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The ILD-GAP Risk Prediction Model Performs Poorly in Myositis-Associated Interstitial Lung Disease

Rebeccah M. Brusca[a], **Iago Pinal-Fernandez**[a,b], **Kevin Psoter**[a], **Julie J. Paik**[a], **Jemima Albayda**[a], **Christopher Mecoli**[a], **Eleni Tiniakou**[a], **Andrew L. Mammen**[a,b], **Lisa Cristopher-Stine**[a], **Sonye Danoff**[a,*], and **Cheilonda Johnson**[a,*]

[a]Johns Hopkins University School of Medicine, 1830 East Monument Street, Suite 500, Baltimore, MD 21224, USA

[b]National Institute of Arthritis and Musculoskeletal and Skin Disease, National Institute of Health, Muscle Disease Unit, Laboratory of Muscle Stem Cells and Gene Regulation, 9000 Rockville Pike Building 50, Bethesda, MD 20892, USA

Abstract

Purpose: Myositis-associated interstitial lung disease (MA-ILD) is associated with increased mortality, but no prognostic model exists in this population. The ILD-GAP index was developed to predict mortality risk across all subtypes of chronic ILD. The purpose of this study was to validate the ILD-GAP risk prediction model in patients with MA-ILD.

Procedures: We completed a retrospective cross-sectional study of patients enrolled in the Johns Hopkins Myositis Center database between 2006 and 2017. Cumulative mortality rates were estimated using the Kaplan-Meier test. Model calibration was determined by using standardized mortality ratios of observed versus expected deaths.

Main Findings: 179 participants with MA-ILD were included. The mean baseline percent predicted forced vital capacity was 65.2 ± 20.6%, forced expiratory volume in the first second 65.4 ± 20.4%, and carbon monoxide diffusing capacity 61.6 ± 20.0%. Thirty-two participants died (17.9%). The ILD-GAP model had poor discriminative performance and calibration.

Conclusions: The ILD-GAP risk prediction model is a poor predictor of mortality among individuals with MA-ILD. The identification of a better predictive model for MA-ILD is needed to help guide care in this patient population.

Keywords

myositis; lung diseases; interstitial; calibration; cross-sectional studies

Corresponding Author: Cheilonda Johnson, MD, Division of Pulmonary, Allergy, & Critical Care Medicine, 3400 Spruce Street, 9054 Gates Building, Philadelphia, PA 19104, Cheilonda.Johnson@uphs.upenn.edu.

*Co-Senior Authors.

COMPETING INTERESTS

None

INTRODUCTION

Myositis is a chronic heterogeneous group of connective tissue disorders associated with dermatologic, cardiovascular and pulmonary morbidity.[1] The prevalence of myositis-associated interstitial lung disease (MA-ILD) is high,[2] and has been associated with increased mortality in this population.[3–6] Despite the known increased mortality among individuals with MA-ILD, risk prediction is challenging given the heterogeneity of disease presentation and progression. The GAP risk prediction model was initially developed for patients with idiopathic pulmonary fibrosis (IPF) as a prognostic guide.[7] The ILD-GAP index was created to better predict mortality across all chronic ILD subtypes, including those with connective tissue disease (CTD).[8] This index added a disease subtype variable to the GAP model and demonstrated good discrimination in a group of individuals with chronic ILD.[8] However, neither the GAP model nor ILD-GAP index have been validated in individuals with MA-ILD. The purpose of this study was to validate the ILD-GAP risk prediction model in this population.

METHODS

We performed a retrospective cross-sectional study of consecutive patients enrolled in the Johns Hopkins Myositis Center database between January 2006 and July 2017. Autoimmune myositis cases included polymyositis (PM), dermatomyositis (DM), and clinically amyopathic dermatomyositis (CADM). Individuals were classified has having clinically evident MA-ILD if they met American Thoracic Society criteria for restriction or diffusing capacity deficits[9] and had evidence of diffuse parenchymal lung disease on high-resolution computed tomography. All participants provided written informed consent; the present study was approved by the Johns Hopkins University IRB (NA_00007454).

Derivation and validation of the ILD-GAP index has been described previously.[8] The predictor variables considered in this model include gender, age, lung physiology variables (forced vital capacity [FVC] and carbon monoxide diffusing capacity [DLCO]), and ILD subtype (IPF, CTD-associated ILD/idiopathic nonspecific interstitial pneumonia, chronic hypersensitivity pneumonitis, or unclassifiable ILD). The ILD-GAP index is calculated by combining points assigned to the variables listed above to obtain a total point score. The total point score is used to classify patients to stages, which correlate with predicted mortality.

All-cause mortality was determined and confirmed through the Social Security Death Index. Lung transplantation was treated as a competing risk. Follow-up time was defined as the date of diagnosis with autoimmune myositis to the date of death or lung transplantation or the last follow-up visit. Cumulative mortality rates were estimated using the Kaplan-Meier test. Model calibration was determined by using standardized mortality ratios of observed versus expected deaths. All calculations were performed using intercooled Stata 13 (StataCorp, College Station, TX).

RESULTS

This study included 179 individuals with MA-ILD. Most participants were women (68.2%) with a mean age of 57.8 ± 12.2 years, and 36.9% of participants were African-American. Ninety-five (53%) had DM, 79 (44%) PM, and 5 (3%) CADM. The mean body mass index was 29.1 ± 6.9 kg/m^2. The mean percent predicted FVC was 65.2 ± 20.6%, forced expiratory volume in the first second (FEV1) 65.4 ± 20.4%, total lung capacity (TLC) 67.1 ± 18.2%, and DLCO 61.6 ± 20.0%. One hundred sixty-eight participants (93.9%) had autoantibodies with anti-Jo-1 being the most common. The median follow-up time was 9 years (range 0-24 years). There were 32 deaths; one participant underwent lung transplantation.

The ILD-GAP model had poor discriminative performance and calibration in this patient population (Table 1). The ILD-GAP model predicted higher mortality rates than that observed in this population at 1, 2 and 3-years.

DISCUSSION

This study of a well-characterized, diverse cohort of participants with MA-ILD showed poor discriminative performance of the ILD-GAP risk prediction model. There are several potential explanations for our findings. The ILD-GAP model was designed to assess three-year risk. In our study population, only 20% of events (death or lung transplantation) occurred within three years of diagnosis, with most occurring after five years. This may be related to differences in overall survival and or response to therapy in this patient population compared to patients with other forms of CTD-ILD. Staging systems derived in this population would need to consider mortality over a longer time period to accurately predict risk. Our study included a relatively large proportion of African-Americans. The racial/ethnic breakdown of the populations of the GAP model and ILD-GAP index are not publically available, but attempts to validate the GAP model among non-Western IPF patients have produced mixed results.[10–12] Race may play a significant role in prognosis among individuals with ILD, specifically MA-ILD, and may be an important variable in future derivation scores. Finally, it may be inappropriate to so heavily weigh lung physiology variables in models designed to assess disease severity in patients with MA-ILD. Autoantibodies, including anti-Jo1, are known to correlate with increased risk of ILD among patients with myositis and may also correlate with disease activity.[5,13] Creatinine kinase and aldolase, which correlate with myositis activity, may also be markers of ILD severity early in the course of disease.[13,14] Inclusion of these biomarkers may increase the validity of a prognostic model for MA-ILD.

We were unable to develop a potential prognostic model due the relatively small number of events compared to potential predictor variables. A longitudinal collaborative multicenter study is needed to generate a risk prediction model in patients with MA-ILD.

CONCLUSIONS

In conclusion, The ILD-GAP risk prediction model is a poor predictor of mortality risk among individuals with MA-ILD. The identification of a better predictive model for MA-ILD is needed to help guide care in this patient population.

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- Neither the GAP model nor ILD-GAP index have been validated in individuals with myositis-associated interstitial lung disease (MA-ILD).
- The ILD-GAP risk prediction model is a poor predictor of mortality among individuals with MA-ILD
- The identification of a better predictive model for MA-ILD is needed to help guide care in this patient population.

Table 1.

One, two and three-year survival probabilities, by ILD-GAP Index

ILD-GAP Index	1-year survival				2-year survival				3-year survival			
	# at Risk	# of Events	Observed (95% CI)	Predicted	# at Risk	# of Events	Observed (95% CI)	Predicted	# at Risk	# of Events	Observed (95% CI)	Predicted
0-1	128	1	99% (94.6-99.9)	96.9%	126	2	98% (92.9-99.2)	93.4%	124	1	97% (91.9-98.8)	89.8%
2-3	39	0	100%	91.2%	39	0	100%	82%	39	1	97% (83.2-99.6)	73.1%
4-5	7	0	100%	81.8%	7	1	86% (33.4-97.9)	65%	7	1	86% (33.4-97.9)	50.8%

Observed = Observed survival in the current MA-ILD cohort

Predicted= Predicted survival based on the original ILD-GAP cohort derivation