Original Article

Prognostic value of the pretreatment systemic immune-inflammation index (SII) in patients with non-small cell lung cancer: a meta-analysis

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Background: The objective of this study is to explore the association between the pretreatment systemic immune-inflammation index (SII) and prognosis in non-small cell lung cancer (NSCLC) patients.

Methods: A systemic literature search of PubMed, EMBASE, the Web of Science, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang, VIP and SinoMed databases was performed from January 1, 1966 to April 15, 2019, to identify potential studies that assessed the prognostic role of the pretreatment SII in NSCLC. The hazard ratio (HR) and 95% confidence interval (CI) were combined to evaluate the correlation of the pretreatment SII with overall survival (OS), disease-free survival (DFS), progression-free survival (PFS) and cancer-specific survival (CSS) in NSCLC patients.

Results: A total of 9 studies involving 2,441 patients were eventually included. An elevated pretreatment SII indicated significantly poorer OS (HR =1.88, 95% CI: 1.50–2.36; P<0.001) with high heterogeneity (I^2=60.6%, P=0.019), DFS/PFS (HR =2.50, 95% CI: 1.20–5.20; P=0.014) with high heterogeneity (I^2=58.2%, P=0.092) and CSS (HR =1.852, 95% CI: 1.185–2.915; P=0.007). Subgroup analyses further verified the above results. In addition, compared with the neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR), the SII showed a much higher prognostic value in NSCLC.

Conclusions: The pretreatment SII may serve as a useful prognostic indicator in NSCLC and contribute to prognosis evaluation and treatment strategy formulation. However, more well-designed studies are warranted to verify our findings.

Keywords: Systemic immune-inflammation index (SII); non-small cell lung cancer (NSCLC); prognosis; meta-analysis

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Introduction

Lung cancer is the most common tumor globally and is characterized by insidious early symptoms, rapid progression and a poor prognosis (1). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases (2). In 2016, the number of patients who died from lung cancer increased to 1.7 million, making it the third leading cause of death worldwide (2,3). Despite developments in the early diagnosis and treatment of lung cancer, the prognosis remains poor due to local recurrence or distal metastases (4).

Clinical studies have demonstrated that the inflammatory response plays an important role in tumor progression,

invasion and metastasis by upregulating inflammation to accelerate tumor angiogenesis and reduce anticancer activities (5). In recent years, inflammatory biomarkers, such as C-reactive protein (CRP), the platelet to lymphocyte ratio (PLR), the neutrophil to lymphocyte ratio (NLR), and the monocyte to lymphocyte ratio (MLR), have been proven to be correlated with cancer prognosis (6). The systemic immune-inflammation index (SII) is a new inflammatory biomarker and is defined as the platelet count × neutrophil count/lymphocyte count (7). According to previous studies, the SII may have high prognostic value in cancer patients (8). However, there still exists no consensus among the pretreatment SII and survival of NSCLC patients. Therefore, we performed the current meta-analysis to determine the prognostic value of the pretreatment SII in NSCLC.

Methods

Search strategy

Relevant studies were searched through PubMed, EMBASE, the Web of Science, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang, VIP and SinoMed databases from the date of establishment until April 15, 2019. The following terms were used: "lung", "pulmonary", "tumor", "cancer", "carcinoma", "neoplasm", "systemic immune-inflammation index" and "SII", and the search strategy used both MeSH terms and free-test words to increase the sensitivity. Furthermore, the references listed in the included studies were also evaluated.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (I) articles assessing the relation between the pretreatment SII and the survival of patients diagnosed with NSCLC pathologically; (II) neutrophil, platelet and lymphocyte counts were measured before any treatments, including neoadjuvant chemoradiotherapy, chemoradiotherapy, surgery and targeted therapy; (III) no clinical or laboratory evidence of infection, hematological or autoimmune diseases; (IV) no use of anti-inflammatory or immunosuppressive drugs; (V) the SII was defined as the neutrophil count × platelet count/lymphocyte count; (VI) the outcomes of interest included overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS) or progression-free survival (PFS) with hazard ratios (HRs) and the corresponding 95% confidence intervals (95% CIs); and (8) Newcastle-Ottawa quality assessment scale (NOS) ≥6 (9).

Exclusion criteria were as follows: (I) letters, meta-analyses, editorials, expert opinions, case reports and reviews; (II) nonhuman studies; and (III) if the data were duplicated or overlapped, only the latest study was included.

Study selection

All searched results were evaluated according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (10). First, titles and abstracts were screened to identify related studies. Then, full tests were reviewed carefully. The study selection was completed by two independent investigators (Yan Wang and Yina Li).

Data extraction and quality assessment

Two authors (Yan Wang and Yina Li) extracted data independently, and any disagreement was resolved by discussion until a consensus was reached. The following information was collected: the name of the first author, year of publication, study period, country, sample size, sex tumor-node-metastasis (TNM) stage, treatment, follow-up period, SII cut-off, outcome, source of HR and HR with 95% CI. Data were collected by using an excel sheet (Microsoft Corporation).

Quality assessment of the included studies was performed according to the NOS by two independent researchers (Yan Wang and Yina Li) (9). Studies with a score of 6 or higher were defined as high-quality studies.

Statistical analysis

All analyses were conducted with STATA (version 12.0; Stata Corporation). HRs and 95% CIs were combined to evaluate the association of the pretreatment SII with prognosis in patients with NSCLC. They were either directly extracted from each study whenever available estimated from Kaplan-Meier (K-M) curves according to the methods reported by Tierney *et al.* (11). The Higgins I^2 statistic and Cochran's Q test were used to evaluate heterogeneity among studies. Significant heterogeneity was defined as $P<0.10$ and/or $I^2>50\%$, and when significant heterogeneity was observed, the random-effects model was used; otherwise, the fixed-effects model was used (12). Begg's funnel plot and Egger's linear regression test were

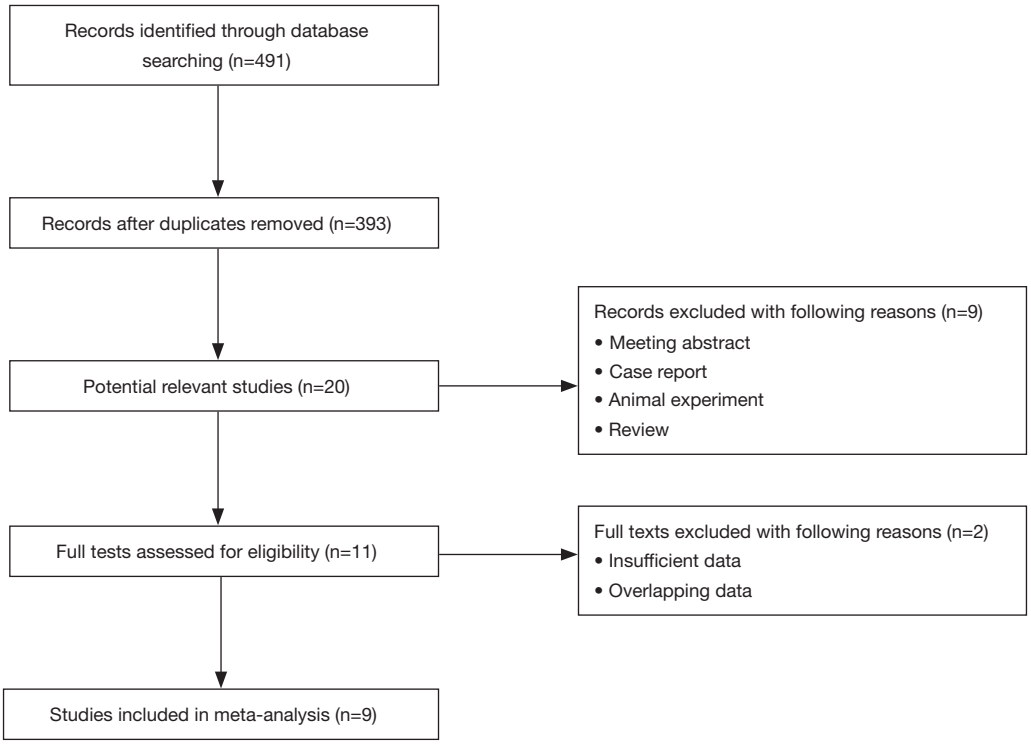

Figure 1 Flow diagram of the literature review.

performed to evaluate publication bias, and significant publication bias was defined as P<0.05 (13).

Results

Characteristics of the included studies

The flow diagram is presented in *Figure 1*. The electronic search yielded 491 studies. After removing duplicates and screening titles and abstracts, 11 studies were assessed by full-tests for eligibility. Finally, a total of 9 articles involving 2,441 patients were included (14-22).

The included studies were all retrospective and published during 2017–2019, with a sample size between 30 and 569. One of the 9 studies was conducted in Japan (18), and the others were conducted in China (14-17,19-22). The SII cut-off values ranged from 395.4 to 1,218.81. More detailed information is shown in *Table 1*.

Meta and subgroup analysis results

A total of 7 studies involving 2,070 patients reported the association of the pretreatment SII with OS in NSCLC patients. The results showed that a high pretreatment SII indicated poor OS (HR =1.88, 95% CI: 1.50–2.36; P<0.001) with high heterogeneity (I^2=60.6%, P=0.019) (*Figure 2*). Subgroup analyses based on the TNM stage and treatment further supported the above results and demonstrated that the TNM stage and treatment method were both potential causes of the significant heterogeneity (*Table 2*).

Three studies involving 351 patients reported the correlation of the pretreatment SII with DFS/PFS. The combined HR was 2.50 (95% CI: 1.20–5.20; P=0.014) with high heterogeneity (I^2=58.2%, P=0.092), which indicated that an elevated pretreatment SII was a negative predictor of DFS/PFS in NSCLC patients (*Figure 3*) (*Table 2*).

Only one study reported the relation between the pretreatment SII and CSS in NSCLC patients and indicated that patients with a high pretreatment SII were more likely to have worse CSS (HR =1.852, 95% CI: 1.185–2.915; P=0.007) (*Table 2*).

Comparison of the prognostic values of the SII with the NLR and PLR

Several studies have also reported an association of the NLR and PLR with OS or DFS/PFS. After comparing the

Table 1 Basic characteristics of included studies

Author	Year	Study period	Study design	Country	Sample size	Sex (F/M)	TNM stage	Treatment	Follow-up, median, [range]	Cut-off	Outcome	Source of HR	NOS score
Tong (14)	2017	2006–2012	Retrospective	China	332	126/206	III	Mixed	22 [2–72]	660	OS	R	8
Gao (15)	2018	2009–211	Retrospective	China	410	143/267	I–IIIA	Surg	54 [3–96]	395.4	OS	R	7
Guo (16)	2018	2013–2016	Retrospective	China	140	45/95	IIIB–IV	CRT	NR	521	OS/PFS	R	6
Li (17)	2019	2013–2016	Retrospective	China	310	148/162	IV	Mixed	NR	1,218.81	OS	R	7
Tomita (18)	2018	2008–2012	Retrospective	Japan	341	168/173	I–III	Surg	NR	471.2	CSS	R	7
Li (19)	2018	2010–2012	Retrospective	China	181	54/127	I–III	Surg	NR	689	OS/DFS	R	8
Wu (20)	2018	2012–2015	Retrospective	China	128	30/98	III–IV	CT	36 [1–62]	604.49	OS	R	7
Wang (21)	2018	2014–2015	Retrospective	China	30	14/16	I–II	Surg	NR	400	DFS	E	6
Guo (22)	2019	2006–2012	Retrospective	China	569	144/425	I–III	Surg	60.3 [0.9–146.7]	419.6	OS	R	7

F, female; M, male; TNM, tumor-node-metastasis; NR, not reported; CRT, chemoradiotherapy; Surg, surgery; CT, chemotherapy; OS, overall survival; PFS, progression-free survival; CSS, cancer specific survival; DFS, disease-free survival; R, reported; E, estimated; HR, hazard ratio; NOS, Newcastle-Ottawa Scale.

SII with the NLR and PLR in NSCLC patients, only the SII was significantly correlated with OS (HR =1.82; 95% CI: 1.41–2.35; P<0.001) and DFS/PFS (HR =1.96; 95% CI: 1.36–2.90; P<0.001) in NSCLC patients, which indicated that the SII was superior to the NLR and PLR in predicting the prognosis of NSCLC patients (*Table 3*).

Sensitivity analysis

Due to the significant heterogeneity among the included studies, a sensitivity analysis was performed, which showed that the pooled results were still stable after excluding any single study (*Figure 4*).

Publication bias

Begg's funnel plot (P>0.999) (*Figure 5*) was symmetric, and the P value of Egger's test was 0.636, which both indicated no significant publication bias.

Discussion

It is well known that the inflammatory response has a close relationship with cancer (23). In recent years, we have found that inflammatory infiltration plays an important role in the development of cancers. In NSCLC, many inflammatory cells, including tumor-associated macrophages, tumor-infiltrating lymphocytes, tumor-associated neutrophils and T, B, and NK cells, compose the tumor stroma (24). These cells also contribute to the enlargement and metastasis of cancer tissue through the cytokines they secrete (25). For example, CXCR2 and CXCL8 can promote the processes of angiogenesis, tumor growth and cell proliferation (26). Due to the convenience, low cost and rapidity of the detection of systemic inflammatory markers, studies on inflammatory biomarkers of cancer prognosis are increasing. There are two types of inflammatory markers: the first type is derived from CRP and ALB, and the second type is derived from leukocyte-related inflammation indexes, such as the PLR, NLR, and SII. The latter have been proven to be clinically important in many types of cancer, such as lung cancer, hepatic carcinoma, gastrointestinal cancer and colorectal cancer (27-30). The SII, defined as platelet × neutrophil/lymphocyte, is a combination of the PLR and NLR and has been demonstrated to show high prognostic value in some malignant solid tumors (31-34).

By reviewing studies about the SII and the prognosis of NSCLC patients, we found that a higher SII indicated

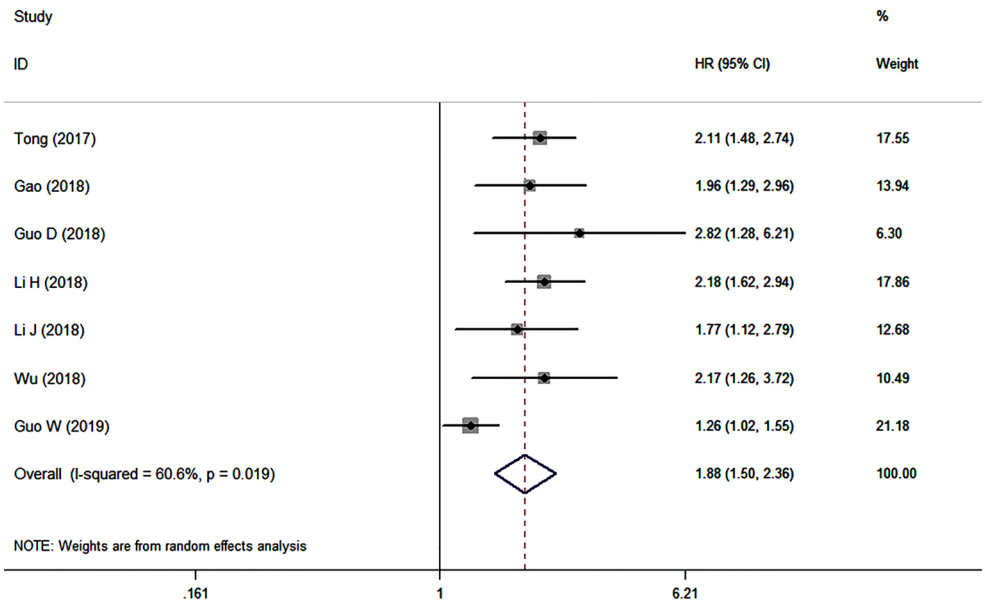

Figure 2 Forest plot of the association between pretreatment SII and overall survival. SII, systemic immune-inflammation index.

Table 2 Meta and subgroup analyses

Analysis	No. of studies	HR (95% CI)	P values for HR	I^2 (%)	P value for heterogeneity
Overall survival	7	1.88 (1.50–2.36)	<0.001	60.6	0.019
TNM stage					
Advanced stage	4	2.18 (1.80–2.65)	<0.001	0.0	0.926
Mixed	3	1.55 (1.15–2.11)	0.004	55.8	0.104
Treatment					
Mixed	2	2.14 (1.73–2.65)	<0.001	0.0	0.875
Surgery	3	1.55 (1.15–2.11)	0.004	55.8	0.104
Chemoradiotherapy	2	2.36 (1.51–3.68)	<0.001	0.0	0.587
Disease-free survival/ progression-free survival	3	2.50 (1.20–5.20)	0.014	58.2	0.092
Cancer specific survival	1	1.852 (1.185–2.915)	0.007	–	–

TNM, tumor-node-metastasis; HR, hazard ratio; CI, confidence interval.

a worse prognosis. Several hypotheses may contribute to this consequence. Neutrophils secrete cytokines and chemokines, such as vascular endothelial growth factor (VEGF), to enhance tumor angiogenesis, promote circulating tumor cell adhesion and facilitate distant metastasis (35). Platelets can prevent circulating tumor cells from immune attack and help circulating tumor cells metastasize via blood transmission (36). Moreover, lymphocytes are involved in the acquired immune system, which is indispensable in the body immune defense and immune surveillance (37). Based on these mechanisms, a higher SII combined with increased counts of neutrophils or platelets or a decreased count of lymphocytes leads to enhanced tumor angiogenesis, adhesion, metastasis and poor immune clearance of cancer cells. Therefore, an elevated pretreatment SII is associated with poor outcomes

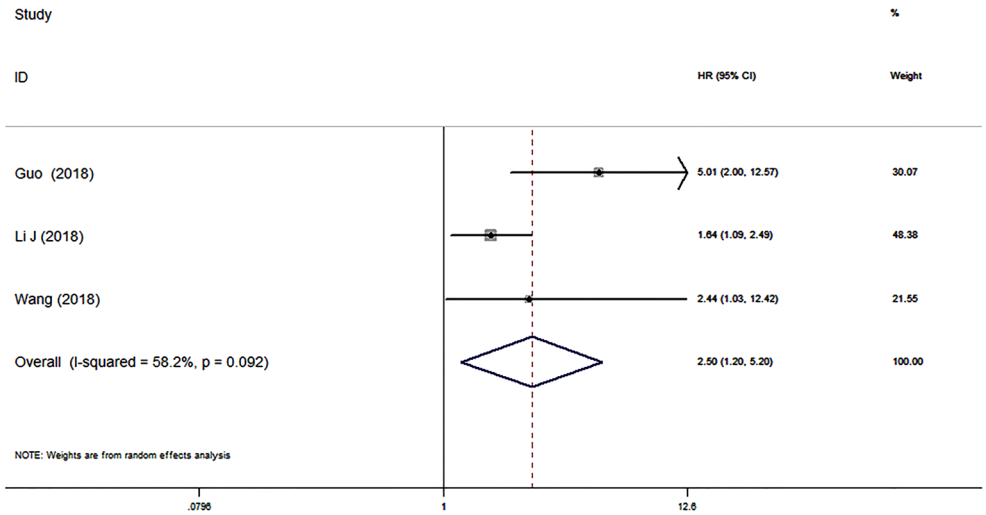

Figure 3 Forest plot of the association between pretreatment SII and disease-free survival/progression-free survival. SII, systemic immune-inflammation index.

Table 3 Comparison of prognostic values of SII with NLR and PLR

Variables	No. of studies	SII		NLR		PLR	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
OS	6	1.82 (1.41–2.35)	<0.001	1.15 (0.83–1.59)	0.395	1.16 (1.01–1.34)	0.042
DFS/PFS	2	1.96 (1.36–2.90)	<0.001	1.02 (0.71–1.47)	0.916	1.01 (0.66–1.55)	0.951

SII, systemic immune inflammation index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; HR, hazard ratio; CI, confidence interval; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival.

in cancer patients.

For patients with severe systemic immune inflammation, some immune checkpoint inhibitors (ICIs), such as nivolumab, pembrolizumab and atezolizumab, are strongly recommended for use, especially in advanced stage or metastatic patients (38,39). Previous studies have proved that ICIs in first-line or second-line treatment could improve the prognosis of advanced NSCLC patients compared with chemotherapy alone (40). Moreover, Mezquita *et al.* demonstrated the prognostic value of inflammatory indexes in ICI-treated patients. They introduced a novel index, the lung immune prognostic index (LIPI), which is based on a lactate dehydrogenase (LDH) level greater than the upper limit of normal and a derived neutrophil/(leukocyte minus neutrophil) (dNLR) ratio greater than 3, and reported that the pretreatment LIPI could serve as a useful indicator for predicting OS and PFS in NSCLC patients who were treated with ICIs (41). Unfortunately, no study has explored the prognostic significance of the SII in NSCLC patients who have received ICI therapy until now, which deserves further investigation in the future. Furthermore, it is also necessary to determine whether ICI treatment is beneficial for early-stage NSCLC patients.

The important clinical significance of the current research is that the pretreatment SII could not only predict the prognostic risks of NSCLC patients but also help develop treatment strategies. In detail, compared with patients with a low pretreatment SII, patients with a high pretreatment SII may be recommended for ICI therapy. However, more research is still needed to further determine the indications of ICI treatment for NSCLC patients.

Our study has certain shortcomings. First, only 9 retrospective articles involving 2,441 patients were included, which may cause bias due to the restricted sample size. Second, all included studies were from China or Japan; therefore, the prognostic value of the SII in NSCLC

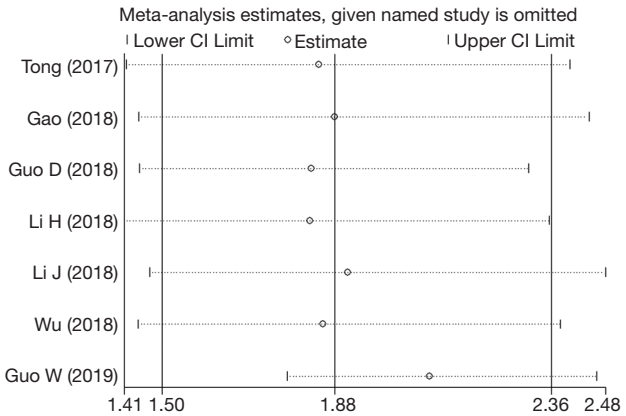

Figure 4 Sensitivity analysis of the association between pretreatment SII and overall survival. SII, systemic immune-inflammation index.

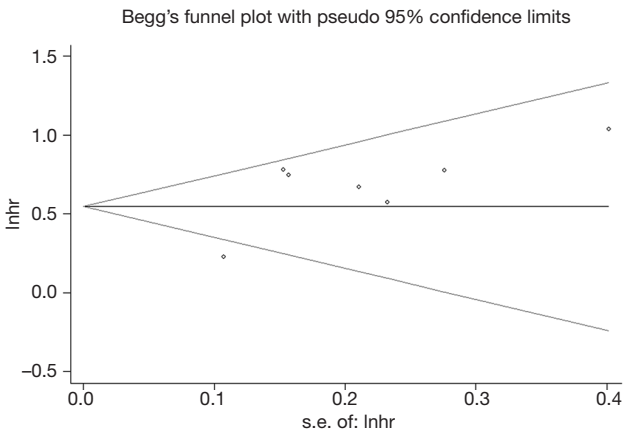

Figure 5 Begg's funnel plot of the association between pretreatment SII and overall survival. SII, systemic immune-inflammation index.

patients from other countries or regions remains unclear. Third, due to the lack of original data, we were unable to conduct more subgroup analyses based on other factors, such as sex, age, and comorbidities.

In conclusion, the pretreatment SII may serve as a useful prognostic indicator in NSCLC and contribute to prognosis evaluation and treatment strategy formulation. However, more prospective and well-designed studies are warranted to verify our findings.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: All procedures performed in studies that involved human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was not required. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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