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ORIGINAL ARTICLE

Platelet Indices and the Causal Relationship with Myeloid Leukemia: a Mendelian Randomization Study with Dual Samples

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SUMMARY

Background: **Platelets are correlated with myeloid leukemia (ML), but to date, there have been no studies confirming the causal relationship between them.**
Methods: **Platelet count (PLT), mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution width (PDW) data were obtained from the GWAS catalog database as exposure factors. Acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) data were obtained from the FinnGen database as outcome indicators. The causal relationship between exposure and outcome was explored using the inverse variance weighted, MR-Egger, weighted median, and simple mode methods of dual-sample Mendelian randomization (MR). The stability and reliability of the results were assessed using Cochran's test, MR-Egger regression, and MR-PRESSO methods.**
Results: **An elevated PCT is positively associated with the risk of CML [$OR_{MR\text{-}Egger}$ = 2.591, 95% CI (1.089 - 6.166), p = 0.032; $OR_{Simple\ mode}$ = 9.873, 95% CI (1.112 - 87.646), p = 0.040]. There was no evidence of heterogeneity or pleiotropy at the gene level. However, there were no causal associations between other indices and CML, and none of the four platelet indices were causally associated with AML.**
Conclusions: **An increase in PCT significantly increases the risk of developing CML, making it a candidate biomarker for clinical screening of CML.**
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KEYWORDS

acute myeloid leukemia, chronic myeloid leukemia, platelet count, mean platelet thrombocyte volume, plateletcrit, platelet distribution width, Mendelian randomization

INTRODUCTION

Myeloid leukemia (ML) is a malignant tumor of the hematopoietic system known for its uncontrolled proliferation of abnormal white blood cells. Its hallmark is the abnormal proliferation and impaired differentiation of hematopoietic progenitor cells in the bone marrow [1]. ML can be classified into two subtypes based on the different stages of cell maturation arrest, namely acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) [2]. AML progresses rapidly, requiring immediate treatment, with a high incidence rate and poor prognosis, with a five-year survival rate of only 24%

[3]. CML is another subtype of leukemia characterized by slow growth and can be treated with medication [4]. CML accounts for 15% of adult leukemia cases, with a global incidence rate of 1.6 to 2 per 100,000 individuals [5].

Platelets are disc-shaped, non-nucleated cells with a diameter of approximately 2 - 3 µm. Their primary function is blood clotting and hemostasis, as well as repairing damaged blood vessels. In clinical practice, platelet count (PLT), mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution width (PDW) are commonly used indicators to evaluate the platelet status of patients [6-8]. The abnormal function of platelets is associated with the occurrence of blood-related diseases such as myocardial infarction, stroke, venous thrombosis, and others [9]. Studies have found that abnormal platelet function is also associated with the occurrence and development of ML [10-12], especially in AML [13]. ML originates from primitive myeloid progenitor cells, which can differentiate into various hematopoietic cells such as red blood cells, white blood cells, and platelet-producing cells. Repsold et al. [14] found that CML patients are often diagnosed with platelet abnormalities, with platelets elevated at diagnosis and decreased after 6 months of treatment, and platelet activation significantly increased after 6 months of treatment compared to diagnosis. Clinical research by Oswald et al. [15] found that fatigue in approximately 91% of AML patients was significantly associated with lower PLT levels. Overall, these studies suggest a correlation between abnormal platelet function and the occurrence and development of ML. However, most studies are currently limited to observational research and cannot provide sufficient evidence of causality due to the presence of confounding factors.

Mendelian randomization (MR) is an emerging and effective statistical method for determining causal relationships using genome-wide association study (GWAS) data, with single nucleotide polymorphisms (SNPs) serving as instrumental variables (IVs) [16]. The characteristics of MR are as follows: 1) genetic variations exist from birth and are not influenced by external factors; 2) SNPs are randomly assigned during meiosis and are not affected by environmental factors or lifestyle; and 3) SNPs have persistent effects on exposure, because they are often associated with specific exposures through biological or metabolic pathways. This study aimed to determine the causal effects of PLT, MPV, PCT, and PDW on the occurrence and development of ML through dual-sample MR analysis and to provide evidence-based support for the identification of early diagnostic markers for ML and subsequent monitoring of platelet management during treatment.

MATERIALS AND METHODS

Study design

This study employs dual-sample Mendelian randomization (MR) to investigate the causal associations between four platelet indices (PLT, MPV, PCT, and PDW) and AML and CML. All GWAS data used in the study are publicly available, with the data for the four platelet indices obtained from the GWAS catalog database (https://gwas.mrcieu.ac.uk/) and AML and CML data sourced from the FinnGen database (https://www.finngen.fi/en/). To minimize bias due to population heterogeneity, all individuals included in this study are of European ancestry. As each included GWAS has obtained ethical and institutional review board approval from local institutions, which can be found in the original publications of each study, no additional ethical approval is required.

Exposure data

The four platelet GWAS datasets obtained from the GWAS catalog database were used to screen for appropriate instrumental variables (IVs), details of which are provided in Table 1. PLT and MPV were derived from the same GWAS study, which utilized REGENIE, a novel machine learning approach, to conduct genome-wide association analysis of 11 million estimated variants associated with 50 quantitative traits and 54 binary traits in 407,746 white British individuals from the UK Biobank [17]. PCT and PDW were derived from another large-scale study that integrated data from the UK Biobank and a large international study. This study included a total of 563,085 individuals of European ancestry and identified 5,106 new genetic mutations independently associated with 29 blood cell phenotypes [18].

Outcome data

The GWAS data for AML and CML are sourced from the FinnGen database, with details provided in Table 1. The CML GWAS data include a total of 218,792 adults of European ancestry (90 AML patients and 218,702 healthy controls), with no gender restrictions, and encompass 16,380,466 SNPs. The AML GWAS data include 218,013 adults of European ancestry, comprising 111 CML patients and 217,902 healthy controls, with no gender restrictions, and encompass 16,380,466 SNPs.

Instrumental variables

By implementing six rigorous filtering steps to meet the three core assumptions of MR analysis and mitigate bias caused by horizontal pleiotropy, we ensured the significance of SNPs associated with the four platelet indices by setting a significance threshold of 5×10^{-8}. Next, to ensure no linkage disequilibrium among IVs, we set clustering parameters ($r^2 < 0.001$, kb = 10,000). Subsequently, to fulfill the assumption of independence, we employed PhenoScanner19 to remove IVs correlated

with confounding factors [19]. Following this, we eliminated palindrome SNPs that may affect MR results during the harmonization process. Finally, we extracted the SNP identifiers along with corresponding data parameters such as effective allele frequencies, effective alleles, exposure and outcome effect estimates, standard errors, and p-values.

MR analysis

The causal relationship between the four platelet indices and ML was evaluated by using MR-Egger, IVW (inverse variance weighted), weighted median, simple mode, and MR-PRESSO. IVW, satisfying three core assumptions (1) strong association with the exposure factor, 2) unrelated to confounding factors, and 3) only related to the exposure and outcome, as shown in Figure 1, calculates the causal effect of individual SNPs using the odds ratio, followed by weighted regression of each SNP's causal effect to accurately estimate the overall causal effect between exposure and outcome. MR-Egger and weighted median serve as supplements to IVW and can also estimate causal effects. MR-Egger tests for horizontal pleiotropy by hypothesis testing of the intercept but with lower precision [20]. MR-Egger and IVW are consistent and require error-free measurement between IV and exposure. Weighted median assumes that 50% of SNPs are valid IVs, estimates the causal effect values of SNPs by taking the median after sorting by weight, and provides a consistent causal effect estimate under this premise. Therefore, weighted median can obtain stable results and reduce type I errors in the presence of horizontal pleiotropy to achieve the most accurate causal estimation [21]. Simple mode is a simple mode of causal effect estimation when there is only one IV. MR-PRESSO provides corrected results after removing horizontal pleiotropy [22]. Finally, for better interpretation of the results, the β and se values were transformed into odds ratios (OR) and the corresponding 95% confidence intervals (CI) were calculated.

Sensitivity analysis

To assess the relationship between instrumental variables (IVs) and the four platelet indices, F-statistics are used to evaluate the strength of each IV. The formula F

$$F = R^{2} \times \frac{(N-2)}{(1-R^{2})}$$

for the F-statistic is as follows:

$$R^{2} = \frac{[2 \times \text{beta}^{2} \times \text{eaf} \times (1-\text{eaf})]}{[2 \times \text{beta}^{2} \times \text{eaf} \times (1-\text{eaf}) + 2 \times \text{se(beta)}^{2} \times \text{N} \times \text{eaf} \times (1-\text{eaf})]};$$

(where beta represents the effect of the gene on exposure; eaf represents the effective allele frequency; se (beta) represents the standard error of the genetic effect, and N represents the sample size [23]. All statistical values of IVs included in this study are greater than 10. MR-Egger regression and MR-PRESSO methods are used to assess potential horizontal pleiotropy among IVs, and Cochran's statistics are employed to evaluate heterogeneity among IVs in IVW and MR-Egger methods.

R software

All MR analyses mentioned above were conducted using the "TwoSampleMR" package (Version: 0.5.6) and "MRPRESSO" package (Version: 1.0) in R software (Version: 4.1.0). The visualization of MR results was performed using the "forestplot" package (Version: 3.1.1) in R software.

RESULTS

IVs tool selection

According to the selection and extraction criteria, 406, 431, 424, and 357 SNPs were ultimately obtained for PLT, MPV, PCT, and PDW, respectively, in association with AML. Similarly, for CML, 406, 431, 424, and 357 SNPs were obtained for PLT, MPV, PCT, and PDW, respectively. All F-values were greater than 10, indicating a low likelihood of weak IV bias in this study.

The causal relationship between platelets and AML

This study utilized dual-sample Mendelian randomization to investigate the causal relationship between PLT, MPV, PCT, PDW, and AML, with the results presented in Figure 2. Only in MR-Egger analysis, a negative association between PLT and AML was observed [OR = 0.317, 95% CI (0.102, 0.986), p = 0.048], while no causal relationship was found between other platelet indices (MPV, PCT, and PDW) and AML. Overall, these findings suggest that an increase in PLT may be a protective factor for AML (Figure 2).

The causal relationship between platelets and CML

The MR results for PLT, MPV, PCT, and PDW in relation to CML are presented in Figure 3. The results indicate that an increase in PCT significantly increases the risk of developing CML [$OR_{MR\text{-}Egger}$ = 2.591, 95% CI (1.089 - 6.166), p = 0.032; $OR_{Simple\ mode}$ = 9.873, 95% CI (1.112 - 87.646), p = 0.040], while there is no causal relationship between PLT, MPV, PDW, and CML. Overall, these findings suggest that an elevation in PCT may be a risk factor for the occurrence of CML.

Results of sensitivity analysis

Sensitivity analysis was conducted to assess the causal relationship between platelet indices (PLT, MPV, PCT, and PDW) and ML, with results presented in Table 2. Cochran's test results indicate that both PMR Egger and PIVW for PLT, MPV, PCT, and PDW with AML and CML are > 0.050, suggesting no heterogeneity for these indices. Horizontal pleiotropy results reveal no genetic pleiotropy for the MR results, except for PLT with AML. Given the significant horizontal pleiotropy between PLT and AML, MR-PRESSO results, after removing horizontal pleiotropy, were used for assessment, indicating no causal relationship between PLT and AML [$OR_{MR\text{-}PRESSO}$ = 2.591, 95% CI (1.089 - 6.166), p = 0.032]. Overall, only one significant result was obtained, indicating that an increase in PCT may be a risk

Table 1. Summary of exposure and outcome GWAS.

Trait	GWAS ID	Year	Population	Sample size	Number of SNPs	Build
PLT [17]	ebi-a-GCST90013980	2021	European	396,621	10,783,695	HG19/GRCh37
MPV [17]	ebi-a-GCST90013981	2021	European	396,616	10,783,695	HG19/GRCh37
PCT [18]	ebi-a-GCST90002400	2020	European	408,112	40,299,196	HG19/GRCh37
PDW [18]	ebi-a-GCST90002401	2020	European	408,112	40,300,122	HG19/GRCh37
AML	finn-b-C3_AML	2021	European	218,792	16,380,466	HG19/GRCh37
CML	finn-b-CML	2021	European	218,013	16,380,466	HG19/GRCh37

PLT - Platelet count, MPV - mean platelet thrombocyte volume, PCT - plateletcrit, PDW - platelet distribution width, AML - acute myeloid leukemia, CML - chronic myeloid leukemia.

Table 2. Results of sensitivity analysis.

Exposure	Outcome	Method	Cochran's Q				Horizontal pleiotropy		
			SNPs	*Q*	*Q_df*	p	*Q*	*Q_df*	p
PLT	AML	MR Egger	406	426.931	404	0.208	0.043	0.017	0.010
PLT		IVW	406	433.981	405	0.154	-	-	-
MPV		MR Egger	431	414.618	429	0.682	-0.027	0.015	0.074
MPV		IVW	431	417.835	430	0.654	-	-	-
PCT		MR Egger	424	456.198	422	0.121	0.003	0.016	0.837
PCT		IVW	424	456.243	423	0.128	-	-	-
PDW		MR Egger	357	348.194	355	0.592	0.003	0.016	0.838
PDW		IVW	357	348.236	356	0.606	-	-	-
PLT	CML	MR Egger	406	403.176	404	0.502	-0.017	0.145	0.253
PLT		IVW	406	404.487	405	0.281	-	-	-
MPV		MR Egger	431	444.492	429	0.293	-0.026	0.014	0.067
MPV		IVW	431	447.9902	430	0.265	-	-	-
PCT		MR Egger	424	385.638	422	0.897	-0.021	0.014	0.119
PCT		IVW	424	388.074	423	0.887	-	-	-
PDW		MR Egger	357	369.309	355	0.290	-0.001	0.015	0.944
PDW		IVW	357	369.315	356	0.302	-	-	-

PLT - platelet count, MPV - mean platelet thrombocyte volume, PCT - plateletcrit, PDW - platelet distribution width, AML - acute myeloid leukemia, CML - chronic myeloid leukemia.

factor for the occurrence of CML.

DISCUSSION

In recent years, as research on ML has deepened, clinical researchers have found that platelets play an important role in its occurrence and development, gradually gaining attention. However, the genetic relationship between the two remains unclear. This study utilized dual-sample MR to explore the causal relationship between four platelet indices (PLT, MPV, PCT, and PDW) and AML and CML. The results show that an increase in PCT significantly increases the risk of developing CML, while no causal relationship was found between PLT, MPV, PDW, and CML. Additionally, there was no causal relationship between the four platelet indices and AML.

Before conducting sensitivity analysis, the study found a negative correlation between PLT and AML. However, due to significant horizontal pleiotropy between them, MR-PRESSO was employed to remove horizon-

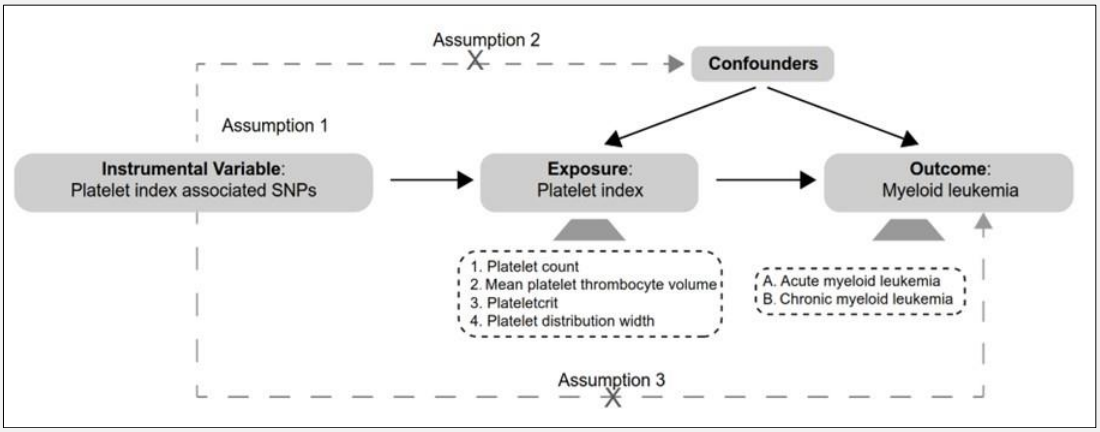

Figure 1. The three core assumptions.

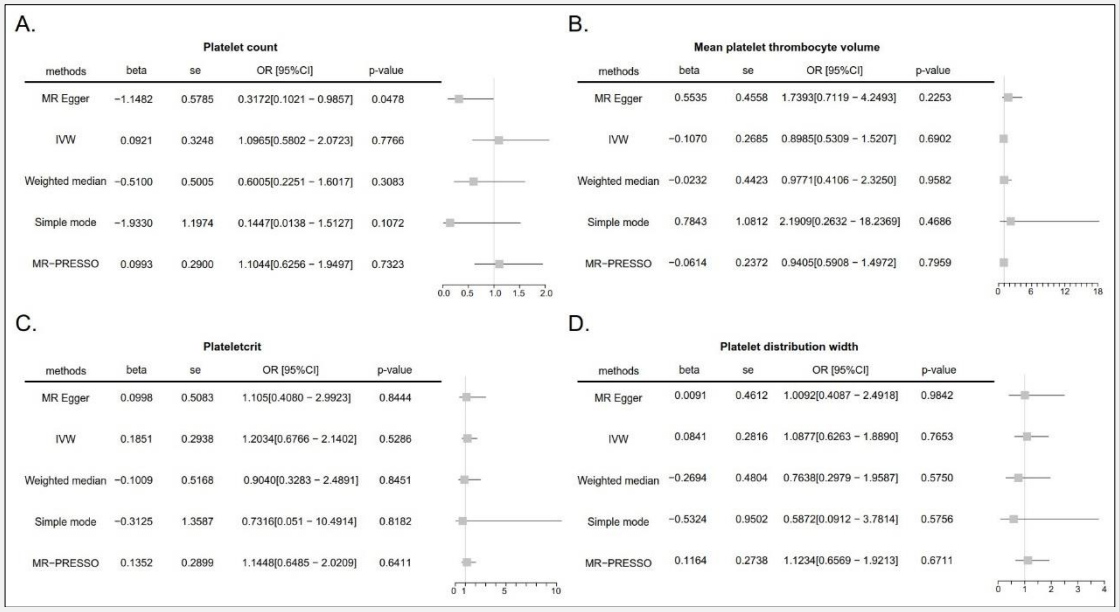

Figure 2. MR results for platelet indices and AML: A) PLT; B) MPV; C) PCT; and D) PDW.

tal pleiotropy. The MR-PRESSO results indicate that there is no causal relationship between the two. The relationship between platelets and AML has been observed in many studies. An observational study in Ukraine found an increase in PLT in AML patients who experienced bleeding [24]. Another study found that the expression levels of PLT, RBC, Hb, and HTC in the AML group were significantly higher than those in the normal group [25]. A retrospective study [26] found that a low PLT count ($\leq$ 40 x 10^9/L) at diagnosis was associated with better 5-year overall survival (OS) outcomes in overall AML patients and intermediate-risk AML pa-

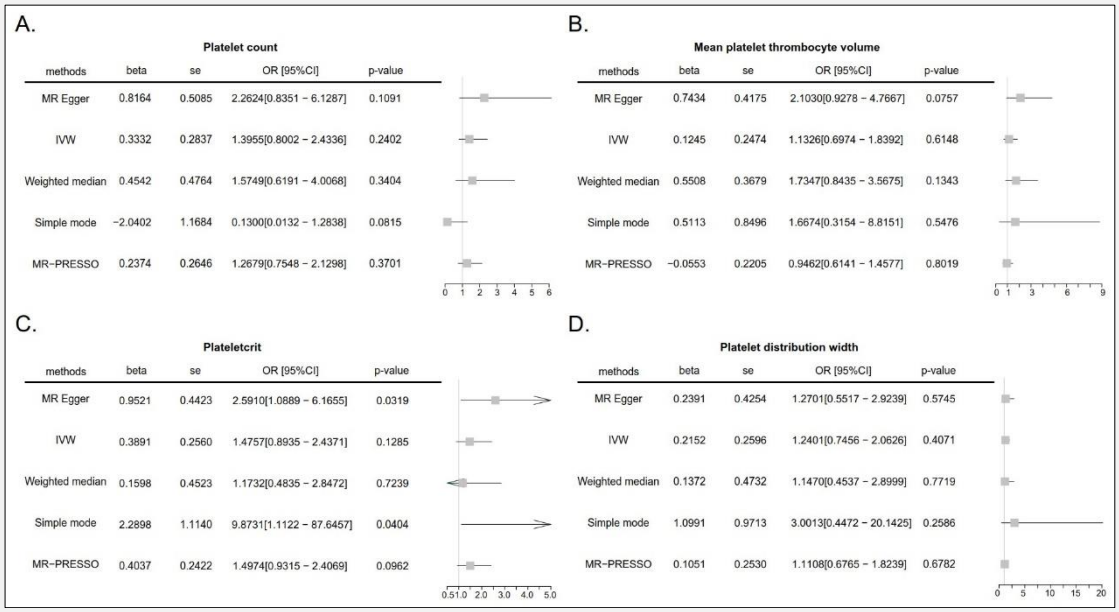

Figure 3. MR results for platelet indices and CML: A) PLT; B) MPV; C) PCT; and D) PDW.

tients (overall AML: 55.1 ± 3.8 vs. 35.3 ± 3.5%, $p < 0.001$; intermediate-risk AML: 64.5 ± 5.4 vs. 41.0 ± 4.8%, $p < 0.001$) and lower 5-year disease-free survival (DFS) recurrence risk (overall AML: 49.1 ± 3.8 vs. 25.7 ± 4.0%, $p < 0.001$; intermediate-risk AML: 60.8 ± 5.6 vs. 28.6 ± 5.6%, $p < 0.001$). Additionally, Trafalis et al. [27] found that patients with initial PLT < 25 x 10^9/L had a higher response to chemotherapy and relatively better prognosis. Overall, it is concluded that an increase in PLT is a risk factor for AML, and a decrease has a favorable therapeutic effect on patient prognosis. This is contrary to the results of our study, possibly due to the presence of some horizontal pleiotropy in the analysis, leading to false positives in MR-Egger. Therefore, based on evidence from sensitivity analysis in this study, we are more inclined to believe that there is no significant causal relationship between platelet indices and AML.

So far, research on PCT and CML has been relatively scarce, and no study has yet established a correlation between the two. Elevated PCT is more commonly associated with clonal thrombocytosis and can serve as an effective diagnostic tool along with MPV and the platelet large cell ratio to differentiate between primary and clonal thrombocytosis disorders [28]. A study conducted in Iraq focusing on the BCR-ABL fusion gene found that compared to CML patients with the b3a2 subtype, CML patients with the b2a2 subtype had significantly higher platelet and PCT percentages, while total white blood cell count was lower [6]. This suggests that the type of BCR-ABL transcript is reflected by different percentages of white blood cells, platelets, and PCT. Al-Kuraishy et al. [29] found significant differences in white blood cell count, platelets, PCT percentage, and red blood cell hemoglobin average concentration between CML patients and healthy individuals. In this analysis, elevated PCT was proposed as a risk factor for CML, which requires further clinical studies to confirm this conclusion.

The correlation between platelet indices and ML has been traditionally explored through clinical studies, which inevitably cannot avoid the influence of other confounding factors. This study, for the first time, employed a two-sample MR approach to investigate the causal relationship between platelet indices and ML. However, MR is a method that infers causality between exposure and outcome using GWAS data, which inherently has both advantages and limitations. Advantages of this study include: 1) meeting the three core assumptions of MR analysis; 2) implementing stringent SNP filtering steps; and 3) utilizing five MR methods to evaluate results and employing Cochran's Q statistic, MR-Egger regression, and leave-one-out analysis to assess all MR results, thus reducing heterogeneity and horizontal pleiotropy. Nevertheless, this study still has the following limitations: 1) the patients included in this study were all of European descent, so the conclusions may not be applicable to other populations; 2) although the SNP sites for the GWAS of the four platelet indices were set at P = 5 x 10 - 8, the final number of SNPs in-

cluded was too high; 3) the AML and CML data from Finland were not sufficiently up-to-date, and there were too few cases of AML and CML; 4) stratification based on the severity of the four platelet indices, gender, and age was not possible; and 5) platelet count exhibited some horizontal pleiotropy with AML, which hindered the results.

In conclusion, this study comprehensively evaluated the causal relationship between four platelet indices (PLT, MPV, PCT, and PDW) and ML using a two-sample MR approach. The results indicate a significant causal relationship between PCT and CML, with no evidence of heterogeneity or horizontal pleiotropy. This suggests that elevated PCT increases the risk of developing CML, with stable and reliable results. Future research should further investigate the variations in PCT among CML patients and its prognostic implications. Additionally, deeper exploration into the biological mechanisms underlying the association between PCT and CML occurrence is warranted, aiming to provide potential biomarkers for the prevention, diagnosis, and treatment of CML.

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Declaration of Interest:
The author declared no competing interest.

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