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Research Article

# Prognostic value of aggregate index of systemic inflammation in acute ischemic stroke mortality

## *Akut iskemik inmede sistemik inflamasyonun toplam indeksinin prognostik değeri*

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## Abstract

**Aim:** Systemic inflammation plays a key role in the pathophysiology of acute ischemic stroke (AIS), influencing disease severity and outcomes. The Aggregate Index of Systemic Inflammation (AISI) is a novel inflammatory biomarker that integrates multiple hematological parameters. This study aimed to evaluate the prognostic value of AISI in predicting 30-day mortality in AIS patients.

**Material and Methods:** This retrospective cohort study included patients diagnosed with AIS in the emergency department of a tertiary care hospital between January 1, 2022, and January 1, 2025. AISI was calculated as (Neutrophil count × Monocyte count × Platelet count) / Lymphocyte count, with all components expressed in absolute values ($\times 10^9$/L). The primary outcome was 30-day all-cause mortality. Logistic regression analysis was performed to assess the independent prognostic value of AISI. Model performance was evaluated using accuracy, sensitivity, specificity, and the area under the receiver operating characteristic curve (AUROC).

**Results:** A total of 663 AIS patients were analyzed, including 573 survivors (86.4%) and 90 non-survivors (13.6%). AISI values were significantly higher in non-survivors compared to survivors (755.4 ± 410.8 vs. 396.7 ± 216.1, $p < 0.001$). Multivariate logistic regression analysis identified AISI as an independent predictor of 30-day mortality (OR: 1.10, 95% CI: 1.02 - 1.19, $p = 0.040$). The AUROC for AISI was 0.820, indicating good discriminatory ability.

**Conclusions:** AISI was found to be an independent predictor of 30-day mortality in AIS patients, highlighting the potential role of systemic inflammation in stroke prognosis. Given its accessibility and ease of calculation, AISI could serve as a useful marker for early risk stratification in clinical practice. However, further prospective, multicenter studies are needed to validate its clinical utility and compare it with other established inflammatory indices.

**Keywords:** acute ischemic stroke, inflammation, mortality

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## Öz

**Amaç:** Sistemik inflamasyon, akut iskemik inmenin (Aİİ) patofizyolojisinde kritik bir rol oynayarak hastalık şiddetini ve sonuçlarını etkiler. Sistemik İnflamasyonun Toplam İndeksi (AISI), birden fazla hematolojik parametreyi entegre eden yeni bir inflamatuvar biyobelirteçtir. Bu çalışmada, AISI'nin Aİİ hastalarında 30 günlük mortaliteyi öngörmedeki prognostik değeri değerlendirilmiştir.

**Gereç ve Yöntemler:** Bu retrospektif kohort çalışmasına, 1 Ocak 2022 ile 1 Ocak 2025 tarihleri arasında üçüncü basamak bir hastanenin acil servisinde Aİİ tanısı alan hastalar dahil edilmiştir. AISI, (Nötrofil sayısı × Monosit sayısı × Trombosit sayısı) / Lenfosit sayısı formülüyle hesaplanmış ve tüm bileşenler mutlak değerler ($\times 10^9$/L) cinsinden ifade edilmiştir. Birincil sonuç değişkeni, 30 günlük tüm nedenlere bağlı mortalite olarak belirlenmiştir. AISI'nin bağımsız prognostik değerini değerlendirmek için lojistik regresyon analizi yapılmış, model performansı doğruluk, duyarlılık, özgüllük ve alıcı işletim karakteristik eğrisi altındaki alan (AUROC) kullanılarak değerlendirilmiştir.

**Bulgular:** Toplam 663 Aİİ hastası analiz edilmiş, bunlardan 573'ü (%86,4) sağ kalırken, 90'ı (%13,6) yaşamını kaybetmiştir. AISI değerleri, yaşamını kaybeden hastalarda sağ kalanlara kıyasla anlamlı olarak daha yüksek bulunmuştur (755,4 ± 410,8 vs. 396,7 ± 216,1, $p < 0,001$). Çok değişkenli lojistik regresyon analizinde AISI, 30 günlük mortalitenin bağımsız bir prediktörü olarak belirlenmiştir (OR: 1,10, %95 GA: 1,02 - 1,19, $p = 0,040$). AISI için AUROC değeri 0,820 olup iyi bir ayırt edici güce işaret etmektedir.

**Sonuçlar:** AISI, Aİİ hastalarında 30 günlük mortalitenin bağımsız bir öngörücüsü olarak belirlenmiş ve sistemik inflamasyonun inme prognozundaki potansiyel rolünü ortaya koymuştur. Erişilebilirliği ve kolay hesaplanabilirliği göz önüne alındığında, AISI klinik uygulamada erken risk sınıflandırması için faydalı bir belirteç olarak kullanılabilir. Ancak, klinik kullanımının doğrulanması ve diğer yerleşik inflamatuvar indekslerle karşılaştırılması için daha fazla prospektif, çok merkezli çalışmaya ihtiyaç vardır.


**Anahtar Kelimeler:** akut iskemik inme, inflamasyon, mortalite

## Introduction

Acute ischemic stroke (AIS) remains a major global health burden and a leading cause of morbidity and mortality worldwide [1-3]. According to the Global Burden of Disease (GBD) 2021 database, the global incidence of ischemic stroke in 2021 was estimated at 7.8 million cases, with an age-standardized incidence rate of 92.39 per 100,000 people. While the incidence of ischemic stroke has shown a relative decline over the past three decades, it continues to contribute significantly to long-term disability and healthcare costs. The disability-adjusted life years (DALYs) associated with ischemic stroke were reported as 70.4 million in 2021, reflecting its substantial impact on global health systems [4]. Despite advances in acute management and secondary prevention strategies, ischemic stroke remains the second leading cause of death globally and disproportionately affects low- and middle-income countries [5]. Given the high disease burden, identifying prognostic markers that facilitate early risk stratification and improve patient outcomes remains a critical area of research.

Inflammation plays a crucial role in the pathophysiology of AIS, contributing to neuronal injury, blood-brain barrier disruption, and secondary brain damage [6]. Systemic inflammatory responses following an ischemic event are associated with poor clinical outcomes, including increased infarct volume, neurological deterioration, and higher mortality rates [7]. Several hematological biomarkers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), have been studied as potential prognostic indicators in stroke patients [8-10]. Recently, the Aggregate Index of Systemic Inflammation (AISI) has been proposed as a novel marker that integrates multiple inflammatory parameters to provide a more comprehensive assessment of systemic inflammation. However, the prognostic utility of AISI in AIS patients remains largely unexplored [11]. Given the strong association between inflammation and stroke outcomes, evaluating the role of AISI in predicting mortality could enhance risk stratification and inform early therapeutic strategies.

We hypothesize that the AISI is an independent predictor of mortality in patients with AIS.

## Material and Methods

This retrospective cohort study included patients diagnosed with AIS in the emergency department of a tertiary care hospital between January 1, 2022, and January 1, 2025. Ethical approval for the study was obtained from the Gazi Yaşargil Education and Research Hosptial's Ethics Committee (349, 07.02.2025). Due to the retrospective nature of the study, the requirement for informed consent was waived.

Patients aged 18 years or older who were diagnosed with AIS based on clinical evaluation and neuroimaging (CT or MRI) findings were included in the study. Those with hemorrhagic stroke, other non-ischemic cerebrovascular events, severe infection, malignancy, or autoimmune disease that could influence inflammatory markers were excluded. Additionally, patients receiving immunosuppressive or corticosteroid therapy or those with missing laboratory parameters necessary for the calculation of the AISI were not included in the final analysis.

Data were retrieved from the hospital's electronic medical records. Baseline demographic characteristics, including age, sex, and comorbid conditions such as hypertension, diabetes mellitus, and atrial fibrillation, were collected. Vital signs at admission, including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature, were recorded. Laboratory parameters, including neutrophil count, lymphocyte count, platelet count, monocyte count, hemoglobin, C-reactive protein (CRP), blood urea nitrogen (BUN), lactate, and creatinine levels, were extracted for analysis.

The AISI was calculated as (Neutrophil count × Monocyte count × Platelet count) / Lymphocyte count, with all components expressed in absolute values ($\times 10^9$/L) [12].

The primary outcome of this study was 30-day all-cause mortality, defined as death occurring within 30 days of hospital admission due to any cause. In cases where hospital records did not contain definitive mortality information, telephone follow-up with patients' relatives was conducted to verify the outcome.

## Statistical Analysis

The data were analyzed using R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were used to summarize the baseline characteristics of the patients. Continuous variables were presented as mean ± standard deviation (SD) for normally distributed data and median (interquartile range [IQR]) for non-normally distributed data. Categorical variables were summarized as frequencies and percentages. To compare continuous variables between the two groups, an independent samples t-test was used for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. Categorical variables were compared using the Chi-square test or Fisher's exact test, depending on the expected frequency. A p-value of <0.05 was considered statistically significant. Multivariate logistic regression was conducted to identify independent risk factors for 30-day mortality, including variables with a p-value <0.20 from univariate analysis. The logistic regression model was fitted using standard procedures. The goodness of fit was assessed using the Hosmer-Lemeshow test, and model performance was evaluated using accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC). The dataset was split into training and test sets in an 80-20 ratio. ROC analysis was performed to evaluate the predictive performance of the AISI in predicting 30-day mortality. The optimal cutoff value for AISI was determined using the Youden index, and sensitivity, specificity, positive likelihood ratio (+LR), and negative likelihood ratio (-LR) were computed.

## Results

In this study, we analyzed a total of 663 patients diagnosed with AIS, consisting of 573 survivors (86.4%) and 90 deceased patients (13.6%). The mean age of survivors was 67.9 ± 11.8 years, significantly lower than that of deceased patients, who had a mean age of 75.9 ± 10.8 years (mean difference 8 years, 95% CI: 5.4 - 10.6, $p < 0.001$). The prevalence of hypertension was significantly higher in deceased patients (92.2%) compared to survivors (71.2%) ($p < 0.001$), while diabetes was more common among deceased patients (21.1%) compared to survivors (10.1%) ($p = 0.002$). Atrial fibrillation also occurred more frequently in deceased patients (17.8%) compared to survivors (5.8%) ($p < 0.001$). Systolic blood pressure was significantly higher in deceased patients (160.7 ± 14.7 mmHg) compared to survivors (149.5 ± 15.2 mmHg), with a mean difference of 11.2 mmHg (95% CI: 7.9 - 14.6), $p < 0.001$. Diastolic blood pressure was also significantly higher in deceased patients (86.9 ± 10.9 mmHg) compared to survivors (84.3 ± 9.8 mmHg), with a mean difference of 2.5 mmHg (95% CI: 0.3 - 4.8), $p = 0.024$. Respiratory rate (20.1 ± 5.5 bpm vs. 15.3 ± 4.1 bpm, $p < 0.001$) and oxygen saturation (91.7 ± 3.3% vs. 95.6 ± 1.9%, $p < 0.001$) were also significantly different between the two groups, with deceased patients showing higher respiratory rates and lower oxygen saturation. No significant difference in temperature was observed between the groups (36.8 ± 0.4°C vs. 36.8 ± 0.5°C, $p = 0.34$) (Table 1).

| **Table 1.** Baseline demographic and clinical characteristics of patients with acute ischemic stroke. | | | | |
|---|---|---|---|---|
| Parameter | Survivor (n=573) | Deceased (n=90) | p | Mean difference (95% CI) |
| Age (years) | 67.9 ± 11.8 | 75.9 ± 10.8 | <0.001 | 8 (5.4 - 10.6) |
| Sex (male) | 348 (60.7%) | 57 (63.3%) | 0.639 | |
| Hypertension | 408 (71.2%) | 83 (92.2%) | <0.001 | |
| Diabetes | 58 (10.1%) | 19 (21.1%) | 0.002 | |
| Atrial fibrillation | 33 (5.8%) | 16 (17.8%) | <0.001 | |
| Systolic BP (mmHg) | 149.5 ± 15.2 | 160.7 ± 14.7 | <0.001 | 11.2 (7.9 - 14.6) |
| Diastolic BP (mmHg) | 84.3 ± 9.8 | 86.9 ± 10.9 | 0.024 | 2.5 (0.3 - 4.8) |
| Heart rate (bpm) | 85.6 ± 10.1 | 84.6 ± 8.6 | 0.407 | |
| Respiratory rate | 15.3 ± 4.1 | 20.1 ± 5.5 | <0.001 | 4.8 (3.9 - 5.8) |
| Oxygen saturation (%) | 95.6 ± 1.9 | 91.7 ± 3.3 | <0.001 | 3.9 (3.4 - 4.4) |
| Temperature (°C) | 36.8 ± 0.4 | 36.8 ± 0.5 | 0.34 | |
| Abbrev.: BP: Blood Pressure; bpm: Beats per minute | | | | |

Laboratory parameters revealed that neutrophil count was significantly higher in deceased patients (7.1 ± 1.5 × $10^9$/L) compared to survivors (5 ± 1.2 × $10^9$/L), with a mean difference of 2.1 × $10^9$/L (95% CI: 1.8 - 2.4), p < 0.001. C-reactive protein (CRP) levels were significantly elevated in deceased patients (17.4 ± 4.7 mg/L) compared to survivors (10 ± 2.8 mg/L), with a mean difference of 7.4 mg/L (95% CI: 6.7 - 8.1), p < 0.001. Lactate levels were significantly higher in deceased patients (3 ± 0.5 mmol/L) compared to survivors (1.8 ± 0.4 mmol/L), with a mean difference of 1.2 mmol/L (95% CI: 1.1 - 1.3), p < 0.001. The AISI was also significantly higher in deceased patients (755.4 ± 410.8) compared to survivors (396.7 ± 216.1), with a mean difference of 358.7 (95% CI: 302.8 - 414.7), p < 0.001. No significant differences were observed for lymphocyte, monocyte, hemoglobin, creatinine, and platelet counts (Table 2).

| **Table 2.** Laboratory parameters of patients with acute ischemic stroke at admission. | | | | |
|---|---|---|---|---|
| Parameter | Survivor (n=573) | Deceased (n=90) | p | Mean difference (95% CI) |
| Neutrophil ($10^9$/L) | 5 ± 1.2 | 7.1 ± 1.5 | <0.001 | 2.1 (1.8 – 2.4) |
| Lymphocyte ($10^9$/L) | 2 ± 0.5 | 2 ± 0.4 | 0.126 | 0.5 (0.4 - 0.6) |
| Monocyte ($10^9$/L) | 0.6 ± 0.1 | 0.6 ± 0.2 | 0.058 | |
| Hemoglobin (g/dL) | 13.8 ± 1.2 | 13.8 ± 1.7 | 0.757 | |
| CRP (mg/L) | 10 ± 2.8 | 17.4 ± 4.7 | <0.001 | 7.4 (6.7 - 8.1) |
| BUN (mg/dL) | 21.2 ± 4 | 21.9 ± 4.6 | 0.146 | |
| Creatinine (mg/dL) | 1.6 ± 0.3 | 1.5 ± 0.4 | 0.127 | |
| Platelet (103/µL) | 251.4 ± 47.4 | 242.6 ± 41.1 | 0.097 | |
| AISI | 396.7 ± 216.1 | 755.4 ± 410.8 | <0.001 | 358.7 (302.8 - 414.7) |
| Abbrev.: RDW: Red Cell Distribution Width, CRP: C-Reactive Protein, BUN: Blood Urea Nitrogen, AISI: Aggregate Index of Systemic Inflammation | | | | |

The multivariate logistic regression analysis revealed that hypertension (odds ratio [OR]: 3.67, 95% CI: 1.50 - 10.43, p = 0.003) and neutrophil count (OR: 2.98, 95% CI: 2.25 - 4.09, p < 0.001) were significant risk factors for 30-day mortality (Table 3).

| **Table 3.** Multivariate logistic regression analysis for predicting 30-day mortality in acute ischemic stroke patients. | | |
|---|---|---|
| Variable | OR (95% CI) | p |
| Hypertension | 3.67 (1.50 - 10.43) | 0.003 |
| BUN | 1.09 (1.00 - 1.19) | 0.044 |
| Neutrophil | 2.98 (2.25 - 4.09) | <0.001 |
| AISI | 1.10 (1.02 - 1.19) | 0.040 |
| Hemoglobin | 1.20 (0.87 - 1.65) | 0.263 |
| Temperature | 1.06 (0.40 - 2.80) | 0.911 |
| Monocyte | 1.84 (0.16 - 21.21) | 0.626 |
| Platelet | 0.99 (0.98 - 1.01) | 0.358 |

The AISI was significantly associated with 30-day mortality (OR: 1.10, 95% CI: 1.02 - 1.19, p = 0.040). Other factors, including BUN, hemoglobin, temperature, monocyte, and platelet counts, were not significant predictors. Model performance on both training and test sets showed an accuracy of 85.12% (95% CI: 82.1% - 87.6%) for the training set, with sensitivity and specificity of 94.50% and 67.28%, respectively. The positive predictive value (PPV) was 90.12%, while the negative predictive value (NPV) was 79.53%. Receiver operating characteristic analysis for AISI revealed an area under the curve (AUROC) of 0.820 (95% CI: 0.770 - 0.870), with an optimal criterion of 512.2 (Figure 1).

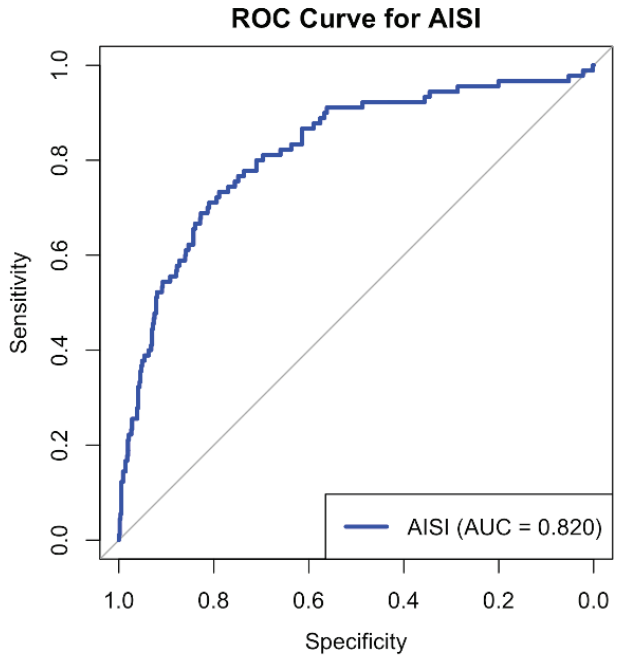


**Figure 1.** Receiver operating characteristic curve for the aggregate index of systemic inflammation (AISI) in predicting 30-day mortality.

Sensitivity was 62.1% (95% CI: 42.3 - 79.3%) and specificity was 88.6% (95% CI: 85.6 - 91%). The positive likelihood ratio (+LR) was 5.47 (95% CI: 3.82 - 7.83) and the negative likelihood ratio (-LR) was 0.43 (95% CI: 0.27 - 0.69) (Table 4).

## Discussion

This study demonstrated that the AISI is an independent predictor of 30-day mortality in acute ischemic stroke patients. Higher AISI values were significantly associated with increased mortality risk, supporting its potential role in risk stratification.

Inflammation plays a pivotal role in the pathophysiology of AIS. Following an ischemic event, a cascade of inflammatory responses is initiated, contributing to both immediate and delayed neuronal injury. The initial phase involves the activation of resident immune cells, particularly microglia, which rapidly respond to ischemic insult by adopting a pro-inflammatory phenotype. This activation leads to the release of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), exacerbating neuronal damage [13]. Concurrently, the ischemic environment disrupts the blood-brain barrier (BBB), increasing its permeability and allowing peripheral immune cells, including neutrophils and monocytes, to infiltrate the brain parenchyma. These infiltrating cells further amplify the inflammatory milieu through the production of reactive oxygen species (ROS) and additional cytokines, leading to oxidative stress and further compromise of neuronal integrity [14]. Recent studies have highlighted the dual role of neuroinflammation in AIS, where it can be both detrimental and beneficial. While acute inflammation contributes to tissue damage, it also facilitates debris clearance and tissue repair processes. The balance between these opposing effects is critical in determining clinical outcomes [15].

**Table 4.** Receiver operating characteristic analysis for aggregate index of systemic inflammation in predicting 30-day mortality.

| Parameter | AUROC | Criterion | Sensitivity (95% CI) | Specificity (95% CI) | +LR (95% CI) | -LR (95% CI) |
|---|---|---|---|---|---|---|
| AISI | 0.820 (0.770 - 0.870) | 512.2 | 62.1 (42.3 - 79.3) | 88.6 (85.6 - 91) | 5.47 (3.82 - 7.83) | 0.43 (0.27 - 0.69) |

AUROC: Area Under Receiver Operating Characteristic Curve; +LR: Positive Likelihood Ratio; -LR: Negative Likelihood Ratio; CI: Confidence Interval

The AISI is a composite inflammatory marker incorporating neutrophil, monocyte, lymphocyte, and platelet counts, reflecting a broader spectrum of immune activation. AISI has been investigated in various clinical conditions, including hypertension, where it has been linked to increased cardiovascular risk, and idiopathic pulmonary fibrosis, where it correlates with disease severity and progression [16,17]. Studies have also explored its role in COVID-19-related inflammation and chronic obstructive pulmonary disease (COPD), suggesting its potential as a generalizable marker of systemic immune activation [18,19].

In the context of AIS, the prognostic value of AISI remains relatively underexplored. However, recent evidence by Göçmen et al. demonstrated that stroke patients exhibit significantly elevated AISI levels compared to healthy controls [11]. Their findings suggest that AISI is particularly high in hemorrhagic stroke cases and that an AISI threshold above 507.45 is associated with increased mortality risk. These findings are in agreement with the results of the present study, where AISI was identified as an independent predictor of 30-day mortality in AIS patients. The ability of AISI to capture multiple inflammatory pathways may explain its prognostic utility, offering a more comprehensive risk stratification tool compared to traditional inflammatory markers. Furthermore, the implementation of AISI in clinical practice, especially in emergency departments and stroke units, may offer practical advantages. As a rapid and cost-effective inflammatory

marker derived from routine hematological tests, AISI could be integrated into early risk stratification protocols. Identifying high-risk AIS patients upon admission may support timely clinical decision-making and resource allocation. Future multicenter studies should explore the generalizability of AISI across diverse patient populations and healthcare settings to better define its clinical utility. While AISI has shown promise as a prognostic indicator, further studies are required to determine its relative performance compared to other inflammation-based indices and to assess its clinical applicability in routine stroke management.

## Limitations of the study

First, its retrospective design may introduce selection bias and limit the ability to establish causal relationships. Second, as a single-center study, the findings may not be generalizable to broader populations, and external validation in multicenter cohorts is needed. Third, the study lacks a control group, which limits the ability to compare AISI levels in stroke patients with those in healthy individuals or patients with other neurological conditions. Fourth, this study focused specifically on AISI and did not compare it with other inflammatory indices such as NLR, PLR, or SII. Future research should evaluate the relative prognostic performance of AISI alongside these markers. Finally, long-term outcomes beyond 30 days were not evaluated, and further studies are required to determine the prognostic value of AISI over extended follow-up periods.

In conclusion, this study demonstrates that the AISI is an independent predictor of 30-day mortality in acute ischemic stroke patients. The significant association between higher AISI values and increased mortality risk highlights the potential role of systemic inflammation in stroke prognosis. As an easily accessible hematological marker, AISI could contribute to early risk stratification in clinical practice. However further prospective, multicenter studies are needed to validate its prognostic utility.

## Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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## Ethical Approval

This study was approved by the Gazi Yaşargil Education and Research Hosptial's ethics committee (ethics committee ruling number: 349, date: 07.02.2025).

## Authors' contribution

NES: Conceptualization, Methodology, Writing, Original Draft. MÖ: Data Collection, Formal Analysis, Supervision, Writing, Review & Editing.Both authors have read and approved the final version of the manuscript.

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