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ORIGINAL RESEARCH

Prognostic Usefulness Of Advanced Lung Cancer Inflammation Index In Locally-Advanced Pancreatic Carcinoma Patients Treated With Radical Chemoradiotherapy

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Background/Aims: Previously advanced lung cancer inflammation index (ALI) has been demonstrated to have prognostic utility in the stratification of patients into distinctive survival groups, but the prognostic value of ALI has never been explored in the setting of locally advanced pancreatic carcinomas (LAPC) treated with concurrent chemoradiotherapy (CCRT). Hence, we aimed to investigate the prognostic value of pre-treatment ALI in LAPC patients who underwent radical CCRT.

Methods: Present retrospective cohort analysis incorporated 141 LAPC patients who received radical CCRT. Accessibility of baseline ALI cutoff(s) impacting survival outcomes was sought by receiver operating characteristic (ROC) curve analysis. Interaction between the ALI and overall- (OS) and progression-free survival (PFS) comprised our primary and secondary endpoints, respectively.

Results: At a median follow-up of 14.4 months (range: 3.2–74.2), the median PFS and OS were 7.5 (%95 CI: 5.9–9.1) and 14.6 months (%95 CI: 11.6–17.6), respectively. ROC curve analyses set the ideal ALI cutoff value at 25.3 (AUC: 75.6%; sensitivity: 72.7%; specificity: 70.3%) that exhibited significant associations with both the OS and PFS results. Patient stratification into two groups per ALI [≤25.3 (N=75) versus>25.3 (N=66)] showed that the ALI>25.3 group had significantly superior median OS (25.8 versus 11.4 months; P<0.001) and PFS (15.9 versus 6.0 months; P<0.001) durations than its ALI≤25.3 counterpart. Other factors exhibiting significantly better OS and PFS rates were N_0 stage (versus N1; P<0.05 for each endpoint) and CA 19-9 ≤90 U/mL (versus >90 U/mL; P<0.05 for each endpoint), respectively. These three factors were additionally asserted to be independent indicators of longer OS (P<0.05 for each) and PFS (P<0.05 for each) in multivariate analyses.

Conclusion: Results of this hypothesis-generating research proposed the pre-CCRT ALI as a novel robust associate of OS and PFS outcomes for LAPC patients undergoing CCRT.

Keywords: locally-advanced pancreas cancer, advanced lung cancer inflammation index, concurrent chemoradiotherapy, prognosis, survival outcomes

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Introduction

Pancreatic carcinoma (PC) is one of the leading sources of cancer-related mortality in Europe and the United States, with overall annual incidence and mortality rates being practically equivalent.[1,2] Although the radical surgery offers the best cure chance, only 20% of all PCs present with resectable disease, while remaining 30%

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and 50% are diagnosed with an unresectable locally advanced- (LAPC) or metastatic PCs, respectively.[3] Sequential chemoradiotherapy and definitive concurrent chemoradiotherapy (CCRT) are the two current treatment choices for medically fit LAPC patients,[4,5] but sadly, the prognosis of such patients remains still grim with an expected median survival of only around 1 year or indeed less even with such aggressive treatments.[2,6]

Pointing out its critical roles in initiation, progression and dissemination steps of carcinogenesis; inflammation has been appreciated as the seventh hallmark of cancer as it can facilitate the acquisition of other hallmarks.[7] Therefore, inflammation is relevant both as a risk factor for cancer development and as a reactionary process of cancer: patients with chronic pancreatitis carry a 13-fold higher risk of PC development.[8] Furthermore, considerable amounts of evidence proposed the systemic inflammation as a basic factor underlying the distinctive patient prognoses following indistinguishable treatment schemes.[9–14] Hence, the prognostic worth of various systemic inflammation markers has been explored in PC patients; including the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), Glasgow prognostic score (GPS), prognostic nutritional index (PNI), and systemic inflammation response index (SIRI).[15–23]

Recently, Jafri et al reported the advanced lung cancer inflammation index (ALI) as another useful prognosticator in metastatic non-small-cell lung cancer patients,[24] which has been subsequently shown to exert comparable prognostic incentive in esophageal-, small-cell lung-, head and neck squamous cell-, metastatic colorectal cancers, and diffuse large B-cell lymphomas.[25–29] However, to our best knowledge, the prognostic value of ALI has never been addressed in unresectable LAPCs treated with definitive C-CRT. Thus, present retrospective analysis aimed to investigate the prognostic value of baseline ALI values in LAPC patients who received definitive C-CRT.

Patients And Methods

Patient Population

We retrospectively reviewed our institutional database maintained and updated by Baskent University Medical Faculty Department of Radiation Oncology to identify unresectable LAPCs treated with radical CCRT between January 2007 and December 2017. Referencing the AJCC staging system (7th ed.), we defined an unresectable LAPC as a primary tumor involving the celiac axis and/or superior mesenteric artery, in particular, the stage III ($T_4N_{0\text{-}1}M_0$) disease. The standard diagnostic and staging workup was as previously reported elsewhere.[30,31] For each patient, the gross tumor volume included the primary tumor and involved lymph nodes apparent on contrast-enhanced CT (short axis ≥ 1.0 cm) and/or PET images, while nodes < 1.0 cm were only included if they were judged to be metabolically active (maximum standard uptake value > 2.5) on PET scan. For eligibility, patients had to meet the following requirements as well: age 18 to 80 years, Eastern Cooperative Oncology Group (ECOG) performance status 0–1, histological adenocarcinoma proof, no previous chemotherapy/RT history, adequate bone marrow and hepatic and renal functions, and body mass index (BMI)>20 kg/m^2.

Ethics, Consent And Permissions

The study was conducted by following the Helsinki Declaration and Rules of Good Clinical Practice, and the study design was approved by the Institutional Ethical Committee review board of Baskent University Medical Faculty before any data collection. According to our institutional standards, all patients provided written informed consent before the initiation of treatment either themselves or legally authorized representatives for collection and analysis of blood samples, pathologic specimens, and publication of their outcomes.

Concurrent Chemoradiotherapy

All patients underwent definitive CCRT as reported previously.[30,31] In brief, a dose of 45 Gy (1.8 Gy/fraction, 5 days/week, for 5 weeks) enclosed the defined planning target volume. Patients treated with elective nodal irradiation were excluded from the analysis. Concurrent with the radiotherapy, all patients received 1–2 courses of cisplatin (N= 37), oral capecitabine (N= 35), continuously infused 5-fluorouracil (N= 29), gemcitabine (N= 21), or cisplatin-based doublet chemotherapy (N= 19). Of those patients, 76 of them received additional 4–6 courses of maintenance gemcitabine (N= 34) or 2–4 courses of cisplatin-based doublet (N= 42) chemotherapy following C-CRT.

Advanced Lung Cancer Inflammation Index Measures

We calculated the ALI by utilizing the total blood count and biochemistry tests obtained on the first day of C-CRT as per

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the Jafri's original definition: ALI = BMI(kg/m2) × Albumin (g/dL)/NLR.[24]

Treatment Response Evaluation

Patients were examined every 3 months for the first 2 years and at 6-month interims, or more frequently, from thereon. Treatment response was first evaluated at 3 months of CCRT by using restaging PET/CT and abdominal MRI/CT scans and the criteria defined by the EORTC 1999 guidelines. Then, each patient was monitored every 3 months for the first 2 years and every 6 months thereafter by total blood count and biochemistry tests, serum CA 19-9 concentrations, and PET/CT until the confirmation of complete metabolic response and abdominal MRI/CT scans in cases with a confirmed complete metabolic response. Patients underwent abdominal ultrasonography, chest CT, cranial MRI, bone scintigraphy examinations, only if indicated.

Statistical Analysis

The primary endpoint of the present analysis was to assess the overall survival (OS: the interval between the first day of CCRT and the dates of death/last follow-up) difference between the patients with high versus low pre-CCRT ALI values. The progression-free survival (PFS: the interval between the first day of CCRT and the dates of any type of disease progression/death/last follow-up) constituted the secondary endpoint. Continuous variables were described with medians and ranges, while frequency distributions were used for categorical variables. Correlations between different groups were compared by Chi-square tests, Student's t-tests, or Spearman correlations, as appropriate. Receiver operating characteristic (ROC) curve analysis was used to determine the accessibility of pre-CCRT ALI cutoff that may stratify the study population into two ALI groups with significantly different OS and PFS results. The potential influence of different risk factors and OS and PFS were analyzed with Kaplan-Meier estimates and log rank tests. Only the factors exhibiting significance on univariate comparisons were included in the multivariate Cox proportional hazard model for assessing the potential interactions between these variables and survival results. For intergroup comparisons, two-sided P-values <0.05 were considered significant.

Results

A total of 141 patients were included in this retrospective cohort analysis (Table 1). The median age was 56 years (range; 32–79 years) for the whole study population with 26 (18.4) of them being>70 years of age. The tumor was mostly confined to the pancreatic head (N=115; 81.6%), while lymph node status was N1 in 65 (46.1%) cases. The CA 19–9 level was higher than >90 U/mL in 99 (70.2%) patients, which was defined as the critical cutoff in the benchmark The Charité Onkologie 001 (CONKO-001) randomized trial.[32]

Median follow-up time was 14.4 months (range: 3.2–74.2) for all patients, and 43 (30.5%) of them were still alive during this final analysis. Locoregional disease control was achieved in 43 (30.5%) patients and 22 (15.6%) patients were free of any disease progression. The median, 2- and 4-year survival rates were 7.5 months, 19.3%, and 10.9% for PFS, and 14.6 months, 31.5%, and 21.1% for OS, respectively (Figure 1).

Using ROC curve analysis, we sought for the presence of separate relevant cutoff(s) for baseline ALI measures which may interact with OS and PFS outcomes in significant manners. Our search revealed ideal cutoffs at 25.3 [Area under the curve (AUC): 75.6%; Sensitivity: 72.7%; Specificity: 70.3%] and 25.5 (AUC: 76.1%; Sensitivity: 74.4%; Specificity: 71.4%) points for PFS and OS, respectively (Figure 2A and B). Because the two values are very similar, we chose the 25.3 as the single common cutoff and grouped the patients into 2 ALI gatherings for further comparative analysis: ALI≤25.3 (N=75) and ALI>25.3 (N=66). Comparative survival analyses per ALI groups exhibited significantly superior median PFS (15.9 versus 6.0 months; P<0.001) and OS (25.8 versus 11.4 months; P<0.001) times favoring the ALI>25.3 group (Figure 2C and D). We additionally examined the accessibility of a potential link between the ALI grouping and the locoregional response rates after CCRT. However, despite the actuarial 1-year locoregional progression-free rates numerically favored the ALI>25.3 group over its ALI≤25.3 counterpart (37.3% versus 28.8%; P=0.16), yet this difference could not reach statistical significance which might be associated with our limited population size rather than proposing no relationship between these two parameters.

Univariate analysis comprising the factors in Table 1, revealed the N0 stage (versus N1), CA 19–9 ≤90 U/mL (versus >90 U/mL), and ALI >25.3 (versus ≤25.3) as the factors exhibiting significant association with longer median OS and PFS durations and numerically superior 2- and 4-year OS and PFS rates (Tables 2 and 3). In a multivariate analysis restricted to these 3 factors, all factors retained their independent prognostic significance on both of the

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Table 1 Baseline Demographics Of 141 Patients With Locally-Advanced Pancreas Cancer

Characteristics	All Patients (N=141)	ALI ≤25.3 (N=75)	ALI >25.3 (N=66)	P-Value
Median age, years (range)	56 (32–79)	55 (32–79)	57 (33–78)	0.71
Age group (N; %)				
< 70 years	115 (81.6)	60 (80.0)	55 (83.3)	0.32
≥ 70 years	26 (18.4)	15 (20.0)	11 (16.7)	
Gender (N; %)				
Female	30 (21.3)	16 (21.4)	14 (21.2)	0.93
Male	111 (78.7)	59 (78.6)	52 (78.8)	
ECOG performance (N; %)				
0	57 (40.4)	30 (40.0)	27 (40.9)	0.79
1	84 (59.6)	45 (60.0)	39 (59.1)	
Tumor location (N; %)				
Head	115 (81.6)	61 (81.3)	54 (81.8)	0.87
Body/Tail	26 (18.4)	14 (18.7)	12 (18.2)	
Median tumor size, cm (range)	3.7 (1.9–7.8)	3.8 (2.1–7.8)	3.5 (1.9–7.6)	0.065
N-stage (N; %)				
0	76 (53.9)	38(50.7)	38 (57.5)	0.23
1	65 (46.1)	37 (49.3)	28 (42.5)	
CA 19-9 (N; %)				
≤90 U/mL	42 (29.8)	23 (30.7)	19 (28.8)	0.68
>90 U/mL	99 (70.2)	52 (69.3)	47 (71.2)	
Median BMI, kg/m^2	21.9	20.5	23.3	0.018
Median albumin, g/dL	3.23	3.03	3.55	0.009
Median NLR	2.76	3.18	2.28	0.003

Abbreviations: ALI, Advanced lung cancer inflammation index; ECOG, Eastern Cooperative Oncology Group; N-stage, Nodal stage; CA 19-9, Cancer antigen 19-9; BMI, Body mass index; NLR, Neutrophil to lymphocyte ratio.

OS (P<0.05, for each factor) and PFS (P<0.05, for each factor) results, respectively (Table 2).

Discussion

The results of current study clearly discovered the pre-CCRT ALI as a novel relevant prognosticator that assembled LAPC patients into two fundamentally distinct OS (25.8 versus 11.4 months; P<0.001) and PFS (15.9 versus 6.0 months; P<0.001) groups following radical CCRT, with results favoring ALI >25.3 over its ≤25.3 counterpart.

In our present study, although the N-stage and CA 19-9 levels were also found to reliably predict clinical outcomes, yet the essential discovery of this first ALI investigation in LAPCs was the emergence of ALI≥25.3 as a novel and independent indicator of superior OS (P<0.001) and PFS (P<0.001) after radical CCRT., yet they Present results gave off an impression of being in great agreement with the results of previous ALI research in various tumor primaries (24–29), though it is quite difficult to achieve solid conclusions in absence of comparative LAPC studies. In the first of ever ALI study, Jafri et al[24] reported that the median PFS (5.1 versus 2.4 months; P<0.001) and OS (8.3 versus 3.4 months; P<0.001) of 173 metastatic non-small-cell lung cancer patients who received palliative chemotherapy were essentially superior within the group with ALI>18 as opposed to its ALI≤18 partner. In a similar study, Feng et al[25] utilized the same ALI cut-off for esophageal squamous cell carcinoma patients treated with surgery and found that the ALI>18 accomplices had significantly higher 5-year cancer-specific survival rate (43.4% versus 21.7%; P<0.001) than the ALI≤18 companion. In a group of 365 small-cell lung cancer patients, He et al[26] assigned the patients to one of ALI ≥19.5 (N=305) or ALI <19.5 (N=60) groups and reported that the median OS was significantly longer in the ALI≥19.5 group (20.14

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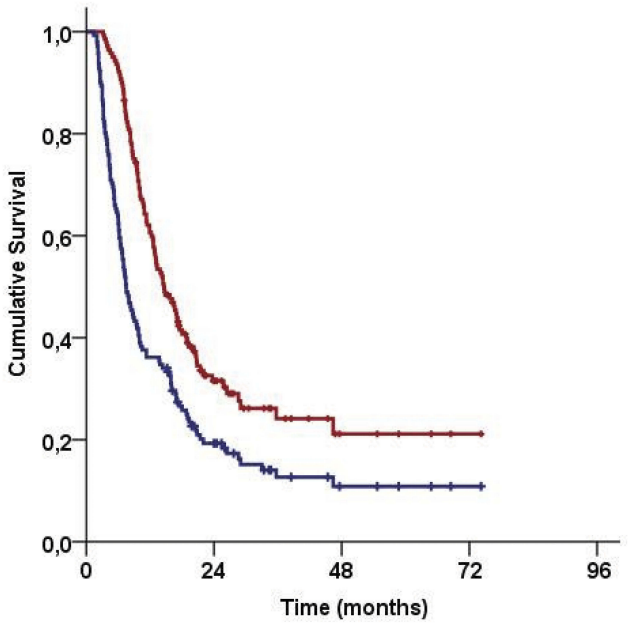


Figure 1 Survival outcomes for the entire study population (Red line: Overall survival; Blue line: Progression-free survival).

versus 10.97 months; P<0.001). Similarly, Jank et al[27] reported that ALI>37.6 was significantly associated with superior 5-year disease-free survival (83.5% versus 47.0; P<0.001) and OS (73.6% versus 44.4; P=0.008) rates after postoperative radiotherapy in 93 head and neck squamous cell carcinomas. Shibutani et al[28] reported significantly better OS rates for the group presenting with ALI>28.9 (P<0.0001) in 159 unresectable metastatic colorectal cancer patients who received combination chemotherapy. Finally, results of Park and colleagues'[29] study comprising 212 diffuse large B-cell lymphoma patients showed that ALI>15.5 was an independent predictor of longer PFS (77.3% versus 58.1%; P=0.006) and OS (80.2% versus 64.2%; P=0.008). Taken together with these investigations, present results indicated the pre-CCRT ALI as a novel biomarker which can reliably predict PFS and OS of unresectable LAPC patients intended to receive radical CCRT, in like manner the other tumor primaries.

The BMI component of the ALI is unequivocally linked with cancer-related sarcopenia, and hence, cancer-related cachexia syndrome which is an indicator of dreadful prognosis. But it might still be contended by some for its weakness for the exact impression of muscle versus fat composition.[33,34] This contention is primarily based on the fact that some patients may have low muscle mass but paradoxically overall heavy body weight due to the high-fat mass; a circumstance alluded to sarcopenic obesity.[35,36] In any case, this issue was assessed by Shibutani et al[28] and found that there was a significant correlation between the BMI and psoas muscle mass index, which is recognized as a more dependable objective measure of body muscle mass.[37] Also, in a previous study Kim et al[38] modified the ALI (mALI) by supplanting the BMI with CT-determined L3 muscle index (L3MI) to quantify the body mass more reliably in consecutively treated small-cell lung cancer patients. Nevertheless, the authors couldn't show any superiority of CT-determined L3MI based mALI over the original ALI and inferred that the original ALI was a simple but strong prognostic indicator of clinical outcomes. These particular findings both affirm and lend further support on the relevancy of our results displayed here, which proposed an excellent prognostic value for ALI in radically treated LAPC patients.

The precise mechanisms underlying the solid connection between the high ALI measures and significantly longer survival rates have not been clarified yet. Nevertheless, because the ALI incorporates BMI, albumin, and NLR, it is clear that ALI incorporates the factors playing pivotal roles in patients' nutritional, immune, and systemic inflammation status. Among these factors, both the low BMI and albumin measures furthermore mirror a pre-cachectic/cachectic patient status that is firmly related with an overtly stimulated systemic inflammatory condition.[39] Similarly, decreased levels of albumin and lymphocytes, and increased levels of neutrophils are altogether the systemic indicators of depressed host immunity with an accompanying overtly enhanced inflammatory condition. In this manner, low ALI levels robustly indicate a combination of poor nutritional and immune and exacerbated systemic inflammation status. In past examinations, every one of these three ominous conditions has been separately shown to be firmly connected with poorer clinical outcomes in many cancer types, including the LAPC.[40,41] Among these indicators of the worse outcome, particularly the systemic inflammation, namely the seventh hallmark of cancer, is universally known to promote cellular proliferation, tumor growth, neo-angiogenesis, invasion, metastasis steps of carcinogenesis, and anti-apoptotic pathways.[42,43] Furthermore, likely attributable to the overt activation of Kras, PC cells have higher basal levels of autophagy than the other cancer cells which promote tumor cell survival, growth, and invasiveness in stressful conditions such as chemotherapy/radiotherapy, nutrient deprivation, hypoxia, metabolic stress, and inflammation.[44,45] In support, Yang et al showed that the PC was regressed with the inhibition of autophagy, which

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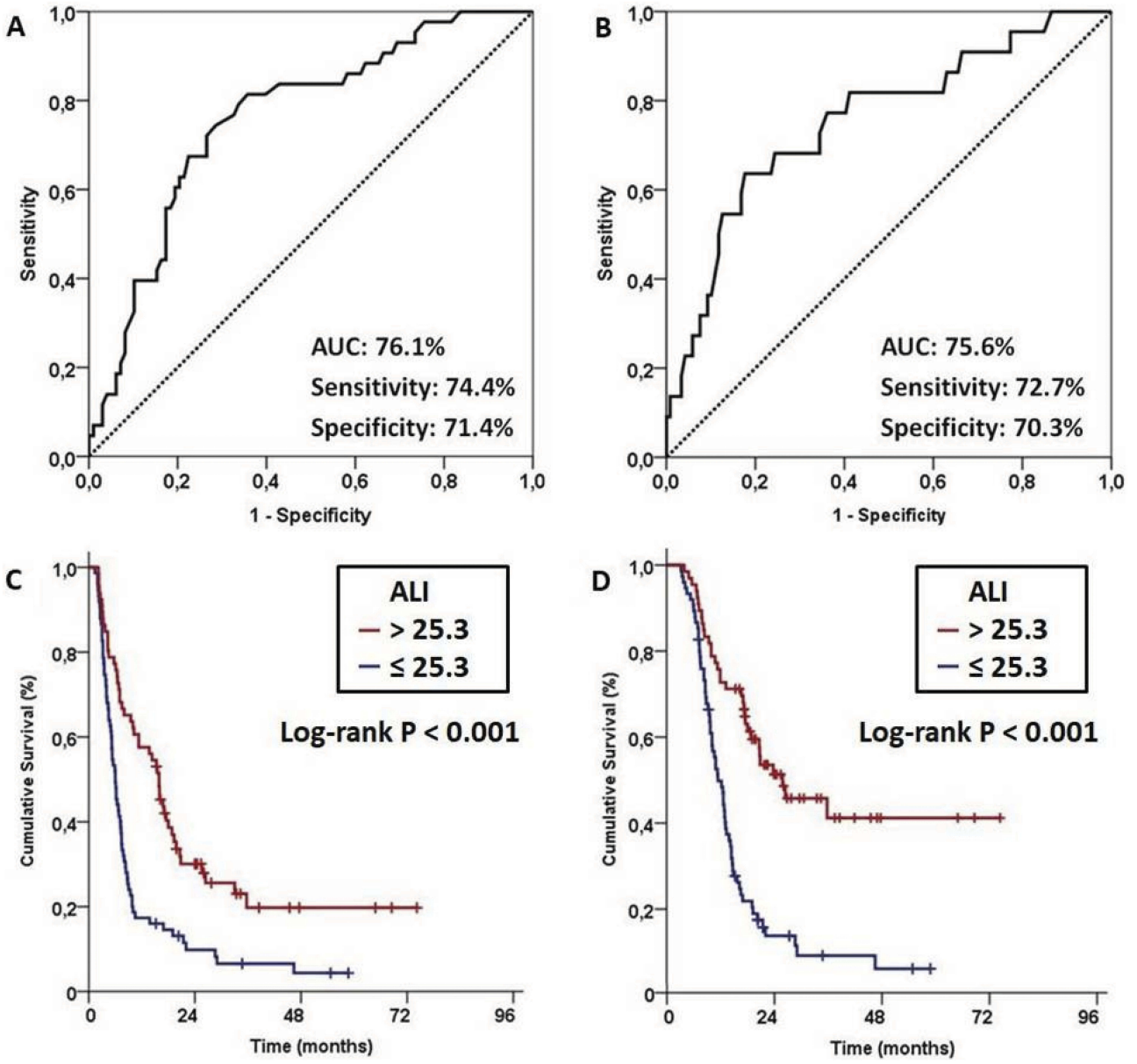


Figure 2 Outcomes of receiver operating characteristic (ROC) curve analyses and survival outcomes per advanced lung cancer inflammation index (ALI): (**A**) ROC curve analysis for progression- free survival, (**B**) ROC curve analysis for overall survival, (**C**) Progression-free survival, and (**D**) Overall survival.

was mediated by macrophage infiltration regulated by the cytokine secreting inflammation regulators.[46] But, uninhibited autophagy was shown to conversely induce resistance to chemotherapy and radiotherapy.[47,48] Consequently, in the light of accessible supporting literature, it is rational to anticipate that a low ALI predicts worse prognosis in radically treated LAPCs by reflecting altogether the hosts' poor nutritional and immune status, and unsuppressed systemic inflammation and autophagy in a highly inflammatory tumor microenvironment. However, despite the availability of rational basic knowledge, the definite connection between the ALI and autophagy in LAPC needs to be further studied before concluding more solidly on this particular issue.

The present study has at least two certain drawbacks. First, this is a single institutional retrospective cohort analysis in a relatively small study population; therefore, our results might be biased by various unpredictable tumor or patient-related factors. Accordingly, they must be valued as hypothetical and ought to be confirmed with future studies in order to remark more conclusively on the prognostic value of ALI in this patients group. And

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Table 2 Outcomes Of Uni- And Multivariate Analyses

Factor	OS			PFS		
	Univariate P-Value	Multiivariate P-Value	HR	Univariate P-Value	Multiivariate P-Value	HR
Age group (<70 vs ≥70 y)	0.55	–	–	0.67	–	–
Gender (Female vs male)	0.83	–	–	0.72	–	–
ECOG (0 vs 1)	0.74	–	–	0.63	–	–
Tumor location (H vs B/T)	0.87	–	–	0.79	–	–
Median tumor size (< vs ≥ 3.7 cm)	0.41	–	–	–	–	–
N-stage (0 vs 1)	0.002	0.007	1.89	0.008	0.014	1.67
CA 19–9 (< vs ≥ 90 U/m/L)	0.011	0.016	1.52	0.017	0.022	1.44
ALI (< vs ≥25.3)	<0.001	<0.001	2.26	<0.001	<0.001	2.65

Abbreviations: OS, Overall survival; PFS, Progression-free survival; HR, Hazard ratio; ECOG, Eastern Cooperative Oncology Group; H, Head; B/H, Body/tail; N-stage, Nodal stage; CA 19-9, Cancer antigen 19-9; ALI, Advanced lung cancer inflammation index.

Table 3 Survival Outcomes According To The Factors Exhibiting Independent Prognostic Value In Multivariate Analysis

Survival	ALI <25.3 (N=75)	ALI ≥25.3 (N=66)	P-Value	N0 (N=65)	N1 (N=76)	P-Value	CA 19–9 ≤90 U/m/L (N=48)	CA 19-9>90 U/mL (N=93)	P-Value
OS									
Median, mo	11.4	25.8	<0.001	20.7	10.9	0.007	18.4	12.1	0.016
2-year (%)	13.8	51.3		49.8	11.1		43.8	26.7	
4-year (%)	6.1	41.2		32.6	8.8		31.1	20.4	
PFS									
Median, mo	6.0	15.9	<0001	10.0	6.0	0.014	9.2	6.4	0.022
2-year (%)	9.8	30.1		30.6	6.7		28.6	15.2	
4-year (%)	4.4	19.7		16.7	5.0		14.1	8.3	

Abbreviations: ALI, Advanced lung cancer inflammation index; N0/1, Nodal stage 0/1; CA 19-9, Cancer antigen 19-9; OS, Overall survival; PFS, Progression-free survival.

second, although the ALI is a dynamic biological marker which may show remarkable variations during and post-CCRT periods due to the changes in host immunity and systemic inflammation response status, and tumor load, yet our research was limited to the pre-CCRT ALI calculations. Since the dynamic ALI fluctuations at any time point during or after the CCRT may reflect either the tumor response or progression much earlier than the emergence of unequivocal radiographic changes; the subsequent studies should particularly concentrate on the ALI dynamics in order to define more relevant cutoff(s) which might serve further useful in prognostic stratification of LAPC patients after CCRT.

Conclusion

The results of this hypothesis-generating retrospective investigation proposed that the pre-CCRT ALI was robustly associated with OS and PFS outcomes in LAPC patients treated with radical CCRT. Hence, if confirmed with further large scale studies, ALI may conceivably be utilized together with the TNM staging system to enhance the prognostic strength of this universally appreciated framework.

Data Sharing Statement

Data cannot be shared publicly because the data is owned and saved by Baskent University Medical Faculty. Data are available from the Baskent University Medical Faculty Institutional Data Access/Ethics Committee (contact via Baskent University Ethics Committee) for researchers who meet the criteria for access to confidential data: contact address, adanabaskent@baskent.edu.tr.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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