INPLASY

Prognostic relevance of systemic immune-inflammation index (SII) in esophageal cancer patients receiving immune checkpoint inhibitors: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 June 2026 and was last updated on 15 June 2026.

INTRODUCTION

Review question / Objective The prognostic relevance of the systemic immune-inflammation index (SII) in esophageal cancer (EC) patients undergoing immune checkpoint inhibitor (ICIs) treatment remains unclear. This meta-analysis aimed to determine the prognostic impact of SII in this specific patient cohort.

Condition being studied (1) Patients were diagnosed with EC (including ESCC or EAC) through histopathological or cytological examination;
(2) Patients received treatment with ICIs, either as monotherapy or in combination with CT, RT, or TT;
(3) SII was calculated based on peripheral blood parameters (PLT × NEU / LYM) obtained prior to ICI treatment;
(4) Studies provided long-term survival data, including OS or PFS;
(5) HR and 95% CI for survival outcomes could be obtained directly from the literature or indirectly through calculation from available data.

METHODS

Participant or population (1) Patients were diagnosed with EC (including ESCC or EAC) through histopathological or cytological Wen;
(2) Patients received treatment with ICIs, either as monotherapy or in combination with CT, RT, or TT;
(3) SII was calculated based on peripheral blood parameters (PLT × NEU / LYM) obtained prior to ICI treatment;
(4) Studies provided long-term survival data, including OS or PFS;
(5) HR and 95% CI for survival outcomes could be obtained directly from the literature or indirectly through calculation from available data.

Intervention (1) Patients were diagnosed with EC (including ESCC or EAC) through histopathological or cytological examination;
(2) Patients received treatment with ICIs, either as monotherapy or in combination with CT, RT, or TT;
(3) SII was calculated based on peripheral blood parameters (PLT × NEU / LYM) obtained prior to ICI treatment;
(4) Studies provided long-term survival data, including OS or PFS;
(5) HR and 95% CI for survival outcomes could be obtained directly from the literature or indirectly through calculation from available data.

Comparator (1) Patients were diagnosed with EC (including ESCC or EAC) through histopathological or cytological examination;
(2) Patients received treatment with ICIs, either as monotherapy or in combination with CT, RT, or TT;
(3) SII was calculated based on peripheral blood parameters (PLT × NEU / LYM) obtained prior to ICI treatment;
(4) Studies provided long-term survival data, including OS or PFS;
(5) HR and 95% CI for survival outcomes could be obtained directly from the literature or indirectly through calculation from available data.

Study designs to be included OS and PFS/DF.

Eligibility criteria
Inclusion criteria:
(1) Patients were diagnosed with EC (including ESCC or EAC) through histopathological or cytological examination;
(2) Patients received treatment with ICIs, either as monotherapy or in combination with CT, RT, or TT;
(3) SII was calculated based on peripheral blood parameters (PLT × NEU / LYM) obtained prior to ICI treatment;
(4) Studies provided long-term survival data, including OS or PFS;
(5) HR and 95% CI for survival outcomes could be obtained directly from the literature or indirectly through calculation from available data.
Exclusion criteria:
(1) Reviews, case reports, case series, conference abstracts, editorials, or commentaries;
(2) Studies with insufficient data to extract or calculate HR and 95% CI for OS or PFS;
(3) Non-clinical studies (e.g., in vitro or animal studies) or non-human studies;
(4) Studies with overlapping or duplicate patient populations (only the most complete or most recent study was included);
(5) Studies that did not report baseline peripheral blood parameters required for SII calculation;
(6) Studies in which patients received neoadjuvant ICI prior to surgery, unless baseline SII was measured before any treatment.

Information sources PubMed, Cochrane Library, CNKI, and EMBASE databases.

Main outcome(s) A total of 1,328 eligible patients were selected from 7 studies. The results indicated a significant association between elevated SII and worse OS and PFS (OS: HR 1.88, 95% CI 1.57–2.24, $p < 0.001$; PFS: HR 1.87, 95% CI 1.26–2.79, $p = 0.002$). Additionally, elevated SII was significantly associated with lower ORR (RR = 0.57, 95% CI 0.38–0.86) and DCR (RR = 0.70, 95% CI 0.57–0.86). Subgroup analyses were conducted to assess the robustness of these findings.

Quality assessment / Risk of bias analysis To evaluate potential publication bias, a combination of funnel plots, Begg's test, and Egger's test was employed. The funnel plots for OS (Figure 3A) and PFS (Figure 3B) both exhibited relatively symmetrical distributions. Begg's test results revealed no significant publication bias for either OS or PFS (OS: $z = 1.69$, $Pr > |z| = 0.091$; after continuity correction: $z = 1.50$, $Pr > |z| = 0.133$; Figure 4A; PFS: $z = 0.49$, $Pr > |z| = 0.624$; after continuity correction: $z = 0.24$, $Pr > |z| = 0.806$; Figure 4B). Egger's test further corroborated these findings, showing no evident publication bias in studies related to OS and PFS (OS: bias coefficient = 4.955382, $P = 0.056$; Figure 5A; PFS: bias coefficient = –0.2824507, $P = 0.624$; Figure 5B). To further assess the possibility of publication bias, a sensitivity analysis was conducted by sequentially excluding each study and performing a cumulative analysis to determine its impact on the overall results. The analysis demonstrated that no single study had a significant effect on the association between SII and OS or PFS in esophageal cancer patients (Figure 6). This finding underscores the robustness of the observed associations, as the results remained consistent and unaffected by the exclusion of individual studies.

Strategy of data synthesis Statistical analyses were performed using Stata SE (version 12.0; StataCorp, College Station, Texas, USA). Heterogeneity across studies was evaluated using Cochran's Q-test and I^2 statistics. A fixed-effects model was applied when heterogeneity was not significant ($P \geq 0.10$ or $I^2 < 50\%$); otherwise, a random-effects model was used ($P < 0.10$ or $I^2 \geq 50\%$). For survival outcomes, pooled HRs with 95% CIs were calculated to assess the association between SII and OS or PFS. Statistical significance was set at $P < 0.05$. Publication bias was assessed

using funnel plot symmetry, Egger's linear regression test, and Begg's rank correlation test, with $P < 0.05$ indicating potential publication bias. Sensitivity analysis was conducted by sequentially omitting individual studies to evaluate the robustness of the pooled results. To explore potential sources of heterogeneity, subgroup analyses were performed based on the following variables: sample size (≥ 100 vs. 830 vs. ≤ 830), and study quality assessed by NOS score (7 vs. 8). These predefined subgroups aimed to determine whether the prognostic value of SII in ESCC patients receiving ICIs remained consistent across different study characteristics.

Subgroup analysis The association between SII and PFS was less consistent, with greater variability across subgroups. Largesample studies (>100 patients) revealed a nonsignificant trend for worse PFS with higher SII (HR = 1.53, 95% CI: 0.84–2.81, P = 0.168) and moderate heterogeneity (I^2 = 61.2%). However, smaller studies (830 yielded a statistically significant association with worse PFS (HR = 1.87, P = 0.002) and low heterogeneity (I^2 = 44.5%), while cutoffs <830 did not reach statistical significance (P = 0.273) and showed extreme heterogeneity (I^2 = 94.1%). Multivariateadjusted results for PFS were significant (HR = 2.65, P = 0.036), whereas univariate analysis was not (P = 0.752), suggesting that after adjusting for confounders, higher SII remains a significant predictor of poorer PFS. These findings suggest that the prognostic role of SII in PFS may depend on cutoff selection, sample size, and adjustment for confounders. Future studies should prioritize standardized cutoffs, larger cohorts, and multivariate designs to clarify its clinical utility for PFS (Table4).

Sensitivity analysis No.

Country(ies) involved China.

Keywords esophageal cancer, immune checkpoint inhibitors, systemic immune-inflammation index, prognosis, meta-analysis.

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