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Prognostic value of the C-reactive protein-albumin-lymphocyte (CALLY) index in idiopathic pulmonary fibrosis: Association with acute exacerbations and mortality

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Abstract:

BACKGROUND AND AIM: The CRP-albumin-lymphocyte (CALLY) index, which combines C-reactive protein (CRP), albumin, and lymphocyte values, serves as a predictive tool for patients with cancer and inflammatory diseases. However, the CALLY index has not been evaluated for its application in idiopathic pulmonary fibrosis (IPF). This study examined the relationship between CALLY scores and acute exacerbations, mortality, and lung function assessment results in patients with IPF.

METHODS: A total of 129 IPF patients diagnosed between January 2020 and December 2023 were studied by reviewing demographic information, test results, and pulmonary function assessments. Patients were enrolled from both outpatient and inpatient services at a single tertiary center. The CALLY index was calculated using the formula: albumin (g/dL) / [CRP (mg/dL) × NLR], with NLR representing the neutrophil-to-lymphocyte ratio. Data on acute exacerbations of IPF (AE-IPF) and all-cause mortality were obtained from longitudinal follow-up records. Participants received follow-up care for a median of 36 months (range: 6-48 months).

RESULTS: Of the 129 patients analyzed, 30 (23.3%) died and 10 (7.8%) experienced AE-IPF during follow-up. The CALLY index was significantly lower in patients with AE-IPF compared to those without (1.41±1.58 vs. 3.48±3.93, p=0.012), and similarly lower in deceased patients compared to survivors (1.85±2.11 vs. 3.79±4.14, p=0.014). Receiver operating characteristic (ROC) curve analysis demonstrated fair discriminatory capacity of the CALLY index for AE-IPF (area under the curve [AUC]: 0.72, cut-off: 0.66, sensitivity: 50.0%, specificity: 85.0%) and mortality (AUC: 0.69, cut-off: 1.19, sensitivity: 58.0%, specificity: 76.0%). The Gender-Age-Physiology (GAP) index showed comparable performance, with AUCs of 0.73 for AE-IPF and 0.75 for mortality, and no significant difference between the two indices (p=0.88 for AE-IPF; p=0.45 for mortality). Among pulmonary function parameters, only diffusing capacity of the lung for carbon monoxide (DLCO%) showed a significant positive correlation with the CALLY index (r=0.265, p=0.0024).

CONCLUSIONS: The CALLY index provides an effective method to evaluate functional deterioration and adverse outcomes in IPF patients while serving as a useful predictive instrument. The CALLY index offers a prognostic value similar to the GAP index using standard laboratory tests. Additional prospective validation studies should be conducted.

Keywords:

Acute exacerbation, all-cause mortality, CALLY index, idiopathic pulmonary fibrosis, inflammation marker, pulmonary function tests

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal disease characterized by continuous lung parenchymal fibrosis, but the exact disease mechanisms remain unclear.[1–3] The clinical course of IPF depends on various factors that extend beyond the primary parenchymal injury. Mortality in IPF may result not only from respiratory failure due to progressive fibrosis or acute exacerbations, but also from cardiovascular events, infections, pulmonary embolism, lung cancer, and other comorbidities.[4] Clinical management of IPF has improved with antifibrotic agents, yet patients still experience diverse disease progression, and their condition often worsens due to acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF), which lead to fatal outcomes.[5,6] Thus, identifying reliable prognostic markers capable of predicting disease progression, AE-IPF occurrence, and all-cause mortality is crucial.

The CRP-albumin-lymphocyte (CALLY) index, which combines C-reactive protein (CRP), albumin, and lymphocyte values, was originally developed for cancer patients but has been tested across various chronic and inflammatory diseases. The CALLY index provides a useful indicator for chronic pulmonary disorders because it integrates measurements of systemic inflammation with nutritional health.[7,8] Importantly, systemic inflammation is not only a feature of IPF progression itself but also reflects overall health status and vulnerability to various complications that contribute to mortality in these patients. The inflammatory burden captured by the CALLY index may therefore predict adverse outcomes regardless of the specific cause of death, as inflammation is a common pathway in respiratory deterioration, infections, cardiovascular complications, and malnutrition—all of which are relevant to IPF prognosis.[9]

However, the prognostic relevance of the CALLY index in IPF has not yet been thoroughly investigated. The CALLY index serves as a valuable prognostic tool because it evaluates both inflammatory markers and nutritional status in IPF patients, who face survival threats from disease progression, acute exacerbations, infections, cardiovascular events, and additional complications. Therefore, this study aimed to explore the relationship between the CALLY index and key clinical outcomes, including AE-IPF and all-cause mortality, and to examine its association with pulmonary function parameters in a well-characterized IPF patient cohort. The CALLY index served as our prediction tool for IPF patient outcomes because it measured both the inflammatory markers of lung disease and the patient's remaining physiological capacity and risk for fatal complications.

Materials and Methods

Study design and patient population

This retrospective observational study was conducted. The study is conducted in a tertiary referral center and included patients who were diagnosed with IPF between 2020 and 2023. The study included patients who received care at both outpatient facilities and inpatient hospital wards. The diagnosis adhered to the 2018 American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT) clinical practice guideline recommendations, based on high-resolution computed tomography (HRCT) patterns and multidisciplinary team assessment.[10]

Inclusion and exclusion criteria

The study included patients who met the following criteria: (1) were at least 18 years old, (2) had IPF confirmed according to the 2018 ATS/ERS/JRS/ALAT guidelines, (3) had all baseline laboratory and pulmonary function test (PFT) results available, and (4) had at least six months of follow-up or had died.

The study excluded patients with active infections during baseline evaluation, those with concurrent malignancies or chronic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus, patients with missing laboratory data for CALLY index calculation, those with insufficient PFT data, patients with less than six months of follow-up without reaching a study endpoint, and patients lost to follow-up. The patient selection process is explained in detail in Figure 1.

Data collection

Demographic information, clinical data, laboratory parameters, and pulmonary function test results were obtained from electronic medical records. Blood samples were collected for laboratory parameters (neutrophil count, lymphocyte count, CRP, and albumin). PFT measurements were performed within two weeks of blood sampling, according to ATS/ERS standards. The CALLY

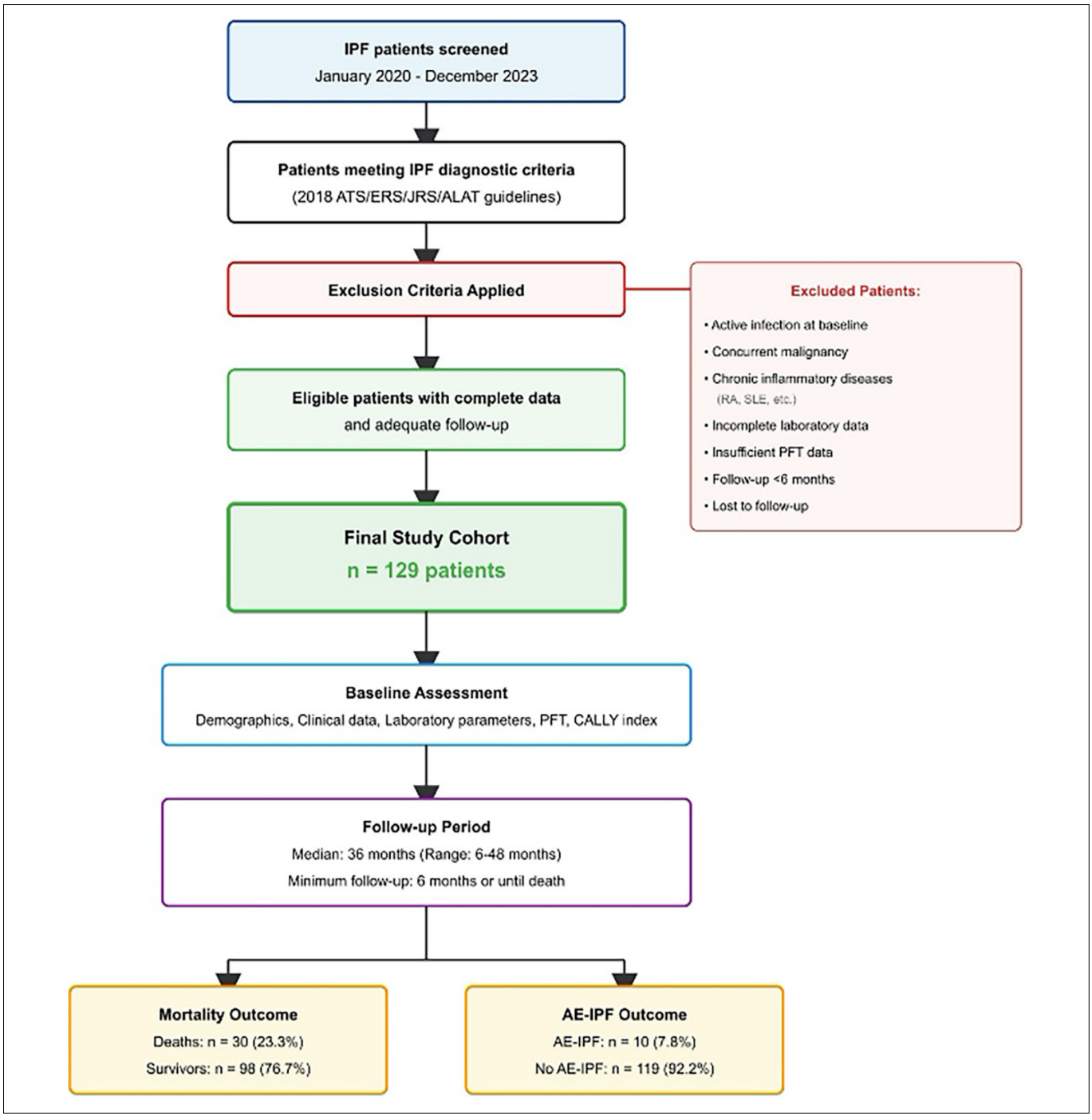

Figure 1: Study flowchart for patient selection and outcomes. Description: Flowchart illustrating the screening and selection process of patients with idiopathic pulmonary fibrosis (IPF) from January 2020 to December 2023, showing exclusion criteria and final cohort outcomes.

IPF: Idiopathic pulmonary fibrosis, AE-IPF: Acute exacerbation of idiopathic pulmonary fibrosis, PFT: Pulmonary function test, RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, ATS: American Thoracic Society, ERS: European Respiratory Society, JRS: Japanese Respiratory Society, ALAT: Latin American Thoracic Society

index was calculated using the following formula: serum albumin (g/dL) divided by the product of C-reactive protein (in mg/dL) and the neutrophil-to-lymphocyte ratio. The GAP (Gender-Age-Physiology) index was calculated using the original scoring system to create a continuous measure combining gender (0–1 points), age (0–2 points), and physiology variables forced vital capacity (FVC%) and diffusing capacity of the lung for carbon monoxide (DLCO%) (0–5 points), producing scores between 0 and 8.[11]

Outcome definitions

The international consensus statement defines acute exacerbations of IPF as a sudden worsening of clinical symptoms with new diffuse alveolar changes.[9] The diagnosis required: (1) a previous or current IPF diagnosis, (2) acute worsening or dyspnea development within 30 days, (3) new bilateral ground-glass opacity and/or consolidation on HRCT, and (4) exclusion of cardiac failure, pulmonary embolism, and identifiable infections.

Mortality was defined as all-cause mortality during the follow-up period. Mortality information was obtained from longitudinal follow-up records and confirmed through hospital records and national death registry data.

Follow-up

All patients were followed for at least six months or until death, with a median follow-up duration of 36 months (range: 6–48 months). While acknowledging that a six-month minimum follow-up may be considered relatively short for IPF studies, this duration was chosen to include patients who experienced early mortality, which is an important outcome in this progressive disease. Regular follow-up visits were scheduled every three months or more frequently based on clinical need.

Statistical analysis

Data normality was assessed using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean±standard deviation (SD) for parametric test analysis. The researchers conducted independent t-tests to evaluate CALLY scores between two patient groups (AE-IPF patients versus non-AE-IPF patients, and deceased patients versus survivors). Pearson's correlation test was used to evaluate the relationship between CALLY index values and PFT measurements, including forced expiratory volume in one second (FEV_1%), FVC%, DLCO%, FEV_1/FVC ratio, and the GAP index. The researchers applied receiver operating characteristic (ROC) curve analysis to determine the best threshold values and to calculate sensitivity, specificity, and area under the curve (AUC) for both AE-IPF prediction and mortality risk assessment. ROC curves were compared using the DeLong test to assess differences in discriminatory performance between the CALLY and GAP indices.

A two-sided p-value <0.05 was considered statistically significant. All analyses were conducted using SPSS software, version 26.0 (IBM Corp., Armonk, NY, USA).

Ethical approval and compliance

The study was approved by the Tekirdağ Namık Kemal Non-interventional Clinical Research Ethics Committee (Approval Number: 2023.157.09.07, Date: 26.09.2023). It was conducted in accordance with the 1964 Declaration of Helsinki. Due to the retrospective design of the study, the requirement for written informed consent was waived.

Results

Patient characteristics

A total of 129 patients diagnosed with IPF were analyzed. The study included detailed baseline information about patients who died and those who developed AE-IPF, together with their corresponding control groups. The patient population consisted mainly of males over 65 years old (72.1%). The two most common presenting symptoms were dyspnea, occurring in 88.4% of patients, and cough, affecting 79.8%. Digital clubbing appeared in 33 patients (25.6%), and its occurrence was more common among patients who died and those with AE- IPF (46.7% vs. 18.4% p<0.001) and (60.0% vs. 22.7% p=0.009) (Table 1).

Clinical outcomes

Patients were followed for a median of 36 months. (Range 6–48 months). During this period, 30 participants (23.3%) died, while 98 patients (76.7%) survived. Acute exacerbations of IPF developed in ten patients (7.8%). Among patients with AE-IPF, 6 (60.0%) died and 4 (40.0%) survived, whereas in the non-AE-IPF group (n=119), 24 patients (20.2%) died and 95 (79.8%) survived. Fisher's exact test revealed that AE-IPF was significantly associated with mortality (p=0.0017).

Laboratory and biomarker analysis

Laboratory results showed that patients with AE-IPF had a lower CALLY index than patients without AE-IPF at baseline (1.41±1.58 vs. 3.48±3.93; p=0.003). Deceased patients also had a lower CALLY index than survivors (1.85±2.11 vs. 3.79±4.14; p=0.001). As the data showed normal distribution, continuous variables were presented as mean±standard deviation (mean±SD) for Pearson correlation coefficient analyses. The GAP index was also significantly higher in both the AE-IPF group (5.0±1.2 vs. 3.8±1.6; p=0.018) and the mortality group (4.9±1.4 vs. 3.5±1.5; p<0.001), with consistent data presentation across all subgroup comparisons (Table 2).

Table 1: Demographics, clinical findings, and symptoms by mortality and acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) status

Variable	Mortality, yes (n=30)		Mortality, no (n=98)		p	AE-IPF, yes (n=10)		AE-IPF, no (n=119)		p
	n	%	n	%		n	%	n	%	
Age (years)					0.14					0.79
<65	4	13.3	29	29.6		3	30.0	31	26.1	
≥65	26	86.7	69	70.4		7	70.0	88	73.9	
Sex					0.41					0.56
Male	22	73.3	65	66.3		6	60.0	82	68.9	
Female	8	26.7	33	33.7		4	40.0	37	31.1	
Comorbidity					0.072					0.38
Yes	6	20.0	35	35.7		2	20.0	40	33.6	
No	24	80.0	63	64.3		8	80.0	79	66.4	
Smoking status					0.55					0.50
Never	11	36.7	31	31.6		4	40.0	38	31.9	
Current	11	36.7	28	28.6		4	40.0	35	29.4	
Former	8	26.6	39	39.8		2	20.0	46	38.7	
Dyspnea					0.69					0.39
Yes	27	90.0	86	87.8		8	80.0	106	89.1	
No	3	10.0	12	12.2		2	20.0	13	10.9	
Cough					**0.007**					0.09
Yes	29	96.7	73	74.5		10	100.0	93	78.2	
No	1	3.3	25	25.5		0	0.0	26	21.8	
Chest pain					0.79					0.12
Yes	7	23.3	20	20.4		4	40.0	23	19.3	
No	23	76.7	78	79.6		6	60.0	96	80.7	
Finger clubbing					**<0.001**					**0.009**
Yes	14	46.7	18	18.4		6	60.0	27	22.7	
No	16	53.3	80	81.6		4	40.0	92	77.3	

Table 2: Laboratory and pulmonary function parameters by mortality and acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) status

Variable	Mortality (mean±SD)		p	AE-IPF (mean±SD)		p
	Yes	No		Yes	No	
Laboratory results						
Neutrophils (×10³/µL)	5.9±2.4	5.1±1.8	0.029	5.9±1.8	5.2±1.9	0.3
Lymphocyte (×10³/µL)	2.0±0.9	2.4±0.6	0.053	1.8±0.7	2.3±0.9	0.09
CRP (mg/dL)	19.4±12.4	7.6±12.7	**0.004**	28.3±46.9	8.9±15.1	**0.003**
Albumin (g/dL)	4.1±0.4	4.2±0.4	0.382	4.2±0.5	4.2±0.4	0.86
CALLY index	1.9±2.1	3.8±4.1	**0.014**	1.4±1.6	3.5±3.9	**0.012**
GAP index	4.9±1.4	3.5±1.5	**<0.001**	5.0±1.2	3.8±1.6	**0.018**
Pulmonary function tests						
FEV_1 (%)	68.1±17.5	78.4±18.7	**0.008**	70.0±12.5	76.4±19.3	0.31
FVC (%)	61.1±17.7	74.1±17.6	**<0.001**	63.9±12.2	71.6±18.8	0.21
DLCO (%)	45.8±17.4	54.1±18.0	**0.026**	41.7±9.6	53.0±18.4	0.058
FEV_1/FVC	88.5±7.8	86.6±10.3	0342	87.4±5.5	87.0±10.1	0.89
FVC/DLCO	1.4±0.5	1.5±0.6	0.494	1.6±0.4	1.5±0.6	0.62

SD: Standard deviation, FEV_1: Forced expiratory volume in one second, FVC: Forced vital capacity, DLCO: Diffusing capacity of the lung for carbon monoxide

Diagnostic performance analysis

Receiver operating characteristic curve analysis showed that the CALLY index provided moderate discrimination for predicting AE-IPF (AUC: 0.72, cut-off: 0.66, sensitivity: 50.0%, specificity: 85.0%, p=0.01). The AUC for mortality prediction was 0.69, with a cut-off of 1.19, sensitivity of 58.0%, and specificity of 76.0%. For AE-IPF prediction, the AUC was 0.73 with a cut-off of

Table 3: Diagnostic performance of the C-reactive protein-albumin-lymphocyte (CALLY) index and the Gender-Age-Physiology (GAP) index for predicting acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) and mortality

Test	Condition	Cut-off value	Sensitivity	Specificity	AUC	p
CALLY index	AE-IPF	0.66	0.50	0.85	0.72	**0.01**
	Exitus	1.19	0.58	0.76	0.69	**0.001**
GAP index	AE-IPF	4.5	0.80	0.67	0.73	**0.002**
	Exitus	4.5	0.71	0.74	0.75	**<0.001**

AE: Acute exacerbation, IPF: Idiopathic pulmonary fibrosis, AUC: Area under the curve

Table 4: Correlation analysis between C-reactive protein-albumin-lymphocyte (CALLY) scores and respiratory parameters

Variable	Correlation coefficient (r)	p
FVC (%)	0.19	**0.0307**
DLCO (%)	0.265	**0.0024**
FEV_1/FVC	0.035	0.6953
FEV_1 (%)	0.198	**0.0249**
GAP	-0.112	0.208
FVC/DLCO	-0.113	0.202

FVC: Forced vital capacity, DLCO: Diffusing capacity of the lung for carbon monoxide, FEV_1: Forced expiratory volume in one second, GAP: Gender-Age-Physiology index

4.5 (p=0.001) (Table 3). The GAP index produced an AUC and sensitivity of 80.0% and specificity of 67.0% (p=0.002) and an AUC of 0.75 for mortality prediction with a cut-off of 4.5 and sensitivity of 71.0% and specificity of 74.0% (p<0.001). The DeLong test for ROC curve comparison revealed no substantial difference between the CALLY and GAP indices in evaluating mortality and acute exacerbation outcomes (p=0.45 and p=0.88, respectively) [Fig. 1].

Correlation with pulmonary function

The CALLY index showed a significant positive correlation with DLCO% (r=0.265; p=0.0024) but no significant correlations were observed with the FEV_1/FVC ratio, the FVC/DLCO ratio, or the GAP index (Table 4).

Discussion

This study evaluated the prognostic value of the CALLY index in patients with IPF through a retrospective cohort analysis. The study results showed that patients with lower CALLY index values experienced both higher rates of acute exacerbations and increased mortality risk. The CALLY index demonstrated a weak but statistically significant relationship with DLCO%, indicating its ability to measure aspects of impaired lung gas exchange.

The observed number of AE-IPF events (n=10, 7.8%) was lower than the number of deaths (n=30, 23.3%), which requires careful consideration. The observed difference between AE-IPF events and deaths supports the conclusion that IPF mortality results from various factors beyond acute exacerbations. Deaths in our cohort likely resulted from multiple causes, including progressive respiratory failure, cardiovascular events, infections, pulmonary embolism, and other complications—all of which are common in IPF patients.[4] Importantly, rather than contradicting the utility of the CALLY index, this observation supports its value as a comprehensive prognostic marker. The CALLY index measures both systemic inflammation and nutritional status, which indicate susceptibility to various serious complications beyond acute exacerbations of IPF. The index demonstrated strong all-cause mortality prediction because it evaluates factors extending beyond acute exacerbation risk.

The clinical progression of IPF shows variable patterns, as acute exacerbations create major health risks that increase mortality rates and disease severity. The small number of AE-IPF cases (n=10) in our study could have reduced statistical power for this outcome, which might have influenced the accuracy of our results. Nonetheless, the CALLY index showed a significant association with AE-IPF despite the study's limited sample size. Identifying affordable and reliable prognostic tools stands as a top clinical priority. The CALLY index, originally developed for oncology and chronic inflammatory conditions, now incorporates systemic inflammation markers (CRP, NLR) and nutritional status indicators (albumin), as these elements play an increasingly recognized role in IPF progression and worsening.[7,8,12] Our findings strengthen the evidence that systemic inflammation contributes meaningfully to disease outcomes, regardless of the specific cause of death or deterioration.

Previous research has shown that inflammation-based indices serve as predictive tools for IPF patient outcomes.

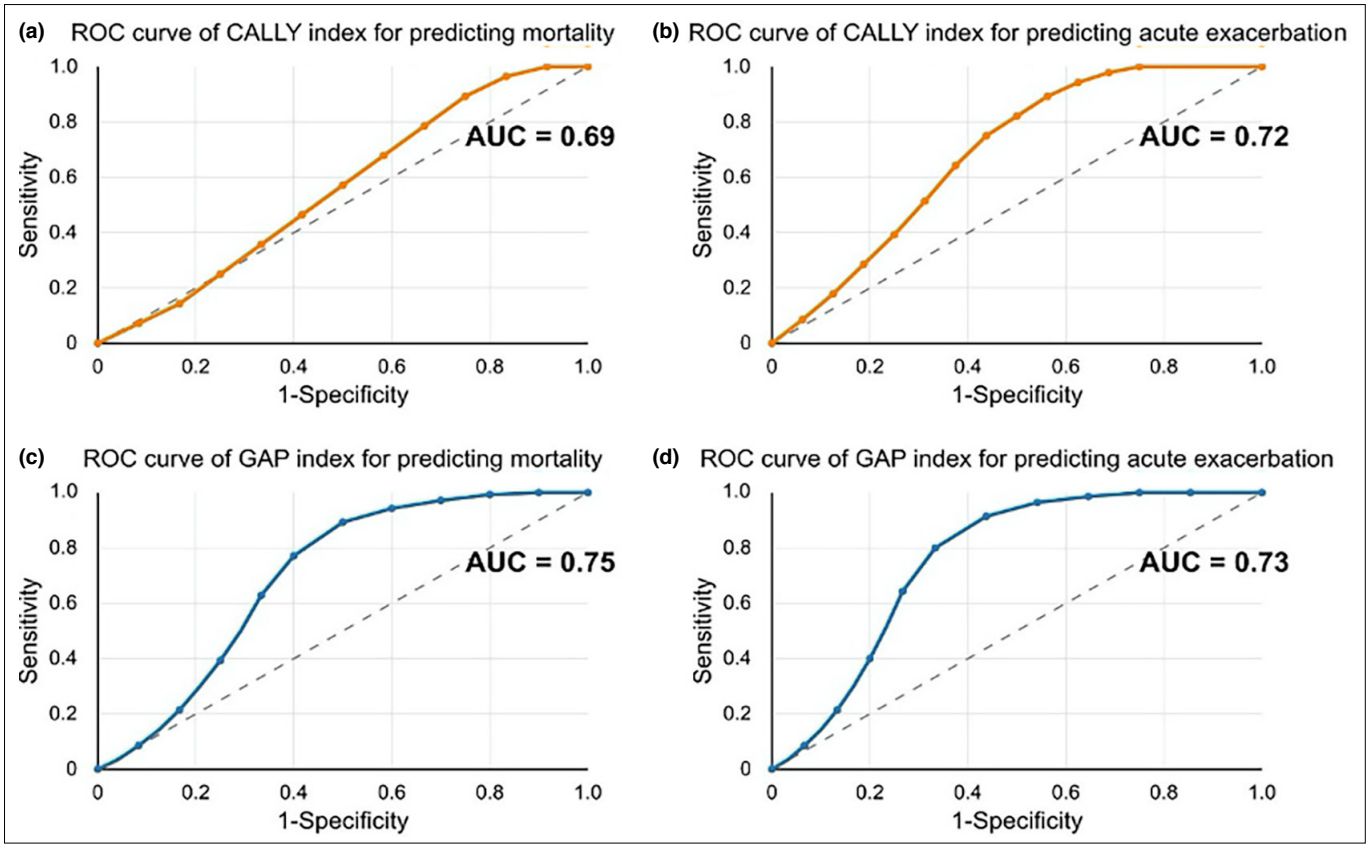

Figure 2: Receiver operating characteristic (ROC) curves for prognostic indices in idiopathic pulmonary fibrosis (IPF). Panel descriptions: (a) C-reactive protein-albumin-lymphocyte (CALLY) index for mortality; (b) CALLY index for acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF); (c) Gender-Age-Physiology (GAP) index for mortality; (d) GAP index for AE-IPF

ROC: Receiver operating characteristic, IPF: Idiopathic pulmonary fibrosis, AE-IPF: Acute exacerbation of idiopathic pulmonary fibrosis, AUC: Area under the curve, GAP: Gender-Age-Physiology index; CALLY: C-reactive protein-albumin-lymphocyte index

[13–18] The Advanced Lung Cancer Inflammation Index (ALI) demonstrated poor predictive value according to Bozkuş and Keskin,[13] whereas Chen et al.[14] reported that NLR, PLR, and monocyte-to-high-density lipoprotein cholesterol ratio (MHR) were independently associated with negative outcomes. Research by Teoh et al.[15] showed that peripheral monocyte counts serve as a mortality risk indicator, while Don and Kaysen[16] established that serum albumin functions as a dual indicator of nutritional health and inflammatory markers. These studies support the CALLY index as a useful composite marker, and our research confirms its value for IPF patients.

When compared with the established GAP index, the CALLY index demonstrated comparable predictive performance. ROC curve analysis showed that both indices had fair discriminatory capacity for AE-IPF (AUC: 0.72 for CALLY vs. 0.73 for GAP) and mortality (AUC: 0.69 for CALLY vs. 0.75 for GAP). The DeLong test showed no significant difference between the two indices for both AE-IPF and mortality outcomes (p=0.88 for AE-IPF; p=0.45 for mortality). Although the confidence intervals were not shown in the Figure 2, the ROC analysis demonstrated overlapping CI values between the indices. The GAP index continues to function as a prognostic tool, yet the CALLY index presents itself as a simpler, practical marker that uses standard laboratory tests and could serve as an alternative or additional tool in resource-constrained environments.

The relatively low cutoff values obtained from our ROC analysis (0.66 for AE-IPF and 1.19 for mortality) merit discussion. The mathematical structure of the CALLY index formula determines these low thresholds, as it includes CRP and NLR values, which tend to rise in IPF patients with systemic inflammation. The CALLY score becomes low in patients with normal albumin levels when their inflammatory markers show elevated values. The index performs better in detecting high-risk patients with inflammatory conditions such as IPF because of its ability to reflect inflammatory burden.[19]

The CALLY index showed a strong relationship with DLCO% but not with other lung function tests, including FVC/DLCO ratio and FEV_1/FVC, likely because DLCO measures both alveolar and vascular problems, linking systemic inflammation to gas exchange abnormalities.[20,21] Spirometric measurements reflect structural fibrotic changes, but these changes do not appear to be influenced by inflammatory pathways.

The study contains several recognized limitations that need to be acknowledged. The single-center design and retrospective approach limit the ability to apply its results to other settings and introduces selection bias in the data. Second, although we had 30 mortality events, which would typically be sufficient for multivariate analysis (generally requiring ten events per variable), we chose to perform only univariate analyses. The decision was based on the relatively small overall sample size (n=129) and the very limited number of AE-IPF events (n=10), which would have resulted in unstable estimates in a multivariate model. We acknowledge that this prevents us from confirming the CALLY index as an independent prognostic factor after adjusting for potential confounders. Future studies with larger cohorts should perform comprehensive multivariate analyses to establish the independent prognostic value of the CALLY index. We also did not evaluate how the CALLY index changes over time, even though ongoing monitoring of this index during different periods could help determine its value as a disease activity and progression indicator. In addition, we did not have detailed information on specific causes of death, which would have allowed for cause-specific mortality analyses and a better understanding of the relationship between the CALLY index and different death etiologies. Future research should include multicenter studies with larger participant groups and time-based data collection to confirm and expand upon these results.

Future studies should validate the CALLY index through prospective multicenter studies involving large patient groups, while also monitoring index values over time. The combination of imaging-based fibrosis scores with molecular biomarkers (Krebs von den Lungen-6 [KL-6] and surfactant protein-D [SP-D]) and established prognostic tools like the GAP index could enhance risk assessment and enable personalized treatment approaches.

Conclusion

The CALLY index serves as an accessible biomarker that shows promise for measuring both systemic inflammation and nutritional health in patients with IPF. Our findings indicate that patients with lower CALLY values face elevated risks of acute exacerbations and all-cause mortality, at levels comparable to the GAP index (AUC: 0.72 vs. 0.73 for AE-IPF; 0.69 vs. 0.75 for mortality, $p>0.05$ for both comparisons). The positive relationship between CALLY index values and DLCO% measurements supports its potential as a valid marker of disease severity. The CALLY index represents a practical risk assessment tool because it relies on affordable laboratory tests that are widely available in healthcare settings worldwide. The CALLY index requires further validation through prospective multicenter studies with larger patient cohorts and follow-up assessments to confirm its clinical utility. Combining the CALLY index with current prognostic tools and new biomarkers will help establish individualized risk evaluation systems for managing this difficult disease.

Ethics Committee Approval

The study was approved by the Tekirdağ Namık Kemal Non-interventional Clinical Research Ethics Committee (No: 2023.157.09.07, Date: 26/09/2023).

Informed Consent

Due to the retrospective design of the study, the requirement for written informed consent was waived.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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Authors declare that no artificial intelligence application was used in the production of the work.

Author Contributions

Concept – N.F., A.Y.; Design – N.F., A.Y., E.P.K., M.F.; Supervision – N.F., A.Y., E.P.K., M.F., L.C.M.; Resource – N.F., E.P.K., M.F., L.C.M.; Materials – N.F., A.Y., E.P.K.; Data Collection and/or Processing - N.F., A.Y., E.P.K., M.F.; Analysis and/or Interpretation - N.F., A.Y., E.P.K., M.F.; Literature Review – N.F., A.Y., M.F.; Writing – N.F., A.Y., M.F.; Critical Review – N.F., A.Y., M.F.

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