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Perioperative Relative Albumin Decline and Post-sampling Remaining Length of Stay After Lung Resection: Findings From the INSPIRE Cohort and an Independent Hospital Cohort

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Abstract

Objectives: Early postoperative albumin decline may reflect the physiological response to lung resection and provide information beyond the preoperative albumin level. We investigated its association with remaining hospital stay and assessed the consistency of this association in an independent hospital cohort.

Methods: This retrospective cohort study used the INSPIRE perioperative database and an independent cohort of lung resection procedures performed at the First Affiliated Hospital of Zhengzhou University between December 2023 and June 2024. Relative albumin decline was calculated from the preoperative and early postoperative measurements. The primary outcome was the interval from postoperative albumin sampling to hospital discharge. In INSPIRE, log-transformed remaining hospital stay was analysed using multivariable linear regression with a 3-degree-of-freedom natural

spline for preoperative albumin and HC3 robust standard errors. The hospital cohort underwent additional adjustment for operative characteristics, comorbidities, pulmonary function and intraoperative blood loss.

Results: Among 3,568 patients in INSPIRE, 3,323 had paired albumin measurements and were included in the primary analysis. Each 10-percentage-point increase in relative albumin decline was associated with a 6.34% longer remaining hospital stay (95% confidence interval [CI], 3.34–9.43; P<0.001). The association persisted after excluding stays longer than 30 days (3.99%; 95% CI, 1.36–6.70) and in inverse probability-weighted analysis (6.22%; 95% CI, 3.20–9.32). In the hospital cohort, the fully adjusted common-sample analysis of 792 procedures showed a corresponding increase of 3.59% (95% CI, 1.28–5.95; P=0.002).

Conclusions: Greater early perioperative relative albumin decline was associated with longer remaining hospital stay after lung resection. This association was consistent across the INSPIRE and independent hospital cohorts. Early albumin change may provide complementary information on postoperative recovery, although its clinical utility requires prospective evaluation.

Keywords: Lung resection; Serum albumin; Relative albumin decline; Remaining hospital stay; Thoracic surgery.

Abbreviations and Acronyms

BMI: body mass index

ASA: American Society of Anesthesiologists

CI: Confidence interval

DLCO: Diffusing capacity of the lung for carbon monoxide

ESS: Effective sample size

FEV_1: Forced expiratory volume in 1 second

HC1: Heteroscedasticity-consistent covariance estimator 1

HC3: Heteroscedasticity-consistent covariance estimator 3

IPW: Inverse probability weighting

IQR: Interquartile range

SD: Standard deviation

SMD: Standardized Mean Difference

1.Introduction

Recovery after lung resection varies considerably between patients. Postoperative length of stay is influenced not only by the procedure itself but also by patients' baseline condition, the extent of surgical injury and subsequent recovery[1]. Serum

albumin is routinely measured in the perioperative period. Although commonly considered a marker of nutritional status, its concentration is also affected by inflammation, changes in capillary permeability and fluid redistribution[2].A postoperative decline in albumin may therefore reflect the early physiological response to surgical injury and capture changes that cannot be fully characterized by a single measurement.

Previous studies in patients undergoing lung resection and other surgical procedures have linked perioperative changes in albumin to postoperative complications and recovery outcomes[3-6].More recent work has examined the associations of preoperative hypoalbuminaemia and postoperative albumin trajectories with hospital outcomes[7-10].However, preoperative albumin primarily reflects patients' baseline status, whereas its relative perioperative decline describes the change occurring around surgery. These measures may convey different clinical information. Whether the relative decline in albumin is independently associated with the remaining length of hospital stay after lung resection, and whether this association persists after accounting for a broader range of patient and procedural characteristics, remains unclear.

We therefore examined the association between the relative decline in albumin from before surgery to the early postoperative period and the time from postoperative albumin sampling to hospital discharge in the INSPIRE perioperative database. We then assessed the consistency of this association in an independent hospital cohort.

The analyses accounted for preoperative albumin, demographic characteristics, procedural factors and the timing of postoperative sampling. The hospital cohort additionally allowed adjustment for resection extent, surgical approach, comorbidities, pulmonary function and intraoperative blood loss. We hypothesized that a greater perioperative decline in albumin would be associated with a longer remaining hospital stay.

2.Methods

2.1 Study Design and Data Sources

This retrospective observational cohort study used the INSPIRE perioperative database to examine the association between perioperative changes in serum albumin and remaining length of hospital stay after lung resection. The findings were assessed in an independent cohort of patients undergoing lung resection at the Department of Thoracic Surgery, the First Affiliated Hospital of Zhengzhou University, China. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The hospital cohort included 910 surgical records from December 2023 through June 2024.

2.2 INSPIRE Cohort Construction

The INSPIRE dataset is a publicly available perioperative research resource comprising approximately 130,000 surgical procedures performed at Seoul National University Hospital between 2011 and 2020. Its data structure, extraction procedures

and technical validation have been described previously. The dataset is distributed through PhysioNet, and version 1.4.2 was used for the present analysis[11-13].The INSPIRE surgical table contained 130,960 records, of which 8,754 were classified as cardiothoracic procedures. Lung resection procedures were identified using prespecified prefix patterns in the ICD-10-PCS procedure codes, yielding 3,815 candidate records. For each patient, the first eligible lung resection was selected as the index procedure. This process resulted in a patient-level cohort of 3,568 patients.

Patients were eligible for the paired-albumin analysis if valid measurements were available within the prespecified preoperative and postoperative sampling windows. The analytic sample for each model was further restricted according to the availability of the covariates required for that analysis.

2.3 Hospital Validation Cohort

The hospital cohort comprised 910 lung resection records. Paired preoperative and postoperative albumin measurements were available for 889 records; 875 also had a valid remaining length-of-stay outcome and met the requirements for the base model. All procedures in this cohort were elective.

This independent cohort was used to assess whether the primary association persisted after adjustment for additional clinical characteristics, including surgical factors, comorbidities and pulmonary function. Because some hospital admission numbers were associated with more than one surgical record, robust standard errors clustered

by admission number were used to account for potential within-patient correlation across records.

2.4 Exposure and Outcome Definitions

In the INSPIRE cohort, preoperative albumin was defined as the last valid measurement within 7 days before the start of surgery. Postoperative albumin was defined as the first valid measurement obtained 6–24 hours after the end of surgery. Albumin concentrations were recorded in g/dL. The hospital cohort used the same definitions for preoperative and postoperative albumin; concentrations were recorded in g/L.

The primary exposure was the relative decline in albumin, which was calculated as (preoperative albumin minus postoperative albumin) multiplied by 100%.For the primary models, this value was divided by 10 so that the estimated effect represented the relative change in remaining hospital stay associated with each 10-percentage-point increase in albumin decline. Preoperative albumin was standardized and modelled using a natural cubic spline with 3 degrees of freedom to allow for a potentially nonlinear association with the outcome.

The primary outcome was the remaining time from postoperative albumin sampling to hospital discharge, expressed in days. The same outcome definition was applied in both cohorts, with the postoperative albumin sampling time as the starting point and the actual discharge time as the endpoint. In the hospital cohort, postoperative

albumin was routinely measured between 6:00 and 8:00 AM on the first postoperative day. Review of the medical records confirmed that these measurements were obtained within 6–24 hours after the end of surgery. Because the interval between the end of surgery and postoperative sampling varied across patients in the INSPIRE cohort, this interval was included as a covariate in the primary model.

Remaining hospital stay was right-skewed in the INSPIRE cohort. Therefore, the outcome was natural log-transformed before linear regression. The same log-transformation approach was used in the hospital cohort to facilitate comparison of relative effect estimates between cohorts.

2.5 Covariates and Model Specification

The primary INSPIRE model adjusted for age, sex, American Society of Anesthesiologists (ASA) physical status, emergency status, operative duration, procedure type, anatomical lung site and the interval between the end of surgery and postoperative albumin sampling. ASA physical status was categorized as I–II, III or higher, or missing. The model was specified as follows:

$$log(T)=f_3(\text{preoperative albumin})+\beta_1(\text{relative albumin decline/10})+\text{age}+\text{sex}+ASAstatus+emergencystatus+operativeduration+proceduretype+\text{anatomical lung site}+\text{sampling interval}+\varepsilon$$

where T denotes the remaining time from postoperative albumin sampling to discharge and f_3 denotes a natural spline with 3 degrees of freedom.

In the hospital cohort, a series of models with progressively expanded covariate adjustment was fitted. Model M0 included preoperative albumin modelled with a 3-degree-of-freedom natural spline, relative albumin decline, age, sex, ASA status and operative duration. Emergency status was not included because all procedures were elective. Model M1 additionally adjusted for extent of resection, surgical approach, pre-existing pulmonary disease, hypertension, diabetes and coronary artery disease. Model M2 added intraoperative blood loss to M1. Model M3 added body mass index (BMI), forced expiratory volume in 1 second as a percentage of predicted (FEV1%) and diffusing capacity of the lung for carbon monoxide as a percentage of predicted (DLCO%) to M1. Model M4 additionally adjusted for intraoperative blood loss in M3.

All hospital models used HC1 robust standard errors clustered by admission number to account for potential correlation between records from the same patient.

2.6 Statistical Analysis

In the INSPIRE cohort, ordinary least-squares linear regression was used to model log-transformed remaining hospital stay, with HC3 heteroscedasticity-robust standard errors. Regression coefficients and their 95% confidence intervals were transformed to percentage changes in remaining hospital stay using $[exp(\beta)-1]\times 100\%$.

Nonlinearity in the association between preoperative albumin and the outcome was assessed by comparing nested models in the same analytic sample, with identical covariates, in which preoperative albumin was entered either as a linear term or as a natural spline with 3 degrees of freedom. Nonlinearity in the association with relative albumin decline was assessed in the same way by comparing the linear specification with a 3-degree-of-freedom natural spline specification.

To assess potential selection bias related to the availability of paired albumin measurements, a logistic regression model was fitted among index patients with complete data for the selection-model covariates. The dependent variable indicated whether paired albumin measurements were available. Covariates included age, sex, ASA status, emergency status, operative duration, procedure type and anatomical lung site. Stabilized inverse probability weights (IPWs) were calculated as the overall proportion of patients with paired measurements divided by each patient's predicted probability of having paired measurements. Predicted probabilities were restricted to the range (10^{-6}) to ($1-10^{-6}$), and no additional weight trimming was performed. The weighted outcome model retained the covariates from the primary model and used HC3 robust standard errors. Covariate balance before and after weighting was assessed using standardized mean differences (SMDs). The distribution of stabilized weights and the effective sample size were also reported.

A sensitivity analysis excluded records with a remaining hospital stay longer than 30 days to assess the influence of prolonged hospitalizations on the primary association.

The uncertainty of the IPW estimate was further evaluated using a full-pipeline bootstrap. Patients or index records with complete data for the selection model were resampled with replacement. In each of 500 bootstrap replicates, the albumin-pairing selection model was refitted, stabilized weights were recalculated and the weighted outcome model was refitted. The random seed was set to 20261020. The 95% percentile confidence interval was derived from the 2.5th and 97.5th percentiles of the bootstrap effect estimates.

As a supplementary analysis, we examined whether the association was also present for the postoperative albumin concentration itself. Postoperative albumin was standardized and modelled per 1-standard-deviation increase. We fitted one model with postoperative albumin as the sole albumin exposure and another including both preoperative and postoperative albumin. The latter estimated the conditional association between postoperative albumin and the outcome at a given preoperative albumin level. Alternative parameterizations of albumin change were also examined as supplementary analyses. These analyses were intended to aid interpretation and were not treated as replacements for the primary exposure or as evidence of causality.

In the hospital cohort, each model was initially fitted using all records with complete data for its respective covariates. To minimize the influence of changes in sample composition when comparing models, M0–M4 were also refitted in the common complete-case sample with data available for all variables included in M1–M4. No imputation was performed in the primary analyses.

All tests were two-sided, and P values less than 0.05 were considered statistically significant. Effect estimates and 95% confidence intervals were emphasized in the reporting of results. Analyses were conducted using R version 4.6.0, with the data.table (version 1.18.4), sandwich (version 3.1-1) and lmtest (version 0.9-40) packages.

3.Results

3.1 Cohort Characteristics and Albumin Measurements

The INSPIRE cohort included 3,568 patients undergoing index lung resection. Preoperative albumin measurements were available for 3,424 patients and postoperative measurements for 3,447. Paired measurements meeting the prespecified definitions were available for 3,323 patients (93.1%); 245 patients had no eligible paired measurements and were excluded from the primary analysis （Figure 1）.

In the paired-albumin cohort, median preoperative albumin was 4.1 g/dL (interquartile range [IQR], 4.0–4.3), and median postoperative albumin was 3.8 g/dL (IQR, 3.5–4.0). The median relative albumin decline was 8.70% (IQR, 4.76%–13.16%; range, −33.33% to 38.30%). The median interval between the end of surgery and postoperative albumin sampling was 14.42 hours (IQR, 6.83–19.25; range, 6–24 hours). Median remaining time from postoperative sampling to discharge was 4.13 days (IQR, 2.65–6.10; range, 0.59–116.15 days).Baseline characteristics of the INSPIRE paired-albumin cohort are shown in Table 1.

The hospital validation cohort comprised 910 surgical records. Paired preoperative and postoperative albumin measurements were available for 889 records, and 875 had a valid remaining length-of-stay outcome and met the requirements for the base model. Median age was 58 years (IQR, 52–65), and 521 records (57.3%) were from female patients. Median preoperative and postoperative albumin concentrations were 41.2 g/L (IQR, 39.1–43.4) and 37.5 g/L (IQR, 35.3–40.1), respectively. Median relative albumin decline was 8.53% (IQR, 1.77%–14.99%). Median remaining hospital stay was 5 days (IQR, 4–6; range, 2–27 days)（Table S1).

Table 1. Characteristics of the INSPIRE Paired-Albumin Cohort

Characteristic	**Overall(N=3,323)**
Age, median (IQR), y	65 (55–70)
Female sex, No. (%)	1,486 (44.7)
ASA physical status, No. (%)	
I–II	2,964 (89.2)
≥III	246 (7.4)
Missing	113 (3.4)
Emergency operation, No. (%)	146 (4.4)
Operation duration, median (IQR), min	125 (95–170)
Procedure type, No. (%)	
Excision	1,535 (46.2)
Resection	1,788 (53.8)
Anatomical site of resection, No. (%)	
Right upper lobe	840 (25.3)
Right middle lobe	235 (7.1)
Right lower lobe	671 (20.2)
Left upper lobe	640 (19.3)

Left lower lobe	405 (12.2)
Right lung	345 (10.4)
Left lung	187 (5.6)
Preoperative albumin, median (IQR), g/dL	4.10 (4.00–4.30)
Postoperative albumin, median (IQR), g/dL	3.80 (3.50–4.00)
Relative albumin decline, median (IQR), %	8.70 (4.76–13.16)
Postoperative sampling time, median (IQR), h	14.42 (6.83–19.25)
Remaining length of stay, median (IQR), d	4.13 (2.65–6.10)

Values are presented as median (interquartile range [IQR]) or number (percentage). The cohort included patients with eligible paired preoperative and postoperative albumin measurements (N = 3323).

Abbreviations: ASA, American Society of Anesthesiologists; IQR, interquartile range.

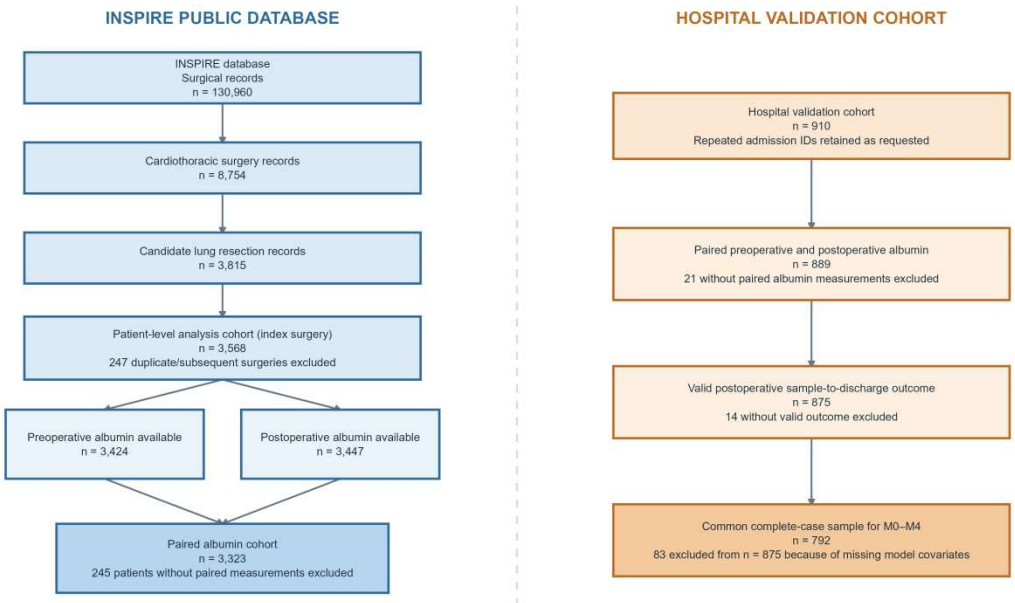

Figure 1. Cohort Flow Diagram

Flow diagram showing the selection of the INSPIRE index lung resection cohort and the paired-albumin analytic cohort. Preoperative albumin was defined as the last valid measurement within 7 days before the start of surgery, and postoperative albumin as the first valid measurement obtained 6–24 hours after the end of surgery.

3.2 Primary INSPIRE Analysis and Nonlinearity

In the primary INSPIRE model, greater relative albumin decline was associated with longer remaining hospital stay after adjustment for age, sex, ASA physical status, emergency status, operative duration, procedure type, anatomical lung site, postoperative sampling interval and preoperative albumin modelled with a 3-degree-of-freedom natural spline. For each 10-percentage-point increase in relative albumin decline, remaining hospital stay was 6.34% longer ($\beta = 0.062$; time ratio, 1.063; 95% confidence interval [CI], 3.34%–9.43%; $P < 0.001$). The model included 3,323 patients and had an R^2 of 0.375 and an adjusted R^2 of 0.371.

Comparison of nested models showed better fit when preoperative albumin was modelled using a 3-degree-of-freedom natural spline rather than a linear term ($F[2, 3304] = 12.08$; $P < 0.001$), supporting a nonlinear association with remaining hospital stay. In contrast, replacing the linear term for relative albumin decline with a 3-degree-of-freedom natural spline did not improve model fit significantly ($F[2, 3304] = 1.34$; $P = 0.262$). The adjusted association with relative albumin decline was therefore adequately represented by a linear term over the observed range, whereas the association with preoperative albumin was nonlinear. The adjusted association between preoperative albumin and remaining hospital stay is shown in Figure 2.

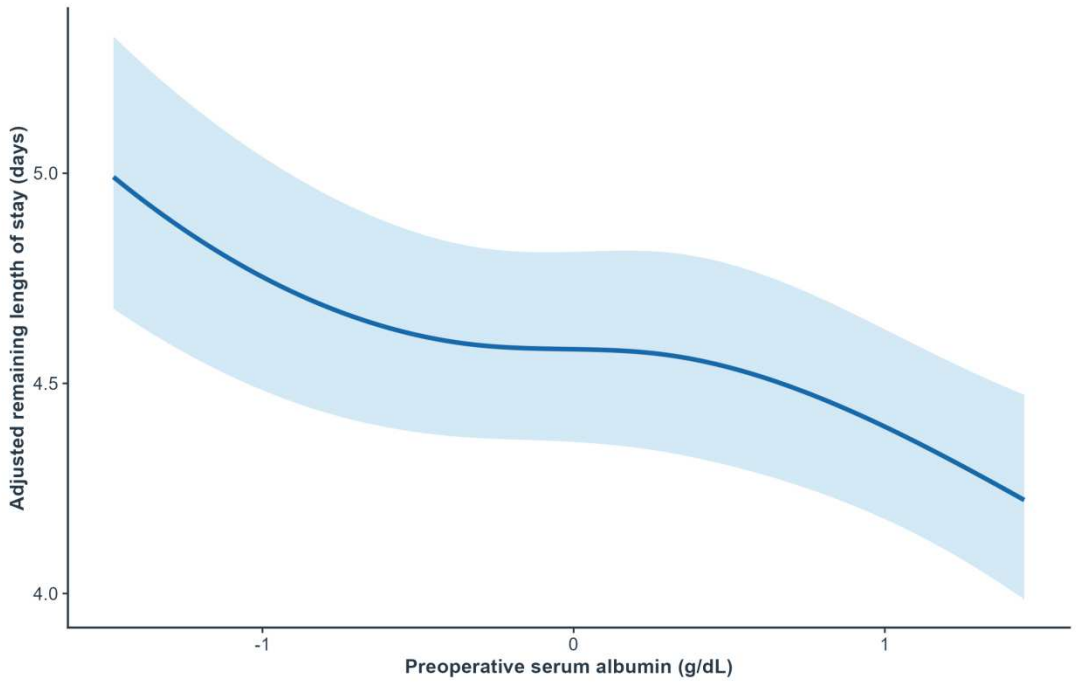

Figure 2. Adjusted Association Between Preoperative Albumin and Remaining Length of Stay

Predicted remaining hospital stay across preoperative serum albumin concentrations, estimated from the primary INSPIRE model with preoperative albumin represented by a natural spline with 3 degrees of freedom. Predictions were calculated using the reference covariate values specified in the prediction dataset. The shaded band represents the 95% confidence interval.

3.3 Sensitivity Analyses and Adjustment for Albumin-Pairing Probability

After excluding records with a remaining hospital stay longer than 30 days, 3,292 patients remained in the sensitivity analysis. Each 10-percentage-point increase in relative albumin decline was associated with a 3.99% longer remaining hospital stay (95% CI, 1.36%–6.70%; P = 0.003). The estimated association was attenuated compared with the primary analysis but remained in the same direction.

Among 3,567 index patients with complete data for the selection model, 3,323 (93.16%) had paired albumin measurements. The selection model included age, sex, ASA physical status, emergency status, operative duration, procedure type and anatomical lung site. Stabilized weights had a mean of 1.000, standard deviation of 0.068, median of 0.980 and range of 0.933–1.593; the 95th percentile was 1.109. The effective sample size after weighting was 3,307.8, equivalent to 99.54% of the paired cohort. SMDs for the measured selection covariates were close to zero after weighting.

In the IPW-weighted primary model, each 10-percentage-point increase in relative albumin decline was associated with a 6.22% longer remaining hospital stay (95% CI, 3.20%–9.32%; $P < 0.001$), consistent with the unweighted primary analysis. All 500 full-pipeline bootstrap replicates were successful. The median bootstrap estimate corresponded to a 6.19% longer remaining hospital stay, with a percentile 95% CI of 3.34%–9.57%. This interval was consistent with the confidence interval from the primary model. Estimates from the primary and sensitivity analyses are summarized in Table 2 and Figure 3.

Table 2. Association Between Relative Albumin Decline and Remaining Hospital Stay in the INSPIRE Cohort

Analysis	Sample	Adjusted Change, % (95% CI)	P Value / Method
Primary spline model	3323	6.34 (3.34 to 9.43)	＜0.001

Sensitivity analysis: remaining stay ≤30 d	3292	3.99 (1.36 to 6.70)	0.003
IPW-weighted primary model	3323 paired; ESS 3308	6.22 (3.20 to 9.32)	＜0.001
IPW bootstrap (500 replicates)	500/500 successful	6.19 (3.34 to 9.57)	Percentile CI

Estimates represent the percentage change in remaining hospital stay for each 10-percentage-point increase in relative albumin decline. The primary and sensitivity models used log-transformed remaining hospital stay and HC3 robust standard errors. The bootstrap estimate represents the median of 500 successful bootstrap replicates, with a percentile-based 95% confidence interval.

Abbreviations: CI, confidence interval; ESS, effective sample size; HC3, heteroscedasticity-consistent covariance estimator 3; IPW, inverse probability weighting.

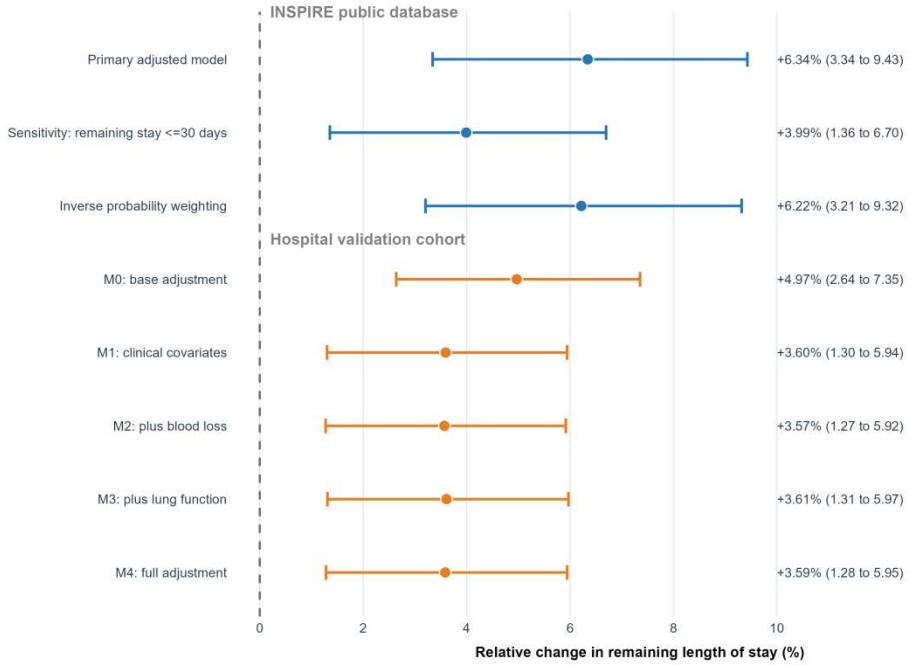

Figure 3. Forest Plot of Relative Albumin Decline Estimates

Adjusted percentage change in remaining hospital stay for each 10-percentage-point increase in relative albumin decline. INSPIRE estimates include the primary model, the sensitivity analysis excluding records with remaining hospital stay longer than 30 days, the IPW-weighted model and the bootstrap estimate. Hospital-cohort estimates

for M0–M4 were obtained from the common sample of 792 surgical records. Horizontal bars indicate 95% confidence intervals.

3.4 Supplementary Analysis of Postoperative Albumin

In supplementary analyses of the same INSPIRE paired-albumin cohort, each 1-standard-deviation increase in postoperative albumin was associated with a 7.31% shorter remaining hospital stay (β = −0.076; time ratio, 0.927; 95% CI, 5.14%–9.44% shorter; P < 0.001).

When preoperative and postoperative albumin were included in the same model, higher postoperative albumin remained associated with shorter remaining hospital stay (5.65% shorter per 1-standard-deviation increase; β = −0.058; time ratio, 0.943; 95% CI, 3.20%–8.04% shorter; P < 0.001). Preoperative albumin was also associated with shorter remaining hospital stay in this model (2.75% shorter per 1-standard-deviation increase; β = −0.028; 95% CI, 0.41%–5.02% shorter; P = 0.021). These analyses are presented as supplementary findings and are summarized in Table 3.

Table 3.Supplementary INSPIRE Analysis of Postoperative Albumin

Model	N	Adjusted Change, % (95% CI) per 1-SD Increase	P Value
M1 postoperative albumin alone	3323	-7.31 (-9.44 to -5.14)	＜0.001

M2 postoperative albumin adjusted for preoperative albumin	3323	-5.65 (-8.04 to -3.20)	＜0.001

Estimates represent the percentage change in remaining hospital stay per 1-standard-deviation increase in albumin concentration. M1 included postoperative albumin as the albumin exposure. M2 included both preoperative and postoperative albumin. Both models were fitted in the INSPIRE paired-albumin cohort (N = 3323) using log-transformed remaining hospital stay and HC3 robust standard errors. These analyses were supplementary and did not replace the primary exposure of relative albumin decline.

Abbreviations: CI, confidence interval; HC3, heteroscedasticity-consistent covariance estimator 3; SD, standard deviation.

3.5 Hospital Cohort Validation

In the hospital cohort, models fitted using all available complete cases included 875 records in M0. Each 10-percentage-point increase in relative albumin decline was associated with a 4.88% longer remaining hospital stay (95% CI, 2.60%–7.22%; P < 0.001).

After additional adjustment for resection extent, surgical approach, pre-existing pulmonary disease and major comorbidities, M1 included 872 records and the estimated association was 3.25% (95% CI, 1.04%–5.51%; P = 0.004). In M2, which additionally adjusted for intraoperative blood loss, the estimate was 3.30% (n = 850; 95% CI, 1.04%–5.62%; P = 0.004). M3 additionally adjusted for BMI, FEV1% and DLCO% and included 812 records; the estimate was 3.51% (95% CI, 1.26%–5.82%; P = 0.002). M4 further included intraoperative blood loss and comprised 792 records; the estimate was 3.59% (95% CI, 1.28%–5.95%; P = 0.002).

To minimize differences in sample composition across models, M0–M4 were refitted in the common complete-case sample of 792 records. In this common sample, the estimated increase in remaining hospital stay per 10-percentage-point increase in relative albumin decline was 4.97% in M0 (95% CI, 2.64%–7.35%; P < 0.001), 3.60% in M1 (95% CI, 1.30%–5.94%; P = 0.002), 3.57% in M2 (95% CI, 1.27%–5.92%; P = 0.002), 3.61% in M3 (95% CI, 1.31%–5.97%; P = 0.002) and 3.59% in M4 (95% CI, 1.28%–5.95%; P = 0.002). Thus, the estimate decreased from 4.97% in the base model to approximately 3.6% after additional clinical adjustment, with similar estimates across M1–M4. Common-sample results are presented in Table 4 and Figure 3.

Table 4.External Cohort: Common-Sample Models for Relative Albumin Decline

Model	N	Adjusted Change, % (95% CI)	P Value
M0: base model	792	4.97 (2.64 to 7.35)	＜0.001
M1: + surgical and comorbidity variables	792	3.60 (1.30 to 5.94)	0.002
M2: M1 + blood loss	792	3.57 (1.27 to 5.92)	0.002
M3: M1 + BMI and lung function	792	3.61 (1.31 to 5.97)	0.002
M4: M3 + blood loss	792	3.59 (1.28 to 5.95)	0.002

All models were fitted in the same 792 surgical records. Estimates represent the percentage change in remaining hospital stay for each 10-percentage-point increase in relative albumin decline. All models used log-transformed remaining hospital stay and HC1 robust standard errors clustered by admission number. Model covariates are defined in the Methods section.

Abbreviations: BMI, body mass index; CI, confidence interval; DLCO%, diffusing capacity of the lung for carbon monoxide as a percentage of predicted; FEV1%, forced expiratory volume in 1 second as a percentage of predicted; HC1, heteroscedasticity-consistent covariance estimator 1.

4.Discussion

4.1 Principal findings

In this study, a greater early postoperative relative decline in serum albumin was associated with a longer remaining hospital stay after lung resection. For each 10-percentage-point increase in relative albumin decline, remaining hospital stay increased by 6.34% in the INSPIRE cohort. The association persisted in an independent hospital cohort after additional adjustment for resection extent, surgical approach, comorbidities, pulmonary function and intraoperative blood loss, although the estimated increase was smaller, at approximately 3.6%. These findings suggest that preoperative albumin and its early postoperative change may provide different types of clinical information. Whereas the preoperative level reflects a patient's baseline condition, the relative decline may capture early physiological changes following surgical injury.

4.2 Comparison with Previous Studies

Previous thoracic surgical studies provide a clinical context for these findings. In a cohort of 533 patients undergoing thoracoscopic anatomical lung resection for lung cancer, Li et al. reported that a decrease in albumin on postoperative day 1 was independently associated with postoperative pulmonary complications[3].A 2026 study of 1,192 patients undergoing thoracoscopic anatomical lung resection further

linked preoperative hypoalbuminaemia to postoperative pulmonary complications and longer hospital stay[7]. A recent meta-analysis also supported an association between preoperative hypoalbuminaemia and pulmonary complications after thoracic surgery[8]. However, these studies primarily examined baseline albumin levels or postoperative complications. They did not directly address whether an early postoperative change in albumin was associated with the subsequent course of hospital stay. Our study extends this evidence by examining remaining hospital stay after albumin sampling as the outcome.

Evidence from other surgical specialties is also relevant. In a prospective study of major abdominal surgery, Labgaa et al. found that the postoperative day 1 decrease in albumin was associated with operative extent, blood loss, operation duration and inflammatory response, as well as postoperative complications and hospital stay[6, 14]. A systematic review by Joliat et al., which included 16 gastrointestinal surgery studies, likewise found an overall association between postoperative albumin decline and complications[5]. Early albumin decline may therefore reflect several overlapping perioperative processes, including surgical stress, inflammation, increased capillary permeability and fluid redistribution[15-17]. It is best regarded as an accessible composite physiological signal rather than a marker specific to any single mechanism[18]. The present study cannot determine the relative contribution of these processes, but the observed association is physiologically plausible.

4.3 Baseline Albumin and Dynamic Change

Our findings also support distinguishing perioperative albumin change from the preoperative baseline level. In a multicentre cohort of patients with early-stage non-small cell lung cancer, Kinoshita et al. reported an association between a postoperative decrease in albumin and long-term disease-free and overall survival[4]. That study examined albumin change over a much longer postoperative period and focused on oncological outcomes, rather than early postoperative change and recovery during the index admission. Nevertheless, both studies suggest that changes in albumin may convey information not fully captured by an isolated concentration measurement. Hypoalbuminaemia itself may also reflect systemic inflammation and underlying disease, rather than nutritional intake alone[2].

In our study, relative albumin decline remained associated with remaining hospital stay after adjustment for preoperative albumin. Preoperative albumin showed a nonlinear association with the outcome, whereas there was no clear evidence of nonlinearity for relative decline. These findings support evaluating baseline albumin and its perioperative change separately. However, because relative decline is calculated from both preoperative and postoperative measurements, the observed association should not be interpreted as evidence of incremental predictive value beyond established clinical variables.

4.4 Consistency in the Independent Hospital Cohort

The independent hospital cohort provides an additional perspective. While INSPIRE offered a larger study population, the hospital cohort allowed adjustment for more

detailed clinical information, including resection extent, surgical approach, underlying pulmonary disease, pulmonary function and intraoperative blood loss. The association between relative albumin decline and remaining hospital stay persisted after these adjustments. Although the estimated effect was smaller than that in the INSPIRE primary analysis, it was not eliminated by the inclusion of these additional variables. This suggests that the association may not be explained solely by the measured operative factors.

The effect estimates should not, however, be assumed to be directly transferable between settings. Differences in patient characteristics, perioperative management, sampling procedures and discharge practices may all influence the magnitude of the association[1, 19]. The hospital cohort therefore provides evidence that the association was also observed in a separate clinical setting with more detailed adjustment, rather than establishing a universally applicable effect size.

4.5 Clinical Implications

These findings do not establish a new threshold for albumin treatment. Rather, they suggest that perioperative assessment should not rely exclusively on a single preoperative or postoperative albumin measurement. Patients with similar postoperative albumin concentrations may have experienced different degrees of decline from their respective baseline levels. When a substantial early postoperative decline is observed, clinicians may consider interpreting it alongside fluid balance, inflammatory markers, chest drainage, respiratory function and mobility.

The present study did not identify an optimal clinical threshold or demonstrate that interventions guided by albumin change improve outcomes. Albumin decline alone should therefore not determine discharge timing or treatment decisions[20-22].

4.6 Strengths and Limitations

This study has several strengths. First, it distinguished preoperative albumin, early postoperative albumin and relative albumin decline, while accounting for the preoperative level in the adjusted models. Second, postoperative albumin sampling was restricted to 6–24 hours after the end of surgery, and the outcome was measured from the sampling time to discharge. This ensured that exposure measurement preceded the period of remaining hospital stay under study. Third, we conducted sensitivity analyses excluding prolonged remaining stays and using inverse probability weighting to address potential selection associated with albumin pairing. Finally, the independent hospital cohort enabled additional adjustment for operative and clinical variables not available in the INSPIRE dataset.

Several limitations warrant consideration. First, the retrospective observational design precludes causal inference and does not eliminate residual confounding. Perioperative fluid administration, transfusion, postoperative inflammation, complications, chest drainage management and functional recovery may influence both albumin change and remaining hospital stay. Second, the primary INSPIRE analysis required paired albumin measurements within prespecified time windows. Patients without eligible measurements may have differed systematically from those included. Although

inverse probability weighting produced estimates similar to the primary analysis, its validity depends on the specification of the selection model and the adequacy of measured covariates. Third, although postoperative sampling was restricted to 6–24 hours and sampling time was included in the models, variation within this window may still have affected the estimated relative decline. Fourth, remaining hospital stay is influenced by discharge criteria, healthcare resources, patient preferences and social support; it should not be regarded as a direct measure of physiological recovery. Finally, the independent hospital cohort was from a single centre, and the findings require evaluation in other healthcare settings.

4.7 Future Directions

Future studies should move beyond reproducing the observed association and assess its potential clinical value. Prospective multicentre studies with standardized albumin sampling should collect detailed information on fluid administration, transfusion, inflammatory markers, postoperative complications and functional recovery. Such data would help clarify the physiological processes underlying albumin decline. Further work should also determine whether adding relative albumin decline to established clinical risk factors improves model discrimination, calibration and clinical decision-making.

5.Conclusion

Among patients undergoing lung resection, a greater early perioperative relative decline in serum albumin was associated with a longer remaining hospital stay. This association persisted across sensitivity analyses in the INSPIRE cohort and was also observed in an independent hospital cohort after adjustment for more detailed operative and clinical variables. Early postoperative albumin change may provide recovery-related information distinct from the preoperative baseline level. Its clinical utility, including any incremental predictive value, requires further prospective evaluation.

Declarations：

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Ethics Approval and Consent to Participate

The original INSPIRE data collection study was approved by the Institutional Review Board of Seoul National University Hospital (approval No. H-2210-078-1368), with a waiver of informed consent because of the retrospective study design. Before public release, the Seoul National University Hospital Data Review Board reviewed the de-identification of the dataset and approved its release (approval No. BD-R-2022-11-02). The present study used version 1.4.2 of the INSPIRE dataset for

secondary analysis and complied with the applicable data-use agreement. No attempt was made to re-identify any individual.

The hospital cohort study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (approval No. 2026-KY-1520-001). Informed consent was waived because of the retrospective design and use of routinely collected clinical data.

Consent for publication

Not applicable.

Author contributions

Penghao Zhao: Conceptualization, Methodology, Data curation, Formal analysis, Visualization, Writing – original draft.

Jiale Wang: Data curation, Investigation, Validation.

Feifan Guo: Investigation, Resources, Validation.

Chunyang Zhang: Conceptualization, Methodology, Supervision, Project administration, Writing – review & editing.

All authors reviewed the manuscript, approved the final version and agree to be accountable for the work.

Competing interests

The authors declare no competing interests.

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Availability of data and materials

The INSPIRE dataset used in this study is publicly available through PhysioNet (version 1.4.2; https://doi.org/10.13026/1eay-yc85). The hospital cohort data are not publicly available because of institutional and patient privacy requirements but may be made available by the corresponding author upon reasonable request, subject to institutional approval and applicable data-sharing regulations.

Clinical trial number

Not applicable.

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