

# Association of *Spatholobus littoralis* Hassk Supplementation with Nutritional Indices and Survival Outcomes in EGFR Wild-Type Lung Adenocarcinoma

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## Abstract

**Introduction:** *Spatholobus littoralis* Hassk. is a natural antioxidant that may help support clinical outcomes in cancer patients. In EGFR wild-type lung adenocarcinoma, where therapeutic options and prognosis remain limited, nutritional status may play an important prognostic role, yet clinical evidence in this setting is scarce. This study evaluated the association of adjunctive *S. littoralis* supplementation with nutritional indices and survival outcomes. **Materials and Methods:** A prospective cohort study was conducted at Ulin General Hospital, Banjarmasin, Indonesia, from May 2023 to May 2024, with follow-up through May 2025. Eligible patients with stage IIIB or higher EGFR wild-type adenocarcinoma received platinum–pemetrexed chemotherapy, with or without *S. littoralis* extract (1000 mg three times daily). Nutritional indices the Prognostic Nutritional Index (PNI) and Controlling Nutritional Status (CONUT) were evaluated before and after three chemotherapy cycles. Comparative analyses were performed using appropriate parametric and non-parametric tests. Primary outcomes were  $\Delta$ PNI,  $\Delta$ CONUT, and progression-free survival (PFS), while overall survival (OS) was treated as a secondary outcome. Survival analyses were conducted using Kaplan–Meier curves with log-rank tests. **Results:** A total of 21 patients with EGFR wild-type lung adenocarcinoma were included. Patients receiving *S. littoralis* supplementation showed non-significant improvements in PNI ( $42.93 \pm 7.93$  to  $46.74 \pm 7.51$ ;  $p = 0.128$ ) and reductions in CONUT scores (1 [0–5] to 1 [0–3];  $p = 0.358$ ) after chemotherapy. However, between-group analysis revealed significantly greater improvement in the *S. littoralis* group, reflected by higher  $\Delta$ PNI (+3.81 vs. –2.21;  $p = 0.043$ ) and lower  $\Delta$ CONUT (–1.36 vs. +0.6;  $p = 0.042$ ). Median PFS was significantly longer in the treatment group (7 vs. 3 months;  $p = 0.012$ ), while OS did not differ (7 vs. 7 months;  $p = 0.542$ ). **Conclusion:** *Spatholobus littoralis* Hassk. supplementation was associated with improved  $\Delta$ PNI,  $\Delta$ CONUT and longer PFS. These findings support its potential as a natural immunonutritional adjuvant in lung cancer care. Larger multicenter trials are required to confirm these findings.

**Keywords:** lung adenocarcinoma- *Spatholobus littoralis* Hassk- Prognostic Nutritional Index- Controlling Nutritional Status

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## Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with adenocarcinoma being the most common histologic subtype of non-small cell lung cancer (NSCLC) [1, 2]. Among its molecular variants, EGFR wild-type tumors show poorer differentiation, limited therapeutic options, and worse prognosis compared to EGFR-mutant types [3]. Beyond tumor-related factors,

nutritional status has been increasingly recognized as an important determinant of treatment response, quality of life, and survival outcomes in lung cancer patients [4]. Malnutrition and cancer cachexia are prevalent in advanced disease and are driven by systemic inflammation and metabolic alterations mediated by cytokines such as TNF- $\alpha$  and IL-6 [5].

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Malnutrition is frequently observed in cancer patients receiving chemotherapy, highlighting the need for routine nutritional monitoring during treatment [6]. Prognostic Nutritional Index (PNI) and Controlling Nutritional Status (CONUT) are simple, blood-based indicators that reflect immune and nutritional conditions. They have been reported as prognostic markers in advanced NSCLC, including associations with progression-free survival (PFS) and overall survival (OS) [7-9].

*Spatholobus littoralis* Hassk (bajakah tampala), a traditional medicinal plant native to Kalimantan, Indonesia, contains high levels of flavonoids, saponins, tannins, and polyphenols with potent antioxidant properties [10]. A review highlighted the complexity of synthetic antioxidant use and recommended prioritizing natural dietary sources, given the controversial outcomes of single-agent supplements such as beta-carotene and vitamin E, which may disrupt physiological redox balance [11]. However, the potential role of *S. littoralis* in improving nutritional or clinical outcomes in lung cancer has not yet been evaluated.

This study was conducted to evaluate whether adjunctive *S. littoralis* supplementation could improve PNI and CONUT values and contribute to better PFS or OS in patients with EGFR wild-type lung adenocarcinoma receiving platinum-based chemotherapy.

## Material and Methods

This prospective cohort study analyzed medical records of patients with histologically confirmed EGFR wild-type lung adenocarcinoma treated at Ulin General Hospital, Banjarmasin, Indonesia, between May 2023 and May 2024, with follow-up until May 2025. Eligible patients were  $\geq 18$  years old and had stage IIIB or higher EGFR wild-type lung adenocarcinoma. All patients completed at least three cycles of either carboplatin–pemetrexed or cisplatin–pemetrexed chemotherapy. The treatment group received adjunctive *Spatholobus littoralis* Hassk (bajakah) at a dose of 1000 mg three times daily during chemotherapy cycles 1–3, and supplementation was not continued beyond the third cycle.

Clinical, laboratory, and imaging data including hematologic profiles, serum albumin, total cholesterol, and CT findings were obtained before and after chemotherapy. Pathological examination confirmed adenocarcinoma in all cases, which may generally exhibit acinar, solid, and lepidic architectural patterns, as well as occasional micropapillary components. Tissue specimens were obtained through bronchoscopic biopsy or CT-guided core needle biopsy and processed as formalin-fixed paraffin-embedded (FFPE) blocks; Cytology-only samples were included for diagnostic confirmation when tissue biopsy was non-diagnostic or contraindicated, and were processed into cell blocks to allow EGFR mutation testing. Mutational analysis covered exons 18–21 and was conducted using DNA-extraction with the Qiagen QIAamp DNA Micro Kit, mutation analysis by PCR–HRM, fragment analysis, direct sequencing, and Idylla™ platform 100% specificity; EGFR mutation testing was

performed on FFPE tumor tissue with a minimum tumor cell content of  $\geq 10\%$ , with macrodissection undertaken when needed.

The Prognostic Nutritional Index (PNI) was calculated as  $(10 \times \text{albumin [g/dL]}) + (0.005 \times \text{lymphocyte count [}/\text{mm}^3\text{)})$ , while the Controlling Nutritional Status (CONUT) score (0–12) was derived from serum albumin, lymphocyte count, and total cholesterol, and categorized as Low (0–1) or High ( $\geq 2$ ). Progression-Free Survival (PFS) was defined as the time from treatment initiation to disease progression or death, and Overall Survival (OS) as the time from treatment start to death from any cause.

## Statistical Analysis

Statistical analyses were performed using SPSS 26.0. Continuous variables were summarized as means with standard deviations or medians with interquartile ranges based on distribution. Given the small sample size and limited reliability of normality testing, both parametric and non-parametric methods were used: paired t-tests or Wilcoxon signed-rank tests for within-group comparisons, and independent t-tests or Mann–Whitney U tests for between-group comparisons. In addition to p-values, 95% confidence intervals were reported, and effect sizes were estimated using Hedges' g for between-group comparisons of change scores ( $\Delta$ PNI and  $\Delta$ CONUT) to account for small sample size. Survival analyses were performed using Kaplan–Meier curves with log-rank tests. An exploratory Cox proportional hazards regression analysis was conducted to estimate hazard ratios (HRs) with 95% confidence intervals.

Patients who were lost to follow-up were censored at the date of their last documented clinical contact. No assumptions were made regarding their survival status beyond that point. A flow summary of patient inclusion, exclusions, and follow-up completion was provided to clarify case handling.

## Ethical

This study received ethical approval from the Health Research Ethics Committee, Faculty of Medicine and Health Sciences, Lambung Mangkurat University, Banjarmasin, Indonesia, with approval number No.112/KEPK-FKIK ULM/EC/VII/2024. In addition, research permission was granted by the Research and Development Division of Ulin General Hospital, Banjarmasin, Indonesia, with approval number No.144/Pulmonologi/Litbang/RSUDU/VII/2024. The principal investigator has been certified in Good Clinical Practice (GCP) to ensure adherence to international ethical and scientific quality standards.

## Results

This prospective cohort study evaluated the effect of adjunctive *Spatholobus littoralis* Hassk. supplementation on nutritional status and survival outcomes in patients with EGFR wild-type lung adenocarcinoma undergoing platinum-based chemotherapy.

Table 1. Characteristics of Research Subjects

Patients Characteristics	Control n (%)	Treatment n (%)	Total	P value
Age, mean±SD (year)	57±10.8	56.5±9.5	56.8±10.0	0.912 <sup>a</sup>
Gender				1.000 <sup>b</sup>
Male	7 (70)	7 (63.6)	14 (66.7)	
Female	3 (30)	4 (36.4)	7 (33.3)	
BMI, mean±SD	18.6±2.4	20.8±4.2	19.8±3.6	0.160 <sup>a</sup>
Smoking Status				0.659 <sup>b</sup>
Yes	7 (70)	6 (54.5)	13 (61.9)	
No	3 (30)	5 (45.5)	8 (38.1)	
Family History of Cancer				-
Yes	0 (0)	0 (0)	0 (0)	
No	10 (100)	11 (100)	21 (100)	
Stage				0.905 <sup>b</sup>
IIIB	3 (30)	2 (18)	5 (23.8)	
IVA	4 (40)	6 (55)	10 (47.6)	
IVB	3 (30)	3 (27)	6 (28.6)	
Metastasis Location				-
Pleural Effusion	5 (50)	8 (72)	13 (61.9)	
Pericardial Effusion	1 (10)	1 (9)	2 (9.5)	
Liver	0 (0)	2 (18)	2 (9.5)	
Bone	2 (20)	0 (0)	2 (9.5)	
Brain	0 (0)	2 (18)	2 (9.5)	
ECOG				1.000 <sup>b</sup>
1	3 (30)	4 (36)	7 (33.3)	
2	7 (70)	7 (64)	14 (66.7)	
Chemotherapy				1.000 <sup>b</sup>
Carboplatin-pemetrexed	8 (80)	8 (73)	16 (76.2)	
Cisplatin-pemetrexed	2 (20)	3 (27)	5 (23.8)	

<sup>a</sup>Independent t-test, <sup>b</sup>Fisher-exact test, PNI: Prognostic Nutritional Index, CONUT: Controlling Nutritional Status

### Study Characteristics

This study enrolled 21 EGFR wild-type lung adenocarcinoma patients in Table 1, stratified into control (n=10) and treatment (n=11) groups. Mean age was 56–57 years, with males predominating (66.7%). Mean BMI was normal in both groups (control: 18.6±2.4 kg/m<sup>2</sup>; treatment: 20.8±4.2 kg/m<sup>2</sup>). Smoking history was prevalent (61.9%), with no familial malignancy reported. Comorbidities included diabetes mellitus (9.5%), hypertension (14%), and cardiovascular disease (9.5%). Most patients presented with stage IVA disease (47.6%), followed by stages IIIB and IVB. Pleural effusion was the most common metastatic site (61.9%), followed by cerebral and hepatic metastases.

### Nutritional indices

Based on Table 2, the control group showed a decline in mean PNI from 46.53 ± 2.48 before chemotherapy to 44.32 ± 2.15 after chemotherapy (p = 0.106). Conversely, the treatment group receiving *S. littoralis* demonstrated an increase in PNI from 42.93 ± 7.93 to 46.74 ± 7.51 (p = 0.128) and regarding CONUT scores, the control

group experienced an increase from a median of 1 (IQR 0–3) to 2.5 (0–4) (p = 0.241), indicating a deterioration in nutritional status. In contrast, the treatment group showed an improvement, with CONUT decreasing from 1 (0–5) to 1 (0–3) (p = 0.358). Although not statistically significant, these changes suggest that *S. littoralis* supplementation may help preserve nutritional status during chemotherapy.

### Between-group comparison

When compared to the control group (Table 3), patients receiving *S. littoralis* showed a significant improvement in nutritional indices. The mean change in PNI increased by +3.81 ± 7.63 in the treatment group versus a decline of -2.21 ± 4.52 in the control group (p = 0.043). Likewise, the CONUT score decreased significantly in the treatment group (-1.36 ± 2.11) compared to an increase in the control group (+0.6 ± 2.01, p = 0.042). The magnitude of effect estimates was substantial (Hedges' g ≈ 0.91), although these estimates should be interpreted cautiously given the small sample size.

Table 2. Nutritional Status Pre and Post Chemotherapy 3 Cycle

Variable	Control		P value	Treatment		P value
	Pre	Post		Pre	Post	
PNI, mean±SD	46.53±2.48	44.32±2.15	0.106 <sup>a</sup>	42.93 ± 7.93	46.74 ± 7.51	0.128 <sup>a</sup>
CONUT, median (IQR)	1 (0-3)	2.5 (0-4)	0.241 <sup>γ</sup>	1 (0-5)	1 (0-3)	0.358 <sup>γ</sup>

<sup>a</sup>Paired t-test, <sup>γ</sup>Wilcoxon test, PNI: Prognostic Nutritional Index, CONUT: Controlling Nutritional Status

Table 3. Nutritional Status Comparison

Variable	Control	Treatment	95% CI	Effect Size (Hedges' g)	P value
Change in PNI	-2.21 ±4.52	+3.81±7.63	0.21 – 11.82	0.91	0.043
Change in CONUT	+0.6±2.01	-1.36 ±2.11	-3.85 to -0.08	0.912	0.042

Unpaired t-test, 95% CI: 95% Confidence Interval; PNI: Prognostic Nutritional Index, CONUT: Controlling Nutritional Status

### Survival outcomes

Kaplan–Meier analysis (Table 4, Figure 1) demonstrated a significant improvement in progression-free survival (PFS) among patients receiving *S. littoralis* (median 7 months, 95% CI: 2.68–11.32) compared with controls (median 3 months, 95% CI: 3.0–5.0;  $p = 0.012$ ). However, no significant difference was observed in overall survival (OS) between the groups (median 7 months in both;  $p = 0.542$ ). Consistent with the Kaplan–Meier findings, Cox proportional hazards regression demonstrated that patients in the control group had a significantly higher risk of progression than those in the treatment group (HR 2.99, 95% CI 1.10–8.15;  $p = 0.032$ ), whereas no significant association was observed for OS (HR 1.35, 95% CI 0.49–3.75;  $p = 0.576$ ). This discrepancy should be interpreted cautiously. Because supplementation was limited to the first three chemotherapy cycles, any biological effect may have been transient or insufficient to influence longer-term outcomes. Alternatively, the observed PFS improvement may represent a fragile early signal or a chance finding, particularly given the small sample size and potential residual confounding.

Overall, the survival differences observed in this study should be regarded as exploratory. The small sample size limits statistical precision and increases susceptibility to random variation, while the very limited number of progression and mortality events produces wide and occasionally unstable confidence intervals. These constraints lead to imprecise Kaplan–Meier estimates that may be highly sensitive to single observations, and the survival results should therefore be interpreted with caution.

Importantly, the observational design and lack of comprehensive multivariable adjustment preclude causal inference. Although exploratory models adjusting for ECOG performance status and clinical stage were performed, residual confounding from unmeasured

clinical, pathological, or treatment-related factors is likely. As such, the associations between *S. littoralis* supplementation, immunonutritional indices, and PFS should be interpreted as correlational rather than causal.

### Nutritional status and survival correlation

Considering that the ROC analysis demonstrated poor discriminative performance of PNI for both progressive status (AUC = 0.389) and outcome status (AUC = 0.107), these results should not be interpreted as diagnostic or predictive models. Therefore, a literature-based PNI cut-off of 52 was applied, supported by a meta-analysis by Li et al. and a large cohort study by Qiu et al. involving 1,416 patients with NSCLC [8]. Patients were subsequently categorized into two PNI groups for comparative analysis (see Supplementary Table S1). Post-chemotherapy PNI status showed no significant association with PFS or OS, with median PFS of 6 months (95% CI: 0.156–11.844) in the PNI≤52 group versus 8 months (95% CI: 8–20) in the PNI>52 group ( $p = 0.340$ ), and median OS of 6 months (95% CI: 0.559–13.441) in the PNI≤52 cohort while no deaths occurred in the PNI>52 group during follow-up. Similarly, post-chemotherapy CONUT status did not significantly correlate with survival outcomes (see supplementary Table S2), as the low-CONUT group demonstrated a median PFS of 7 months (95% CI: 3.901–10.099) compared with 4 months in the high-CONUT group ( $p = 0.260$ ), with OS showing a similar pattern (7 vs. 4 months;  $p = 0.186$ ). Kaplan–Meier curves (Figure 2) show numerically longer PFS and OS among patients with higher post-chemotherapy PNI (>52) and lower CONUT scores (0–1), although these differences were not statistically significant.

Table 4. PFS vs OS Between Control and Treatment Group

Variabel	Control	Treatment	Log-rank p	HR (95% CI)	Cox p
PFS, MST (95%CI), months	3 (3-5)	7 (2.684-11.316)	0.012	2.99 (1.10-8.15)	0.032
OS, MST (95%CI), months	7 (2.351-11.649)	7 (0-18.476)	0.542	1.35 (0.49-3.75)	0.576

PFS: progression-free survival, OS: overall survival, MST: median survival time

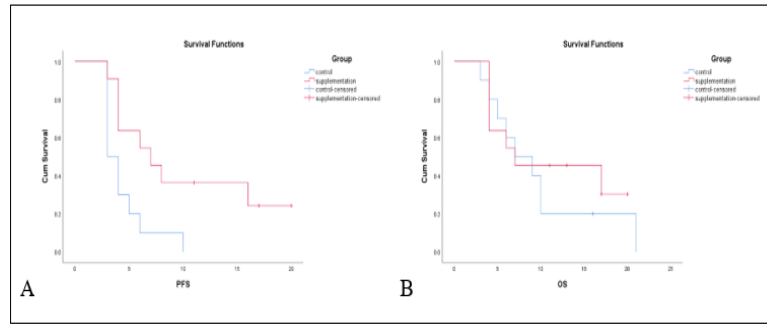


Figure 1. Kaplan–Meier Survival Curves Comparing (A) Progression-free Survival (PFS) and (B) Overall Survival (OS) between the Control and *Spatholobus Littoralis* Hassk Supplementation Groups. The supplementation group was associated with longer PFS compared with the control group (log-rank  $p = 0.012$ ), whereas no significant difference in OS was observed (log-rank  $p = 0.542$ ).

## Discussion

This prospective cohort study suggests that adjunctive *Spatholobus littoralis* Hassk. supplementation may help preserve immunonutritional status and delay disease progression in patients with EGFR wild-type lung adenocarcinoma receiving platinum–pemetrexed chemotherapy. Although baseline characteristics appeared broadly similar between groups, the small sample size limits the ability to establish true baseline equivalence. Residual confounding from unmeasured clinical or pathological factors may therefore remain.

PNI and CONUT are widely recognized immunonutritional indices associated with systemic inflammation, nutritional reserve, and survival outcomes in NSCLC. Prior studies report commonly used thresholds between 45–53 for PNI and  $<2$  for low CONUT scoring, with low PNI and elevated CONUT consistently linked to poorer prognosis [12–14]. The predominance of mild malnutrition and generally preserved immunonutritional status in this cohort aligns with earlier data showing that many advanced adenocarcinoma patients maintain relatively favorable baseline indices [8, 9].

In this study, patients receiving *S. littoralis* demonstrated improved  $\Delta$ PNI and  $\Delta$ CONUT compared

with controls, alongside a longer median PFS. These findings raise the possibility that preservation of nutritional and inflammatory balance may contribute to better tolerance of chemotherapy or slower disease progression. However, the biological plausibility remains speculative. This study did not assess pharmacokinetic, mechanistic, or biomarker outcomes, and evidence for antioxidant, immunomodulatory, or antitumor activity of *S. littoralis* is derived primarily from in vitro and in silico studies demonstrating cytotoxicity, flavonoid-mediated antioxidant effects, or STAT3-related interactions [15–17]. These experimental data provide theoretical support but do not establish the mechanisms through which *S. littoralis* may influence clinical trajectories in humans.

Despite the observed PFS difference, no significant OS benefit was detected. This is not unexpected, as OS is strongly influenced by post-progression therapies, access to second-line regimens [18], treatment adherence, and supportive care factors that were not fully captured in this study. The limited and short duration of supplementation (restricted to cycles 1–3) may also have resulted in a transient biological effect insufficient to influence long-term survival. Alternatively, the PFS improvement may represent an early fragile signal or a chance observation,

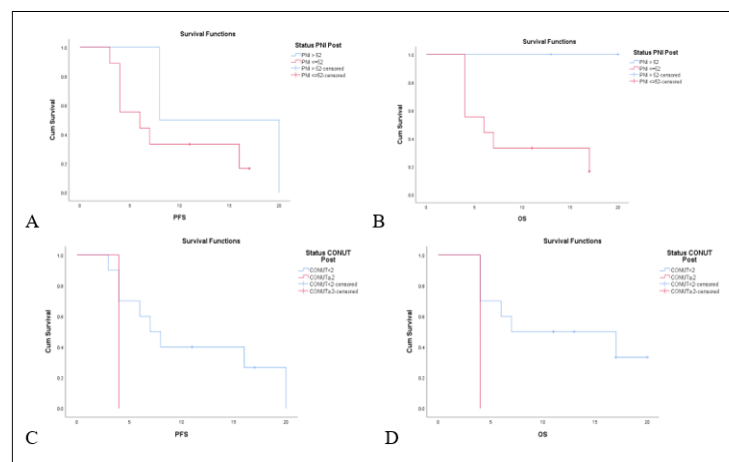


Figure 2. Kaplan–Meier Survival Curves Comparing (A) Progression-free Survival (PFS) and (B) Overall Survival (OS) between Patients with Post-chemotherapy PNI  $>52$  and PNI  $\leq 52$ . No significant differences were observed for either PFS (log-rank  $p = 0.340$ ) or OS (log-rank  $p = 0.104$ ). Kaplan–Meier survival curves comparing (C) PFS and (D) OS between patients with low CONUT (0–1) and high CONUT ( $\geq 2$ ) status also showed no significant differences (PFS: log-rank  $p = 0.260$ ; OS: log-rank  $p = 0.186$ ).

particularly given the small number of events and the potential for residual confounding.

Subgroup analyses based on post-chemotherapy PNI and CONUT values did not yield statistically significant associations with PFS or OS, though numerical trends favored higher PNI and lower CONUT. Prior meta-analyses consistently link reduced PNI and elevated CONUT to worse clinical outcomes in NSCLC [8–10, 19, 20], but the limited sample, wide confidence intervals, and event scarcity in this cohort reduce the reliability of subgroup estimates. The ROC analysis further illustrated instability, yielding an AUC < 0.5, which is likely attributable to the small number of events and should therefore be interpreted purely as exploratory. Literature-based thresholds were consequently used rather than data-derived cut-offs.

The survival analyses must also be interpreted with caution. The wide and sometimes unstable confidence intervals reflect the very small number of progression and mortality events, leading to imprecise Kaplan–Meier estimates that are highly sensitive to single observations.

In addition, Cox proportional hazards regression was performed as an exploratory approach to estimate hazard ratios; however, no comprehensive multivariable adjustment was undertaken. The observational design and absence of comprehensive multivariable adjustment further limit causal inference. The associations observed between supplementation, nutritional indices, and PFS should therefore be interpreted as correlational rather than causal.

This study has additional limitations. Pathological factors such as detailed histologic patterns, primary tumor burden, and metastatic distribution were not formally quantified. Treatment-related details including number of cycles completed, dose reductions or delays, and supportive care utilization were also not systematically recorded, despite their potential influence on nutritional indices and survival outcomes. Routine testing for ALK, ROS1, and PD-L1 was not available, limiting molecular characterization. The small sample size, and multiple exploratory statistical comparisons further increase the risk of type I error and reduce the reliability of significance testing. Loss to follow-up introduces the possibility of non-random censoring and selection bias, given that censoring was based solely on the last available clinical encounter.

Taken together, this study provides preliminary evidence that *S. littoralis* supplementation may help maintain immunonutritional indices and delay disease progression in EGFR wild-type lung adenocarcinoma receiving platinum-based chemotherapy. However, these findings must be interpreted cautiously given the exploratory design, small sample size, limited event numbers, and potential residual confounding. Larger, adequately powered randomized trials with integrated mechanistic evaluations are required to validate these preliminary observations.

### Limitation

This study has several limitations. First, the small sample size reduces statistical power and limits the reliability of subgroup analyses, increasing the likelihood of type I and type II errors. As a pilot exploratory cohort without a formal power calculation, all findings should be viewed as hypothesis-generating.

Second, several potential confounders were not fully captured, including detailed pathological factors (such as precise histologic architecture, primary tumor burden, and metastatic distribution) and treatment-related variables (including chemotherapy dose intensity, cycle completion, and use of supportive care). These unmeasured elements may influence both survival outcomes and immunonutritional indices.

Third, molecular profiling was incomplete, as testing for biomarkers such as ALK rearrangements, ROS1 fusions, and PD-L1 expression was not routinely performed and depended on test availability during the study period. The lack of comprehensive molecular characterization limits the interpretation of prognostic heterogeneity within the cohort.

Fourth, the short and discontinuous duration of supplementation restricted to chemotherapy cycles 1–3 may have yielded transient effects insufficient to influence long-term outcomes. Differences in post-progression therapies, which were not standardized, may also have contributed to variability in overall survival.

Lastly, loss to follow-up raises the possibility of non-random censoring and selection bias, as patients with incomplete follow-up were censored at their last recorded visit. The very small number of events further amplifies the instability of survival estimates and widens confidence intervals.

In conclusion, adjunctive *Spatholobus littoralis* Hassk. supplementation was associated with improved PNI and CONUT scores and longer PFS in patients with EGFR wild-type lung adenocarcinoma undergoing platinum based chemotherapy. Although overall survival did not differ significantly between groups, the observed associations with improved nutritional indices and longer progression free survival need for further investigation in larger, well-designed studies. Such studies are required to validate these findings and to better define the clinical relevance of *S. littoralis* in advanced lung cancer.

### Declarations

#### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

#### Clinical Trial Registration

Not applicable.

#### Conflicts of Interest / Competing Interests

The authors declare that they have no conflicts of interest.

### Availability of Data and Material

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

### Code Availability

Not applicable.

### Authors' Contributions

F.R.A. contributed to the study conception, design, clinical evaluation, perform data analysis, and final drafting of the manuscript. H.H. contributed to the study conception, verified the clinical data, and final drafting. A.A., I.N., and M.I. provided critical input on statistical interpretation and manuscript final drafting. All authors critically reviewed the manuscript and approved the final version for submission.

### Ethics Approval

This study was approved by the Ethics Committee of the Faculty of Medicine, Lambung Mangkurat University.

### Consent to Participate

Written informed consent was obtained from all participants prior to enrollment, and the study was conducted in accordance with the Declaration of Helsinki.

### Consent for Publication

Not applicable

### Originality Declaration for Figures

All figures included in this manuscript are original and were created by the authors specifically for this study. No previously published or copyrighted images were used.

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### Declaration on Generative AI and AI-Assisted Technologies in the Writing Process

Generative AI and AI-assisted technologies were used solely for grammatical editing. The authors reviewed and edited the final manuscript and take full responsibility for its content and originality.

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