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# Albumin-to-D-dimer ratios: A novel prognostic factor for evaluating first-line chemotherapy efficacy in advanced lung adenocarcinoma patients

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The prognosis of advanced lung adenocarcinoma (LUAD) remains unfavorable, with chemotherapy constituting a primary treatment modality. Discerning the efficacy of chemotherapy for advanced LUAD is imperative. Prior investigations have demonstrated the prognostic value of albumin and D-dimer individually for malignancies; however, the predictive capacity of albumin-to-D-dimer ratios (ADR) for advanced LUAD subjected to first-line platinum-based chemotherapy remains unexplored. A cohort of 313 patients with advanced LUAD was retrospectively examined in this study, spanning from January 2017 to January 2021. ADR threshold values were ascertained via receiver operating characteristic analysis, followed by the evaluation of the association between pretreatment ADR and clinicopathological characteristics, disease control rate (DCR), and overall response rate (ORR) pertinent to first-line chemotherapy. Prognostic factors for progression-free survival (PFS) were determined employing Cox univariate and multivariate analyses. Subsequently, survival data were illustrated utilizing the Kaplan-Meier method and scrutinized through the log-rank test across the entire and subgroup populations. ADR demonstrated a superior area under the curve (AUC) value relative to albumin and D-dimer individually and exhibited enhanced prognostic predictive capability compared to albumin-to-fibrinogen ratios (AFR) for advanced LUAD (AUC: 0.805 vs. 0.640, DeLong test: $p<0.001$). ADR yielded a cut-off value of 16.608. A greater proportion of non-smokers was observed within the high-ADR group (ADR>16.608) compared to the low-ADR group (ADR≤16.608). Patients in the high-ADR group displayed elevated BMI and $Na^+$ levels and reduced neutrophil count, monocyte count, globulin, and alkaline phosphatase (all $p<0.05$). Notably, the high-ADR group exhibited heightened DCR (96.7% vs. 89.2%, $p=0.008$) and ORR rates (70.1% vs. 51.0%, $p=0.001$) relative to the low-ADR group. Multivariate analysis outcomes indicated that high ADR constituted an independent risk factor for PFS (hazard ratio: 0.24, $p<0.001$). Furthermore, patients in the high-ADR cohort displayed a significantly prolonged median PFS (254 vs. 142 days, $p<0.0001$) compared to their low-ADR counterparts. In subpopulations exhibiting favorable implications for PFS, as determined by multivariate analysis, high-ADR patients consistently demonstrated extended PFS durations relative to the low-ADR group (all $p<0.0001$). Collectively, our findings suggest that ADR constitutes a novel and promising prognostic indicator for advanced LUAD patients, surpassing the accuracy of albumin and D-dimer individually and AFR. ADR thus serves as a potent instrument for assessing treatment effects and PFS in advanced LUAD patients undergoing first-line chemotherapy.

*Key words: albumin-to-D-dimer ratios; albumin-to-fibrinogen ratios; lung adenocarcinoma; first-line chemotherapy; prognosis; progression-free survival*

Lung carcinoma represents the second most prevalent neoplastic malignancy, boasting the highest mortality rate [1, 2]. Notably, the incidence of lung adenocarcinoma (LUAD) has surged disproportionately, rendering it the most ubiquitous subtype among lung carcinomas [3]. For incipient-stage LUAD, surgical intervention has garnered widespread acceptance as the principal therapeutic approach [4]. Alas, the majority of LUAD patients receive diagnoses at comparatively advanced stages (stage III or IV), potentially precluding surgical excision [5]. In recent decades, novel therapeutic modalities for advanced LUAD have rapidly emerged and evolved. Targeted treatments and immunotherapy have piqued considerable interest due to their enhanced tolerability and efficacy [6, 7]. Nevertheless, even among East Asian populations, the prevalence of epidermal growth factor receptor (EGFR) mutations does not surpass 50%, while the frequency of anaplastic lymphoma kinase (ALK) mutations remains substantially lower, not exceeding 10% [8, 9]. Substantial evidence indicates that fewer than 40% of LUAD patients exhibit high PD-L1 expression, rendering immunotherapy ineffective for a majority of patients [7, 10, 11]. In summation, platinum-based chemotherapeutic regimens remain the predominant choice for a preponderance of patients afflicted with advanced LUAD [12]. Given the inherent variability in chemotherapeutic efficacy, the identification of prognostic markers correlated with chemotherapeutic response is imperative to facilitate early optimization of treatment regimens, thereby ameliorating the prognosis of patients with advanced LUAD [13].

Systemic inflammation, malnutrition, and coagulation aberrations frequently manifest as comorbidities in neoplastic patients [14–16]. Heightened systemic inflammation, malnutrition, and a hypercoagulable state contribute to tumorigenesis, progression, recurrence, metastasis, and drug resistance, culminating in diminished survival duration [17–21]. Albumin, a potent hepatically synthesized protein, has gained widespread recognition as a serum inflammatory and nutritional marker employed to prognosticate mortality in neoplastic patients [22–24]. Among the fibrinolytic and coagulation factors present within the tumor microenvironment, fibrinogen and D-dimer, which also reflect tumor patients' inflammatory responses and coagulation aberrations, may serve as prognostic indicators for these individuals [25–28]. The albumin-to-fibrinogen (AFR) and albumin-to-D-dimer ratios (ADR) concurrently capture the inflammatory, nutritional, and coagulation status of cancer patients, potentially offering superior prognostic accuracy compared to albumin, fibrinogen, and D-dimer in isolation. A plethora of literature supports the reliability of AFR and ADR as prognostic markers for neoplastic patients [29–34].

Furthermore, it is well-established that fibrinogen undergoes conversion into fibrin, which subsequently undergoes cross-linking and eventual degradation into D-dimer [35]. Given the protracted nature of tumor progression to advanced stages, fibrinogen may initially be converted solely into fibrin during the tumor's incipient stage, with fibrin subsequently cross-linking and degrading into D-dimer during the advanced stage. Consequently, the association between D-dimer and advanced tumors may be more robust than that between fibrinogen and advanced tumors. Nonetheless, scant research exists on the capacity of ADR to predict the therapeutic efficacy in advanced LUAD and its comparative performance against AFR. Thus, the present investigation endeavors to elucidate the prognostic value of ADR in advanced LUAD patients undergoing first-line chemotherapy.

## Patients and methods

**Patients.** From January 2017 through January 2021, a retrospective analysis was conducted on data from 313 advanced LUAD patients admitted to the Shenyang Fifth People's Hospital, who underwent first-line platinum-based chemotherapy. The enrollment criteria included: 1) histopathological confirmation of advanced LUAD, devoid of prior anti-neoplastic intervention or lung cancer-related surgical management; 2) stage III–IV classification based on the 8th edition of the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) guidelines; 3) completion of a minimum of two cycles of first-line platinum-based chemotherapy; 4) refusal of EGFR, ALK or other target gene testing, or presence of wild-type test results. Exclusion criteria for the final analysis encompassed: 1) incomplete data; 2) utilization of approved anti-inflammatory and anticoagulant medications prior to chemotherapy; 3) severe renal or hepatic dysfunction, infection, myocardial infarction, or thrombosis; 4) presence of cerebral metastases. The first-line chemotherapy regimen consisted of cisplatin, carboplatin, or lobaplatin in conjunction with pemetrexed, paclitaxel, or docetaxel.

This study has received approval from the Institutional Ethics Review Board of Shenyang 5$^{th}$ People Hospital. As this was a retrospective study, the requirement for informed consent was waived. The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Data collection.** Clinical data prior to first-line chemotherapy, including blood samples, age, sex, smoking history, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) score, TNM tumor staging, tumor metastasis, chemotherapy response, and progression-free survival (PFS), were gathered. Pre-treatment fasting peripheral blood specimens were obtained between 6:00–8:00 am, 1–3 days preceding chemotherapy initiation. The normal range of BMI is 18.5–24 kg/m$^2$. Established reference ranges for blood biomarkers are as follows: albumin (40–55 g/l), fibrinogen (2–4 g/l), D-dimer (0–0.5 mg/l), hemoglobin (115–150 g/l),

erythrocyte count (3.5–5.5×$10^{12}$/l), neutrophil counts (1.8–6.3×$10^{9}$/l), lymphocyte count (1.1–3.2×$10^{9}$/l), monocyte count (0.1–0.6×$10^{9}$/l), thrombocyte counts (100–300×$10^{9}$/l), creatinine (CREA, 41–81 μmol/l), blood urea nitrogen (BUN, 3.1–8.8 mmol/l), globulin (20–30 g/l), total bilirubin (0–23 μmol/l), alkaline phosphatase (50–135 U/l), fasting plasma glucose (3.9–6.1 mmol/l), $Na^{+}$ (135–145 mmol/l), and $K^{+}$ (3.5–5.5 mmol/l). The albumin-to-fibrinogen ratio (AFR) was defined as albumin (g/l) divided by fibrinogen (g/l), and the albumin-to-D-dimer ratio (ADR) as albumin (g/l) divided by D-dimer (mg/l).

The first-line chemotherapy response was evaluated after every 2 chemotherapy cycles, in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Patient follow-ups were conducted until the first-line chemotherapy failed, patients were lost to follow-up, expired, or the follow-up period terminated. The study concluded in December 2022. The first-line chemotherapy response was categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The disease control rate (DCR) was calculated as the proportion of patients achieving CR, PR, and SD statuses. This metric is designed to capture the full spectrum of positive outcomes from the treatment under investigation, extending beyond tumor reduction (CR and PR) to include cases where disease progression is halted (SD). The overall response rate (ORR), was defined as the sum of CR and PR instances alone, highlighting the proportion of patients who achieved tumor size reduction as a direct effect of the treatment. PFS was calculated as the duration from therapy initiation to first-line chemotherapy failure, last follow-up, or time of death.

**Statistical analysis.** Analyses were conducted utilizing GraphPad Prism 9.4 (GraphPad Software), SPSS software 21.0 (SPSS Inc., Chicago, IL, USA), and R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Measurements were expressed as median (25th percentile, 75th percentile) for data exhibiting skewed distribution, and as mean ± standard deviation for data following a normal distribution. The area under the curve (AUC) values for AFR and ADR were determined via receiver operating characteristic (ROC) curve analysis, with the DeLong test employed to compare ROC curve performance between AFR and ADR. Utilize Youden's index to ascertain the optimal cut-off value for prognostic factors. Appropriate tests, including the independent samples t-test, chi-square test, and Mann-Whitney U-test, were used as necessary. Prognostic determinants of PFS were computed employing Cox univariate and multivariate analyses. Survival data were plotted using the Kaplan-Meier method and analyzed via the log-rank test. A p-value <0.05 was deemed statistically significant.

## Results

**Determination of optimal threshold values and patient stratification.** Utilizing ROC curves, we ascertained the AUC values for albumin, fibrinogen, D-dimer, AFR, and ADR with respect to the patients' median PFS of 215 days (Figure 1). In summary, the AUC values for albumin, fibrinogen, D-dimer, AFR, and ADR were 0.716, 0.602, 0.795, 0.640, and 0.805, respectively. Owing to the significantly superior AUC value of ADR compared to AFR (0.805 vs. 0.640, DeLong test: p<0.001), our subsequent investigations focused solely on ADR. Employing Youden's index, the optimal threshold value for ADR was established as 16.608. Consequently, patients exhibiting an ADR>16.608 were assigned to the high-ADR group (low-risk group), while those with lower values were stratified into the low-ADR group (high-risk group).

**Association of clinicopathological characteristics with ADR.** The median age for the entire cohort was 60 years,

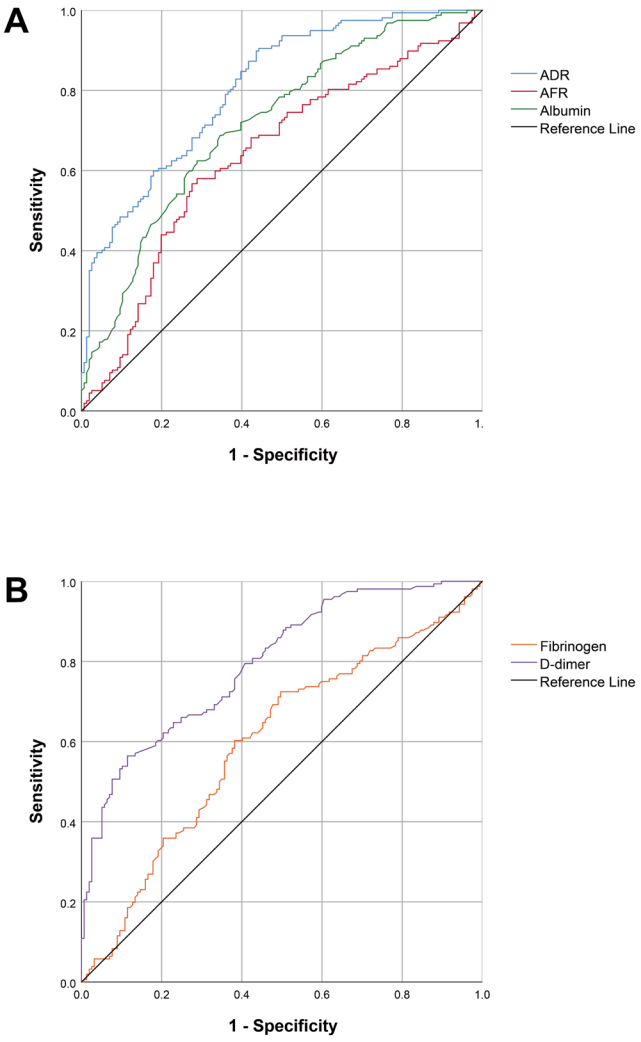


**Figure 1. Illustration of A) the albumin, albumin-to-fibrinogen ratio (AFR), and albumin-to-D-dimer ratio (ADR), and B) fibrinogen and D-dimer levels in patients with advanced lung adenocarcinoma using receiver operating characteristic (ROC) curves.**

**Table 1. Correlation of pretreatment ADR with clinicopathological parameters.**

| | Total | Low-ADR | High-ADR | p-value |
|---|---|---|---|---|
| Total (n) | 313 | 102 | 211 | |
| Age (years, median) | 60 (53.00–67.00) | 62 (53.75–67.00) | 60 (52.00–67.00) | 0.395 |
| Sex (n) | | | | |
| Male | 183 (58.5%) | 67 (65.7%) | 116 (55.0%) | 0.072 |
| Female | 130 (41.5%) | 35 (34.3%) | 95 (45.0%) | |
| Body Mass Index (kg/m², median) | 22.77 (20.90–24.91) | 21.97 (19.44–24.57) | 22.92 (21.30–24.98) | 0.001 |
| Smoking (n) | | | | |
| Nonsmokers | 184 (58.8%) | 49 (48.1%) | 135 (64.0%) | 0.019 |
| Cessation | 88 (28.1%) | 34 (33.3%) | 54 (25.6%) | |
| Persistent use | 41 (13.1%) | 19 (18.6%) | 22 (10.4%) | |
| ECOG (n) | | | | |
| 0 | 71 (22.7%) | 19 (18.6%) | 52 (24.6%) | 0.233 |
| 1 | 242 (77.3%) | 83 (81.4%) | 159 (75.4%) | |
| The quantity of organs impacted by metastatic dissemination (n) | | | | |
| 0–1 | 201 (64.2%) | 58 (56.9%) | 143 (67.8%) | 0.059 |
| ≥2 | 112 (35.8%) | 44 (43.1%) | 68 (32.2%) | |
| TNM stage (n) | | | | |
| III | 32 (10.2%) | 10 (9.8%) | 22 (10.4%) | 0.865 |
| IV | 281 (89.8%) | 92 (90.2%) | 189 (89.6%) | |
| Hemoglobin (g/l, median) | 134.00 (123.00–145.00) | 132.00 (118.75–143.25) | 135.00 (125.00–145.00) | 0.124 |
| Erythrocyte count (×10¹²/l, mean) | 4.51±0.52 | 4.47±0.51 | 4.54±0.52 | 0.269 |
| Neutrophil counts (×10⁹/l, median) | 4.85 (3.80–6.33) | 5.31 (4.19–7.07) | 4.59 (3.52–5.83) | 0.001 |
| Lymphocyte count (×10⁹/l, median) | 1.54 (1.21–1.89) | 1.45 (1.17–1.82) | 1.58 (1.29–1.90) | 0.084 |
| Monocyte count (×10⁹/l, median) | 0.47 (0.37–0.66) | 0.56 (0.41–0.82) | 0.45 (0.35–0.60) | <0.001 |
| Thrombocyte counts (×10⁹/l, median) | 263.00 (213.00–322.50) | 267.00 (204.50–335.00) | 259.00 (216.00–316.00) | 0.396 |
| CREA (μmoI/l, median) | 60.00 (51.15–67.00) | 57.82 (49.00–65.08) | 60.90 (52.00–68.40) | 0.043 |
| BUN (mmol/l, median) | 5.20 (4.15–6.91) | 5.10 (4.01–6.65) | 5.27 (4.34–7.10) | 0.286 |
| Globulin (g/l, median) | 29.60 (26.45–33.30) | 30.50 (26.88–34.53) | 29.40 (26.20–32.70) | 0.046 |
| Total bilirubin (μmol/l, median) | 10.20 (7.90–12.95) | 10.18 (7.50–12.73) | 10.40 (7.90–13.30) | 0.581 |
| Alkaline phosphatase (U/l, median) | 93.00 (74.15–126.95) | 107.50 (81.00–176.25) | 91.00 (71.00–112.00) | <0.001 |
| Fasting plasma glucose (mmol/l, median) | 5.20 (4.78–5.93) | 5.31 (4.73–5.90) | 5.29 (4.79–5.94) | 0.875 |
| $Na^+$ (mmol/l, median) | 140.00 (137.60–142.00) | 139.00 (136.48–141.00) | 140.10 (138.00–142.00) | <0.001 |
| $K^+$ (mmol/l, mean) | 4.16±0.42 | 4.18±0.44 | 4.15±0.41 | 0.496 |

Abbreviations: ADR-albumin-to-D-dimer ratio; ECOG-eastern cooperative oncology group; TNM-tumor-node-metastasis; CREA-creatinine; BUN-blood urea nitrogen

with a predominance of male participants. A higher proportion of non-smokers was observed within the high-ADR group as compared to the low-ADR group (64.0% vs. 48.1%, p=0.019). Patients in the high-ADR group exhibited elevated BMI (22.92 vs. 21.97 kg/m², p=0.001), CREA (60.90 vs. 57.82 μmol/l, p=0.043), and $Na^+$ (140.10 vs. 139.00 mmol/l, p<0.001). Conversely, lower levels of neutrophil count (4.59 vs. 5.31×10⁹/l, p=0.001), monocyte count (0.45 vs. 0.56×10⁹/l, p<0.001), globulin (29.40 vs. 30.50 g/l, p=0.046), and alkaline phosphatase (91.00 vs. 107.50 U/l, p<0.001) were observed in comparison to the low-ADR group (Table 1).

**Association of ADR with first-line chemotherapy outcomes.** Following first-line chemotherapy, no patients achieved CR. The high-ADR group exhibited a greater proportion of SD, PR, and a reduced proportion of PD relative to the low-ADR group (p=0.001) (Figure 2A). Compared to the low-ADR group, patients in the high-ADR group demonstrated a higher DCR (96.7% vs. 89.2%, p=0.008) and ORR rates (70.1% vs. 51.0%, p=0.001) (Figures 2B, 2C).

**Prognostic determinants portend patient progression-free survival.** As delineated in Table 2, univariate analyses yielded that ADR (p<0.001), gender (p=0.016), BMI (p=0.023), extent of metastatic organ involvement (p=0.003), hemoglobin (p=0.005), erythrocyte count (p<0.001), neutrophil count (p<0.001), monocyte count (p=0.008), thrombocyte count (p=0.004), alkaline phosphatase (p<0.001), and $Na^+$ (p<0.001) served as prognostic indicators for PFS among the investigated cohort. Variables exhibiting p values below 0.5 in univariate analysis were incorporated into the multivariate analysis.

Multivariate assessment revealed that ADR>16.60 (Hazard ratio [HR]: 0.24, p<0.001), female gender (HR: 0.71,

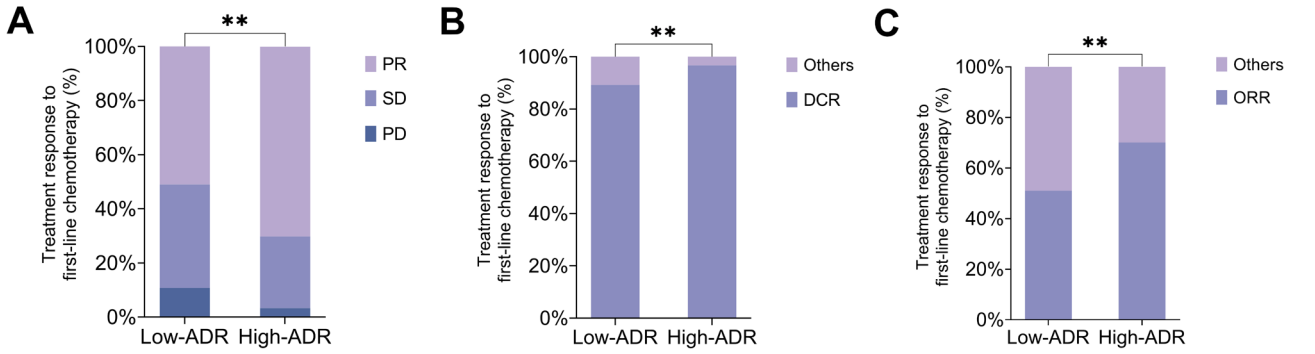


**Figure 2. Association between the pretreatment albumin-to-D-dimer ratio (ADR) and A) progressive disease (PD), stable disease (SD), partial response (PR), B) disease control rate (DCR), and C) overall response rate (ORR). Statistical significance **p<0.01.**

**Table 2. Associations between PFS and ADR alongside additional clinicopathological determinants.**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | p-value | Hazard ratio | 95% CI | p-value |
| Age (>60 years) | 1.09 | 0.84–1.41 | 0.528 | | | |
| Sex (female) | 0.72 | 0.55–0.94 | 0.016 | 0.71 | 0.53–0.95 | 0.020 |
| BMI (≥18.5 kg/m$^2$) | 0.56 | 0.34–0.93 | 0.023 | 0.62 | 0.35–1.11 | 0.107 |
| Smoking (cessation or persistent use) | 1.18 | 0.90–1.52 | 0.24 | | | |
| ECOG (=1) | 1.20 | 0.87–1.65 | 0.267 | | | |
| The quantity of organs impacted by metastatic dissemination (≥ 2) | 1.49 | 1.15–1.96 | 0.003 | 1.28 | 0.97–1.69 | 0.083 |
| TNM stage (IV) | 1.49 | 0.93–2.43 | 0.099 | | | |
| Hemoglobin (<115 g/l) | 1.75 | 1.19–2.62 | 0.005 | 0.93 | 0.55–1.58 | 0.800 |
| Erythrocyte count (≥3.8×10$^{12}$/l) | 0.36 | 0.21–0.63 | <0.001 | 0.41 | 0.20–0.82 | 0.012 |
| Neutrophil count (>6.3×10$^9$/l) | 1.82 | 1.36–2.47 | <0.001 | 1.24 | 0.85–1.8 | 0.270 |
| Lymphocyte count (<1.1×10$^9$/l) | 1.43 | 0.99–2.05 | 0.054 | | | |
| Monocyte count (>0.6×10$^9$/l) | 1.45 | 1.1–1.93 | 0.008 | 0.87 | 0.61–1.23 | 0.433 |
| Thrombocyte count (≤300×10$^9$/l) | 0.67 | 0.51–0.88 | 0.004 | 0.75 | 0.56–1.00 | 0.046 |
| CREA (>81 μmol/l) | 0.66 | 0.4–1.09 | 0.105 | | | |
| BUN (>8.8 mmol/l) | 0.85 | 0.58–1.23 | 0.384 | | | |
| Globulin (>30 g/l) | 1.08 | 0.83–1.4 | 0.558 | | | |
| Total bilirubin (>23 μmol/l) | 2.33 | 0.58–9.48 | 0.233 | | | |
| Alkaline phosphatase (≤135 U/l) | 0.47 | 0.35–0.65 | <0.001 | 0.69 | 0.49–0.97 | 0.033 |
| Fasting plasma glucose (>6.1 mmol/l) | 0.93 | 0.68–1.27 | 0.625 | | | |
| $Na^+$ (≥135 mmol/l) | 0.26 | 0.15–0.46 | <0.001 | 0.45 | 0.25–0.81 | 0.008 |
| $K^+$ (<3.5 mmol/l) | 0.95 | 0.55–1.67 | 0.872 | | | |
| ADR (>16.60) | 0.23 | 0.17–0.32 | <0.001 | 0.24 | 0.17–0.34 | <0.001 |

Abbreviations: ADR-albumin-to-D-dimer ratio; PFS-progression-free survival; ECOG-eastern cooperative oncology group; TNM-tumor-node-metastasis; CREA-creatinine; BUN-blood urea nitrogen

p=0.020), erythrocyte count ≥3.8×10$^{12}$/l (HR: 0.41, p=0.012), thrombocyte count ≤300×10$^9$/l (HR: 0.75, p=0.046), alkaline phosphatase ≤135 U/l (HR: 0.69, p=0.033), and $Na^+$ ≥135 mmol/l (HR: 0.45, p=0.008) independently conferred favorable implications on PFS.

**Association between ADR and progression-free survival.** The median PFS for participants encompassed within this investigation was 215 days. Patients belonging to the high-ADR cohort exhibited a markedly extended median PFS (254 vs. 142 days, p<0.0001) in comparison to their low-ADR counterparts. As delineated in Figure 3, at the 400-day juncture, 18% of high-ADR patients had not yet experienced disease progression, whereas disease progression was observed in 100% of the low-ADR cohort.

A subgroup assessment was employed to ascertain whether ADR values could further prognosticate subpopulations with favorable implications on PFS, derived from the aforementioned multivariate analysis, exhibiting the following demographic attributes: female gender, erythrocyte count ≥3.8×10$^{12}$/l, thrombocyte count ≤300×10$^9$/l, alkaline

phosphatase ≤135 U/l, and $Na^+$ ≥135 mmol/l. Within all subgroups, high-ADR patients consistently demonstrated a prolonged PFS duration relative to the low-ADR group (all p<0.0001) (Figure 4).

## Discussion

Perturbations in inflammation, malnourishment, and coagulation system aberrations frequently manifest in lung carcinoma, portending unfavorable prognostic outcomes [15, 36–39]. Diminished serum albumin concentrations, emblematic of inflammatory and nutritional derangements, correspond to the grim prognosis of numerous virulent neoplasms [22, 40]. Conversely, the elevation in D-dimer levels, indicative of hypercoagulable and inflammatory states, is associated with suboptimal survival across a diverse array of malignancies [41–44]. The composite measure, ADR, encompasses both albumin and D-dimer concentrations, potentially capturing a more comprehensive representation of the concomitant inflammatory, nutritional, and hemostatic perturbations in oncologic patients. Consequently, its accuracy may surpass that of individual albumin and D-dimer assessments. Nevertheless, the extant literature remains sparse in this regard.

To the best of our knowledge, this investigation represents the inaugural exploration of ADR's association with therapeutic responsiveness and prognostic outcomes in advanced LUAD patients undergoing first-line chemotherapeutic intervention. In the present analysis, ROC curve methodology facilitated the determination of an optimal cut-off value, revealing a superior AUC for ADR compared to albumin, D-dimer, and AFR in prognosticating PFS among patients. Consequently, ADR may constitute a more potent prognostic indicator than albumin, D-dimer in isolation, or AFR. The study population was subsequently stratified into high-ADR and low-ADR cohorts according to the designated ADR cut-off values. Notably, both DCR and ORR were markedly elevated in the high-ADR cohort relative to their low-ADR counterparts among patients receiving first-line chemotherapy. In a multivariable assessment, ADR emerged as an independent predictor of PFS in the context of advanced LUAD. Ultimately, survival analyses disclosed a significantly improved prognosis for high-ADR patients

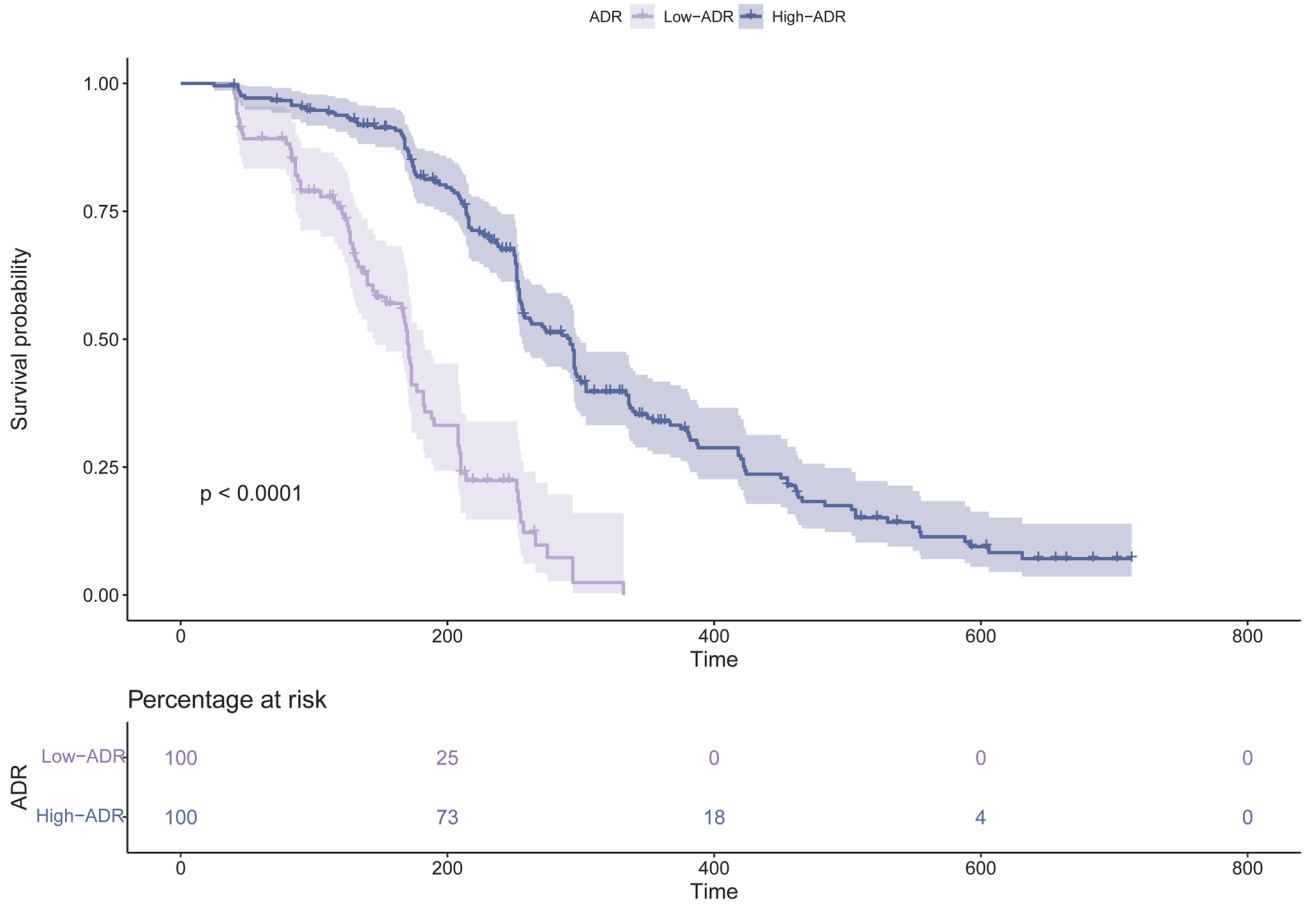


**Figure 3. Kaplan-Meier curves depicting progression-free survival based on different thresholds of the albumin-to-D-dimer ratio (ADR).**

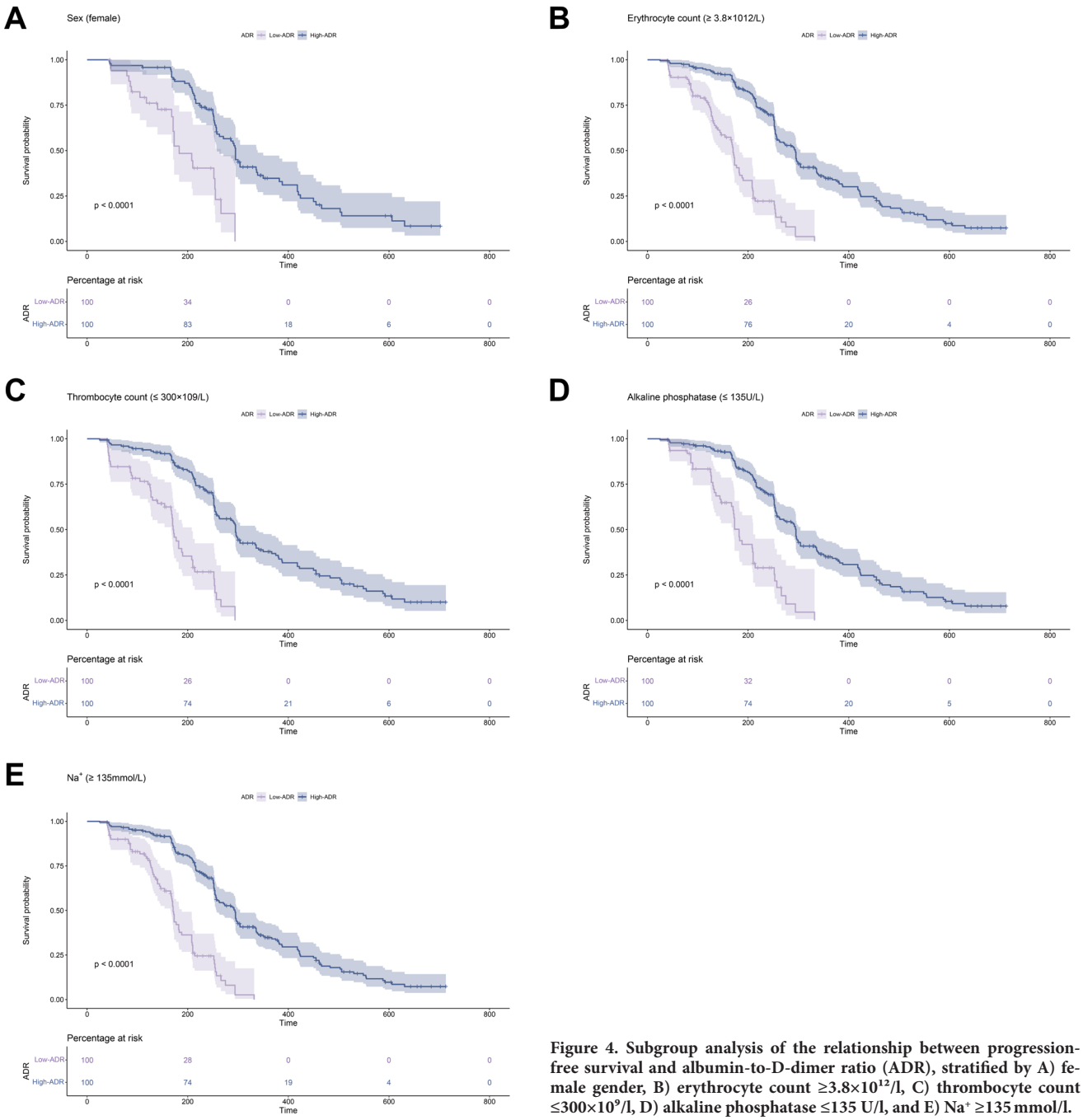


**Figure 4. Subgroup analysis of the relationship between progression-free survival and albumin-to-D-dimer ratio (ADR), stratified by A) female gender, B) erythrocyte count ≥3.8×10$^{12}$/l, C) thrombocyte count ≤300×10$^{9}$/l, D) alkaline phosphatase ≤135 U/l, and E) $Na^{+}$ ≥135 mmol/l.**

compared to their low-ADR counterparts. This observation remained robust even within subgroups exhibiting favorable PFS implications.

Analogous findings have been documented in investigations of alternative neoplastic entities, including nasopharyngeal carcinoma and gastric cancer [32–34]. Nevertheless, the intricate mechanisms underpinning the relationships between ADR and therapeutic responsiveness and prognostic outcomes in oncological contexts remain elusive. Plausibly, exacerbated systemic inflammation, malnourishment, and hypercoagulable states might collectively engender tumorigenesis, disease progression, relapse, metastasis, and chemoresistance, culminating in attenuated survival durations [17–21].

The significance of inflammation in tumorigenesis has been extensively investigated. Inflammatory maladies often

result in the augmented expression of proinflammatory cytokines, such as interleukin-6, tumor necrosis factor, and interleukin-1β, thereby heightening cancer risk [45]. Inflammation is instrumental in the initiation, invasion, and metastasis of neoplasms. An inflammatory milieu teeming with immune cells, chemokines, and cytokines engulfs the tumor, fostering the expansion of malignant cells. These factors, generated by neoplastic cells or their adjacent tissues, precipitate malignant progression. During tumorigenesis, inflammation may facilitate neoplasm proliferation and metastasis by inhibiting apoptosis and stimulating angiogenesis [46]. Chemotherapy-induced inflammation is a frequent occurrence in oncological therapy, potentially leading to tumor-acquired resistance, therapeutic failure, and metastasis [47, 48]. Prior research has indicated that attenuating inflammatory responses might enhance the prognosis of neoplastic patients [45]. It has been documented that D-dimer levels markedly rise in the context of inflammatory disorders [49, 50]. Concurrently, inflammation impedes albumin synthesis, culminating in reduced albumin concentrations [51].

Malnutrition preceding therapy manifests in 26–40% of lung carcinoma cases, contingent upon the evaluative instrument employed – the Nutritional Status Assessment Questionnaire: Subjective Global Assessment (SGA), Patient-Generated SGA, or Mini Nutritional Assessment [52–54]. Anorexia is a predominant symptom among lung cancer patients, with up to 98% of individuals with advanced disease reporting this affliction [55]. The malnourished state, attributable to inadequate nutrient ingestion or aberrant absorption, adversely influences survival prognosis, quality of life, and treatment-induced sequelae [52, 54]. Investigations conducted on patients awaiting pulmonary carcinoma surgery revealed that malnourished individuals experienced diminished survival duration and elevated postoperative complication risk compared to those with optimal nutritional status [56, 57]. Fortunately, reports indicate that lung cancer patients can derive benefits from nutritional amelioration following targeted nutritional support [58]. Albumin, an indicator reflecting patients' nutritional status, contributes to cellular growth stabilization, DNA replication, diverse biochemical change buffering, and functions as an antioxidant against carcinogens [59]. As the most copious serum protein, albumin serves as a valuable biomedicine factor in determining patients' nutritional condition.

Blood coagulation activation in early-stage lung cancer patients influences the clinical trajectory of the malignancy [60]. Constituents of the fibrinolytic and coagulation systems may facilitate tumor cell proliferation, survival, and angiogenesis [20, 21]. Thrombin and additional enzymes within the coagulation cascade can promote angiogenesis, augmenting oxygen and nutrient supply via the bloodstream to the tumor, thereby fostering tumor growth [61]. Antigens have been reported to play a crucial role in lung cancer, exerting not only antithrombotic effects but also enhancing patient prognosis [62, 63]. In this investigation, we determined that ADR exhibits superior prognostic predictive capacity compared to AFR for advanced LUAD (AUC: 0.805 vs. 0.640, DeLong test: $p<0.001$), potentially due to fibrinogen undergoing conversion into fibrin, which subsequently cross-links and degrades into D-dimer. Considering the protracted nature of tumor progression to advanced stages, fibrinogen may initially be converted exclusively into fibrin during the neoplasm's incipient phase, with fibrin subsequently cross-linking and degrading into D-dimer during the advanced phase. As this study's research subjects are all patients with advanced LUAD, D-dimer proves superior to fibrinogen in predicting patient outcomes, and our findings corroborate this assertion. We observed that the AUC value for D-dimer is significantly greater than that of fibrinogen (0.795 vs. 0.602). However, elucidating the underlying mechanism necessitates further investigation.

As delineated herein, individuals afflicted with malignant pathologies frequently exhibit chronic inflammation, compromised nutritional status, and a hypercoagulable milieu. Diminished albumin concentrations indicate pervasive inflammation and pronounced malnourishment, whereas elevated D-dimer levels correlate with exacerbated inflammatory responses and coagulation aberrations. In this investigation, the amalgamation of albumin and D-dimer, as opposed to their independent assessment, facilitated the enhanced prognostic capacity of ADR in determining survival outcomes for advanced LUAD patients.

Our study boasts several merits. Primarily, this constitutes the inaugural report highlighting ADR's capacity to prognosticate the efficacy of first-line chemotherapy and PFS in advanced LUAD patients. Secondly, the study's results revealed that ADR possessed a superior AUC value compared to albumin and D-dimer alone, potentially attributable to ADR encapsulating a composite of inflammatory, nutritional, and coagulative patient indicators, thereby augmenting its prognostic prowess. This marks the first instance wherein ADR superseded albumin and D-dimer as a prognostic factor for PFS. Thirdly, even within subpopulations demonstrating favorable PFS implications via multivariate analysis, ADR remains a robust prognostic determinant. These insights may prompt clinicians to focus on patients who may otherwise be overlooked due to ostensibly favorable prognostic indicators. Clinicians might be able to use ADR values as one of several tools to inform predictions about treatment responses, potentially allowing for more individualized treatment plans for LUAD patients. Our results suggest that higher ADR values could be indicative of a better prognosis and a more favorable response to certain chemotherapeutic agents. Conversely, lower ADR values might suggest a need for alternative treatment strategies, possibly including more aggressive or different chemotherapy combinations, earlier intervention with targeted therapies, or inclusion in clinical trials for new therapeutic agents. Additionally, the attributes of ADR, such as its cost-effectiveness, accessibility, and reproducibility, could, in the future, offer valuable advantages for

its application as a prognostic tool, pending further research to confirm its efficacy.

Despite these strengths, the current study is not without limitations. Initially, the retrospective and single-center nature of this investigation necessitates further prospective research. Additionally, the study's modest sample size calls for expanded, multicenter investigations to corroborate findings.

In conclusion, the ADR demonstrated a correlation with DCR and ORR rates following first-line chemotherapy and PFS. ADR levels may serve as a facile, non-invasive clinical prognostic biomarker in advanced LUAD patients.

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