The Prognostic Significance of Leukocyte Count on All-Cause and Cardiovascular Disease Mortality: A Systematic Review and Meta-Analysis

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White blood cells (WBCs) act as mediators of inflammatory responses and are commonly measured in hospitals. Although several studies have reported a relation between WBC count and mortality, no systematic review or meta-analysis has been conducted. This study aimed to identify an association between WBC count and mortality. We conducted a systematic search on Embase using keywords such as "white blood cell" and "mortality." We analyzed the hazard ratios (HRs) for WBC count of 1.0 × 10^9 cells/L regarding 2 criteria: the cause of mortality and the follow-up period. A total of 13 of 222 articles comprising a total of 62,904 participants were included in this study, meeting the criteria set. A positive association was observed between WBC count and mortality, as indicated by an HR of 1.10 (95% confidence interval [CI] 1.08 to 1.13). In additionally, WBC count emerged as a significant predictor of mortality in both groups, with an HR of 1.10 (95% CI 1.07 to 1.12) for patients with cardiovascular disease and an HR of 1.12 (95% CI 1.07 to 1.17) for the general population or patients with COVID-19. Furthermore, a higher WBC count demonstrated a significant association with long-term all-cause mortality (HR 1.09, 95% CI 1.07 to 1.12) and long-term cardiovascular mortality (HR 1.05, 95% CI 1.02 to 1.07). Similarly, a significant association was found between higher WBC count and short-term all-cause mortality (HR 1.12, 95% CI 1.09 to 1.16) and cardiovascular mortality (HR 1.12, 95% CI 1.07 to 1.17). Further research is necessary to explore the relation between WBC count and disease progression or death and to establish causality between elevated WBC count and disease progression. **(Am J Cardiol 2023;203:226–233)**

The leukocyte count serves as mediators of inflammatory responses and play a crucial role in the host's defense. Therefore, they are routinely used as a nonspecific biomarker for acute inflammatory responses. Furthermore, several studies suggest that white blood cell (WBC) count could serve as a predictive marker for certain diseases, such as coronary heart disease[1,2] and a marker for disease severity in conditions such as chronic obstructive pulmonary disease.[3,4] The WBC count is a common component of routine blood tests in most hospitals. It is an easily accessible test because of its low cost and straightforward procedure. As such, changes in WBC count, if clinically significant, could be valuable in diagnosing and monitoring a patient's condition. An increase in WBC count is generally indicative of active inflammation, whereas leukopenia may be an epiphenomenon or may indicate an underlying systemic disease.[5,6] Moreover, WBC count has been shown to be associated with the prognosis of patients with certain diseases and the general population. It was reported that higher total WBC counts are an independent predictor of all-cause mortality.[7] In addition, an increase in total WBC count has been linked to poor outcomes in patients with stable coronary disease, acute coronary syndromes, and acute myocardial infarction.[8–10] An acute increase in the WBC count typically reflects systemic inflammation and is associated with increased mortality. Furthermore, a chronic elevation in the WBC count indicates danger. Prolonged elevation of WBCs can indicate the sustained activation of their cytotoxic mechanism, leading to tissue damage.[11] WBC count is an essential indicator because of its accessibility. However, no systematic review or meta-analysis has established the relation between the WBC count and short-term or long-term mortality. Hence, the objective of this study was to investigate all-cause and cardiovascular-specific mortality in relation to the differences in the WBC count.

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See page 231 for Declaration of Competing Interest.

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Methods

This study was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guideline.[12] The protocol of the article is registered with international prospective register of systematic reviews (registration number: CRD42022329742).

We conducted a search of the Embase and Medline databases on January 31, 2022, to identify studies examining the relation between WBC count and mortality. To establish our search strategy, we used medical subject headings terms and entry terms related to WBC and mortality in PubMed. We limited our search to titles and abstracts for a more precise retrieval. To ensure relevance to our study, we excluded nonarticle types and nonhuman subjects using the appropriate search options. The search strategy used for Embase and Medline is as follows: ('white blood cell*':ti OR 'white cell*':ti OR 'blood corpuscle*':ti OR wbc:ti OR leukocyte*:ti) AND (mortalit*:ti OR 'case fatality rate*':ti OR 'death rate*':ti) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim.

The following criteria were used to exclude studies: nonarticles, articles in press, nonhuman subjects, systematic reviews or meta-analyses, irrelevant studies, studies that were not randomized controlled trials or cohort studies, and studies that did not include hazard ratios (HRs) for WBC count as a continuous variable. Cohort studies were chosen owing to the lack of relevant randomized controlled trials. Cross-sectional studies, case-control studies, case series, case reports, and review articles were excluded. To reduce heterogeneity between studies, only those that treated WBC count as a continuous variable were included. In addition, HR was selected as the effect measure, and only studies that adjusted for at least age and gender were included. Therefore, any studies that did not include the adjusted HR for the WBC count as a continuous variable were excluded.

A total of 3 authors (Park, Yoo, and Lee) conducted an independent review of each article. The articles underwent a 3-stage review process, which included title, abstract, and full-text review. After the initial review, the articles were evaluated as a group through discussion. Disagreements were resolved through discussion, and decisions were made unanimously.

A total of 3 authors (Park, Yoo, and Lee) conducted a full review of the included studies and extracted basic information such as author, year of publication, research design, country, number of subjects, target population, research period, and HRs.

The risk of bias in the cohort studies was assessed using the Newcastle−Ottawa scale. A total of 3 authors (Park, Yoo, and Lee) evaluated all articles, and any disagreements were resolved through discussion, with unanimous decisions made.

To conduct a quantitative analysis, it is necessary to standardize the measurement unit of the WBC count to ensure that the HR is comparable across studies. By unifying the measurement unit to 1.0×10^9 cells/l, it allows the extraction of the adjusted HR of mortality based on a consistent change in leukocyte count of 1.0×10^9 cells/L.

The statistical analysis was performed using RevMan version 5.4.1, the Cochrane Collaboration's review manager (Cochrane Training, United Kingdom). A total of 3 authors (Park, Yoo, and Lee) independently reviewed all procedures using the same tool and resolved discrepancies through discussion. Statistical heterogeneity was assessed using the I^2 statistic, and a random-effects model was used when the I^2 value was >50%, whereas a fixed-effects model was used when the I^2 value was <50%.[13] A meta-analysis was conducted using the inverse variance method for weighting. The results were presented using a forest plot to visualize the integrated HR estimates.

A subgroup analysis was conducted based on 2 criteria: period and cause of mortality. A total of 4 subgroups were created based on whether the period was short term or long term (short term defined as <1 year) and whether the cause of mortality was all-cause or cardiovascular disease (CVD)−specific. The 4 subgroups were analyzed separately.

Publication bias was evaluated by visually inspecting the funnel plots. In addition, the Egger regression test was conducted to statistically assess publication bias.[14]

The grading of recommendations assessment, development, and evaluation approach was used to assess the certainty of the analysis.[15] A total of 8 factors were thoroughly considered, including the risk of bias, inconsistency, indirectness, imprecision, and publication bias as factors reducing the quality of evidence and large magnitude of an effect, plausible residual confounding, and dose-response gradient as factors improving the quality of evidence. The 3 authors (Park, Yoo, and Lee) evaluated all factors, and decisions were made unanimously.

Results

A Medline and Embase search yielded 222 articles based on their titles and abstracts. During the screening process, 143 records were identified, excluding duplicates, nonarticle studies, and nonhuman studies. Of the remaining 121 articles, those that were irrelevant, had inadequate data, or used inappropriate study designs were excluded. Finally, 13 studies were included based on the selection criteria outlined in Figure 1. These studies were conducted between 1992 and 2020, with 8 targeting patients with CVD and 5 targeting either the general population or patients with COVID-19. A study each on disabled older patients and older popluation were categorized under "general population" for analysis. Except for 2 studies conducted worldwide across 20 different countries, the remaining 5 were conducted in the United States; 2 in China; and 1 each in Taiwan, Korea, the United Kingdom, and Italy. All included studies measured WBC count as a continuous variable. The characteristics of the included studies are listed in Table 1.

Figure 2 presents the results of the overall analysis on the correlation between WBC count and mortality. WBC count was found to be a significant predictor of mortality rate (HR 1.10, 95% confidence interval [CI] 1.08 to 1.12, heterogeneity $I^2 = 72\%$, $p < 0.001$). In addition, WBC count was also found to be a significant predictor of mortality in both groups, with an HR of 1.10 (1.07 to 1.12, $I^2 = 80\%$) for patients with CVD and an HR of 1.12 (1.07 to 1.17, $I^2 = 0\%$) for the general population or patients with COVID-19.

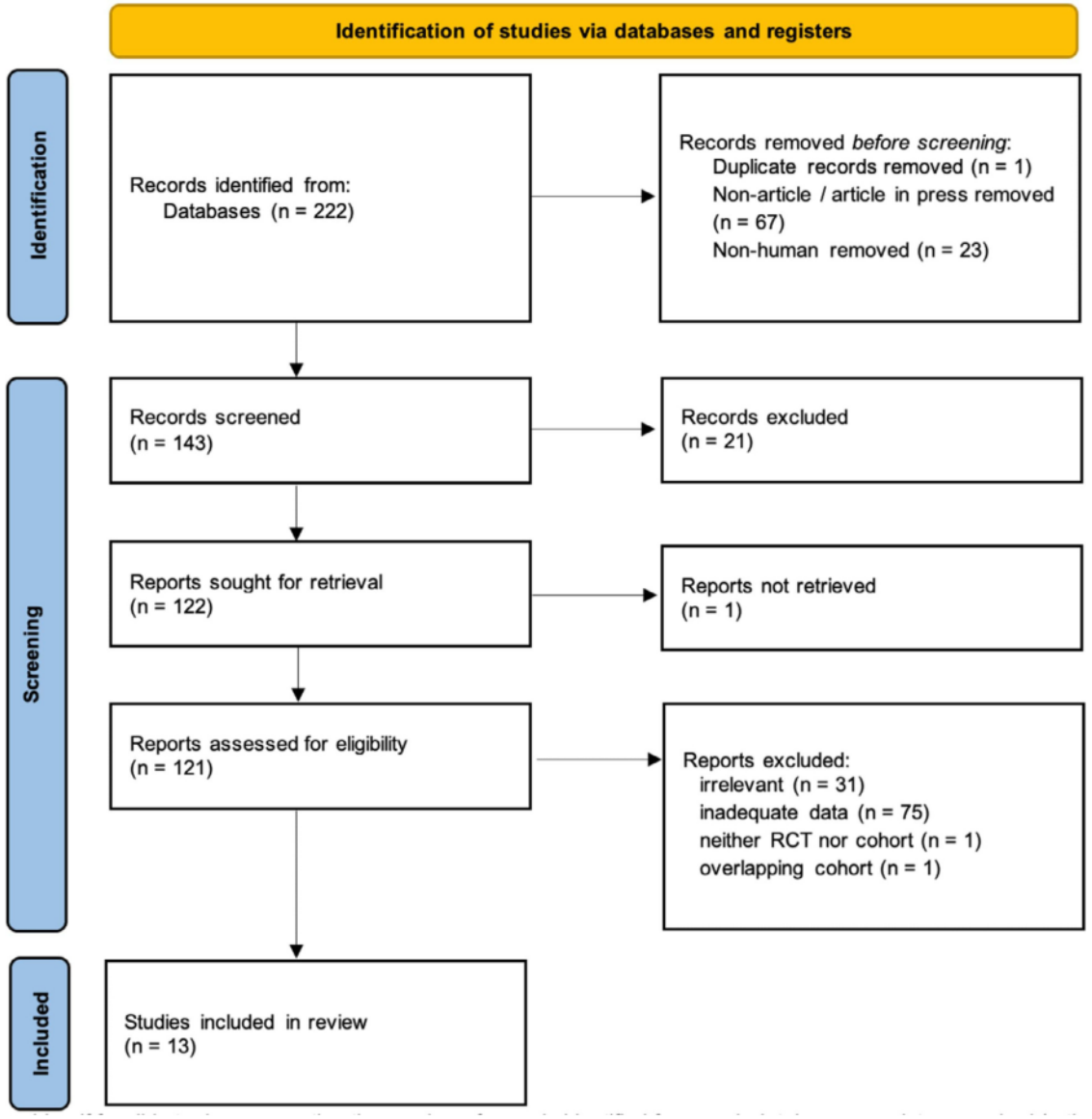
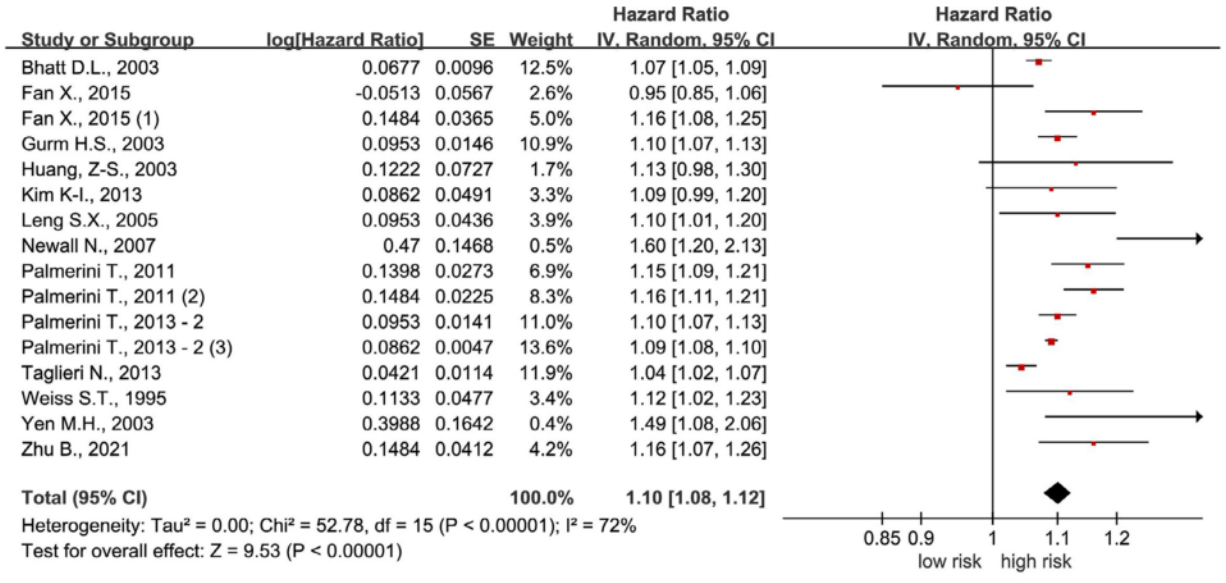


Figure 1. Study selection flow chart of included studies.

Table 1
Characteristics of the studies included in the meta-analysis

Author, year	Study design	Country	Sample size	Target population	Study duration (mean or median)
Bhatt D.L., 2003[41]	Cohort	U.S.A.	10,480	CVD	6 months
Fan X., 2015[26]	Cohort	China	570	CVD	30 days, 1.89 years
Gurm H.S., 2003[42]	Cohort	20 different countries	2,279	CVD	3 years
Huang, Z-S., 2003[29]	Cohort	Taiwan	8,447	General population	65.5 months
Kim K-I, 2013[28]	Cohort	Korea	9,996	Older population	44.9 months
Leng S.X., 2005[16]	Cohort	U.S.A.	624	Disabled older population	5 years
Newall N., 2007[43]	Cohort	U.K.	3,024	CVD	1 year
Palmerini T., 2011[44]	Cohort	U.S.A.	3,345	CVD	30 days, 1 year
Palmerini T., 2013-2[45]	Cohort	U.S.A.	13,678	CVD	30 days, 1 year
Taglieri N., 2013[46]	Cohort	Italy	1,315	CVD	3 years
Weiss S.T., 1995[30]	Cohort	USA	1,956	General population	22.5 years
Yen M.H., 2003[47]	Cohort	20 different countries	2,282	CVD	12 months
Zhu B., 2021[27]	Cohort	China	163	COVID-19	NS

CVD = cardiovascular disease; NS = not specified.



Footnotes

(1) Fan X., 2015 (1) shows the data of long-term overall mortality.

(2) Palmerini T., 2011 (2) shows the data of short-term cardiovascular disease mortality.

(3) Palmerini T., 2013-2 (3) shows the data of short-term cardiovascular disease mortality.

Figure 2. Forest plot for an overall meta-analysis on the effect of WBC count on mortality.

A subgroup analysis was performed based on the overall mortality, cardiovascular mortality, and short-term and long-term mortality. Studies with mortality follow-up of more than 1 year were categorized as long term, whereas studies with mortality follow-up of less than 1 year were categorized as short term. As listed in Table 2, the results indicate that WBC count is a significant predictor of mortality in all subgroup analyses. The HR was 1.09 (95% CI 1.07 to 1.12, I^2 = 39%) for the long-term overall mortality, and the HR was 1.05 (95% CI 1.02 to 1.07, I^2 = 16%) for long-term cardiovascular mortality. The HR was 1.12 (95% CI 1.09 to 1.16, I^2 = 78%) for the short-term overall mortality and the HR was 1.12 (95% CI 1.07 to 1.17, I^2 = 52%) for short-term cardiovascular mortality.

Based on the Newcastle−Ottawa scale, the 13 included studies were categorized as being of good, fair, or poor quality. A total of 7 studies were evaluated as fair quality, 4 as good quality, and 2 as poor quality. Detailed quality assessments are listed in Table 3.

A funnel plot for the overall analysis between WBC count and mortality is presented in Figure 3. The plot shows that there is no obvious asymmetry, suggesting the absence of significant publication bias. This result is supported by the Egger regression test, which also indicates no significant publication bias (p = 0.124).

According to our assessment using the grading of recommendations assessment, development, and evaluation approach, the certainty of the outcome of interest, mortality, is very low (Table 4). This is because of the presence of several factors that reduce the quality of evidence, including risk of bias and inconsistency. Specifically, most of the included studies had a fair quality, and there was considerable heterogeneity across the studies.

Discussion

This study aimed to investigate the relation between WBC count and mortality. As demonstrated in Figure 2, it suggests that mortality increases proportionally with the number of WBCs. The subgroup analysis showed that the WBC count was a significant predictor of both short-term and long-term mortality, and the risk was particularly prominent in the short term.

An elevated WBC count has been identified as a prognostic factor that affects mortality, alongside risk factors such as tobacco use, total cholesterol levels, and high-density lipoprotein cholesterol levels.[16] The mechanisms underlying the association between elevated WBC counts and increased mortality are not fully understood, but several hypotheses have been proposed. A hypothesis suggests that

Table 2
Subgroup analysis of mortality according to cause and period

	Long-term all-cause mortality	Short-term all-cause mortality	Long-term CVD-cause mortality	Short-term CVD-cause mortality
Number of studies	5	7	2	2
Hazard Ratio (HR)	1.09	1.12	1.05	1.12
95% CI	1.07 − 1.12	1.09 − 1.16	1.02 − 1.07	1.07 − 1.17
heterogeneity (I^2)	39%	78%	16%	52%

Table 3
Newcastle-Ottawa quality assessment of included in the meta-analysis

Author, year	Selection				Comparability		Outcomes			Quality*
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at the start	Main factor (age)	Additional factor	Assessment of outcomes	Length of follow up	Adequacy of follow up	
Bhatt D.L., 2003[41]	0	1	1	0	1	1	-	1	1	Fair
Fan X., 2015[26]	0	1	1	0	1	1	1	1	1	Fair
Gurm H.S., 2003[42]	0	1	1	0	1	1	1	1	1	Fair
Huang, Z-S., 2003[29]	1	1	1	1	1	1	1	1	-	Good
Kim K-I, 2013[28]	1	1	1	1	1	1	1	1	1	Good
Leng S.X., 2005[16]	0	1	1	0	1	1	1	1	1	Fair
Newall N., 2007[43]	0	1	1	0	1	1	1	1	1	Fair
Palmerini T., 2011[44]	0	1	1	0	1	1	1	1	1	Fair
Palmerini T., 2013[45]	0	1	1	0	1	1	1	1	1	Fair
Taglieri N., 2013[46]	0	1	1	1	1	1	1	1	1	Good
Weiss S.T., 1995[30]	0	1	1	1	-	-	1	1	1	Poor
Yen M.H., 2003[47]	0	1	1	1	1	1	1	1	1	Good
Bhatt D.L., 2003[41]	0	1	-	0	1	1	1	-	1	Poor

* Good quality:3 or 4 stars in the selection domain AND 1 or 2 stars in the compatibility domain AND 2 or 3 stars in the outcome/exposure domain; fair quality:2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain; poor quality:0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 stars in the outcome/exposure domain

chronic systemic inflammation resulting from increased activity of pro-inflammatory factors, particularly, interleukin-6, activates the immune system and contributes to the increased mortality.[17] Another potential mechanism is the increased mortality associated with clinical or subclinical diseases that could alter WBC levels.[18]

A previous studies have established a positive and linear association between elevated WBC count and all-cause mortality.[19] Furthermore, several studies have shown that when WBC count was treated as a categorical variable, the group with the highest WBC count had a higher risk of all-cause mortality than other groups.[20–22] Similarly, other studies have reported a positive association between WBC count and CVD-related mortality, with WBC count serving as an independent predictor.[20,23–25]

A total of 7 of the studies included in our analysis were conducted on patients with ischemic heart disease. Fan et al[26] (2015) was conducted on patients with acute aortic dissection (AAD), Zhu et al[27] (2021) on patients with COVID-19, Leng et al[16] (2005) on disabled older patients, Kim et al[28] (2013) on older patients, and Huang et al[29] (2003) and Weiss et al[30] (1995) on the general population. Each of these diseases was associated with an increased number of WBC after an inflammatory response. These findings support the significance of our results.

Ischemic heart disease is a condition in which blood supply to the myocardium is insufficient. It is most caused by an atherosclerotic plaque in the coronary artery. The pathogenesis of atherosclerosis is closely related to an inflammatory response.[31] Hypercholesterolemia, a risk factor for coronary

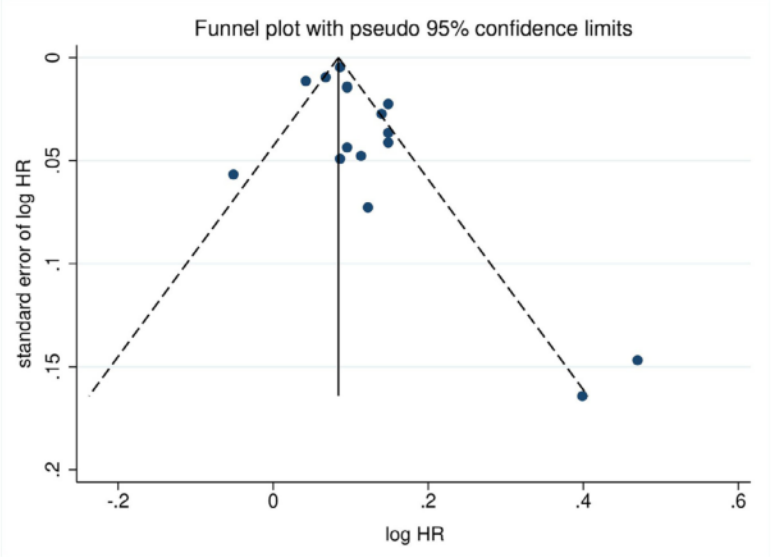


Figure 3. Funnel plot for an overall meta-analysis on the effect of WBC count on mortality.

Table 4
GRADE approach for certainty assessment of overall analysis between WBC count and mortality

Outcomes	Certainty assessment							No. of participants	Effect	Certainty
	No. of studies	Study design	Risk of bias	Inconsistency	Indirections	Imprecision	Other considerations		Relative (95% CI)	
WBC-mortality	13	Observational	Serious*	Serious†	Not serious	Not serious	Dose-response gradient	62,904‡	HR 1.10 (1.08-1.12)	Low

CI = confidence interval; HR = hazard ratio.
* Not all prognostic factors were controlled and the adjusted factors across studies does not match.
† Heterogeneity 72%.
‡ WBC count was treated as continuous variable.

artery disease, promotes low-density lipoprotein accumulation in the intima, which initiates an inflammatory response in the arterial wall.[32] Endothelial cells activated by inflammation express leukocyte adhesion molecules, which attract leukocytes.[33] Recruited monocytes mature into macrophages, which then turn into foam cells and produce inflammatory cytokines.[34] Infarction of the coronary artery induces systemic inflammatory response, and the myocardium is damaged. This condition is called acute myocardial infarction (AMI). After AMI occurs, the number of peripheral blood mononuclear cells increases, and these cells infiltrate into the damaged region. Peripheral blood mononuclear cells are known to be associated with left ventricular remodeling after AMI.[35] Percutaneous coronary intervention, a mechanical way of reperfusion in patients with AMI, is also related to the provocation of inflammatory response. Coronary angioplasty elevates neutrophil, monocyte, and platelet adhesion molecule expression.[36]

Although acute aortic syndromes are predisposed by many different risk factors, atherosclerosis is mainly related to AAD in the older population. The weakening of the intima of the aorta because of predisposing risk factors leads to a tear. Blood moves into the middle tunic through the tear, which results in the dissection or rupture of the aorta.[37] In an induced aortic dissection model, Kurihara et al[38] (2012) showed that infiltration of neutrophils and their secretion of matrix metalloproteinase-9 may play a role in the initiation of AAD.

COVID-19 is a relatively recent issue, and further studies are needed to determine the underlying pathophysiology. Current studies suggest that a higher WBC count is associated with mortality in patients with COVID-19,[39] but there is also a hypothesis that survival depends on lymphocyte restoration.[40]

There are several limitations in our study. First, although more than 13 studies were conducted on WBC count and mortality, studies in which leukocyte counts were divided by categorical variables could not be combined and were excluded in the selection process. WBC is a highly nonspecific biomarker because elevated levels would simply indicate the presence of infection, inflammation, or a sick patient. Moreover, among the selected studies, 8 focused on patients with CVD and other 5 studies included general population or patients with COVID-19. Because of the heterogeneity of the chosen subjects across these studies, there may be limitations in generalizing the findings of this study.

Furthermore, given that the certainty of outcome was assessed as low, it is important to exercise caution when interpreting the results of the study. Further research may be necessary to increase the certainty of the findings and to gain a better understanding of the relation between the variables in question. Despite the limitations, our research process yielded a significant correlation.

The objective of this meta-analysis was to determine whether a clinically significant relation exists between WBC count and mortality. Although the study is limited by the fact that only age and gender were the commonly adjusted factors, the results indicate that a higher WBC count is associated with increased mortality across various populations, regardless of time. This positive correlation is more pronounced in short-term mortality than in long-term mortality. Consequently, WBC count should be considered when predicting prognosis or determining a treatment plan. Further research is required to establish the specific relation between WBC count and disease progression or death, and the causality between the elevation of WBC count and disease progression should be thoroughly examined. Although the study was limited to all-cause and CVD mortality, the relevance of WBC count to mortality from more diverse causes should be explored. Further research that evaluates WBC count together with other biomarkers may reveal a stronger prognostic factor.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed in this study.

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