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Leukemia and risk of stroke: a Mendelian randomization analysis

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Abstract

Background Observational studies suggest an association between leukemia and stroke, but causality remains unclear. Certain leukemia types may increase stroke risk, but variations exist in stroke and mortality rates across leukemia subtypes. This study employed Mendelian randomization (MR) to investigate links between leukemia subtypes and stroke.

Methods We conducted a two-sample Mendelian randomization (TSMR) study utilizing genetic variants linked to various subtypes of leukemia as instruments to investigate their causal effects on stroke, specifically ischemic stroke (IS) and intracerebral hemorrhage (ICH). The leukemia dataset comprised 456,276 subjects from the UK Biobank, while the stroke dataset was sourced from the FINNGEN consortium, encompassing 212,774 participants.

Results In the present study, there was suggestive evidence that genetically predicted chronic lymphocytic leukemia (CLL) is associated with ischemic stroke (odds ratio, 1.02; 95% confidence intervals, 1.01–1.05; $P=0.024$), but no significant association was observed with intracerebral hemorrhage (ICH) (0.74; 0.99–1.03; $P=0.237$). Additionally, chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) was no significant associations between with stroke according to genetical prediction even if heterogeneity test and pleiotropic test was performed.

Conclusions Our Mendelian randomization analysis revealed that chronic lymphocytic leukemia (CLL) was associated with an increased risk of ischemic stroke (IS) but not intracerebral hemorrhage (ICH). Conversely, there was no evidence supporting causal associations of chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), or acute myeloid leukemia (AML) with either type of stroke. These findings enhance our comprehension of the intricate interplay between various leukemia subtypes and the risk of stroke. Further research is essential to delve into the underlying mechanisms and potential clinical implications of these observed associations.

Keywords Leukemia, Stroke, Mendelian randomization, Causality

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Background

Leukemia is a type of hematological malignancy characterized by the excessive production of abnormal leukocytes, which are atypical white blood cells that do not function as normal immune cells. This abnormal proliferation of leukocytes hinders the bone marrow's ability to generate an adequate number of red blood cells, platelets, and healthy white blood cells [1, 2]. This disruption occurs due to the occupation of space within the bone marrow by these abnormal cells [3]. As a result, individuals with leukemia may experience a range of symptoms related to impaired immune function, anemia, and a higher risk of bleeding or infection [4].

Stroke is a highly debilitating neurological condition that poses a significant global health burden, particularly in low- and middle-income regions [5]. It is a major contributor to both mortality and disability, accounting for approximately 10% of disability-adjusted life-years lost and 5% of annual deaths worldwide. As the prevalence of stroke continues to rise, it becomes increasingly important to identify the underlying risk factors and potential protective factors associated with this condition [6]. By understanding these factors, we can develop effective strategies for stroke prevention and ultimately reduce the impact of this devastating disease on individuals and communities.

Previous observational studies have indicated a potential link between leukemia and stroke, implying that individuals with specific leukemia subtypes may face an elevated risk of stroke [7–9]. However, it is important to note that some studies have also reported an increased risk of stroke in leukemia patients undergoing treatment [10]. These findings highlight the complexity of the relationship between leukemia and stroke, and the need for further research to better understand the underlying mechanisms and establish causality. One of the limitations of these previous studies is the challenge of excluding potential confounding biases, which may influence the observed associations. Additionally, the inability to infer causality is another limitation, as observational studies cannot establish a cause-and-effect relationship.

The two-sample Mendelian randomization (MR) method has emerged as a widely utilized approach for assessing causal relationships between risk factors and disease outcomes [11–13]. By leveraging the random allocation of alleles from parents to offspring, MR takes advantage of the inherent nature of genetic inheritance, which is less susceptible to confounding factors. Additionally, the issue of reverse causation is circumvented as genotypes established during zygote formation remain unaffected by subsequent diseases [14]. Building on the success of a recent Mendelian randomization (MR) study that highlighted the utility of genetic instruments in elucidating causal relationships between physical activity and disease risk [15], we note that no studies have yet employed MR to explore the relationship between leukemia and stroke. In this context, we utilize a similar methodology within a large-scale study design to investigate the impact of leukemia on stroke risk. Specifically, we focus on ischemic stroke and intracerebral hemorrhage as subtypes of stroke. By satisfying the necessary assumptions, our study aims to estimate the causal effect of leukemia on stroke, providing valuable insights for predicting stroke risk in individuals with leukemia. This innovative approach holds promise for advancing our understanding of the complex relationship between leukemia and stroke, ultimately informing clinical decision-making and improving patient outcomes.

Methods

Exposure and instrumental variables

We conducted a search in the UK Biobank repository for genome-wide association study (GWAS) data pertaining to various subtypes of leukemia. Our investigation unveiled 23 single nucleotide polymorphisms (SNPs) linked to acute lymphoblastic leukemia (ALL), 20 SNPs associated with acute myeloid leukemia (AML), 18 SNPs associated with chronic lymphocytic leukemia (CLL), and 11 SNPs associated with chronic myelogenous leukemia (CML), all demonstrating strong genome-wide significance ($P < 5 \times 10$^-6). Besides, the SNP with the lowest P value for association with each leukemia was chosen if SNPs are in linkage disequilibrium (LD) (based on a distance window of 10,000 kB and an $r^2 < 0.01$). To address potential bias stemming from weak instrumental variables, we calculated the F statistic for all instrumental variables and retained only those with F values exceeding 10 (Table 1, Table S1). Furthermore, all SNPs were retrieved from the dbSNP public database to exclude the impact of palindromic SNPs on the research results. We gathered concise statistics, including estimates of effect size and standard errors, for ALL, AML, CLL, and CML based on published GWAS data. SNPs identified as significantly associated with leukemia subtypes in our analysis were utilized as instrumental variables for subsequent exploration.

Data sources

The disease outcomes data were sourced from the FINNGEN consortium for ischemic stroke (25,398 cases and 339,920 controls) [16]; and from the UK Biobank for intracerebral hemorrhage (ICH) (655 cases and 455,693 controls) [17]. Stroke cases were enrolled between 2017 and 2023, with a median participant age of 63 years. The stroke subtypes were documented by centrally trained and certified investigators utilizing the web-based

Table 1 Genome-wide association studies and information of single nucleotide polymorphisms used as instrumental variable in the Mendelian randomization analyses of leukemia in relation to stroke

Traits	nSNPs	Ethnics	Sample size	Data sources	F-statistic (mean)	Reference
Acute Lymphoblastic Leukemia	23	Europeans	450,369	UK Biobank	23.24	(L et al., 2021)
Acute Myeloid Leukemia	20	Europeans	453,144	UK Biobank	22.87	(L et al., 2021)
Chronic Lymphocytic Leukemia	18	Europeans	451,228	UK Biobank	27.36	(L et al., 2021)
Chronic Myeloid Leukemia	11	Europeans	454,486	UK Biobank	23.22	(L et al., 2021)

nSNPs: number of single nucleotide polymorphisms

F-statistic (mean): the mean F-statistic of instrumental variables

Table 2 Description of stroke outcomes

Stroke	Consortium or study	Sample size	Ethnics	Year
Ischemia stroke	FINNGEN	25,398/339,920	Europeans	2022
Intracerebral hemorrhage	UK Biobank	655/455,693	Europeans	2021

Sample size: Reports case/controls

Causative Classification of Stroke (CCS) protocol (Table 2).

Mendelian randomization analysis

This study utilized a two-sample Mendelian randomization (MR) approach, leveraging summary-level data comprising beta coefficients and standard errors obtained from leukemia genotype regression and analogous data from disease outcome genotype regression [18]. The abundance of publicly available data from the global GWAS collaborative group has popularized the two-sample MR method. To ensure the efficacy of genetic variation as a tool for causal inference, the MR method employed must adhere to three fundamental assumptions: genetic variation is linked to the exposure; genetic variation is unrelated to confounding factors; genetic variation influences the risk of the outcome solely through the exposure and not via other pathways (Fig. 1).

We first harmonized the effect of exposure and outcome data sets containing combined information on SNPs, phenotype, effect allele, effect size, standard error for selected SNPs. In the main analyses, we calculated the odds ratio (OR) and 95% confidence intervals (CIs) for IVs by dividing the per-allele log-OR of Strokes by the per-allele difference in four subtypes of leukemia for each genetic variant respectively, using four different MR methods in which the conventional fixed effect inverse variance weighted method (IVW) is in a key position to get causal estimates. Besides, simple median method, weighted median method and MR-Egger

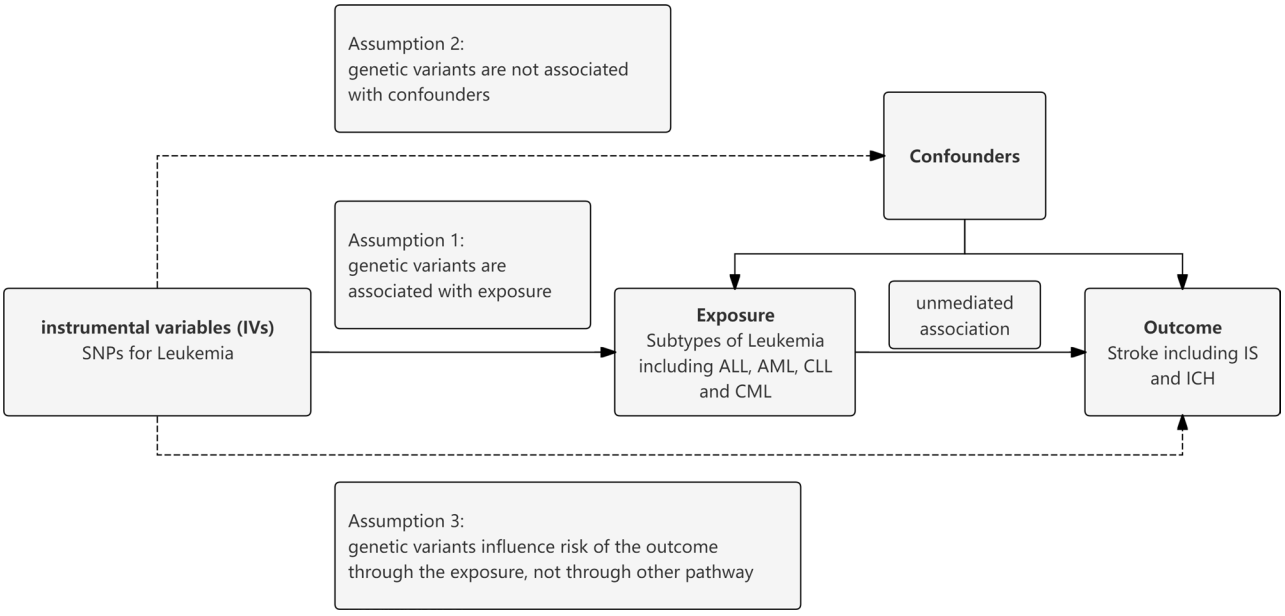

Fig. 1 Assumptions of a Mendelian randomization analysis for leukemia subtypes and stroke risk are depicted in the diagram. Broken lines symbolize potential pleiotropic or direct causal effects between variables that could breach Mendelian randomization assumptions. ALL = Acute Lymphoblastic Leukemia, AML = Acute Myeloid Leukemia; CLL = Chronic Lymphocytic Leukemia, CML = Chronic Myeloid Leukemia; IS = Ischemia stroke; ICH = Intracerebral hemorrhage

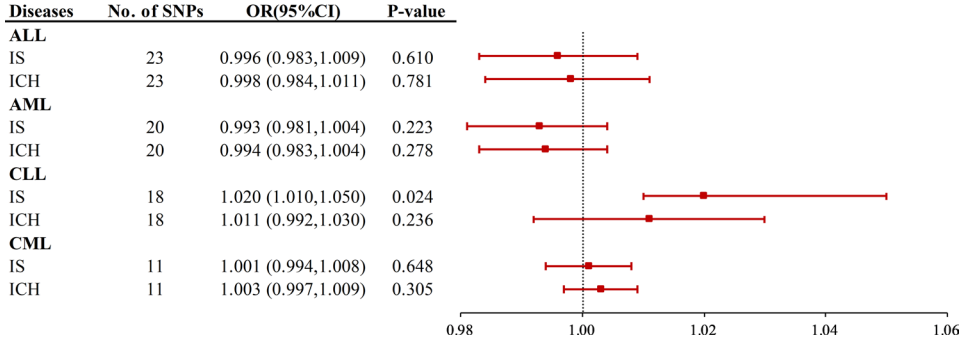

Fig. 2 Odds ratio for association of genetically predicted subtypes of Leukemia with Stroke. OR: odds ratio; CI: confidence internal. OR (95% CI) means risk of cardiovascular diseases per 1 SD increase of continuous factors or per 1 unit log odds increase of binary factors. SNPs = single nucleotide polymorphisms; ALL = Acute Lymphoblastic Leukemia, AML = Acute Myeloid Leukemia; CLL = Chronic Lymphocytic Leukemia, CML = Chronic Myeloid Leukemia; IS = Ischemia stroke; ICH = Intracerebral hemorrhage

regression method are performed as sensitivity analyses. The weighted median method has a high tolerance for pleiotropy, which provides a consistent estimate if at least 50% of the weight comes from valid SNPs. To see if there is directional pleiotropy existing in the IVW estimates, the MR-Egger analysis was conducted to test whether there is evidence of the intercept parameter being different from zero. In the absence of directional pleiotropy, the IVW estimates of each SNP should be distributed symmetrically near the point estimation, indicating that there is no systematic bias in the results. Heterogeneity in odds ratio was quantified using the I^2 test.

Result

Ischemia stroke

The study revealed potential evidence of a genetically predicted CLL risk on ischemic stroke (IVW OR, 1.03; 95% CI, 1.01–1.05; $P = 0.024$). Both the simple median and weighted median methods demonstrated a consistent effect pattern. MR-Egger analysis confirmed the absence of directional pleiotropy ($P = 0.695$). Heterogeneity tests using MR Egger and Inverse variance weighted methods indicated no significant heterogeneity ($P = 0.241$, $P = 0.287$). However, no significant association was found between ischemic stroke and genetically predicted ALL (IVW OR, 1.00; 95% CI, 0.98–1.01; $P = 0.611$), genetically predicted AML (IVW OR, 0.99; 95% CI, 0.98–1.00; $P = 0.223$), or genetically predicted CML (IVW OR, 1.00; 95% CI, 0.99–1.01; $P = 0.649$). These findings lacked sufficient data for alternative MR methods and sensitivity analyses (Fig. 2).

Intracerebral hemorrhage

No significant association was observed between the four subtypes of leukemia and ICH, including genetically predicted ALL (IVW OR, 1.33; 95% CI, 0.58–3.05; $P = 0.501$), genetically predicted AML (IVW OR, 1.00; 95% CI, 1.00–1.01; $P = 0.231$), genetically predicted CLL (IVW OR, 1.23; 95% CI, 0.77–1.97; $P = 0.381$), and genetically predicted CML (IVW OR, 0.85; 95% CI, 0.48–1.52; $P = 0.589$) (Fig. 2). Sensitivity analysis yielded consistent results, indicating no correlation between the four subtypes of leukemia and ICH.

Discussion

In the present study, we for the first time explored the causal relationships between ALL, AML, CLL, CML, and stroke risk utilizing a Mendelian randomization approach. Our analysis indicated that CLL could potentially act as a risk factor for ischemic stroke, as evidenced by the MR results. However, our study did not find any supportive evidence linking ALL, AML, or CML to stroke risk using this methodology and the selected SNPs.

Several observational studies have investigated the correlation between leukemia and stroke. A prospective study involving 820,491 leukemia patients revealed a significant increase in the risk of ischemic stroke (standardized incidence rate (SIR) 3.0, 95% confidence interval (CI) 2.5–3.7) and intracerebral hemorrhage (SIR 13, 95% CI 10–16) compared to individuals without leukemia [19]. Furthermore, data from U.S. hospitalizations for acute ischemic stroke over the past decade indicated that 12.7% of these patients had a history of cancer, with 47.2% having non-metastatic solid cancer, 34.0% having metastatic cancer of any type, and 18.8% having leukemia [20]. Another retrospective study involving 841 acute myeloid leukemia (AML) patients in Taiwan demonstrated a higher risk of hemorrhagic stroke among AML patients compared to the general population [21]. It is crucial to underscore that while these findings suggest a potential association between leukemia and stroke, limited research has explored the relationship between ischemic stroke and various subtypes of leukemia.

To our knowledge, no prior MR study has examined the link between leukemia and stroke. Our findings regarding the potential association between CLL and ischemic stroke align with those of a prospective population-based retrospective study involving 7,265 participants, which indicated that individuals hospitalized with CLL face an elevated risk of stroke [22]. Likewise, in a single cohort longitudinal retrospective study, 13.79% ($n = 381$) of patients with ischemic stroke were found to have CLL [23]. In addition, a prospective study spanning 32 months suggest that people with CLL have a higher risk of experiencing ischemic stroke episodes, compared to those without CLL [24]. Age is a crucial factor to consider when interpreting these findings. CLL is predominantly diagnosed in individuals aged 40 and above, with a median age at diagnosis surpassing 70 years [25]. Additionally, age itself is an independent risk factor for IS [26]. Therefore, the association between CLL and IS may be influenced by age-related factors. Patients with CLL often experience a state of chronic low-grade inflammation characterized by elevated levels of inflammatory markers, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) [27]. This inflammatory milieu can contribute to endothelial cell dysfunction, which may lead to vasoconstriction and alterations in hemodynamics, thereby increasing the risk of atherosclerosis [28]. At the same time, their blood viscosity may increase, which can adversely affect blood flow velocity and circulation. This elevation in viscosity is associated with a heightened risk of ischemic stroke [29, 30]. Furthermore, the substantial release of procoagulants resulting from the lysis of cancer cells further elevates the risk of thrombosis and ischemic stroke. This risk is compounded by hemodynamic changes and vascular damage, which reinforce this mechanism [31, 32]. Bruton's tyrosine kinase (BTK) inhibitors, such as ibrutinib, are considered first-line treatment options for CLL and have demonstrated significant efficacy in improving patient prognosis [29, 33]. However, the associated complications warrant careful consideration. A recent meta-analysis revealed that the risk of atrial fibrillation in patients treated with ibrutinib is approximately four times greater than that in the control group [34]. Atrial fibrillation is associated with a fivefold increase in stroke incidence and a twofold increase in mortality. Regardless of whether atrial fibrillation is persistent or intermittent, the risk of stroke remains elevated [35–37]. Ischemic strokes can be classified based on etiological subtypes (large artery atherosclerosis, cardioembolic, small-vessel occlusion, etc.), which may have different risk profiles associated with leukemia. But an updated GWAS dataset is needed to provide sufficient detail for such an analysis to reveal more specific associations.

Nevertheless, We did not identify a significant association between CLL and intracerebral hemorrhage, in contrast to the conclusions drawn from previous observational studies that indicated leukemia might elevate the risk of intracerebral hemorrhage [19]. The current MR analysis did not find evidence of associations between other leukemia subtypes and ischemic stroke or intracerebral hemorrhage. Our findings contradict some previous observational studies indicating an increased risk of stroke with acute myeloid leukemia (AML) [7, 38], a and fatal intracranial hemorrhage with acute lymphoblastic leukemia (ALL) and chronic myelogenous leukemia (CML) [21, 23]. These results are inconsistent with epidemiological conclusions [39, 40]. Our null results suggest that the observed links between leukemia and stroke in prior observational studies may have been false positives, likely due to reverse causation or confounding factors. By utilizing genetic variants strongly associated with leukemia, our analysis accounted for the majority of the variance, revealing genuine null associations. However, the potential for pleiotropy from the numerous variants may dilute this association. Therefore, further large-scale intervention trials are warranted to investigate the impact of leukemia on stroke. Emerging evidence suggests that leukemia per se has a limited impact on stroke risk, with the various complications and treatments associated with leukemia potentially driving the heightened stroke risk in affected patients [41–44]. Patients with leukemia often experience thrombocytopenia and coagulation abnormalities, predisposing them to an increased stroke risk [45]. Additionally, the inflammatory response triggered by leukemia can disrupt vascular endothelial cell function, promoting thrombosis and stroke [44]. Furthermore, treatment modalities for leukemia, including chemotherapy, radiotherapy, and stem cell transplantation, may also elevate the risk of stroke [41, 46]. Therefore, mitigating complications and implementing prophylactic anticoagulation during treatment could help reduce the incidence of stroke in leukemia patients [47].

This study boasts several notable strengths. Firstly, it represents the first systematic assessment of the causal impact of leukemia on stroke development using MR methods. The MR analysis provides a reliable approach for establishing causal estimates by reducing confounding factors and remaining immune to reverse causal effects or confounders. Furthermore, we employed sensitivity analyses, including the simple median method, weighted median method, and MR-Egger method, in addition to the conventional IVW method. These additional analyses were conducted to ensure the consistency of causal estimates, emphasizing the robustness of our findings. Thirdly, the study benefits from utilizing summary

statistics from GWAS, enabling larger sample sizes compared to epidemiological studies. Larger sample sizes enhance statistical power, leading to more reliable causal estimates.

However, despite meeting the core assumptions, MR studies, despite their strengths, are subject to certain limitations. Firstly, genetic variants identified in GWAS may have small phenotypic effects, potentially resulting in weak instrument bias, which is influenced by the strength of the genetic instruments, typically assessed by the F statistic. Secondly, population stratification poses another limitation, involving variations in allele frequencies and disease prevalence among different ethnic groups. Thirdly, MR studies require large sample sizes to guarantee sufficient power, a calculation that can be complex to ascertain [48].

In conclusion, our study presents evidence that challenges the conclusions of prior research suggesting that leukemia and its subtypes elevate the risk of stroke. This discrepancy implies that confounding variables may have exerted a substantial influence on the outcomes of previous observational studies. Consequently, larger-scale investigations that mitigate the influence of confounding factors are imperative to delve deeper into the causal association between leukemia and stroke.

Abbreviations

OR	Odds ratio
CIs	Confidence intervals
GWAS	Genome-wide association studies
IVW	Inverse variance weighted
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myeloid Leukemia
IS	Ischemia stroke
ICH	Intracerebral hemorrhage
MR	Mendelian randomization
RCT	Randomized controlled trial
SNPs	Single nucleotide polymorphisms
BTK	Bruton's tyrosine kinase

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04079-7.

Supplementary Material 1

Supplementary Material 2

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Author contributions
HN and CY designed the research. YXY, HN and CY had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. YXY, ZJR and ZX wrote the paper and performed the data analysis. All authors agree to publish.

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Data availability
All data used in the present study were obtained from genome wide association study summary statistics which were publicly released by genetic consortia.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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