

Early Postoperative Changes in Routine Blood Biomarkers and Postoperative Complications After Lung Resection: A Retrospective Cohort Study

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Research Article

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Abstract

Background

Early inflammatory and immune responses after lung resection may be associated with postoperative complications. However, whether changes in routine blood biomarkers over the perioperative period provide information on early postoperative risk beyond single time-point measurements remains unclear. This study evaluated the associations of changes in white blood cell count, lymphocyte percentage, albumin, and red cell distribution width from before surgery to 24 h after surgery with postoperative complications, and assessed whether these dynamic measures provided incremental discrimination beyond baseline clinical variables.

Methods

Patients undergoing lung resection were retrospectively included. Preoperative measurements were defined as the most recent laboratory results obtained within 7 days before surgery, and postoperative measurements were those obtained 24 h after surgery. Changes (Δ) were calculated as the postoperative value minus the preoperative value. The primary outcome was any postoperative complication; secondary outcomes included postoperative pulmonary complications (PPC), postoperative length of stay, and chest tube duration. Logistic regression was used to assess the associations of biomarker changes with overall postoperative complications and PPC. Three prespecified nested models were developed sequentially using clinical variables alone, clinical variables plus Δ WBC, and clinical variables plus Δ WBC and Δ Lymphocyte. Incremental discrimination was assessed using receiver operating characteristic curves, DeLong tests, and likelihood ratio tests. Internal optimism correction was performed using 1000 bootstrap resamples, with additional calibration and decision curve analyses.

Results

Among 908 patients included in the primary analysis, 223 (24.6%) developed at least one postoperative complication. At 24 h after surgery, median WBC increased from 5.57 (IQR, 4.71–6.69) to 10.54 (8.40–12.91) $\times 10^9/L$, lymphocyte percentage decreased from 31.90% (26.50–37.90) to 8.70% (6.00–12.80), and albumin decreased from 41.20 (39.05–43.40) to 37.60 (35.30–40.10) g/L. After adjustment, Δ WBC was associated with overall postoperative complications (OR, 1.13; 95% CI, 1.08–1.19; $P < 0.001$) and PPC (OR, 1.12; 95% CI, 1.07–1.18; $P < 0.001$). Δ Lymphocyte was also independently associated with overall postoperative complications (OR, 0.97; 95% CI, 0.95–0.99; $P = 0.001$) and PPC (OR, 0.98; 95% CI, 0.96–0.99; $P = 0.009$). The AUC of the clinical model was 0.729, increasing to 0.761 after addition of Δ WBC ($P = 0.002$) and to 0.764 after further addition of Δ Lymphocyte ($P = 0.410$). The optimism-corrected C-indexes from 1000 bootstrap resamples were 0.702, 0.734, and 0.737, respectively.

Conclusions

Changes in routine blood biomarkers at 24 h after lung resection were independently associated with postoperative complications, with Δ WBC showing the clearest incremental discrimination beyond baseline

clinical variables. Δ WBC may have potential as an early adjunct to conventional clinical risk assessment, although its clinical utility requires validation in independent cohorts.

1. Background

Lung resection is an important treatment for lung cancer and other localized pulmonary diseases (1, 2). Despite advances in minimally invasive surgery, perioperative anesthetic management, and enhanced recovery strategies, postoperative complications remain an important cause of delayed recovery, with particular attention given to postoperative pulmonary complications (PPC) (3, 4). Previous studies have shown that patients who develop PPC have longer hospital stays and are at increased risk of intensive care admission, readmission, and adverse long-term outcomes (5, 6).

Current risk assessment for postoperative complications relies largely on preoperative clinical variables, including age, pulmonary function, ASA classification, smoking history, comorbidity burden, and extent of resection(7, 8). Although these variables capture patients' baseline risk, they do not fully reflect the early physiological response to surgical trauma(9, 10). During the first 24 h after surgery, substantial inflammatory responses, redistribution of immune cells, and changes in intravascular volume may occur. Therefore, the magnitude of change between preoperative and early postoperative measurements may provide information beyond that captured by a single absolute measurement(11) .

Postoperative leukocytosis, lymphopenia, and a decrease in serum albumin are common changes after surgery(12). Previous thoracic surgical studies have suggested that early postoperative lymphopenia is associated with the risk of postoperative pneumonia, while perioperative changes in serum albumin may also be associated with PPC (13, 14). However, previous studies have generally focused on individual biomarkers, and few have compared changes in multiple routinely measured biomarkers within the same analytical framework. More importantly, statistical association in a multivariable model does not necessarily indicate that a biomarker improves risk discrimination(15). Therefore, from a clinical perspective, it is important to determine whether dynamic biomarker changes provide additional discriminatory information beyond established clinical variables.

Accordingly, this study used 24 h after surgery as the key time point for the early physiological response and examined the associations of changes in WBC count, lymphocyte percentage, albumin, and RDW from before surgery to 24 h after surgery with postoperative complications. We further assessed whether the dynamic biomarkers that provided the most information could improve risk discrimination beyond a baseline clinical model. We hypothesized that a greater postoperative increase in WBC count and a greater decrease in lymphocyte percentage would be associated with a higher risk of postoperative complications.

2. Methods

2.1 Study population and study design

This was a single-center retrospective cohort study. We retrospectively included patients who underwent lung resection at the Department of Thoracic Surgery, the First Affiliated Hospital of Zhengzhou University, between December 2023 and June 2024 and had available perioperative laboratory data. The original database included

910 patients. According to the prespecified completeness criteria for the primary analysis variables, 2 patients were excluded because key preoperative (T0) biomarker data were unavailable, leaving 908 patients for the primary association analyses. ROC and nested model analyses were performed in a common complete-case cohort of 904 patients. Complete postoperative length-of-stay data were available for 892 patients.

2.2 Biomarker measurement and outcome definitions

Preoperative blood measurements (T0) were defined as the most recent laboratory results obtained within 7 days before surgery. Postoperative measurements (T1) were obtained 24 h after surgery. Four routinely measured biomarkers were evaluated: white blood cell count (WBC), lymphocyte percentage, albumin, and red cell distribution width (RDW).

The change in each biomarker was defined as:

$$\Delta \text{biomarker} = T1 - T0$$

Thus, a positive Δ WBC indicated an increase in WBC after surgery, whereas a negative Δ Lymphocyte indicated a decrease in lymphocyte percentage from before to after surgery.

The primary outcome was any postoperative complication, defined as the presence of at least one postoperative complication documented in the database. The secondary outcome was postoperative pulmonary complications (PPC), including pneumonia, atelectasis, acute respiratory distress syndrome (ARDS), pulmonary embolism, and reintubation. The criteria used to define PPC were based on the joint definitions of the Society of Thoracic Surgeons and the European Society of Thoracic Surgeons (16). Postoperative length of stay and chest tube duration were analyzed as continuous outcomes.

2.3 Clinical variables and statistical analysis

The primary multivariable models prespecified age, sex, BMI, ASA classification, comorbidity burden, smoking index, clinical stage, neoadjuvant therapy, and extent of resection. Age and BMI were analyzed as continuous variables. Smoking index was categorized as 0, 1–200, 201–400, and > 400. ASA classification was categorized as 1, 2, and 3–4. Comorbidity burden was categorized as 0, 1, 2, and ≥ 3 conditions. Clinical stage was categorized as stage 0, I, II, III–IV, and unknown. Neoadjuvant therapy was categorized as no or yes, and extent of resection as sublobar resection or lobectomy/pneumonectomy. Sensitivity analyses additionally included surgical approach, operation time, and intraoperative blood loss in the primary model, followed by a second sensitivity analysis that further included FEV1% predicted.

Continuous variables were summarized as mean $\pm$ standard deviation or median (IQR), as appropriate, and categorical variables as number (percentage). Patients were stratified according to the presence or absence of postoperative complications, and standardized mean differences were also calculated. Changes between preoperative and 24-h postoperative measurements were assessed using paired statistical tests.

Separate logistic regression models were fitted for overall postoperative complications and PPC, with each Δ biomarker entered as the main exposure. Crude ORs were first estimated, followed by adjustment for the prespecified clinical variables. The four dynamic biomarkers were entered into separate models to assess their independent associations while avoiding unnecessary model complexity. Results are presented as ORs with 95% CIs.

Postoperative length of stay showed a right-skewed distribution and was analyzed using log-linear regression, with a Gamma regression model used as a sensitivity analysis. Chest tube duration was analyzed using the corresponding continuous-outcome model.

2.4 Incremental discrimination and internal validation

To assess whether dynamic biomarker changes provided additional information beyond conventional clinical variables, three prespecified nested models were constructed. Model 1 included age, sex, BMI, ASA classification, comorbidity burden, smoking index, clinical stage, neoadjuvant therapy, and extent of resection. Model 2 additionally included Δ WBC, and Model 3 further included Δ Lymphocyte. All three models were fitted in the same complete-case cohort of 904 patients to ensure that ROC comparisons were not affected by differences in sample size.

The area under the receiver operating characteristic curve (AUC) was used to assess discrimination, and correlated ROC curves were compared using the DeLong test. Likelihood ratio tests were used to compare overall model fit between nested models.

Internal optimism correction was performed using 1000 bootstrap resamples. Apparent C-index, bootstrap optimism, and optimism-corrected C-index were reported. Calibration curves were generated using bootstrap resampling, and the Brier score, calibration slope, and calibration intercept were reported. Decision curve analysis was performed across threshold probabilities of 0.05–0.50 to explore the potential net clinical benefit of the models. DCA and Brier score analyses were considered internal, apparent analyses rather than external validation.

All statistical analyses were performed using R version 4.6.0. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

3. Results

3.1 Study population and baseline characteristics

The original database included 910 patients (Figure 1). After excluding 2 patients with missing key preoperative (T0) biomarker data, 908 patients were included in the primary analysis. Baseline characteristics are summarized in Table 1. Overall, 223 patients (24.6%) developed at least one postoperative complication. The mean age was 57.43 ± 11.18 years, and 520 patients (57.3%) were female. The mean BMI was 24.36 ± 3.22 kg/m². Most patients had an ASA classification of 2 (76.5%), 57.7% had clinical stage I disease, 93.4% had not received neoadjuvant therapy, and 51.8% underwent sublobar resection. Patients with postoperative complications differed from those without complications in age, sex, smoking index, ASA classification, clinical stage, neoadjuvant therapy, extent of resection, operation time, and intraoperative blood loss.

Table 1. Baseline and perioperative characteristics according to postoperative complication status

Variable	Overall (n=908)	No complication (n=685)	Complication (n=223)	<i>P</i> value	SMD
Age, years	57.43 ± 11.18	56.76 ± 11.24	59.50 ± 10.77	0.001	0.249
Sex, n (%)				<0.001	0.449
Female	520 (57.3)	429 (62.7)	91 (40.8)		
Male	388(42.7)	255 (37.3)	132 (59.2)		
Smoking index, n (%)				<0.001	0.341
0	719 (79.2)	566 (82.6)	153 (68.6)		
1–200	28 (3.1)	20 (2.9)	8 (3.6)		
201–400	43 (4.7)	28 (4.1)	15 (6.7)		
>400	118 (13.0)	71 (10.4)	47 (21.1)		
ASA, n (%)				<0.001	0.313
1	103 (11.3)	89 (13.0)	14 (6.3)		
2	695 (76.5)	527 (76.9)	168 (75.3)		
3–4	110 (12.1)	69 (10.1)	41 (18.4)		
Comorbidity burden, n (%)				0.17	0.166
0	449 (49.4)	347 (50.7)	102 (45.7)		
1	289 (31.8)	220 (32.1)	69 (30.9)		
2	128 (14.1)	91 (13.3)	37 (16.6)		
≥3	42 (4.6)	27 (3.9)	15 (6.7)		
Clinical stage, n (%)				<0.001	0.546
Stage 0	249 (27.4)	217 (31.7)	32 (14.3)		
Stage I	524 (57.7)	389 (56.8)	135 (60.5)		
Stage II	55 (6.1)	25 (3.6)	30 (13.5)		
Stage III–IV	54 (5.9)	33 (4.8)	21 (9.4)		
Unknown	26 (2.9)	21 (3.1)	5 (2.2)		
Neoadjuvant therapy, n (%)				0.016	0.183
No	848 (93.4)	648 (94.6)	200 (89.7)		
Yes	60 (6.6)	37 (5.4)	23 (10.3)		
Surgical approach, n (%)				0.999	0.008
Single-port VATS	762 (84.4)	575 (84.3)	187 (84.6)		

Multi-port/Robotic/Thoracotomy	141 (15.6)	107 (15.7)	34 (15.4)		
Extent of resection, n (%)				<0.001	0.69
Sublobar resection	470 (51.8)	409 (59.7)	61 (27.4)		
Lobectomy/Pneumonectomy	438 (48.2)	276 (40.3)	162 (72.6)		
Operation time, min	93.0 [71.0, 122.0]	88.0 [67.0, 115.0]	110.0 [89.5, 140.5]	<0.001	0.657
Blood loss, mL	50.0 [20.0, 50.0]	50.0 [20.0, 50.0]	50.0 [30.0, 95.0]	<0.001	0.248
FEV1, % predicted	77.75 ± 7.53	78.04 ± 7.39	76.80 ± 7.88	0.041	0.162

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; FEV1, forced expiratory volume in 1 second; SMD, standardized mean difference; VATS, video-assisted thoracoscopic surgery.

Values are mean ± SD, median [IQR], or n (%), as appropriate. P values were derived from Student's t-test, Wilcoxon rank-sum test, chi-square test, or Fisher's exact test, as appropriate. SMD values describe the magnitude of between-group differences. Percentages are based on non-missing observations; surgical approach had 5 missing values.

3.2 Acute changes in routine blood biomarkers at 24 h after surgery

All four biomarkers showed statistically significant changes from before surgery to 24 h after surgery, although the magnitude of change and its relationship with clinical outcomes differed across biomarkers (Table 2, Figure 2).

The median WBC count increased from 5.57 (IQR, 4.71–6.69) ×10⁹/L before surgery to 10.54 (8.40–12.91) ×10⁹/L at 24 h after surgery, with a ΔWBC of 4.91 (2.70–7.14) ×10⁹/L. Lymphocyte percentage decreased from 31.90% (26.50–37.90) to 8.70% (6.00–12.80), with a ΔLymphocyte of –22.90 (–28.80 to –16.30) percentage points. Albumin decreased from 41.20 (39.05–43.40) g/L to 37.60 (35.30–40.10) g/L, with a ΔAlbumin of –3.50 (–6.25 to –0.70) g/L.

In contrast, RDW decreased from 13.00% (12.60–13.60) to 12.90% (12.50–13.50%), with a median ΔRDW of only –0.10 (–0.40 to 0.20) percentage points. Although the paired comparison was statistically significant, the absolute magnitude of change was small, suggesting limited clinical relevance.

Table 2. Acute postoperative changes in routine blood biomarkers

Biomarker	n	T0	T1	Δ (T1–T0)	Δ No complication (n=685)	Δ Complication (n=223)	P (paired)	P (between groups)
WBC ($\times 10^9/L$),	906	5.57 [4.71, 6.69]	10.54 [8.40, 12.91]	4.91 [2.70, 7.14]	4.53 [2.59, 6.61]	6.09 [3.41, 8.49]	<0.001	<0.001
Lymphocyte (%)	906	31.90 [26.50, 37.90]	8.70 [6.00, 12.80]	-22.90 [-28.80, -16.30]	-22.80 [-28.80, -16.20]	-23.00 [-28.75, -16.85]	<0.001	0.731
Albumin (g/L)	899	41.20 [39.05, 43.40]	37.60 [35.30, 40.10]	-3.50 [-6.25, -0.70]	-3.50 [-6.35, -0.80]	-3.45 [-6.02, -0.48]	<0.001	0.597
RDW (%)	906	13.00 [12.60, 13.60]	12.90 [12.50, 13.50]	-0.10 [-0.40, 0.20]	-0.10 [-0.40, 0.20]	-0.10 [-0.30, 0.20]	<0.001	0.608

Abbreviations: Δ , change from T0 to T1; IQR, interquartile range; RDW, red blood cell distribution width; T0, preoperative value obtained within 7 days before surgery; T1, value obtained 24 h after surgery; WBC, white blood cell count.

Values are median [IQR]. T0 denotes the preoperative measurement obtained within 7 days before surgery; T1 denotes the measurement obtained 24 h after surgery. Δ was calculated as T1–T0. P values for paired comparisons were derived from paired Wilcoxon signed-rank tests; P values for between-group comparisons of Δ were derived from Wilcoxon rank-sum tests. Available paired observations were used for each biomarker, and the number of observations may therefore vary between biomarkers.

3.3 Associations of dynamic biomarkers with postoperative complications and PPC

In the analysis of overall postoperative complications (Table 3), Δ WBC showed the most consistent association. For each $1 \times 10^9/L$ increase in Δ WBC, the crude OR was 1.13 (95% CI, 1.08–1.18; $P < 0.001$), and the association remained unchanged after adjustment for age, sex, BMI, ASA classification, comorbidity burden, smoking index, clinical stage, neoadjuvant therapy, and extent of resection (OR, 1.13; 95% CI, 1.08–1.19; $P < 0.001$). For PPC, the adjusted OR for Δ WBC was 1.12 (95% CI, 1.07–1.18; $P < 0.001$).

Δ Lymphocyte was not significantly associated with overall postoperative complications in the crude model (OR, 0.99; 95% CI, 0.98–1.01; $P = 0.272$), but showed an independent association after adjustment for clinical variables (OR, 0.97; 95% CI, 0.95–0.99; $P = 0.001$). For PPC, the adjusted OR was 0.98 (95% CI, 0.96–0.99; $P = 0.009$). Because Δ Lymphocyte was defined as T1–T0, more negative values indicate a greater decrease in lymphocyte percentage. Thus, an $OR < 1$ should not be interpreted as a protective effect of lymphocyte decline; rather, it indicates that greater lymphocyte depletion was associated with a higher risk of postoperative complications.

Neither Δ Albumin nor Δ RDW showed consistent evidence of an association with overall postoperative complications or PPC. The adjusted OR for Δ Albumin was 1.02 (95% CI, 0.98–1.06; $P = 0.427$) for overall

postoperative complications and 1.01 (95% CI, 0.97–1.06; P=0.545) for PPC. Δ RDW was likewise not significantly associated with either outcome.

After additionally adjusting for surgical approach, operation time, and intraoperative blood loss, the association of Δ WBC with overall postoperative complications remained stable (OR, 1.13; 95% CI, 1.08–1.19; P<0.001), while Δ Lymphocyte remained statistically significant (OR, 0.98; 95% CI, 0.96–1.00; P=0.028). After further adjustment for FEV1% predicted, the OR for Δ WBC was 1.16 (95% CI, 1.11–1.22; P<0.001) and that for Δ Lymphocyte was 0.97 (95% CI, 0.95–0.99; P=0.002), whereas Δ Albumin and Δ RDW remained non-significant. Overall, the direction and magnitude of the main associations were broadly consistent across the sensitivity analyses (Table S1).

Table 3. Associations of early postoperative blood biomarker changes with postoperative complications

Exposure	Crude OR (95% CI)	Crude P	Adjusted OR (95% CI)	Adjusted P
Any postoperative complication				
Δ WBC ,per 1 $\times 10^9$ /L	1.13 (1.08–1.18)	<0.001	1.13 (1.08–1.19)	<0.001
Δ Lymphocyte ,per 1 percentage point	0.99 (0.98–1.01)	0.272	0.97 (0.95–0.99)	0.001
Δ Albumin ,per 1 g/L	1.00 (0.97–1.04)	0.862	1.02 (0.98–1.06)	0.427
Δ RDW ,per 1 percentage point	1.15 (0.91–1.46)	0.248	1.15 (0.89–1.47)	0.271
Postoperative pulmonary complications				
Δ WBC, per 1 $\times 10^9$ /L	1.11 (1.07–1.16)	<0.001	1.12 (1.07–1.18)	<0.001
Δ Lymphocyte, per 1 percentage point	0.99 (0.98–1.01)	0.484	0.98 (0.96–0.99)	0.009
Δ Albumin, per 1 g/L	1.00 (0.96–1.04)	0.994	1.01 (0.97–1.06)	0.545
Δ RDW, per 1 percentage point	1.08 (0.84–1.38)	0.523	1.06 (0.82–1.38)	0.639

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; OR, odds ratio; RDW, red blood cell distribution width; WBC, white blood cell count.

Δ was defined as T1–T0. Each biomarker change was entered separately into the logistic regression model. Adjusted models included age, sex, BMI, smoking-index category, ASA category, comorbidity burden, clinical stage, neoadjuvant therapy, and extent of resection. For Δ Lymphocyte, more negative values indicate greater postoperative lymphocyte depletion; therefore, an OR below 1 should not be interpreted as a protective effect of lymphocyte decline.

3.4 Secondary recovery outcomes

Among the 892 patients with complete postoperative length-of-stay data (Table S2), the median postoperative length of stay was 5 days (IQR, 4–6), with a mean of 5.68 ± 2.33 days and a range of 2–27 days, indicating a markedly right-skewed distribution. Patients who developed postoperative complications had a longer hospital

stay than those without complications, with median lengths of stay of 6 (IQR, 5–9) and 5 (IQR, 4–6) days, respectively (Mann–Whitney $P<0.001$).

In multivariable analyses, Δ WBC, Δ Lymphocyte, and Δ RDW were not consistently associated with postoperative length of stay. Δ Albumin showed a small but statistically significant association with length of stay: each 1 g/L increase in Δ Albumin was associated with a 0.55% relative reduction in postoperative length of stay (95% CI, -1.04% to -0.06%; $P=0.027$), with a consistent direction of association in the Gamma model ($P=0.039$). Given the small effect size, this finding was considered exploratory. None of the dynamic biomarkers showed an independent association with chest tube duration.

3.5 Incremental discrimination, internal validation, calibration, and decision curve analysis

Among the 904 patients in the common complete-case cohort (Table 4), the baseline clinical model had an AUC of 0.729 (95% CI, 0.692–0.767). After adding Δ WBC, the AUC increased to 0.761 (95% CI, 0.724–0.797), with a Δ AUC of 0.031 (DeLong $P=0.002$), indicating significant incremental discrimination beyond the conventional clinical variables (Figure 3A).

Further addition of Δ Lymphocyte increased the AUC to 0.764 (95% CI, 0.729–0.800), an absolute increase of only 0.003 over the clinical + Δ WBC model (DeLong $P=0.410$). Thus, although Δ Lymphocyte remained independently associated with postoperative complications in multivariable logistic regression, its addition to Δ WBC did not significantly improve risk discrimination.

Likelihood ratio testing provided complementary evidence. Adding Δ WBC to the clinical model significantly improved model fit (deviance difference, 33.744; $P=6.286 \times 10^{-9}$), while further addition of Δ Lymphocyte produced an additional deviance difference of 4.245 ($P=0.0394$). The deviance difference between the clinical model and Model 3 was 37.989 ($P=5.634 \times 10^{-9}$). These findings suggest that Δ Lymphocyte may provide some additional information for overall model fit, although this did not translate into a detectable improvement in AUC.

In the 1000-resample bootstrap internal validation analysis (Figure 3B), the apparent C-indexes of the three models were 0.729, 0.761, and 0.764, with optimism estimates of 0.028, 0.026, and 0.027, respectively. The corresponding optimism-corrected C-indexes were 0.702, 0.734, and 0.737. The apparent Brier scores were 0.162, 0.155, and 0.154, respectively. The optimism-corrected calibration slopes were approximately 0.848, 0.862, and 0.858, with corresponding calibration intercepts of -0.147, -0.129, and -0.132, indicating some degree of optimism and calibration deviation.

Decision curve analysis (Figure 3C) showed a modest net-benefit advantage for the model including Δ WBC over the baseline clinical model across a broad range of intermediate threshold probabilities, whereas the curves for the models with and without Δ Lymphocyte were closely aligned. As the DCA was based on apparent model performance, these findings should be considered exploratory and not evidence of established clinical benefit.

Table 4. Incremental discrimination and internal validation of nested clinical models

Panel A. Discrimination and internal validation

Model	Model specification	AUC (95% CI)	Δ AUC	DeLong P value	LRT P value	Bootstrap optimism	Optimism-corrected C-index
Model 1	Clinical variables	0.729 (0.692–0.767)	—	—	—	0.028	0.702
Model 2	Clinical variables + Δ WBC	0.761 (0.724–0.797)	0.031	0.002	<0.001	0.026	0.734
Model 3	Clinical variables + Δ WBC + Δ Lymphocyte	0.764 (0.729–0.800)	0.004	0.410	0.039	0.027	0.737

Panel B. Calibration

Model	Apparent Brier score	Optimism-corrected calibration intercept	Optimism-corrected calibration slope
Model 1	0.162	−0.147	0.848
Model 2	0.155	−0.129	0.862
Model 3	0.154	−0.132	0.858

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; C-index, concordance index; LRT, likelihood ratio test.

Model 1 included age, sex, BMI, ASA category, comorbidity burden, smoking-index category, clinical stage, neoadjuvant therapy, and extent of resection. Model 2 additionally included Δ WBC; Model 3 additionally included Δ Lymphocyte. Models were fitted in the same complete-case cohort of 904 patients. Δ AUC and DeLong P values compare each model with the preceding model. For Model 3 versus Model 1, the Δ AUC was 0.035 ($P=0.001$). LRT P values compare nested models with the preceding model; the Model 3 versus Model 1 comparison was $P<0.001$. Internal validation was performed using 1000 bootstrap resamples. Bootstrap optimism estimates were 0.028, 0.026, and 0.027 for Models 1, 2, and 3, respectively. Brier scores were calculated from apparent predictions; calibration intercepts and slopes are optimism-corrected internal estimates.

4. Discussion

4.1 Principal findings

This study evaluated changes in four routinely measured blood biomarkers during the first 24 h after lung resection and their associations with postoperative complications. Three main findings emerged.

First, substantial changes in routine blood biomarkers were observed within 24 h after lung resection, with the most pronounced changes being an increase in WBC count and a decrease in lymphocyte percentage,

accompanied by a marked reduction in albumin, whereas the absolute change in RDW was small. Second, after adjustment for major clinical risk factors, Δ WBC remained consistently associated with both overall postoperative complications and PPC, while Δ Lymphocyte also showed an independent association. In contrast, Δ Albumin and Δ RDW showed no consistent associations with the primary outcomes. Third, from a risk stratification perspective, Δ WBC showed the clearest incremental value among the dynamic biomarkers, increasing the AUC of the clinical model from 0.729 to 0.761. Although adding Δ Lymphocyte further improved model fit, it did not significantly increase the AUC.

These findings suggest that postoperative biomarker changes provide information that is distinct from single time-point measurements(17, 18) . However, statistical association with postoperative complications does not necessarily mean that adding a biomarker to a clinical model will improve risk discrimination. In the present study, Δ WBC demonstrated both a consistent association with postoperative complications and incremental discriminatory value, making it the most clinically relevant early dynamic biomarker among those evaluated.

4.2 Interpretation of findings and comparison with previous studies

Surgical trauma can induce a marked systemic stress response within a short period, including the release of inflammatory mediators, leukocyte mobilization, and changes in immune-cell distribution(19-21) . Therefore, an increase in WBC count after surgery does not in itself indicate infection and should not necessarily be regarded as an abnormal response (11, 22) . A more relevant finding in the present study was that the magnitude of the increase in WBC count from before surgery to 24 h after surgery was consistently associated with the risk of postoperative complications. This suggests that Δ WBC may reflect the intensity of the early systemic response to surgical trauma rather than serve as a surrogate for any specific postoperative complication.

Compared with a single preoperative WBC measurement, a change-based measure may have the potential advantage of accounting, at least in part, for differences in individual baseline levels. Preoperative WBC counts may vary considerably between patients, and the magnitude of the physiological shift during the first 24 h after surgery may therefore provide additional information. However, this interpretation is biologically plausible rather than directly demonstrated by the present data. Given the observational design, the association between Δ WBC and postoperative complications should not be interpreted as causal.

Postoperative lymphopenia was also a prominent finding in this study. Previous thoracic surgical research has shown that early postoperative lymphopenia is associated with postoperative pneumonia and PPC(13) . Our findings were broadly consistent with this observation: Δ Lymphocyte remained independently associated with overall postoperative complications and PPC after adjustment for clinical variables. However, its incremental discriminatory value was substantially lower than that of Δ WBC. Notably, although adding Δ Lymphocyte to the model resulted in a modest improvement in model fit according to the likelihood ratio test, it did not significantly improve the AUC according to the DeLong test. This illustrates that a biomarker may carry independent statistical information without materially improving the ranking of patients according to risk. This distinction is relevant when assessing the clinical value of candidate biomarkers.

Albumin also decreased substantially after surgery in our cohort, but Δ Albumin was not consistently associated with the primary complication outcomes after adjustment. Previous studies have reported an association between perioperative albumin changes and PPC after lung cancer resection(14) . The discrepancy between those findings and ours may reflect differences in patient characteristics, extent of resection, complication

profiles, sampling time points, or residual confounding. Thus, our findings do not rule out albumin as a potential postoperative biomarker but may indicate that its prognostic relevance varies across patient populations and clinical settings.

RDW showed a different pattern. Although the preoperative-to-24-h postoperative change was statistically significant, the median change was only -0.10 percentage points, and Δ RDW was not independently associated with overall postoperative complications or PPC. This finding also illustrates that statistical significance does not necessarily imply clinical importance, particularly when the magnitude of an observed change is very small. A small P value alone should therefore not be given substantial biological or clinical interpretation when the underlying change is minimal.

4.3 Clinical implications

The most direct potential clinical implication of our findings is that the change in WBC count at 24 h after surgery can be obtained from routine postoperative blood testing without requiring additional resources. Compared with specialized biomarkers, WBC count is routinely measured in the perioperative setting and is inexpensive, readily available, and easily repeatable.

If these findings are reproduced in independent cohorts, a greater Δ WBC may serve as a simple signal for early postoperative risk stratification. In patients who already have a higher baseline risk, a marked increase in WBC count may warrant closer monitoring of respiratory status, signs of infection, and postoperative recovery.

However, our findings do not support the use of Δ WBC as a stand-alone diagnostic marker for postoperative complications or the initiation or modification of antibiotic treatment on the basis of Δ WBC alone. Its more appropriate role is as a complement to conventional clinical variables rather than a replacement for them. Given the degree of calibration deviation observed in the present models and the apparent nature of the DCA, clinical decisions based on specific risk thresholds should await external validation.

4.4 Strengths and limitations

This study has several strengths. First, we used paired preoperative and 24-h postoperative measurements from the same patients, focusing on dynamic changes rather than single absolute measurements. Second, the primary association analyses used prespecified clinical variables for adjustment, and the stability of the main findings was examined in sensitivity analyses incorporating surgical approach, operation time, blood loss, and FEV1% predicted. Third, we did not equate statistical association with clinical predictive value; instead, ROC analysis, the DeLong test, likelihood ratio tests, bootstrap internal validation, calibration, and DCA were used to assess the incremental value of the dynamic biomarkers from complementary perspectives.

Several limitations should also be considered. First, the retrospective design is subject to selection bias, information bias, and residual confounding; therefore, the observed associations should not be interpreted as causal. Second, this was a single-center study. Although bootstrap internal validation was performed, the models have not yet undergone independent external validation, limiting their generalizability. Third, PPC was primarily identified from predefined postoperative complication records in the database, and the specific diagnostic criteria and timing of individual events should be further verified against the original clinical records. Fourth, only a single early postoperative time point was assessed. Thus, we could not determine whether

persistent inflammation, the rate of recovery, or a subsequent second peak might have greater prognostic value. Fifth, the calibration slopes were below 1, suggesting some degree of model optimism or overfitting, and the current results should therefore not be interpreted as demonstrating clinical-ready model performance. Finally, the ROC analyses were based on a common complete-case cohort, and missing data in some variables may have introduced bias associated with complete-case analysis.

Importantly, the aim of this study was not to develop a complex prediction tool containing as many biomarkers as possible. Rather, the findings support further external validation of Δ WBC as the most consistent signal and evaluation of its stability across different extents of resection, surgical approaches, levels of pulmonary function, and baseline-risk groups.

5. Conclusions

Marked changes in routine blood biomarkers occur within 24 h after lung resection, characterized by an increase in WBC count and decreases in lymphocyte percentage and albumin. After adjustment for major clinical factors, Δ WBC remained consistently associated with overall postoperative complications and PPC and provided the clearest incremental discrimination beyond the baseline clinical model. Δ Lymphocyte was also independently associated with postoperative complications, but its addition to Δ WBC resulted in limited improvement in AUC.

Accordingly, dynamic changes in routine blood biomarkers at 24 h after surgery, particularly Δ WBC, may serve as early markers for risk stratification after lung resection. Further prospective studies and independent external validation are needed before these findings can be incorporated into clinical decision-making pathways.

Abbreviations

ASA

American Society of Anesthesiologists

AUC

area under the receiver operating characteristic curve

BMI

body mass index

CI

confidence interval

C

index—concordance index

DCA

decision curve analysis

FEV1

forced expiratory volume in 1 second

IQR

interquartile range

LRT

likelihood ratio test

OR

odds ratio

PPC

postoperative pulmonary complication

RDW

red cell distribution width

SMD

standardized mean difference

T0

preoperative measurement

T1

postoperative 24–h measurement

VATS

video–assisted thoracoscopic surgery

WBC

white blood cell count

 Δ

change from T0 to T1

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of The First Affiliated Hospital of Zhengzhou University. Owing to the retrospective nature of this study, the requirement for written informed consent was waived by the committee. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Data use agreements were signed among participating institutions.

Clinical trial number

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to privacy/ethical restrictions on patient medical record data but are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

Funding

Not applicable.

Authors' contributions

Penghao Zhao and Chunyang Zhang collected the data. Penghao Zhao designed the study. Penghao Zhao analyzed the data. Penghao Zhao and Chunyang Zhang interpreted the data. Penghao Zhao prepared the manuscript, and Chunyang Zhang revised it critically. All authors read and approved the final manuscript.

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Figures

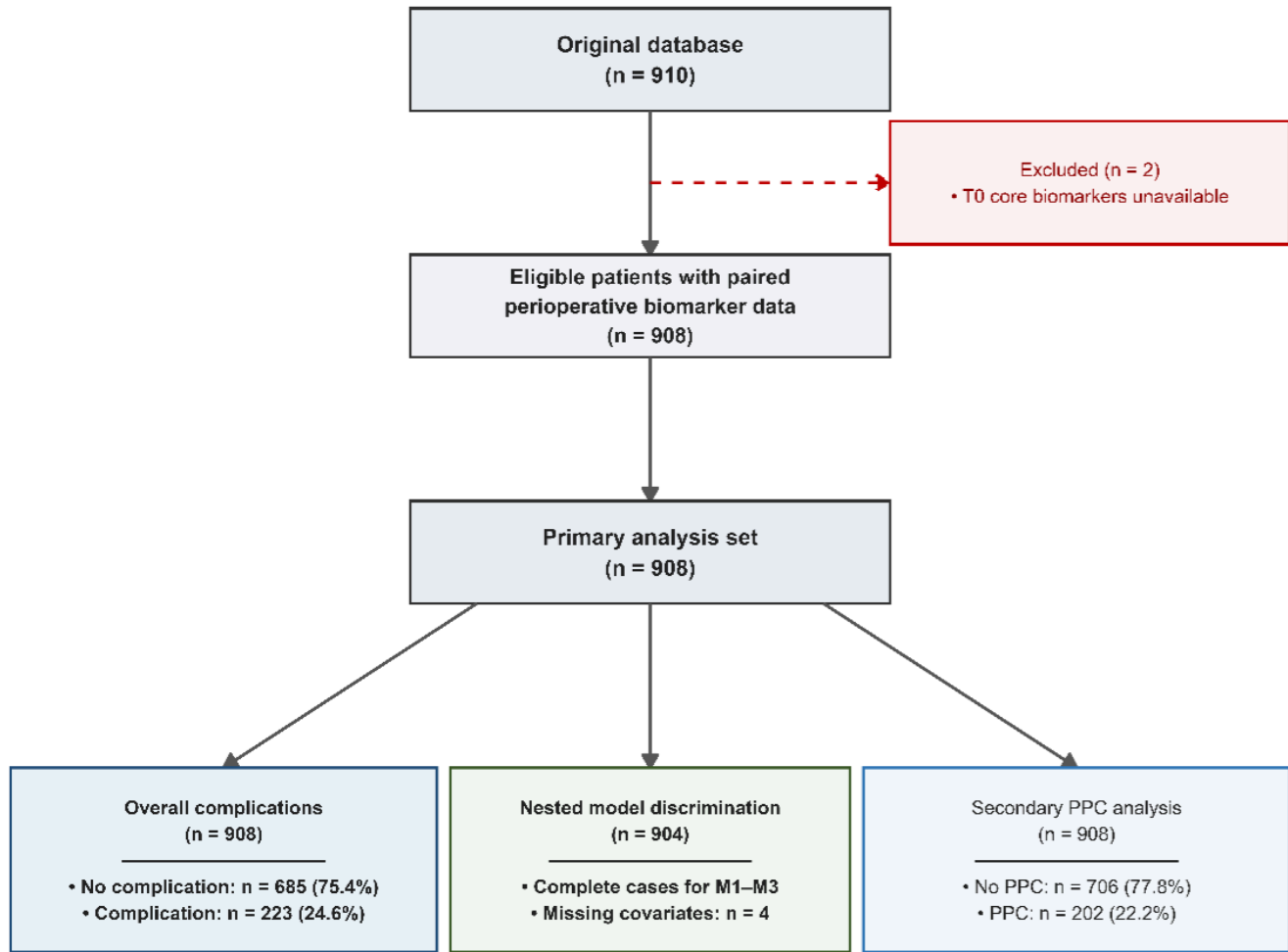


Figure 1

Study flow diagram.

Flowchart detailing patient selection and cohort stratification. Among 910 patients in the initial database, 2 were excluded due to missing preoperative (T0) baseline biomarker data, yielding a primary analysis set of 908 eligible patients with paired perioperative biomarker data. The cohort was evaluated across three specific analytical tracks: (left) the primary outcome cohort (n = 908) stratified by overall postoperative complications; (middle) the complete-case cohort (n = 904) utilized for nested discrimination model analyses (Models 1–3), excluding 4 patients with missing baseline covariates; and (right) the secondary outcome cohort (n = 908) evaluated for postoperative pulmonary complications (PPC).

PPC: postoperative pulmonary complication.

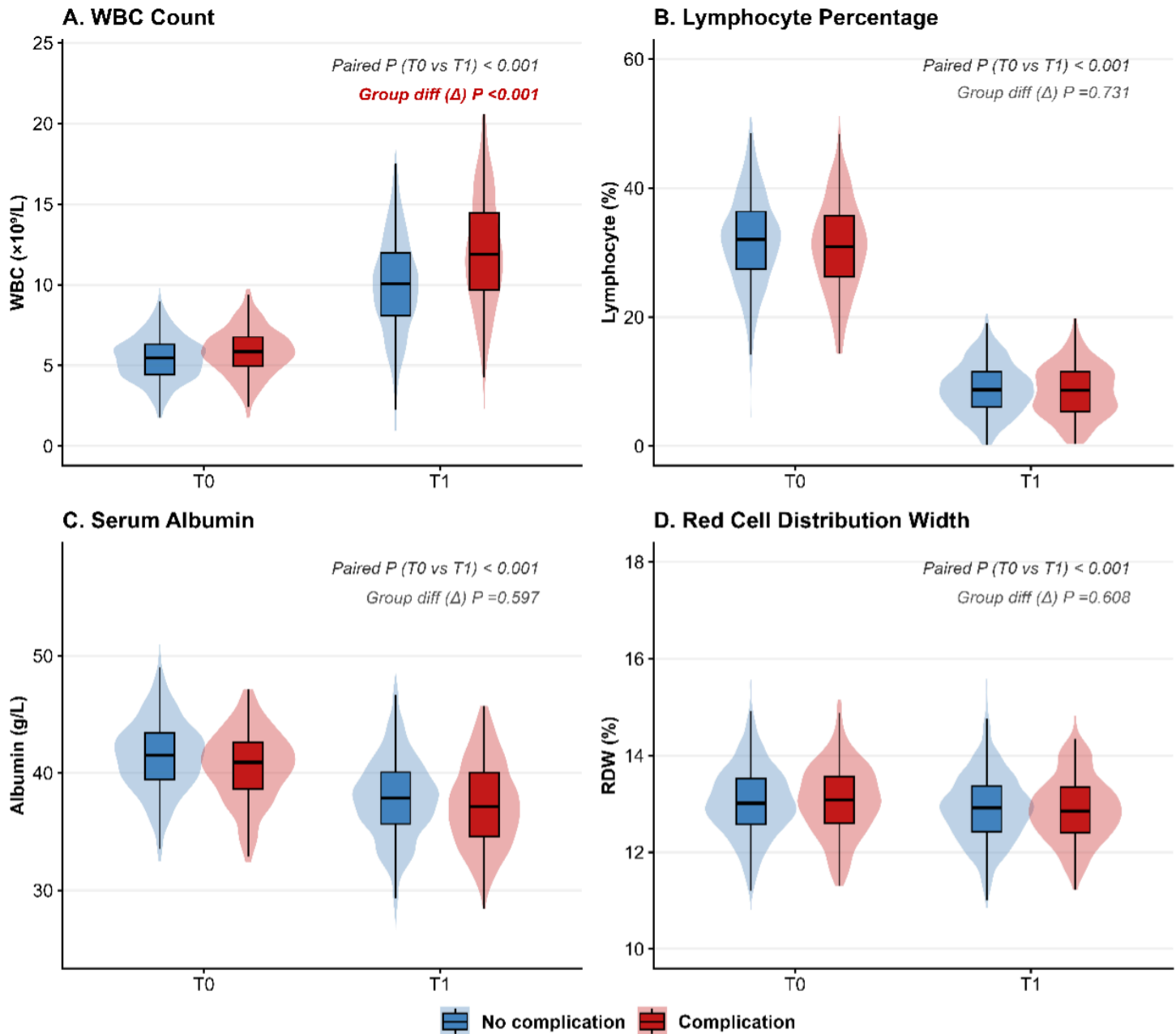


Figure 2

Acute perioperative dynamics of inflammatory and nutritional biomarkers.

Comparison of biomarker levels between baseline (T0, preoperative) and 24 hours postoperatively (T1) stratified by overall complication status. (A) White blood cell (WBC) count, (B) Lymphocyte percentage, (C) Serum albumin level, and (D) Red cell distribution width (RDW). Violin plots depict data kernel density distributions; overlaid boxplots represent the median and interquartile range (IQR). Paired Wilcoxon signed-rank tests were used for within-group comparisons (T0 vs T1), and Mann–Whitney U tests were used to evaluate acute change ($\Delta = T1 - T0$) differences between groups. Statistically significant group differences (Δ) are highlighted in bold red.

WBC: white blood cell; RDW: red cell distribution width.

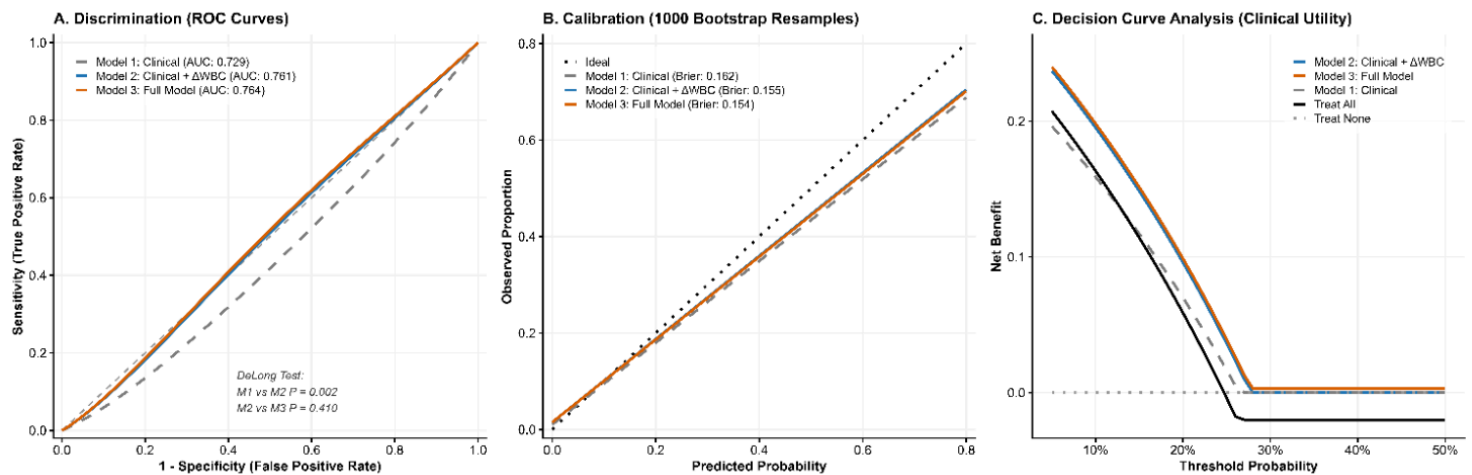


Figure 3

Incremental discrimination and decision curve analysis of early postoperative blood biomarker dynamics

(A) Receiver operating characteristic (ROC) curves evaluating model discrimination for overall complications. Addition of Δ WBC to the baseline clinical model (Model 1) significantly improved discrimination (Model 2 AUC = 0.761 vs Model 1 AUC = 0.729; DeLong P = 0.002). Incorporating Δ Lymphocyte (Model 3) provided minimal incremental discrimination over Model 2 (AUC = 0.764; DeLong P = 0.410). **(B)** Bootstrap optimism-corrected calibration curves based on 1,000 resamples illustrating agreement between predicted probabilities and observed complication proportions. Brier scores for Model 1, Model 2, and Model 3 were 0.162, 0.155, and 0.154, respectively. **(C)** Decision curve analysis showed a modest net-benefit advantage of Model 2 over Model 1 across a range of intermediate threshold probabilities, whereas Model 3 provided little additional net benefit beyond Model 2.

AUC: area under the receiver operating characteristic curve; WBC: white blood cell.

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