DOI: 10.67692/IODT.26.2734



Integrated Oncology Diagnostics & Treatment
Volume 1, Issue 2, 2026 | Pages 151-166 | ISSN: 2979-5575
Published by Pinnacle Academic Publishing, United Kingdom

SYSTEMATIC REVIEW

Composite Nutritional–Inflammatory Indices and Overall Survival Across the Esophageal Cancer Treatment Continuum

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Abstract

Background: Malnutrition and systemic inflammation are near-universal in esophageal cancer and are captured by composite blood-based indices—the prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio (NLR), geriatric nutritional risk index (GNRI)/nutritional risk index (NRI), and the newer global immune-nutrition-inflammation index (GINI). Published syntheses have each addressed a single index, usually within a single treatment setting, leaving unclear whether prognostic performance is preserved as treatment has diversified from surgery alone to chemoradiotherapy- and immunotherapy-based regimens.

Objectives: To compare, across the surgical, chemo(radio)therapy, and immunotherapy-based treatment settings, the association between an adverse composite nutritional-inflammatory index category and overall survival in esophageal cancer.

Methods: We conducted a rapid evidence synthesis with exploratory random-effects meta-analysis. Because a fully systematic, protocol-registered, dual-reviewer search was not undertaken, this work is deliberately reported as a rapid synthesis rather than as a PRISMA-compliant systematic review. Eligible reports were cohort studies of patients with esophageal cancer providing a categorical (adverse vs favourable) hazard ratio (HR) with 95% confidence interval (CI) for overall survival according to pretreatment PNI, NLR, GNRI/NRI, or GINI. All estimates were direction-standardised to express the hazard associated with the adverse category. One estimate per independent cohort was pooled using a random-effects (DerSimonian–Laird) model, pre-specified by treatment setting; duplicate and institutionally overlapping cohorts were excluded from the primary analysis and examined in sensitivity analyses. Certainty was rated using GRADE.

Results: Fifteen study-index observations derived from 14 unique cohorts (3,904 patients) were eligible for narrative synthesis; eight independent cohorts (2,450 patients) contributed to the primary meta-analysis. An adverse index category was associated with worse overall survival (pooled HR 2.39, 95% CI 2.02–2.82; I^2=0%), with consistent point estimates in the surgery-alone (HR 2.23, 95% CI 1.81–2.76), chemo(radio)therapy (HR 2.36, 95% CI 1.69–3.28), and immunotherapy-based subgroups (HR 3.47, 95% CI 2.16–5.58). The estimate was stable on leave-one-out analysis (HR 2.27–2.45) and across three pre-specified sensitivity analyses (HR 2.39–2.45). However, the surgery-alone 95% prediction interval crossed unity (0.89–5.59), and the apparent absence of heterogeneity (I^2=0%) is more plausibly an artifact of a small, restrictively selected estimate set than evidence of true homogeneity. Certainty of evidence was low.

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Received 19 August 2026
Revised 15 September 2026
Accepted 19 October 2026
Published 1 November 2026

DOI: 10.67692/IODT.26.2734

How to cite: Chileshe M, Mulenga T. Composite Nutritional–Inflammatory Indices and Overall Survival Across the Esophageal Cancer Treatment Continuum. Integr Oncol Diagn Treat. 2026;1(2):151-166. DOI: 10.67692/IODT.26.2734

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Conclusions: Adverse composite nutritional-inflammatory index status is associated with approximately a doubling of mortality hazard at every point on the esophageal cancer treatment continuum, including under immunotherapy. Given a non-exhaustive search, an exclusively retrospective and predominantly East Asian evidence base, study-specific cut-offs, and low GRADE certainty, these findings are hypothesis-generating and support prospective, protocol-driven validation rather than immediate clinical adoption.

Keywords: Esophageal Neoplasms; Nutrition Assessment; Prognostic Nutritional Index; Neutrophil-Lymphocyte Ratio; Immune Checkpoint Inhibitors; Prognosis.

INTRODUCTION

Esophageal cancer remains among the most lethal gastrointestinal malignancies, with overall 5-year survival below 25% despite therapeutic advances.[1] Squamous cell carcinoma and adenocarcinoma differ substantially in geographic distribution and risk-factor profile, and global incidence and mortality patterns continue to diverge as adenocarcinoma rises in Western populations while squamous cell carcinoma predominates in East Asia.[2]

Contemporary management spans a continuum rather than a single modality. Patients may undergo primary resection, neoadjuvant or definitive chemoradiotherapy, or immune checkpoint inhibitor (ICI) therapy; adjuvant nivolumab is now standard for residual disease after neoadjuvant chemoradiotherapy and surgery,[3] and nivolumab-based combinations are an established first-line option in advanced squamous cell disease.[4] Malnutrition and systemic inflammation accompany the disease at every point along this continuum, driven by dysphagia, tumour-related catabolism, and treatment toxicity.

Composite blood-based indices capture this nutritional-inflammatory axis from routinely available laboratory values: PNI, NLR, GNRI/NRI, and, most recently, GINI. Existing quantitative syntheses have each been confined to a single index—chiefly GNRI[5] or NLR within the neoadjuvant setting[6]—and typically to a single treatment context. Whether these indices perform comparably to one another, and whether performance is preserved in the immunotherapy era, has not been directly examined.

We therefore undertook a rapid evidence synthesis with exploratory meta-analysis to compare the association between an adverse composite index category and overall survival across the surgical, chemo(radio)therapy, and immunotherapy-based treatment settings. We state at the outset that the search was structured but not exhaustive, and that the analysis is framed as hypothesis-generating; the methodological consequences of this choice are addressed explicitly in the Methods and Discussion, and are reported in line with transparent reporting standards for evidence syntheses.[7]

METHODS

Design and Reporting Framework

We conducted a rapid evidence synthesis with exploratory random-effects meta-analysis. We deliberately do not describe this work as a systematic review and do not claim PRISMA 2020 compliance, because three constituent requirements were not met: no protocol was prospectively registered; the literature search was structured but non-exhaustive; and screening and extraction were performed by a single reviewer without independent duplication. We adopted the rapid-review framing rather than retrofitting systematic-review terminology because transparent labelling of search intensity is a precondition for readers to calibrate confidence in a synthesis of this kind.[7]

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Eligibility Criteria

Reports were eligible if they enrolled patients with histologically confirmed esophageal squamous cell carcinoma or adenocarcinoma; reported a pretreatment or preoperative PNI, NLR, GNRI, NRI, or GINI dichotomised into adverse and favourable categories by a study-defined cut-off; and reported overall survival as a hazard ratio with 95% confidence interval, or with data permitting its calculation. Reports were excluded if esophageal cancer patients could not be separated from a predominantly gastric or gastro-esophageal-junction cohort, or if they were case reports, narrative reviews, or conference abstracts lacking extractable data. Studies meeting clinical eligibility but reporting the association only on a continuous per-unit scale, or without a recoverable 95% confidence interval, were retained for narrative synthesis and excluded from pooling.

Index Definitions

PNI was defined by Onodera et al as 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per mm^3).[8]

GNRI was derived by Bouillanne et al from the Nutritional Risk Index using an ideal-weight correction: 1.489 × albumin (g/L) + 41.7 × (actual/ideal body weight).[9] We treated the closely related NRI within the same index family for synthesis purposes. NLR is the ratio of absolute neutrophil to lymphocyte counts.

GINI combines both axes as (C-reactive protein × platelet × monocyte × neutrophil)/(albumin × lymphocyte); the literature applies this identical formula under two near-identical names, which we treated as one construct.[10]

Search and Selection

We searched PubMed/PMC, publisher websites, and the reference lists of existing index-specific meta-analyses using iterative topic-based queries combining index terms, esophageal cancer population terms, and survival or prognosis terms. Searching proceeded until additional queries returned no new eligible reports. Because searching was iterative rather than a single pre-specified strategy executed across named databases on a fixed date, the total number of records screened was not logged and is not reported; we regard reporting an unverifiable screening count as less acceptable than reporting none. The consequence—that eligible studies were probably missed, and that missed studies may differ systematically from those found—is treated as a primary limitation.

Data Extraction and Direction Standardisation

For each eligible report we extracted first author, year, country, treatment setting, index and cut-off, sample size, outcomes reported, and the categorical hazard ratio with 95% confidence interval for overall survival. Where a report used the favourable category as the reference (yielding HR<1 for the adverse category), we inverted the estimate and its interval bounds so that all pooled effects express the hazard of death associated with the adverse (low-nutritional or high-inflammatory) category. This applied to one pooled estimate, which is identified in Table 1.

Handling of Non-Independent Cohorts

Two threats to independence were identified and handled before pooling. First, one report contributed two estimates (PNI and GNRI) derived from the same 1,265 patients; pooling both would count that cohort twice and falsely narrow the confidence interval. Second, two surgical reports originated from the same institution over overlapping accrual periods and are likely to

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share patients. For the primary analysis we therefore retained a single estimate per independent cohort, selecting the index reported first in the source article for the dual-estimate cohort and the larger cohort where institutional overlap was suspected. Both decisions were tested in pre-specified sensitivity analyses, and the naive double-counted analysis is reported alongside the primary result for transparency.

Methodological Appraisal

We did not perform a formal ROBINS-I assessment, which requires full-text access to design and confounding details that could not be verified for every included report. Instead we applied a transparent, criterion-based appraisal across five items verifiable from the published abstract and methods: study design; single- versus multi-centre recruitment; sample size; whether the index cut-off was derived from the study's own outcome data; and whether the reported hazard ratio was adjusted in a multivariable model. Each item is reported factually in Table 2 rather than converted into a summary bias judgement, so that readers can weight the studies themselves.

Statistical Analysis

Log-transformed hazard ratios were pooled using a random-effects model with the DerSimonian–Laird estimator of between-study variance,[11] pre-specified by treatment setting. Heterogeneity was quantified by the Cochran Q test and the I^2 statistic, and 95% prediction intervals were computed where three or more cohorts contributed. We conducted leave-one-out analysis and three pre-specified sensitivity analyses addressing index selection, institutional overlap, and dominance by the largest cohort.

Small-study effects were assessed by Egger's regression test of the intercept.[12] We report this test for the overall analysis only, and note that with eight cohorts it falls below the conventional threshold of ten studies and is substantially underpowered; a non-significant result should therefore not be read as evidence against publication bias. Certainty of evidence was rated using GRADE, beginning at low certainty for an exclusively observational evidence base.[13] Analyses were performed in Python 3.12 (SciPy, NumPy); the analysis code is available from the corresponding author.

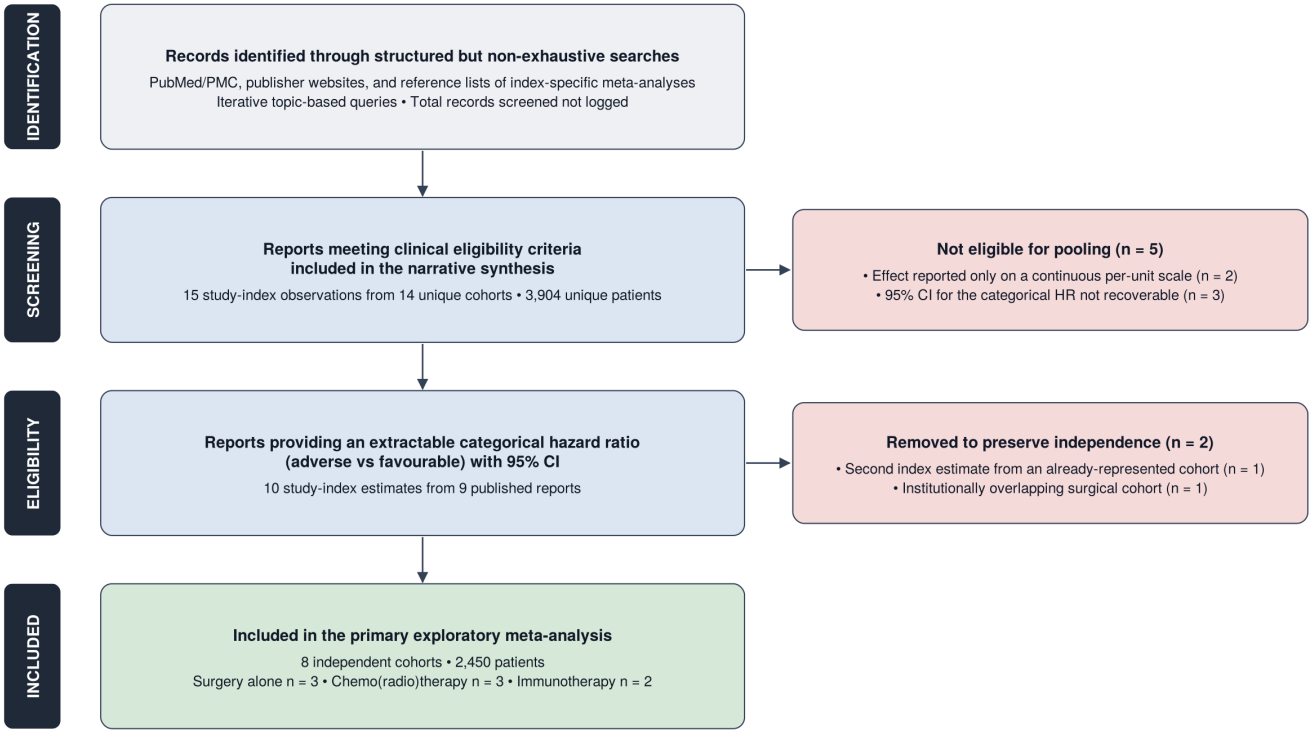
RESULTS

Study flow and included cohorts

Fifteen study-index observations derived from 14 unique cohorts (3,904 unique patients) met the clinical eligibility criteria and are included in the narrative synthesis (Figure 1). Ten of these reported an extractable categorical hazard ratio with a 95% confidence interval. Two estimates were removed to preserve independence—one duplicate index estimate from an already-represented cohort, and one institutionally overlapping surgical cohort—leaving eight independent cohorts (2,450 patients) in the primary meta-analysis. The remaining five eligible reports could not be pooled because the effect was reported only on a continuous per-unit scale (n=2) or because the confidence interval for the categorical estimate was not recoverable from the published report (n=3).

DOI: 10.67692/IODT.26.2734

Figure 1. Flow of study identification, eligibility, and inclusion in the exploratory meta-analysis. HR, hazard ratio; CI, confidence interval. Total records screened are not reported because searching was iterative rather than a single pre-specified strategy; see Methods.



Included cohorts were conducted in China, Japan, Taiwan, and South Korea and published between 2016 and 2025 (Table 1). All fifteen study-index observations originated from retrospective designs; none from prospective or randomised studies. Sample sizes in the pooled set ranged from 78 to 1,265 patients. Three pooled cohorts evaluated patients treated with surgery alone, three with definitive or neoadjuvant chemo(radio)therapy, and two with immunotherapy-based regimens, spanning all four index families.

Table 1. Characteristics of the 15 eligible study-index observations (14 unique cohorts).

Study	Country	Treatment setting	Index (cut-off)	N	HR (95% CI)[a]	Status in analysis
Yoon et al, 2021[14]	South Korea	Surgery alone	PNI (high-risk vs no-risk)	1,265	2.32 (1.77–3.06)	Pooled
Yoon et al, 2021[14]	South Korea	Surgery alone	GNRI (high-risk vs no-risk)	1,265	2.54 (1.64–3.93)	Excluded[b] (same cohort); sensitivity A
Kato et al, 2024[15]	Japan	Surgery alone	GNRI (<98 vs ≥98)	187	2.18 (1.36–3.51)	Pooled
Xiao et al, 2016[16]	China	Surgery alone (basaloid ESCC)	NLR (>1.77 vs ≤1.77)	121	2.03 (1.26–3.27)	Pooled

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Study	Country	Treatment setting	Index (cut-off)	N	HR (95% CI)[a]	Status in analysis
Yamamoto et al, 2025[17]	Japan	Surgery alone	GINI (≥5,000 vs <5,000)	180	2.11 (1.25–3.54)	Excluded[c] (overlaps Kato); sensitivity B
Ho et al, 2021[18]	Taiwan	Definitive CRT (inoperable)	NLR (>3.56 vs ≤3.56)	101	2.36 (1.39–4.00)	Pooled
Bo et al, 2016[19]	China	Definitive RT (age ≥60 y)	GNRI (high-risk vs no-risk)	239	2.70 (1.51–4.82)	Pooled
Tang & Yang, 2025[20]	China	Neoadjuvant therapy + surgery	NRI, preoperative (low vs high)	319	2.01 (1.07–3.76)	Pooled
Wu et al, 2023[21]	China	Immunotherapy (ICI)	PNI (<40.6 vs ≥40.6)	78	2.44 (1.01–5.89)[d]	Pooled
Gao et al, 2022[22]	China	Immunotherapy (anti-PD-1)	NLR (≥5 vs <5)	140	4.01 (2.28–7.06)	Pooled
Hirahara et al, 2018[23]	Japan	Surgery alone	PNI (<49.2 vs ≥49.2)	169	2.25 (interval not recoverable)	Narrative only[e]
Nakatani et al, 2017[24]	Japan	Neoadjuvant chemotherapy + surgery	PNI, preoperative (low vs high)	66	Significant on multivariable analysis; estimate not recoverable	Narrative only[e]
Feng et al, 2024[25]	China	Neoadjuvant immunochemotherapy	GNRI (low vs high)	224	0.29 as published[f] (interval not recoverable)	Narrative only[e]
Wang et al, 2025[26]	China	Immunotherapy (metastatic/ unresectable)	GNRI (continuous, per unit)	677	0.65 per unit (0.53–0.79)	Narrative only[f]
Feng et al, 2025[27]	China	Neoadjuvant immunochemotherapy	GINI (continuous, per unit)	138	1.01 per unit (p=0.012)	Narrative only[f]

CI, confidence interval; CRT, chemoradiotherapy; ESCC, esophageal squamous cell carcinoma; GINI, global immune-nutrition-inflammation index; GNRI, geriatric nutritional risk index; HR, hazard ratio; ICI, immune checkpoint inhibitor; N, sample size; NLR, neutrophil-to-lymphocyte ratio; NRI, nutritional risk index; PNI, prognostic nutritional index; RT, radiotherapy.

[a] All hazard ratios are direction-standardised to express the hazard of death associated with the adverse (low-nutritional or high-inflammatory) category, except where the row explicitly states the value as published.

[b] Excluded from the primary analysis to avoid counting the same 1,265 patients twice; substituted for the PNI estimate in sensitivity analysis A.

[c] Same institution (Yokohama City University) and overlapping accrual period as Kato et al; excluded from the primary analysis and substituted in sensitivity analysis B.

[d] Direction-standardised by inversion from the published HR of 0.41 (95% CI 0.17–0.99) for high versus low PNI.

[e] Clinically eligible but not poolable: the 95% confidence interval for the categorical estimate could not be recovered from the published report.

DOI: 10.67692/IODT.26.2734

[f] Clinically eligible but not poolable: effect reported only on a continuous per-unit scale, not convertible to the categorical comparison used in this synthesis. The Feng 2024 value of 0.29 is reproduced as published (favourable category as reference) and was not inverted because no interval was available for interval-level standardisation.

All 15 study-index observations derive from retrospective designs; the Yoon et al 2021 report contributed PNI and GNRI estimates from the same 1,265-patient cohort. Superscript numerals refer to the reference list.

Methodological characteristics

The criterion-based appraisal is presented in Table 2. All fifteen study-index observations derive from retrospective designs, and thirteen were single-centre. Most importantly, eleven of the fifteen derived the index cut-off from their own outcome data by receiver-operating-characteristic or X-tile analysis rather than applying a pre-specified external threshold—a data-dependent procedure that systematically inflates apparent effect size and is the single most important methodological limitation of this literature. All pooled estimates were adjusted in a multivariable model. A formal ROBINS-I assessment was not performed because full-text verification of design and confounding detail could not be confirmed for every report; the five criteria above are reported factually rather than converted into a summary bias judgement, so that readers may weight studies themselves. No included study reported external validation of its cut-off in an independent cohort.

Table 2. Criterion-based methodological appraisal of the 15 eligible study-index observations.

Study	Design	Centres	N	Cut-off derived from study's own outcome data	Multivariable-adjusted HR
Yoon et al, 2021[14]	Retrospective	Single	1,265	No (pre-specified risk bands)	Yes
Kato et al, 2024[15]	Retrospective	Single	187	No (established cut-off <98)	Yes
Xiao et al, 2016[16]	Retrospective	Single	121	Yes (ROC)	Yes
Yamamoto et al, 2025[17]	Retrospective	Single	180	Yes (ROC)	Yes
Ho et al, 2021[18]	Retrospective	Single	101	Yes (ROC)	Yes
Bo et al, 2016[19]	Retrospective	Single	239	No (established risk bands)	Yes
Tang & Yang, 2025[20]	Retrospective	Single	319	Yes (ROC)	Yes
Wu et al, 2023[21]	Retrospective	Single	78	Yes (X-tile)	Yes
Gao et al, 2022[22]	Retrospective	Multi	140	Yes (ROC)	Yes
Hirahara et al, 2018[23]	Retrospective	Single	169	Yes (ROC)	Yes
Nakatani et al, 2017[24]	Retrospective	Single	66	Yes (ROC)	Yes
Feng et al, 2024[25]	Retrospective	Single	224	Yes (ROC)	Yes
Wang et al, 2025[26]	Retrospective	Single	677	Yes (ROC)	Yes
Feng et al, 2025[27]	Retrospective	Single	138	Yes (ROC)	Yes

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Study	Design	Centres	N	Cut-off derived from study's own outcome data	Multivariable-adjusted HR
Yoon et al, 2021 (GNRI)[14]	Retrospective	Single	1,265	No (pre-specified risk bands)	Yes

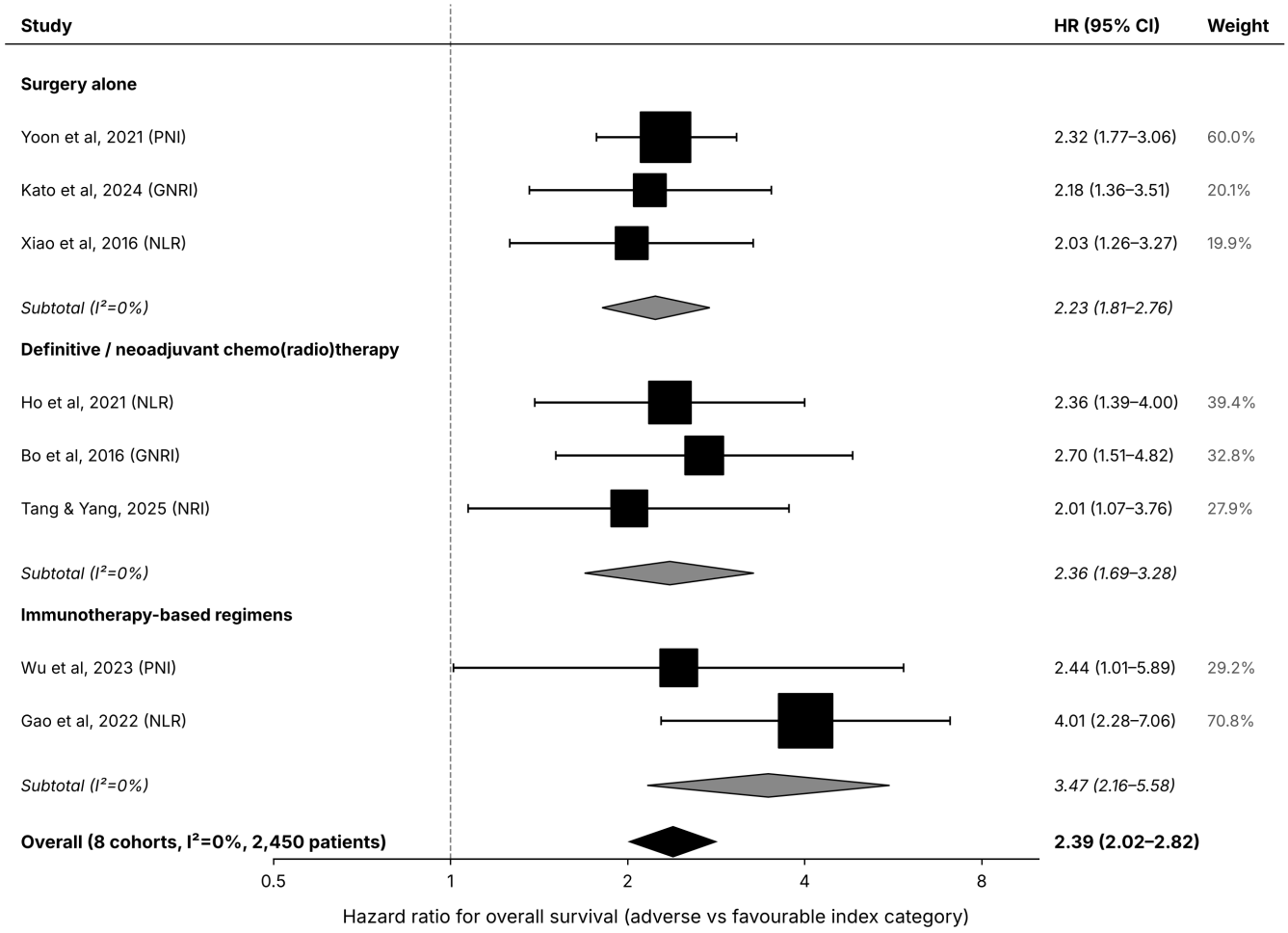
HR, hazard ratio; N, sample size; ROC, receiver operating characteristic.

Derivation of the cut-off from the study's own survival data (11 of 15 observations) is a data-dependent procedure that systematically inflates apparent effect size and is the dominant methodological weakness of this literature.

Primary analysis

Across eight independent cohorts, an adverse composite index category was associated with a pooled hazard ratio for death of 2.39 (95% CI 2.02–2.82; Figure 2). The Cochran Q test was non-significant (Q=4.33, df=7, p=0.741) with I^2=0% and τ^2=0, and the 95% prediction interval was 1.20–4.77. As addressed in the Discussion, we interpret this apparent absence of heterogeneity cautiously rather than as a strength.

Figure 2. Forest plot of the primary analysis: eight independent cohorts by treatment setting. Squares denote study-specific hazard ratios, sized by random-effects weight; grey diamonds denote subgroup pooled estimates and the black diamond denotes the overall pooled estimate. HR>1 indicates worse survival with the adverse index category. Random-effects (DerSimonian–Laird) model throughout.



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Subgroup analysis by treatment setting

Point estimates were consistent across all three pre-specified settings: surgery alone (k=3, HR 2.23, 95% CI 1.81–2.76), definitive or neoadjuvant chemo(radio)therapy (k=3, HR 2.36, 95% CI 1.69–3.28), and immunotherapy-based regimens (k=2, HR 3.47, 95% CI 2.16–5.58). Each subgroup confidence interval excluded unity. However, the 95% prediction interval for the surgery-alone subgroup crossed unity (0.89–5.59), as did that for the chemo(radio)therapy subgroup (0.66–8.42), indicating that a future study in either setting could plausibly observe no association. No prediction interval could be computed for the immunotherapy subgroup, which contained only two cohorts. Formal testing for subgroup differences was not performed, as two to three cohorts per stratum provide no meaningful power to detect interaction.

Sensitivity and leave-one-out analyses

The pooled estimate was robust across all eight leave-one-out iterations (HR 2.27–2.45), with the lower bound of the confidence interval remaining above 1.9 throughout. Three pre-specified sensitivity analyses gave concordant results: substituting the alternative index estimate for the dual-estimate cohort yielded HR 2.45 (95% CI 2.03–2.97); substituting the alternative institutionally overlapping surgical cohort yielded HR 2.39 (95% CI 2.01–2.82); and excluding the dominant cohort entirely, which contributed 37% of the weight, yielded HR 2.43 (95% CI 1.97–3.00). For transparency, the naive analysis retaining all ten estimates—which double-counts one cohort and one institution—yielded a spuriously more precise HR of 2.38 (95% CI 2.05–2.77); the narrowing of that interval relative to the primary analysis illustrates the artificial precision that unit-of-analysis error introduces (Table 3).

Table 3. Primary, subgroup, sensitivity, and leave-one-out results.

Analysis	Cohorts (k)	Patients	Pooled HR (95% CI)	I^2	95% prediction interval
Primary analysis (all settings)	8	2,450	2.39 (2.02–2.82)	0%	1.20–4.77
Subgroup: surgery alone	3	1,573	2.23 (1.81–2.76)	0%	0.89–5.59
Subgroup: chemo(radio)therapy	3	659	2.36 (1.69–3.28)	0%	0.66–8.42
Subgroup: immunotherapy-based	2	218	3.47 (2.16–5.58)	0%	Not estimable (k=2)
Sensitivity A: alternative index for dual-estimate cohort	8	2,450	2.45 (2.03–2.97)	0%	1.21–4.97
Sensitivity B: alternative overlapping surgical cohort	8	2,443	2.39 (2.01–2.82)	0%	1.19–4.79
Sensitivity C: dominant cohort excluded	7	1,185	2.43 (1.97–3.00)	0%	1.14–5.17
Leave-one-out range (8 iterations)	7 each	—	2.27–2.45	0%	—
Naive analysis retaining all estimates[a]	10	3,895[b]	2.38 (2.05–2.77)	0%	1.25–4.53

CI, confidence interval; HR, hazard ratio; k, number of cohorts.

All estimates from a random-effects (DerSimonian–Laird) model. Prediction intervals require k≥3 and are not estimable for the immunotherapy subgroup.

[a] Presented for transparency only and not used for any inference: this analysis double-counts one cohort (two indices from the same 1,265 patients) and one institution. Its narrower

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confidence interval relative to the primary analysis illustrates the artificial precision produced by unit-of-analysis error.

[b] Patient total is inflated by double-counting and does not represent independent patients.

Egger's regression test of the intercept for the primary analysis: intercept 0.47, standard error 0.90, p=0.621. With k=8 this test is substantially underpowered and is not interpreted as evidence against publication bias.

Small-study effects

Egger's regression test of the intercept was non-significant for the overall analysis (intercept 0.47, standard error 0.90, p=0.621). With only eight cohorts this test has very low power, and we explicitly do not interpret it as evidence against publication bias.[12] Given that small positive prognostic-biomarker studies are substantially more likely to be published than small null ones, undetected small-study effects remain a plausible contributor to the pooled estimate.

Certainty of evidence

GRADE certainty for the primary outcome was rated low (Table 4). Starting from low certainty for an exclusively observational evidence base, we downgraded one level for risk of bias, reflecting near-universal data-dependent cut-off derivation, and one level for indirectness, reflecting the pooling of four distinct indices with non-interchangeable thresholds across a predominantly East Asian population. We upgraded one level for a large magnitude of effect, all subgroup point estimates exceeding a hazard ratio of 2.0. Certainty for the immunotherapy subgroup, resting on two small cohorts, was rated very low.[13]

Table 4. GRADE summary of findings for overall survival.

Outcome	Cohorts (patients)	Pooled HR (95% CI)	Certainty	Rationale
Overall survival, all settings	8 (2,450)	2.39 (2.02–2.82)	⨁⨁◯◯ Low	Observational start (low); −1 risk of bias (in-sample cut-off derivation in 11/15 observations); −1 indirectness (four non-interchangeable indices, predominantly East Asian); +1 large effect (all estimates HR>2)
Overall survival, surgery alone	3 (1,573)	2.23 (1.81–2.76)	⨁⨁◯◯ Low	As above; prediction interval crosses unity, but effect magnitude and consistency retained
Overall survival, chemo(radio)therapy	3 (659)	2.36 (1.69–3.28)	⨁◯◯◯ Very low	As above, with −1 further for imprecision (k=3; prediction interval 0.66–8.42 crosses unity)
Overall survival, immunotherapy-based	2 (218)	3.47 (2.16–5.58)	⨁◯◯◯ Very low	As above, with −1 further for imprecision (k=2, 218 patients; heterogeneity and prediction interval not estimable)

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CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio.

All evidence began at low certainty, deriving exclusively from retrospective observational cohorts.

⨁⨁⨁⨁ High; ⨁⨁⨁◯ Moderate; ⨁⨁◯◯ Low; ⨁◯◯◯ Very low.

No outcome reached moderate or high certainty. These ratings do not support incorporation of these indices into treatment-selection decisions.

Narrative synthesis of non-pooled studies

Five eligible reports could not be pooled. In 169 patients undergoing curative esophagectomy, a low PNI was an independent predictor of both overall and cancer-specific survival, with a reported hazard ratio of 2.25 for overall survival, but the published report provided p-values without a recoverable confidence interval.[23] In 66 patients receiving neoadjuvant chemotherapy, preoperative—but not pretreatment—PNI was independently prognostic for overall and recurrence-free survival, again without an extractable categorical interval.[24]

Two reports from the immunotherapy setting are directly relevant to the question posed by this synthesis but were reported on incompatible scales. In 224 patients receiving neoadjuvant immunochemotherapy, GNRI was independently associated with both overall and disease-free survival (reported hazard ratio 0.29 for the favourable category), without a recoverable interval.[25] In 677 patients receiving immunotherapy for metastatic, recurrent, or unresectable disease—by some margin the largest cohort identified in this review—GNRI modelled continuously independently predicted overall survival (HR 0.65 per unit, 95% CI 0.53–0.79) and outperformed PD-L1 expression for survival prediction.[26] That the largest and most contemporary cohort in this literature could not enter the quantitative analysis is a material limitation of the pooled estimate.

Evidence for GINI outside the surgical setting remains limited to a single cohort of 138 patients receiving neoadjuvant immunochemotherapy, in which pretreatment GINI independently predicted both pathological response and overall survival, but only as a continuous per-unit estimate (HR 1.01 per unit, p=0.012) reflecting the very large numeric range of this multiplicative index.[27] The newest index in this family therefore has essentially no categorical, poolable evidence base beyond primary surgery, and conclusions about GINI should be regarded as preliminary.

DISCUSSION

Across eight independent retrospective cohorts comprising 2,450 patients, an adverse composite nutritional-inflammatory index category was associated with approximately a doubling of the hazard of death, and this association was of similar magnitude whether patients were treated with surgery alone, chemo(radio)therapy, or immunotherapy-based regimens. The finding was stable across leave-one-out and three pre-specified sensitivity analyses.

The consistency across settings is biologically coherent. Malnutrition and systemic inflammation converge on impaired anti-tumour immune surveillance and reduced treatment tolerance, a relationship established in the cancer cachexia literature,[28] and would be expected to compromise outcomes irrespective of treatment modality. Because PNI, GNRI, and NLR each combine markers of the same two underlying axes—nutritional reserve and inflammatory or immune competence—in modestly different mathematical forms, the similar hazard

DOI: 10.67692/IODT.26.2734

magnitudes we observed most likely reflect overlapping biological signal rather than four independent sources of prognostic information. This has a direct practical implication: measuring several of these indices in the same patient is unlikely to add incremental value over measuring one well.

Our estimates are directionally concordant with, though numerically larger than, prior index-specific syntheses: a GNRI-focused meta-analysis in esophageal cancer reported a pooled overall-survival hazard ratio of 1.75 (95% CI 1.45–2.10) across eleven studies,[5] and an NLR-focused synthesis restricted to the neoadjuvant setting reported 1.99 (95% CI 1.43–2.76) across eleven studies.[6] Those syntheses each drew on more studies than ours within their narrower scope. We regard the larger point estimates in our analysis as more likely to reflect selection of a small number of strongly positive, categorically reported cohorts than a true difference in the underlying association—an interpretation that argues for caution rather than for emphasising our higher figure.

The apparent absence of heterogeneity (I^2=0%, τ^2=0) in every stratum deserves scepticism rather than celebration. It is implausible that four different biomarkers, applied at study-specific cut-offs across three treatment settings and four countries, generate truly homogeneous effects. A more credible explanation is that our restrictive pooling criteria—admitting only categorical estimates with recoverable intervals—selected a narrow and mutually similar subset of a genuinely heterogeneous literature, while I^2 is known to be unreliable and biased toward zero when few studies contribute. The wide prediction intervals, two of which cross unity, convey the underlying uncertainty far better than I^2 does and should be regarded as the more informative statistic.[29]

The strengths of this work are its explicit organisation around the treatment continuum rather than a single modality; direction-standardised pooling that avoided conflating categorical with continuous estimates; explicit detection and removal of duplicate and institutionally overlapping cohorts, with the naive double-counted analysis reported alongside for comparison; and transparent labelling of search intensity and certainty.[7]

The limitations are substantial and constrain interpretation. The search was structured but non-exhaustive, conducted without a registered protocol, and screened by a single reviewer, so eligible studies were probably missed and the possibility that they differ systematically from those included cannot be excluded. Only eight cohorts entered the primary analysis, with two to three per subgroup, precluding subgroup-interaction testing and leaving the immunotherapy estimate resting on 218 patients. All included evidence is retrospective and predominantly East Asian, limiting generalisability to Western populations where adenocarcinoma predominates. Eleven of fifteen observations derived cut-offs from their own outcome data, which inflates apparent effect sizes across this entire literature. Five eligible reports—including the largest and most contemporary immunotherapy cohort, and the only immunotherapy-era GINI evidence—could not be pooled. Egger’s test is uninterpretable at this number of studies.[12] Finally, the design permits no causal inference: whether correcting an adverse index before treatment improves survival is entirely untested.

These findings do not support using composite indices to select or withhold any oncological treatment modality, and we would specifically caution against interpreting the numerically larger immunotherapy-subgroup estimate as evidence that these indices matter more before ICI therapy, since it rests on two small cohorts with overlapping confidence intervals. What the evidence does reasonably support is pragmatic: these indices cost nothing beyond a routine

DOI: 10.67692/IODT.26.2734

complete blood count and albumin, and an adverse value is a reasonable trigger for formal nutritional assessment and supportive-care referral alongside standard treatment.[10]

Priorities for future research follow directly from the limitations above. Prospective, protocol-registered cohorts are needed in non-East-Asian and adenocarcinoma-predominant populations; cut-offs require external derivation and validation rather than in-sample optimisation; investigators should report categorical alongside continuous estimates so that findings remain poolable, which would immediately have admitted three of our five excluded reports; and head-to-head comparison of indices within single cohorts is needed to establish whether any offers incremental value over the others. Whether nutritional intervention modifies outcome in patients identified as high-risk by these indices is an interventional question that this literature cannot answer and that no included study addressed.[28]

CONCLUSION

In this rapid evidence synthesis, an adverse composite nutritional-inflammatory index category was associated with approximately double the hazard of death across the surgical, chemo(radio)therapy, and immunotherapy-based esophageal cancer treatment continuum, with a pooled hazard ratio of 2.39 (95% CI 2.02–2.82) and low GRADE certainty. Given a non-exhaustive search, an exclusively retrospective and predominantly East Asian evidence base, near-universal in-sample cut-off derivation, and prediction intervals that cross unity in two of three settings, these results are hypothesis-generating. They justify prospective validation with externally derived cut-offs, not immediate incorporation into treatment-selection algorithms.

Declarations

Funding: This research received no external funding.

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

Author Contributions: M.C. conceived the review question, led the literature search and record screening, extracted and tabulated data, drafted the Introduction and Narrative Synthesis sections, and participated in revising the manuscript. T.M. developed the methodological and analytical framework, performed the random-effects meta-analysis including subgroup, leave-one-out, and sensitivity analyses, computed prediction intervals, led the GRADE assessment, drafted the Methods, Results and Discussion, and supervised the overall project. Both authors verified every included reference against the primary published source, independently re-checked all numerical results, and read and approved the final version of the manuscript. T.M. is the corresponding author and accepts full responsibility for the integrity of the work and the decision to submit for publication.

Data Availability Statement: All data supporting this synthesis are extracted from previously published reports and are presented in full in Tables 1–4 and Figures 1–2. The Python analysis code used to compute all pooled estimates, prediction intervals, leave-one-out iterations and sensitivity analyses, together with the extracted study-level dataset, is available from the corresponding author on reasonable request.

Ethics Approval: Not applicable. This work is a synthesis of previously published aggregate data and did not involve human subjects, identifiable patient data, or primary data collection; institutional ethics approval was therefore not required.

Use of Artificial Intelligence: A large language model was used to assist with iterative literature identification, drafting of the manuscript, and computation of the pooled estimates. All included references were verified by the authors against the published source records, and all

DOI: 10.67692/IODT.26.2734

reported numerical results were independently checked by the authors. The authors accept full responsibility for the content, integrity, and conclusions of this work.

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