Original Research

Albumin-to-alkaline phosphatase ratio as a novel prognostic indicator for patients undergoing minimally invasive lung cancer surgery: Propensity score matching analysis using a prospective database

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ABSTRACT

Objectives: To evaluate prognostic significance of albumin-to-alkaline phosphatase ratio (AAPR) for patients undergoing video-assisted thoracoscopic surgery (VATS) lobectomy for non-small-cell lung cancer (NSCLC) by a propensity score-matching (PSM) analysis.

Methods: This PSM study was conducted on the prospectively-maintained database in our institution between December 2013 and March 2015. Overall survival analyses and further subgroup analyses were both performed to distinguish the differences in postoperative survival between patients stratified by an optimal cutoff of AAPR. Multivariable Cox proportional hazards regression models were established to determine the independent prognostic factors.

Results: There were 390 patients with operable NSCLCs included. An AAPR of 0.57 was identified as the optimal cutoff regarding to postoperative survival. Both overall survival (OS) and disease-free survival (DFS) in patients with AAPR ≤ 0.57 were significantly shortened compared to those in patient with AAPR > 0.57 (Log-rank $P < 0.001$). Patients with AAPR ≤ 0.57 had significantly lower rates of OS and DFS than those of patients with AAPR > 0.57 ($P < 0.001$). These differences still remained significant after subgroup analyses and PSM analyses. Multivariate analyses on the entire cohort and the PSM cohort commonly indicated that low preoperative AAPR could be an independent prognostic factor for unfavorable OS and DFS of resected NSCLCs.

Conclusions: AAPR can serve as a novel risk stratification tool to refine prognostic prediction for surgical NSCLC. It may help surgeons to screen high-surgical-risk patients and further formulate individualized treatment schemes.

1. Introduction

1.1. Rationale

Lung cancer is the leading cause of malignancy-related deaths worldwide, and non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases [1–4]. Surgical resection is widely accepted as the optimal therapeutic option for early-stage NSCLCs and contributes to the multidisciplinary treatments for locally-advanced NSCLCs. Despite substantial advances in surgical techniques and combined treatment modalities, the clinical prognosis of NSCLC still remains frustrating, with a poor overall survival (OS) rate around 15–18% [1–5]. A better understanding of possible prognostic factors will be extremely crucial to assist thoracic surgeons to identify the patients who are considered at high probability of unfavorable outcomes and further draw up an appropriate treatment plan in advance. Nowadays, a range of peripheral hematological and biochemical markers, which can be conveniently acquired with a less invasion of the blood in routine clinical practice, have been increasingly utilized for the prognostic prediction in numerous cancers [6–13].

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Emerging evidence indicates that serum albumin (sALB), a reliable indicator for patients' nutritional conditions, can also reflect host systemic inflammatory response when formulating various immune-nutritional scoring systems with other putative laboratory biomarkers [14]. In addition, alkaline phosphatase (ALP), which is a kind of the hydrolase concentrated in liver, bile duct and kidney, has also been increasingly utilized as a predictor of mortality for cancer patients independently with distant metastasis [14,15]. Taken together, a novel prognostic index based on the continuous variables of sALB and ALP, termed the albumin to alkaline phosphatase ratio (AAPR), has been recently proposed among patients receiving chemo-radiotherapy for hepatocellular carcinoma, nasopharyngeal carcinoma and small cell lung cancer (SCLC), showing a great efficacy for prognostic prediction [14,16–18]. Preoperative AAPR was also reported to serve as a potent prognostic indicator for patients undergoing radical surgery for digestive and urothelial cancers [15,19,20]. However, until recently, there has been no study addressing on the clinical significance of AAPR for either short-term or long-term survival after curative resection for NSCLC.

1.2. Objectives

Propensity score-matching (PSM) analysis is a validated alternative method matching each subject between intervention groups with comparable baseline characteristics to minimize confounding influence in observational studies [18,21]. Therefore, we performed the present PSM study to elucidate the prognostic significance of preoperative AAPR for patients undergoing video-assisted thoracoscopic surgery (VATS) lobectomy for NSCLCs.

2. Materials and methods

2.1. Study design and protocol

This single-center cohort study was conducted on our institutional prospectively-maintained dataset. The study protocol was approved by our regional ethics committee (ID: 2016-255). We wrote it in compliance with the STROCSS - Strengthening the Reporting of Cohort Studies in Surgery statement (Appendix Data 1) [22].

2.2. Patient selection

2.2.1. Settings

We reviewed the survival data of consecutive patients who had underwent VATS lobectomy for operable NSCLCs at our unit between December 2013 and March 2015. All clinicopathological characteristics were derived from our medical records.

2.2.2. Inclusion and exclusion criteria

We established the following eligibility criteria to determine the appropriateness of the patients included:

 i. The target diseases were operable primary NSCLCs. Patients with any concomitant or previous malignancy were not considered;
 ii. Only standardized single-lobectomy with systematic mediastinal lymph node dissection operated by a completely VATS procedure would be included;
 iii. Patients who received neoadjuvant or adjuvant chemotherapy were not considered, in order to avoid potential confounding influence from perioperative anti-cancer therapy, which might complicate actual roles of AAPR for postoperative outcomes;
 iv. Patients who experienced major intraoperative morbidities, resulting in unexpected conversion to thoracotomy, were excluded due to their potential confounding influence on postoperative outcomes;
 v. The laboratory indexes must be obtained within 5 days before

surgery. Patients with loss of laboratory records were not included;
 vi. Patients who were lost to follow-up were not considered in order to guarantee the accuracy and objectivity of the survival data obtained;

2.2.3. Follow-up investigation

Patients were followed up starting on the operation day. The most routine appointments, including physical examination, laboratory testing, chest computed tomography (CT), upper abdominal CT and brain magnetic resonance imaging or CT, were provided in compliance with our institutional policies [21]. In addition, a regular telephone follow-up would be prepared if patients could not come to the outpatient clinic.

This follow-up assessment was performed every 3 months for the first 2 years and every 6 months for the next 3 years. The terminal follow-up date was updated to December 2018.

2.3. Outcome data, measures and definitions

2.3.1. Patient characteristics

Baseline information included the age, gender, body mass index (BMI), smoking history and tumor location. Preoperative underlying comorbidities included the respiratory comorbidity, cardio-cerebrovascular comorbidity and diabetes mellitus. Respiratory comorbidity was defined as the existence of one or more respiratory diseases, including chronic obstructive pulmonary disease, emphysema, lung bullae, asthma, tuberculosis, pneumonia (including bacterial/viral/fungal respiratory tract infections, obstructive pneumonia and aspiration pneumonia), bronchiectasis, lung abscess and interstitial lung diseases. Cardio-cerebrovascular comorbidity included the hypertension, coronary heart diseases, peripheral arterial diseases, stroke, aortic aneurysm and chronic heart failure.

In addition, we assessed the following 5 pathological variables: histological subtypes, differentiation degrees, tumor invasion (T-stage), lymph node metastasis (LNM) and TNM-stage, all of which were defined according to the Union for International Cancer Control 7th Edition [23].

2.3.2. Establishment and grouping criteria of serum markers

The levels of sALB and ALP were gathered from preoperative blood sampling to extrapolate the AAPR (calculated by sALB/ALP). We further employed the *Cutoff Finder*, a freely available Website-based R software (http://molpath.charite.de/cutoff), to determine the optimal cutoff value of AAPR regarding to postoperative survival. Moreover, the lower range of normal measurement at 40 g/L was applied to dichotomize the sALB level according to its clinical meaning to define the 'hypoalbuminemia'. The normal range of ALP (male: 45–125U/L; female: 50–135U/L) in routine clinical practice was also utilized to divide the patients into the normal ALP group and the abnormal ALP group.

Then we compared patient baseline characteristics and survival outcomes between 2 groups stratified by the threshold value of AAPR. Subgroups analyses was further performed according to patients' age, gender, BMI, smoking status, presence of comorbidity, histological subtypes, differentiation degrees, T-stages, LNM and TNM-stages.

2.3.3. Outcomes of interest

The primary outcomes of interest were overall survival (OS) and disease-free survival (DFS). OS was defined as the survival time from the operation day to the date of death from any cause or to the time of censoring at the latest follow-up date. DFS was defined as the survival time from the operation day to the diagnosis of cancer recurrence or metastasis.

Our secondary outcomes included any Clavien-Dindo grade ≥ II complication developed within 30 days after surgery, which was judged in compliance with the Society of Thoracic Surgeons and the European Society of Thoracic Surgeons joint definitions [24]. We categorized all

Table 1
Patient characteristics.

Characteristics	Entire cohort				Propensity score-matched cohort			
	Total ($N = 390$)	AAPR > 0.57 ($N = 178$)	AAPR ≤ 0.57 ($N = 212$)	P_1-value	Total ($N = 310$)	AAPR > 0.57 ($N = 155$)	AAPR ≤ 0.57 ($N = 155$)	P_2-value
Age (Years)								
≤ 65	224 (57.4%)	106 (59.6%)	118 (55.7%)	0.44	173 (55.8%)	92 (59.4%)	81 (52.3%)	0.21
> 65	166 (42.6%)	72 (40.4%)	94 (44.3%)		137 (44.2%)	63 (40.6%)	74 (47.7%)	
Gender								
Female	147 (37.7%)	70 (39.3%)	77 (36.3%)	0.54	126 (40.6%)	60 (38.7%)	66 (42.6%)	0.49
Male	243 (62.3%)	108 (60.7%)	135 (63.7%)		184 (59.4%)	95 (61.3%)	89 (57.4%)	
Body mass index (kg/m^2)								
≤ 24	225 (57.7%)	96 (53.9%)	129 (60.8%)	0.17	183 (59.0%)	84 (54.2%)	99 (63.9%)	0.11
> 24	165 (42.3%)	82 (46.1%)	83 (39.2%)		127 (41.0%)	71 (45.8%)	56 (36.1%)	
Smoking status								
Never	200 (51.3%)	100 (56.2%)	100 (47.2%)	0.095	176 (56.8%)	88 (56.8%)	88 (56.8%)	1.0
Current/former	190 (48.7%)	78 (43.8%)	112 (52.8%)		134 (43.2%)	67 (43.2%)	67 (43.2%)	
Presence of comorbidity								
Absent	127 (32.6%)	65 (36.5%)	62 (29.2%)	0.13	105 (33.9%)	60 (38.7%)	45 (29.0%)	0.093
Present	263 (67.4%)	113 (63.5%)	150 (70.8%)		205 (66.1%)	95 (61.3%)	110 (71.0%)	
Tumor location								
Right upper lobe	143 (36.7%)	65 (36.5%)	78 (36.8%)	0.24	120 (38.7%)	54 (34.8%)	66 (42.6%)	0.38
Left upper lobe	76 (19.5%)	43 (24.2%)	33 (15.6%)		69 (22.3%)	41 (26.5%)	28 (18.1%)	
Right lower lobe	88 (22.6%)	35 (19.7%)	53 (25.0%)		63 (20.3%)	33 (21.3%)	30 (19.4%)	
Left lower lobe	50 (12.8%)	22 (12.4%)	28 (13.2%)		38 (12.3%)	17 (11.0%)	21 (13.5%)	
Right middle lobe	33 (8.5%)	13 (7.3%)	20 (9.4%)		20 (6.5%)	10 (6.5%)	10 (6.5%)	
Histological subtypes								
Adenocarcinoma	296 (75.9%)	150 (84.3%)	146 (68.9%)	< 0.001	258 (83.2%)	129 (83.2%)	129 (83.2%)	1.0
Non-adenocarcinoma	94 (24.1%)	28 (15.7%)	66 (31.1%)		52 (16.8%)	26 (16.8%)	26 (16.8%)	
Differentiation degree								
Moderate/high	306 (78.5%)	143 (80.3%)	163 (76.9%)	0.41	257 (82.9%)	127 (81.9%)	130 (83.9%)	0.65
Low	84 (21.5%)	35 (19.7%)	49 (23.1%)		53 (17.1%)	28 (18.1%)	25 (16.1%)	
Tumor invasion (T-stage)								
T_1	181 (46.4%)	93 (52.2%)	88 (41.5%)	0.034	166 (53.5%)	83 (53.5%)	83 (53.5%)	1.0
T_{2-3}	209 (53.6%)	85 (47.8%)	124 (58.5%)		144 (46.5%)	72 (46.5%)	72 (46.5%)	
Lymph node metastasis (N-stage)								
N_0	313 (80.3%)	153 (86.0%)	160 (75.5%)	0.010	260 (83.9%)	130 (83.9%)	130 (83.9%)	1.0
N_{1-2}	77 (19.7%)	25 (14.0%)	52 (24.5%)		50 (16.1%)	25 (16.1%)	25 (16.1%)	
TNM-stage								
I	267 (68.5%)	142 (79.8%)	125 (59.0%)	< 0.001	240 (77.4%)	120 (77.4%)	120 (77.4%)	1.0
II-IIIa	123 (31.5%)	36 (20.2%)	87 (41.0%)		70 (22.6%)	35 (22.6%)	35 (22.6%)	
Albumin (g/L)								
≤ 40	80 (20.5%)	20 (11.2%)	60 (28.3%)	< 0.001	56 (18.1%)	15 (9.7%)	41 (26.5%)	< 0.001
> 40	310 (79.5%)	158 (88.8%)	152 (71.7%)		254 (81.9%)	140 (90.3%)	114 (73.5%)	
Alkaline phosphatase (U/L)								
Normal range	366 (93.8%)	162 (91.0%)	204 (96.2%)	0.033	292 (94.2%)	139 (89.7%)	153 (98.7%)	0.001
Abnormal range	24 (6.2%)	16 (9.0%)	8 (3.8%)		18 (5.8%)	16 (10.3%)	2 (1.3%)	

AAPR: albumin-to-alkaline phosphatase ratio.

Clavien-Dindo grade II complications only requiring pharmacological intervention as the minor morbidity. The Clavien-Dindo grade ≥ III complications requiring endoscopy, surgical intervention or life support were categorized as the major morbidity. The details of individual complications had been reported in our previous studies [25–32].

2.4. Surgical procedure and perioperative care

Our VATS lobectomy was operated through a 3-portal access using a modified 'hilum-first-fissure-last' thoracoscopic technique known as 'single-direction lobectomy' [21]. Mechanical staplers were implemented in all included patients to divide the incomplete inter-lobar fissures and close the bronchial stumps.

All of our patients were routinely managed in compliance with a standardized clinical pathway, including short-term invasive pulmonary physiotherapy, antibiotic prophylaxis, respiratory drug intervention, breath training, venous thromboembolism prophylaxis and surgical pain control, all of which had been described in our previous studies [21,33]. One chest tube was placed on the suction device (-10-20 cm H_2O) at the end of the operation, and then either removed or converted to water seal according to our institutional policies after chest radiography done on postoperative day 1. Chest tube removal

would be allowed with a 24-h pleural drainage < 200 mL and air leak cessation detected from pleural drainage systems. Our discharge criteria had been fully described in the previous study [26].

2.5. Statistical analysis

We used the Pearson's chi-squared test or Fisher's exact-test to compare perioperative parameters. The survival analyses of OS and DFS were performed using the Kaplan-Meier method, and differences in survival time were determined by the Log-rank test.

In the PSM analysis, we employed a nearest-neighbor matching algorithm through caliper matching with its designated distance at 0.20 standard deviation of the logit of the propensity score (PS). We used this PSM method to achieve balance in clinicopathological characteristics that significantly differed between patients with stratified by the cutoff of AAPR. In the PSM model, the confounders must not be influenced by elements of AAPR, suggesting that both sALB and ALP were not considered for PS balance [34]. The 1:1 matched pairs were finally created based on their PSs.

A univariate Cox proportional hazards regression analysis was initially conducted to evaluate the relationships between patient characteristics and postoperative survival. Finally, preoperative AAPR and

other clinicopathological variables with univariate $P < 0.05$ would be included in the multivariate Cox proportional hazards regression model to determine the independent prognostic factors for OS and DFS. Hazard ratio (HR) with its 95% confidence interval (CI) was then obtained.

In addition, we performed a receiver operating characteristic (ROC) analysis to evaluate the discriminatory powers of AAPR, sALB and ALP for the prediction of postoperative survival and then compare their areas under ROC curves (AUCs).

We utilized the IBM SPSS 22.0 software (IBM SPSS Statistics, Version 22.0. Armonk, NY: IBM Corp) and the STATA 12.0 (STATA Corporation, College Station, TX, USA) to accomplish above statistical analyses. Statistical significance was indicated by *P*-value < 0.05.

3. Results

3.1. Basic information and outcomes

3.1.1. Patient characteristics

During the study period, there were 390 patients undergoing VATS lobectomy for operable primary NSCLCs met the eligibility criteria and completed the entire follow-up assessment. Their baseline characteristics are presented in Table 1.

Our cohort consists of 243 male (ratio = 62.3%) and 147 female (ratio = 37.7%) patients, with a mean age of 63.0 ± 7.6 years and mean BMI of 23.3 ± 2.9 kg/m^2, and 190 patients were active smokers (ratio = 48.7%). There were 263 patients suffered from one or more underlying comorbidities (ratio = 67.4%). Lung adenocarcinoma was diagnosed in 296 patients (ratio = 75.9%), followed by squamous cell carcinoma (SCC) in 79 patients (ratio = 20.3%) and other subtypes in 15 patients (ratio = 3.8%). LNM was found in 77 patients postoperatively by the pathological criteria (ratio = 19.7%). The majority of included patients were diagnosed with TNM-stage I NSCLCs (n = 267, ratio = 68.5%).

3.1.2. AAPR evaluation

The mean sALB and ALP of our cohort was 42.4 ± 3.5 g/L and 78.8 ± 22.4 U/L, respectively. Accordingly, the mean AAPR of the entire cohort was 0.58 ± 0.17. According to the bio-statistical results generated from the *Cutoff Finder*, we recognized that a wide range of cutoff points of AAPR showed statistical significance (203 of 214 tests, 94.9%; Fig. 1). An AAPR at 0.57 was determined to be the optimal cutoff value regarding to postoperative survival. Therefore, there were 178 patients divided into the high AAPR group (AAPR > 0.57:
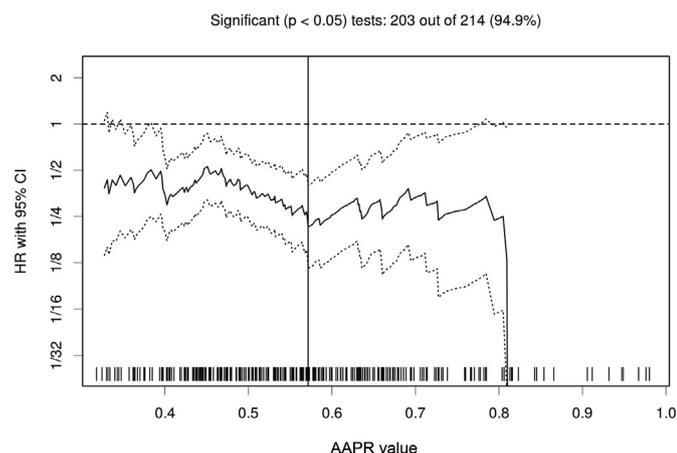
ratio = 45.6%), whereas the remaining 212 patients were divided into the low AAPR group (AAPR ≤ 0.57: ratio = 54.4%)(Table 1).

3.1.3. Surgical outcomes

The median follow-up period in this study was 50.0 months (range 12–66 months). In the entire cohort, the OS and DFS rate until the latest follow-up date was 82.3% and 74.1%, respectively. In addition, there were 115 patients experienced Clavien-Dindo grade ≥ II complications postoperatively, with an overall morbidity rate at 29.5%. The minor morbidity and major morbidity rate was 28.2% (n = 110) and 6.7% (n = 26), respectively. No patient dead within the hospitalization (Table 2).

3.2. Preoperative AAPR and patient characteristics

Table 1 shows the differences in patient characteristics between 2 groups of AAPR. We found that patients with AAPR ≤ 0.57 had significantly higher ratios of hypoalbuminemia, normal ALP, SCC, LNM, T$_{2-3}$ stage and TNM-stage II-IIIa tumors compared to patients with AAPR > 0.57. No significant difference was found in the other clinicopathological variables between these 2 groups.

We performed a PSM to balance the confounding bias in histological subtypes, LNM, T-stage and TNM-stage tumors between patients with AAPR ≤ 0.57 and with AAPR > 0.57. Accordingly, the present PSM analysis generated 155 well-matched pairs between 2 groups of AAPR. All of covariates were adequately balanced in the matched data after PSM (Table 1; Fig. 2).

3.3. Preoperative AAPR and postoperative complications

In the entire cohort, there was no significant difference in overall morbidity (30.2% vs. 28.7%; $P = 0.74$), minor morbidity (28.8% vs. 27.5%; $P = 0.79$) or major morbidity (6.6% vs. 6.7%; $P = 0.96$) between patients with AAPR ≤ 0.57 and with AAPR > 0.57 (Table 2).

In the 155 PSM pairs, no significant difference was found in either overall morbidity (27.7% vs. 27.1%; $P = 0.90$), minor morbidity (25.8% vs. 27.1%; $P = 0.80$) or major morbidity (7.7% vs. 5.2%; $P = 0.36$) between patients with AAPR ≤ 0.57 and with AAPR > 0.57 (Table 2).

3.4. Preoperative AAPR and survival outcomes

3.4.1. Before PSM

In the entire cohort, the median OS time in patients with AAPR ≤ 0.57 and with AAPR > 0.57 was 49.0 (range 12–59) and 51.0 (range 24–66) months, respectively. The OS rate in patients with AAPR ≤ 0.57 and with AAPR > 0.57 was 72.6% and 93.3%, respectively. Moreover, the median DFS time in patients with AAPR ≤ 0.57 and with AAPR > 0.57 was 48.0 (range 12–58) and 50.6 (range 16–66) months, respectively. The DFS rate in patients with AAPR ≤ 0.57 and with AAPR > 0.57 was 66.5% and 82.6%, respectively.

The survival analyses demonstrated that both OS and DFS in patients with AAPR ≤ 0.57 were significantly shortened compared to those in patients with AAPR > 0.57 (Log-rank-*P* < 0.001; Fig. 3A and B). In the further subgroup analysis, AAPR ≤ 0.57 was found to be significantly associated with worse postoperative survival in all the subgroups stratified by patients' clinicopathological characteristics (Appendix Table 1).

3.4.2. After PSM

In the PSM cohort, patients with AAPR ≤ 0.57 and with AAPR > 0.57 had a median OS time of 49.0 (range 12–59) and 52.0 (range 24–66) months, respectively. The OS rate in patients with AAPR ≤ 0.57 and with AAPR > 0.57 was 93.5% and 72.9%, respectively. Furthermore, the median DFS time in patients with AAPR ≤ 0.57 and with AAPR > 0.57 was 49.0 (range 12–58) and 51.0 (range 16–66)

Significant (p < 0.05) tests: 203 out of 214 (94.9%)

Fig. 1. Hazard ratios for OS based on the cutoff points of AAPR in the entire cohort of included patients. The vertical line designates the optimal cutoff value with the most significant (log-rank test) split. The plot was generated from the *Cutoff Finder*.

Table 2
Postoperative complications.

| Characteristics	Entire cohort				Propensity score-matched cohort			
	Total ($N = 390$)	AAPR > 0.57 ($N = 178$)	AAPR ≤ 0.57 ($N = 212$)	P_1-value	Total ($N = 310$)	AAPR > 0.57 ($N = 155$)	AAPR ≤ 0.57 ($N = 155$)	P_2-value
Any complication (Clavien-Dindo Grade ≥ II)								
Absent	275 (70.5%)	127 (71.3%)	148 (69.8%)	0.74	225 (72.6%)	113 (72.9%)	112 (72.3%)	0.90
Present	115 (29.5%)	51 (28.7%)	64 (30.2%)		85 (27.4%)	42 (27.1%)	43 (27.7%)	
Minor morbidity (Clavien-Dindo Grade II)								
Absent	280 (71.8%)	129 (72.5%)	151 (71.2%)	0.79	228 (73.5%)	113 (72.9%)	115 (74.2%)	0.80
Present	110 (28.2%)	49 (27.5%)	61 (28.8%)		82 (26.5%)	42 (27.1%)	40 (25.8%)	
Major morbidity (Clavien-Dindo Grade ≥ III)								
Absent	364 (93.3%)	166 (93.3%)	198 (93.4%)	0.96	290 (93.5%)	147 (94.8%)	143 (92.3%)	0.36
Present	26 (6.7%)	12 (6.7%)	14 (6.6%)		20 (6.5%)	8 (5.2%)	12 (7.7%)	

AAPR: albumin-to-alkaline phosphatase ratio.
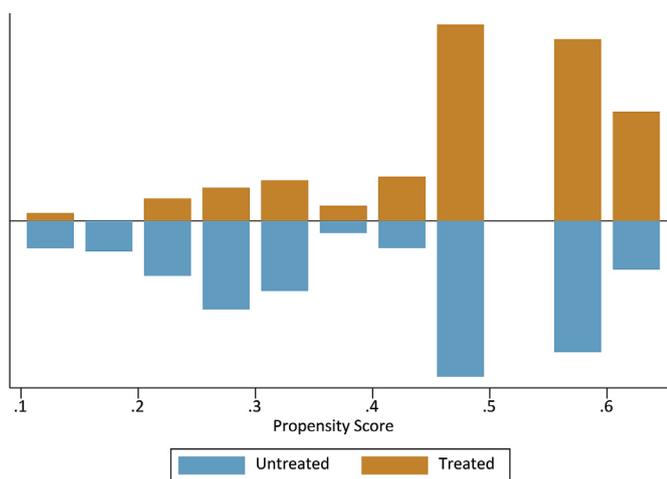
Fig. 2. Mirrored histogram showing PS distribution and overlapping between unmatched and matched samples in 2 groups of AAPR.

months, respectively. Patients with AAPR ≤ 0.57 and with AAPR > 0.57 had a DFS rate at 91.0% and 67.1%, respectively.

The survival analyses demonstrated that both OS and DFS in patients with AAPR ≤ 0.57 were significantly shortened compared to those in patients with AAPR > 0.57 (Log-rank $P < 0.001$; Fig. 3C and D). Further subgroup analysis showed that AAPR ≤ 0.57 was significantly associated with poorer postoperative survival in all subgroups stratified by gender, BMI, smoking status, coexistence of comorbidity, histological subtypes, differentiation degrees, LNM, T-stage and TNM-stage tumors, and in the subgroup of elderly people (Appendix Table 1).

3.5. Univariate and multivariate analyses of prognostic factors for OS

The univariate Cox proportional hazards regression analysis showed that AAPR ≤ 0.57 ($P < 0.001$), sALB ≤ 40 g/L ($P = 0.001$), age > 65 years ($P = 0.020$), male gender ($P = 0.007$), smoking history ($P = 0.009$), presence of comorbidity ($P = 0.019$), LNM ($P < 0.001$), T$_{2-3}$-stage ($P < 0.001$) and more advanced TNM-stage ($P < 0.001$) tumors were significantly associated with worse OS of the entire cohort (Table 3). A multivariate Cox proportional hazards regression model was then established on these significant clinicopathological variables and demonstrated that AAPR ≤ 0.57 (HR = 3.23; 95%CI = 1.67–6.25; $P < 0.001$), LNM (HR = 2.70; 95%CI = 1.43–5.12; $P = 0.002$) and T$_{2-3}$-stage tumor invasion (HR = 2.49; 95%CI = 1.29–4.81; $P = 0.007$) could serve as independent prognostic factors for OS of resected NSCLCs (Table 3).

In the PSM cohort, the univariate Cox proportional hazards regression analysis showed that AAPR ≤ 0.57 ($P < 0.001$), sALB ≤ 40 g/L ($P = 0.007$), age > 65 years ($P < 0.001$), male gender ($P = 0.034$),

smoking history ($P = 0.043$), presence of comorbidity ($P = 0.008$), SCC ($P = 0.027$), LNM ($P < 0.001$), T$_{2-3}$-stage ($P < 0.001$) and more advanced TNM-stage ($P < 0.001$) tumors were significantly associated with the poorer OS (Table 3). Finally, multivariate Cox proportional hazards regression analysis demonstrated that AAPR ≤ 0.57 (HR = 5.26; 95%CI = 2.56–11.11; $P < 0.001$), age > 65 years (HR = 2.18; 95%CI = 1.15–4.13; $P = 0.016$), T$_{2-3}$-stage (HR = 2.39; 95%CI = 1.21–4.72; $P = 0.012$) and more advanced TNM-stage tumors (HR = 5.85; 95%CI = 2.47–13.89; $P < 0.001$) were the independent prognostic factors for unfavorable OS of resected NSCLCs (Table 3).

3.6. Univariate and multivariate analyses of prognostic factors for DFS

In the univariate Cox proportional hazards regression model, we found that AAPR ≤ 0.57 ($P < 0.001$), sALB ≤ 40 g/L ($P = 0.010$), age > 65 years ($P = 0.005$), male gender ($P = 0.030$), smoking history ($P = 0.006$), presence of comorbidity ($P = 0.002$), SCC ($P = 0.013$), LNM ($P < 0.001$), T$_{2-3}$-stage ($P < 0.001$) and more advanced TNM-stage ($P < 0.001$) tumors were significantly associated with worse DFS of the entire cohort (Table 4). On the basis of above significant clinicopathological factors, the multivariate Cox proportional hazards regression analysis determined that AAPR ≤ 0.57 (HR = 1.67; 95%CI = 1.06–2.63; $P = 0.026$), age > 65 years (HR = 1.61; 95%CI = 1.07–2.41; $P = 0.023$) and LNM (HR = 2.32; 95%CI = 1.30–4.16; $P = 0.004$) could independently predict worse DFS of the entire cohort.

After PSM, AAPR ≤ 0.57 ($P < 0.001$), sALB ≤ 40 g/L ($P = 0.019$), age > 65 years ($P < 0.001$), male gender ($P = 0.045$), smoking history ($P = 0.032$), presence of comorbidity ($P = 0.010$), LNM ($P < 0.001$), T$_{2-3}$-stage ($P < 0.001$) and more advanced TNM-stage ($P < 0.001$) tumors were found to be significantly associated with worse DFS of the PSM cohort in the univariate Cox proportional hazards regression analysis (Table 4). Finally, a multivariate Cox proportional hazards regression model based on these clinicopathological characteristics suggested that AAPR ≤ 0.57 (HR = 4.76; 95%CI = 2.50–9.09; $P < 0.001$), age > 65 years (HR = 1.99; 95%CI = 1.16–3.44; $P = 0.013$) and more advanced TNM-stage tumors (HR = 6.54; 95%CI = 2.90–14.71; $P < 0.001$) were the independent prognostic factors for unfavorable DFS of resected NSCLCs (Table 4).

3.7. Discriminatory powers of serum indicators

With regard to the prediction of OS, AAPR got an AUC at 0.68 (95%CI = 0.61–0.74; $P < 0.001$) in the entire cohort and at 0.69 (95%CI = 0.62–0.76; $P < 0.001$) in the PSM cohort, respectively. The AUCs of all serum markers are presented in Fig. 4A and B. AAPR hold the largest AUCs compared with those of sALB and ALP, and was the only significant discriminator for OS in the PSM cohort.

With regard to the prediction of DFS, the AUC of AAPR was 0.61 (95%CI = 0.54–0.67; $P = 0.002$) in the entire cohort and was 0.68
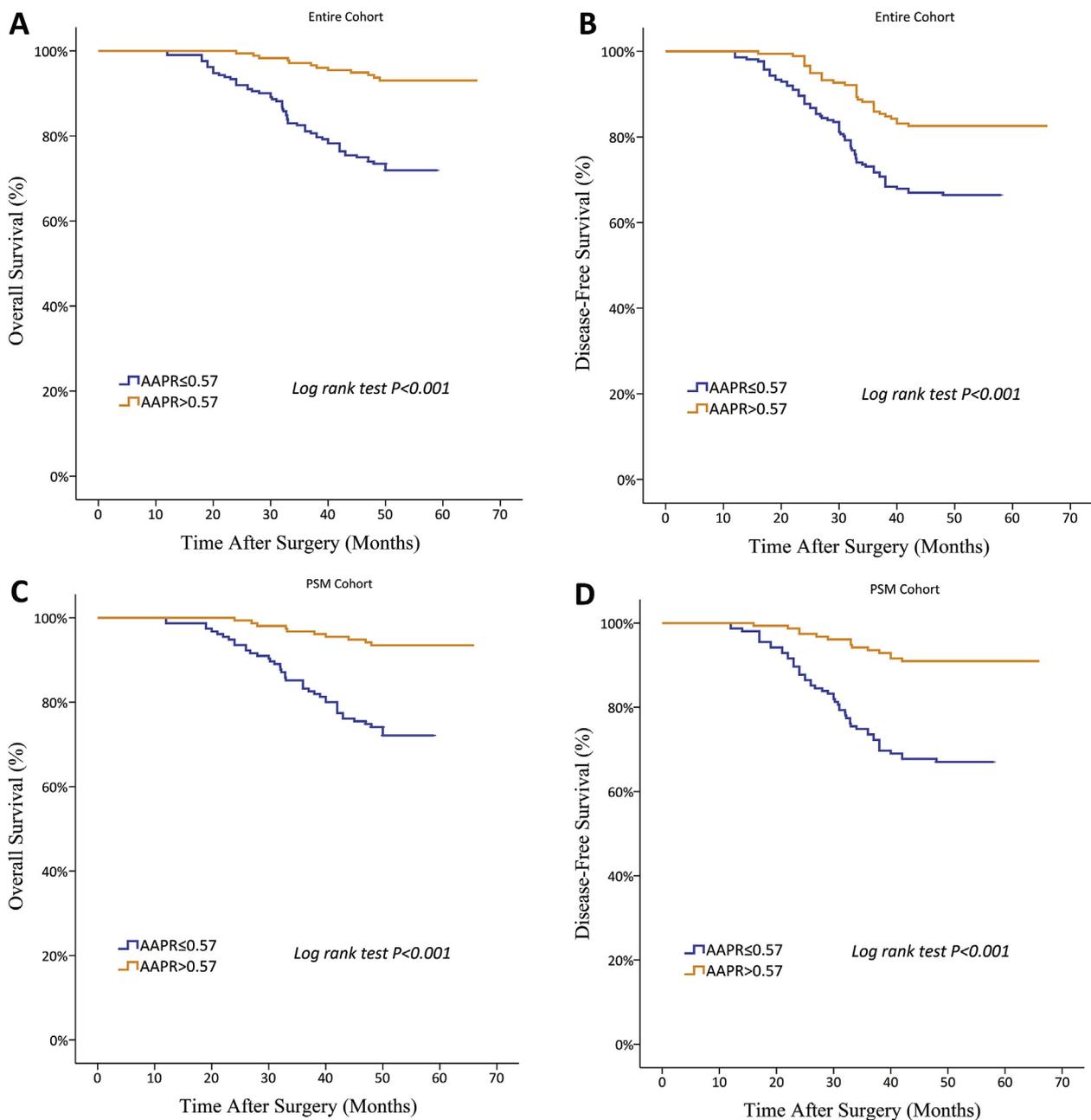
Fig. 3. Survival analyses of **(A)** OS and **(B)** DFS between 2 groups of AAPR in the entire cohort; Survival analyses of **(C)** OS and **(D)** DFS between 2 groups of AAPR in the PSM cohort.

(95%CI = 0.61–0.75; *P* < 0.001) in the PSM cohort, respectively. Fig. 4C and D illustrate the AUCs of AAPR, sALB and ALP. AAPR had the largest AUCs among all the serum indicators, and was the only significant discriminator for DFS in both the entire cohort and the PSM cohort.

4. Discussion

4.1. Key results and interpretations

AAPR is characterized by a simple and effective integration of 2 serum biomarkers, namely sALB and ALP, both of which can be conveniently and inexpensively obtained in routine clinical practice. This scoring system was initially established to reflect patients' liver function reserve and present a great prognostic value [16]. Since its first introduction onto prognostic prediction, the clinical significance of AAPR

has been validated across a variety of malignancies [14–20].

Chan et al. [16] firstly developed the AAPR assessment tool in patients who underwent curative resection for hepatocellular carcinoma and further validated the strong prognostic significance of low preoperative AAPR for both unfavorable OS and DFS of resected hepatocellular carcinoma. Subsequently, Pu et al. [15] introduced the AAPR to the patients undergoing curative resection for pancreatic ductal adenocarcinoma for accurate prognostic prediction. Low preoperative AAPR was also identified to act as an independent prognostic indicator for postoperative OS of pancreatic ductal adenocarcinoma. Similarly, in the latest cohort study conducted on 303 patients who had received cholangiocarcinoma surgery, Xiong et al. [19] further confirmed potent prognostic roles of preoperative AAPR for OS of resected cholangiocarcinoma. Most recently, Li et al. [14] firstly focused on the prognostic value of dynamic AAPR in patients receiving chemo-radiotherapy for limited-stage SCLC. The authors retrospectively analyzed the survival

Table 3

Prognostic significance of clinicopathological parameters for overall survival of operable non-small-cell lung cancer.

Characteristics	Entire cohort				Propensity score matched cohort			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate 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)								
≤65	Reference				Reference			
>65	1.75 (1.09–2.81)	0.020	1.56 (0.94–2.59)	0.082	2.85 (1.59–5.08)	<0.001	2.18 (1.15–4.13)	0.016
Gender								
Female	Reference				Reference			
Male	2.17 (1.24–3.79)	0.007	1.65 (0.75–3.62)	0.21	1.94 (1.05–3.58)	0.034	1.18 (0.50–2.81)	0.71
Body mass index (kg/m^2)								
≤24	Reference				Reference			
>24	0.96 (0.60–1.55)	0.88			0.85 (0.49–1.47)	0.57		
Smoking status								
Never	Reference				Reference			
Current/former	1.92 (1.18–3.11)	0.009	1.45 (0.72–2.92)	0.30	1.76 (1.02–3.05)	0.043	1.13 (0.50–2.52)	0.77
Presence of comorbidity								
Absent	Reference				Reference			
Present	2.02 (1.13–3.63)	0.019	1.34 (0.72–2.50)	0.36	2.63 (1.28–5.39)	0.008	1.44 (0.67–3.11)	0.35
Tumor location								
Upper	Reference				Reference			
Lower/middle	0.80 (0.50–1.28)	0.36			0.72 (0.42–1.24)	0.24		
Histological subtypes								
Adenocarcinoma	Reference				Reference			
Non-adenocarcinoma	1.71 (0.94–3.11)	0.076			2.0 (1.08–3.69)	0.027	1.17 (0.55–2.49)	0.69
Differentiation degree								
Moderate/high	Reference				Reference			
Low	1.22 (0.71–2.11)	0.48			1.34 (0.69–2.62)	0.38		
Tumor invasion								
T$_1$	Reference				Reference			
T$_{2-3}$	4.33 (2.36–7.87)	<0.001	2.49 (1.29–4.81)	0.007	3.86 (2.06–7.25)	<0.001	2.39 (1.21–4.72)	0.012
Lymph node metastasis								
N$_0$	Reference				Reference			
N$_{1-2}$	5.27 (3.29–8.44)	<0.001	2.70 (1.43–5.12)	0.002	4.33 (2.48–7.55)	<0.001	1.17 (0.50–2.76)	0.72
TNM-stage								
I	Reference				Reference			
II-IIIa	6.33 (3.79–10.53)	<0.001	1.84 (0.87–3.88)	0.11	7.63 (4.33–13.51)	<0.001	5.85 (2.47–13.89)	<0.001
Albumin to alkaline phosphatase ratio								
≤0.57	Reference				Reference			
>0.57	0.21 (0.12–0.39)	<0.001	0.31 (0.16–0.60)	<0.001	0.21 (0.11–0.42)	<0.001	0.19 (0.090–0.39)	<0.001
Albumin (g/L)								
≤40	Reference				Reference			
>40	0.43 (0.26–0.71)	0.001	0.65 (0.37–1.13)	0.13	0.45 (0.25–0.80)	0.007	0.94 (0.47–1.86)	0.86
Alkaline phosphatase (U/L)								
Normal range	Reference				Reference			
Abnormal range	1.49 (0.47–4.76)	0.50			3.32 (0.46–23.81)	0.23		

CI: confidence interval; HR: hazard ratio.

data of a small limited-stage SCLC cohort and found that both pre- and post-operative AAPR were independent predictive factors for both OS and DFS. Moreover, AAPR could also improve the prediction accuracy of TNM stage for patent mortality risk stratification. However, there was no study reported to assess the clinical significance of AAPR for surgical NSCLCs until recently.

To our knowledge, the present study was the first PSM study to demonstrate prognostic roles of preoperative AAPR for the survival of patients with operable NSCLCs. In our series, an AAPR at 0.57 was determined as the optimal cutoff value regarding to postoperative survival and further used to divide all patients into the low AAPR group and high AAPR group to reflect the intensity of host immune-nutritional and liver function reserve. Patients with AAPR ≤ 0.57, who were considered to have a higher probability to suffer from hypoalbuminemia and a sharp increase in ALP, had less favorable pathological characteristics compared to those of patients with AAPR > 0.57, including the significantly higher ratios of LNM, T$_{2-3}$ stage and TNM-stage II-IIIa tumors. This phenomenon might suggest a potential efficacy of low AAPR to reflect more aggressive behaviors of NSCLC.

The highlight of our study was to demonstrate the predictive ability of AAPR for the prognosis of resected NSCLCs through both

multivariate Cox proportional hazards regression analysis and PSM analysis, in order to minimize potential confounding bias as much as possible. After matching PSs of clinicopathological characteristics between 2 groups of AAPR, a total of 155 well-matched pairs were identified for further analyses. Finally, our multivariate Cox proportional hazards regression models commonly showed that the prognostic value of AAPR for both OS and DFS did not only remain strongly reliable in the entire cohort but also successfully validated in the PSM cohort. Such powerful prognostic roles were identified in almost all the subgroups stratified according to patients' clinicopathological features. More importantly, AAPR hold the best discriminatory ability for predicting postoperative survival and was the only independent prognostic factor after eliminating confounding influence by PSM. Taken together, our findings strongly suggested that a lower preoperative AAPR could serve as an excellent discriminator for unfavorable prognosis of resected NSCLCs.

In this study, we found no difference in postoperative complications between patients stratified by preoperative AAPR. We speculated that the great majority of the included patients were treated with more aggressive medications under the supervision of attending physicians during the hospitalization but generally received less professional care

Table 4

Prognostic significance of clinicopathological parameters for disease-free survival of operable non-small-cell lung cancer.

Characteristics	Entire cohort				Propensity score matched cohort			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate 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)								
≤65	Reference				Reference			
>65	1.75 (1.18–2.58)	0.005	1.61 (1.07–2.41)	0.023	2.53 (1.52–4.21)	< 0.001	1.99 (1.16–3.44)	0.013
Gender								
Female	Reference				Reference			
Male	1.61 (1.05–2.47)	0.030	1.01 (0.52–1.96)	0.98	1.73 (1.01–2.95)	0.045	1.05 (0.48–2.27)	0.91
Body mass index (kg/m^2)								
≤24	Reference				Reference			
>24	0.87 (0.59–1.29)	0.50			0.74 (0.45–1.20)	0.22		
Smoking status								
Never	Reference				Reference			
Current/former	1.74 (1.17–2.59)	0.006	1.21 (0.64–2.31)	0.56	1.71 (1.05–2.78)	0.032	1.03 (0.51–2.05)	0.94
Presence of comorbidity								
Absent	Reference				Reference			
Present	2.14 (1.31–3.49)	0.002	1.54 (0.92–2.56)	0.098	2.22 (1.21–4.07)	0.010	1.30 (0.69–2.46)	0.41
Tumor location								
Upper	Reference				Reference			
Lower/middle	0.86 (0.58–1.27)	0.45			0.67 (0.41–1.09)	0.11		
Histological subtypes								
Adenocarcinoma	Reference				Reference			
Non-adenocarcinoma	1.69 (1.11–2.56)	0.013	1.16 (0.72–1.86)	0.54	1.12 (0.75–1.67)	0.57		
Differentiation degree								
Moderate/high	Reference				Reference			
Low	1.50 (0.97–2.31)	0.070			1.23 (0.67–2.26)	0.50		
Tumor invasion								
T$_1$	Reference				Reference			
T$_{2-3}$	2.24 (1.47–3.42)	< 0.001	1.35 (0.83–2.19)	0.22	2.51 (1.50–4.20)	< 0.001	1.48 (0.84–2.62)	0.18
Lymph node metastasis								
N$_0$	Reference				Reference			
N$_{1-2}$	3.99 (2.69–6.91)	< 0.001	2.32 (1.30–4.16)	0.004	5.33 (3.26–8.72)	< 0.001	1.10 (0.53–2.28)	0.80
TNM-stage								
I	Reference				Reference			
II-IIIa	3.95 (2.65–5.88)	< 0.001	1.72 (0.90–3.26)	0.10	7.69 (4.61–12.65)	< 0.001	6.54 (2.90–14.71)	< 0.001
Albumin to alkaline phosphatase ratio								
≤0.57	Reference				Reference			
>0.57	0.46 (0.30–0.70)	< 0.001	0.60 (0.38–0.94)	0.026	0.24 (0.13–0.43)	< 0.001	0.21 (0.11–0.40)	< 0.001
Albumin (g/L)								
≤40	Reference				Reference			
>40	0.57 (0.37–0.88)	0.010	0.77 (0.48–1.24)	0.28	0.52 (0.30–0.90)	0.019	0.92 (0.49–1.70)	0.78
Alkaline phosphatase (U/L)								
Normal range	Reference				Reference			
Abnormal range	2.35 (0.74–7.41)	0.16			4.29 (0.60–31.25)	0.15		

CI: confidence interval; HR: hazard ratio.

and health tips after discharge from hospital. Therefore, a better maintenance of patient immune-nutritional reserve during the perioperative period might attenuate the predictive power of AAPR for in-hospital outcomes.

As an integrated indicator based on sALB and ALP, the biological reasons underlying potent prognostic value of preoperative AAPR may be elucidated by a combination of the following two plausible mechanisms.

Firstly, sALB is known as a negative acute-phase protein and routinely employed to reflect patient nutritional status. Hypoalbuminemia represents not only an undernourished condition but also a sustained systemic inflammatory response as the synthesis of sALB could be suppressed by malnutrition and inflammation [14,35]. Preoperative malnutrition has shown evident effects in terms of tissue vulnerability, delayed wound healing and increased susceptibility to infectious complications [23]. Besides, the excessive protein catabolism induced by surgery can further impair global immune-nutritional function and physiological homeostasis. Thus, patients with low sALB level are less likely to have an adequate response to the surgical stress because of their compromised ability to withstand an acute injury, resulting in dramatically increased risks of adverse events.

Secondly, as one of major markers that generally reflect the hepatic protein synthesis, serum ALP level can be easily affected by the liver function damage from chronic wasting diseases and the cancer-related inflammatory microenvironment [19]. Emerging evidence shows that an elevated level of ALP could also act as a reliable indicator for the oxidative stress, one of the major products of inflammation, which could produce reactive oxygen species that damage DNA, proteins and lipids and promote high mutagenic metabolic activities, resulting in more aggressive cancer genesis, proliferation and metastasis [15,35]. Therefore, as many studies recently demonstrated, an elevated serum ALP may play a vital role for the prediction of an adverse prognosis of cancers [14–20].

4.2. Generalizability

Our findings can facilitate thoracic surgeons to better distinguish the patients who are at high surgical risk by incorporating an AAPR index into traditional stratification tools before curative resections for NSCLC. Moreover, an optimized prognostic prediction by early recognizing preoperative AAPR can provide a great help to settle more accurate personalized therapeutic schemes, in order to enhance the
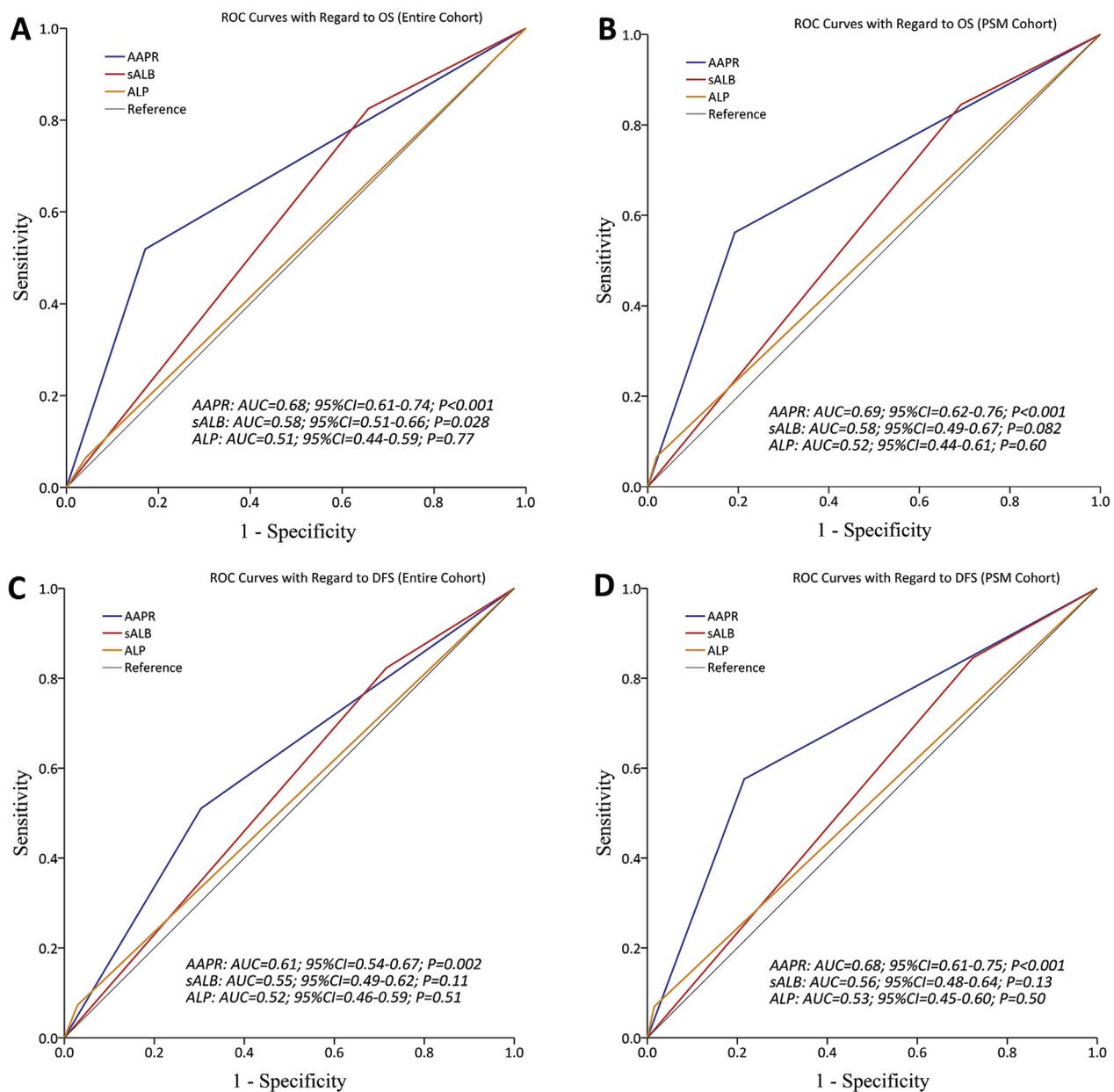
Fig. 4. ROC curves showing the discriminatory power of serum biomarkers for predicting OS **(A)** in the entire cohort and **(B)** in the PSM cohort; ROC curves showing the discriminatory power of serum biomarkers for predicting DFS **(C)** in the entire cohort and **(D)** in the PSM cohort.

surgical tolerability and limit the unfavorable survival.

4.3. Limitations

Several limitations in this study must be acknowledged as follows:

First, our study was subject to the inherent limitations of any single-center data analysis without external validation. Potential selection bias might complicate our findings, although we had included the patients in compliance with fairly strict eligibility criteria and further performed a 1:1 PSM analysis to avoid any confounding influence. We recommend that more prospective validating studies with much better control of perioperative parameters are needed to verify the predictive power of AAPR in resected NSCLCs.

Second, other putative inflammatory prognostic markers such as the C-reactive protein, fibrinogen and cytokines were not gathered in our analysis because they might not be routinely measured in routine clinical practice. Several common risk scales involving these biomarkers could not be estimated to help to interpret our results.

Therefore, further prospective studies are highly desirable to estimate the prognostic significance of AAPR in combination with such laboratory markers.

Third, we utilized a validated Web-based bio-statistical tool to derive the optimal cutoff of AAPR (0.57) as the grouping criterion of our NSCLC series since no consensus had been recommended on the reference values for AAPR. The dichotomized cutoffs of AAPR varied across currently available studies.

Fourth, comprehensive and professional hepatobiliary imaging and function tests might not be considered in every surgical patients included in our thoracic surgery department. Thus, the complete details regarding to the presence and severity of hepatobiliary disorders before surgery were not available for the entire cohort of patients.

Fifth, ALP existed in several isoforms that originate from the liver and bone tissues account for the majority of serum ALP in humans. Unfortunately, in the present study, an ALP isoenzyme analysis was not routinely performed to differentiate between liver and bone origins of an elevated level of total serum ALP. We recommend that a differential

diagnosis on the proportions between liver and bone ALP may further help to understand the potential mechanisms underlying the potent prognostic value of AAPR in surgical NSCLC in the future.

Finally, our results were derived from patients who underwent VATS lobectomy for NSCLCs. These findings should be further investigated among conventional thoracotomy cases.

5. Conclusions

In conclusion, the present study demonstrates that preoperative AAPR may serve as an excellent prognostic biomarker for both OS and DFS following VATS lobectomy for NSCLCs. The AAPR can be employed as a simplified, effective and routinely operated risk stratification tool to provide readily available and objective information for the prognostic prediction of resected NSCLCs. Owing to several inherent limitations of the study design, more large-scale prospective analyses are warranted to substantiate and validate our findings in the future.

Author contribution

Conception and design: SJ Li, GW Che, LX Liu;

Provision of study materials or patients: SJ Li, H Du, GW Che, LX Liu;

Collection and assembly of data: SJ Li, WB Zhang, YJ Li, GW Che;

Data analysis and interpretation: SJ Li, WY Lv, H Du;

Statistical analysis: SJ Li, WY Lv, H Du, YJ Li;

Manuscript writing: SJ Li, WY Lv, YJ Li, H Du, WB Zhang;

Manuscript editing: SJ Li, WY Lv, GW Che, LX Liu;

Manuscript review: GW Che, LX Liu

Final approval of manuscript: SJ Li, WY Lv, H Du, YJ Li, WB Zhang, GW Che, LX Liu.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.07.008.

Appendix

Table 1
Subgroup analyses (Log-rank test) for postoperative survival between patients stratified by preoperative AAPR of 0.57

Characteristics	Mean survival months with 95%CI of the entire cohort			Mean survival months with 95%CI of the PSM cohort		
	AAPR > 0.57 (N = 178)	AAPR ≤ 0.57 (N = 212)	Log rank P_1-value	AAPR > 0.57 (N = 155)	AAPR ≤ 0.57 (N = 155)	Log rank P_2-value
Age (Years)						
≤ 65	64.0 (62.5–65.5)	53.1 (50.9–55.3)	0.002	64.0 (62.4–65.6)	55.6 (53.7–57.6)	0.11
> 65	58.6 (57.3–59.9)	48.1 (45.4–50.7)	< 0.001	58.6 (57.1–60.1)	46.6 (43.5–49.7)	< 0.001
Gender						
Female	64.8 (63.4–66.1)	52.3 (49.7–54.8)	0.013	64.6 (62.9–66.2)	52.2 (49.4–55.1)	0.033
Male	58.1 (56.8–59.4)	50.0 (47.7–52.3)	< 0.001	58.2 (56.8–59.6)	50.4 (47.8–53.0)	< 0.001
Body mass index (kg/m^2)						
≤ 24	58.4 (57.2–59.5)	51.2 (49.0–53.4)	0.001	58.6 (57.4–59.7)	52.0 (49.7–54.4)	0.003
> 24	64.3 (62.6–65.9)	50.6 (47.8–53.5)	< 0.001	64.0 (62.1–65.9)	50.3 (46.9–53.6)	< 0.001
Smoking status						
Never	64.9 (63.9–66.0)	51.4 (49.1–53.7)	< 0.001	64.8 (63.6–66.0)	51.6 (49.2–54.0)	0.001
Current/former	54.9 (53.3–56.4)	50.1 (47.6–52.7)	< 0.001	55.0 (53.3–56.6)	50.2 (47.1–53.3)	< 0.001
Presence of comorbidity						
Absent	64.7 (63.1–66.2)	51.8 (48.9–54.7)	0.017	65.0 (63.7–66.4)	53.3 (50.7–55.9)	0.026
Present	58.2 (56.9–59.4)	50.6 (48.4–52.8)	< 0.001	58.0 (56.5–59.4)	50.6 (48.1–53.1)	< 0.001
Histological subtypes						
Adenocarcinoma	58.6 (57.7–59.5)	53.1 (51.2–55.1)	< 0.001	58.6 (57.7–59.6)	52.8 (50.7–54.9)	< 0.001
Squamous cell carcinoma	63.3 (59.7–66.9)	46.5 (43.1–49.9)	0.003	63.1 (59.2–67.0)	46.1 (41.1–51.1)	0.002
Differentiation degree						
Moderate/high	63.8 (62.4–65.1)	52.0 (50.1–54.0)	< 0.001	63.9 (62.5–65.3)	52.5 (50.3–54.6)	< 0.001

Table 1 (*continued*)

Characteristics	Mean survival months with 95%CI of the entire cohort			Mean survival months with 95%CI of the PSM cohort		
	AAPR > 0.57 (N = 178)	AAPR ≤ 0.57 (N = 212)	*Log rank P_1-value*	AAPR > 0.57 (N = 155)	AAPR ≤ 0.57 (N = 155)	*Log rank P_2-value*
Low	57.4 (56.3–58.5)	48.2 (44.3–52.1)	0.001	57.3 (55.9–58.7)	47.7 (42.9–52.6)	0.001
Tumor invasion (T-stage)						
T_1	65.3 (64.3–66.3)	55.1 (53.4–56.8)	0.007	65.2 (64.1–66.3)	55.0 (53.2–56.8)	0.009
T_{2-3}	56.5 (54.9–58.0)	48.2 (45.6–50.8)	< 0.001	56.5 (54.8–58.2)	47.3 (43.9–50.8)	< 0.001
Lymph node metastasis (N-stage)						
N_0	65.0 (64.1–65.9)	53.4 (51.8–55.1)	< 0.001	65.2 (64.3–66.1)	52.8 (50.9–54.7)	< 0.001
N_{1-2}	49.4 (46.1–52.7)	42.9 (38.6–47.2)	0.019	49.4 (46.1–52.7)	43.0 (37.1–48.8)	0.021
TNM-stage						
I	65.4 (64.6–66.1)	54.4 (52.7–56.1)	< 0.001	65.7 (65.0–66.3)	54.3 (52.5–56.0)	< 0.001
II-IIIa	53.6 (50.3–56.9)	46.0 (42.8–49.1)	0.020	53.4 (50.1–56.8)	40.8 (36.2–45.4)	< 0.001

AAPR: albumin-to-alkaline phosphatase ratio; CI: confidence interval; PSM: propensity score matching.

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