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Prognostic role of serum CA-125 and CA19-9 in lung transplant candidates with interstitial lung disease: a retrospective cohort study

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ABSTRACT

Background Advanced interstitial lung disease (ILD) often necessitates lung transplantation, and identifying accessible prognostic markers is essential for effective management. However, the link between serum tumour markers and survival in waitlisted lung transplant candidates with advanced ILD remains underexplored.

Objective To evaluate associations between serum tumour marker levels and long-term survival in lung transplant candidates with advanced ILD.

Methods This study included 282 patients with end-stage ILD who were waitlisted for lung transplantation from November 2012 to March 2021. Baseline data and serum tumour marker levels were assessed before listing. Vital status and transplant outcomes were retrospectively reviewed as of 31 May 2023. Associations between tumour markers, clinical variables and mortality were analysed using Cox proportional hazards models with competing risk regression.

Results During a median wait time of 17.8 months (IQR: 7.8–44.1), 107 patients received transplants, 38 survived on the list and 137 died while waiting. Multivariable analysis identified higher CA-125 levels (HR 1.03, 95% CI 1.01 to 1.06, p=0.001), older age (HR 1.03, 95% CI 1.01 to 1.06, p=0.001), female gender (HR 1.43, 95% CI 1.01 to 2.04, p<0.04), elevated C-reactive protein (HR 1.17, 95% CI 1.03 to 1.34, p=0.01) and cerebrovascular disease (HR 2.03, 95% CI 1.38 to 2.98, p=0.01) as significant predictors of mortality.

Conclusion Among waitlisted lung transplant candidates with advanced ILD, elevated serum carbohydrate antigen (CA)-125 and CA19-9 levels are associated with higher mortality risk. Routine assessment of these markers may enhance risk stratification for this patient population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Advanced interstitial lung disease is a severe condition that frequently requires lung transplantation.
⇒ The identification of accessible prognostic markers is crucial for effective management.
⇒ Yet, the role of tumour markers as prognostic indicators in lung transplant candidates with advanced interstitial lung disease remains underexplored.

WHAT THIS STUDY ADDS

⇒ Carbohydrate antigen (CA)-125 and CA19-9 are strongly associated with an increased risk of mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Based on these findings, measuring tumour markers may aid physicians in decision-making regarding lung transplant allocation.

INTRODUCTION

Interstitial lung disease (ILD) is a group of chronic respiratory disorders marked by inflammation and/or fibrosis in the lung interstitium.[1–3] When ILD reaches an advanced stage, outcomes are generally poor.[1–3] The course of pulmonary fibrosis varies widely and unpredictably: some patients decline rapidly, others slowly and some remain stable for extended periods.[1–4] Monitoring advanced ILD typically involves high-resolution CT (HRCT) and lung function tests (LFTs).[5] However, these measures have limitations, including high cost, radiation exposure and less-than-optimal patient performance, restricting their usefulness. Therefore, there is a crucial need for additional markers to enhance prognostication.

Serum tumour markers are commonly used for cancer screening and monitoring. However, several studies have reported abnormal levels of these markers in patients with non-malignant respiratory disorders, including ILD.[6–11] Elevated levels of tumour markers have been associated with the severity and progression of ILD,[7–10 12–15] and elevated levels of specific tumour markers, such as carbohydrate antigen (CA)-125,[12 16] CA19-9[7 12] and carcinoembryonic antigen (CEA),[11] have been linked to a higher risk of death. Notably, these studies often focused on specific types

of ILD and evaluated only certain tumour markers. Moreover, the prognostic significance of tumour markers in patients with advanced ILD who are candidates for lung transplantation has not been thoroughly investigated.

The aim of this study was to assess the potential associations between levels of serum tumour markers and long-term survival in waitlisted lung transplant candidates with advanced ILD.

MATERIALS AND METHODS

Study population and design

The study was conducted at Rabin Medical Center, a tertiary care university hospital in Petach Tikva, that has served as Israel's national centre for lung transplantation since 1997. The eligible study population consisted of 293 patients with advanced ILD who were placed on the lung transplantation waiting list between November 2012 and March 2021. Of these, 11 were excluded: 5 patients with cancer, 3 who had a re-transplantation and 3 without available tumour marker measurements. The remaining 282 patients were included in the study. The selection of lung transplant candidates was performed according to international guidelines.[17] Patients with a known diagnosis of cancer were excluded, as they were not referred to the lung transplant clinic nor registered for transplantation.

Patient and public involvement

Patients and members of the public were not involved in the design or conduct of the study.

Data collection and follow-up protocol

Before placement of patients on the transplant list, their demographic and clinical data were recorded and laboratory tests, LFTs and right heart catheterisation (RHC) were performed. The registered laboratory data included serum concentrations of C-reactive protein (CRP) and tumour markers CA-125, CA19-9, CA15-3 and CEA. LFT parameters included forced expiratory volume in 1 s (FEV1), forced vital capacity, FEV1/FVC ratio, total lung capacity (TLC), residual volume (RV) and diffusing lung capacity for carbon monoxide (DLCO). Additionally, the 6-minute walk test (6MWT) was conducted. RHC provided data on cardiac output (CO), cardiac index (CI), pulmonary capillary wedge pressure, mean pulmonary arterial pressure (MPAP) and pulmonary vascular resistance (PVR).

Patients underwent evaluation at the ambulatory clinic every 3–4 months on average; more frequent visits were scheduled based on clinical need. Follow-up procedures consisted of a comprehensive medical interview, physical examination and LFTs. Chest HRCT and echocardiographic examinations were routinely conducted every 12 months. At the end of the follow-up period on 31 May 2023, vital status and lung transplantation data were retrospectively collected from the electronic medical records, Ministry of Internal Affairs and the Israeli Transplant Registry.

Laboratory analysis of serum tumour markers

Venous blood samples were collected into tubes containing separating gel and analysed within 8 hours. The concentrations of CA-125, CA19-9, CA15-3 and CEA were quantified using a validated immunoassay (Elecsys Cobas e 601 analyser, Roche Diagnostics, Indianapolis, Indiana, USA). The test principle was a sandwich immunoassay with a total duration of 18 min. During the first incubation of the sample with the antigen, a biotinylated monoclonal marker-specific antibody and a monoclonal marker-specific antibody labelled with a ruthenium complex formed the sandwich complex. During the second incubation, after the addition of streptavidin-coated microparticles, the complex bound to the solid phase via the interaction of biotin and streptavidin. The reaction mixture was aspirated into the measuring cell where the microparticles were magnetically captured onto the surface of the electrode. Applying a voltage to the electrode induced chemiluminescent emission, which was measured by a photomultiplier. Reference values ranged from 0 to 35 U/mL for CA125, 0–39 U/mL for CA19-9, 0–30 U/mL for CA15-3 and 0–5 ng/mL for CEA.

Outcome measures

The primary outcome measure of the study was case-specific mortality of any cause following placement on the lung transplant waiting list.

Statistical analysis

The results for quantitative data were expressed as mean±SD, while qualitative data were presented as number (percentage). Statistical significance was set at $p \leq 0.05$.

To assess associations between serum CA-125 and CA19-9 levels and LFT parameters, specifically FVC%, FEV1% and TLC%, we conducted linear regression analyses. These models were adjusted for age and sex to control for potential confounding factors.

We evaluated risk factors for mortality among waitlisted lung transplant candidates using a competing-risk regression analysis, applying the Fine and Gray model to account for lung transplantation as a competing event. Survival curves were generated for patients with elevated versus normal levels of each tumour marker, using reference values established for cancer screening.

The impact of potential confounders on the association between tumour markers (analysed as continuous variables) and case-specific mortality was further assessed using the Cox proportional hazards model with competing-risk regression. In this model, HRs for each tumour marker represent the relative risk of mortality associated with each unit increase in serum levels.

Correlation coefficient (r) was calculated to evaluate correlations of serum tumour marker levels with age, CRP values, distance on the 6MWT and LFT. Additionally, a sensitivity analysis was performed, stratifying patients by disease type—idiopathic pulmonary fibrosis (IPF) versus other forms of ILD (non-IPF)—to examine the consistency of associations between serum tumour marker levels and survival outcomes across different ILD diagnosis.

All statistical analyses were conducted using SAS software, V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Baseline characteristics

Table 1 presents the baseline demographic, clinical, laboratory, LFT and RHC data of the 282 waitlisted lung transplant candidates with advanced ILD included in the study. The mean age of the cohort was 58.6±10.2 years; 58.2% were men. The most frequent underlying cause of ILD was IPF. Non-IPF disorders included mainly autoimmune diseases and non-specific interstitial pneumonia. Mean laboratory values were as follows: CA-125, 63.2±80.9 U/mL; CA19-9, 159.7±567.7 U/mL; CA15-3, 91.4±71.0 U/mL; and CEA, 6.2±5.6 ng/mL.

Association with pulmonary function tests

In linear regression analyses, serum CA-125 levels were not significantly associated with FVC% (beta coefficient: −0.010, p=0.3), FEV1% (beta coefficient: 0.005, p=0.4), or TLC% (beta coefficient: −0.002, p=0.6). Similarly, serum CA19-9 levels showed no significant associations with FVC% (beta coefficient: −0.015, p=0.4), FEV1% (beta coefficient: 0.024, p=0.1) or TLC% (beta coefficient: −0.013, p=0.2). These findings indicate that CA-125 and CA19-9 levels do not have a significant association with pulmonary function measures in this cohort.

Survival analysis

Over the median waiting time of 17.8 months on the lung transplant list (IQR: 7.8–44.1), 107 patients (37.9%) underwent lung transplantation, 38 (13.5%) survived while waiting for a transplant and 137 (48.6%) died while waiting for a transplant.

Table 2 shows the results of the univariate analysis with competing risk regression. The following variables were significantly associated with all-cause mortality in the whole cohort: older age (HR 1.04; 95% CI 1.01 to 1.06, p<0.001), higher body mass index (HR 1.12, 95% CI 1.03 to 1.22, p=0.008), having diabetes mellitus (HR 1.45, 95% CI 1.03 to 2.04, p=0.03), having cerebrovascular disease (HR 3.87, 95% CI 3.02 to 4.94, p<0.001) and higher values of CA-125 (HR 1.30, 95% CI 1.08 to 1.56, p=0.005) CA19-9 (HR 1.14, 95% CI 1.03 to 1.26, p=0.01), CRP (HR 1.21, 95% CI 1.07 to 1.36, p=0.001), MPAP (HR 1.01, 95% CI 1.01 to 1.03, p=0.02) and PVR (HR 1.10, 95% CI 1.04 to 1.16, p<0.001). Better survival

Table 1 Baseline demographic, clinical, laboratory, LFT and RHC data of waitlisted lung transplant candidates with advanced ILD

Variable	Whole cohort (N=282)
Age (years)	58.6±10.2
Body mass index (kg/m^2)	31±4.8
Male sex (%)	164 (58.2)
Underlying cause for advanced ILD	
IPF	183 (64.9)
Non-IPF disorder	99 (35.1)
Autoimmune	26 (9.2)
Non-specific interstitial pneumonia	23 (8.1)
Sarcoidosis	15 (5.3)
Occupational	12 (4.3)
Hypersensitivity pneumonitis	5 (1.8)
Others	18 (6.4)
Comorbid conditions	
Hypertension n, (%)	76 (27.0)
Diabetes mellitus n, (%)	87 (30.9)
Positive smoking history n, (%)	86 (30.5)
Cerebrovascular disease	3 (1)
Coronary artery disease	122 (43.2)
Pulmonary embolism	6, (2.1)
Laboratory data	
Serum CA-125 (normal 0–35 U/mL)	63.2±80.9
Serum CA19-9 (normal 0–39 U/mL)	159.7±567.7
Serum CA15-3 (normal 0–30 U/mL)	91.4±71
Serum CEA (normal 0–5 ng/mL)	6.2±5.6
Serum CRP (normal 0–5 mg/dL)	2.78±13.6
6-minute walk test distance (metres)	287.4±122.6
LFT data	
FEV1 (% of predicted value)	50.8±17.3
FVC (% of predicted value)	49.4±17.0
FEV1/FVC ratio	1.2±5.6
TLC (% of predicted value)	55.6±16.6
RV (% of predicted value)	70.9±39.6
DLCO (% of predicted value)	35.8±24.0
RHC data	
CO (L/min)	4.3±1.3
CI (L/min/m^2)	2.6±2.8
PCWP (mm Hg)	9.2±5.8
MPAP (mm Hg)	26.4±11.2
PVR (WU)	4.3±2.8

Data are presented as means±SD, or n (%).
CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CI, cardiac index; CO, cardiac output; CRP, C-reactive protein; DLCO, diffusing lung capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LFT, lung function test; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterisation; RV, residual volume; TLC, total lung capacity; WU, wood units.

Table 2 Variables evaluated for association with all-cause mortality among 282 waitlisted lung transplant candidates with advanced ILD (univariate analysis)

Variable	HR	95% CI	P value
Age (years)	1.04	1.01 to 1.06	**<0.001**
Male sex	0.76	0.55 to 1.06	0.1
Body mass index (kg/m^2)	1.12	1.03 to 1.22	**0.008**
Comorbid conditions			
Hypertension	1.21	1.03 to 204	0.2
Diabetes mellitus	1.45	1.03 to 2.04	**0.03**
Positive smoking history	1.01	0.99 to 1.02	0.2
Cerebrovascular disease	3.87	3.02 to 4.94	**<0.001**
Coronary artery disease	1.22	0.87 to 1.71	0.2
Pulmonary embolism	1.98	0.63 to 6.15	0.2
Laboratory data			
Serum CA-125 (U/mL)	1.30	1.08 to 1.56	**0.005**
Serum CA19-9 (U/mL)	1.14	1.03 to 1.26	**0.01**
Serum CA15-3 (U/mL)	1.10	0.90 to 1.35	0.34
Serum CEA (ng/mL)	1.20	0.97 to 1.57	0.07
Serum CRP (mg/dL)	1.21	1.07 to 1.36	**0.001**
6MWT distance (metres)	0.99	0.99 to 1.00	**<0.001**
LFT data			
FEV1 (% of predicted value)	0.99	0.98 to 1.01	0.9
FVC (% of predicted value)	0.96	0.98 to 1.00	0.26
FEV1/FVC ratio	0.98	0.93 to 0.99	**0.008**
TLC (% of predicted value)	0.98	0.97 to 0.99	**0.02**
RV (% of predicted value)	0.98	0.97 to 0.99	**0.006**
RHC data			
DLCO (% of predicted value)	0.82	0.96 to 0.99	**0.01**
CO (L/min)	1.01	0.68 to 0.98	**0.03**
CI (L/min/m^2)	0.99	0.98 to 1.04	0.3
PWCP (mm Hg)	1.01	0.96 to 1.03	0.93
MPAP (mm Hg)	1.10	1.00 to 1.03	**0.02**
PVR (WU)	0.99	1.04 to 1.16	**<0.001**

Bold entries in the table indicate a p value<0.05.
CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CI, cardiac index; CO, cardiac output; CRP, C-reactive protein; DLCO, diffusing lung capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, hazard ratio; ILD, interstitial lung disease; LFT, lung function test; MPAP, mean pulmonary arterial pressure; 6MWT, 6-minute walk test; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterisation; RV, residual volume; TLC, total lung capacity; WU, wood units.

was significantly associated with a longer 6MWT distance (HR 0.99, 95% CI 0.99 to 1.00, p<0.001), higher FEV1/FVC ratio (HR 0.96, 95% CI 0.93 to 0.99, p=0.008) and higher values of TLC (HR 0.98, 95% CI 0.97 to 0.99, p=0.02), RV (HR 0.98, 95% CI 0.97 to 0.99, p=0.006), DLCO (HR 0.98, 95% CI 0.96 to 0.99, p=0.01) and CO (HR 0.82, 95% CI 0.68 to 0.98, p=0.03).

Figure 1 illustrates the survival curves in the study population, evaluated by the Fine and Gray model, according to normal versus elevated levels of CA-125 and CA19-9. Case-specific cumulative mortality was significantly higher among patients with increased compared with normal levels of serum CA-125 (p=0.007, figure 1A): 25.8% versus 12.7% at 1 year, 40.3% versus 22.6% at 2 years and 48.3% versus 27.6% at 3 years. Mortality rates were also increased in patients with elevated versus normal CA19-9 values (p=0.002, figure 1B): 32.5% versus 9.4% at 1 year, 43.9% versus 22.1% at 2 years, 50.6% versus 28.4% at 3 years. There were no significant differences in survival between patients with high versus normal values of CA15-3 or CEA (data not shown).

Pearson's correlation analysis revealed a significant positive correlation between CRP levels and the serum tumour markers CA-125 (r=0.81, p=0.01) and CA19-9 (r=0.94, p=0.004) in our cohort. However, no significant correlations were found between the levels of individual tumour markers and age, distance on the 6MWT, CRP levels or LFT parameters (data not shown).

In the multivariable logistic regression analysis conducted on the entire patient cohort, considering covariates such as CA19-9, CA-125, age, sex, CRP, diabetes mellitus, cerebrovascular disease, the (continuous) variables most significantly associated with mortality were levels of higher CA-125 (HR 1.03, 95% CI 1.01 to 1.06, p=0.001), older age (HR 1.03, 95% CI 1.01 to 1.06, p=0.001), female gender (HR 1.43, 95% CI 1.01 to 2.04, p<0.04), higher CRP (HR 1.17, 95% CI 1.03 to 1.34, p=0.01) and having cerebrovascular disease (HR 2.03, 95% CI 1.38 to 2.98, p=0.01).

Sensitivity analysis by disease type

In a sensitivity analysis by disease type, elevated CA-125 levels were significantly associated with higher mortality in the IPF group (HR 1.317, 95% CI 1.030 to 1.684, p=0.0281), with age also being a significant factor (HR 1.062, 95% CI 1.021 to 1.105, p=0.0031). In contrast, CA19-9 was not significantly linked to survival in patients with IPF. For the non-IPF group, CA-125 levels showed a non-significant trend towards increased mortality (HR 1.392, 95% CI 0.970 to 1.998, p=0.0728), while age and CA19-9 levels were not significantly associated with survival outcomes.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the prognostic significance of tumour markers in waitlisted lung transplant candidates with advanced ILD. The results yielded a strong association of elevated serum CA-125 and CA19-9 levels with an increased risk of mortality.

Increased levels of circulating tumour markers have been previously reported in patients with non-malignant

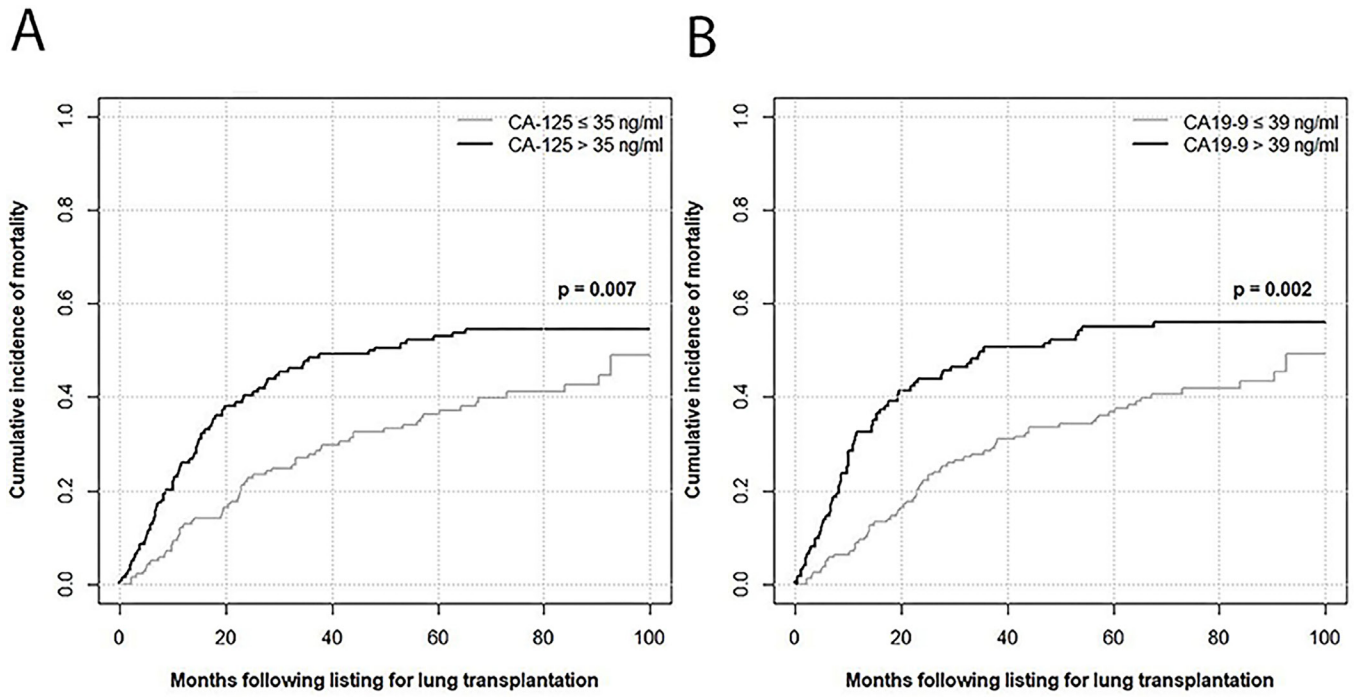

Figure 1 Cumulative incidence of case-specific mortality among waitlisted lung transplant candidates according to high versus normal levels of CA-125 (A) and CA19-9 (B). CA, carbohydrate antigen.

pulmonary disorders,[6] including ILD.[6–11] However, there is little solid information regarding an association of elevated levels of serum tumour markers with survival in this population. Kodama *et al*[6] reported that among 50 patients with idiopathic interstitial pneumonia and collagen disease-related pulmonary fibrosis, higher-than-normal CA19-9 levels were associated with increased long-term mortality. Maher *et al*[12] demonstrated that elevated concentrations of serum CA-125 and CA19-9, compared with stable concentrations over time, were powerful predictors of mortality in 127 patients with IPF. Additionally, Alqalyoobi *et al*[16] studied the relationship between serum CA-125 and progression-free survival, defined as death, lung transplant or a ≥10% relative decline in FVC, in 307 patients with connective tissue disease-associated and unclassifiable ILD.[16] High CA-125 levels were found to be significantly associated with poor survival. Furthermore, Rusanov *et al*[18] demonstrated that tumour markers are elevated in candidates for lung transplantation and tend to decrease following the transplant procedure. Finally, Kwon *et al*[11] evaluated the prognostic role of CA-125, CA19-9 and CEA in 294 patients with ILD and found that elevated values of each marker were associated with increased long-term mortality on univariate analysis.[11] On multivariate analysis, performed for CEA only due to missing CA-125 and CA19-9 data, higher CEA levels remained significantly associated with mortality.

The findings of our study generally align with previous reports, although several differences in design are noteworthy. Some of the prior investigations included a relatively small patient population, focused on type-specific ILD or lacked information about certain tumour markers.

When we conducted a sensitivity analysis stratifying patients into IPF and non-IPF groups, we observed notable differences in the prognostic significance of serum tumour markers. Elevated CA-125 levels were significantly associated with increased mortality in the IPF group, whereas CA19-9 did not demonstrate a similar association. This variation likely reflects disease-specific heterogeneity between IPF and non-IPF conditions. IPF is characterised by a distinct pathophysiological profile, including progressive fibrosis and unique molecular pathways, which may explain the stronger prognostic relevance of CA-125 in this subgroup. In contrast, non-IPF conditions include a mix of autoimmune, hypersensitivity and occupational lung diseases, potentially reducing the impact of any single biomarker. Additionally, the smaller sample size of the non-IPF subgroup may have limited the statistical power to detect significant associations. These findings highlight the need for larger, multicentre studies to confirm the prognostic utility of tumour markers across ILD subtypes and to clarify the underlying mechanisms driving these disease-specific differences.

We propose that measuring CA-125 and CA19-9 could aid in identifying patients at the highest risk of waitlist mortality, irrespective of age and severity of LFT and RHC parameters. Serum tumour marker assessment is a widely available and cost-effective laboratory tool, and its incorporation into the routine management of lung transplant candidates with ILD could contribute to prioritising donor transplant allocation. However, the applicability of our findings needs to be validated through further research.

The pathophysiological mechanisms underlying the associations of CA-125 and CA19-9 with poor survival in the patient with ILD population are not fully understood. Several studies have shown that elevated levels of CA-125[7 10] and CA19-9[9 10 13] correlate with parameters of ILD severity, such as decline in pulmonary function and extent of HRCT findings. Additionally, an increase in levels of CA-125[14] and CA19-9[12 15] over time has been identified as a potential predictor of ILD progression. In an immunohistochemical study of patients with progressive IPF, Maher *et al*[12] noted an overexpression of CA-125 and CA19-9 within the metaplastic epithelium of the fibrotic lungs. In patients with advanced ILD, the striking expression of these tumour markers in the more severe fibrotic pulmonary lesions may contribute to their more significant elevation in serum concentrations and an increased risk of mortality. Thus, elevated serum levels of CA-125 and CA19-9 may be considered markers of damage severity, which would explain their association with poor prognosis.

In our cohort, we did not find a significant correlation between tumour marker levels (CA-125 and CA19-9) and disease severity as measured by lung function parameters. This may be explained by the advanced disease stage of our population, composed exclusively of patients waitlisted for lung transplantation. At such an advanced stage, lung function parameters may no longer adequately differentiate disease severity, as these patients often exhibit uniformly severe disease. Furthermore, tumour markers were measured only at the time of waitlisting, which does not account for potential fluctuations in their levels over time. These fluctuations may correlate with changes in LFTs, providing additional prognostic information. It is also possible that elevated tumour marker levels reflect systemic processes, such as inflammation, fibrosis-related epithelial injury or immune dysregulation, which are not directly captured by LFTs. Prior studies[12 16] may have observed stronger correlations due to their inclusion of a broader spectrum of ILD severity, allowing for more variability in both lung function and marker levels. Longitudinal studies tracking tumour markers and dynamic changes in LFTs could help clarify the interplay between these markers and disease progression.

While CA-125 and CA19-9 were associated with mortality, CEA and CA15-3 were not. Previous studies have explored the role of these markers in ILD, particularly in rheumatoid arthritis-associated ILD (RA-ILD) and connective tissue disease-related ILD. For instance, Wang *et al*[19] found that elevated levels of CA125 were more prevalent in patients with RA-ILD than in those with RA alone, while CEA levels were not significantly higher in the RA-ILD population. Moreover, El-Din Mohamed *et al*[20] observed that CA15-3 levels were significantly higher in the reticulation group compared with the honeycombing group in patients with ILD. They suggested that this may be because reticulation represents active fibrosis, whereas honeycombing indicates established fibrosis.

These findings suggest that while CA15-3 may reflect disease activity, its utility in predicting mortality in ILD is less clear, and CEA may be less relevant in non-malignant ILD. The lack of prognostic value for these markers in terms of mortality may be due to differences in their biological roles at different stages of ILD or variability in their expression across different types of ILD. Additionally, the smaller sample sizes of patients with elevated CEA and CA15-3 in these studies may have limited the statistical power to detect significant associations. Further studies with larger sample sizes are needed to clarify the prognostic role of these markers in ILD.

In our cohort, we did not find a significant correlation between tumour marker levels (CA-125 and CA19-9) and disease severity as measured by lung function parameters. This may be explained by the advanced disease stage of our population, composed exclusively of patients waitlisted for lung transplantation. At such an advanced stage, lung function parameters may no longer adequately differentiate disease severity, as these patients often exhibit uniformly severe disease. Furthermore, tumour markers were measured only at the time of waitlisting, which does not account for potential fluctuations in their levels over time. These fluctuations may correlate with changes in LFTs, providing additional prognostic information. It is also possible that elevated tumour marker levels reflect systemic processes, such as inflammation, fibrosis-related epithelial injury or immune dysregulation, which are not directly captured by LFTs. Prior studies may have observed stronger correlations due to their inclusion of a broader spectrum of ILD severity, allowing for more variability in both lung function and marker levels. Longitudinal studies tracking tumour markers and dynamic changes in LFTs could help clarify the interplay between these markers and disease progression.

Our findings revealed a strong positive correlation between CRP levels and serum tumour markers CA-125 and CA19-9 in patients with advanced ILD. This association is consistent with previous research showing that inflammation markers, such as CRP, correlate with elevated tumour markers in non-malignant pulmonary conditions, including ILD. Zheng *et al*[21] reported that levels of CA19-9, CA-125 and CRP are higher in patients with RA-ILD than in those without ILD. Liu *et al*[22] found that elevated CA-125 levels in patients with systemic sclerosis-associated ILD (SSc-ILD) who also had high baseline CRP were associated with shorter survival and predicted long-term declines in FVC independently of potential confounders. Stock *et al*[23] also demonstrated an association between elevated CRP levels and 5-year mortality across four groups: RA-ILD, SSc-ILD, IPF and fibrotic hypersensitivity pneumonitis.

Importantly, we believe that CA-125 and CA19-9 offer incremental prognostic value beyond CRP. In our multivariable logistic regression analysis, CA-125 retained a significant association with mortality even after adjusting for CRP. We hypothesise that CA-125 not only reflects the effects of systemic inflammation but also captures

the extent of tissue damage and fibrosis. Maher *et al*[12] highlighted that these biomarkers, secreted predominantly by metaplastic epithelium in fibrotic lung lesions, act as markers of epithelial damage and remodelling in IPF. Their histological evidence demonstrated increased expression of CA-125 and CA19-9 within metaplastic bronchial epithelium and honeycomb cysts, further supporting their role as indicators of disease progression. Further studies are warranted to validate the independent prognostic utility of CA-125 and CA19-9 and to explore their potential as therapeutic targets or as markers for treatment response in advanced ILD.

Strengths and limitations

The present study has several strengths. First, it represents a pioneering effort to investigate the prognostic utility of various tumour markers among a relatively large population of patients with advanced ILD, who are candidates for lung transplantation. Second, our study includes patients with a wide spectrum of ILD aetiologies, reflecting a real-world population of waitlisted lung transplant candidates. Third, we evaluated the prognostic significance of tumour markers as both continuous and dichotomised (high vs normal level) variables. Finally, the associations of CA-125 and CA19-9 with poor survival were confirmed by multivariate analysis with adjustment for crucial potential cofounders such as age, gender and CRP level.

The study was limited by its retrospective, single-centre design, which restricts the ability to establish causal relationships and limits the generalisability of the findings to other medical centres. Multicentre prospective studies are required to validate these results and enhance the external validity of our conclusions. Additionally, tumour markers were measured only at the time of waitlisting for lung transplantation, which does not account for potential fluctuations in marker levels over time. Such fluctuations could affect the markers' prognostic accuracy. Longitudinal assessments of serum tumour markers would provide a clearer understanding of their dynamics and prognostic implications in patients with advanced ILD.

CONCLUSIONS

Among waitlisted lung transplant candidates with advanced ILD, elevated serum levels of CA-125 and CA19-9 are strongly associated with an increased risk of mortality. We suggest that measuring these markers may aid physicians in decision-making regarding lung transplant allocation.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Rabin Medical Center (approval number: RMC-0375-23). Informed consent was not required due to the retrospective nature of the study and the anonymised data used, as approved by the ethics committee.

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