

Anastomotic leakage and long-term survival after minimally invasive esophagectomy: a retrospective cohort study

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Abstract

Background

Whether anastomotic leakage affects long-term survival after esophagectomy for esophageal squamous cell carcinoma remains disputed. We assessed the association between anastomotic leakage and overall survival after minimally invasive esophagectomy using complementary methods for confounding control.

Methods

We retrospectively analyzed 618 patients with esophageal squamous cell carcinoma who underwent curative-intent minimally invasive esophagectomy (2012–2017) without neoadjuvant therapy at a single high-volume center. Anastomotic leakage ($n = 96$) was analyzed using inverse probability of treatment weighting, time-dependent Cox regression, propensity score matching, landmark analysis, conditional survival, restricted mean survival time, and E-value analysis. A nomogram was constructed for risk stratification.

Results

Anastomotic leakage occurred in 15.5% of patients. Inverse probability of treatment weighting showed leakage was independently associated with poorer overall survival (hazard ratio 1.907, 95% confidence interval 1.318–2.759, $p < 0.001$), corroborated by time-dependent Cox (1.926), multivariable Cox (1.926), and propensity score matching (2.195). Multi-time-point landmark analyses demonstrated significant associations at every timepoint (3–24 months, all $p \leq 0.012$), with no evidence that the effect changed over time ($p = 0.44$). Five-year restricted mean survival time was 7.65 months shorter with leakage. Graded by treatment intensity, the adjusted hazard ratio was 1.56 (95% confidence interval 0.97–2.49) for conservatively managed leaks and 2.55 (1.54–4.22) for leaks requiring interventional or surgical management (p for trend < 0.001). A nomogram incorporating leakage achieved a C-index of 0.715 (95% CI 0.691–0.716) versus 0.697 for tumour-node-metastasis staging alone, with an integrated discrimination improvement of 0.056 at 3 years.

Conclusions

Anastomotic leakage was independently associated with inferior overall survival after minimally invasive esophagectomy for esophageal squamous cell carcinoma, with significant prognostic impact persisting across all postoperative landmark timepoints. These findings support continued efforts to prevent leakage and suggest a role for risk-stratified surveillance after leakage.

Background

Esophageal cancer is the seventh most common malignancy and sixth leading cause of cancer death worldwide, with esophageal squamous cell carcinoma (ESCC) predominating in East Asia [1]. Despite advances in minimally invasive esophagectomy (MIE), long-term survival remains poor, underscoring the need for modifiable prognostic factors.

Anastomotic leakage (AL) occurs in 5%-25% of esophagectomy cases [2]. Beyond immediate morbidity, AL may adversely affect long-term survival.

The literature is inconsistent. Several studies report an independent association between AL and diminished overall survival (OS) [3, 4, 5, 6, 7, 8], whereas others find no independent association after adjustment and attribute the apparent decrement to confounding [9, 10, 11].

Whether treating AL as a time-fixed versus time-dependent exposure alters the estimated effect on survival remains unresolved [12, 13].

Two features of this literature make the estimates difficult to compare. The first is that leakage occurs after surgery rather than at baseline, so any analysis that enters it as a fixed exposure assigns patients who died before a leak could declare itself to the unexposed group, creating a stretch of follow-up during which death was impossible [12, 13]. The second is that the adjustments available in routine datasets seldom reach the factors most likely to matter: how severe the leak was, how promptly it was controlled, and how much nutritional reserve the patient had.

We therefore applied complementary analytical approaches that address different sources of bias—inverse probability of treatment weighting (IPTW), time-dependent Cox regression, propensity score matching (PSM), restricted mean survival time (RMST) and E-value analysis—and hypothesised that AL is independently associated with overall survival after MIE for ESCC, with estimates robust across analytical approaches.

Methods

Study design and patient population

This retrospective cohort study was conducted at Fujian Medical University Union Hospital, a high-volume tertiary referral centre. We reviewed consecutive ESCC patients undergoing curative-intent MIE (2012–2017), with follow-up censored on 17 July 2019, excluding those with invalid or missing survival data. MIE was adopted for its favorable perioperative profile relative to open esophagectomy [14, 15]. The exposure was AL status. As this was a retrospective review of a consecutive series, no a priori sample-size calculation was performed and all eligible patients were included.

Definitions and variable ascertainment

AL was defined as clinical or radiological evidence of anastomotic disruption confirmed by contrast esophagography, endoscopy, or computed tomography [16]. Overall survival (OS) was defined as the interval from surgery to death from any cause.

Because no severity grade had been recorded prospectively, we derived a treatment-based grade for each leak retrospectively from the recorded reintervention field, following the structure of the Esophageal Complications Consensus Group (ECCG) classification [16]: type I, no intervention or conservative management only (nil by mouth, dressing changes, nutritional support or medical treatment); type II, interventional management without thoracotomy (percutaneous or intercostal drain placement, endoscopic stenting or dilation); type III, surgical reintervention (re-exploration, debridement or repair by thoracoscopy, thoracotomy or cervical approach). Entries were classified with a prespecified rule set applied to the free-text records; 29 of the 96 leaks had no recorded reintervention and were classified as type I.

Baseline covariates considered were age, sex, smoking history, pathological T and N stage (from which pathological TNM stage was derived according to the 8th edition of the American Joint Committee on Cancer [AJCC] staging manual for oesophageal cancer), lymphovascular invasion (LVI), perineural invasion (PNI), tumour differentiation, body mass index (BMI), intraoperative blood loss, operative duration, and preoperative carcinoembryonic antigen (CEA). Anastomosis was predominantly cervical (McKeown, 73.9%), intrathoracic (Ivor-Lewis) in 7.8%, and unrecorded in 18.3%. For the multivariable model and nomogram we pre-specified anastomotic leakage and the seven covariates with established prognostic relevance (age, sex, smoking history, T3-4 stage, N stage as N0/N1/N2/N3, LVI and PNI); the five other candidates were excluded because none was associated with overall survival in univariable analysis (tumour differentiation $p = 0.28$, BMI $p = 0.91$, blood loss $p = 0.19$, operative time $p = 0.054$, CEA $p = 0.90$).

Smoking history was defined as any recorded cigarette use, that is, a recorded smoking duration greater than zero years or a recorded consumption greater than zero cigarettes per day. Patients were classified as smokers when either field indicated use, because 13 patients had one of the two fields missing while the other was clearly positive (for example, 20 cigarettes per day with duration unrecorded).

Statistical methodology

Continuous variables are summarised as mean $\pm$ standard deviation when approximately normally distributed and as median (interquartile range) otherwise, and are compared with the Mann-Whitney U test. Survival was estimated by the Kaplan-Meier method with log-rank comparison. Multivariable associations used Cox proportional hazards regression, and restricted mean survival time was estimated as described by Royston and Parmar [17]. Of 618 patients, 26 (4.2%) were excluded from multivariable analyses: 21 with an unrecorded T or N category and 5 with Tis disease and recorded staging. A further 12 patients with Tis disease also had unrecorded staging and are counted within the 21, giving 17 Tis tumours in total and leaving 592 patients for multivariable analysis.

The primary analysis used IPTW with propensity scores from logistic regression modeling the covariates listed above [18]. Weights were trimmed at the 1st/99th percentile and the weighted Cox model additionally adjusted for the same covariates, giving a doubly robust estimate. Variance was estimated with robust (sandwich) standard errors. Balance was confirmed by standardized mean differences (SMD) below 0.10 (Supplementary Table S1). The effective sample size after weighting was 290 (49% of 592), as expected given the 15.4% prevalence of leakage; weights ranged from 1.08 to 10.13, and no extreme weights were observed. As a further sensitivity analysis we repeated the weighted analysis using overlap weights [19], which constrain weights between 0 and 1 and yield exact covariate balance.

To circumvent immortal time bias, AL was modelled as a time-varying covariate in a start-stop format [12, 13]. As the exact onset date was not recorded, onset was assumed at postoperative day 7, consistent with the median time to clinical diagnosis [4, 20]; sensitivity analyses using days 1, 3, 14 and 21 yielded hazard ratios of 1.898–1.926 (all $p < 0.001$).

As sensitivity analyses, 1:1 PSM used nearest-neighbor matching with a caliper of 0.15 SD. Additional analyses included landmark analyses at 3, 6, 9, 12, 18 and 24 months; the 3-month landmark is mathematically equivalent to excluding 90-day mortality, as no death occurred within the first 15 postoperative days. Competing-risks regression was not performed because cause-of-death data were unavailable. E-values were computed to quantify the resilience of the primary estimate to unmeasured confounding [21]. Robustness was assessed by sequentially adding covariate blocks (age and sex; T and N stage; lymphovascular and perineural invasion; smoking) to the unadjusted model.

The proportional hazards assumption was assessed using Schoenfeld residuals. Because the landmark estimates drifted upward with time, we also tested for a time-dependent effect of AL using a flexible parametric Poisson spline model (3 df), cross-checked with step functions at 12, 18 and 24 months.

The relative excess risk due to interaction (RERI) was calculated [22] with 1000-bootstrap resampling. Pulmonary infection was defined as postoperative pneumonia within 30 days. Subgroup analyses were stratified by N stage, LVI, PNI, T stage, sex, age, smoking, BMI (< 24 vs ≥ 24 kg/m²) and preoperative CEA (> 5 vs ≤ 5 ng/mL). Interaction tests introduced AL $\times$ subgroup product terms into the multivariable Cox model, comparing nested models by likelihood ratio test; Bonferroni correction was applied for 18 comparisons ($\alpha = 0.0028$), with p values reported alongside the forest plot in Supplementary Figure S1.

Prognostic model. A nomogram for 3- and 5-year overall survival was constructed from the multivariable Cox model fitted in the 617 patients with complete data for all eight prespecified predictors (anastomotic leakage, age, sex, smoking history, T3-4 stage, N stage, LVI and PNI). Discrimination was quantified by Harrell's concordance index and by Uno's time-dependent area under the receiver operating characteristic curve at 3 and 5 years. Optimism was corrected using 2000 bootstrap resamples, from which the calibration slope was also obtained; calibration was displayed graphically by predicted-risk groups. Reclassification was summarised by the integrated discrimination improvement. The prediction model is reported in accordance with the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement.

All analyses were performed in Python 3.13 using lifelines 0.29.0, scikit-learn 1.5.0, and scipy 1.13.0. This observational study was reported per the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, with the completed checklist provided as Supplementary Material. Large language model tools were used only for language editing; no scientific content, data, results or conclusions were generated by these tools, and all output was reviewed and verified by the authors, who take full responsibility for the content.

Results

Patient characteristics and perioperative burden

Of 633 consecutive patients undergoing MIE (2012–2017), 15 with invalid survival data were excluded, leaving 618 for the primary survival analysis (96 with AL, 15.5%; 522 without). Three analytic cohorts were therefore derived: the full 618 for unadjusted analyses, 592 for multivariable Cox and IPTW, and 617 for the nomogram (1 patient excluded for missing smoking history). Of the 26 patients excluded from multivariable analysis, 5 had experienced AL, so the 592-patient analytic cohort comprised 91 patients with AL and 501 without, as shown in Table 1. A participant flow diagram is provided as Supplementary Figure S4. Baseline characteristics are in Table 1 and stratified by sex in Supplementary Table S2.

Table 1. Baseline clinicopathological characteristics

Characteristic	AL (n=91)	Non-AL (n=501)	p value
Age (years)	60.4±6.8	58.9±8.2	0.141
Male sex	72 (79.1)	374 (74.7)	0.437
Smoking history	56 (61.5)	273 (54.5)	0.258
T3-4 stage	59 (64.8)	263 (52.5)	0.039
N+ stage	42 (46.2)	237 (47.3)	0.93
LVI+	22 (24.2)	91 (18.2)	0.231
PNI+	22 (24.2)	72 (14.4)	0.028
BMI ≥24 kg/m²	27 (29.7)	123 (24.6)	0.367
CEA >5 ng/mL	11 (12.1)	42 (8.4)	0.348
LN yield ≥15	74 (81.3)	399 (79.6)	0.822

Abbreviations: AL, anastomotic leakage; BMI, body mass index; CEA, carcinoembryonic antigen; LN, lymph node; LVI, lymphovascular invasion; N, nodal stage; PNI, perineural invasion; T, tumour stage

AL was associated with prolonged hospital stay (37.1 vs 20.4 days, $p<0.001$), higher costs (10.96 vs 8.39 $\times 10^4$ CNY (Chinese yuan), $p<0.001$) and increased pulmonary infection (62.6% vs 27.0%, $p<0.001$)

(Supplementary Table S3). Operative time, blood loss and other complications were comparable. Leakage rates were comparable between cervical (15.8%) and intrathoracic (14.9%) anastomoses ($p=0.42$).

Primary analysis and temporal profile

After a median follow-up of 49.0 months, estimated by the reversed Kaplan-Meier method (observed follow-up range 0.5-88.2 months; interquartile range 24.4-59.1 months), 165 patients (26.7%) had died in the 618-patient cohort and 161 (27.2%) among the 592 with complete covariate data. Survival was lower with leakage throughout follow-up (Figure 1A).

In univariate Cox regression, AL was associated with inferior OS (hazard ratio [HR] = 1.969, $p<0.001$) and remained an independent prognostic factor after multivariable adjustment (HR = 1.926, 95% confidence interval (CI) 1.340–2.770; $p<0.001$; Table 2). Modelling AL as a time-varying covariate gave an identical estimate, because no patient died within the first 15 postoperative days (earliest death, day 16); the immortal-time window thus contained no events, leaving the partial likelihood unchanged.

Table 2. Survival analyses of AL and overall survival.

Analytical approach	HR	95% CI	p value	Sample size
Multivariable Cox (original)	1.926	1.340-2.770	<0.001	592
IPTW-weighted multivariable Cox (primary; doubly robust)	1.907	1.318-2.759	<0.001	592
Overlap-weighted Cox (sensitivity)	1.960	1.368-2.808	<0.001	592
Time-dependent Cox	1.926	1.340-2.770	<0.001	592
1:1 PSM Cox (sensitivity)	2.195	1.305-3.692	0.0030	182 (91 pairs)
3-month landmark (excluding 90-day mortality)	1.851	1.272-2.694	0.0013	586
6-month landmark	1.859	1.271-2.719	0.0014	582
9-month landmark	1.930	1.304-2.856	0.0010	572
12-month landmark	1.749	1.132-2.701	0.0117	552
18-month landmark	2.126	1.324-3.413	0.0018	512
24-month landmark	2.644	1.573-4.446	<0.001	447

Note: landmark analyses were significant at all timepoints (3–24 months). The 683 intervals in time-dependent Cox reflect 91 AL patients contributing 2 intervals each plus 501 non-AL patients ($91 \times 2 + 501 = 683$), consistent with the 592-patient cohort.

Abbreviations: AL, anastomotic leakage; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; OS, overall survival; PSM, propensity score matching

Figure 2 summarises the hazard ratios from all survival analyses. Sequential covariate adjustment yielded stable AL hazard ratios of 1.901–1.969 (all $p < 0.01$) (Supplementary Table S4).

After IPTW, all covariates were balanced ($SMD < 0.10$). The IPTW-weighted, covariate-adjusted Cox model confirmed the association (HR = 1.907, 95% CI 1.318–2.759; $p < 0.001$) (Table 2, Figure 1B). Repeating the analysis with overlap weights gave a consistent estimate (HR = 1.960, 95% CI 1.368–2.808; $p < 0.001$).

The 3-month landmark, mathematically equivalent to excluding 90-day mortality, confirmed the association persisted beyond perioperative mortality (HR = 1.851, 95% CI 1.272–2.694; $p = 0.0013$;

n=586); the 12-month landmark was also significant (HR = 1.749, 95% CI 1.132–2.701; p=0.012).

1:1 PSM (91 pairs) was significant (HR = 2.195, p=0.003), consistent with primary analyses.

Alternative AL onset assumptions (days 1, 3, 7, 14 and 21) gave hazard ratios of 1.898–1.926 (all p<0.001), identical up to day 14 and marginally lower at day 21, when one earlier death was reclassified as unexposed. No consistent evidence emerged that the effect varied over follow-up: the Schoenfeld test for AL gave p=0.87, the spline time-dependent term gave p=0.44, and step functions at 12, 18 and 24 months gave p=0.38, 0.48 and 0.097, with the early-versus-late contrast reversing by cut point. Only 72 deaths occurred after 24 months, so the penalty was persistent rather than progressive.

Landmark analyses at 3, 6, 9, 12, 18 and 24 months showed significant associations at every timepoint (HRs 1.749–2.644, all p≤0.012; Figure 3A). Point estimates drifted upward at later landmark timepoints, but formal testing gave no statistically significant time-dependent change, as reported above; the 24-month landmark comprised 447 patients with 72 subsequent deaths.

Among patients surviving beyond 12 months, the conditional probability of surviving to 36 months was 71.2% (AL) versus 82.1% (non-AL); beyond 24 months, the probability of reaching 48 months was 69.2% versus 87.0% [23].

RMST differences were –2.91 months at 36 months (95% CI –5.08 to –0.78; bootstrap p = 0.005), –5.06 months at 48 months (95% CI –8.63 to –1.61) and –7.65 months at 60 months (95% CI –12.49 to –3.39; bootstrap p = 0.0025). Because only 19 patients with leakage remained at risk at 60 months, compared with 121 without, that estimate rests on extrapolation beyond the observed follow-up and should be interpreted with caution; the 48-month estimate is the more reliable summary of the absolute deficit.

The E-value for the primary IPTW estimate was 3.22 (1.97 for the corresponding lower confidence bound). An unmeasured confounder would need to be associated with both leakage and mortality by a risk ratio of at least this magnitude to explain the association fully. Because several candidate confounders—leak severity, nutritional reserve and adjuvant therapy—could plausibly approach this magnitude, we regard the estimate as reasonably, but not entirely, robust to unmeasured confounding.

Leak severity and survival

Of the 96 leaks, 66 (68.8%) were managed conservatively (type I), 23 (24.0%) required interventional drainage (type II) and 7 (7.3%) required surgical reintervention (type III). Death occurred in 22 of 66 type I leaks (33.3%), 16 of 23 type II leaks (69.6%) and 4 of 7 type III leaks (57.1%).

Compared with patients without leakage, the adjusted hazard ratio was 1.557 (95% CI 0.973–2.490; p = 0.065) for type I leaks and 2.549 (95% CI 1.539–4.222; p < 0.001) for type II–III leaks (Supplementary Figure S5). Treating severity as an ordinal variable gave a hazard ratio of 1.589 per grade (95% CI 1.258–2.007; p < 0.001), and five-year survival was 71.3%, 62.6% and 27.1% among patients with no leak, type I

and type II–III leaks respectively (log-rank $p < 0.001$). The contrast between type II–III and type I leaks did not reach statistical significance (hazard ratio 1.637, 95% CI 0.859–3.121; $p = 0.134$), and these analyses are exploratory given the numbers in the higher grades.

Beyond leak severity, pathological stage modified the anastomotic-leak–survival association. Five-year overall survival (OS) by pathological TNM stage (AJCC 8th edition) and AL status is summarised in Table 3. The AL-associated survival deficit widened with advancing stage—from a negligible difference in stage I (90.7% vs 86.7%) to a 35.8-percentage-point gap in stage III (23.2% vs 59.0%)—with AL-positive stage III patients faring worst. Because the stage I and II AL-positive groups were small ($n=24$ and $n=34$), these estimates are descriptive and should not be read as evidence of stage-specific effect modification.

Table 3. Five-year overall survival by pathological TNM stage and anastomotic leakage status.

TNM stage	AL-positive	AL-negative
Stage I	90.7% (n=24)	86.7% (n=200)
Stage II	55.2% (n=34)	67.2% (n=118)
Stage III	23.2% (n=34)	59.0% (n=187)
All patients	51.7% (n=96)	71.6% (n=522)

Abbreviations: AL, anastomotic leakage; OS, overall survival. Five-year OS estimated by the Kaplan–Meier method. Twenty-one patients with undocumented pathological stage were excluded from the stage-stratified rows; the 'All patients' row reflects the entire cohort ($n=618$). Pathological stage was derived from pathological T and N categories per AJCC 8th edition (oesophagus): stage I = Tis/T1 N0, T1 N1, T2 N0; stage II = T2 N1, T3 N0; stage III = T3 N1, T4 any N, or any T with N2/N3 (T4 subclass not documented).

Subgroup analyses and combined effects

Subgroup analyses (Supplementary Table S5 and Supplementary Figure S1) showed the adverse AL effect was most pronounced in high-risk strata. After Bonferroni correction ($\alpha=0.0028$), it remained significant with nodal disease (HR = 2.442), lymphovascular invasion (HR = 2.558), perineural invasion (HR = 4.801), smoking (HR = 2.638) and BMI below 24 kg/m² (HR = 2.150).

The AL×smoking interaction was nominally significant ($p=0.004$) but did not meet the Bonferroni-corrected threshold of 0.0028; because 18 comparisons were tested, we regard this interaction as exploratory.

The effect appeared amplified with CEA above 5 ng/mL (HR = 4.879), although this did not survive Bonferroni correction. It was significant with BMI below 24 kg/m² (HR = 2.150, 95% CI 1.418–3.260; $p<0.001$) but not at or above 24 kg/m² (HR = 1.178, 95% CI 0.522–2.656; $p=0.694$) [24].

In males, AL was associated with worse survival (multivariable HR = 1.944, $p=0.001$); in females the association was not significant (HR = 1.58, 95% CI 0.62–4.04; $p=0.335$), likely reflecting limited power. The AL $\times$ sex interaction was nonsignificant ($p=0.69$; Supplementary Figure S1).

Mortality was lowest with neither complication and highest with both (22.5% vs 50.0%), intermediate in single-complication groups (35.1% and 28.8%; trend $p<0.001$). RERI was -0.084 (95% CI -1.734 to 1.285), indicating no additive interaction (Figure 4).

Nomogram and risk stratification

A nomogram incorporating AL with age, sex, smoking history, T stage, N stage, LVI and PNI predicted 3- and 5-year OS (Figure 5). It was developed in the 617 patients with complete model variables; the 21 patients with an unrecorded T or N category and the 17 with Tis disease were classified as non-advanced. To gauge the influence of this assumption, we note that estimates from the 592-patient cohort, from which all of these patients were excluded, were materially identical to those from the primary analysis (multivariable HR 1.926 versus IPTW 1.907).

The nomogram achieved a C-index of 0.715 (95% CI 0.691–0.716) in the 617 patients with complete model variables, compared with 0.697 for T and N stage alone. Bootstrap validation with 2000 resamples gave an optimism of 0.015, an optimism-corrected C-index of 0.700 and a calibration slope of 0.903 (95% CI 0.743–1.080), indicating minimal overfitting and good calibration. The increment in discrimination over TNM staging was modest (Δ C-index 0.018); nevertheless, adding leakage to the TNM model significantly improved model fit (likelihood ratio $\chi^2 = 14.7$, $df = 1$, $p < 0.001$) and yielded an integrated discrimination improvement of 0.056 at 3 years and 0.066 at 5 years. Calibration curves are in Supplementary Figure S2.

Decision curve analysis showed greater net benefit than TNM alone across threshold probabilities of 0.1–0.5 (Supplementary Figure S3).

Risk stratification identified three groups with 5-year mortality of 13.6% (low), 27.7% (intermediate) and 52.5% (high) (Figure 1C; Supplementary Table S6). Compared with the low-risk group, the adjusted hazard ratios were 2.23 (95% CI 1.35–3.68) for the intermediate-risk group and 5.27 (3.31–8.39) for the high-risk group.

Discussion

Principal findings

In this cohort, anastomotic leakage carried a durable prognostic penalty: an IPTW-adjusted hazard ratio of 1.907, reproduced by every sensitivity analysis. The penalty was not uniform: it was concentrated in leaks that required interventional or surgical management (HR 2.55, 95% CI 1.54–4.22), whereas

conservatively managed leaks carried a smaller and statistically non-significant excess risk (HR 1.56, 95% CI 0.97–2.49). The excess hazard was present at every landmark timepoint with no time-dependent change on formal testing, and among patients alive at 12 months the conditional probability of surviving a further 24 months (to 36 months) was 11 percentage points lower with a leak (71.2% versus 82.1%). Patients with nodal disease, lymphovascular or perineural invasion, and smokers bore the largest excess risk.

Reconciliation with prior literature: the methodological dimension

The literature remains split. Fransen et al. [4] reported an independent survival disadvantage after leakage (HR 1.68), as did a meta-analysis in the European Journal of Cardio-Thoracic Surgery (EJCTS) [3] and a more recent propensity-matched series [25]. By contrast, Zeng et al. [9] found no association (HR 1.08), and a 1539-patient European cohort reported a null estimate for long-term survival (HR 0.994, 95% CI 0.849–1.176) [2]. Three features plausibly account for this divergence. First, case mix differs: the null studies were predominantly adenocarcinoma and included open, transthoracic and transhiatal approaches, whereas our cohort was exclusively ESCC treated by minimally invasive McKeown resection; leak rates were nevertheless comparable across studies (15.5% here versus 19% in the largest null cohort), implying that differences in outcome reflect differences in population and in the severity distribution of leaks rather than in leak frequency. Second, treating leakage as a baseline exposure invites immortal time bias [12, 13]. Third, and most importantly, no study in this field has assigned severity prospectively with a standardised instrument; if the excess hazard is concentrated in leaks requiring intervention, studies enrolling different proportions of such leaks will necessarily diverge. We examined this possibility directly in the severity-stratified analysis described below.

The severity-stratified analysis suggests a further explanation. If the excess hazard is concentrated in leaks that require intervention, cohorts containing a smaller proportion of such leaks will attenuate, or fail to detect, the association. This may partly reconcile our positive estimate with the null result reported in a 1539-patient European cohort [2], in which both the case mix and the distribution of surgical approaches differed substantially from ours. It also implies that the prognostic penalty is not a uniform property of anastomotic leakage: conservatively managed leaks in this cohort carried a hazard ratio of 1.56 that did not reach statistical significance, whereas leaks requiring intervention carried a hazard ratio of 2.55, and five-year survival fell from 71.3% to 27.1% across that gradient. If confirmed, this would redirect attention from leakage per se to the early recognition and control of the leakage that matters most. Because severity was graded retrospectively, this gradient should be regarded as hypothesis-generating; prospective cohorts using standardised ECCG or SEAL grading are needed to establish it.

Modelling leakage as a time-varying covariate gave a hazard ratio (1.926) virtually identical to the conventional model, unsurprising when leakage declares itself around day 7 against a median follow-up of 49.0 months. We emphasise that this analysis is not an independent corroboration: because no death

occurred within the first 15 postoperative days, it is mathematically equivalent to the time-fixed model in this dataset. Its contribution is to show that immortal time bias does not explain our estimate, and therefore that immortal time bias is unlikely to explain the null results of earlier studies either. Sequential adjustment left the estimate unchanged (1.901–1.969), arguing against residual confounding by measured covariates.

Oncological mechanisms: why anastomotic leakage may impact survival

Mechanistic explanations for a survival deficit persisting after clinical resolution of a leak are likely biological rather than mechanical. Sustained systemic inflammation may create a microenvironment permissive to tumour proliferation and metastatic seeding [26, 27, 28], while the nutritional cost of prolonged fasting and parenteral nutrition depletes the reserve on which immune competence depends [29]. A third pathway is delayed or omitted adjuvant therapy: the convalescence imposed by a leak often precludes treatment within the safe window. Because adjuvant data were unavailable, this mechanism remains hypothetical [26, 27].

Our subgroup data fit this framework. The smoking interaction is biologically coherent, as smoking impairs healing and amplifies inflammation. The outsized hazard with CEA above 5 ng/mL (HR 4.879) suggests leakage harms most where tumour biology is already adverse, though this subgroup was small [30]. The stronger association with a lymph node yield of 15 or more (HR 1.820) likely reflects more accurate staging [31].

Clinical and translational implications

For the operating surgeon the message is that leakage should be regarded not merely as a cause of early morbidity but as a marker of substantially reduced long-term survival. Meticulous technique, early detection and aggressive management remain priorities [32], and patients who leak warrant closer clinical and oncological surveillance. Whether intensified surveillance improves outcome is untested, and our observational data do not establish that preventing a leak prolongs survival.

The stage-dependent gradient was steepest in stage III, where leakage was associated with a 35.8-percentage-point reduction in 5-year OS (23.2% vs 59.0%); these patients may merit intensified surveillance and earlier recurrence work-up.

The nomogram offers one way to formalise that surveillance. Discrimination improved only modestly over TNM staging (C-index 0.715 versus 0.697; optimism-corrected 0.700), yet the model separated three strata with five-year mortality of 13.6%, 27.7% and 52.5%, and adding leakage significantly improved both model fit and integrated discrimination. Whether these strata can guide follow-up intensity remains untested; pending external validation we regard the model as hypothesis-generating.

Study limitations

Several limitations temper these conclusions. The design is retrospective and single-centre. Leak severity was graded retrospectively from recorded reinterventions rather than assigned prospectively with a validated instrument such as ECCG or SEAL; 29 of 96 leaks had no recorded reintervention and were classified as type I, so some severe leaks may have been misclassified as mild. Any such misclassification would attenuate rather than exaggerate the severity gradient we observed. Leak onset was assumed at day 7, although sensitivity analyses across days 1 to 21 were reassuring. Adjuvant therapy data were unavailable, leaving one mechanistic pathway untested, and without cause-of-death information we could not perform competing-risks analysis. We analysed overall survival only; disease-free and cancer-specific survival were not available, so the excess hazard cannot be attributed specifically to recurrence rather than to non-cancer deaths. Median follow-up was 49.0 months, but only 19 patients with leakage remained at risk at 60 months, so the 60-month estimates rest on extrapolation. Ninety-day mortality in this high-volume cohort was 1.0% (6 deaths among 592 patients), lower than the 30-day mortality reported in comparable series, and 15 patients were excluded for invalid survival data; we cannot fully exclude under-ascertainment of early postoperative deaths. The nomogram awaits external validation.

Future research should externally validate the nomogram in independent, preferably multicentre, cohorts and prospectively test whether intensified surveillance or earlier initiation of adjuvant therapy in stage III patients who develop anastomotic leakage improves long-term survival.

Conclusions

Across complementary analytical approaches, AL was independently associated with poorer overall survival after MIE for ESCC (IPTW-adjusted HR = 1.907). The association persisted across all landmark timepoints (3–24 months) without attenuation and was corroborated by conditional survival gradients and RMST deficits. Patients with perineural invasion, nodal disease or a smoking history bore the greatest excess risk. Because these data are observational, they support but do not establish a causal contribution of postoperative complications to long-term survival; confirmation will require prospective cohorts with standardised leak severity grading and with data on recurrence and adjuvant therapy.

Abbreviations

AL: Anastomotic leakage; ESCC: Esophageal squamous cell carcinoma; MIE: Minimally invasive esophagectomy; OS: Overall survival; IPTW: Inverse probability of treatment weighting; PSM: Propensity score matching; RMST: Restricted mean survival time; LVI: Lymphovascular invasion; PNI: Perineural invasion; HR: Hazard ratio; CI: Confidence interval; SMD: Standardized mean difference; CEA: Carcinoembryonic antigen; BMI: Body mass index.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Fujian Medical University Union Hospital (Ethics No. 2024KY060). The requirement for informed consent was waived owing to the retrospective study design.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available owing to institutional restrictions, but are available from the corresponding author on reasonable request. De-identified participant data and analysis code will be deposited in a public repository on publication.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceptualization: K.P., S.C.; Methodology: K.P., G.H.; Software: K.P., G.H.; Validation: K.P., G.H., P.Z.; Formal analysis: G.H., K.P.; Investigation: G.H., P.Z.; Resources: M.K.; Data curation: G.H., P.Z.; Writing—original draft: K.P.; Writing—review and editing: all authors; Visualization: K.P., G.H.; Supervision: P.Z., M.K.; Project administration: M.K.; Funding acquisition: M.K. K.P. and G.H. contributed equally as co-first authors.

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analysis. All AI-generated content was reviewed and verified by the authors, who take full responsibility for the content. The scientific content, study design, statistical analyses, and interpretation of results were entirely authored by the investigators.

Authors' information

Not applicable

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Figures

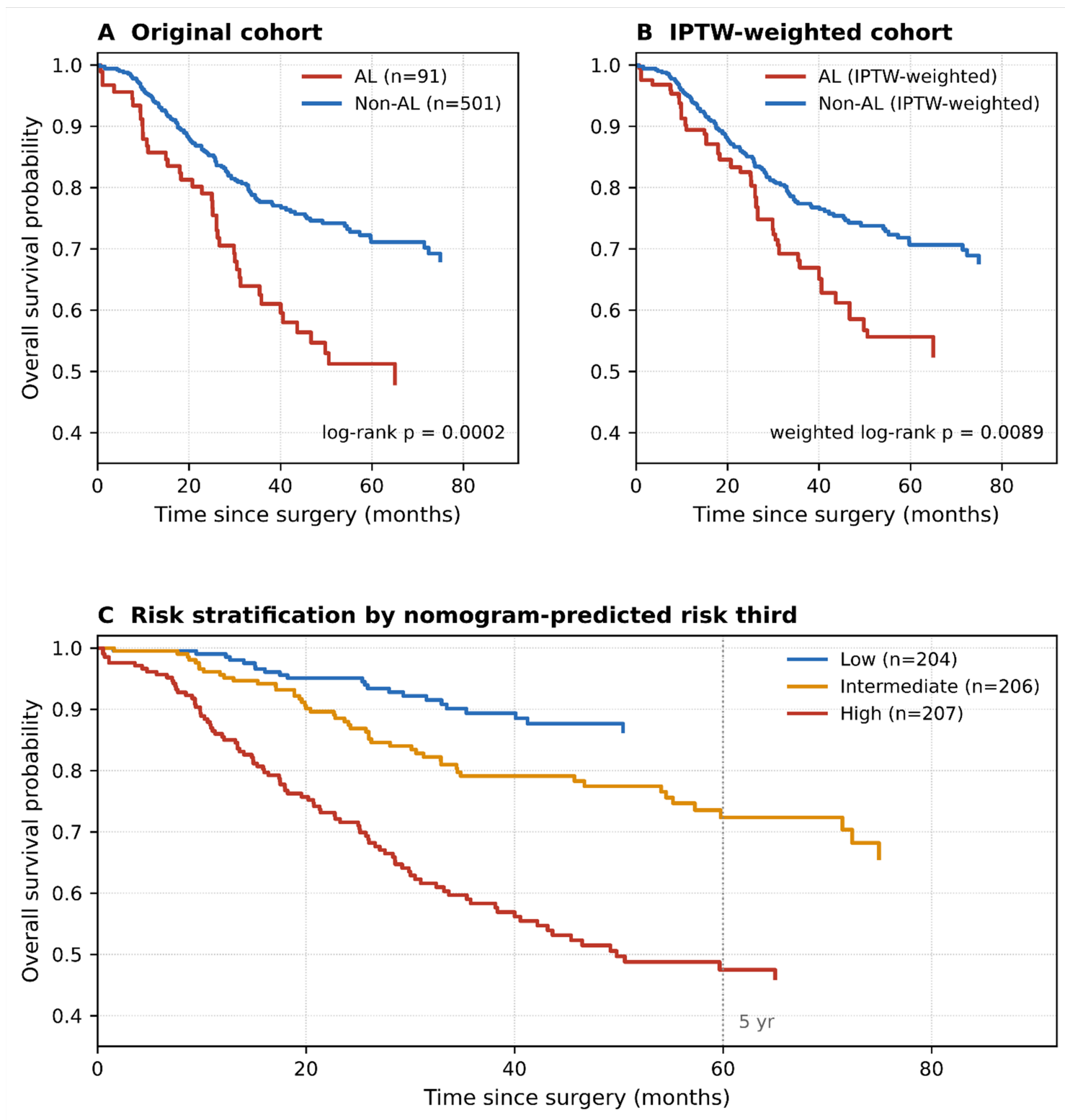


Figure 1

Kaplan-Meier survival curves. (A) Unadjusted cohort. (B) IPTW-weighted cohort. (C) Risk stratification by nomogram-predicted score tertiles. Five-year mortality by stratum: low 13.6%, intermediate 27.7%, high 52.5% (n=204, 206, 207). Panels A and B show the 592-patient analytic cohort; panel C the 617 patients with complete nomogram variables. AL, anastomotic leakage; IPTW, inverse probability of treatment weighting.

Summary of survival analyses evaluating anastomotic leakage and ov

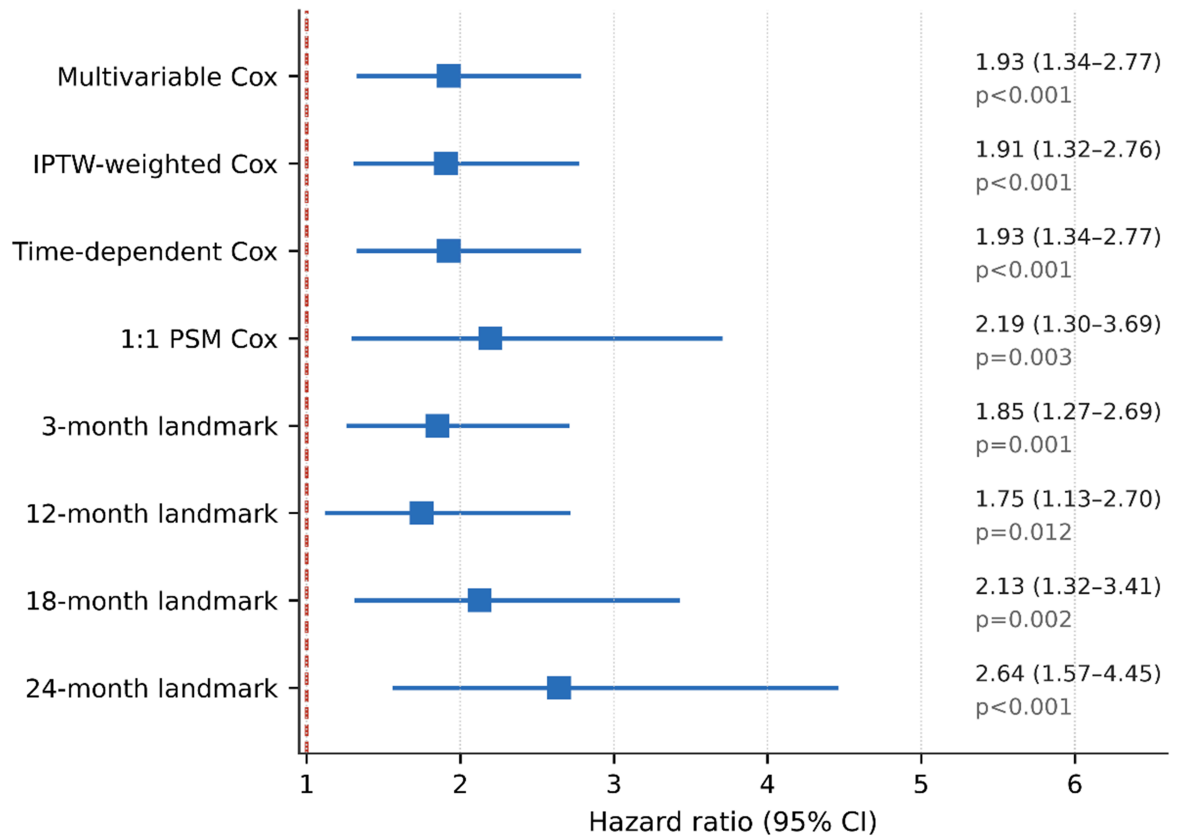


Figure 2

Forest plot of all survival analyses. Blue squares denote significant results ($p < 0.05$); gray squares non-significant. The dashed red line indicates $HR = 1.0$. IPTW, inverse probability of treatment weighting; PSM, propensity score matching.

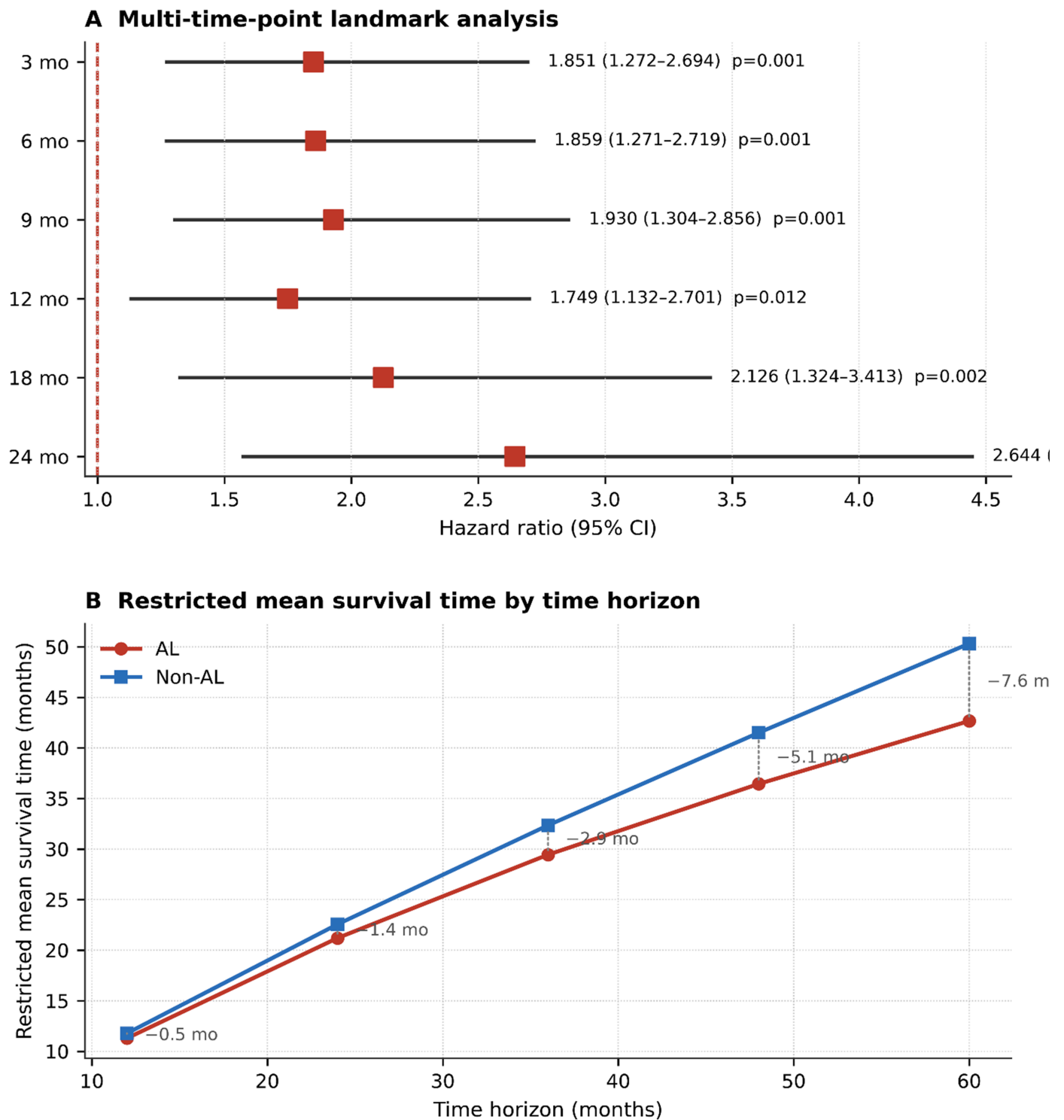


Figure 3

Temporal profile of the AL–survival association. (A) Landmark hazard ratios (95% CI) at 3, 6, 9, 12, 18 and 24 months (all $p \leq 0.012$). (B) Restricted mean survival time (RMST) differences from 12 to 60 months: -2.91 months at 36 months (95% CI -5.08 to -0.78), -5.06 months at 48 months (95% CI -8.63 to -1.61) and -7.65 months at 60 months (95% CI -12.49 to -3.39). Numbers at risk at 60 months were 19 with leakage and 121 without. AL, anastomotic leakage; RMST, restricted mean survival time.

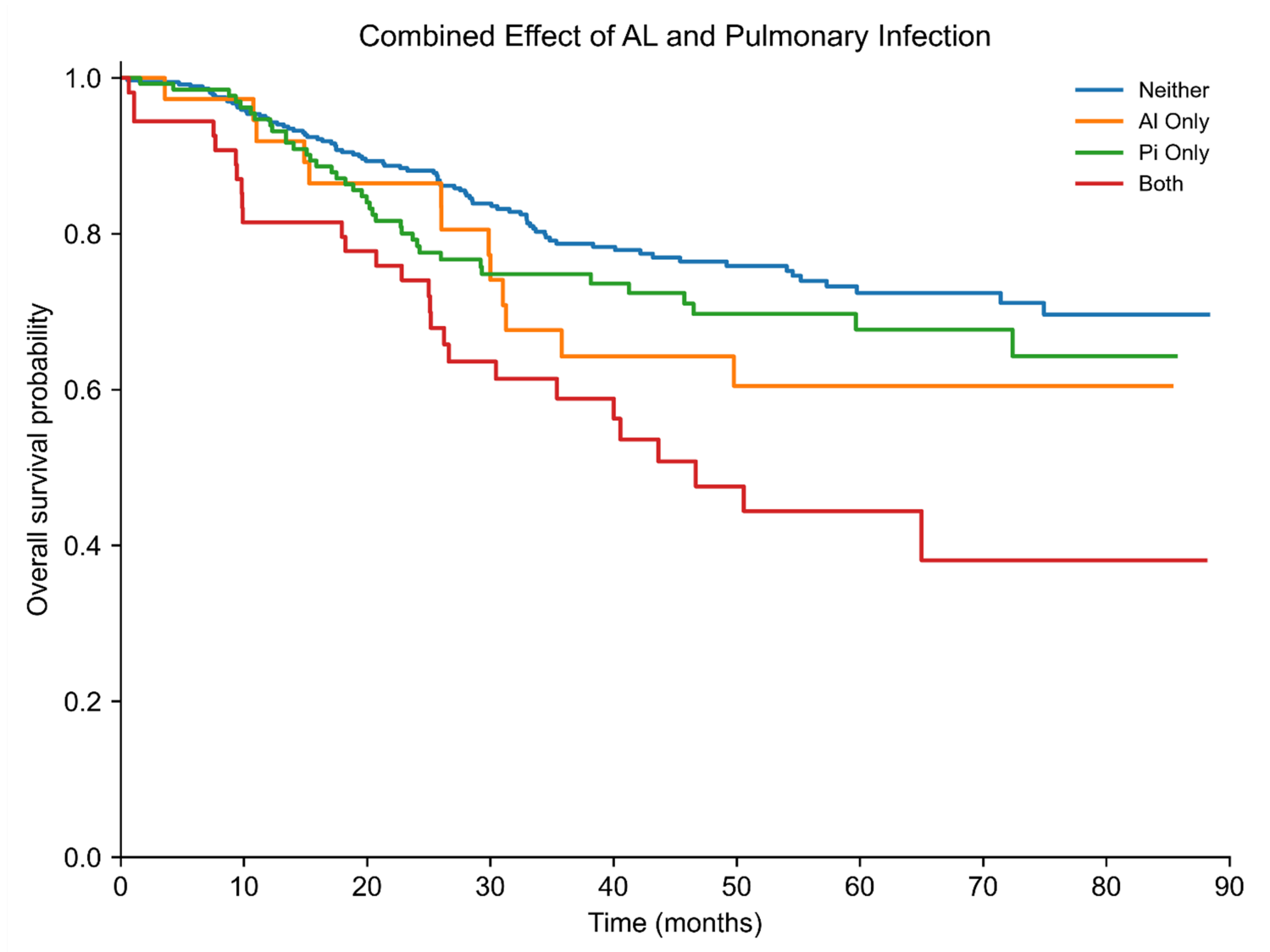
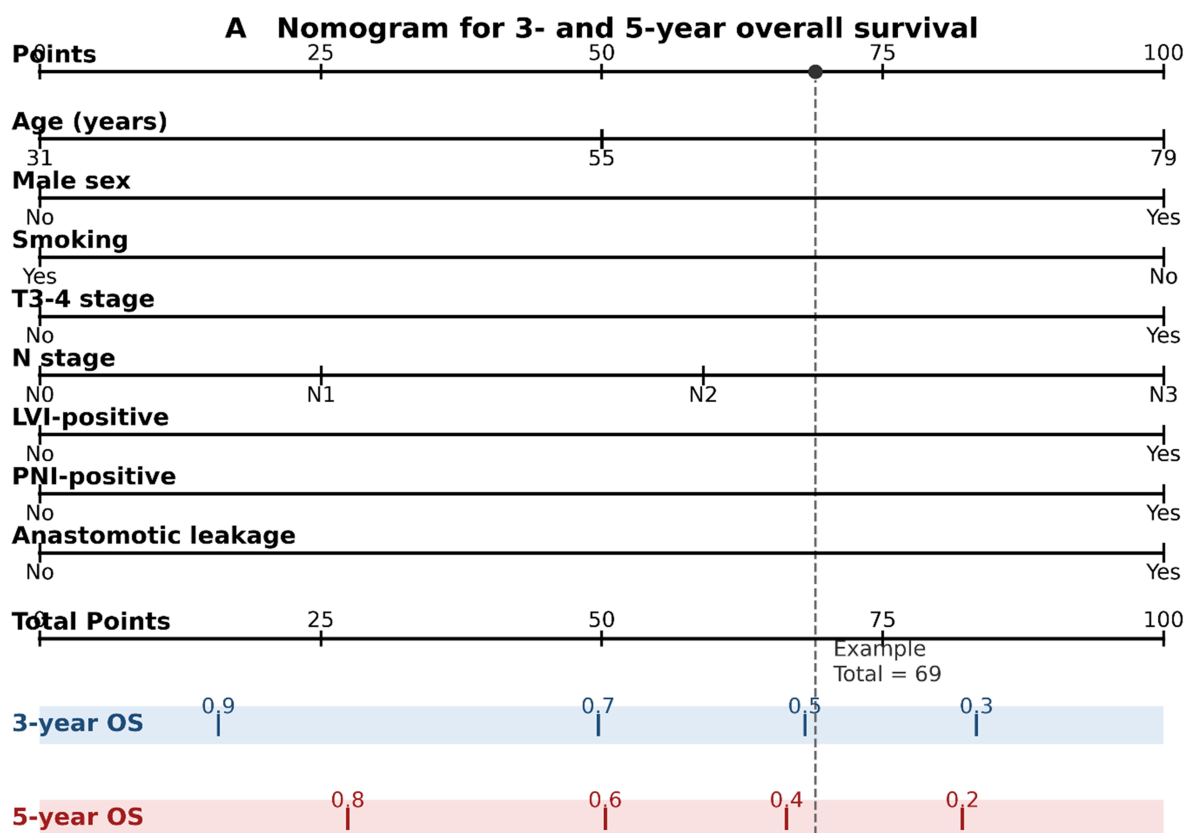


Figure 4

Combined effect of anastomotic leakage (AL) and pulmonary infection on survival. Groups: neither (n=369), AL only (n=37), infection only (n=132), both (n=54). Mortality was 22.5%, 35.1%, 28.8% and 50.0%, respectively (trend $p < 0.001$). AL, anastomotic leakage.



B Risk stratification and worked example

Observed mortality by nomogram-predicted risk third

Risk third	n	3-year	5-year
Low	204	10.6%	13.6%
Intermediate	206	20.9%	27.7%
High	207	41.7%	52.5%

Worked example

65-year-old male smoker with T3-4 disease, N1 stage and anastomotic leakage:
Total Points = 69 → 3-year OS = 49%, 5-year OS = 37%

C-index = 0.715. Risk thirds were defined by tertiles of nomogram-predicted 5-year overall survival; observed mortality was estimated by the Kaplan-Meier method. AL, anastomotic leakage; LVI, lymphovascular invasion; OS, overall survival; PNI, perineural invasion.

Figure 5

Prognostic nomogram for 3-year (blue) and 5-year (red) overall survival after MIE for ESCC. (A) Variable axes with point contributions: anastomotic leakage, age, sex, smoking history, T3-4 stage, N stage, LVI and PNI. (B) Risk stratification and worked example. LVI, lymphovascular invasion; OS, overall survival; PNI, perineural invasion.

Supplementary Files

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