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A novel predictor in patients with coronary chronic total occlusion: systemic immune-inflammation index: a single-center cross-sectional study

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SUMMARY

OBJECTIVE: Severe inflammation is reportedly associated with subsequent cardiovascular events, including in patients with coronary artery disease. This study aimed to examine the prognostic value of systemic immune-inflammation index and determine mortality and clinical outcomes in patients with chronic coronary total occlusion.

METHODS: Our study evaluated 366 consecutive coronary total occlusion patients. The clinical end points were all-cause mortality and major adverse cardiovascular events, which include target vessel revascularization, myocardial infarction, and cerebrovascular events during 105 months follow-up.

RESULTS: The study findings showed 59 (16.1%) all-cause death, 22 (6%) target vessel revascularization cases, 32 (8.7%) myocardial infarction cases, and 13 (3.6%) cerebrovascular events cases, with a median follow-up of 49 months (26–74). Multivariate logistic regression analysis showed that systemic immune-inflammation index was not associated with target vessel revascularization, myocardial infarction, and cerebrovascular events. Multivariate Cox regression analysis found systemic immune-inflammation index to be associated with all-cause death. Kaplan-Meier analysis showed a lower survival rate and myocardial infarction-free survival time in patients with higher systemic immune-inflammation index scores.

CONCLUSION: Although systemic immune-inflammation index is a preferable tool for the detection of mortality, it failed to give adverse outcomes. Larger multicenter studies are thus warranted to investigate the effect of systemic immune-inflammation index on clinical outcomes.

KEYWORDS: Inflammation. Inflammation mediators. Coronary artery disease. Prognosis. Atherosclerosis.

INTRODUCTION

Coronary chronic total occlusion (CTO) is defined as occlusion of coronary artery with Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow lasting longer than 3 months in the distal segment of the completely occluded vessel due to atherosclerosis[1]. CTO lesions such as fibrocalcific and thrombotic plaques have been reported in approximately one-third of patients undergoing diagnostic coronary angiography[2].

Coronary chronic total occlusion is associated with poor clinical outcomes, such as ischemia, heart failure, and increased risk of death[3-5]. Moreover, prediction of clinical events in CTO, particularly inflammation, has always been a topic of interest.

In the literature, blood markers have been used to investigate potential complications in patients with CTO[6]. However, an easily measurable marker is still needed in practice for the prediction of clinical events. In addition to routinely used scoring systems, some researchers have used hematological markers for predicting future events as well as comorbidities and risk factors in coronary artery disease (CAD)[7-8].

Systemic immune-inflammation index (SII), which is calculated based on peripheral lymphocyte, neutrophil, and platelet counts, is a recently developed index used for concurrent evaluation of immune and inflammatory responses. SII has been reported to predict adverse cardiovascular events (CVEs) in CAD patients[9]. It has been shown to be a marker for predicting clinical events in patients with acute myocardial infarction (MI)[10]. However, the relationship between SII and clinical outcomes in CTO patients remains unclear. The present study aimed to investigate the prognostic significance of SII as a new inflammatory marker and determine its relationship with cardiovascular clinical outcomes in CTO patients.

METHODS

Study design

This was a single-center, retrospective, and cross-sectional study. All-cause mortality was accepted as the primary end point, while target vessel revascularization (TVR), recurrent

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myocardial infarction (MI), and cerebrovascular events (CVEs) were considered secondary end points. Demographic and clinical characteristics including age, gender, follow-up period, clinical outcomes, and relevant laboratory values were retrieved from hospital records.

Subjects

Patients who underwent routine angiography for CAD and were incidentally diagnosed with CTO in our clinic between 2011 and 2020 were included in the study. Patients with hematological diseases, systemic inflammatory diseases, malignancies, chronic kidney diseases, chronic liver diseases, heart failure with ejection fraction (EF) <40%, and acute or chronic infections were excluded from the study (Figure 1A). Each patient or their family was informed about the study criteria, both verbal and nonverbal ways. The study protocol was approved by the Local Ethics Committee, and the study was conducted in accordance with the ethical rules for human experimentation stated in the Declaration of Helsinki (2013).

Protocol

Angiograms and clinical data of patients were retrieved from hospital databases. Angiograms were analyzed by three independent operators experienced in angiography.

Outcomes and follow-up

All-cause mortality was defined as any death recorded from the date of enrollment to the date of the last follow-up visit. Time to TVR was defined as the time from the opening of the target vessel to thrombus or restenosis formation in the vessel. Time to MI was defined as the time to the development of the first MI after the CTO procedure. Time to CVE was defined as the time to the first ischemic or hemorrhagic stroke attack after the CTO procedure.

Additional definitions

Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2. Hypertension (HT), dyslipidemia, and diabetes mellitus (DM) were defined according to the 10th Revision Codes of the *International Classification of Diseases*.

Blood samples and inflammatory indexes

Blood samples were analyzed using a hematology analyzer (Abbott Cell-Dyn 3700, IL, USA). SII was calculated using the following formula: neutrophil count × platelet count / lymphocyte counts[11].

Statistical analysis

Data were analyzed using SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables. Continuous variables were expressed as mean±standard deviation (SD) or median (interquartile range), and categorical variables were expressed as percentages. Multiple groups were compared using one-way analysis of variance (ANOVA) test or Kruskal-Wallis test, and categorical variables were compared using chi-square test or Fisher's exact test as appropriate. Multivariate logistic regression was performed to examine the association between SII and clinical outcomes. The SII values transformed by the natural logarithm were used in the models due to skewed distributions. A $p<0.05$ was considered statistically significant. Cox regression analysis was performed to identify the predictors of all-cause mortality. Clinical outcomes were assessed by the Kaplan-Meier method.

RESULTS

A total of 366 patients (69.4% male) were enrolled in the study, with a mean age of 62.26±11.09 years. Median follow-up was 49 (26–74) months. Patients were divided into three tertiles based on the SII levels as follows: 340.84±84.65 in tertile 1 (lower), 620.19±86.44 in tertile 2 (middle), and 1314±748.94 in tertile 3 (upper). Baseline clinical characteristics, outcomes, and laboratory findings of the patients according to SII tertiles are shown in Table 1. Patients in the upper SII group were older and had a higher prevalence of DM and all-cause mortality (Table 1). The upper and middle SII values were positively associated with higher admission white blood cell count, platelets levels, and neutrophils levels and were negatively associated with lower admission hemoglobin, lymphocytes, serum albumin, and triglycerides levels (Table 1). The prevalence of all-cause mortality was significantly higher among patients in the upper SII group when compared to patients in the lower SII group (Figure 1B).

Ln SII and Ln WBC levels were not associated with the resulted clinical outcomes (Table 1). In the Cox regression analysis, SII, age, and albumin level were found to be predictors of mortality (Table 1). The upper SII group had a higher incidence of all-cause mortality and MI, and significant differences between Kaplan-Meier curves were measured using the log-rank test (Figure 2).

DISCUSSION

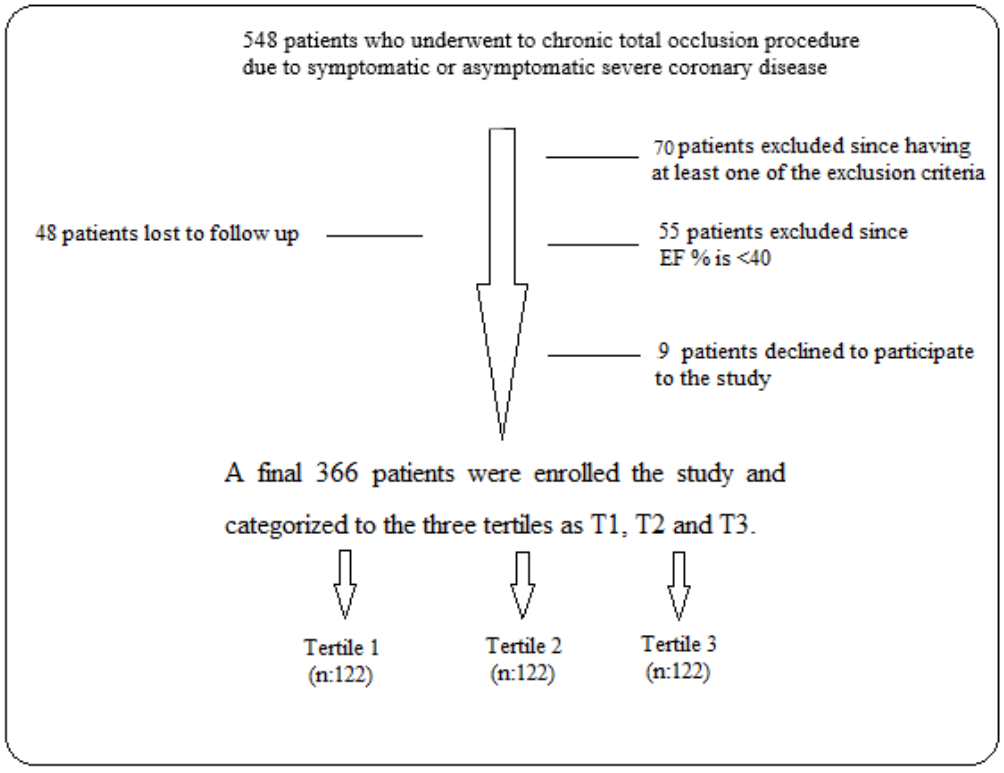
This cohort study was performed in order to determine if SII is independently associated with risks for all-cause death, TVR,

Table 1. Clinical characteristics and outcomes of the patients.

	Total (N=366)	Tertile 1 (N=122)	Tertile 2 (N=122)	Tertile 3 (N=122)	p
Age	62.26±11.09	60.46±10.57	62.39±10.49	63.94±11.95	**0.049**
Male	254 (69.4%)	89 (73%)	89 (73%)	76 (62.3%)	0.114
Hypertension	131 (35.8%)	37 (30.3%)	41 (33.6%)	53 (43.4%)	0.084
Diabetes mellitus	111 (30.3%)	36 (29.5%)	25 (20.5%)	50 (41%)	**0.002**
All-cause death	59 (16.1%)	10 (8.2%)	22 (18%)	27 (22.1%)	**0.01**
Myocardial infarction	32 (8.7%)	10 (8.2%)	6 (4.9%)	16 (13.1%)	0.074
Target vessel revascularization	22 (6%)	8 (6.6%)	6 (4.9%)	8 (6.6%)	0.824
Cerebrovascular event	13 (3.6%)	2 (1.6%)	4 (3.3%)	7 (5.7%)	0.22
Follow-up period (months)	49 (26–74)	46 (26–80)	55.5 (29.75–75)	40 (19–67.2)	**0.02**
Laboratory findings of the patients					
White blood cell count (×10³ µL)	9.58±2.55	8.27±2.28	8.44±1.91	10.45±2.81	**<0.001**
Hemoglobin (g/dl)	13.74±1.89	14.1±1.74	13.95±1.82	13.17±1.98	**<0.001**
Platelets (×10³ µL)	257.77±84.64	218.31±66.45	251.19±61.15	303.81±98.52	**<0.001**
Lymphocytes (×10³ µL)	2.3±0.87	2.84±0.97	2.17±0.63	1.9±0.7	**<0.001**
Neutrophils (×10³ µL)	5.83±2.28	4.39±1.29	5.39±1.34	7.7±2.54	**<0.001**
GFR (mL/min/1.73m²)	85.24±24.61	87.45±24.18	87.13±22.92	81.15±26.29	0.079
Glucose (mg/dl)	143.85±85.24	141.14±75.57	135.09±62.7	155.33±82.19	0.091
Creatine (mg/dl)	1.02±0.72	0.96±0.55	1.01±0.77	1.08±0.82	0.4
Serum albumin (g/dl)	3.64±0.46	3.75±0.42	3.65±0.41	3.51±0.5	**<0.001**
SII (P*N/L)	758±599	340.84±84.65	620.19±86.44	1314±748.94	**<0.001**
Multivariable logistic regression analysis according to the clinical outcomes#					
		Ln SII adjusted		Ln WBC adjusted	
Outcome	n	OR (95%CI)	p	OR (95%CI)	p
TVR	22	0.96 (0.19–4.86)	0.963	0.8(0.16–4.02)	0.790
MI	32	2.52 (0.63–10)	0.192	2.34 (0.59–9.28)	0.226
CVE	13	6.41 (0.78–52)	0.082	2.21 (0.26–18.2)	0.461
Cox proportional hazard regression analysis of all-cause death regression models during 105 months of follow-up in the study population					
		Univariate		Multivariate	
		OR (95%CI)	p	OR (95%CI)	p
Age		1.065 (1.040–1.091)	**<0.001**	1.051 (1.025–1.077)	**<0.001**
Sex		1.24 (0.727–2.113)	0.430		
Hypertension		1.66 (0.996–2.767)	**0.052**	1.075 (0.624–1.850)	0.795
Diabetes mellitus		1.170 (0.682–2.007)	0.568		
Dyslipidemia		0.955 (0.346–2.637)	0.930		
Chronic kidney disease		3.265 (1.603–6.647)	0.001	1.340 (0.594–3.026)	0.481
Smoker		0.681 (0.361–1.284)	0.235		
Albumin		0.252 (0.153–0.415)	**<0.001**	0.418 (0.230–0.761)	**0.004**
Ln SII		5.842 (2.242–15.225)	**<0.001**	2.822 (1.028–7.748)	**0.044**

CI: confidence interval; OR: odds ratio.Bold indicates statistically significant value.
#Ln SII or Ln WBC adjusted with age, sex, hypertension, diabetes mellitus, dyslipidemia, chronic renal failure, and smoking in multivariable logistic regression analysis.

A



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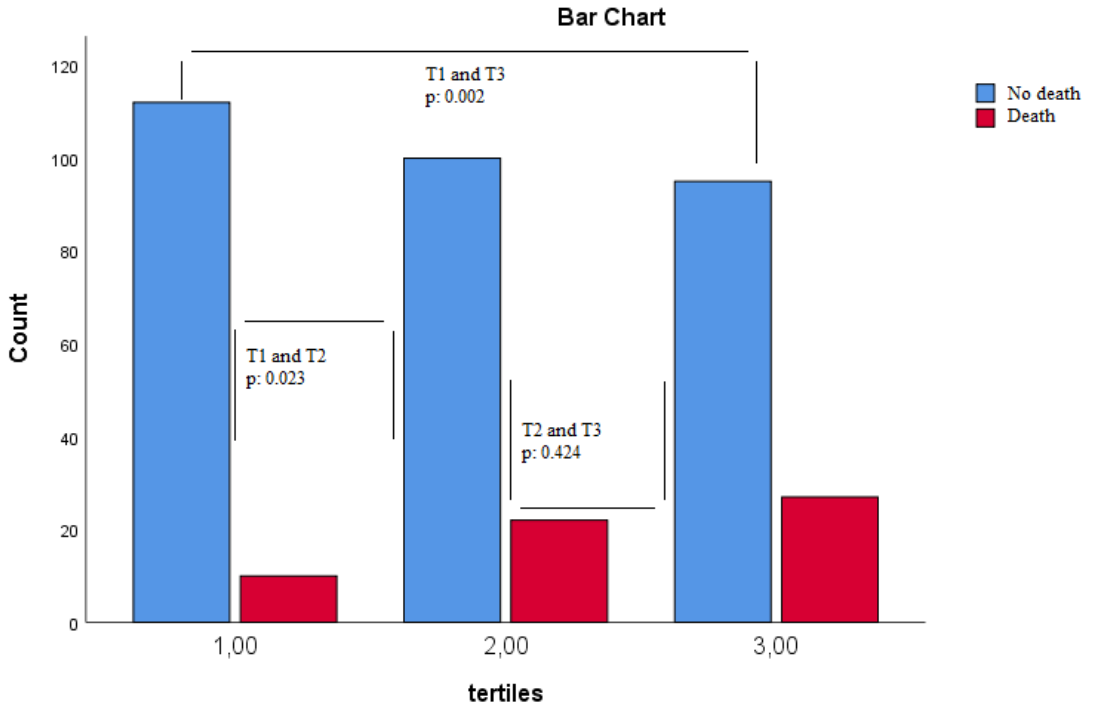

Figure 1. Study flowchart and comparison of groups according to the all-cause death.

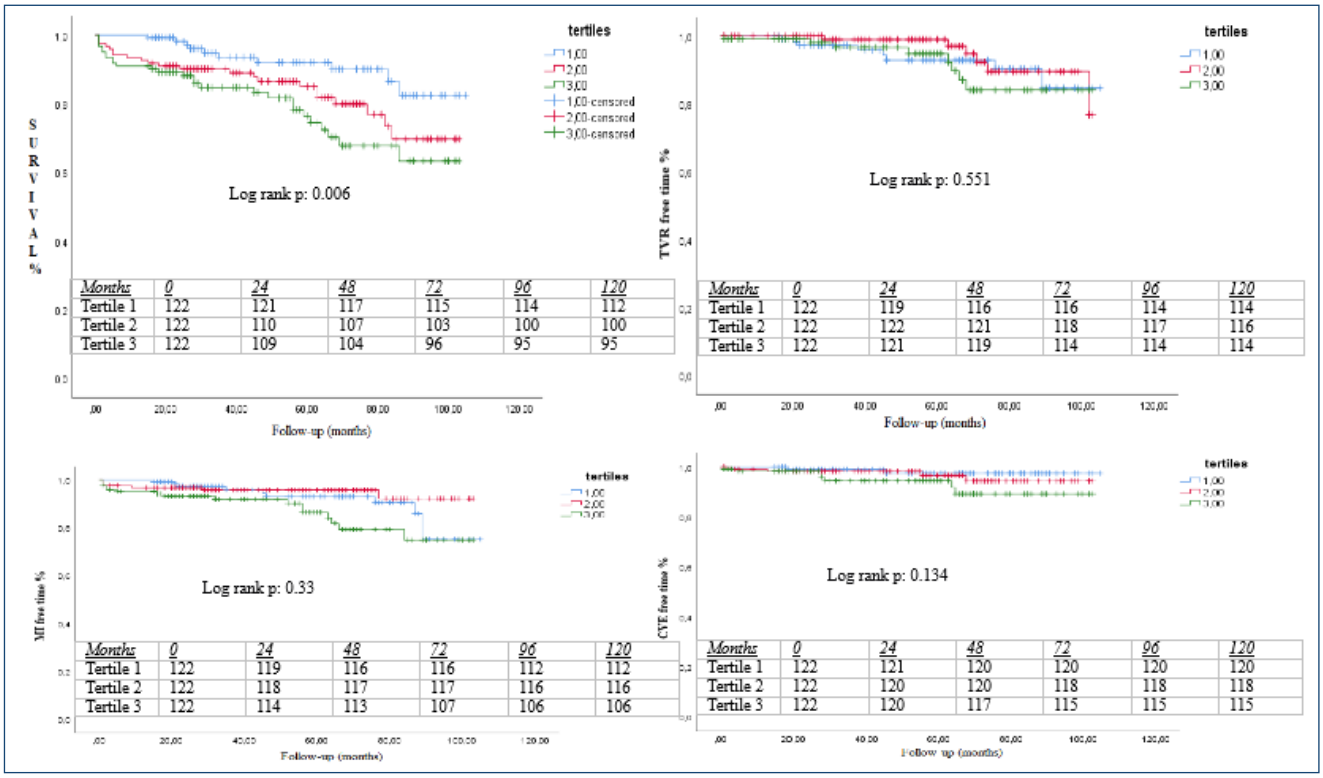

Figure 2. Kaplan-Meier analysis of groups according to the survival, target vessel revascularization (TVR), myocardial infarction (MI), and cerebrovascular events (CVEs).

MI, and CVE in CTO patients. This study presented two main findings: (i) SII was found to be an indicator of survival and (ii) SII was not associated with TVR, MI, and CVE.

Atherosclerosis is strongly associated with inflammation[12,13]. Moreover, atherosclerotic plaque includes a sophisticated interaction between innate immunity and adaptive immunity[14,15]. Components of innate immune system including neutrophils and lymphocytes initiate inflammation in the endothelium. Neutrophils may release pro-oxidant and pro-inflammatory mediators and thereby cause the formation of neutrophil extracellular traps, which have a potential to produce plaque formation and enhance thrombus balance[16]. Platelets also play an important role in the pathogenesis of CAD and acute coronary syndrome[17]. Occlusive platelets aggregate and endothelial damage contributes to the etiology of atherosclerosis. Platelets are biomarkers of CAD that help predict the prothrombotic potential and blood vulnerability[18]. Inflammatory markers with one or two components are relatively poor predictors of prognosis in atherosclerotic diseases[19]. Hence, SII, an inflammatory index calculated from inflammatory cells (e.g., neutrophils, platelets, and lymphocytes), might more comprehensively indicate the balanced status of immune-inflammatory conditions.

Clinical data linking inflammatory markers with the presence of a CTO lesion are highly limited and, to the best of our knowledge, there are very few studies on this subject. Gebhard et al. investigated the prognostic significance of preprocedural leukocyte count and its power to predict cardiovascular risk in CTO patients[20]. Although the study included a larger cohort of 1262 patients (475 of whom had at least a CTO lesion) when compared to our study, the clinical outcomes such as death and adverse cardiac events were evaluated based on only the leukocyte count. In our study, however, these clinical outcomes were investigated with a stronger multiparameter model (i.e., SII). Moreover, in the same study, leukocyte count, age, GFR, and Syntax score were found to be significant predictors of all-cause mortality, while only leukocyte count and Syntax score were significant predictors of major adverse cardiac events (MACEs). In our study, SII, age, and albumin level were associated with all-cause mortality. In addition, unlike in that study, no correlation was found between SII and leukocyte count and adverse cardiac clinical outcomes such as TVR, MI, and CVE. In a study by Okuya et al., a relationship was found between serum uric acid level and TVR[21]. In our study, however, uric acid level was not studied. In another study, a correlation was shown between neutrophil-to-lymphocyte ratio (NLR) and

coronary dissection, instant restenosis, coronary slow-flow phenomenon (CSFP), and MACE ratio in CTO patients[22].

It is difficult to show the specific mechanism on how inflammation affects prognosis in patients with CTO from the results of this observational study. It is known that MI indirectly causes a systemic inflammatory response[23]. Given the low rates of successful percutaneous coronary intervention (PCI) in CTO patients, both the existing ischemia and the inflammation indirectly caused by this ischemia affect the clinical course in CAD and may worsen the prognosis[24]. In our study, however, functional severity of ischemic burden was not determined and thus no causal relationship could be established among MI, inflammatory status, and prognosis in CTO patients.

Our study has some strength. A key finding was that our study was the first to reveal the association of SII with mortality and clinical outcomes including TVR, MI, and CVE in patients CTO, in which SII can be regarded as a mixed indicator of three blood cells in the "cross-talk" of thrombocytosis, inflammation, and immunity in the pathological process of CVEs when compared to other types of blood cells. Second, the follow-up period of the study is relatively long. Finally, the patient population in the study was highly heterogeneous and the study did not focus on a specific patient group but included a wide range of patients such as those who underwent PCI, those who underwent bypass surgery, and those who had a failed CTO intervention and were medically followed up due to SAP, USAP, NSTEMI, and STEMI.

Certain design limitations are also inherent in the present study. First, as a single-center, retrospective study with a small patient cohort, unknown confounding factors might have affected the outcomes regardless of adjustments. Second, only a single value of preprocedural SII was used in the study and no data were available regarding the changes in SII value during subsequent follow-up. Last but the most important limitation, prominent markers of inflammation such as interleukin 6 (IL-6), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were not studied.

CONCLUSIONS

The results indicated that higher SII is independently associated with higher future risk of all-cause mortality in CTO patients, while its relationship with clinical outcomes was not shown. SII improved the risk of mortality compared to traditional risk factors. SII could be used as an easy and practical indicator for identifying high-risk CTO patients. Further multicenter and larger scale studies are needed to perform clinical risk assessment of CTO.

AUTHORS' CONTRIBUTIONS

MD: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **MÖ**: Conceptualization, Visualization, Data curation, Investigation, Methodology, Supervision, Validation.

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