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ORIGINAL ARTICLE

Harnessing Genomic and Bioinformatic Data to Broaden Understanding of Leukaemia Across Continents

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Abstract

Background/Aim: Leukaemia is a malignant disease of blood cells found in the bone marrow, which can be divided into acute lymphocytic leukaemia and myelocytic leukaemia. Current management of acute leukaemia still uses chemotherapy as the main therapy but has many side effects, therefore a new approach is needed to identify genetic factors involved in leukaemia. The aim of this study was to investigate gene variations that have potential pathogenic properties in leukaemia.
Methods: This study used genome-wide association study (GWAS) data obtained from the National Human Genome Research Institute (NHGRI) to search for genomic variants associated with leukaemia. The data was then screened using *SNPnexus* to detect potentially protein-damaging variants. Furthermore, the gene expression of these variants was analysed using the *GTEx portal*.
Results: Of the 2115 genomic variants found, four were deleterious, namely rs12140153, rs140386498, rs757110 and rs2066827, representing four different genes, namely *PATJ, MINDY1, ABCC8* and *CDKN1B*. Alterations in the expression of *PATJ, MINDY1, CDKN1B* and *ABCC8* genes affect the brain and leukaemia development. *PATJ* maintains brain cell integrity, *MINDY1* regulates gene expression, *CDKN1B* controls the cell cycle and *ABCC8* regulates glucose levels. Their deregulation is associated with neurological dysfunction and leukaemia. Variation in allele frequencies showed differences between continents, with rs757110 and rs2066827 having higher expression than rs12140153 and rs140386498. Variant gene expression also varied between tissues, with rs757110 and rs2066827 showing higher expression than rs12140153 and rs140386498.
Conclusion: This study successfully identified four genomic variants by harnessing a genomic and bioinformatic database, which are associated with leukemia and demonstrated variations in gene distribution and expression across different populations and tissues.

Key words: Leukaemia; Genome-wide association study; Polymorphism, single nucleotide; Genes; *PATJ; MINDY1; ABCC8; CDKN1B.*

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Introduction

Leukaemia is a malignant disease of blood cells found in the bone marrow, characterised by proliferation of white blood cells with manifestations of abnormal blood cells in the peripheral blood.[1] Acute leukaemia can be divided into acute lymphocytic leukaemia (LLA) and acute myelocytic leukaemia (LMA).[2] Leukaemia can be classified by the type of bone marrow af-

fected. Lymphoblastic leukaemia consists of immature lymphocytes and lymphocyte stem cells that originate from the bone marrow but infiltrate the spleen or spleen, lymphatic nodes, central nervous system and other tissues,[1] whereas myeloid leukaemia consists of pluripotent myeloid cells that originate from the bone marrow. In Indonesia, especially in Yogyakarta, the incidence of LLA is 20.8/1,000,000 while LMA is 8/1,000,000. This figure creates a proportion of LMA in the incidence of acute leukaemia of 27.7 %. This proportion is considered quite high.[3]

Management of acute leukaemia until now still uses chemotherapy as the main therapy.[4, 5] Acute leukaemia chemotherapy is divided into several stages, namely remission induction stage, consolidation or intensification stage, central nervous system prophylaxis stage and long-term maintenance stage.[6, 7] Drugs used for chemotherapy currently have many side effects, especially on the haematopoietic and gastrointestinal systems.[8] In the American Cancer Society (ACS) data, there was an increase in leukaemia cases from 2016 to 2017 in the United States.[9] In 2016 there were 24,500 deaths, in 2018 there were around 60,300 new cases with 24,370 deaths. In 2019 there were 61,780 new cases and 22,840 deaths. In Indonesia, according to WHO in 2019, the incidence of leukaemia was 35,870 cases in the last five years with 11,314 deaths.[10] West Sumatra shows a leukaemia prevalence of 2.4 %, which is the second highest incidence after Yogyakarta province 4.9 %.

It is important to find alternative treatments with fewer side effects. Leukaemia is a complex disease with many subtypes, such as acute lymphoblastic leukaemia (LLA) and acute myelocytic leukaemia (LMA).[11] It is important to understand more about these subtypes and how they affect prognosis and treatment. The aim of this study was to investigate gene variations that have potential pathogenic properties in leukaemia. The approach taken in this study was the use of genomic and bioinformatic data.[12]

Methods

Identifying genomic alterations is crucial in understanding the makeup of the human genome and the intricacies of disease. In this investigation, the incorporation of bioinformatics-centred methodologies was used to include changes associated with leukaemia disease.[13, 14] This study

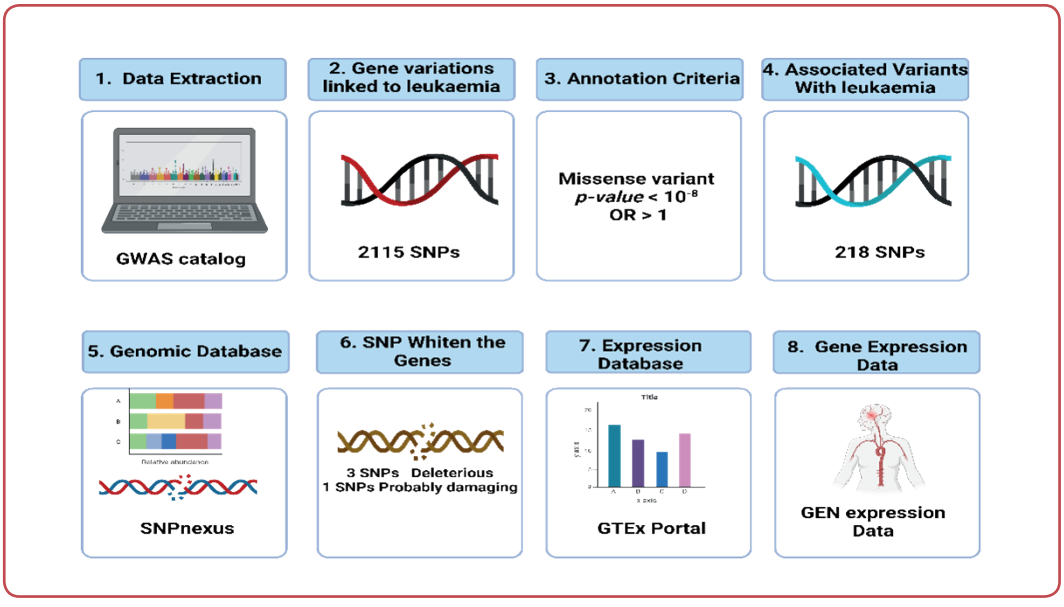

Figure 1: Process of single nucleotide polymorphisms (SNPs) data capture for leukaemia with genome-wide association study (GWAS) catalogue

was conducted using genome-wide association study (GWAS) data obtained from the National Human Genome Research Institute (NHGRI) to inform this research. The word "leukemia" was used in the search process and resulted in 2115 genomic variants. Next was to eliminate duplication in genomic variants. This facilitates research to be more focused on the specific genome that can damage and to pay more attention to 218 variants that are suspected to be detrimental to health to select these data using *SNPnexus* (https://www.snp-nexus.org) to make it easier to detect variants that are likely to experience protein changes that result in leukaemia disease. This was done on 28 December 2023. There are 3 single nucleotide polymorphisms (SNPs) that have deleterious properties from the data collected from *SNPnexus* and 1 polymorphism that is probably damaging. After selection (odds ratio (OR) < 0.05 was considered as significant) , the next researcher conducted a gene expression test using the *GTEx* portal (http://www.gtexportal.org/home/). This was done to see gene expression found in human tissue. The methodological steps used to screen for leukaemia-associated variants are summarised in the various stages of the bioinformatics pathway (Figure 1).

Results

From the data of 218 leukaemia SNPs (Table 1) that were assumed to be damaging from the GWAS catalogue, the same gene / duplication was separated and four SNP variants that cause damage to the protein were obtained. These SNPs represent four different genes including: *PATJ*, *MINDY1*, *ABCC8* and *CDKN1B* with the highest probability of damage being *ABCC8* as it has the largest predicted damage of 0.64.

Table 1 shows data collected from a database of 2115 genomes. From the data provided (Table 2 and 3) it can be seen that rs12140153 on the continent of Africa and East Asia is not common in population, as well as for rs140386498 on three continents namely Africa, America and East Asia. The opposite happened to rs757110 - the distribution of alleles throughout the world was quite large at 27 % and the spread on the South Asian continent was 42 %. For rs2066827 the distribution reached 36 % for all continents, with an average distribution of 22 % for the African and American continents; 24 % for Europe; 32 % for South Asia and the least distribution was in East Asia – 6 %.

The *GTEx portal* was used to identification of gene expression from SNPs associated with leukaemia (Figure 2-5). This analysis was useful for knowing the distribution of genes in each

Table 1: Leukaemia-associated single nucleotide polymorphisms (SNPs) and their effect on protein levels

SNP	Chromosomes	Gene	Score	Prediction
rs12140153	chr1	*PATJ*	0.020	Deleterious
rs140386498	chr1	*MINDY1*	0.040	Deleterious
rs757110	chr11	*ABCC8*	0.640	Probably damaging
rs2066827	chr12	*CDKN1B*	0.200	Deleterious

Table 2: Allele frequency distribution of the four single nucleotide polymorphisms (SNPs) cross (%)

SNP	All	Africa	America	East Asia	Europe	South Asia
rs12140153	7	0	2	None	7	5
rs140386498	0	None	0	None	2	1
rs757110	27	2	31	36	35	42
rs2066827	36	22	22	6	24	32

Table 3: Allele frequency distribution of the four single nucleotide polymorphisms (SNPs) across continents

SNP	Allele		Allele frequency				
	REF alleles	ALT alleles	Africa	America	East Asia	Europe	South Asia
rs12140153	G	T	none	0.022	none	0.067	0.047
rs140386498	A	T	none	0.003	none	0.017	0.006
rs757110	C	A	0.975	0.693	0.639	0.648	0.585
rs2066827	T	G	0.784	0.218	0.056	0.243	0.319

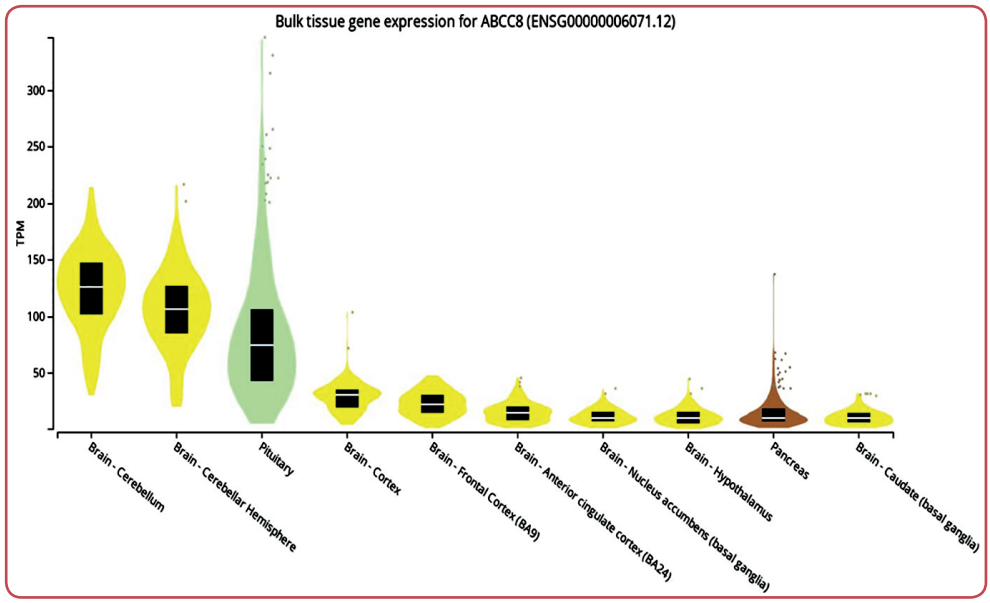

Figure 2: Tissue gene expression for ABCC8 according to GTEx portal database

TPM: transcripts per million;

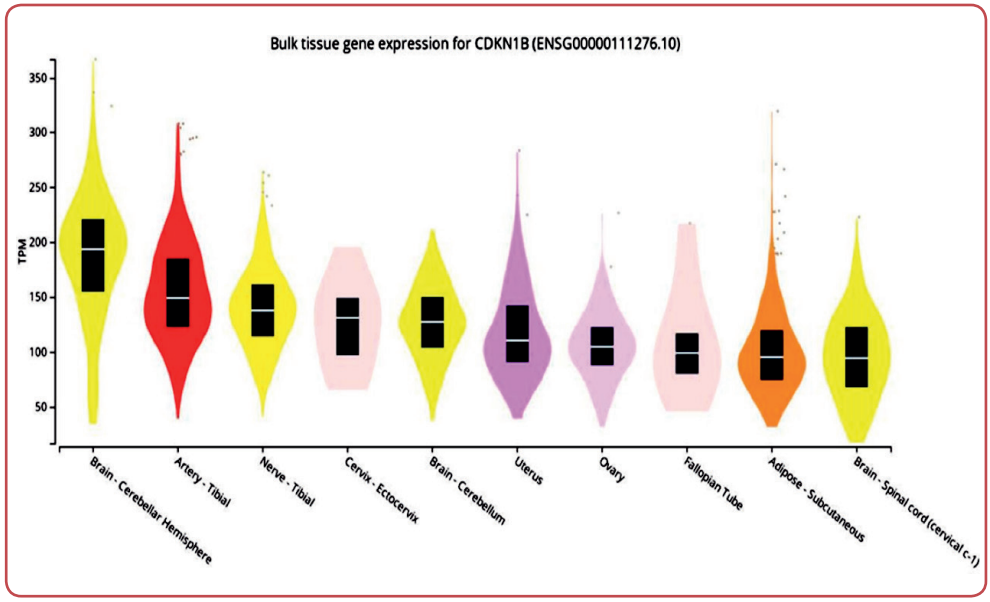

Figure 3: Tissue gene expression for CDKN1B according to the GTEx portal database

TPM: transcripts per million;

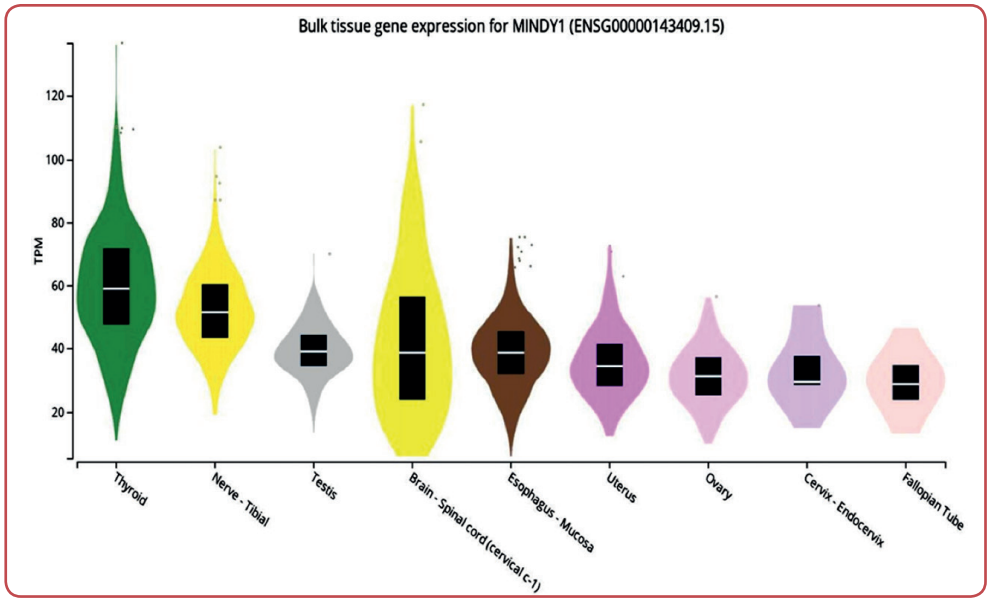

Figure 4: Tissue gene expression for MINDY1 according to GTEx portal database
TPM: transcripts per million;

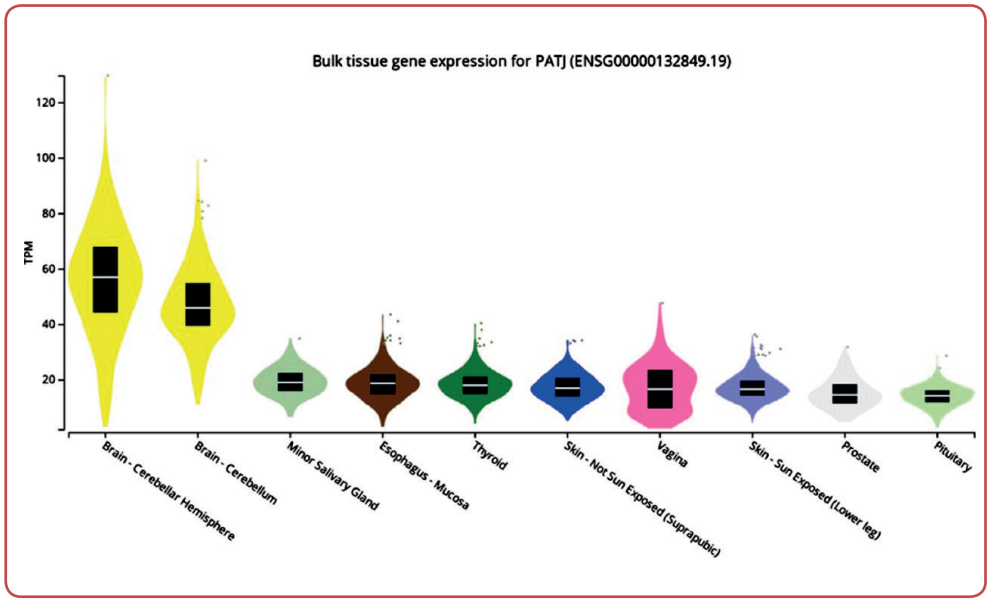

Figure 5: Tissue gene expression for PATJ according to GTEx portal database
TPM: transcripts per million;

tissue of the human body to facilitate further analysis. For the *ABCC8* gene, the distribution is mostly in the brain, pancreas and pituitary gland. For the *CDKN1B* gene, the distribution is in the brain, arteries, uterus, nerves, cervix, ovaries and adipose. The *MINDY1* gene has a distribution in the thyroid gland, uterine mouth, ovaries, brain, uterus, testes and fallopian tubes. And the distribution for the *PATJ* gene includes the brain, thyroid, vagina, prostate, oesophagus, skin and salivary gland.

Discussion

The aim of this research was to investigate gene variations that have the potential to have pathogenic properties in leukaemia. The approach taken in this research was the use of genomic and bioinformatic data. The *ABCC8* gene is located on chromosome 11p15.1 which encodes the SUR1 protein. The first type of *ABCC8* mutase that affects membrane channel expression disrupts

SUR1 synthesis or maturation, causing the protein not to reach the plasm membrane.[15, 16] This mutation can also cause impaired SUR1 inflammation.[17]

CDKN1B is an essential element of cell cycle control and a known tumour suppressor.[18, 19] In addition, germ line mutations of *CDKN1B* cause a multiple endocrine neulasia 1-like (MEN1) phenotype.[20] The *CDKN1B* gene encodes the p27 protein which is assumed to play a role as a negative regulator of the cell cycle.[21] This protein belongs to the CDK inhibitor family that binds to the cyclin/CDK complex, thus inhibiting cell division. Experiments by in a murine model showed that p27 deficiency affects chromosome stability and results in decreased mitotic cells.[22] As chromatin damage increases, Rad51 -dependent double-stranded DNA damage repair appears to be inhibited in p27-deficient cells leading to chromosomal instability.[23]

MINDY1 is a gene that has been studied in the context of leukaemia. It has been found to play an important role in promoting embryonic stem cell self-renewal.[24] In addition, *MINDY1* has been identified as a deubiquitinating enzyme that maintains liver cancer stem cell lines. It is highly expressed in liver cancer stem cells and its knockout leads to reduced stemness and inhibition of tumour growth.[25] *MINDY1* has also been found to be a member of the *MINDY1* deubiquitinating enzyme family, which is highly selective in leaving K48-associated polyuB and may have a specialised role in regulating proteostasis.[26] In breast cancer, *MINDY1* has been identified as a potential deubiquitylase of oestrogen receptor α (ERα) and its high expression is associated with poor prognosis. Furthermore, *MINDY1* has been shown to interact with and stabilise YAP, a key effector of the Hippo pathway in bladder cancer.[27]

PATJ is a gene that has been studied in the context of leukaemia. Altered function of RBPJ-corepressors, including *PATJ,* may contribute to the development of leukaemia, especially acute myeloid leukaemia (AML).[28] In addition, changes in *PATJ* expression have been observed in malignant melanoma, another type of skin cancer *PATJ* plays a role in epithelial morphogenesis and polarity, specifically in establishing tight junctions by providing a link between its lateral and apical components. Reduction of *PATJ* expression leads to delayed tight junction formation and cell polarisation defects.[29, 30] *PATJ* plays a role in epithelial morphogenesis and polarity, particularly in the formation of tight junctions by providing a link between their lateral and apical components.[31] Reduced PATJ expression results in delayed tight junction formation and cell polarisation defects. However, the specific role of the *PATJ* gene in leukaemia is as a gene with the potential to cause leukaemia.[30, 32]

Alterations in the expression of *PATJ, MINDY1*, *CDKN1B* and *ABCC8* genes affect brain function and leukemia progression. *PATJ* helps maintain brain cell integrity, *MINDY1* regulates gene expression through histone modification, *CDKN1B* controls the cell cycle by inhibiting cyclindependent kinases and *ABCC8* regulates glucose levels. Deregulation of these genes can lead to neurological dysfunction and uncontrolled proliferation of leukaemia cells. The current study presents several strengths and limitations in its investigation of leukaemia. Among its strengths, the research effectively utilised comprehensive data sources, specifically *GWAS data* from the National Human Genome Research Institute (NHGRI), which provided a robust dataset for identifying genomic variants associated with leukaemia. The study successfully identified four potentially pathogenic genomic variants, enhancing the understanding of the genetic factors involved in leukaemia. Additionally, it conducted a cross-population analysis that highlighted variations in allele frequency distribution and gene expression across different populations and tissues, offering valuable insights into the diversity of leukaemia manifestations globally. The application of advanced bioinformatics tools, such as SNPnexus for screening protein-damaging variants and the GTEx portal for gene expression analysis, further strengthened the reliability of the findings. Moreover, by identifying genetic factors associated with leukaemia, the study holds potential clinical implications for developing new diagnostic and therapeutic strategies to address the limitations of current chemotherapy treatments.

However, the study also has notable limitations. Its focus on a specific set of four deleterious variants may overlook other significant variants that could contribute to leukaemia. Furthermore, the reliance on existing *GWAS data* and bioinformatic tools introduces potential biases or limitations inherent in those datasets or analytical methods. The lack of functional validation means that while genomic variants were identified, there is no experimental evidence confirming their role

in leukaemia pathogenesis, which is crucial for establishing causality. Additionally, since the allele frequency distribution was only analysed across certain continents, the findings may not be generalisable to all populations, potentially missing variations in other regions. Although gene expression variability was observed, the study did not explore the underlying mechanisms driving these differences, leaving gaps in understanding how these factors interact with leukaemia development. Lastly, by primarily focusing on genomic variations, the investigation did not consider other potential factors such as environmental influences or epigenetic modifications that may also play a role in leukaemia risk and progression.

Conclusion

Four deleterious genomic variations were found, namely rs12140153, rs140386498, rs757110 and rs2066827, representing four different genes, namely *PATJ, MINDY1, ABCC8* and *CDKN1B3*. The allele frequency distribution of such variations shows variation between continents, with rs757110 and rs2066827 having a wider distribution than rs12140153 and rs140386498. Gene expression of such variation also varies between tissues, with rs757110 and rs2066827 having higher expression than rs12140153 and rs1403864984. The rs757110 and rs2066827 polymorphisms showed greater expression levels compared to rs12140153 and rs1403864984. This research is important to understand more about these gene subtypes and how each gene can cause damage and lead to leukaemia and help in the prognosis and treatment process.

Ethics

This study was a secondary analysis based on the currently existing dataset from the *GWAS* catalogue, *HaploReg*, *GTEx Portal* and *Ensembl* and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper. *GWAS* catalogue, *HaploReg, GTEx Portal* and *Ensembl* were available databases that contain patient data which were obtained through ethical clearance. Researcher are permitted to download relevant data free of charge for research purposes and to publish studies based on those data. Since our study relied solely on open-source data, we confirm that there were no ethical concerns or conflicts of interest.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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