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*Original Article*

# Gamma-Glutamyl Transpeptidase to Platelet Ratio Is a Novel and Independent Prognostic Marker for Resectable Lung Cancer: A Propensity Score Matching Study

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**Background: We report this propensity score matching (PSM) analysis to assess prognostic roles of preoperative gamma-glutamyl transpeptidase to platelet ratio (GPR) in video-assisted thoracoscopic (VATS) lobectomy for stage I-II non-small-cell lung cancer (NSCLC).**
**Methods: The PSM-based study conducted on our single-center prospectively collected database from January 2014 to August 2015 provided Kaplan–Meier survival analyses using the log-rank test to discriminate differences in overall survival (OS) and disease-free survival (DFS) between patients stratified by preoperative GPR.**
**Results: Our study includes 379 patients diagnosed with operable primary stage I-II NSCLC. A GPR value at 0.16 was recognized as the optimal cutoff point for prognostic prediction. Both OS and DFS of patients with GPR ≥0.16 were significantly shortened when compared to those of patients with GPR <0.16. Patients with GPR ≥0.16 had significantly lower 5-year rates of OS and DFS than those of patients with GPR <0.16 ($P$ <0.001). Significant associations between GPR and unfavorable survival still are validated in the PSM analysis. Multivariable Cox regression models on both the entire cohort and the PSM cohort consistently demonstrated that an elevated preoperative GPR could be an independent prognostic marker for both OS and DFS of resectable NSCLC.**
**Conclusions: GPR may be an effective and noninvasive prognostic biomarker in VATS lobectomy for surgically resectable NSCLC.**

**Keywords:** gamma-glutamyl transpeptidase to platelet ratio, non-small-cell lung cancer, video-assisted thoracoscopic surgery, prognosis

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## Introduction

Non-small-cell lung cancer (NSCLC) is one of the worldwide leading causes of deaths from solid malignancy.[1–6] Up to date, surgical resection has been generally considered as the most preferred treatment option for resectable early-stage NSCLC. However, despite dramatic advances in elective therapeutic techniques, clinical prognosis of NSCLC, reaching at a poor 5-year survival rate around 15%–18%, still remains frustrating.[2–5] Therefore, an early identification of putative prognostic markers will be essentially critical to help surgeons precisely recognize the patients who are at a higher risk suffering from unfavorable surgical outcomes and further draw up an individualized treatment plan in advance.[2–5]

The tumor burden traditionally characterized by a range of well-known pathologic factors, including the differentiation grade, tumor invasion, lymph node metastasis, and TNM-stage classification, is not the only determining factor for the prognosis of carcinoma.[2–5] Current evidence recognizes that a validated combination of peripheral blood and biochemistry biomarkers, which can be conveniently gained with minimal invasion of the blood, has been increasingly applied to develop kinds of clinical risk scoring systems providing effective information for the prognostic prediction of surgically resectable NSCLC.[1–7]

Most recently, gamma-glutamyl transpeptidase to platelet ratio (GPR) has been reported to emerge as a novel noninvasive biomarker with acceptable accuracy to estimate the severity of liver fibrosis and the development of acute-on-chronic liver failure.[8–11] Preoperative GPR has also been further identified to possess a credible prognostic significance in patients undergoing curative resection for hepatocellular carcinoma.[12–15] However, there is no study yet tried to explore clinical implications of GPR in the other fields of surgical oncology. We speculate that GPR may also have a potentially predictive impact on survival outcomes of resectable NSCLC.

Given such concerns, we determined to conduct this propensity score matching (PSM) cohort study to demonstrate the prognostic value of preoperative GPR in surgically resectable primary stage I-II NSCLC.

## Materials and Methods

### Study design and protocol

The present study was performed on our prospectively collected institutional database. We declared that all relevant procedures were approved by the Institutional Review Board and performed in compliance with the Helsinki Declaration (ID: 2016-255). We finished this study according to the Strengthening the Reporting of Cohort Studies in Surgery 2019 Guidelines.[16]

### Patient selection

*Settings*

We reviewed the consecutive patients who had undergone completely video-assisted thoracoscopic (VATS) lobectomy for operable stage I-II NSCLC within our academic institution between January 2014 and August 2015.

*Inclusion and exclusion criteria*

We carried out the following inclusion and exclusion criteria to determine the appropriateness of the patients included:

i. Only standard single lobectomy with systemic mediastinal lymph node dissection performed by a completely VATS procedure would be considered;
ii. We set up the target disease as surgically resectable primary stage I–II NSCLC. Furthermore, patients with any concomitant or previous malignancy were not included;
iii. Patients who underwent neoadjuvant chemotherapy or chemo-radiotherapy, adjuvant chemotherapy or chemo-radiotherapy, or molecular targeted therapy were not included in this analysis with the aim to control potential interfering influence from anti-cancer therapies during preoperative and postoperative follow-up period;
iv. The laboratory data must be obtained within 5 days before surgery. Patients with loss of clinical biochemistry records were not included;
v. Patients who were lost out of follow-up were not included with the aim to guarantee the accuracy and objectivity of the survival data collected.

### Follow-up assessment

As for each patient included, we designed a standardized follow-up plan since the operation day. We had prepared the most conventional appointments in compliance with our institutional protocols, including routine physical examination, laboratory index testing, chest computed tomography, upper abdominal computed tomography, and brain computed tomography or magnetic resonance imaging.[2–5] In addition, a regular telephone follow-up

would be an alternative if patients cannot go to the outpatient clinic.

The follow-up assessment was operated every 3 months for the first 2 years and every 6 months for the next 3 years. Our latest date regarding follow-up was until March 2019.

## Outcome data, measures, and definitions

*Patient characteristics*

Perioperative baseline characteristics included the age, body mass index (BMI), gender, smoking status, alcohol consumption, and tumor-located lobes.

The preoperative underlying comorbidities estimated were composed of respiratory comorbidity (i.e., chronic obstructive pulmonary disease (COPD), pneumonia, emphysema, asthma, bullae, abscess, tuberculosis, interstitial pulmonary diseases, and bronchiectasis), cardiocerebrovascular comorbidity (i.e., coronary heart disease, hypertension, peripheral artery disease, stroke, aortic aneurysm, and chronic heart failure), hepatic comorbidity (i.e., chronic hepatitis B and hepatitis C, severe hepatocirrhosis and fatty liver, and hepatic parasitic infections), and diabetes mellitus.[2–5)]

We further extracted four mostly assessed pathologic factors: histologic subtypes, differentiation grade, T-stage and lymph node metastasis (N-stage), all of which were defined according to the Union for International Cancer Control 7th Edition.[2–5)]

*Laboratory markers with grouping criteria*

Blood sampling was performed before surgery by our experienced nurses. The levels of gamma-glutamyl transpeptidase (GGT) (IU/L), serum albumin (g/L) and hemoglobin (g/L), and the amounts of peripheral red blood cell (RBC), neutrophil, lymphocyte and platelet, were all obtained from complete blood count and biochemistry tests. The GPR index was calculated by the level of GGT divided by platelet count.

The optimal cutoff point of GPR with respect to postoperative survival was determined by the *Cutoff Finder*, a freely available website-based R software (http://molpath.charite.de/cutoff), as what we previously reported in a prognostic marker study.[3)] Then, we classified the patients with GPR < this threshold value and the patients with GPR ≥ this threshold value into the low GPR group and the high GPR group.

In addition, when performing the subsequent survival analyses, we also applied our institutional normal ranges of peripheral platelets (100–300 $\times$ $10^9$/L) and GGT (<45 IU/L) to divide all included patients into the normal range group and the abnormal range group, respectively.

*Outcomes of interest*

Our primary outcome data included the overall survival (OS) and the disease-free survival (DFS). On the one hand, OS was the survival time between the operation day and the date of death from any cause or of censoring at the last follow-up date. On the other hand, DFS was the survival time from the operation day to the date detecting any cancer recurrence or distant metastasis.[2–5)]

Our secondary goals were Clavien-Dindo Classification grade ≥2 complications occurred within 30 days postoperatively, all of which were diagnosed in accordance to the STS-ESTS joint definition.[17,18)] We classified all grade 2 complications which only required drug treatment into the minor morbidity. Meanwhile, we classified all grade ≥3 complications which required surgical, endoscopic treatment or life support into the major morbidity.[17)]

## Surgical technique and perioperative care

A standardized three-portal VATS lobectomy was operated via a modified fissureless thoracoscopic surgical technique named the "single-direction lobectomy." The whole operative protocols and systemic mediastinal lymph node dissection had been previously described.[19)] All of the elective patients who were intend to undergo VATS lobectomy at our unit were generally managed in compliance with a standardized pathway composing of the antibiotic prophylaxis, breath training, respiratory drug intervention, invasive physiotherapy, surgical pain control, venous thromboembolism prophylaxis, and chest tube management, all of which had been previously described.[20)]

## Statistical analysis

We determined the Pearson's chi-squared test or Fisher's exact test to compare the categorical covariates analyzed and the Mann–Whitney U test to compare the continuous data analyzed (mean ± standard deviation [SD]). The survival analyses regarding OS and DFS were carried out through the Kaplan–Meier method with log-rank test to assess differences in survival months.

With respect to PSM, a nearest-neighbor matching algorithm via caliper matching with its designated distance at 0.20 SD of the logit of propensity score was employed, to achieve balance in the clinic-pathologic covariates significantly differed between the two GPR groups. In addition, this PSM model required that any of

the confounders estimated must not be influenced by any element comprising of GPR, suggesting that any peripheral blood markers obtained from complete blood count and biochemistry tests would not be considered for propensity score balancing.[2,3,5] A 1:1 matched pair was finally created according to the propensity scores.

Univariable Cox proportional hazards regression analysis was initially conduct to explore potential correlations between perioperative covariates and survival outcomes. Then, only those covariates with $P$ <0.10 were chosen for establishment of multivariable Cox proportional hazards regression models to identify putatively reliable prognostic factors for both OS and DFS. Hazard ratio (HR) with its 95% confidence interval (CI) was then derived.

We used the STATA 12.0 (STATA Corporation, College Station, TX, USA) and SPSS 22.0 (IBM SPSS Statistics, Armonk, NY, USA: IBM Corp) software to accomplish all of above statistical analyses. Statistical significance would be indicated if $P$ <0.05.

## Results

### Patient characteristics and outcomes

*Basic information and surgical outcomes*

Between January 2014 and August 2015, there were totally 379 patients who had received radical thoracoscopic lobectomy met all predetermined inclusion criteria and completed our follow-up assessment, as presented in **Supplementary Table 1**.

Our cohort includes 236 male and 143 female patients, with a mean age at 62.8 ± 7.5 years and mean BMI at 23.4 ± 2.8 kg/m$^2$. There were 185 patients having an active or former smoking history, and meanwhile, 19 patients are currently heavy drinkers. Lung adenocarcinoma (LAC) and squamous cell carcinoma (SCC) were diagnosed in 291 and 88 patients, respectively. LNM was confirmed in 73 patients postoperatively according to the pathological criteria.

The median follow-up time was 50.0 (range: 18–66) months, with the OS and DFS rate until the terminal follow-up date at 84.4% and 76.0%, respectively. As for short-term outcomes occurred within the hospitalization, 109 patients developed Clavien-Dindo grade ≥2 complications postoperatively, with an overall morbidity rate at 28.8%. The minor morbidity and major morbidity rate was 28.0% (n = 106) and 6.1% (n = 23), respectively (**Supplementary Table 2**). The in-hospital mortality rate was 0% since no patient died during the hospitalization.

*Groups classified by the cutoff point of GPR*

The bio-statistical results generated by the *Cutoff Finder* showed that there were 24.7% of the available cutoff points regarding GPR were recognized to hold statistical significance for predicting the survival of our series (41 out of 166 tests; **Supplementary Fig. 1**). A GPR at 0.16 was finally identified as the optimal cutoff value with the most significant discriminatory power to predict postoperative survival outcomes, as shown in **Supplementary Fig. 1**. Then, according to this threshold value of GPR, we divided 235 patients with GPR <0.16 into the low GPR group and the rest 144 patients with GPR ≥0.16 into the high GPR group (**Supplementary Table 1**).

### Preoperative GPR and patient characteristics

**Supplementary Table 1** presents all the demographic characteristics between the two GPR groups. We found that patients in the GPR ≥0.16 group had a significantly higher mean BMI but decreased counts of peripheral lymphocytes, and had significantly higher ratios of male gender, smoking history, cardio-cerebrovascular comorbidity, and diabetes when compared to those of patients in the GPR <0.16 group. No significant difference was found in the other clinic-pathologic covariates or laboratory markers between the two GPR groups.

Accordingly, we further applied a PSM to balance potential confounding bias in the above covariates significantly differed between patients with GPR <0.16 and GPR ≥0.16, including the BMI, gender, smoking status, cardio-cerebrovascular comorbidity, and diabetes, as shown in **Supplementary Table 1**. Finally, our PSM model generated a total of 84 well-matched pairs (**Supplementary Tables 1 and 2**). All clinic-pathologic covariates involved were adequately balanced among the matched cohorts after PSM.

### Postoperative complications between the two GPR groups

In the entire cohort, there was no significant difference between patients in the GPR <0.16 group and the GPR ≥0.16 group in terms of overall morbidity (26.4% vs. 32.6%; $P$ = 0.19), minor morbidity (25.1% vs. 32.6%; $P$ = 0.11), or major morbidity (6.0% vs. 6.2%; $P$ = 0.91). After PSM, no significant difference was either showed between the 84 well-matched pairs in terms of overall morbidity (22.6% vs. 32.1%; $P$ = 0.17), minor morbidity (22.6% vs. 32.1%; $P$ = 0.17), or major morbidity (1.2% vs. 2.4%; $P$ = 1.0) (**Supplementary Table 2**).

### Survival outcomes between the two GPR groups

*Entire cohort*

For the entire cohort, the mean OS time of the GPR <0.16 group and the GPR ≥0.16 group was 58.4 (95% CI = 56.5–60.8) and 57.4 (95% CI = 56.0–58.4) months, respectively. The 5-year OS rate of patients with GPR <0.16 and with GPR ≥0.16 was 88.5% and 77.8%, respectively. Furthermore, the mean DFS time of the GPR <0.16 group and the GPR ≥0.16 group was 54.6 (95% CI = 53.1–56.9) and 53.9 (95% CI = 50.9–56.1) months, respectively. The 5-year DFS rate of patients with GPR <0.16 and with GPR ≥0.16 was 80.9% and 68.1%, respectively.

The Kaplan–Meier survival analysis revealed that patients with GPR ≥0.16 had significantly poorer OS (log-rank $P = 0.003$) and DFS (log-rank $P = 0.002$) when compared to those of patients with GPR <0.16 (**Fig. 1A** and **1B**). In addition, an increased GGT also showed a significant relationship with unfavorable OS (log-rank $P = 0.026$), but no significant correlation was found between GGT level and postoperative DFS (log-rank $P = 0.060$) (**Fig. 1C** and **1D**). No significant difference was showed in either OS (log-rank $P = 0.75$) or DFS (log-rank $P = 0.81$) between patients with normal and abnormal ranges of platelets (**Fig. 1E** and **1F**).

*PSM cohort*

In the PSM cohort, patients in the GPR <0.16 group and the GPR ≥0.16 group had a mean OS time at 58.8 (95% CI = 57.8–59.7) and 52.2 (95% CI = 49.3–55.2) months, respectively. The 5-year OS rate of the GPR <0.16 group and the GPR ≥0.16 group was 92.9% and 73.8%, respectively. Meanwhile, the mean DFS time of patients in the GPR <0.16 group and the GPR ≥0.16 group was 56.7 (95% CI = 54.9–58.6) and 48.6 (95% CI = 45.1–52.0) months, respectively. Patients in the GPR <0.16 group and the GPR ≥0.16 group had a 5-year DFS rate at 86.9% and 64.3%, respectively.

The Kaplan–Meier survival analysis on the PSM cohort demonstrated that both OS (log-rank $P = 0.001$) and DFS (log-rank $P < 0.001$) of the GPR ≥0.16 group were significantly shortened when compared to those of the GPR <0.16 group (**Fig. 2A** and **2B**). As for the GGT level and platelet counts, no significant correlation was revealed between any of these peripheral blood biomarkers and survival results after PSM (**Fig. 2C–2F**).

### Prognostic factors for OS of resectable NSCLC

*Entire cohort*

The univariable Cox regression analysis for the entire cohort indicated per unit increase in age ($P = 0.012$), RBC ($P = 0.040$), neutrophils ($P < 0.001$), lymphocytes ($P = 0.001$), serum albumin ($P = 0.004$), and hemoglobin ($P = 0.004$), and male gender ($P = 0.004$), smoking history ($P = 0.004$), GPR ≥0.16 ($P = 0.004$), SCC ($P = 0.004$), LNM ($P < 0.001$), and $T_{2\text{-}3}$ stage tumor ($P < 0.001$) were significantly associated with postoperative OS (**Table 1**). The multivariable Cox regression analysis further demonstrated that per unit increase in neutrophils (HR = 1.19; 95% CI = 1.06–1.33; $P = 0.003$) and lymphocytes (HR = 0.34; 95% CI = 0.17–0.68; $P = 0.002$), and GPR ≥0.16 (HR = 1.92; 95% CI = 1.08–3.42; $P = 0.026$), $T_{2\text{-}3}$ stage tumor (HR = 2.94; 95% CI = 1.45–5.98; $P = 0.003$) and LNM (HR = 5.31; 95% CI = 3.03–9.31; $P < 0.001$) could serve as the independent prognostic factors for OS of resectable NSCLC. Neither GGT level nor peripheral platelet presented a significant prognostic impact on postoperative OS (**Table 1**).

*PSM cohort*

In the univariable Cox regression model based on the PSM cohort, we found that per unit increase in RBC ($P = 0.007$), lymphocytes ($P < 0.001$), and hemoglobin ($P = 0.005$), and male gender ($P = 0.009$), smoking history ($P = 0.016$), GPR ≥0.16 ($P = 0.002$), LNM ($P < 0.001$), and $T_{2\text{-}3}$ stage tumor ($P = 0.016$) showed significant relationships with postoperative OS (**Table 1**). Multivariable Cox regression model on the PSM cohort finally determined that per unit increase in peripheral lymphocytes (HR = 0.22; 95% CI = 0.07–0.67; $P = 0.008$) and hemoglobin (HR = 0.952; 95% CI = 0.914–0.991; $P = 0.017$), and GPR ≥0.16 (HR = 3.80; 95% CI = 1.35–10.72; $P = 0.012$) and LNM (HR = 10.63; 95% CI = 4.15–27.22; $P < 0.001$) could be independently predictive of postoperative OS. No significant impact was observed regarding the other peripheral blood biomarkers on OS of resectable NSCLC (**Table 1**).

### Prognostic factors for DFS of resectable NSCLC

*Entire cohort*

In the univariable Cox regression model for the entire cohort, per unit increase in age ($P = 0.003$), neutrophils ($P < 0.001$), and lymphocytes ($P = 0.009$), and male

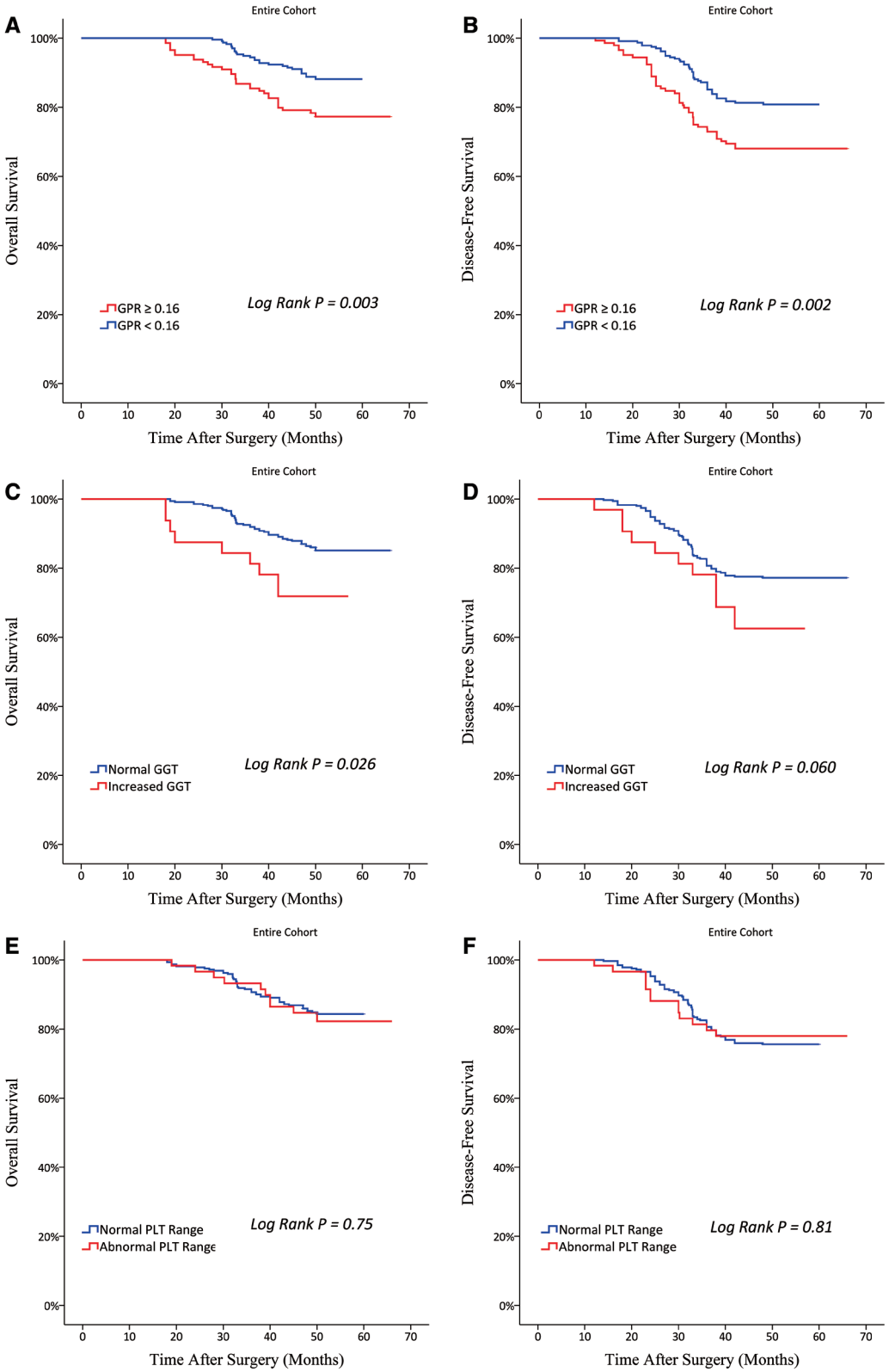


**Fig. 1** Kaplan–Meier survival analyses of **(A)** OS and **(B)** DFS between the GPR <0.16 group and the GPR ≥0.16 group; **(C)** OS and **(D)** DFS between the normal GGT group and the increased GGT group; **(E)** OS and **(F)** DFS between the normal platelet count range group and the abnormal platelet count range group in the entire cohort. DFS: disease-free survival; GGT: gamma-glutamyl transpeptidase; GPR: gamma-glutamyl transpeptidase to platelet ratio; OS: overall survival

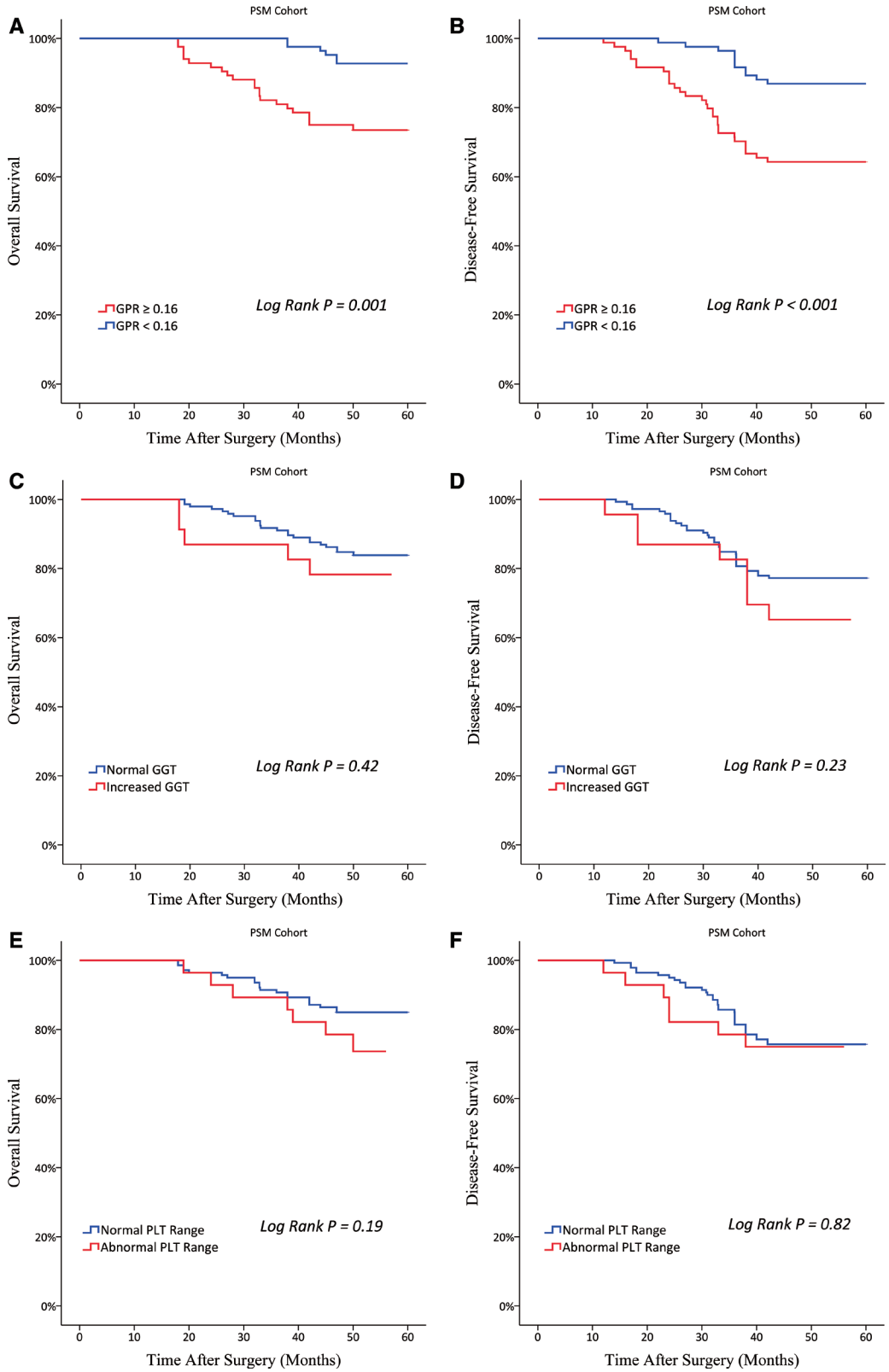


**Fig. 2** Kaplan–Meier survival analyses of **(A)** OS and **(B)** DFS between the GPR <0.16 group and the GPR ≥0.16 group; **(C)** OS and **(D)** DFS between the normal GGT group and the increased GGT group; **(E)** OS and **(F)** DFS between the normal platelet count range group and the abnormal platelet count range group in the PSM cohort. DFS: disease-free survival; GPR: gamma-glutamyl transpeptidase to platelet ratio; OS: overall survival; PSM: propensity score matching

**Table 1 Prognostic significance of perioperative parameters for the overall survival of surgically resectable non-small-cell lung cancer**

| Characteristics | Entire cohort | | | | Propensity score matched cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable analysis | | Multivariable analysis | | Univariable analysis | | Multivariable analysis | |
| | HR with 95% CI | *P* value | HR with 95% CI | *P* value | HR with 95% CI | *P* value | HR with 95% CI | *P* value |
| Age (years) (per unit increase) | 1.048 (1.011–1.086) | 0.012 | 1.033 (0.990–1.077) | 0.13 | 1.035 (0.984–1.088) | 0.18 | | |
| Gender | | | | | | | | |
| Female | Reference | | | | Reference | | | |
| Male | 2.54 (1.35–4.79) | 0.004 | 1.47 (0.54–4.03) | 0.45 | 4.92 (1.49–16.30) | 0.009 | 3.78 (0.76–18.72) | 0.10 |
| Body mass index (kg/m$^2$) (per unit increase) | 0.994 (0.907–1.088) | 0.89 | | | 1.027 (0.906–1.165) | 0.68 | | |
| Smoking status | | | | | | | | |
| Never | Reference | | | | Reference | | | |
| Current/former | 2.23 (1.30–3.83) | 0.004 | 1.08 (0.46–2.50) | 0.86 | 2.74 (1.21–6.23) | 0.016 | 1.07 (0.30–3.79) | 0.92 |
| Heavy alcohol consumption | | | | | | | | |
| Never | Reference | | | | Reference | | | |
| Current/former | 3.20 (0.44–23.07) | 0.25 | | | 22.25 (0.03–17101) | 0.36 | | |
| Respiratory comorbidity | | | | | | | | |
| Absent | Reference | | | | Reference | | | |
| Present | 1.11 (0.66–1.86) | 0.70 | | | 1.18 (0.53–2.60) | 0.69 | | |
| Cardio-cerebrovascular comorbidity | | | | | | | | |
| Absent | Reference | | | | Reference | | | |
| Present | 1.61 (0.97–2.68) | 0.068 | 1.09 (0.61–1.92) | 0.78 | 1.18 (0.55–2.51) | 0.68 | | |
| Hepatic comorbidity | | | | | | | | |
| Absent | Reference | | | | Reference | | | |
| Present | 1.65 (0.66–4.13) | 0.28 | | | 1.19 (0.41–3.43) | 0.75 | | |
| Diabetes mellitus | | | | | | | | |
| Absent | Reference | | | | Reference | | | |
| Present | 1.08 (0.49–2.37) | 0.86 | | | 1.66 (0.58–4.79) | 0.35 | | |
| Tumor location | | | | | | | | |
| Upper | Reference | | | | Reference | | | |
| Lower/middle | 1.28 (0.77–2.13) | 0.34 | | | 1.75 (0.83–3.71) | 0.14 | | |
| Red blood cell count ($10^{12}$/L) (Per unit increase) | 0.64 (0.42–0.98) | 0.040 | 0.67 (0.32–1.40) | 0.29 | 0.55 (0.36–0.85) | 0.007 | 1.77 (0.58–5.34) | 0.31 |
| Neutrophil count ($10^9$/L) (Per unit increase) | 1.26 (1.13–1.39) | <0.001 | 1.19 (1.06–1.33) | 0.003 | 1.15 (0.97–1.35) | 0.11 | | |
| Lymphocyte count ($10^9$/L) (Per unit increase) | 0.39 (0.23–0.67) | 0.001 | 0.34 (0.17–0.68) | 0.002 | 0.23 (0.11–0.48) | <0.001 | 0.22 (0.07–0.67) | 0.008 |
| Serum albumin (g/L) (Per unit increase) | 0.90 (0.83–0.97) | 0.004 | 0.965 (0.887–1.050) | 0.41 | 0.93 (0.83–1.03) | 0.17 | | |
| Hemoglobin (g/L) (Per unit increase) | 0.979 (0.962–0.997) | 0.021 | 0.989 (0.961–1.019) | 0.48 | 0.965 (0.942–0.990) | 0.005 | 0.952 (0.914–0.991) | 0.017 |
| Platelet count ($10^9$/L) (Per unit increase) | 0.999 (0.995–1.003) | 0.64 | | | 0.998 (0.992–1.004) | 0.53 | | |
| Gamma-glutamyl transpeptidase (IU/L) (Per unit increase) | 1.001 (0.997–1.005) | 0.75 | | | 0.999 (0.992–1.006) | 0.81 | | |

| Characteristics | Entire cohort | | | | Propensity score matched cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable analysis | | Multivariable analysis | | Univariable analysis | | Multivariable analysis | |
| | HR with 95% CI | *P* value | HR with 95% CI | *P* value | HR with 95% CI | *P* value | HR with 95% CI | *P* value |
| Gamma-glutamyl transpeptidase to platelet ratio | | | | | | | | |
| <0.16 | Reference | | | | Reference | | | |
| ≥0.16 | 2.11 (1.27–3.53) | 0.004 | 1.92 (1.08–3.42) | 0.026 | 4.25 (1.73–10.49) | 0.002 | 3.80 (1.35–10.72) | 0.012 |
| Histological subtypes | | | | | | | | |
| Adenocarcinoma | Reference | | | | Reference | | | |
| Squamous cell carcinoma | 2.19 (1.29–3.71) | 0.004 | 1.30 (0.68–2.48) | 0.43 | 1.96 (0.90–4.24) | 0.089 | 1.22 (0.46–3.27) | 0.69 |
| Differentiation grade | | | | | | | | |
| Moderate/poor | Reference | | | | Reference | | | |
| Well | 0.77 (0.43–1.39) | 0.38 | | | 0.66 (0.30–1.45) | 0.30 | | |
| Tumor invasion (T-stage) | | | | | | | | |
| $T_1$ | Reference | | | | Reference | | | |
| $T_{2-3}$ | 4.39 (2.28–8.45) | <0.001 | 2.94 (1.45–5.98) | 0.003 | 3.03 (1.23–7.48) | 0.016 | 2.76 (0.96–7.92) | 0.059 |
| Lymph node metastasis (N-stage) | | | | | | | | |
| $N_0$ | Reference | | | | Reference | | | |
| $N_1$ | 6.10 (3.65–10.18) | <0.001 | 5.31 (3.03–9.31) | <0.001 | 9.52 (4.29–21.12) | <0.001 | 10.63 (4.15–27.22) | <0.001 |
| Any Clavien-Dindo Grade ≥2 complication | | | | | | | | |
| Absent | Reference | | | | Reference | | | |
| Present | 1.19 (0.66–2.14) | 0.56 | | | 1.82 (0.69–4.78) | 0.23 | | |

CI: confidence interval; HR: hazard ratio

gender (*P* = 0.024), smoking history (*P* = 0.003), cardio-cerebrovascular comorbidity (*P* = 0.003), GPR ≥0.16 (*P* = 0.003), and LNM (*P* <0.001) were found to be significantly associated with postoperative DFS (**Table 2**). The subsequent multivariable Cox regression analysis indicated that per unit increase in peripheral neutrophils (HR = 1.18; 95% CI = 1.07–1.30; *P* = 0.001) and lymphocytes (HR = 0.56; 95% CI = 0.35–0.91; *P* = 0.019), and GPR ≥0.16 (HR = 1.59; 95% CI = 1.03–2.47; *P* = 0.040) and LNM (HR = 4.37; 95% CI = 2.82–6.77; *P* <0.001) could independently predict the DFS of resectable NSCLC. No significant influence regarding either GGT level or peripheral platelet was observed on postoperative DFS (**Table 2**).

*PSM cohort*

After eliminating the confounding biases by PSM, the univariable Cox regression analysis on the well-matched cohort found that per unit increase in age (*P* = 0.026) and lymphocytes (*P* = 0.009), and male gender (*P* = 0.009), smoking history (*P* = 0.013), GPR≥0.16 (*P* = 0.001), and LNM (*P* <0.001) were found to be significantly associated with postoperative DFS (**Table 2**). Multivariable Cox regression analysis finally determined that per unit increase in age (HR = 1.066; 95% CI = 1.012–1.123; *P* = 0.017), GPR ≥0.16 (HR = 2.62; 95% CI = 1.25–5.48; *P* = 0.011), and LNM (HR = 8.57; 95% CI = 4.08–18.01; *P* <0.001) could perform as the independent prognostic indicators for DFS of resectable NSCLC. No significant prognostic impact was observed regarding the other peripheral blood biomarkers in the PSM cohort (**Table 2**).

## Discussion

### Key results and interpretations

Accumulative evidence has indicated reliable clinical implications of all kinds of risk assessment tools for the prognostic prediction based on peripheral blood biomarkers from routine laboratory tests in numerous types of cancer. As a novel prognostic scoring system consisting of peripheral platelet counts and GGT level, the GPR has been designed as a noninvasive surrogate for liver

**Table 2 Prognostic significance of perioperative parameters for the disease-free survival of surgically resectable non-small-cell lung cancer**

| Characteristics | Entire Cohort | | | | Propensity score matched cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable analysis | | Multivariable analysis | | Univariable analysis | | Multivariable analysis | |
| | HR with 95%CI | *P* value | HR with 95%CI | *P* value | HR with 95%CI | *P* value | HR with 95%CI | *P* value |
| Age (Years) (Per unit increase) | 1.044 (1.014–1.075) | 0.003 | 1.027 (0.995–1.059) | 0.10 | 1.049 (1.006–1.095) | 0.026 | 1.066 (1.012–1.123) | 0.017 |
| Gender | | | | | | | | |
| Female | Reference | | | | Reference | | | |
| Male | 1.70 (1.07–2.69) | 0.024 | 1.16 (0.56–2.42) | 0.69 | 2.95 (1.31–6.66) | 0.009 | 2.69 (0.79–9.18) | 0.12 |
| Body mass index (kg/m$^2$) (Per unit increase) | 1.003 (0.934–1.077) | 0.94 | | | 1.013 (0.914–1.123) | 0.80 | | |
| Smoking status | | | | | | | | |
| Never | Reference | | | | Reference | | | |
| Current/former | 1.89 (1.24–2.89) | 0.003 | 1.72 (0.83–3.54) | 0.14 | 2.30 (1.19–4.44) | 0.013 | 1.11 (0.42–2.96) | 0.83 |
| Heavy alcohol consumption | | | | | | | | |
| Never | Reference | | | | Reference | | | |
| Current/former | 1.20 (0.44–3.27) | 0.72 | | | 1.18 (0.36–3.84) | 0.78 | | |
| Respiratory comorbidity | | | | | | | | |
| Absent | Reference | | | | Reference | | | |
| Present | 1.27 (0.84–1.92) | 0.26 | | | 1.04 (0.55–1.99) | 0.90 | | |
| Cardio-cerebrovascular comorbidity | | | | | | | | |
| Absent | Reference | | | | Reference | | | |
| Present | 1.86 (1.23–2.81) | 0.003 | 1.36 (0.86–2.14) | 0.19 | 1.37 (0.74–2.56) | 0.32 | | |
| Hepatic comorbidity | | | | | | | | |
| Absent | Reference | | | | Reference | | | |
| Present | 1.14 (0.61–2.15) | 0.68 | | | 1.19 (0.55–2.58) | 0.65 | | |
| Diabetes mellitus | | | | | | | | |
| Absent | Reference | | | | Reference | | | |
| Present | 1.03 (0.55–1.93) | 0.93 | | | 1.59 (0.67–3.79) | 0.29 | | |
| Tumor location | | | | | | | | |
| Upper | Reference | | | | Reference | | | |
| Lower/middle | 1.17 (0.78–1.77) | 0.45 | | | 0.78 (0.36–1.70) | 0.53 | | |
| Red blood cell count ($10^{12}$/L) (Per unit increase) | 0.83 (0.57–1.21) | 0.34 | | | 0.70 (0.45–1.10) | 0.12 | | |
| Neutrophil count ($10^9$/L) (Per unit increase) | 1.21 (1.11–1.32) | <0.001 | 1.18 (1.07–1.30) | 0.001 | 1.13 (0.97–1.31) | 0.12 | | |
| Lymphocyte count ($10^9$/L) (Per unit increase) | 0.57 (0.37–0.87) | 0.009 | 0.56 (0.35–0.91) | 0.019 | 0.37 (0.20–0.69) | 0.002 | 0.44 (0.19–1.00) | 0.050 |
| Serum albumin (g/L) (Per unit increase) | 0.968 (0.910–1.030) | 0.31 | | | 1.001 (0.909–1.102) | 0.99 | | |
| Hemoglobin (g/L) (Per unit increase) | 0.990 (0.976–1.004) | 0.15 | | | 0.982 (0.961–1.003) | 0.088 | 0.978 (0.954–1.002) | 0.076 |
| Platelet count ($10^9$/L) (Per unit increase) | 0.999 (0.996–1.003) | 0.65 | | | 0.998 (0.993–1.003) | 0.45 | | |
| Gamma-glutamyl transpeptidase (IU/L) (Per unit increase) | 1.00 (0.997–1.004) | 0.79 | | | 1.00 (0.996–1.004) | 0.98 | | |

| Characteristics | Entire Cohort | | | | Propensity score matched cohort | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariable analysis | | Multivariable analysis | | Univariable analysis | | Multivariable analysis | |
| | HR with 95%CI | *P* value | HR with 95%CI | *P* value | HR with 95%CI | *P* value | HR with 95%CI | *P* value |
| Gamma-glutamyl transpeptidase to platelet ratio | | | | | | | | |
| <0.16 | Reference | | | | Reference | | | |
| ≥0.16 | 1.88 (1.24–2.83) | 0.003 | 1.59 (1.03–2.47) | 0.040 | 3.30 (1.65–6.59) | 0.001 | 2.62 (1.25–5.48) | 0.011 |
| Histological subtypes | | | | | | | | |
| Adenocarcinoma | Reference | | | | Reference | | | |
| Squamous cell carcinoma | 1.51 (0.96–2.37) | 0.072 | 1.36 (0.79–2.34) | 0.26 | 1.25 (0.63–2.49) | 0.53 | | |
| Differentiation grade | | | | | | | | |
| Moderate/poor | Reference | | | | Reference | | | |
| Well | 0.63 (0.40–0.99) | 0.045 | 0.89 (0.52–1.51) | 0.65 | 0.66 (0.34–1.28) | 0.22 | | |
| Tumor invasion (T-stage) | | | | | | | | |
| $T_1$ | Reference | | | | Reference | | | |
| $T_{2-3}$ | 2.12 (1.36–3.30) | 0.001 | 1.47 (0.91–2.39) | 0.12 | 1.55 (0.81–2.96) | 0.18 | | |
| Lymph node metastasis (N-stage) | | | | | | | | |
| $N_0$ | Reference | | | | Reference | | | |
| $N_1$ | 4.25 (2.80–6.44) | <0.001 | 4.37 (2.82–6.77) | <0.001 | 7.37 (3.92–13.87) | <0.001 | 8.57 (4.08–18.01) | <0.001 |
| Any Clavien-Dindo Grade ≥2 complication | | | | | | | | |
| Absent | Reference | | | | Reference | | | |
| Present | 1.32 (0.85–2.03) | 0.21 | | | 1.04 (0.52–2.08) | 0.90 | | |

CI: confidence interval; HR: hazard ratio

biopsy to estimate the severity of liver fibrosis.[8–11] Since its first introduction onto the clinical practice, a significant prognostic value of preoperative GPR has been currently validated in patients with resectable hepatocellular carcinoma.[12–15]

To our knowledge, the present study was the first to demonstrate the prognostic significance of preoperative GPR for the prediction regarding both OS and DFS of patients who had undergone VATS lobectomy for resectable stage I-II NSCLC. The highlight of this study was to systematically demonstrate the prognostic strength of the GPR scoring system for survival outcomes after VATS lobectomy through both multivariable Cox proportional hazards regression analysis and PSM analysis to eliminate possible confounding bias risks. PSM is well known as a validated alternative that matches each subject between study groups with comparable baseline parameters to minimize potential confounding influence within observational investigations.[2,3,5,21] We further matched the propensity score of perioperative clinic-pathologic parameters between the low GPR group and the high GPR group, and then, a total of 84 well-matched pairs were generated for subsequent survival analyses.

Finally, a higher preoperative GPR was found to be significantly associated with worse OS and DFS in our series. We further identified that the evident prognostic value of GPR for both OS and DFS did not only remain strongly stable in the entire cohort but also successfully validated in the PSM cohort. Furthermore, when compared to the other peripheral hematologic biomarkers, including the GGT and platelets estimated individually, GPR also held a much better predicting ability for postoperative survival in both the entire cohort and the PSM cohort based on a validated combination of the data regarding GGT and platelets. Taken together, our findings strongly supported that GPR could serve as a simplified, convenient, and non-invasive discriminator for the prognosis after VATS lobectomy for resectable stage I-II NSCLC.

In our study, there was no difference identified in postoperative morbidity between patients classified by preoperative GPR. We hypothesized that might be because the great majority of the included surgical inpatients were treated with more aggressive medications under the

supervision of our attending physicians during the hospitalization but generally received less professional care and health tips after discharge from hospital. Therefore, the predictive value of GPR for short-term postoperative complications might be largely attenuated due to a better maintenance of patients' immune-nutritional status during the in-hospital period.

**Generalizability**

Our PSM analysis provides the evidence supporting a GPR score as an adjunctive marker with most common prognostic assessment tools to help thoracic surgeons to distinguish the patients at a higher surgical risk suffering from worse postoperative prognosis of resectable stage I-II NSCLC. In addition, a more precise prognostic prediction by early estimating preoperative GPR can remind our physicians to settle more personalized therapeutic schemes for specific high surgical risk patients in advance to limit unfavorable survival.

## Limitations

Our study has a few limitations that need to be acknowledged.

First, the present study had intrinsic limitations of any other single-institution study without external validation. Although we had established fairly strict eligibility criteria and tried both multivariable Cox regression remodeling and PSM to eliminate possible confounding influence, several selection biases might still confuse our results, and meanwhile, the relatively small sample size might also attenuate the analytical strength.

Second, the value of GPR was measured at a single time point preoperatively. It would also be clinically meaningful to study the changes in this index within postoperative follow-up period. The dynamic prognostic roles of GPR in resectable NSCLC were considered to be the subject of the future research directions.

Third, some specific laboratory markers, such as C-reactive protein, fibrinogen, and cytokines, were not adequately assessed in this analysis since they were not routinely measured in our institutional practice. Several most common risk scales using some of these biomarkers, like modified Glasgow prognostic score, might contribute to in-depth interpretations of our results based on more biochemistry data collected. Thus, potential significance of GPR in combination with such laboratory parameters was highly desirable for evaluation.

Finally, we applied a validated R-based bio-statistical tool to determine the optimal cutoff point regarding GPR (0.16) in our stage I-II NSCLC series. The dichotomized cutoff values of GPR might vary across the currently available evidence.

## Conclusions

In conclusion, the present study demonstrates that preoperative GPR serves as an independent prognostic indicator for both OS and DFS following VATS lobectomy for resectable stage I-II NSCLC. The GPR may be utilized as a simplified, noninvasive, and convenient blood-obtained biomarker offering clinically meaningful information to help for the prognostic prediction of surgical NSCLC. We recommend that more prospective validation analyses based on a larger sample availability are urgently needed to substantiate and validate our findings in the future.

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## Disclosure Statement

The authors declare that they have no conflict of interest.

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