Original Article

# Survival predictors of interstitial lung disease in India: Follow-up of Interstitial Lung Disease India registry

*Sheetu Singh[1], Mohan Bairwa[2], Bridget F. Collins[3], Bharat Bhushan Sharma[4], Jyotsana M Joshi[5], Deepak Talwar[6], Nishtha Singh[7], Khushboo Pilania[8], Parthasarathi Bhattacharya[9], Neeraj Gupta[10], Ravindran Chetambath[11], Aloke G. Ghoshal[12], Surya Kant[13], Parvaiz A Koul[14], Raja Dhar[15], Rajesh Swarnakar[16], Virendra Singh[7], Ganesh Raghu[3]*

*Author affiliations at the end*

## ABSTRACT

**Background:** Predictors of survival for interstitial lung disease (ILD) in the Indian population have not been studied. The primary objective of the study was to assess the Modified-Gender Age and Physiology (M-GAP) score to predict survival in patients with ILD seen in clinical practice. We also analyzed the role of demographic and radiological characteristics in predicting the survival of patients with ILD. **Materials and Methods:** In the ILD India registry, data were collected from 27 centers across 19 cities in India between March 2012 and June 2015. A single follow-up was conducted at 18 centers who agreed to participate in the follow-up in 2017. M-GAP score (range 0–5) was calculated with the following variables: age (≤60 years 0, 61–65 years 1, and >65 years 2), gender (female 0, male 1), and forced vital capacity% (>75% 0, 50%–75% 1, and >75% 2). A score of 0–3 and score of 4 and 5 were classified into Stage 1 and 2, respectively. Other predictors of survival, such as the history of tuberculosis, smoking, and the presence of honeycombing on computed tomography scan, were also evaluated. **Results:** Nine hundred and seven patients were contacted in 2017. Among them, 309 patients were lost to follow-up; 399 were alive and 199 had died. M-GAP was significantly associated with survival. Similarly, other predictors of survival were ability to perform spirometry (hazard ratio [HR]: 0.49, 95% confidence interval [CI]: 0.34–0.72), past history of tuberculosis (HR: 1.57, 95% CI: 1.07–2.29), current or past history of smoking (HR: 1.51, 95% CI: 1.06–2.16), honeycombing (HR: 1.81, 95% CI: 1.29–2.55), a diagnosis of connective tissue disease -ILD (HR: 0.41, 95% CI: 0.22–0.76), and sarcoidosis (HR: 0.24, 95% CI: 0.08–0.77). **Conclusion:** In a subgroup of patients with newly diagnosed ILD enrolled in ILD India registry and who were available for follow-up, M-GAP score predicted survival. Honeycombing at the time of diagnosis, along with accurate history of smoking, and previous history of tuberculosis were useful indices for predicting survival.

**KEY WORDS:** Hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, interstitial lung disease, survival

**Address for correspondence:** Dr. Sheetu Singh, 167 Officers' Campus Extension, Sirsi Road, Jaipur - 302 012, Rajasthan, India. E-mail: sheetusingh@yahoo.co.in

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## INTRODUCTION

Interstitial lung disease (ILD) is a heterogenous group of disease with survival depending on a multitude of factors such as age, sex, vital capacity, honeycombing in computed tomography (CT) scan, and type of ILD. Subsequent to the diagnosis of ILD, prognostication and survival prediction are expected. Various scores have been developed for predicting survival.[1-4] These scores should

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include accurate predictors and be practically feasible and simple. The Gender, Age, and Physiology (GAP) index score includes forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO) as physiologic markers to predict survival for patients with ILD and is widely used.[5] FVC measurement has been used to assess the primary outcome of treatment response in most clinical trials and spirometry is readily available in clinical practice. Several technical factors associated with DLCO measurement may account for the DLCO to be the most variable lung function test between and within centers.[6] Besides, DLCO may also not be readily available in all ambulatory settings, especially in India. Kobayashi *et al*. have described a "modified GAP score" (M-GAP) including FVC, age, and gender, but excluding DLCO to predict acute exacerbations and survival in patients with lung cancer and ILD [Figure 1].[7] We have explored the utility of the M-GAP score and other survival predictors among patients with new-onset ILD (without lung cancer) in the ILD India registry[8] with the hope that this may be a useful index in clinical practice.

## MATERIALS AND METHODS

The ILD India registry recruited 1084 consecutive consenting patients with new-onset ILD from 27 centers across 19 cities in India (March 2012–June 2015).[8] Adult patients with cough, dyspnea, and bilateral diffuse parenchymal lung disease on high-resolution CT (HRCT) of the chest and without active infection such as pulmonary tuberculosis and malignancy were included. Diagnoses were validated with multidisciplinary discussions (MDD) conducted at the Center for ILD, University of Washington, Seattle.[8] The study was approved by the institutional review board and the Clinical Trials Registry of India (CTRI/2013/05/003674).

| | | |
|---|---|---|
| G | Gender | |
| | Female | 0 |
| | Male | 1 |
| A | Age, years | |
| | ≤60 y | 0 |
| | 61-65 y | 1 |
| | >65 y | 2 |
| P | Physiology, FVC % predicted | |
| | >75% | 0 |
| | 50-75% | 1 |
| | <50% | 2 |

| m-GAP score | |
|---|---|
| Stage 1 | Score 0-3 |
| Stage 2 | Score 4-5 |

**Figure 1:** Modified Gender Age Physiology score used to assess the prognosis of patient with interstitial lung disease

Follow-up data were collected from patients enrolled in 18 participating centers [Figure 2] using a detailed case report form. Analysis was done for the entire data set including those patients who could not perform spirometry. A subanalysis was also done on patients who could perform spirometry to analyze M-GAP in prognosticating the disease. The M-GAP score (range 0–5) was calculated with the following variables: age (≤60 years 0, 61–65 years 1, and >65 years 2), gender (female 0, male 1), and FVC% (>75% 0, 50%–75% 1, and <50% 2).[7] A Stage of I or II M-GAP was assigned based on score between 0–3 and 4–5, respectively. The GAP score (range 0–8) included in addition to the above DLCO (>55%: 0, 36%–55%: 1, <35%: 2, and cannot perform: 3).[5] A Stage of I, II, or III GAP was assigned on the basis of score between 0–3, 4–5, and 6–8, respectively. Honeycombing was defined as layered, cystic spaces that share walls. Emphysema was noted as a feature by the radiologist as focal lucencies, not bounded by visible walls, measuring up to 1 cm and located within the secondary pulmonary lobule (centrilobular), all parts of the lobule (panacinar), and adjacent to pleura and septal lines (paraseptal). A past history of tuberculosis was confirmed by examining old records of the patients, including chest X-ray, sputum for acid-fast bacilli, or mycobacterial cultures. Current or past history of tobacco smoking was defined as patients smoking tobacco for at least 6 months.

SPSS version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA) was used for analyses. Kaplan–Meier survival curves and log-rank tests were used to compare survival time. The

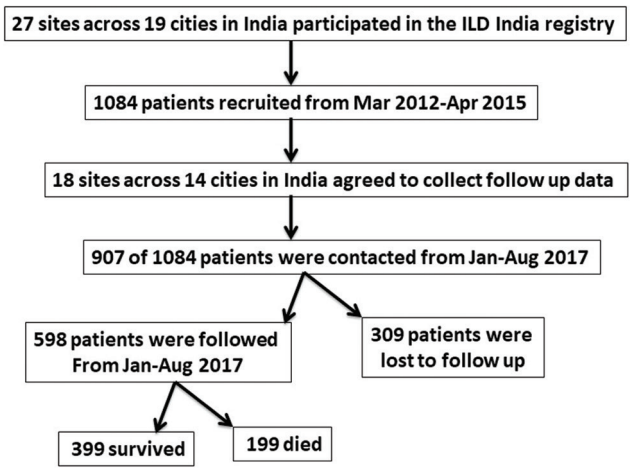


**Figure 2:** Flowchart depicting the recruitment of patients in the Interstitial Lung Disease India registry and subsequently in the follow-up

Cox regression hazard model was used to identify various predictors of survival of ILD patients.

## RESULTS

Nine hundred and seven patients were contacted from January 01, 2017, to August 31, 2017; 309 had been lost to follow-up; 399/530 were alive; and 199 had died (28 and 171 patients died due to nonrespiratory and respiratory causes, respectively) [Figure 2]. The demographic details of the patients who died and survived are elaborated in Table 1. Among the 598 total patients who had follow-up data inclusive of spirometry, 288 (48.2%) had hypersensitivity pneumonitis (HP), 84 (14%) had idiopathic pulmonary fibrosis (IPF), 94 (15.7%) had connective tissue disease-ILD (CTD-ILD), 41 (6.9%) had sarcoidosis, and 91 (15.2%) had other ILDs. The common comorbidities manifested at the time of follow-up visit were gastroesophageal reflux disease (72, 12.0%), pulmonary artery hypertension by echocardiograph findings (72, 12.0%), diabetes mellitus (33, 5.5%), osteoporosis (22, 3.7%), sleep apnea (13, 2.2%), cardiac conditions (11,1.8%), depression (9,1.5%), pulmonary tuberculosis (7, 1.2%), and neoplasm (1, 0.2%). A total of 185/598 (30.9%) patients were hospitalized due to worsening respiratory conditions. Of the 399 patients who were alive on follow-up, 201 (50.4%) had quit working due to worsened respiratory status; 53 (13.3%) were on supplemental oxygen; 216 (54.1%) were sedentary and not engaged in exercise activities such as daily walks, exercise, or yoga; and 186 (46.6%) were vaccinated both for influenza and pneumococcal vaccines. The median survival for patients with ILD was 21.6 months (8.3–34.9). The ability to perform spirometry was associated with better survival (3-year survival rate 67.8%, 95% confidence interval [CI]: 63.3–72.3) [Figure 3]. On Cox regression analysis, it was found that the ability to perform spirometry was associated with lower risk of mortality (hazard ratio [HR]: 0.49, 95% CI: 0.34–0.72, $P < 0.001$). The risk was adjusted for age, sex, residence, honeycombing, history of tuberculosis, smoking history, and subtype of ILD.

Analysis of subset of patients who were able to perform spirometry was done on 530 patients (366 survived, 164 died); M-GAP Stage 1 and 2 were calculated. India in general appears to be poor with 54.5% (95% CI: 47.4%–61.6%) survival at 4 years (IPF – 31%, 95% CI: 16.7%–45.2%; HP – 51.6%, 95% CI: 40.3%–63%, CTD-ILD – 79.1%, 95% CI: 66.1%–92.1%; and sarcoidosis – 90%, 95% CI: 78.7%–101.3%) [Table 2]. Table 3 shows the survival rates as per the M-GAP stage 1 and 2 for HP and IPF. The other subtypes had few numbers in the two stages of M-GAP, thereby analysis was not possible.

Figures 4-7 show the Kaplan–Meier survival curves. The predictors of survival [Table 4] using Cox proportional hazard model (adjusted for duration of disease symptoms, residence, and radiological evidence of emphysema) were M-GAP (HR: 1.65, 95% CI: 1.14–2.39), past history of tuberculosis (HR: 1.57, 95% CI: 1.07–2.29), current or past history of smoking (HR: 1.51, 95% CI: 1.06–2.16), and presence of honeycombing in HRCT scan images of the chest (HR: 1.81, 95% CI: 1.29–2.55). Patients with a diagnosis of CTD-ILD (HR: 0.41, 95% CI: 0.22–0.76) and sarcoidosis (HR: 0.24, 95% CI: 0.08–0.77) had better survival than patients with other types of ILD. GAP and M-GAP both were significant in bivariate analysis denoted by Kaplan–Meier graphs. However, on multivariate

**Table 1: Characteristics of the patients of the Interstitial Lung Disease India registry followed up from January to August 2017**

| Characteristics | Patients died (*n*=199) | Patients survived (*n*=399) |
|---|---|---|
| Age (years) | 58.6±14.1 | 54.1±13.0 |
| Sex (males/females) | 111/99 | 144/255 |
| Total duration of illness (months) | 46.8±35.8 | 49.8±37.4 |
| FVC (L) | 1.5±0.6 | 1.70±0.70 |
| Current or ex-smoker | 65 | 55 |
| ILD diagnosis | | |
| HP | 98 | 190 |
| CTD-ILD | 14 | 80 |
| IPF | 47 | 37 |
| NSIP | 15 | 24 |
| Sarcoidosis | 3 | 38 |
| Occupational ILD | 8 | 11 |
| Other | 14 | 19 |
| Radiological parameters | | |
| Reticulations | 168 | 289 |
| Ground glass haziness | 121 | 269 |
| Air trapping | 29 | 96 |
| Honeycombing | 104 | 111 |
| Consolidation | 13 | 41 |
| Mediastinal LAD | 38 | 103 |

CTD: Connective tissue disease, ILD: Interstitial lung disease, HP: Hypersensitivity pneumonitis, IPF: Idiopathic pulmonary fibrosis, LAD: Lymphadenopathy, FVC: Forced vital capacity, NSIP: Nonspecific interstitial pneumonia

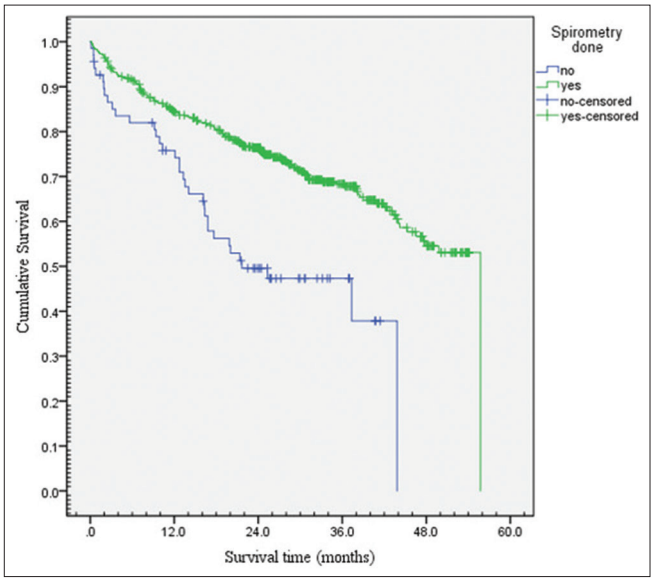


**Figure 3:** Kaplan–Meier survival curves for difference in survival based on ability to perform spirometry

**Table 2: Disease-specific survival for 1, 2, 3, and 4 years**

| Subtype of ILD | 95% CI | | | |
|---|---|---|---|---|
| | 1-year survival | 2-year survival | 3-year survival | 4-year survival |
| IPF | 75.3 (65.7-85.0) | 60.9 (49.7-72.1) | 46.9 (34.3-59.6) | 31.0 (16.7-45.2) |
| HP | 83.3 (78.6-88.1) | 76.1 (70.6-81.6) | 66.9 (60.1-73.7) | 51.6 (40.3-63.0) |
| CTD-ILD | 95.4 (90.9-99.8) | 90.4 (84.1-96.7) | 84.4 (75.5-93.3) | 79.1 (66.1-92.1) |
| Sarcoidosis | - | 94.7 (87.6-101.8) | - | 90.0 (78.7-101.3 |
| Other types of ILD | 79.7 (70.9-88.6) | 67.5 (57.0-78.1) | 65.8 (55.0-76.6) | 49.5 (30.9-68.0) |
| Cumulative | 84.5 (81.4-87.6) | 76.4 (72.7-80.1) | 68.3 (63.8-72.8) | 54.5 (47.4-61.6) |

CI: Confidence interval, CTD: Connective tissue disease, ILD: Interstitial lung disease, HP: Hypersensitivity pneumonitis, IPF: Idiopathic pulmonary fibrosis

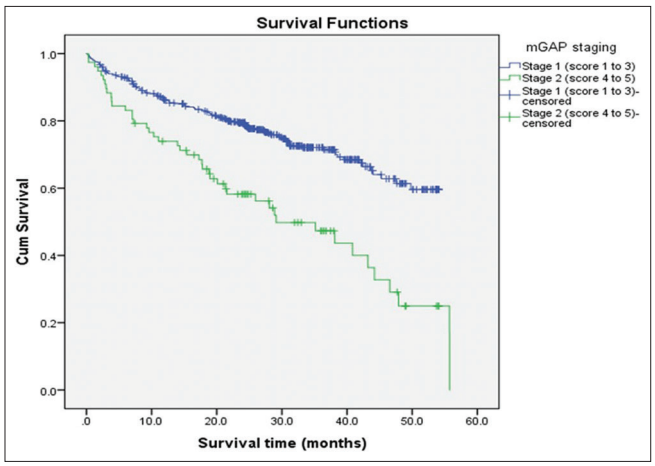


**Figure 4:** Kaplan–Meier survival curves depicting the difference in survival in modified Gender Age Physiology Stage 1 versus 2

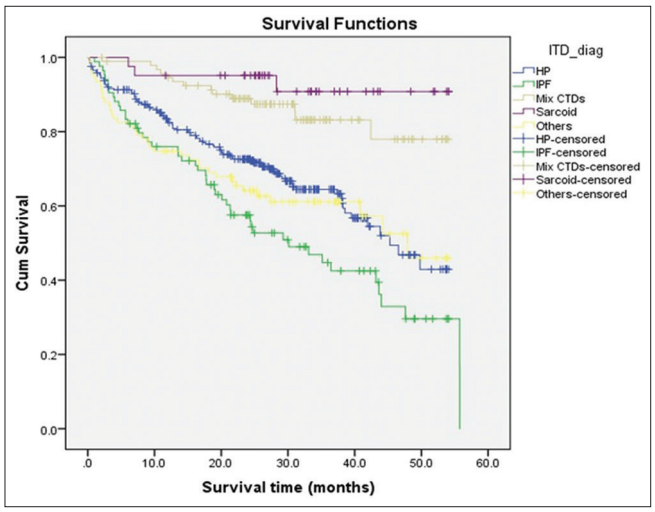


**Figure 6:** Kaplan–Meier survival curves depicting survival difference for various interstitial lung disease subtypes

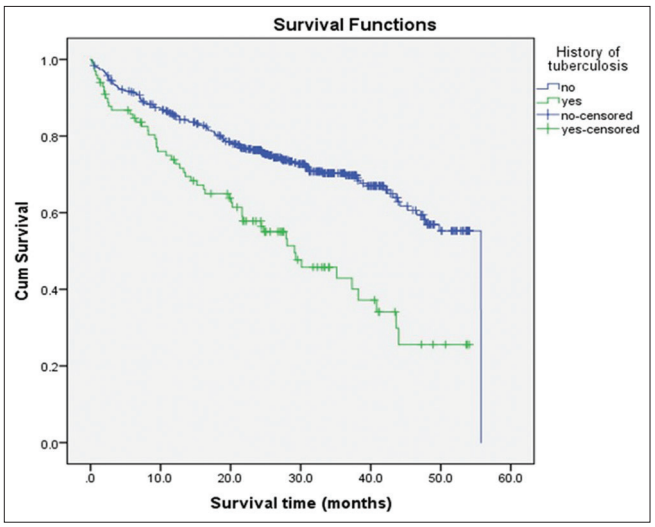


**Figure 5:** Kaplan–Meier survival curves depicting survival difference for presence versus absence of past history of pulmonary tuberculosis

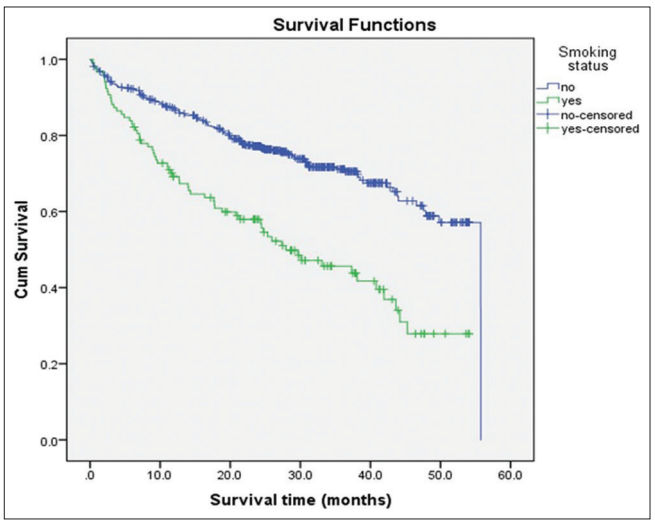


**Figure 7:** Kaplan–Meier survival curves for difference in survival for current and past history of tobacco smoking

analysis, only M-GAP was significant (small number in the GAP group).

## DISCUSSION

ILD India registry is the first prospective ILD registry in India. It has also been the largest follow-up study analyzing the data gathered from 598 patients. Survival for ILD in India, appears to be poor with up to 46% mortality at 4 years. A novel score, i.e., M-GAP, was analyzed in this population to predict survival. It predicted 1-year survival of 85% and 71% for Stage I and II, respectively, for patients with HP 78% and 71% for Stage I and II, respectively, for patients with IPF. The predictors associated with worse survival include honeycombing, current or past history of smoking, and past history of pulmonary tuberculosis.

**Table 3: Survival up to 3 years for the followed-up patients in the interstitial lung disease India registry as per the Modified Gender Age Physiology stage for hypersensitivity pneumonitis and idiopathic pulmonary fibrosis**

| Subtype of ILD | Survival | M-GAP stage | |
|---|---|---|---|
| | | Stage I (Score 0-3) | Stage II (Score 4-5) |
| HP | 1 year | 85.4 (80.6-90.3) | 70.6 (55.3-85.9) |
| | 2 years | 79.1 (73.4-84.7) | 58.3 (41.6-75.0) |
| | 3 years | 71.6 (64.6-78.6) | 39.5 (20.5-58.5) |
| IPF | 1 year | 77.7 (66.1-89.3) | 71.3 (54.4-88.1) |
| | 2 years | 64.4 (50.8-78.1) | 54.9 (35.7-74.1) |
| | 3 years | 46.9 (31.2-62.7) | 48.1 (27.0-69.1) |

M-GAP: Modified Gender Age Physiology, HP: Hypersensitivity pneumonitis, IPF: Idiopathic pulmonary fibrosis, ILD: Interstitial lung disease

**Table 4: Multivariate Cox proportional hazard model for predicting survival among interstitial lung disease patients from Interstitial Lung Disease Registry India, 2012-2017#**

| Variables | Hazard ratio* | 95% CI limits | | *P* |
|---|---|---|---|---|
| | | Lower | Upper | |
| History of TB | 1.57 | 1.07 | 2.29 | **0.020** |
| History of smoking | 1.51 | 1.06 | 2.16 | **0.024** |
| Honeycombing | 1.81 | 1.29 | 2.55 | **0.001** |
| M-GAP staging | 1.65 | 1.14 | 2.39 | **0.008** |
| Diagnosis | | | | |
| HP | 1.00 | - | - | - |
| IPF | 1.04 | 0.69 | 1.57 | 0.847 |
| CTD-ILD | 0.41 | 0.22 | 0.76 | **0.005** |
| Sarcoidosis | 0.24 | 0.08 | 0.77 | **0.016** |
| Others** | 1.06 | 0.67 | 1.66 | 0.806 |

*In years, #Adjusted for patient's age, sex, residence, and emphysema, **Pneumoconiosis, organizing pneumonia, Langerhan's cell histiocytosis, lymphangioleiyomyomatosis, desquamative interstitial pneumonia, pulmonary alveolar proteinosis, lymphocytic interstitial pneumonia, respiratory bronchiolitis associated ILD, alveolar microlithiasis and unclassifiable ILD. M-GAP: Modified Gender Age Physiology, HP: Hypersensitivity pneumonitis, IPF: Idiopathic pulmonary fibrosis, CTD: Connective tissue disease, ILD: Interstitial lung disease, CI: Confidence interval. Bold Values: Highlighted values indicate significant difference noted with values <0.05

Diagnosis of CTD-ILD and sarcoidosis was associated with better survival.

The duration between the first symptom and diagnosis of ILD was almost 4 years at the time of recruitment in the registry, indicating a delay in the diagnosis. Delayed diagnosis leads to the progression of the disease, which is substantiated by the fact that 17% of the ILD India registry patients had resting oxygen saturation <90% and mean FVC 57% (±23%) at baseline. It is much lower than the indices of patients of a single-center large study, having a mean FVC of 73% (±21%) and oxygen saturation ranging from 95% to 98%.[9] In addition to delayed diagnosis and advanced disease, other variables in clinical practices such as lack of standardized ILD care guidelines, lack of defined survival predictors, and high prevalence of pulmonary infections such as tuberculosis may also contribute the high mortality.[10]

Despite the limited lung biopsies in the patients who were enrolled in the ILD-India registry–a point criticized,[11,12] the diagnosis was ascertained by MDD and the disease course of various subtypes of ILD is consistent with that known from previous literature. Except HP and sarcoidosis, the prevalence of IPF, CTD-ILD, non-IPF IIPs, and other ILDs are in comparable range.[9] Higher mortality observed in the HP group (vs. sarcoidosis group) in our study precludes the possibility of sarcoidosis being misdiagnosed as HP. Similarly, lower mortality in the HP group (vs. IPF group) may preclude the possibility of IPF being misdiagnosed as HP.

GAP score index has been used to predict survival in patients with IPF.[5] In their study, Ley *et al*. predicted 1-year mortality of 6%, 16%, and 39% for GAP Stages 1, 2, and 3, respectively.[5] The ILD-GAP score was a modification of the GAP score, which was primarily developed for IPF.[13] The ILD-GAP also took into account the type of ILD in addition to gender, age, FVC, and DLCO. In yet another model, longitudinal fall in FVC along with the GAP score index was noted in the longitudinal-GAP model.[14] Similarly, CT-GAP included CT fibrosis score in addition to parameters recorded in the GAP score.[15] However, all these scores required the measurement of DLCO, an investigation that had limited availability in community settings and a significant variability. The M-GAP was initially developed to prognosticate 43 patients of IPF who developed lung cancer, as they were not subjected to diffusion studies.[7] The 1-year survival in this study was 42%. In our pilot study, we explored the potential of the M-GAP score, eliminating the DLCO value, as a simplified version of the GAP score index to assess prognosis.[7] An M-GAP Stage II was associated with worse outcomes with lesser 1-year survival than Stage I (1-year survival for Stage I and II is 85% vs. 71%, respectively, for HP; 78% vs. 71% for IPF) [Table 3]. The traditional GAP score was not associated with survival correlation among ILD patients in our study. This may be because of relatively small number of patients in the study had DLCO measurements available to calculate the GAP score ($n$ = 106, 20%). In addition, the GAP score was developed for IPF, whereas all patients in our sample did not have IPF. The M-GAP successfully predicted 1-year survival for patients with Stage I and II diseases.

In addition to M-GAP, as a secondary objective, the other survival predictors were also assessed for the Indian population. Patients of ILD with a past history of pulmonary tuberculosis are quite common in India, a comorbid condition that was associated with significantly worse survival. Concomitant lung damage due to posttubercular sequelae and ILD may be reason of the poor outcome. Another significant predictor of poor survival was the history of tobacco smoking currently or in the past. Associated lung damage due to smoking may be a possible reason, though in previous studies it has been reported on the contrary.[2,4] Previous studies have suggested no prognostic effect of concomitant emphysema in patients with IPF. However, none of these studies have

been on Indian population. The genetic and environmental factors also play a role in disease behavior. Fibrosis and honeycombing have been established as poor predictors in previous studies also.[16] The inability to perform spirometry was associated with poor survival probably due to advanced disease, rendering the patient unable to perform the technique. This is the largest article from the Indian subcontinent highlighting the survival predictors for patients with ILD.

Limitations of this study include a selection bias in the patient cohort: data analyzed were in the cohort of patients in whom a single follow-up data were available during a fixed duration of time, i.e., January 1, 2017–August 31, 2017. While 34.1% of the patients were lost to follow-up, the baseline clinical characteristics of the 598 total patients with follow-up data available were similar to those of the original cohort of 1084 patients. Third, the M-GAP score used in the study has not been validated. The M-GAP may be criticized for including only FVC as a functional index. However, FVC has been used quite widely. Conventionally, IPF was classified into mild, moderate, and severe in various clinical trials and early classification systems based on FVC.[17-23] It has been shown that 5%–10% fall in FVC is associated with worse survival in patients with IPF, and a 2%–6% change in FVC is called the minimal clinically important difference.[24]

## CONCLUSION

Acknowledging the limitations, observations from this study provide valuable insight into the predictors of survival among patients with ILD using simple clinical parameters in the Indian population. Advanced disease at the time of presentation and frequent change of doctors are ground realities of ILD patients in the clinical practice of a common pulmonologist in India. The M-GAP score can be easily calculated with routine, bedside clinical parameters and may be particularly useful in resource-limited settings where DLCO cannot be easily obtained. Further, the prognostic markers, including smoking history, past history of tuberculosis, inability to perform spirometry, and honeycombing on HRCT, are poor prognostic markers, and should be sought actively when evaluating a patient during first consultation. While our findings suggest the clinical utility of the mGAP, further studies are warranted to compare with the GAP index in the same population and validate our observations.

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### Conflicts of interest

There are no conflicts of interest.

*[1]Department of Chest and Tuberculosis, SMS Medical College, Jaipur, Rajasthan, India, [2]Department of Community Medicine, All India Institute of Medical Sciences, New Delhi, India, [3]Department of Medicine, Center for Interstitial Lung Diseases, University of Washington, Seattle, WA, USA, [4]Department of Medicine, SMS Medical College, Jaipur, Rajasthan, India, [5]Department of Pulmonary Medicine, Topiwala National Medical College and BYL Nair Hospital, Mumbai, Maharashtra, India, [6]Department of Pulmonary and Sleep Care Medicine, Metro Multispeciality Hospital, Noida, Uttar Pradesh, India, [7]Department of Pulmonary Medicine, Asthma Bhawan, Jaipur, Rajasthan, India, [8]Jankharia Imaging Center, Mumbai, Maharashtra, India, [9]Department of Respiratory Medicine, Institute of Pulmocare and Research, Kolkata, West Bengal, India, [10]Department of Respiratory Medicine, JLN Medical College and Hospital, Ajmer, Rajasthan, India, [11]Department of Pulmonary Medicine, Government Medical College, Kozhikode, Kerala, India, [12]Department of Respiratory Medicine, National Allergy Asthma Bronchitis Institute, Kolkata, West Bengal, India, [13]Department of Pulmonary Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India, [14]Department of Internal and Pulmonary Medicine, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India, [15]Department of Pulmonology and Critical Care, Fortis Hospital, Kolkata, West Bengal, India, [16]Department of Respiratory, Critical Care, Sleep Medicine and Interventional Pulmonology, Getwell Hospital and Research Institute, Nagpur, Maharashtra, India*

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