37	0.0000
High platelet group	2974	6.71 $\pm$ 2.72	6.61 – 6.81	0.0000
Low platelet group	2980	5.86 $\pm$ 1.75	5.80 – 5.92	0.0000

Table 13. Description of white blood cell count in different subgroups of the NHANES database

Subgroup	N	Mean $\pm$ SD	95% CI	P value
Overall	2839	6.85 $\pm$ 2.32	6.76 – 6.93	0.0000
Male	1392	6.91 $\pm$ 2.66	6.77 – 7.05	0.0002
Female	1447	6.79 $\pm$ 1.95	6.69 – 6.89	0.0000
Older age group	1388	6.81 $\pm$ 2.62	6.67 – 6.95	0.0054
Younger age group	1451	6.89 $\pm$ 2.00	6.78 – 6.99	0.0000
Hypertension	1475	7.00 $\pm$ 2.49	6.87 – 7.13	0.0011
No hypertension	1361	6.68 $\pm$ 2.11	6.57 – 6.79	0.0000
High total cholesterol group	1350	6.80 $\pm$ 2.32	6.68 – 6.93	0.0000
Low total cholesterol group	1396	6.85 $\pm$ 2.30	6.73 – 6.97	0.0000
High platelet group	1401	7.27 $\pm$ 1.99	7.16 – 7.37	0.0001
Low platelet group	1438	6.44 $\pm$ 2.55	6.31 – 6.57	0.0005
High WBC group	1414	8.41 $\pm$ 2.30	8.29 – 8.53	0.3243
Low WBC group	1425	5.30 $\pm$ 0.85	5.26 – 5.35	0.0000
Married	1636	6.82 $\pm$ 2.39	6.70 – 6.93	0.0000
Unmarried	1201	6.89 $\pm$ 2.23	6.76 – 7.02	0.0253
Less than high school	787	7.07 $\pm$ 2.52	6.89 – 7.25	0.1233
High school or above	2050	6.76 $\pm$ 2.24	6.67 – 6.86	0.0000
White	1119	7.17 $\pm$ 2.67	7.01 – 7.33	0.0037

Subgroup	N	Mean $\pm$ SD	95% CI	P value
Black	774	6.37 $\pm$ 2.18	6.22 – 6.53	0.1361
Mexican American	226	7.22 $\pm$ 1.90	6.98 – 7.47	0.1066
Other race	720	6.74 $\pm$ 1.88	6.61 – 6.88	0.0000

Subgroup descriptions of WBC are provided in **Table 9** (CHARLS) and **Table 10** (NHANES). In interaction analyses, nationality, sex, age, BMI, diabetes, smoking, stroke, and CKD significantly modified the WBC-RCII association (all interaction $p < 0.05$), whereas race/ethnicity and hypertension status were significant effect modifiers in NHANES.

3.6. Survival analysis

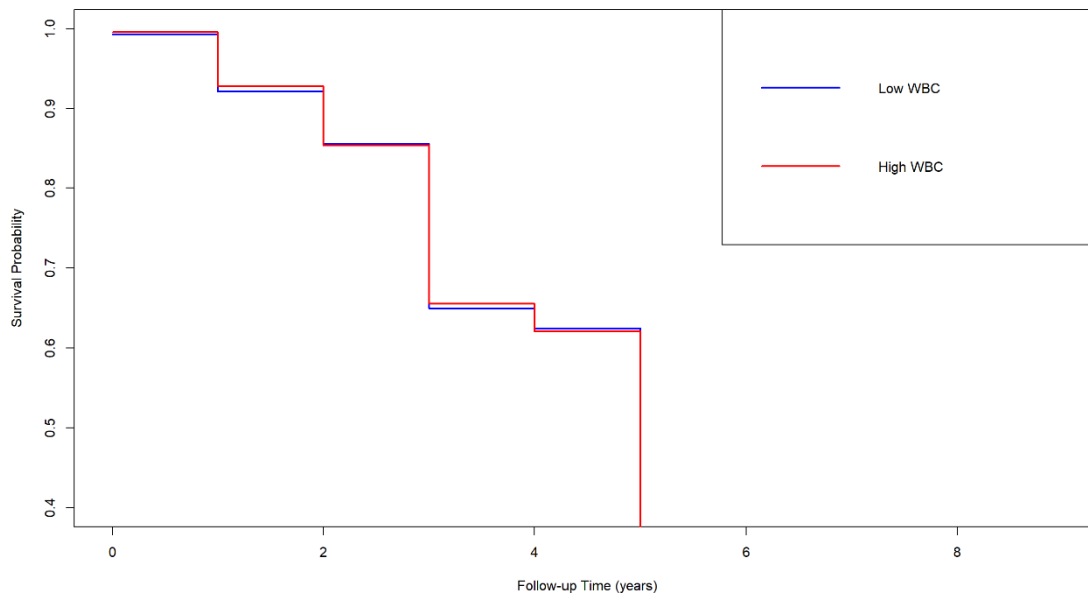


Figure 3. Kaplan-Meier survival curves for high WBC and low WBC.

Kaplan-Meier analysis of CHARLS longitudinal data (Figure 3) revealed a distinct interactive pattern. In the high RCII group, high and low WBC strata showed overlapping survival curves. In contrast, within the low RCII stratum, individuals with high WBC had markedly worse long-term survival, with a roughly 10–12 percentage point absolute risk difference emerging by year 8. This indicates that WBC offers incremental prognostic value specifically among those with a low residual cholesterol inflammatory burden.

4. Discussion

This study systematically evaluated the association between WBC and RCII by mining data from the CHARLS and NHANES databases. The principal findings can be summarized at three levels: first, in cross-sectional analyses, WBC exhibited a robust positive association with RCII in both populations, independent of traditional risk factors; second, restricted cubic spline analysis revealed that this association is nonlinear, displaying differentiated risk gradients across WBC intervals; third, longitudinal survival analysis further demonstrated that the prognostic value of WBC is highly dependent on the RCII background—among individuals with low RCII, elevated WBC can identify a group with significantly increased long-term

mortality risk, whereas among those with high RCII, WBC virtually loses additional risk discrimination capacity. This “context-dependent” interactive pattern is the most central finding of this study.

The positive association aligns with prior research on systemic inflammatory markers and cardiovascular residual risk. Evidence indicates that WBC, as a basic inflammatory marker, is closely linked to insulin resistance, endothelial dysfunction, and increased risk of future cardiovascular events^[13]. On the other hand, remnant cholesterol (RC), as an important atherogenic lipid component, has been shown to independently promote inflammatory responses and increase metabolic syndrome risk^[14]. By linking WBC with the composite indicator RCII, our study further reveals that the systemic inflammatory state characterized by WBC and the “lipid residual risk-chronic inflammation” axis characterized by RCII exhibit significant synchrony^[15].

The underlying mechanism may be rooted in the “lipid-inflammation” cycle, a core pathobiological process^[16]. Under conditions of chronic low-grade inflammation, an elevated WBC (especially neutrophils and monocytes) marks sustained immune activation, and the released pro-inflammatory cytokines such as IL-6 and TNF- α directly disrupt lipid metabolic homeostasis^[17]. These inflammatory signals can stimulate the liver to increase VLDL synthesis while inhibiting lipoprotein lipase activity, impairing the clearance of triglyceride-rich lipoproteins and their remnants (i.e., RC), thereby driving RC accumulation in the blood^[18]. This accumulated RC, especially after oxidative modification, is not an inert metabolic product^[19]; it can act as a potent inflammatory stimulus, recognized and phagocytosed by macrophages within the vascular wall, which in turn activates intracellular signaling pathways such as the NLRP3 inflammasome and triggers the release of additional cytokines like IL-1 β , further exacerbating systemic inflammation^[20]. Thus, inflammation and disordered lipid metabolism constitute a self-reinforcing cycle^[21]: inflammation promotes RC generation and retention, while RC acts as “fuel” to continuously aggravate the inflammatory response^[22]. The synchronous elevation of WBC and RCII in this study is a population-level manifestation of this cycle—WBC reflects the level of activated immune cells in circulation^[23], while RCII quantifies the composite lipid-inflammatory burden jointly characterized by RC and CRP^[24].

The Chinese-American differences revealed in this study point to deeper mechanisms that multiple factors may modulate, and this basic mechanistic framework helps explain such cross-national heterogeneity^[25]. First, differences in obesity types and fat distribution characteristics likely play a role. The obesity prevalence is higher in the U.S. population, with a predominance of subcutaneous fat accumulation; the obesity profile in the Chinese population differs markedly, primarily manifesting as a relatively lower obesity rate but a tendency for fat to accumulate in visceral adipose tissue, particularly in the abdominal area. Visceral adipose tissue is a potent source of inflammatory cytokines, and its inflammatory spillover effects may act more strongly on the liver, simultaneously exacerbating systemic inflammation (WBC elevation) and the generation of lipoprotein remnants, leading to a tighter “coupling” between WBC and RCII in the Chinese cohort. Second, differences in diet and gut microbiota may contribute: the U.S. diet is rich in saturated fats and refined carbohydrates, while the Chinese diet is primarily grain-based with higher dietary fiber. Third, genetic factors—owing to racial differences—the frequencies of relevant loci that significantly influence lipid metabolism and inflammatory response pathways may differ, modulating an individual’s metabolic response to inflammatory stimuli.

Comparison with previous studies also highlights the innovations of this research. Most prior studies either analyzed the relationship between lipid profile and inflammation separately or focused on lipid

modulation in specific immune responses such as allergy^[26]. In contrast, our study employs the composite indicator RCII and, for the first time, brings overall immune system activity (represented by WBC) and systemic residual inflammatory risk into the same analytical framework. Furthermore, through a design combining cross-sectional and longitudinal cohorts, we significantly enhance the credibility of the conclusions.

From a clinical application perspective, this study emphasizes that while focusing on the cardiovascular risk reflected by multidimensional composite indicators such as RCII, the independent value of classic hematological indicators like WBC should not be overlooked. Although WBC, as a coarse-grained inflammatory marker, has limited specificity, it features low testing cost, wide accessibility, and good applicability across populations. Therefore, WBC fluctuations can serve as a low-cost, high-efficiency screening tool to help clinicians identify potential high inflammatory response states at an early stage, especially in settings where resources are limited or refined biomarker testing is unavailable.

Nevertheless, several limitations should be acknowledged. First, although WBC count is a convenient hematological parameter, it lacks specificity; the impact of different leukocyte subtypes (e.g., neutrophils, lymphocytes) on RCII and cardiovascular risk may differ considerably. Future studies incorporating derived indicators such as the neutrophil-to-lymphocyte ratio may provide more refined information. Second, because publicly available databases were used, some variables relied on self-report and may be subject to recall bias or measurement error. Third, some of the cross-national differences observed in this study are difficult to fully explain through existing mechanisms and may involve unmeasured confounders.

Based on these findings and limitations, future research directions may include the following: first, prospective cohorts are needed to validate the predictive value of baseline WBC for long-term RCII changes or cardiovascular events, clarifying their temporal sequence and clinical utility; second, studies incorporating more precise inflammatory markers (e.g., IL-6, TNF- α) and detailed lipoprotein particle subfraction analyses should be conducted to reveal the specific molecular pathways underlying the WBC-RCII association; third, in cohorts with genomics, metabolomics, and microbiomics data, machine learning methods should be employed to explore the decisive biological and environmental factors contributing to cross-national heterogeneity and their interactions.

5. Conclusion

Through analysis of large-scale population data, this study reveals a significant nonlinear positive association between peripheral WBC and RCII levels, highly consistent across Chinese and U.S. populations. Notably, subgroup and survival analyses indicate that among individuals with lower RCII, even a slight rise in WBC is significantly associated with increased mortality risk, suggesting a special state of “low RCII but high inflammatory burden” that may relate to microvascular dysfunction or metabolic stress not fully captured by RCII. Clinically, WBC serves as a low-cost, accessible screening tool to identify high-risk inflammatory states, particularly in resource-limited settings. Pathophysiologically, the nonlinear association provides new insights into the “lipid-inflammation” cycle, positioning WBC not as a mere bystander but as a participant and driver of this vicious cycle. In summary, WBC is a valuable supplementary indicator when combined with RCII for multidimensional risk assessment in middle-aged and older adults. Future studies exploring WBC subtypes and anti-inflammatory interventions in low-RCII individuals may offer new entry points for

primary CVD prevention strategies.

Disclosure statement

The author declares no conflict of interest.

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