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Original Article

Systemic immune-inflammation index as a prognostic marker in pancreatic ductal adenocarcinoma: a metaanalysis

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ABSTRACT

Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy with limited durable treatment options despite evolving multimodal and systemic strategies. Systemic inflammation has emerged as a clinically relevant determinant of outcomes in several cancers. The systemic immune-inflammation index (SII; platelet count x neutrophil count / lymphocyte count) integrates key circulating immune cell populations and may serve as an accessible prognostic biomarker in PDAC.

Methods: A systematic search of PubMed was performed for studies published up to 11 April 2025. Eligible full-text English studies reported hazard ratios (HRs) with 95% confidence intervals (CIs) for overall survival (OS) according to SII (typically high versus low SII, defined by a study-specific cutoff). Pooled HRs were calculated using an inverse-variance random-effects model. Heterogeneity was assessed using Cochran's Q and the I^2 statistic. Small-study effects were evaluated by funnel plot inspection and Egger's regression test.

Results: Seventeen studies (18 datasets) comprising 4218 patients were included. Elevated SII was associated with worse OS (pooled HR 1.58, 95% CI 1.19 - 2.08; $p < 0.01$). Between-study heterogeneity was substantial ($I^2 = 89.9\%$). Funnel plot inspection did not suggest major asymmetry, and Egger's test did not provide statistical evidence of small-study effects ($p = 0.072$).

Conclusions: Elevated SII is associated with poorer overall survival and represents a practical prognostic biomarker derived from routine laboratory testing. Considerable heterogeneity across studies—likely driven by differences in case mix, treatment context, and SII cutoff definitions—underscores the need for standardized thresholds and prospective, harmonized validation studies.

Introduction

Pancreatic ductal adenocarcinoma (PDAC), which accounts for >90% of exocrine pancreatic malignancies, ranks among the most aggressive solid tumors worldwide [1]. Although its incidence is lower than that of several other common cancers, PDAC is already a leading cause of cancer-related mortality and is projected to rise further [1,2]. Five-year survival remains low and declines sharply with advancing stage [3,4].

Chronic inflammation is recognized as a hallmark of tumorigenesis and metastatic progression in PDAC [5]. Inflammatory conditions such as chronic pancreatitis are associated with a markedly increased PDAC risk, and systemic inflammatory responses are increasingly linked to tumor progression, immune suppression, and treatment resistance [5].

Because PDAC often presents with non-specific or silent symptoms, many patients are diagnosed with locally advanced or metastatic disease, and only a minority are eligible for curative-intent resection [6]. Contemporary PDAC management is increasingly multimodal. For localized and borderline-resectable disease, treatment is organized around surgical eligibility, neoadjuvant or adjuvant combination chemotherapy, selective chemoradiotherapy, perioperative optimization, and enhanced-recovery or prehabilitation strategies [7,8]. For locally advanced or metastatic disease, cytotoxic chemotherapy remains the principal systemic backbone. In contrast, immunotherapy and precision-medicine approaches have produced meaningful benefit only in selected molecularly defined subgroups and remain constrained by the immunosuppressive PDAC microenvironment and treatment-related toxicity considerations [9–13].

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Table 1
The main features of the studies included in the analysis of SII and outcome measures in PDAC patients.

Authors	Publication Date	Patient No	Treatment	Country	Age (mean)	Gender (M/F)	Stage (T1–2/ T3–4)	SII Cutoff	Histology	Method for cutoff selection	Survival endpoint	Study design
Topkan E	2024	163	concurrent chemoradiotherapy (C—CRT)	Turkey	57	36/127	163/0	538	Pancreas	ROC analysis	OS	retrospective
Yur M	2023	163	No treatment was allowed	Turkey	60.12 ± 12.55	52/64	60/56	704	mixed periampullary cohort including pancreatic-head tumors	ROC analysis	OS	retrospective
Schlanger D	2022	312	surgical resection	Romania	63.4 ± 9.4	Not reported	Not reported	819.78/ 803.40/ 803.40	Pancreas	ROC analysis	OS	retrospective
Bittoni A	2021	234	first-line chemotherapy	Italy	67	131/103	Not reported	1200	Pancreas	ROC analysis	OS	retrospective
Ke Z	2019	419	Not reported	China	61	269/150	Not reported	440	Pancreas	ROC analysis	OS	retrospective
Gerd J	2020	324	surgical resection	University of Vienna	68,5	169/155	306/18	873	Pancreas	ROC analysis	OS	retrospective
Jing L	2020	27	treated with SBRT (Stereotactic Body Radiation Therapy)	China	58	18/9	Not reported	821.9	Pancreas	ROC analysis	OS	prospective
Pranav M	2020	419	neoadjuvant therapy	USA	65.17	209/210	311/98	900	Pancreas	ROC analysis	OS	retrospective
Jin S	2021	122	treated with ICB	China	56	87/35	11/111	566	Pancreas	ROC analysis	OS	retrospective
Chuanlong X	2021	135	Whipple surgery	China	56.6 ± 8.8	78/57	Not reported	900	Pancreas	ROC analysis	OS	retrospective
Aziz M	2019	170	surgical resection	Netherlands	65,5	96/74	23/136	900	Pancreas	cutoff with the lowest −2 log likelihood	OS	retrospective
Han R	2022	243	palliative surgical resection and non-surgical treatment	China	61,74	152/91	78/165	533	Pancreas	median values	OS	retrospective
Yifan Y	2025	384	IAIC	China	59	183/85	Not reported	785.78	Pancreas	ROC analysis	OS	retrospective
Qing C	2023	164	surgery	China	63.8	91/73	77/87	563	Pancreas	ROC analysis	OS	retrospective
Guanhua C	2024	364	surgical resection	China	51	164/200	Not reported	523.95	Pancreas	ROC analysis	OS	retrospective
Merve K	2025	75	Patients diagnosed with metastatic pancreatic adenocarcinoma	Turkey	62±10	26/49	Not reported	768	Pancreas	ROC analysis	OS	retrospective
Mengyi J	2025	500	Patients with PDAC	China	63	308/192	308/190	348.305	Pancreas	median values	OS	retrospective

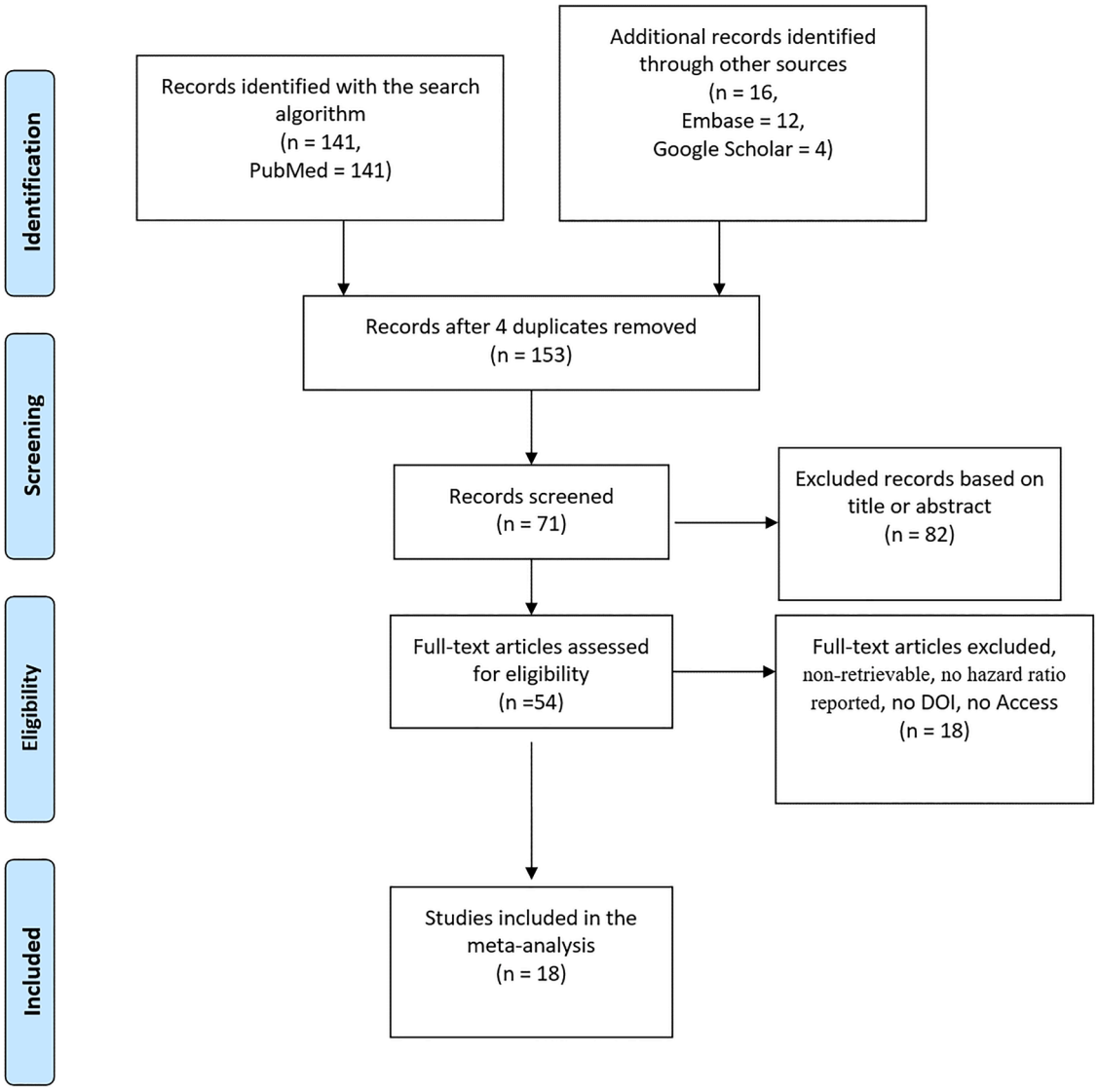

Fig. 1. Flow-chart of the study selection process. Selection of studies for the Systemic Immune-Inflammation index (SII).

From a translational perspective, the value of SII lies not in replacing established prognostic factors, but in providing a simple pre-treatment readout of the host inflammatory state. SII can be obtained before surgery, neoadjuvant therapy, chemotherapy, or supportive interventions and can be interpreted alongside stage, performance status, bilirubin, nutritional status, and treatment intent. This positioning makes SII clinically attractive, but it also makes standardization essential: a biomarker measured with different cutoffs across heterogeneous treatment settings cannot be assumed to have a single universal prognostic threshold.

In this context, inexpensive and readily available biomarkers derived from routine blood tests offer practical advantages because they can be obtained before treatment and do not require specialized assays. Inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and SII have been proposed as prognostic biomarkers in PDAC [14–16]. SII is calculated as platelet count x neutrophil count / lymphocyte count, capturing tumor-promoting inflammation (neutrophilia and thrombocytosis) alongside reduced antitumor immune surveillance (lymphopenia) [17].

Across multiple tumor types, elevated SII has been associated with unfavorable outcomes [18–26]. In PDAC, evidence suggests that SII may help identify patients at higher risk of early recurrence or progression—particularly valuable because many conventional prognostic factors become available only after surgical pathology [27].

Previous meta-analyses have evaluated SII in pancreatic cancer, including a 2021 report that analyzed nine datasets and linked elevated SII with poorer overall and progression-free survival [28]. To update and extend this evidence base, we performed a meta-analysis to quantify the association between elevated SII and overall survival in PDAC across published cohorts and to characterize between-study heterogeneity.

Methods

Literature retrieval

A custom Python script was used to query PubMed for potentially eligible studies published up to 2025. The following search strings were applied: "PDAC AND systemic immune–inflammation index", "pancreas SII AND prognosis", "pancreatic ductal adenocarcinoma AND SII AND survival OR hazard ratio", and "pancreatic cancer AND systemic inflammation AND markers". The script accessed PubMed via the query URL format https://pubmed.ncbi.nlm.nih.gov/?term={query}&sort=date&size=200, and extracted bibliographic fields (title, authors, publication date, DOI when available) into an Excel file. The code is publicly available on GitHub (https://github.com/Pahi95/pubmedscrapp). Because only published, aggregate data were used,

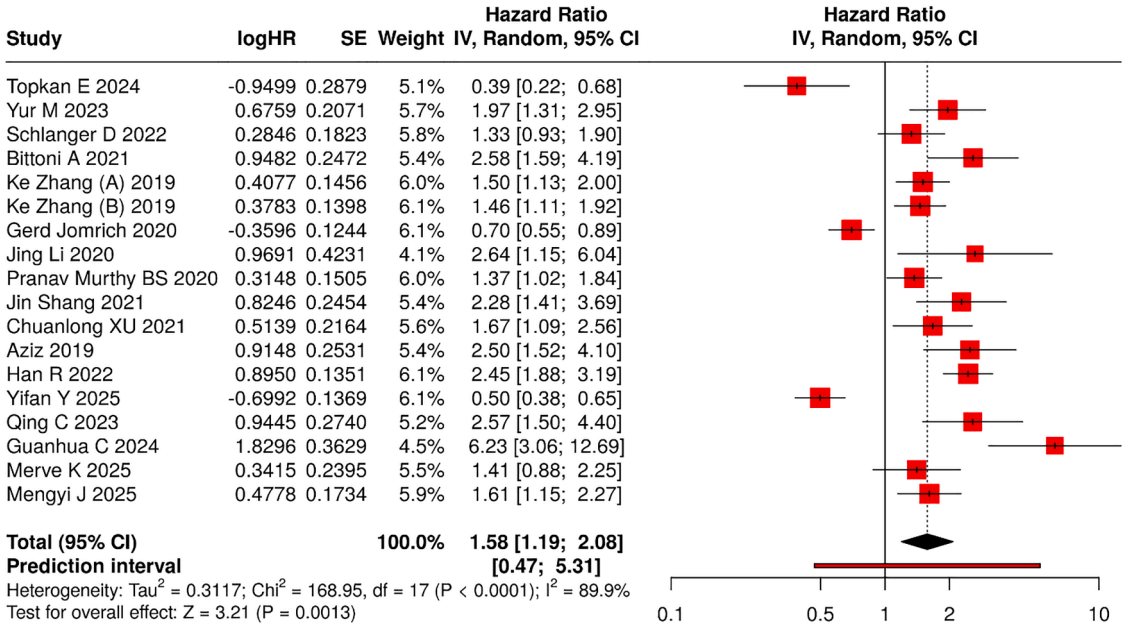

Fig. 2. Forest plot of the association between elevated SII and overall survival (OS) in patients with PDAC across 17 studies (18 datasets; random-effects model).

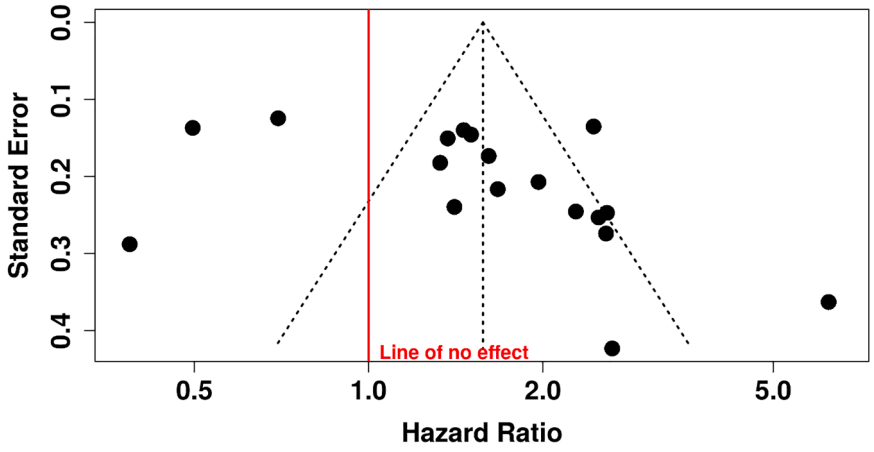

Fig. 3. Funnel plot for the association between SII and OS. Egger's regression did not show statistically significant small-study effects (p = 0.072), although mild visual asymmetry should be interpreted cautiously.

Table 2
Exploratory pooled hazard ratios for non-SII clinical covariates reported across included studies.

Variables	No. Of datasets	No of patients	Effect model	HR (95% CI)	P-value	Heterogeneity I^2%	Heterogeneity *P*-value
Location (Head vs Body/Tail)	9	2294	Random	0,98 (0,85 - 1,12)	0,74	23,9%	0,23
Stage	10	2487	Random	1,40 (1,16 - 1,69)	<0,01	34,1%	0,13
NLR	11	2691	Random	1,36 (1,03 - 1,81)	0,0331	91,2%	<0,01
SII	18	4218	Random	1,58 (1,19 - 2,08)	<0,01	89,9%	<0,01
Age	13	3337	Random	1,00 (0,98 - 1,03)	0,8	67,8%	<0,01
Sex (M/F)	13	3074	Random	1,08 (0,99 - 1,19)	0085	0%	0.57

ethical approval and patient consent were not required. Further publication search was conducted manually on Embase, Google Schoolar and Scopus. The search was limited to English-language full texts.

Eligibility criteria

Studies were eligible if they (i) were full-text articles published in English; (ii) enrolled patients with pancreatic ductal adenocarcinoma (PDAC); and (iii) reported hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for overall survival (OS) according to SII (typically high versus low SII based on a study-defined cutoff).

We excluded studies without sufficient survival data to extract HRs and CIs, conference abstracts, letters, editorials, reviews, case reports, preclinical studies, and studies primarily focused on basic science.

Histology was checked during full-text review. Studies were retained when the cohort was described as pancreatic cancer/PDAC or when extractable pancreatic/PDAC survival data were available. One included publication [29] enrolled a mixed periampullary cohort, including

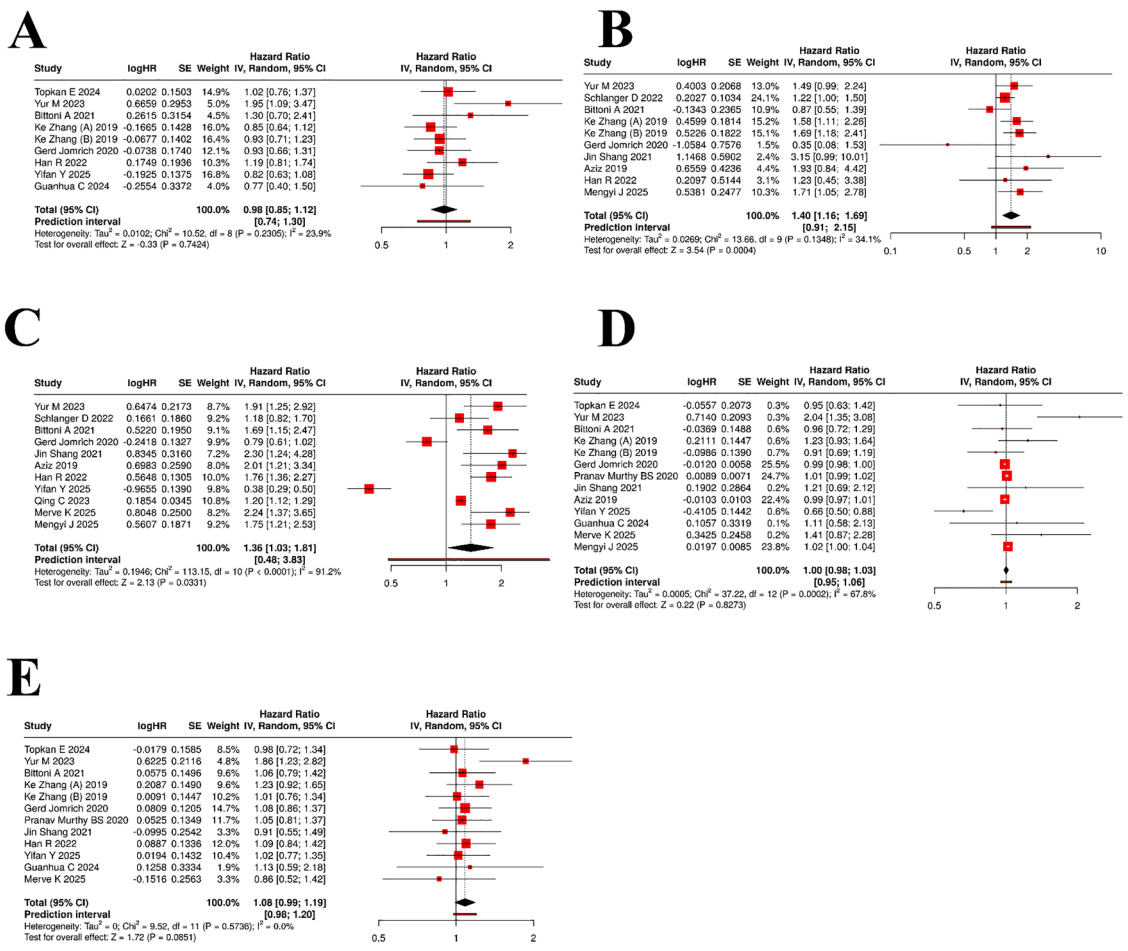

Fig. 4. Exploratory pooled analyses of non-SII prognostic covariates reported across included studies: (A) tumor location, (B) disease stage, (C) NLR, (D) age, and (E) sex. These analyses provide clinical context only and do not test whether the association between SII and OS differs across subgroups.

pancreatic-head tumors, and was therefore flagged in Table 1 and in the risk-of-bias assessment as a potential histology-related source of indirectness. No additional study was excluded on histology alone in the current pooled analysis.

Study selection and data extraction

Titles and abstracts of retrieved records were screened, followed by full-text assessment of potentially eligible studies. From each included study, we extracted: first author, publication year, sample size, treatment context, country, age, sex distribution, TNM stage distribution (when reported), SII cutoff value and cutoff derivation method, histology, study design, survival endpoint, and HRs with 95% CIs.

The TNM classification describes primary tumor extent (T), nodal involvement (N), and distant metastasis (M), and is used to stage disease, guide treatment selection, and estimate prognosis.

Risk-of-bias assessment

Study-level risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) framework because SII was evaluated as a prognostic factor. The following domains were considered: study participation, study attrition, measurement of prognostic factors, measurement of outcomes, confounding, and statistical analysis/reporting. Overall judgments were assigned as low, moderate, or high risk based on the highest-impact concerns across domains. No study was excluded solely based on risk-of-bias judgment.

Statistical analysis

Overall survival (OS) was the primary endpoint. The prognostic impact of SII was summarized using pooled hazard ratios (HRs) and 95% confidence intervals (CIs). Heterogeneity was assessed using Cochran's Q test and quantified with the I^2 statistic [30]. Statistically significant heterogeneity was defined as Q-test $p < 0.10$ and/or $I^2 > 50\%$. Given anticipated clinical and methodological diversity, a random-effects model (inverse-variance weighting) was used for pooling. Potential small-study effects were explored using funnel plot inspection and Egger's regression test. Because only aggregate published estimates were available and the number of studies within clinically comparable strata was limited, heterogeneity was interpreted qualitatively rather than by formal meta-regression.

Exploratory pooled analyses of additional prognostic covariates reported in the included studies (tumor location, stage, NLR, age, and sex) were conducted only to contextualize survival risk in the included literature. These hypothesis-generating analyses reflect the pooled association of each covariate with OS and should not be interpreted as subgroup analyses or effect-modification analyses of the SII-OS association unless stratified SII-specific estimates are available.

Sensitivity analysis

A leave-one-out sensitivity analysis was performed to evaluate the influence of each individual dataset on the pooled SII–OS estimate.

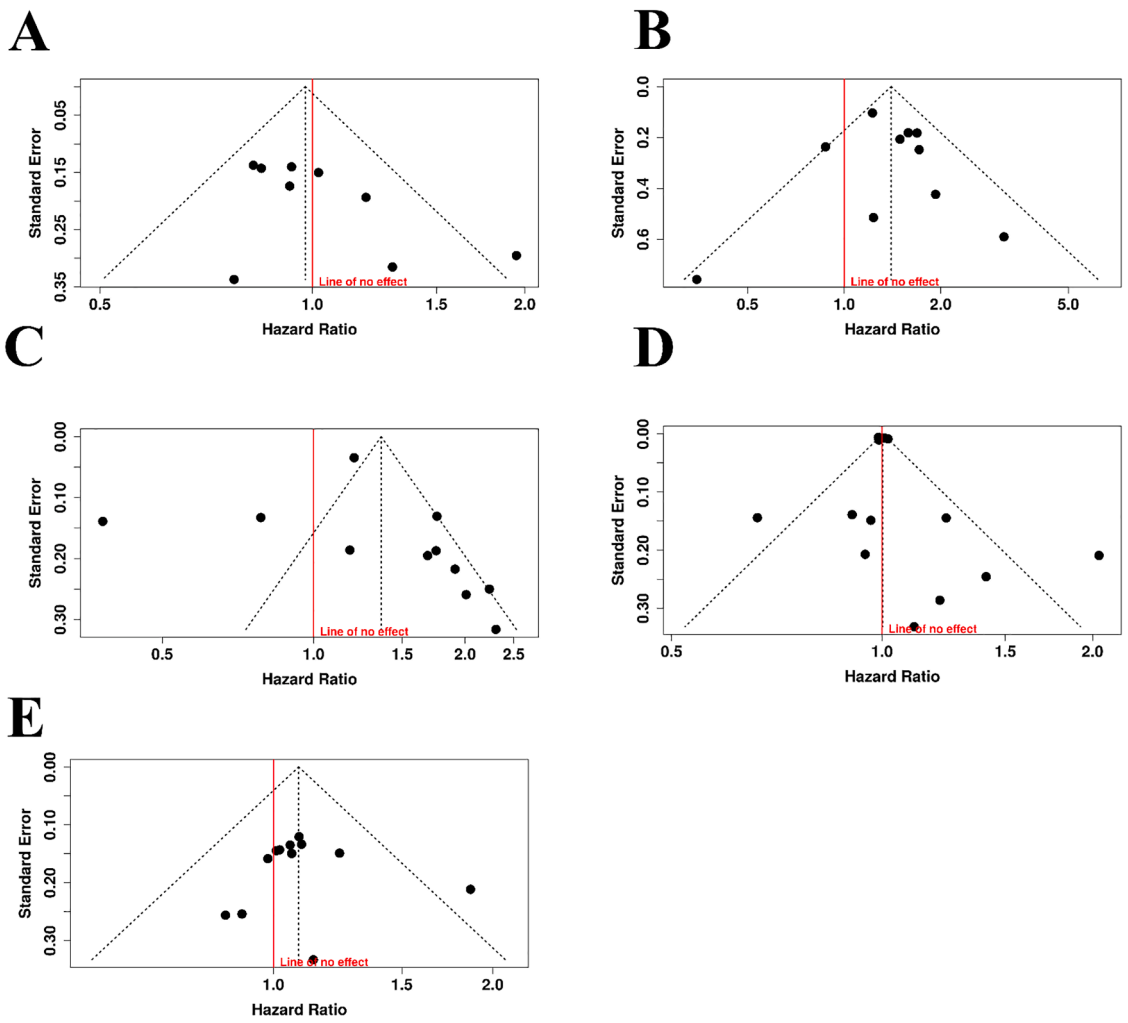

Fig. 5. Funnel plots for exploratory pooled analyses of non-SII clinical covariates: (A) tumor location, (B) disease stage, (C) NLR, (D) age, and (E) sex. Findings should be interpreted cautiously because the number of datasets differs by covariate and these analyses were not designed to evaluate SII effect modification.

Software

All metaanalyses were performed using MetaAnalysisOnline (https://meta-analysisonline.com).

Sensitivity analyses were conducted to evaluate the robustness of the primary SII–OS association. First, the primary random-effects model was repeated after excluding the mixed periampullary cohort, as this study introduced histology-related indirectness in a PDAC-focused meta-analysis. Second, leave-one-out analysis was used to assess whether any single dataset drove the pooled estimate. Formal meta-regression was not performed because only aggregate published estimates were available, and the number of clinically comparable datasets within treatment, cutoff, and disease-stage strata was limited.

Results

Study selection and characteristics

A total of 156 records were retrieved. After title/abstract screening, 54 articles underwent full-text review. Seventeen studies published between 2019 and 11 April 2025 met the eligibility criteria and were included (Fig. 1) [29,31–46]. Together, these studies comprised 4218 patients (18 datasets).

Sixteen studies were retrospective cohort analyses, and one was a prospective study. Nine studies were conducted in China, three in Turkey, and one each in Romania, Italy, Austria, the United States, and the Netherlands. Key study characteristics are summarized in Table 1. The 2025 Jiang and Zhou cohort was retained in the included-study set and is represented in Table 1 as the Mengyi J study.

Risk-of-bias assessment

The QUIPS assessment indicated predominantly moderate study-level risk of bias, mainly because of the retrospective design, data-driven cutoff selection, incomplete adjustment for major clinical confounders, and incomplete reporting of disease-stage or treatment-context variables. The mixed periampullary cohort was judged to have a high risk in the study participation/domain applicability assessment. The risk-of-bias summary is presented in Table 3.

Association of SII with overall survival

Across 18 datasets, elevated SII was associated with worse overall survival (pooled HR 1.58, 95% CI 1.19–2.08; $p < 0.01$) (Fig. 2). Heterogeneity was substantial ($I^2 = 89.9\%$; Q-test $p < 0.01$), indicating considerable between-study variability in effect sizes.

Funnel plot inspection suggested possible mild visual asymmetry, but Egger's regression did not reach conventional statistical significance (intercept: 4.25, 95% CI −0.08 to 8.59; $t = 1.924$; $p = 0.072$). Therefore, there was no statistical evidence of small-study effects, although the

Table 3
Leave-one-out sensitivity analysis.

Publication left out	HR (95% CI)	P-value	Heterogenity I^2%	Heterogenity *P*-value
Topkan E	1,69 (1,29–2,23)	0,0002	89,3	<0,01
Yur M	1,56 (1,16–2,08)	0,0028	90,3	<0,01
Schlanger D	1,6 (1,19–2,14)	0,0019	90,5	<0,01
Bittoni A	1,53 (1,15–2,04)	0,0034	90,1	<0,01
Ke Zhang (A)	1,58 (1,17–2,14)	0,0026	90,5	<0,01
Ke Zhang (B)	1,59 (1,18–2,15)	0,0026	90,5	<0,01
Gerd Jomrich	1,66 (1,26–2,18)	0,0003	88,3	<0,01
Jing Li	1,54 (1,16–2,05)	0,0028	90,4	<0,01
Pranav Murthy BS	1,59 (1,18–2,15)	0,0023	90,5	<0,01
Jin Shang	1,54 (1,16–2,06)	0,0031	90,3	<0,01
Chuanlong XU	1,57 (1,17–2,11)	0,0024	90,5	<0,01
Aziz	1,54 (1,15–2,04)	0,0033	90,2	<0,01
Han R	1,53 (1,15–2,03)	0,0032	89,2	<0,01
Yifan Y	1,69 (1,32–2,15)	0,0001	85,3	<0,01
Qing C	1,53 (1,15–2,04)	0,0033	90,2	<0,01
Guanhua C	1,47 (1,12–1,94)	0,0052	89,4	<0,01
Merve K	1,59 (1,19–2,13)	0,0019	90,5	<0,01
Mengyi J	1,58 (1,17–2,12)	0,0025	90,5	<0,01

borderline p-value warrants cautious interpretation (Fig. 3).

Exploratory pooled analyses of other prognostic covariates

To provide clinical context across the included literature, we pooled reported HRs for selected covariates when available (Table 2; Fig. 4). These exploratory analyses were hypothesis-generating and were not designed to test whether the prognostic association between SII and OS differed across subgroups. Advanced disease stage was associated with poorer OS (HR 1.40, 95% CI 1.16–1.69; p = 0.0004), with low-to-moderate heterogeneity. Tumor location (head vs body/tail) was not consistently associated with OS (HR 0.98, 95% CI 0.85–1.12; p = 0.74). NLR was associated with poorer OS (HR 1.36, 95% CI 1.03–1.81; p = 0.0331) with substantial heterogeneity (I2 = 91.2%). Age (HR 1.00, 95% CI 0.98–1.03; p = 0.80) and sex (HR 1.08, 95% CI 0.99–1.19; p = 0.085) were not significantly associated with OS.

Publication bias in exploratory analyses

Across exploratory covariate analyses, funnel plots and Egger's tests did not provide consistent statistical evidence of small-study effects. Because these analyses were secondary and based on fewer datasets than the primary SII analysis, their publication-bias assessments should be interpreted cautiously (Fig. 5).

Sensitivity analysis

A leave-one-out sensitivity analysis confirmed the robustness of the primary SII–OS association (Table 3). Sequential omission of each individual dataset yielded pooled hazard ratios ranging from 1.47 (95% CI 1.12–1.94; after excluding Guanhua et al.) to 1.69 (95% CI 1.29–2.23 after excluding Topkan et al.; 95% CI 1.32–2.15 after excluding Yifan et al.), all closely aligned with the overall pooled estimate (HR 1.58, 95% CI 1.19–2.08). The pooled effect remained statistically significant in every iteration (all $p \leq 0.005$), and no single study, when removed, shifted the estimate outside this narrow range or reversed the direction of the association. These findings indicate that the pooled SII–OS estimate was not driven by any individual cohort. Between-study heterogeneity remained substantial throughout (I^2 = 85.3–90.5%, all $p < 0.01$), indicating that no single dataset accounted for the observed heterogeneity. The largest reduction in heterogeneity occurred after omission of Yifan et al. (I^2 = 85.3%), which also produced the highest pooled estimate, identifying this dataset as a modest contributor to between-study variability (Table 4).

Discussion

This metaanalysis of 17 studies (18 datasets; 4218 patients) indicates that elevated systemic immune–inflammation index (SII) is associated with poorer overall survival in pancreatic ductal adenocarcinoma (PDAC). SII integrates platelet, neutrophil, and lymphocyte counts and may capture tumor-driven inflammation (neutrophilia and thrombocytosis) alongside impaired adaptive immune surveillance (lymphopenia), thereby providing a composite measure of the host–tumor inflammatory milieu [17–19,24].

Our pooled estimate supports and extends prior reports linking high SII to adverse outcomes in pancreatic cancer [28]. Importantly, SII can

Table 4
QUIPS risk-of-bias assessment for the included studies.

Study	Participation	Attrition	SII measurement	OS measurement	Confounding	Analysis/reporting	Overall
Topkan et al. 2024	Low	Low	Low	Low	Low	Moderate	Moderate
Yur et al. 2023	High	Low	Low	Low	Moderate	Moderate	High
Schlanger et al. 2022	Low	Low	Low	Low	High	Moderate	High
Bittoni et al. 2021	Low	Moderate	Low	Low	Moderate	Moderate	Moderate
Zhang/Ke et al. 2019	Low	Low	Low	Low	Low	Moderate	Moderate
Jomrich et al. 2020	Low	Low	Low	Low	Moderate	Moderate	Moderate
Li et al. 2020	Moderate	Low	Low	Low	High	Moderate	High
Murthy et al. 2020	Low	Low	Low	Low	Low	Moderate	Moderate
Shang et al. 2021	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Xu et al. 2021	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Aziz et al. 2019	Low	Low	Low	Low	Low	Moderate	Moderate
Han et al. 2022	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Yang et al. 2025	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Chen et al. 2023	Low	Low	Low	Low	Moderate	Moderate	Moderate
Lu et al. 2024	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Kuday Ozkan et al. 2025	Low	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Jiang and Zhou 2025	Low	Low	Low	Low	Moderate	Moderate	Moderate

be calculated from routine complete blood counts and is therefore inexpensive, widely available, and potentially useful for pre-treatment risk stratification.

However, heterogeneity was substantial ($I^2 = 89.9\%$), emphasizing that the magnitude of association varies across cohorts. Differences in SII cutoffs and cutoff selection methods, treatment context (resection, neoadjuvant therapy, chemotherapy, chemoradiotherapy, immunotherapy), disease stage distributions, histologic eligibility, and clinical confounders (e.g., cholestasis or infection) may contribute to variability. These hypotheses were not tested with formal subgroup analysis or meta-regression in the present aggregate-data analysis. Bilirubin levels have been reported to influence the prognostic value of SII in resectable pancreatic cancer, underscoring the importance of clinically informed adjustment and standardized reporting [41].

In exploratory pooled analyses of other prognostic covariates reported in the included studies, advanced stage was associated with worse overall survival, whereas tumor location, age, and sex were not consistently associated. These findings provide context but do not substitute for true subgroup analyses of the SII–OS association; evaluating effect modification would require stratified SII estimates or individual patient data.

Several limitations should be considered. The search strategy was restricted to English-language full-text articles, which may have missed eligible studies. Most included studies were retrospective, used heterogeneous, often data-driven SII cutoffs, and differed in treatment context, disease stage, adjustment variables, and the exclusion of inflammatory confounders. QUIPS assessment indicated mainly moderate study-level risk of bias, with confounding adjustment and cutoff selection as recurring concerns. The mixed periampullary cohort introduced histology-related indirectness; therefore, the PDAC-focused sensitivity analysis should be interpreted alongside the primary estimate. Finally, substantial heterogeneity persisted even after sensitivity analyses, indicating that SII should not yet be considered a standardized clinical decision threshold.

Despite these limitations, the aggregated evidence indicates that SII is a practical prognostic marker associated with overall survival in PDAC. Prospective studies with standardized cutoff definitions and robust adjustment for confounders are warranted to define how SII can best be integrated into clinical decision-making and risk-adapted treatment strategies.

Conclusions

Elevated systemic immune–inflammation index (SII) is associated with poorer overall survival in patients with pancreatic ductal adenocarcinoma. Given its low cost and availability from routine blood testing, SII may support pre-treatment risk stratification. Standardized cutoffs and prospective validation are needed before routine clinical implementation.

Ethical approval/exemption statement

This study is a systematic review and meta-analysis based exclusively on previously published studies. All data analyzed were obtained from publicly available sources and did not involve any direct patient contact or the collection of new individual-level data. As such, the study does not involve human subjects research requiring ethical approval, in accordance with local and international guidelines. Therefore, ethical approval and informed consent were not required for this research.

CRediT authorship contribution statement

Bence Pachinger-Molnár: Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization. **Otília Menyhárt:** Writing – review & editing, Writing – original draft, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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