CA 19-9 serum levels in patients with end-stage idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases (ILDs): Correlation with functional decline

Elisabetta Balestro1, Gioele Castelli1, Nicol Bernardinello1, Elisabetta Cocconcelli1, Davide Biondini1, Federico Fracasso1, Federico Rea1, Marina Saetta1, Simonetta Baraldo1 and Paolo Spagnolo1

Abstract

Idiopathic pulmonary fibrosis presents a progressive and heterogeneous functional decline. CA 19-9 has been proposed as biomarker to predict disease course, but its role remains unclear. We assessed CA 19-9 levels and clinical data in end-stage ILD patients (48 IPF and 20 non-IPF ILD) evaluated for lung transplant, to correlate these levels with functional decline. Patients were categorized based on their rate of functional decline as slow (n = 20; ΔFVC%pred ≤ 10%/year) or rapid progressors (n = 28; ΔFVC%pred ≥ 10%/year). Nearly half of the entire patients (n = 32; 47%) had CA 19-9 levels ≥ 37kU/L. CA 19-9 levels in IPF were not different from non-IPF ILD populations, however, the latter group had a median CA 19-9 level above the normal cut-off value of 37 KU/L (60 [17–247] kU/L). Among IPF patients, CA 19-9 was higher in slow than in rapid progressors with a trend toward significance (33 vs 17kU/L; p = 0.055). In the whole population, CA19-9 levels were inversely related with ΔFVC/year (r = -0.261; p = 0.03), this correlation remained in IPF patients, particularly in rapid progressors (r = -0.51; p = 0.005), but not in non. Moreover, IPF rapid progressors with normal CA 19-9 levels showed the greater ΔFVC/year compared to those with abnormal CA 19-9 (0.95 vs. 0.65 L/year; p = 0.03). In patients with end-stage ILD, CA 19-9 may represent a marker of disease severity, whereas its level is inversely correlated with functional decline, particularly among IPF rapid progressors.

Keywords

Idiopathic pulmonary fibrosis, interstitial lung disease, CA 19-9, serum biomarkers, lung transplantation

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown etiology associated with significant morbidity and mortality.1 The clinical course of IPF is highly heterogeneous and unpredictable with some patients progressing rapidly (rapid progressors),...
others declining slowly (slow progressors), and others experiencing episodes of sudden worsening following periods of relative stability.1–3 Such variable disease course makes it challenging to predict the trajectory of IPF in individual patients and several studies have tried to identify tools to predict both disease progression and risk of mortality. A number of risk models have been developed that incorporate demographic, clinical and physiological variables, including the du Bois’ model and the Gender, Age, Physiology (GAP) index.4,5 Though undoubtedly valuable, these scoring systems are not able to predict disease behavior. Change in forced vital capacity (FVC) is a reliable, valid and reproducible measure of disease progression as well as an independent predictor of mortality and treatment response.6–8 However, considerable inter-individual and intraindividual variability exists in the rate of FVC decline over time in patients with IPF.9,10 These issues highlight the need for additional and more reliable non-invasive tools to improve risk stratification and prediction of outcome in IPF.

Significant advances in the pathogenesis of IPF over the last two decades have led to the identification of several potential predictors of disease behavior, such as KL-6, CCL18 and MMP-7.11,12 However, they are neither able to predict disease progression nor are they routinely available in clinical practice.13 Recently, Maher and colleagues have conducted a large prospective study of patients with IPF to investigate the predictive power of selected biomarkers and to identify individuals with IPF at risk of progression or death. Among all biomarkers examined, including cytokines, chemokines, growth factors, extracellular matrix proteins and markers of epithelial injury, the authors found that serum levels of Carbohydrate Antigen 19-9 (CA 19-9), a marker of epithelial damage, was significantly associated to disease progression in the first year of follow-up.14 However, it is unclear whether CA 19-9 will maintain the same prognostic power throughout the natural history of the disease. With this background, the aim of our study was to investigate the role of serum CA 19-9 levels in IPF patients with advanced disease referred to our lung transplant center and its relation with different patterns of functional decline (rapid vs. slow progression as assessed by the rate of FVC decline). In addition, we evaluated the significance of CA 19-9 levels in patients with interstitial lung disease (ILD) other than IPF who also displayed a progressive fibrosing phenotype.

Material and methods

Study population

The study population included a well-characterized cohort of patients with end-stage IPF and non-IPF ILD referred to our center and evaluated for lung transplantation. Clinical, laboratory and lung function data were retrospectively collected at the time of listing for transplant. In all patients, the diagnosis of IPF or non-IPF ILD was made following multidisciplinary discussion and in accordance with the ATS/ERS/JRS/ALAT guidelines on IPF.1

CA 19-9 levels were determined by the solid-phase, two-site chemiluminescent enzyme immunoassay with levels above 37 kU/L considered abnormal.15 Measurements were performed by an experienced technician blinded to clinical information.

All causes of increased CA 19-9 levels, such as gastrointestinal cancers and concomitant nonmalignant diseases (i.e. extra-hepatic cholestasis, hepatic cirrhosis or gallbladder disease) were carefully investigated by the examinations routinely performed during the lung transplant evaluation and excluded. FVC changes in the year before referral (median follow-up value 13 months) were used to phenotype patients as either “rapid” (n = 39, decline in % predicted FVC >10% per year) or “slow” (n = 29, decline in % predicted FVC ≤10% per year) progressors, as previously reported 3. The absolute fall in FVC in mL normalized per year was also calculated. Additional functional parameters such as diffusing capacity of the lung for carbon monoxide (DLco) and 6-minute walking test were available for only a minority of patients and were therefore excluded from the analysis.

Statistical analysis

All continuous variables were tested for normality. To compare clinical and functional data between IPF and non-IPF ILD patients, and between rapid and slow progressors, Mann–Whitney U test was used when normality assumptions were not met. In IPF patients, analyses were also performed after treatment stratification (treated versus untreated). Correlation coefficients between functional and laboratory data were calculated using the nonparametric Spearman’s rank method. ROC curves for CA 19-9 were performed using Youden J test.
All data were analyzed using SPSS Software version 25.0 (New York, NY, US: IBM Corp. USA). p-values <0.05 were considered statistically significant.

Results

The study population included 68 patients referred to our center for potential listing for lung transplantation. Forty-eight (n = 48) patients had IPF (age 60 [54–62] years) and 20 (n = 20) patients had ILD other than IPF (age 57 [55–60] years), including idiopathic Non-Specific Interstitial Pneumonia (n = 9), chronic Hypersensitivity Pneumonitis (n = 6), pulmonary Sarcoidosis (n = 3) and Pleuroparenchymal Fibroelastosis (n = 2). Nearly half of IPF patients (n = 23, 48%) were on antifibrotic therapy. Clinical, functional characteristics and CA 19-9 levels of the entire study population and of different subgroups are shown in Table 1.

Values are expressed as numbers and (%) or median and interquartile range as appropriate.

As expected, most patients were males and former smokers, with a similar smoking history between IPF and non-IPF ILD patients (p = 0.44). Patients with IPF and non-IPF ILD differed in terms of age at diagnosis (55 vs. 51 years), but did not differ significantly with regard to time from diagnosis to referral (36 vs. 35 months). Patients with IPF and non-IPF ILD were comparable with regard to degree of lung function decline; indeed, although patients with non-IPF ILD had slightly lower values of FVC at referral (37 vs. 48% pred), the two groups had a similar FVC loss per year (400 vs. 460 mL).

In the entire study population, 32 patients (47%) presented CA 19-9 levels above the cut-off value (37 kU/L). Levels of CA 19-9 were not significantly different in IPF patients than in non-IPF ILD patients (26 [7–106] vs. 60 [17–247], p = 0.14) (Figure 1A); however, the latter group had a median CA 19-9 level above the normal cut-off value of 37 KU/L (60 [17–247] kU/L). The established cut-off of 37 KU/L is derived from studies in malignancies, though it has also been applied to IPF. We then applied a ROC curve analysis to our data, which resulted in best threshold value at 24.6 kU/L, with a modest accuracy. An analysis of the cohort in relation to this threshold is presented in Table S1 (supplementary material).

Given the heterogeneous clinical course of IPF patients, in further analyses we evaluated CA 19-9 levels in patients stratified by the rate of their functional decline (i.e., slow [S, n = 20] or rapid [R, n = 28] progressors).

The median FVC decline %pred/year before referral was 17% in rapid progressors (absolute FVC decline 0.72 L) and 2% in slow progressors (absolute FVC decline 0.13 L). Slow and rapid progressors were similar with regard to age at diagnosis (55 vs. 56 years), age at listing (59 vs. 60 years) as well as time from diagnosis to referral (36 vs. 36 months). Similarly, there were no between group differences with regard to number of patients on antifibrotic therapy (9 [45%] vs. 14 [50%]). Conversely, FVC both as absolute value (L) and %predicted at referral was significantly lower in rapid progressors than in slow progressors (1.70 L vs. 2.11 L, p = 0.02; 43% vs. 55% %pred., p = 0.005 respectively). Interestingly, rapid progressors displayed lower serum levels of CA 19-9 compared to slow progressors, although this difference did not reach statistical significance (17 [3–70] kU/L vs. 33 [16–415] kU/L, p = 0.055 respectively) (Figure 1B).

We then analyzed the correlation between CA 19-9 values and loss of FVC L/year before referral in the entire patient population, in the IPF and non-IPF ILD subgroups as well as in rapid and slow progressors. We observed an inverse correlation between CA 19-9 levels and FVC L/year in the entire study population (r = -0.261, p = 0.031) (Figure 2). This negative correlation remained significant in patients with IPF (r = -0.335, p = 0.020), but not in those with non-IPF ILD (r = 0.100, p = 0.67) (Figure 3). Noteworthy, CA 19-9 serum levels were inversely correlated with FVC L/year among rapid (r = -0.515, p = 0.005), but not slow progressors (r = 0.239, p = 0.31) (Figure 4).

Finally, when rapid progressors were considered, we observed that patients with CA 19-9 levels below 37 kU/L (n = 17) experienced a significantly more rapid FVC decline L/year compared to patients with CA 19-9 >37 kU/L (n = 11) (0.95 vs. 0.65 L/year; p = 0.03) (Figure 5).

When we compared clinical and functional characteristics between IPF patients with and without antifibrotic treatment, we did not observe any statistical significance with the exception of age at diagnosis, which was lower in untreated patients. In particular CA 19-9 levels were similar between treated and untreated patients (supplementary material, Table S2).

Discussion

In this study, we assessed CA 19-9 serum levels in patients with end-stage IPF and compared them with
|                          | Entire population (n = 68) | IPF (n = 48) | Non-IPF ILD (n = 20) | IPF—Slow progressor (n = 20) | IPF—Rapid progressor (n = 28) | p value |
|--------------------------|-----------------------------|--------------|----------------------|-------------------------------|--------------------------------|---------|
| Male—n (%)               | 54 (80)                     | 42 (88)      | 12 (60)              | 18 (90)                       | 24 (86)                       | ns      |
| Age at diagnosis—years   | 54 (49–59)                  | 55 (51–59)   | 51 (48–54)           | 55 (51–59)                    | 56 (47–59)                    | ns      |
| Smoking history—pack years | 6 (0–25)                   | 6 (0–24)     | 0 (0–25)             | 17 (1–28)                     | 5 (0–18)                      | ns      |
| Former—n (%)             | 40 (59)                     | 31 (65)      | 9 (45)               | 15 (75)                       | 16 (57)                       | ns      |
| Nonsmokers—n (%)         | 28 (41)                     | 18 (35)      | 11 (55)              | 5 (25)                        | 12 (43)                       | ns      |
| Age at referral—years    | 59 (55–61)                  | 60 (54–62)   | 57 (55–60)           | 59 (56–61)                    | 60 (49–62)                    | ns      |
| CA 19-9 referral—kU/L    | 32 (11–180)                 | 26 (7–106)   | 60 (17–247)          | 33 (16–415)                   | 17 (3–70)                     | 0.05    |
| >37 kU/L—n (%)           | 32 (47)                     | 20 (42)      | 12 (60)              | 9 (45)                        | 11 (39)                       | ns      |
| <37 kU/L—n (%)           | 36 (53)                     | 28 (58)      | 8 (40)               | 11 (55)                       | 17 (61)                       | ns      |
| FVC at referral—L        | 1.70 (1.24–2.18)            | 1.84 (1.38–2.27) | 1.34 (0.95–1.69)     | 2.11 (1.77–2.46)              | 1.70 (1.25–2.06)              | 0.02    |
| FVC at referral—%pred.   | 46 (35–57)                  | 48 (36–58)   | 37 (34–55)           | 55 (49–62)                    | 43 (34–52)                    | 0.005   |
| FVC decline per year—L   | 0.43 (0.20–0.89)            | 0.46 (0.18–0.93) | 0.40 (0.20–0.72)     | 0.13 (0.03–0.26)              | 0.72 (0.50–1.20)              | <0.0001 |
| FVC decline per year—%pred. | 12 (5–19)                | 11 (5–19)    | 11 (3–14)           | 2 (3–7)                       | 17 (13–24)                    | <0.0001 |
| Time from diagnosis to referral, months | 35 (23–65)       | 36 (26–59)   | 35 (18–151)          | 36 (23–57)                    | 36 (25–67)                    | ns      |

Values are expressed as numbers and (%) or median and interquartile range as appropriate.
those of patients with end-stage non-IPF ILD undergoing evaluation for lung transplantation. In addition, we stratified data analysis based on the rate of FVC decline over the 12-month period (slow vs. rapid progressors) preceding listing for transplantation. Nearly half (n = 32, 47%) of our entire study population had CA19-9 levels higher than the cut-off value of 37 kU/L. Somewhat unexpectedly, CA 19-9 levels correlated inversely with the rate of FVC decline; this correlation remained intact among the IPF population and, further subgrouping these patients, only in the group of rapid progressors. In addition, among rapid progressors, those with CA 19-9 levels below the cut-off of 37 kU/L had statistically more rapid FVC decline in the year before referral than rapid progressors with high CA19-9 levels (0.95 vs. 0.65 L/year p = 0.03).

In a large prospective, longitudinal cohort of treatment-naive patients with IPF, Maher and coworkers assessed an array of biomarkers, with the aim to identifying potential predictors of clinical outcome. Specifically, by using a multiplex immunoassay, they quantified a panel of 123 possible biomarkers with putative pathogenic roles in IPF. The protein that most clearly distinguished progressive from stable disease was CA 19-9 and this was the only biomarker that remained significant after multivariate correction for the others 123 variables. Notably, in the Maher’s study, CA19-9 was significantly increased in patients with progressive disease (mean value: 53 U/mL) than in those with stable disease whose CA 19-9 levels remained within normal limits (22 U/mL). In a different study, Rusanov and coworkers collected

Figure 1. CA 19-9 levels (logarithmic expression of kU/L). a) CA 19-9 levels in patients with IPF and patients with ILD (non-IPF). White box indicates IPF and gray box ILD (non-IPF). b) CA 19-9 levels in patients with slow progression and rapid progression of IPF. White box indicates slow progressor and gray box rapid progressor (non-IPF). Horizontal bars represent median values; bottom and top of each box plot 25th and 75th; brackets show 10th and 90th percentiles; points and triangles indicate outliers. The red line represents the 37 kU/L cut-offs in logarithmic expression.

Figure 2. Correlation between CA 19-9 levels (kU/L) and ΔFVC L/year in the entire population (IPF and ILD non-IPF). The black line represents the correlation in the entire population. Spearman’s rank correlation: r = −0.261, p = 0.03 in the entire population.
samples from patients with progressive IPF referred for lung transplantation and observed increased CA 19-9 levels (121 ± 28 kU/L).\textsuperscript{16} Taken together, these observations suggest that CA 19-9 levels tend to progressively increase over the disease course.

CA 19-9 has been primarily evaluated as a tumor marker, especially in gastro-enteric tumors\textsuperscript{17}; however, increased serum levels of CA 19-9 have been shown in a number of non-malignant diseases such as extra-hepatic cholestasis, hepatic cirrhosis or gall-bladder disease.\textsuperscript{18} With regard to respiratory diseases, increased CA19-9 levels have been observed in idiopathic non-specific interstitial pneumonia, hypersensitivity pneumonitis and sarcoidosis.\textsuperscript{19} Totani and colleagues measured CA 19-9 levels in the serum, bronchoalveolar lavage fluid (BALF) and epithelial lining fluid (ELF) of 31 patients with IPF.\textsuperscript{20} Serum CA19-9 levels correlated positively with disease extent on chest X-ray, number of BALF neutrophils as well as ELF CA 19-9 levels. Notably, serum CA 19-9 did not correlate with markers of disease activity such as serum LDH, KL-6, SP-A, and SP-D, suggesting that serum CA 19-9 levels may reflect progression rather than activity of pulmonary fibrosis. In a Japanese study, Kodama and coworkers analyzed CA 19-9 in 554 patients diagnosed with either lung cancer (n = 323) or nonmalignant pulmonary disease (n = 231), including, among others, idiopathic interstitial pneumonia and connective tissue disease-associated ILD.\textsuperscript{21} 30.7% of patients with lung cancer and

![Figure 3](image3.png)

*Figure 3. Correlation between CA 19-9 levels (kU/L) and ΔFVC L/year in IPF and non-IPF ILD patients. The black line represents the correlation. a) Correlation in IPF patients. Spearman’s rank correlation: \( r = -0.335, p = 0.02 \). b) Correlation in non-IPF ILD patients. Spearman’s rank correlation: \( r = -0.101, p = 0.67 \).*

![Figure 4](image4.png)

*Figure 4. Correlation between CA 19-9 levels (kU/L) and ΔFVC L/year in IPF patients with rapid and slow progression. The black line represents the correlation. a) Correlation in rapid progressors. Spearman’s rank correlation: \( r = -0.515, p = 0.005 \). b) Correlation in slow progressors. Spearman’s rank correlation: \( r = 0.239, p = 0.31 \).*
38.9% of patients with nonmalignant lung disease displayed CA 19-9 higher than the cut-off level of 37 U/mL. Several studies have shown that patients with IPF have a significantly higher risk to develop lung cancer compared with the general population, with incidence rates ranging between 3% and 22% and prevalence rates exceeding 50%. Therefore, in the presence of elevated levels of tumor markers, it is imperative to carefully screen IPF patients with advanced disease (before listing for lung transplant, as was the case in our entire study population) for an occult neoplasm. The mechanisms leading to elevation of CA 19-9 levels in ILDs are unknown. One hypothesis is that excessive CA 19-9 is released by regenerating epithelial cells in damaged lungs. Low levels of CA 19-9 have also been reported for severely damaged lungs but this could be due to the loss of the ability to regenerate the alveolar epithelium in some patients. At present, the determinants of the elevated CA 19-9 levels in ILD and its correlation with poor prognosis remain speculative.

In our study, pre-transplant serum levels of CA 19-9 between rapid and slow progressors trended toward significance (p = 0.055). Interestingly, CA 19-9 levels inversely correlated with FVC loss among rapid, but not slow progressors. In addition, among rapid progressors, patients with CA 19-9 levels below the cut-off displayed the greater FVC loss in the year before referral (0.95 vs. 0.65 L/year; p = 0.03). This seems apparently in contrast from previous literature, where rapid progressors, in the first year after diagnosis, presented higher CA 19-9 serum levels. However, our study captures the end-stage disease scenario, searching if this prognostic value remains along the disease course. In fact, analyses were conducted in the end stage of the natural history of the disease that was never investigated in relation to disease progression. Differently, Maher and coauthors investigated patients with IPF at diagnosis and followed them for 1 year to determine disease progression. In our investigation we wanted to capture the later phase of the disease when marked fibrosis with architectural distortion of the lung has already happened. The inverse correlation between CA 19-9 levels and functional decline, particularly among IPF rapid progressors raised an interesting hypothesis. We can speculate that rapid progressors, especially those with the greater functional loss, may experience a very rapid evolution toward epithelial-to-mesenchymal transition. As CA 19-9 is a marker of bronchial epithelial proliferation, exhausted cells from rapid progressors in severely damaged lungs may not be able to regenerate and produce sufficient amount of CA 19-9. Conversely, in Maher’s study, the positive correlation between CA 19-9 levels and progression may reflect the active phase of the disease (initial phase) with extensive regeneration of epithelial cells. Our observation highlights the potential utility of measuring CA 19-9 at different time points during the disease course to evaluate its role as a prognostic biomarker. However, the contribution of additional mechanisms that drive the disease toward a rapid decline cannot be excluded. We have previously shown that rapid progressors are characterized by the activation of both innate and adaptive immune responses leading to a prominent immune inflammatory response. Therefore, the accelerated disease course of rapid progressors may go beyond epithelial proliferation and be detected by biomarkers of immune dysregulation such as CCL8, alveolar macrophage activation (M2), CCL18 and Toll-like receptors.

The results of our study should be interpreted in the light of several limitations. First, this was a
retrospective cohort study, therefore data were collected from medical records, which may introduce inaccuracies. However, every effort was made to reduce this risk. Antifibrotic treatment (i.e., pirfenidone and nintedanib) slow down functional decline and disease progression of patients with IPF. In our study, nearly half of patients (48%) were on antifibrotic therapy as they were part of an historical cohort from the pre-antifibrotics era. However, the percentage of patients on antifibrotic therapy was equally distributed between slow and rapid progressors, and no statistical difference were found in any of the subgroups. The study included a relatively small number of patients. However, it should be noticed that only a small minority of the IPF population is referred to and evaluated for lung transplantation. On the other hand, our study cohort is phenotypically very well defined and includes deliberately patients for whom lung function data were fully available. We measured CA 19-9 levels at a single time point (i.e. referral for transplant); however, Maher and colleagues observed similar CA 19-9 levels at baseline and after 3 months later suggesting that there may not be a progressive increase of CA 19-9 levels over a short period of time. Whether this is the case in the longer term remains to be elucidated. Finally, our study included a highly selected subgroup of patients; therefore, our findings may not be generalizable to the entire IPF patient population due to the great variability of natural history and disease phenotypes.

Notwithstanding these limitations, our study suggest that CA 19-9 levels may be variable during the course of IPF, with increased levels in the end-stage disease. However, there could be a possible decline in secretion in those lungs, which reached a loss of epithelial regeneration. Further prospective studies are needed to validate these findings about CA 19-9 role in IPF prognosis and assess whether they hold true outside the setting of end-stage IPF patients undergoing evaluation for lung transplantation.

**Abbreviations list**

| Abbreviation | Description |
|--------------|-------------|
| IPF          | Idiopathic Pulmonary Fibrosis |
| ILD          | Interstitial Lung Disease |
| CA 19-9      | Carbohydrate Antigen 19-9 |
| FVC          | Forced Vital Capacity |

**Authors’ note**

All authors take responsibility for the content of the manuscript, including data and analysis.

**Author contributions**

Conceptualization, Elisabetta Balestro; Data curation, Gioele Castelli, Nicol Bernardinello, Federico Fracasso; Formal analysis, Gioele Castelli, Nicol Bernardinello, Federico Fracasso, Simonetta Baraldo, Davide Biondini; Funding acquisition, Paolo Spagnolo; Investigation, Elisabetta Balestro; Elisabetta Cocconcelli; Writing—review & editing, Elisabetta Balestro, Simonetta Baraldo, Marina Saetta, Federico Rea and Paolo Spagnolo.

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**ORCID iD**

Elisabetta Balestro https://orcid.org/0000-0003-1373-8197
Gioele Castelli https://orcid.org/0000-0002-5925-4035

**Supplemental material**

Supplemental material for this article is available online.

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