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ORIGINAL ARTICLE

Clinical Utility of the CALLY Index versus EASIX Score for Malignancy Prediction in Mediastinal Pathologies

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ABSTRACT

Background: **Mediastinoscopy is considered the gold standard for evaluating mediastinal lymph nodes due to its high diagnostic accuracy. However, its invasive nature highlights the need for non-invasive tools to predict malignancy. The CALLY index and EASIX score are promising prognostic biomarkers derived from routine laboratory data, yet their utility in differentiating between benign and malignant mediastinal pathologies remains underexplored.**

Methods: **This retrospective cohort study included patients who underwent mediastinoscopy between January 2014 and January 2024. Histopathological results were classified as benign or malignant. Preoperative laboratory parameters were used to calculate the CALLY index and EASIX score. The diagnostic performance of these scores was assessed using receiver operating characteristic (ROC) curve analysis, and multivariate logistic regression was conducted to evaluate their independent predictive value.**

Results: **Among 285 patients, 235 (82.5%) had benign pathologies and 50 (17.5%) had malignant pathologies. The CALLY index demonstrated significant predictive value, with an area under the curve (AUC) of 0.746 and an optimal cutoff value of 1.37, providing a sensitivity of 82.0% and a specificity of 61.7%. In contrast, the EASIX score showed no significant association with malignancy (AUC: 0.485). Multivariate logistic regression analysis confirmed the independent predictive value of the CALLY index (odds ratio: 0.431, $p < 0.001$), while the EASIX score was not identified as a significant predictor ($p = 0.419$).**

Conclusions: **The CALLY index may serve as a useful, non-invasive tool for preoperative risk stratification in mediastinal pathology, whereas the EASIX score demonstrated limited utility in this context. Future multicenter prospective studies are needed to validate these findings and explore their integration into clinical workflows.**

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KEYWORDS

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INTRODUCTION

Mediastinoscopy remains the gold standard for the evaluation of mediastinal lymph nodes in lung cancer, offering high diagnostic accuracy and enabling direct tissue sampling essential for accurate staging. Despite the increasing adoption of minimally invasive techniques such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) [1,2], mediastino-

scopy continues to play an indispensable role, particularly in cases where EBUS results are inconclusive or when malignancy is strongly suspected [3]. However, given the procedural risks, there is an increasing need for reliable, non-invasive tools to assist in malignancy prediction. Recent advances, including liquid biopsy and circulating tumor DNA (ctDNA) technologies, highlight the growing emphasis on minimally invasive diagnostic strategies [4,5]. Nonetheless, cost, accessibility, and technical limitations often restrict their widespread application in routine clinical practice. Therefore, easily obtainable and cost-effective serum biomarkers remain highly attractive options for risk stratification. The C-reactive protein-albumin-lymphocyte (CALLY) index and the Endothelial Activation and Stress Index (EASIX) score are promising examples, both derived from routine laboratory parameters and previously validated as prognostic indicators in various malignancies [6-10]. However, their diagnostic utility in mediastinal pathology has not yet been systematically evaluated. This study aimed to assess the potential role of these indices in predicting malignancy in patients undergoing mediastinoscopy, thereby addressing an important gap in the current literature.

MATERIALS AND METHODS

Study design and patient selection

Our institution has over two decades of experience in mediastinal pathology evaluation, having performed the first mediastinoscopy in 2005 [11]. This study was designed as a retrospective cohort analysis. Data were collected from patients who underwent mediastinoscopy between January 2014 and January 2024 at our institution. Patients were included if they had histopathologically confirmed mediastinal lymph node pathology, classified as either benign or malignant. Preoperative laboratory data, including complete blood count (CBC) and biochemical parameters, were required for inclusion.

Patients were excluded if they had incomplete or missing laboratory data, had received chemotherapy, radiotherapy, or other therapeutic interventions prior to mediastinoscopy, or had systemic inflammatory or infectious conditions such as sepsis at the time of evaluation. All eligible patients within the study period were included; no formal power calculation was performed due to the retrospective design.

Data collection and biomarker calculation

Demographic data, including age and gender, as well as preoperative laboratory parameters (C-reactive protein [CRP], albumin, lymphocyte count, lactate dehydrogenase [LDH], creatinine, and platelet count) were obtained from electronic medical records. The histopathological outcomes of mediastinoscopy were categorized as benign or malignant based on pathology reports.

Two prognostic indices were calculated using preoperative laboratory values as follows:

CALLY Index: (Albumin x Lymphocyte)/(CRP x 10^4)

EASIX Score: (LDH x Creatinine)/Platelet

Patients were then classified into two groups according to their histopathological results: the benign group and the malignant group.

Ethical considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Antalya Training and Research Hospital Medical Ethics Committee (approval number: 2025-083). Due to the retrospective nature of the study, the requirement for informed consent was waived.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median with interquartile range, depending on the distribution of the data. Group comparisons were performed using the independent *t*-test or Mann-Whitney U test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables, as appropriate.

The diagnostic performance of the CALLY index and EASIX score in predicting malignancy was assessed using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC), sensitivity, specificity, and optimal cutoff values were calculated for each score. The optimal cutoff values were determined using the Youden Index (J = Sensitivity + Specificity - 1), which identifies the threshold that provides the best balance between sensitivity and specificity.

Additionally, multivariate logistic regression analysis was performed to evaluate the independent predictive value of the CALLY index and EASIX score for malignancy. Results were reported as odds ratios (OR) with corresponding 95% confidence intervals (CI). A two-tailed p-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 27 (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA).

RESULTS

A total of 285 patients underwent mediastinoscopy between January 2014 and January 2024. Of the 235 patients with benign pathologies, 27.2% were female, while 24% of the 50 patients with malignant pathologies were female. There was no statistically significant difference between the groups in terms of gender distribution ($p = 0.391$) or age distribution ($p = 0.843$). The mean creatinine level was 1.13 ± 0.31 in patients with malignant pathologies, compared to 1.21 ± 0.35 in those with benign pathologies, which was significantly higher in the benign group ($p = 0.040$). The descriptive characteristics of the patients are summarized in Table 1.

A comparison of EASIX and CALLY scores between

Table 1. Descriptive characteristics.

	Benign (n = 235)	Malign (n = 50)	p-value
Female (n, %)	64 (27.2%)	12 (24.0%)	0.391
Age (mean ± SD)	44.17 ± 14.03	39.90 ± 14.14	0.843
Lactate Dehydrogenase (mean ± SD)	192.47 ± 88.42	194.24 ± 86.67	0.559
Creatinine (mean ± SD)	1.21 ± 0.35	1.13 ± 0.31	0.040
White Blood Cell (mean ± SD)	10.77 ± 5.93	10.98 ± 4.98	0.867
Hemoglobin (mean ± SD)	13.02 ± 2.07	13.25 ± 1.91	0.653
Hematocrit (mean ± SD)	38.41 ± 5.59	38.76 ± 5.25	0.710
Platelets (mean ± SD)	233.09 ± 88.64	240.60 ± 106.48	0.232
Neutrophil (mean ± SD)	5.93 ± 3.94	6.19 ± 3.63	0.980
Lymphocyte (mean ± SD)	2.06 ± 1.97	2.00 ± 1.21	0.990
Monocyte (mean ± SD)	0.98 ± 0.93	0.95 ± 0.57	0.991
Albumin (mean ± SD)	42.80 ± 3.11	38.34 ± 3.35	0.218
C-reactive protein (CRP) (mean ± SD)	56.10 ± 43.02	88.46 ± 36.70	0.658

Table 2. Comparison of EASIX and CALLY scores.

	Benign (n = 235)	Malign (n = 50)	p-value
EASIX (median IQR)	0.99 (0.85)	0.91 (0.83)	0.724
CALLY (median IQR)	1.84 (2.76)	0.75 (0.72)	< 0.001

Table 3. ROC analysis.

	AUC	p-value	Cutoff	Sensitivity	Specificity
EASIX	0.485	0.746	1.21	42.0%	63.9%
CALLY	0.746	< 0.001	1.37	82.0%	61.7%

Table 4. Multivariate logistic regression analysis for malignancy.

	B	S.E.	Wald	p-value	Odds Ratio
EASIX	0.096	0.116	0.652	0.419	1.098
CALLY	-0.842	0.197	18.228	< 0.001	0.431

benign and malignant patients was performed revealing no significant difference in EASIX scores (p = 0.724). Table 2 presents the comparison of EASIX and CALLY scores based on the benign or malignant status of the patients.

The area under the curve (AUC) for the EASIX score was calculated as 0.485, with a cutoff value of 1.21. For the CALLY score, the AUC was determined to be 0.746, with a cutoff value of 1.37. Table 3 summarizes the results of the ROC analysis including sensitivity and specificity, while Figure 1 illustrates the ROC curve.

Multivariate regression analysis revealed that the odds

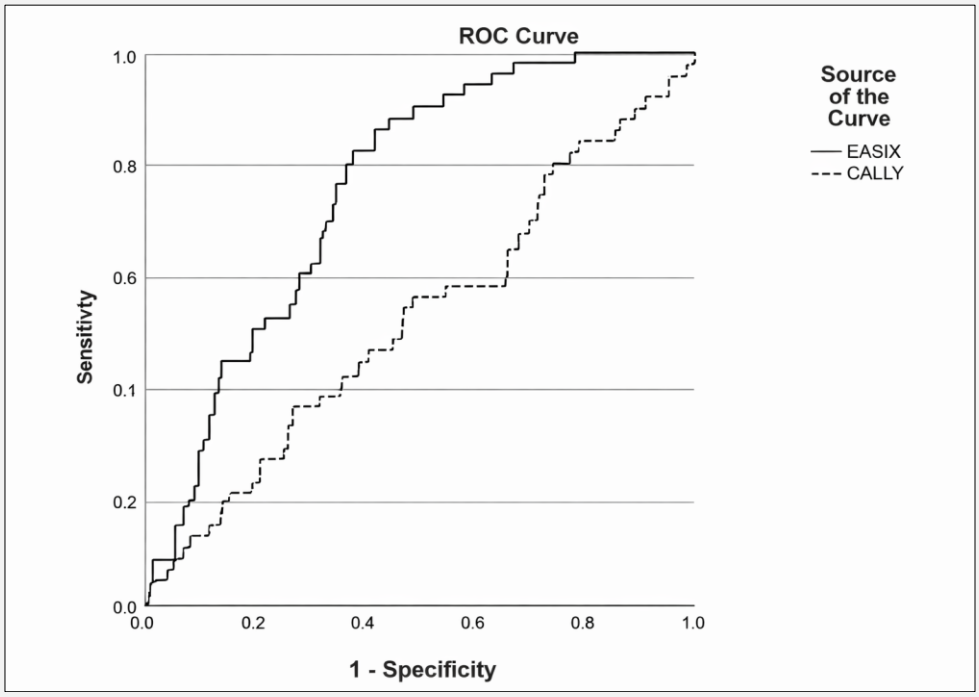

Figure 1. ROC curve.

ratio for detecting malignancy was 1.098 for the EASIX score ($p = 0.419$) and 0.431 for the CALLY score ($p < 0.001$). The results of the multivariate regression analysis are presented in Table 4.

DISCUSSION

This study evaluated the diagnostic utility of the CALLY and EASIX scores in distinguishing between benign and malignant mediastinal pathologies in patients undergoing mediastinoscopy. Although current guidelines for mediastinal staging in non-small cell lung cancer (NSCLC) recommend the use of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) as the first-line invasive diagnostic modality, mediastinoscopy remains the gold standard, particularly when EBUS-TBNA results are inconclusive or when there is a high clinical suspicion of malignancy [3]. While mediastinoscopy is widely regarded as a safe and routine procedure, it is not devoid of risks. Socci et al. [12] have systematically categorized the most common perioperative complications into six groups: bleeding, left recurrent laryngeal nerve palsy, infection, pneumothorax, tracheal perforation, and esophageal perforation, with the first three being the most prevalent. These complications, although infrequent, can range from minor to catastrophic, underscoring the necessity for meticulous surgical technique and thorough preoperative planning to mitigate potential morbidity. Given the procedural risks, even in experienced hands, the identification and validation of reliable, non-invasive biomarkers for malignancy prediction have become an essential priority. Such tools could refine patient selection, reduce unnecessary invasive procedures, and ultimately improve both diagnostic efficiency and patient safety.

In this context, novel non-invasive diagnostic tools such as circulating tumor DNA (ctDNA) analysis and liquid biopsies have demonstrated significant promise [4,5]. However, despite their high specificity, widespread implementation remains limited by logistical and economic constraints. Consequently, laboratory-based indices such as the CALLY and EASIX scores, which leverage routinely available clinical parameters, offer a practical and cost-effective alternative for initial risk stratification.

Inspired by previous studies demonstrating the predictive value of serum tumor markers such as carcinoembryonic antigen (CEA) and cytokeratin fragment 21-1 (CYFRA 21-1) in assessing mediastinal lymph node metastasis in lung cancer [13], we explored the potential role of the CALLY index and EASIX score as non-invasive laboratory-based predictors.

Both indices are derived from routine laboratory parameters and have been previously validated as prognostic markers in various malignancies, including gastric, breast, pancreatic, and esophageal cancers, as well as in hematological disorders such as multiple myeloma [6-10]. To the best of our knowledge, this is the first study to systematically investigate the diagnostic utility of the CALLY and EASIX scores for malignancy prediction in mediastinal pathologies, thereby addressing a critical and previously unexplored gap in the literature.

Our findings demonstrated that the CALLY index is a significant predictor of malignancy in mediastinal pathologies, with an AUC of 0.746 and an optimal cutoff value of 1.37, yielding a sensitivity of 82.0% and a specificity of 61.7%. These results are consistent with previous research highlighting the prognostic significance of the CALLY index, which integrates nutritional status (via albumin), immune response (lymphocyte count), and systemic inflammation (CRP levels) into a single score [7-9]. The combination of these parameters may offer a more comprehensive reflection of the tumor microenvironment and host immune response, thereby enhancing its predictive capacity for malignancy.

In contrast, the EASIX score, which is calculated using LDH, creatinine, and platelet count, did not show significant predictive value in this cohort, with an AUC of 0.485. The EASIX score has primarily been validated as a prognostic marker in conditions associated with endothelial dysfunction, such as hematological malignancies and systemic inflammatory diseases [10]. Its limited performance in predicting malignancy in mediastinal lymphadenopathy may be attributed to the distinct pathophysiological mechanisms between solid tumors and endothelial-related processes.

The results of the multivariate logistic regression analysis further supported these findings, confirming the independent predictive value of the CALLY index, while the EASIX score did not emerge as a significant factor. These findings suggest that the CALLY index, as an easily obtainable and cost-effective biomarker, may assist clinicians in the preoperative assessment of patients with mediastinal masses, potentially reducing the need for invasive diagnostic procedures in selected cases.

Study Limitations

This study has several limitations that should be acknowledged. First, the retrospective design may introduce selection bias, and unmeasured confounding factors could have influenced the results. Second, the single-center nature of the study limits the generalizability of the findings to broader populations. Third, although patients with overt systemic inflammatory or infectious conditions were excluded, subclinical inflammatory states may still have affected the biomarker levels used in the calculation of the CALLY and EASIX scores.

Additionally, this study did not include longitudinal follow-up or survival analysis, which could further validate the prognostic significance of these indices. Finally, we did not assess the potential additive value of combining the CALLY index with imaging modalities such as PET-CT or EBUS-TBNA, which may further enhance diagnostic accuracy.

Future Directions

Future prospective studies with larger, multicenter cohorts are warranted to validate these findings and to explore the integration of the CALLY index into clinical decision-making algorithms. Moreover, studies evaluating the combination of the CALLY index with other biomarkers or imaging techniques could provide a more comprehensive approach to mediastinal lymph node assessment. Incorporating these biomarkers into risk stratification models may optimize patient selection for invasive diagnostic procedures and improve clinical outcomes.

CONCLUSION

In conclusion, the CALLY index demonstrated significant predictive value for distinguishing between benign and malignant mediastinal pathologies, offering a practical, non-invasive tool for preoperative risk assessment. In contrast, the EASIX score did not show utility in this setting. These findings support the potential role of the CALLY index as an adjunct to current diagnostic approaches, although further validation in larger, prospective studies is needed before routine clinical implementation.

Ethics Statement:

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Antalya Training and Research Hospital Medical Ethics Committee (Approval Number: approval number: 2025-083). Due to the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

Data Availability Statement:

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

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Declaration of Interest:
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