ERJ Express. Published on May 3, 2018 as doi: 10.1183/13993003.00255-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

African-American Race and Mortality in Interstitial Lung Disease: A Multicenter Propensity-Matched Analysis

Ayodeji Adegunsoye, Justin M. Oldham, Shashi K. Bellam, Jonathan H. Chung, Paul A. Chung, Kathleen M. Biblowitz, Steven Montner, Cathryn Lee, Scully Hsu, Aliya N. Husain, Rekha Vij, Gokhan Mutlu, Imre Noth, Matthew M. Churpek, Mary E. Strek

Please cite this article as: Adegunsoye A, Oldham JM, Bellam SK, *et al*. African-American Race and Mortality in Interstitial Lung Disease: A Multicenter Propensity-Matched Analysis. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.00255-2018).

African-American Race and Mortality in Interstitial Lung Disease: A Multicenter Propensity-Matched Analysis

Ayodeji Adegunsoye, MD, MS[1]; Justin M. Oldham, MD, MS[2]; Shashi K. Bellam, MD[3]; Jonathan H. Chung, MD[4]; Paul A. Chung, DO[5]; Kathleen M. Biblowitz, MD[5]; Steven Montner, MD[4]; Cathryn Lee, MD[1]; Scully Hsu, BS[1]; Aliya N. Husain, MD[6]; Rekha Vij, MD[1]; Gokhan Mutlu, MD[1]; Imre Noth, MD[1]; Matthew M. Churpek, MD, MPH, PhD[1,7]*; Mary E. Strek, MD[1]*

1. Section of Pulmonary & Critical Care, Department of Medicine; The University of Chicago, Chicago, IL
2. Division of Pulmonary, Critical Care & Sleep Medicine, Department of Medicine, University of California at Davis
3. Division of Pulmonary & Critical Care, Department of Medicine; NorthShore University HealthSystem, Evanston, IL
4. Department of Radiology; The University of Chicago
5. Department of Medicine; NorthShore University HealthSystem, Evanston, IL
6. Department of Pathology; The University of Chicago
7. Department of Public Health Sciences; The University of Chicago

*These authors contributed equally

Corresponding Author:

Ayodeji Adegunsoye, MD, MS

Section of Pulmonary & Critical Care,

Department of Medicine,

The University of Chicago,

5841 S. Maryland Ave

Chicago, IL 60637

deji@uchicago.edu

Funding: This investigation was supported by an NIH grant (T32-HL007605)

Final approval of the submitted manuscript and accountability for all aspects of the work: All authors (AA, JMO, SKB, JHC, PAC, KMB, SM, CL, SH, ANH, RV, GM, IN, MMC, MES)

Conflict of Interest Disclosures: Drs. Adegunsoye, Chung JH, Montner, Lee, Bellam, Chung P, Biblowitz, along with Ms. Hsu, have nothing to disclose. Dr. Oldham has received speaking and advisory board fees from Genentech and Boehringer Ingelheim. Dr. Vij has received a grant from Genentech to study the genomics of autoimmune interstitial lung diseases. Dr. Noth has received honoraria for advisory boards with Boehringer Ingelheim, InterMune, Anthera within the last 12 months related to IPF. He has also received speaking honoraria from GSK and receives consulting fees for Immuneworks. He also has study contracts with the NIH, Stromedix, Sanofi, and BI for the conduct of clinical trials in IPF. Dr. Strek has received institutional funding for interstitial lung disease research from Boehringer-Ingelheim, Genentech, Gilead and MedImmune and has served on an advisory board for Boehringer-Ingelheim. Dr. Churpek is supported by a career development award from the National Heart, Lung, and Blood Institute (K08 HL121080), has received honoraria from Chest for invited speaking engagements and also has a patent pending (ARCD. P0535US.P2) for risk stratification algorithms for hospitalized patients.

Abbreviation List

AA = African-American; CI = Confidence Interval; CHP= chronic hypersensitivity pneumonitis; CTD = connective tissue disease; DLCO = diffusion capacity of the lung for carbon monoxide; FVC = forced vital capacity; HR = hazard ratio; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IPAF = interstitial pneumonia with autoimmune features; IPF = idiopathic pulmonary fibrosis; IRB = institutional review board; PFT = pulmonary function testing; SD = standard deviation

Author's contributions:

Conception and design: AA, JMO, IN, MES, MMC

Acquisition of data for the work: AA, JMO, SKB, JHC, PAC, KMB, SM, CL, SH, ANH, RV, GM, IN, MMC, MES

Analysis and interpretation: AA, JMO, IN, MES, MMC

Drafting the manuscript for important intellectual content: AA, JMO, SKB, JHC, PAC, KMB, SM, CL, SH, ANH, RV, GM, IN, MMC, MES

Critical revision for important intellectual content: All authors (AA, JMO, SKB, JHC, PAC, KMB, SM, CL, SH, ANH, RV, GM, IN, MMC, MES)

Abstract

We studied whether African-American race is associated with younger age and decreased survival time at diagnosis of interstitial lung disease (ILD).

We performed a multicenter, propensity score matched analysis of patients with an ILD diagnosis followed at five US hospitals between 2006–2016. African-Americans were matched with patients of other races based on a time-dependent propensity score calculated from multiple patient, physiologic, diagnostic, and hospital characteristics. Multivariable logistic regression models were used. All-cause mortality and hospitalizations were compared between race-stratified patient cohorts with ILD, and sensitivity analyses were performed.

The study included 1,640 patients with ILD, 13% of whom were African-American, followed over 5,041 person-years. When compared with patients of other races, African-Americans with ILD were younger at diagnosis (56 years vs. 67 years), but in the propensity-matched analyses had greater survival (HR=0.46; 95%CI=0.28-0.77; *P*=0.003) despite similar risk of respiratory hospitalizations (RR=1.04; 95%CI=0.83-1.31; *P*=0.709), and similar GAP-ILD (gender-age-physiology-ILD) scores at study entry. Sensitivity analyses in a separate cohort of 9,503 patients with code-based ILD diagnosis demonstrated a similar association of baseline demographic characteristics with all-cause mortality.

We conclude that African-Americans demonstrate a unique phenotype associated with younger age at ILD diagnosis and perhaps longer survival time.

Key Words: interstitial lung disease, mortality, pulmonary fibrosis, race/ethnicity

Introduction

The interstitial lung diseases (ILD) are a heterogeneous group of diffuse parenchymal lung disorders with shared clinical, radiographic, and pathologic features[1]. While some ILDs manifest with parenchymal inflammation at disease onset, others lead to fibrotic destruction. Such changes to the pulmonary parenchyma can lead to severe impairment of lung function and concomitant high mortality. While geographic differences in disease burden and variable recognition have led to substantial variation in the reported incidence of ILD, the global prevalence and mortality continue to rise with the aging population worldwide[2, 3].

Racial differences in disease risk and mortality are important determinants of population health and can result in health disparities[4, 5]. African-Americans are the largest minority race in the U.S., now encompassing over 40 million people[6]. African-American race has been associated with high rates of respiratory impairment and worsened survival in numerous pulmonary disease conditions[7, 8]. The US Centers for Disease Control and Prevention reports a three-fold increase in asthma-related deaths among African-Americans compared to European-Americans[6, 9]. African-Americans have earlier onset of COPD, worsened lung function decline, and greater mortality risk with lung cancer when compared to European-Americans[10-12]. Likewise, the severity of connective tissue diseases (CTD) and associated risk for pulmonary involvement is greater among African-Americans[13, 14].

The majority of epidemiological studies characterizing patients with ILD and evaluating survival have been conducted in populations with a Caucasian predominance[15-18]. One such study suggested that patients of African descent are less likely to develop the most severe form of ILD, idiopathic pulmonary fibrosis (IPF) but that death from IPF occurs at a younger age in African-Americans[16]. It remains unclear however, whether racial differences influence survival across the wide spectrum of ILD. We anticipated that similar to other pulmonary disorders, earlier onset of ILD and worsened outcomes in African-Americans might prompt the need for earlier therapeutic intervention. Thus, we hypothesized that independent of access to care, African-American race is associated with younger age at ILD diagnosis and increased mortality when compared to other races.

Methods

Study Design and Population

This retrospective cohort study included all adult patients (≥18 years) at five US hospitals with a multidisciplinary diagnosis of ILD (University of Chicago Hospital) and independently adjudicated ILD diagnosis (Evanston Hospital, Highland Park Hospital, Glenbrook Hospital, and Skokie Hospital) from January 2006 through July 2016. The electronic medical record, which contained inpatient and outpatient data, was used to ascertain supportive evidence of ILD, race category, and determine vital status. The categorization of race was implemented per the federally defined US Census Bureau standards on race (White, Black or African-American, American-Indian or Alaska Native, Asian, and Native Hawaiian or Other Pacific

Islander) and ethnicity (Hispanic or not Hispanic) [19]. No individuals identified as American-Indian or Native Hawaiian in the study cohort. The remaining categories were stratified into African-American (non-Hispanic black), and non-African-American (non-Hispanic white, non-Hispanic Asian, and Hispanic) cohorts. The study was reviewed and approved by the local institutional review boards (IRB #16-1062;#17-025), which waived informed consent.

Multidisciplinary diagnosis (MDD) of ILD

To assess our findings, patients with ICD-9 code-based ILD diagnosis at the tertiary hospital (University of Chicago Hospital) underwent a multidisciplinary evaluation using available clinical data, pulmonary function tests (PFTs), high-resolution computed tomography (HRCT) scans, and surgical lung biopsies according to current ATS/ERS criteria. An assessment of multidisciplinary ILD diagnosis (MDD-ILD) was performed by pulmonologists in conjunction with rheumatologists, dedicated chest radiologists, and a thoracic pathologist. Patients with an eventual multidisciplinary diagnosis of sarcoidosis were excluded, as the majority of patients with pulmonary sarcoidosis lack parenchymal lung disease. Ascertainment of race was performed by separate reassessment of clinician-documented race at the time of PFTs.

As the four non-tertiary hospitals are suburban community hospitals that do not perform multidisciplinary discussions to determine ILD diagnosis, an independent “adjudication” panel of two academic pulmonologists with expertise in ILD (J.M.O., R.V.) evaluated clinical data including PFT results and HRCT scans to confirm the diagnosis of ILD in all patients

who received an ICD-9 code-based ILD diagnosis from a pulmonologist at that center, and had clinical information available for review. All adjudicators were blinded to race, hospitalization, and mortality data. Each panel member reviewed all available records to determine whether the study participant had ILD. Among discordant cases (n=60), a third independent pulmonologist (I.N.) with ILD expertise reviewed the available data for eventual classification. Based on review of this information, patients classified as having ILD (n=488) were included in the analyses (agreement=92.6%, kappa=0.84 for ILD diagnosis). An ILD diagnosis was adjudicated by panel members when the available medical records that were reviewed demonstrated pulmonologist-diagnosed ILD with (1) radiographic evidence of pulmonary fibrosis, (2) HRCT ground-glass opacities with restrictive pulmonary defect, or (3) auscultatory crackles with restrictive pulmonary defect +/- DLCO impairment or oxygen requirement (Table E1).

Propensity Score Matching

To minimize potential confounding, African-Americans were matched to non-African-Americans using propensity score matching by calculating the probability of identification as African-American, given the study covariates on cohort entry. We selected covariate predictors for race in our propensity score based on previously identified socioeconomic factors associated with race and mortality in similar investigations that evaluated the influence of African American race on mortality[20-22]. These were factors that had a plausible direct or indirect relation to both race and mortality. Covariates for assessing the primary outcome of the study included demographic characteristics, ILD subtype, and pulmonary function measures of

disease severity. Random frequency matching using the propensity score was performed which increased the likelihood that all matches were of equal quality. The final cohort consisted of ~3:2 frequency-matched participants of African-American race to non-African-Americans.

Follow-up and Study Outcomes

Patients entered the cohort on the date of initial ILD evaluation at the center. For the primary outcome, all patients were followed up until occurrence of death, lung transplantation, end of the study period, or loss to follow-up. Person-time was averaged at 30 days per month from initial ILD evaluation to study endpoint. The primary outcome was all-cause mortality during the study follow-up period, and secondary outcomes included all-cause hospitalizations and respiratory hospitalizations. Survival was also evaluated by constructing transplant-free, transplant-excluded, and transplant-as-a-competing-risk-event Cox regression models (data not shown). The gender age physiology-ILD (GAP-ILD) score was assessed at initial presentation as an index of clinical disease severity[23].

Mortality Ascertainment

Manual review of hospital documentation, death occurrence records and IRB-approved telephone confirmation was performed for ascertainment of vital status in cases of loss to follow-up. Vital status was confirmed using medical records and social security death index.

Statistical Analyses

In the study cohort, hypothesis testing was conducted between pairs of variables using 2-tailed T-tests for continuous variables and Fisher exact tests for categorical variables. All-cause and respiratory hospitalization risks were computed using Poisson regression models.

A propensity score (PS) was generated for each patient using the *'teffects'* package in Stata[24, 25] by constructing a parsimonious unconditional logistic regression model that adjusted for potential confounding variables for ILD disease severity and mortality. Final model selection was based on the assessment of optimal covariate balance by comparing the standardized differences between groups after the propensity score was computed. The final model chosen adjusted for age, gender, body mass index, smoking status (ever vs never), percent predicted forced vital capacity (FVC), percent predicted diffusing capacity of the lung for carbon monoxide (DLCO), ILD subtype, and hospital center. We excluded referral status, income level and insurance status from the PS due to poor covariate balance, but did include these variables along with immunosuppressive therapy in subsequent outcome modeling. Patient selection for outcome modeling was performed using the PS with robust estimates of the variance-covariance matrix to calculate the 95% confidence interval level. We tested fully adjusted models for effect modification by the individual components of the GAP-ILD score (age, gender, percent predicted FVC, percent predicted DLCO and ILD subtype) using multiplicative interaction terms. Outcome modeling included random-effects analyses to control for heterogeneity between hospital centers. Patient stratification by center was

performed to assess consistency of study results across centers. Post-estimation tests demonstrated goodness of fit for all models.

Time to all-cause mortality was analyzed using Cox proportional hazards models with robust standard errors to account for familial correlation in our cohorts. Survival time was calculated as time from initial ILD evaluation to death, lung transplantation, loss to follow-up or end of study period. Survival time was censored on July 31, 2016 or at the time a patient underwent lung transplantation or was lost to follow-up. Survival curves are plotted using the Kaplan–Meier survival estimator. Hazard ratios and odds ratios are reported relative to study participants of non-African-American race.

Sensitivity analyses were performed in patients with code-based ILD diagnosis that did not meet the initial inclusion criteria of MDD-ILD (University of Chicago Hospital) or independently adjudicated ILD diagnosis (Evanston Hospital, Highland Park Hospital, Glenbrook Hospital, and Skokie Hospital). Additional sensitivity analyses assessing sub-populations of the MDD-ILD and adjudicated ILD cohorts for the primary outcome were conducted. All *P*-values were 2-sided and a level of .05 was considered statistically significant. All statistical analyses were performed in Stata (StataCorp 2017; R.15, StataCorp, College Station, Texas).

Results

Of the 1,823,338 patients evaluated across all study centers between January 2006 and July 2016, 11,143 adult patients had an ICD-9 diagnosis code for ILD (Fig.E1). Among these, 1,640 patients had MDD or independently adjudicated ILD and were evaluated during 5,041 person-years of follow-up. All adult age groups were represented (median age, 68 years [25th-75th percentiles, 59-75 years]), and 821 (50%) were male.(Table 1).

Prevalence and Baseline Characteristics of African-Americans

Overall, there were 222 (13.5%) patients that identified as African-Americans during the study period (Table 1). Compared to the non-African-American population, the African-American population differed with regard to baseline characteristics, lung function, and ILD sub-category (Table 1). African-American patients were younger than non-African-Americans (58 years vs 68 years), had the lowest male prevalence (25%), the greatest prevalence of positive antinuclear antibody titers (60%), and the lowest prevalence of CAD (7%)(*P*<0.001)(Table 1)(Fig.1A). African-Americans also had substantially decreased measures of lung function– TLC (65%), FVC (57%), DLCO (46%), six-minute walk distance (1007ft.), and the least prevalence of traction bronchiectasis (24%)(*P*<0.001)(Table 1). When socioeconomic factors were assessed, in comparison to non-African-Americans, the majority of African-American patients had incomes below the national median

(72.9% vs 35.5%;*P*<0.001) and fewer African-Americans were referred from out of state (10.4% vs 15.6%;*P*=0.042). African-Americans had greater odds of having CTD-ILD (OR=6.28; 95%CI =4.32-9.12;*P*<0.001), or interstitial pneumonia with autoimmune features (IPAF)(OR=1.66; 95%CI=1.07-2.58;*P*=0.023), but decreased odds of IPF (OR=0.21; 95%CI=0.13-0.32;*P*<0.001), or chronic hypersensitivity pneumonitis (CHP)(OR=0.28; 95%CI=0.12-0.62;*P*<0.001)(Table E2).

Mortality in African-Americans with Interstitial Lung Disease

In African-Americans with ILD, annual mortality rates increased with increasing age, peaking in the seventh decade of life during the study period. (Fig.E2). When assessing the primary outcome, survival of African-American patients was greater than that of non-African-Americans with ILD (Fig.1A, 1B).

The mean survival time among African-American patients was 103 months (95%CI, 96–110 months) compared to 85 months (95%CI, 81–88 months) in non-African-Americans. Mortality was 19% (42 deaths) in African-Americans compared to 27% (377 deaths) in non-African-Americans over the ten-year study period. Lung transplantation occurred in 5% (10 patients) of African-American vs 4% (55 patients) of non-African-American patients (Table 2).

Before propensity score matching, the univariate and multivariable Cox hazards for all-cause mortality were decreased in African-American patients (HR=0.5, 95%CI=0.4-0.7;*P*<0.001, and HR=0.4, 95%CI=0.3-0.6;*P*<0.001, respectively)(Table 2)(Fig.2A). This decreased mortality was also observed in the code-based ILD subset without multidisciplinary or adjudicated ILD (HR=0.7, 95%CI=0.7-0.8;*P*<0.001) (Fig.2B). When specific ILD subtypes were examined, African-American race was associated with a consistent trend to improved mortality except in patients with IPF (Fig.2C – 2F).

After propensity score matching, the unadjusted PS model constructed for the MDD and independently adjudicated ILD cohort included 306 patients (Table 3). In primary outcome analysis of the unadjusted PS model, African-Americans had improved survival when compared with patients of other races (HR=0.51; 95%CI=0.32-0.80;*P*=0.004)(Table 4)(Fig.3). The improvement in survival remained consistent after adjusting for baseline demographic characteristics, physiologic indices of disease severity using the GAP-ILD score, ILD subtype, referral status, use of immunosuppressive therapy, income level and type of insurance (HR=0.46; 95%CI=0.28-0.77;*P*=0.003)(Table 4).

Sensitivity analyses that assessed the baseline characteristics of the African-American population and tested study assumptions were performed in those patients with only a code-based ILD diagnosis with consistent results to those from the primary analysis (Table E3). Additional sensitivity analyses were performed in patients with MDD or adjudicated-ILD diagnosis adjusting for antifibrotic therapy, ANA seropositivity, total lung capacity (TLC), six-minute walk distance, and honeycomb fibrosis on HRCT yielded similar findings consistent at both tertiary and non-tertiary medical centers and yielded similar results even after substratifying by age, gender, GAP-ILD score, and presence or absence of honeycombing (Tables E4)(Fig.E3A-C). Although missing covariates were infrequent in our cohort (<5%), additional data analysis accounting for these covariate values with multiple imputation using chained equations yielded similar results (data not shown).

All-Cause Hospitalization

Among patients with MDD or adjudicated ILD, 40.6% (n=692) were hospitalized during the study period. African-American patients had decreased risk for all-cause hospitalization (RR=0.81; 95%CI=0.72–0.91;*P*<0.001), when compared to non-African-American patients (Table 2). This decreased risk remained consistent even after adjusting for baseline demographic characteristics, physiologic indices of disease severity using the GAP-ILD score, ILD subtype, referral status, use of immunosuppressive therapy, income level and type of insurance (RR=0.78; 95%CI=0.69-0.90;*P*<0.001)(Table 2).

Respiratory Hospitalization

Respiratory hospitalizations constituted 50% (n=345) of all hospitalizations. Respiratory hospitalizations per patient (2.1 vs 1.8;*P*=0.306) and risk for respiratory hospitalization (RR=1.04; 95%CI=0.86-1.27;*P*=0.658) were similar between African-American and non-African-American patients (Table 2). Similar findings were observed after race- and gender-specific cohort sub-classification (Fig.4A). However, African-Americans hospitalized for respiratory causes had decreased mortality risk when compared to others (Fig.4B).

Discussion

We have shown in a large, well-characterized multicenter cohort with diverse forms of ILD that African-American race is associated with: 1) younger age at ILD diagnosis; 2) decreased all-cause mortality; 3) decreased risk for all-cause hospitalization; and 4) similar rates of respiratory hospitalization in patients with ILD. This novel study illuminates distinct clinical features and outcomes that characterize African-Americans with ILD while providing new insights into understanding disease etiopathogenesis. Results of this study have implications for both ILD clinical care and research.

The primary outcome of improved all-cause mortality among African-Americans with ILD in our study remained consistent across tertiary and non-tertiary health care centers, and increased diagnostic specificity by replacing code-based diagnoses with MDD-ILD or adjudication of ILD diagnosis appeared to magnify this effect. However, although we adjusted for center-level effects in our analyses, the inability to account for symptom duration before initial evaluation, the potential for subsequent referral from non-tertiary health care centers to other tertiary ILD centers, and the low prevalence of AA at these centers, all preclude broad conclusions about this observation.

Poor clinical outcomes in patients of African-American race are a unique public health challenge, which has been linked to socioeconomic disparities in access to

care. As African-Americans and Caucasians receive care disproportionately at different centers, we selected several medical centers at divergent geographical locations, which distinctly differed in the prevalence of their African-American patient populations. In addition to socioeconomic factors, the high rates of respiratory impairment and decreased pulmonary function indices among African-Americans are well-described factors contributing to disparities in health care. Therefore, we derived propensity models attempting to capture several elements that enabled assessment of the independent effects of race. Our statistical models by which we matched on the propensity to be African-American accounted for demographic and pulmonary indices, while further adjusting for socio-economic status, geographical location, access to care and immunosuppression use. The consistently improved survival in African-Americans across these models despite similar rates of respiratory hospitalization suggests the effect of intrinsic patient-specific factors that transcend socioeconomic differences and use of immunosuppressive therapy.

Although epidemiological studies link mortality risk to geographical variations in disease prevalence, the observed prevalence of CTD-ILD among African-Americans in our study is consistent with that previously described by others[26, 27]. The odds ratio for a diagnosis of autoimmune-associated forms of ILD among African-Americans in our cohort (CTD-ILD, OR=5.9) was similar to that of patients of African descent with CTD/vasculitis ILDs in a recent French study (Afro-Caribbeans, OR=4.4)[27]. The relatively low frequency of IPF observed among

African-Americans in our cohort (OR=0.3) is similar to that of Swigris et al. which demonstrated that African-Americans were significantly less likely to carry an ICD-9 diagnosis of IPF (OR=0.5)[16]. Our findings are also consistent with the ASCEND and CAPACITY trials, in which African-American patients constituted less than 9% of the IPF population[28, 29]. Similar to previous studies in IPF and scleroderma, African-Americans in our ILD cohort presented at an earlier age and had reduced lung function[13, 26, 30]. Yet, African-Americans with CTD-ILD in our cohort had a significant survival benefit that may have been associated with factors previously described to improve survival in CTD-ILD such as reduced prevalence of pulmonary fibrosis at presentation, differential autoantibody profiles or shared genetic variants [30-32].

Durheim et al. recently showed that all-cause hospitalizations and respiratory hospitalizations predict survival in patients with IPF[33]. Similarly, our findings demonstrate increased mortality in ILD patients with respiratory hospitalization; however, this detrimental effect was less severe in African-American patients (Fig.3B). Interestingly, the association of African-American race with improved survival despite comparable rates of respiratory hospitalizations in our study is similar to that from a recent post-hoc analysis of patients with acute respiratory distress syndrome by Jolley et al., in which African-Americans who received conservative fluid management had better survival. This might suggest that the survival benefit observed in African-Americans with ILD occurs in those hospitalized for respiratory causes, or could be indicative of a unique African-American

phenotype with distinct baseline characteristics which confer a survival advantage in advanced lung disease and should be fully explored in larger prospective studies.

Our study has several limitations. First, we excluded patients with sarcoidosis from our analysis as our study was designed to evaluate interstitial lung diseases and the majority of patients with sarcoidosis have early stage disease and lack parenchymal lung involvement. Second, patient identification at all study centers was performed retrospectively using code-based ILD diagnoses, which have been described to have a low diagnostic specificity[34]. However, we focused our analysis on the subset with a MDD-ILD and performed independent adjudication of diagnoses for all ILD patients from the non-tertiary centers. Due to the challenges of making an accurate assessment of specific ILD subtypes from heterogeneous data acquired retrospectively over a decade at these non-tertiary centers, the adjudication process was limited to diagnosing the presence of ILD in study participants, but not determining ILD subtypes at these centers. Therefore, the original ILD subtype diagnosis made by the local pulmonologist was utilized. Third, the balancing achieved by our propensity scoring was only performed on identified confounders rather than all possible confounders. Thus, some of the results of our study could be attributable to unmeasured confounding, even with the use of propensity scores, which are often used to measure treatment effects in observational studies. Fourth, race is a complex sociobiological construct that often reflects the patients' perception of their familial origin, cultural environment and genetic makeup. We verified ethnic identification at initial pulmonary evaluation

using independent documentation of race by clinicians at the time pulmonary function tests were performed. Fifth, all hospitals in our study were located in the Greater Chicagoland area and our results could have been influenced by unmeasured environmental or geographic factors despite adjusting for residential location in our propensity score analyses. Future studies analyzing a distinct cohort are needed.

Conclusion

ILD in adult African-American patients is characterized by a unique phenotype with diagnosis at a younger age but with improved survival time when compared to non-African-Americans. This survival disparity may be influenced by familial, immunological or other biologic mechanisms and the underlying potential pathways require further investigation.

Acknowledgments

Our profound appreciation goes to the support staff of the University of Chicago Respiratory Clinical Research Unit, the Interstitial Lung Disease Clinic (Nancy Trojan, Catherine Brown, and Spring Maleckar) and NorthShore University HealthSystems, Evanston, IL (Mohammad Imran Beig, Daisy Zhu, and Naomi BenIsrael Olive), for their assistance with this study. We also extend our gratitude to the patients with ILD who made these research endeavors possible.

References

1. American Thoracic S, European Respiratory S. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *American journal of respiratory and critical care medicine* 2002: 165(2): 277-304.
2. Raghu G, Chen SY, Yeh WS, Maroni B, Li Q, Lee YC, Collard HR. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11. *Lancet Respir Med* 2014: 2(7): 566-572.
3. Hutchinson JP, McKeever TM, Fogarty AW, Navaratnam V, Hubbard RB. Increasing global mortality from idiopathic pulmonary fibrosis in the twenty-first century. *Annals of the American Thoracic Society* 2014: 11(8): 1176-1185.
4. Dressler WW, Oths KS, Gravlee CC. RACE AND ETHNICITY IN PUBLIC HEALTH RESEARCH: Models to Explain Health Disparities. *Annual Review of Anthropology* 2005: 34(1): 231-252.
5. Schraufnagel DE, Blasi F, Kraft M, Gaga M, Finn PW, Rabe KF, Health AECoDiR. An official American Thoracic Society/European Respiratory Society policy statement: disparities in respiratory health. *Am J Respir Crit Care Med* 2013: 188(7): 865-871.
6. Centers for Disease Control and Prevention. National Center for Health Statistics. Atlanta, GA: US Department of Health and Human Services, CDC: 2017. 2017.
7. Vaz Fragoso CA, McAvay G, Gill TM, Concato J, Quanjer PH, Van Ness PH. Ethnic differences in respiratory impairment. *Thorax* 2014: 69(1): 55-62.
8. Cooke CR, Erickson SE, Eisner MD, Martin GS. Trends in the incidence of noncardiogenic acute respiratory failure: the role of race. *Crit Care Med* 2012: 40(5): 1532-1538.
9. Heron M, Hoyert DL, Murphy SL, Xu J, Kochanek KD, Tejada-Vera B. Deaths: final data for 2006. *Natl Vital Stat Rep* 2009: 57(14): 1-134.
10. Haiman CA, Stram DO, Wilkens LR, Pike MC, Kolonel LN, Henderson BE, Le Marchand L. Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med* 2006: 354(4): 333-342.
11. Dransfield MT, Davis JJ, Gerald LB, Bailey WC. Racial and gender differences in susceptibility to tobacco smoke among patients with chronic obstructive pulmonary disease. *Respir Med* 2006: 100(6): 1110-1116.
12. Foreman MG, Zhang L, Murphy J, Hansel NN, Make B, Hokanson JE, Washko G, Regan EA, Crapo JD, Silverman EK, DeMeo DL, Investigators CO. Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPDGene Study. *Am J Respir Crit Care Med* 2011: 184(4): 414-420.
13. McNearney TA, Reveille JD, Fischbach M, Friedman AW, Lisse JR, Goel N, Tan FK, Zhou X, Ahn C, Feghali-Bostwick CA, Fritzler M, Arnett FC, Mayes MD. Pulmonary

involvement in systemic sclerosis: associations with genetic, serologic, sociodemographic, and behavioral factors. *Arthritis Rheum* 2007: 57(2): 318-326.
14. Mittoo S, Gelber AC, Christopher-Stine L, Horton MR, Lechtzin N, Danoff SK. Ascertainment of collagen vascular disease in patients presenting with interstitial lung disease. *Respir Med* 2009: 103(8): 1152-1158.
15. A. Goodwin GJ. Idiopathic Pulmonary Fibrosis Occurs More Frequently In Caucasian Than In Black Patients - A
Systematic Review. *Am J Respir Crit Care Med* 2015: 191(2015: A1562).
16. Swigris JJ, Olson AL, Huie TJ, Fernandez-Perez ER, Solomon J, Sprunger D, Brown KK. Ethnic and racial differences in the presence of idiopathic pulmonary fibrosis at death. *Respiratory medicine* 2012: 106(4): 588-593.
17. Kropski JA, Blackwell TS, Loyd JE. The genetic basis of idiopathic pulmonary fibrosis. *Eur Respir J* 2015: 45(6): 1717-1727.
18. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Patterns of interstitial lung disease and mortality in rheumatoid arthritis. *Rheumatology (Oxford)* 2017: 56(3): 344-350.
19. Arias E, Heron M, Xu J. United States Life Tables, 2014. *Natl Vital Stat Rep* 2017: 66(4): 1-64.
20. Xian Y, Holloway RG, Noyes K, Shah MN, Friedman B. Racial differences in mortality among patients with acute ischemic stroke: an observational study. *Ann Intern Med* 2011: 154(3): 152-159.
21. Spertus JA, Jones PG, Masoudi FA, Rumsfeld JS, Krumholz HM. Factors associated with racial differences in myocardial infarction outcomes. *Ann Intern Med* 2009: 150(5): 314-324.
22. Silber JH, Rosenbaum PR, Clark AS, Giantonio BJ, Ross RN, Teng Y, Wang M, Niknam BA, Ludwig JM, Wang W, Even-Shoshan O, Fox KR. Characteristics associated with differences in survival among black and white women with breast cancer. *JAMA* 2013: 310(4): 389-397.
23. Ryerson CJ, Vittinghoff E, Ley B, Lee JS, Mooney JJ, Jones KD, Elicker BM, Wolters PJ, Koth LL, King TE, Jr., Collard HR. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. *Chest* 2014: 145(4): 723-728.
24. StataCorp. Stata Statistical Software: Release 15. College Station, TX: StataCorp SE; 2017. 2017.
25. Garrido MM, Kelley AS, Paris J, Roza K, Meier DE, Morrison RS, Aldridge MD. Methods for constructing and assessing propensity scores. *Health services research* 2014: 49(5): 1701-1720.
26. Gelber AC, Manno RL, Shah AA, Woods A, Le EN, Boin F, Hummers LK, Wigley FM. Race and association with disease manifestations and mortality in scleroderma: a 20-year experience at the Johns Hopkins Scleroderma Center and review of the literature. *Medicine (Baltimore)* 2013: 92(4): 191-205.
27. Duchemann B, Annesi-Maesano I, Jacobe de Naurois C, Sanyal S, Brillet PY, Brauner M, Kambouchner M, Huynh S, Naccache JM, Borie R, Piquet J, Mekinian A, Virally J, Uzunhan Y, Cadranel J, Crestani B, Fain O, Lhote F, Dhote R, Saidenberg-Kermanac'h N, Rosental PA, Valeyre D, Nunes H. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of Greater Paris. *Eur Respir J* 2017: 50(2).

28. King TE, Jr., Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW, Group AS. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014: 370(22): 2083-2092.
29. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, King TE, Jr., Lancaster L, Sahn SA, Szwarcberg J, Valeyre D, du Bois RM, Group CS. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011: 377(9779): 1760-1769.
30. Steen V, Domsic RT, Lucas M, Fertig N, Medsger TA, Jr. A clinical and serologic comparison of African American and Caucasian patients with systemic sclerosis. *Arthritis Rheum* 2012: 64(9): 2986-2994.
31. Solomon JJ, Ryu JH, Tazelaar HD, Myers JL, Tuder R, Cool CD, Curran-Everett D, Fischer A, Swigris JJ, Brown KK. Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD). *Respir Med* 2013: 107(8): 1247-1252.
32. Juge PA, Borie R, Kannengiesser C, Gazal S, Revy P, Wemeau-Stervinou L, Debray MP, Ottaviani S, Marchand-Adam S, Nathan N, Thabut G, Richez C, Nunes H, Callebaut I, Justet A, Leulliot N, Bonnefond A, Salgado D, Richette P, Desvignes JP, Liote H, Froguel P, Allanore Y, Sand O, Dromer C, Flipo RM, Clement A, Beroud C, Sibilia J, Coustet B, Cottin V, Boissier MC, Wallaert B, Schaeverbeke T, Dastot le Moal F, Frazier A, Menard C, Soubrier M, Saidenberg N, Valeyre D, Amselem S, consortium F, Boileau C, Crestani B, Dieude P. Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis. *Eur Respir J* 2017: 49(5).
33. Durheim MT, Collard HR, Roberts RS, Brown KK, Flaherty KR, King TE, Jr., Palmer SM, Raghu G, Snyder LD, Anstrom KJ, Martinez FJ, investigators IP. Association of hospital admission and forced vital capacity endpoints with survival in patients with idiopathic pulmonary fibrosis: analysis of a pooled cohort from three clinical trials. *Lancet Respir Med* 2015: 3(5): 388-396.
34. Ley B, Urbania T, Husson G, Vittinghoff E, Brush DR, Eisner MD, Iribarren C, Collard HR. Code-based Diagnostic Algorithms for Idiopathic Pulmonary Fibrosis. Case Validation and Improvement. *Ann Am Thorac Soc* 2017: 14(6): 880-887.

Table 1. Baseline Characteristics & Demographics of Population with ILD diagnosis+ (n=1640).

Characteristics	Pooled Population				
	AA patients	Non-AA patients			*P*-Value*
	Black (n=222)	White (n=1251)	Hispanic (n=92)	Asian (n=75)	
Age, mean (±SD)	57.5 (13.2)	68.4 (11.5)	62.7 (12.7)	64.3 (14.9)	<0.001
Male, No. (%)	56 (25.2)	687 (54.9)	42 (45.7)	36 (48.0)	<0.001
Ever smoker, n (%)	97 (43.7)	579 (46.3)	40 (43.5)	15 (20.0)	0.777
BMI, mean (SD)	30.5 (7.5)	29.4 (6.4)	30.0 (5.4)	26.2 (6.2)	0.014
Clinical features					
Crackles, n (%)	137 (71.7)	802 (80.4)	67 (81.7)	44 (75.9)	0.532
Clubbing, n (%)	22 (9.9)	147 (11.8)	13 (14.1)	8 (10.7)	0.400
Positive ANA Titer **, n (%)	121 (59.6)	378 (43.3)	37 (52.1)	16 (40.0)	<0.001
Co-morbid diseases					
Coronary Artery Disease, n (%)	13 (7.3)	269 (25.5)	13 (16.7)	12 (18.2)	<0.001
Diabetes, n (%)	38 (21.4)	181 (17.1)	19 (24.4)	20 (30.3)	0.331
Gastroesophageal reflux, n (%)	86 (40.2)	521 (43.7)	39 (44.3)	25 (34.3)	0.407
Lung Function					
TLC %, mean (SD)	64.6 (16.2)	73.4 (17.8)	64.7 (14.0)	66.7 (18.4)	<0.001
FVC %, mean (SD)	56.8 (16.2)	69.4 (18.8)	61.5 (17.8)	61.1 (20.1)	<0.001
DLCO %, mean (SD)	46.1 (18.5)	50.7 (21.6)	48.2 (21.6)	44.2 (17.3)	0.016
6MWT distance, mean (SD)	1007 (365)	1114 (407)	1110 (309)	973 (406)	0.009
HRCT fibrosis	163 (78.4)	1071 (82.4)	269 (25.5)	269 (25.5)	0.163
Reticulation, n (%)	135 (64.9)	786 (68.6)	62 (74.7)	40 (56.3)	0.328
Traction bronchiectasis, n (%)	50 (24.0)	410 (35.8)	34 (41.0)	25 (35.2)	<0.001
Honeycomb pattern fibrosis, n (%)	75 (36.1)	442 (38.6)	37 (44.6)	25 (35.2)	0.446
ILD sub-category					
IPF, n (%)	28 (12.6)	555 (44.4)	38 (41.3)	33 (44.0)	<0.001
CHP, n (%)	8 (3.6)	123 (9.8)	13 (14.1)	3 (4.0)	0.003
IPAF, n (%)	34 (15.3)	129 (10.3)	10 (10.9)	8 (10.7)	0.029
CTD-ILD, n (%)	104 (46.9)	134 (10.7)	20 (21.7)	7 (9.3)	<0.001
Unclassifiable/Others, n (%)	48 (21.6)	307 (24.5)	11 (12.0)	23 (30.7)	0.429
Oxygen therapy, n (%)	66 (29.7)	398 (31.8)	25 (27.2)	19 (25.3)	0.661
Immunosuppressive therapy, n (%)	120 (55.8)	563 (46.4)	46 (50.6)	42 (57.5)	0.020
Antifibrotic therapy, n (%)	4 (1.8)	101 (8.1)	5 (5.4)	3 (4.0)	0.001

+No individuals identified as American-Indian or Native-Hawaiian in the study

*comparing African-Americans (AA) to Non-AA categories; n=1640 in pooled population; tertiary medical center, n=1152 (AA=195, non-AA=957); non-tertiary medical center, n=488 (AA=27, non-AA=461)

**positive antinuclear antibody (ANA) titer >1:320 ; ILD – interstitial lung disease

Exceptions for count variables: crackles, n=1329; clubbing, n=1369; coronary artery disease (CAD), n=1380; diabetes, n=1380; gastroesophageal reflux, n=1568; total lung capacity (TLC), n=1271; forced vital capacity (FVC), n=1504; diffusing capacity of the lung for carbon monoxide (DLCO), n=1425; six-minute walk test (6MWT), n=793; high-resolution computed tomography (HRCT), n=1508.

Table 2. Association between African-American Race, Mortality, All-Cause Hospitalizations, and Respiratory Hospitalizations

Characteristics	AA patients (n=222)	Non-AA patients (n=1418)	*P*-value
Mortality			
Mean survival time, (95% CI), months	103 (96 – 110)	85 (81 – 88)	<0.001
Mortality, No. (%)	42 (18.9)	377 (26.6)	0.015
Absolute mortality rate (events/person-years)	0.04	0.09	<0.001
Relative mortality risk*, (unadjusted)	0.51	--	<0.001
Relative mortality risk*, (adjusted+)	0.42	--	<0.001
Lung Transplantation, No. (%)	10 (4.5)	55 (3.9)	0.657
All-Cause Hospitalizations			
Hospitalization count, (no. per hospitalized patient)	336 (2.9)	1785 (3.1)	0.588
Hospitalization rate (events/person-years)	0.35	0.44	<0.001
Relative risk of hospitalization^, (unadjusted)	0.81	--	<0.001
Relative risk of hospitalization^, (adjusted+)	0.78	--	<0.001
Respiratory Hospitalizations			
Respiratory hospitalization count, (no. per hospitalized patient)	125 (2.1)	516 (1.8)	0.306
Respiratory hospitalization rate (events/person-years)	0.13	0.13	0.709
Relative risk of respiratory hospitalization^, (unadjusted)	1.04	--	0.658
Relative risk of respiratory hospitalization^, (adjusted)	1.04	--	0.709
GAP-ILD score, median (IQR)	4 (1-8)	4 (0-8)	0.511

ILD=interstitial lung disease; GAP=gender, age, physiology; OR= odds ratio; IQR=interquartile range; SE=standard error

* computed using Cox proportional hazard models

+ adjusted for baseline demographic characteristics – body mass index, age, gender, percent predicted forced vital capacity, percent predicted diffusing capacity of the lung for carbon monoxide, ILD subtype; GAP-ILD score, immunosuppressive therapy, antifibrotic therapy, and socioeconomic determinants of access to care

^ computed using Poisson regression models

Table 3. Comparison of Select Baseline Variables Between African American (AA) patients and Non-AA patients in the Original (Unmatched) and the Matched ILD Data Sets

Variable	Original (Unmatched) data			Matched data			
	AA Patients (n=222)	Non-AA patients (n=1418)	*P* Value	AA Patients (n=180)	Non-AA patients (n=126)	*S diff**	*P* Value
Age, yrs (±SD)	57.5 (13.2)	67.8 (11.9)	<0.001	56.6 (12.6)	57.8 (13.1)	0.087	0.408
Male, No. (%)	56 (25.2)	765 (54.0)	<0.001	44 (24.4)	37 (29.4)	0.052	0.337
BMI, mean (SD)	30.5 (7.5)	29.2 (6.4)	0.014	30.4 (7.5)	30.4 (6.2)	0.005	0.961
Ever smoker, n (%)	97 (43.7)	634 (44.7)	0.777	86 (47.9)	57 (45.2)	0.033	0.661
Disease severity index							
GAP-ILD score [*G*ender, *A*ge, *P*hysiology (FVC, DLCO), *ILD* subtype], mean (SD)	4.2 (1.7)	4.2 (1.7)	0.802	4.3 (1.7)	4.2 (1.8)	0.023	0.683
Socioeconomic factors							
Out of state referral, n (%)	23 (10.4)	221 (15.6)	0.042	22 (12.2)	15 (11.9)	<0.001	0.933
Income level below national median, n (%)	161 (72.9)	501 (35.5)	<0.001	134 (74.4)	87 (69.1)	0.039	0.300
Medicare with private insurance, n (%)	99 (45.6)	462 (33.3)	<0.001	82 (45.6)	57 (45.2)	0.022	0.956
Tertiary hospital center, n (%)	195 (87.8)	957 (67.5)	<0.001	156 (86.7)	106 (84.1)	0.068	0.533
Immunosuppressive therapy, n (%)	120 (55.8)	651 (47.3)	0.020	115 (63.9)	80 (63.5)	0.070	0.943

FVC=forced vital capacity; DLCO=diffusing capacity of the lungs for carbon monoxide; ILD=interstitial lung disease.
SD=standard deviation; *S diff=standardized difference comparing the frequency matched cohort to the unmatched cohort.

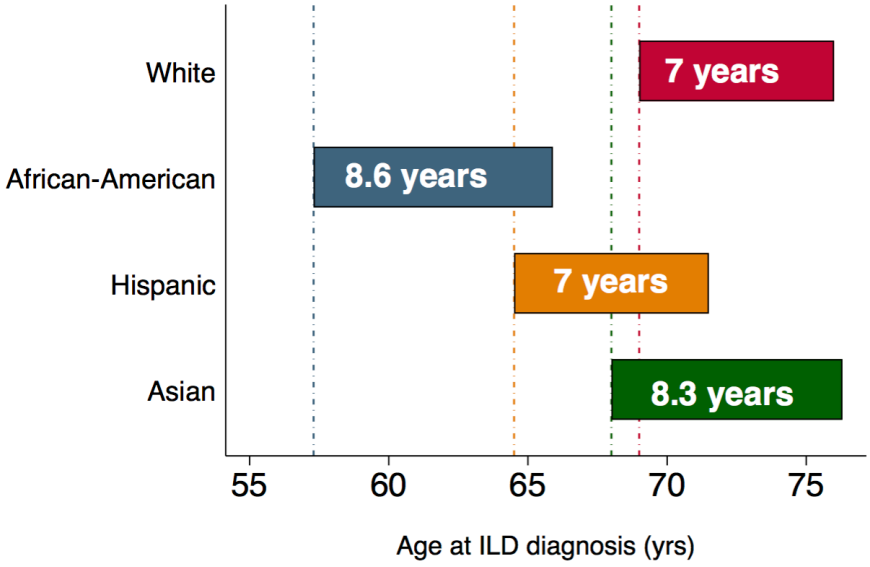
Table 4. Propensity Score Matched Model Demonstrating Association between African-American Race and Mortality

Propensity Score Models[#]	HR	95% CI	*P*-value
Unadjusted model	0.51	0.32-0.80	0.004
Adjusted model*	0.48	0.29-0.79	0.004
Plus referral status	0.48	0.29-0.79	0.004
Plus immunosuppressive therapy	0.48	0.29-0.79	0.004
Plus income level	0.47	0.29-0.78	0.003
Plus insurance type	0.46	0.28-0.77	0.003

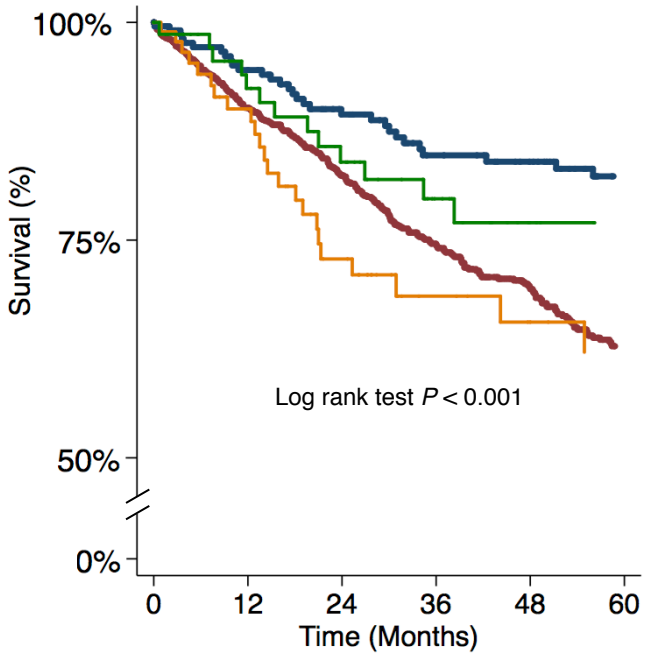
* adjusted for baseline demographic characteristics – body mass index, age, gender, percent predicted forced vital capacity, percent predicted diffusing capacity of the lung for carbon monoxide, ILD subtype; GAP-ILD score, and hospital center.

after propensity score matching, n=306 in pooled population; tertiary medical center, n=262 (AA=156, non-AA=106); non-tertiary medical center, n=44 (AA=24, non-AA=20)

A.



B.



White	1233	864	619	452	347	248
Afr.American	222	177	142	119	109	86
Hispanic	92	63	41	25	21	18
Asian	73	59	46	32	21	17

**No individuals identified as American-Indian or Native-Hawaiian in the study*

Figure 1. (a) Survival time from ILD diagnosis stratified by race/ethnicity. (b) Survival stratified by race among patients with ILD. Time zero (0) = initial ILD evaluation at study center. ILD= interstitial lung disease

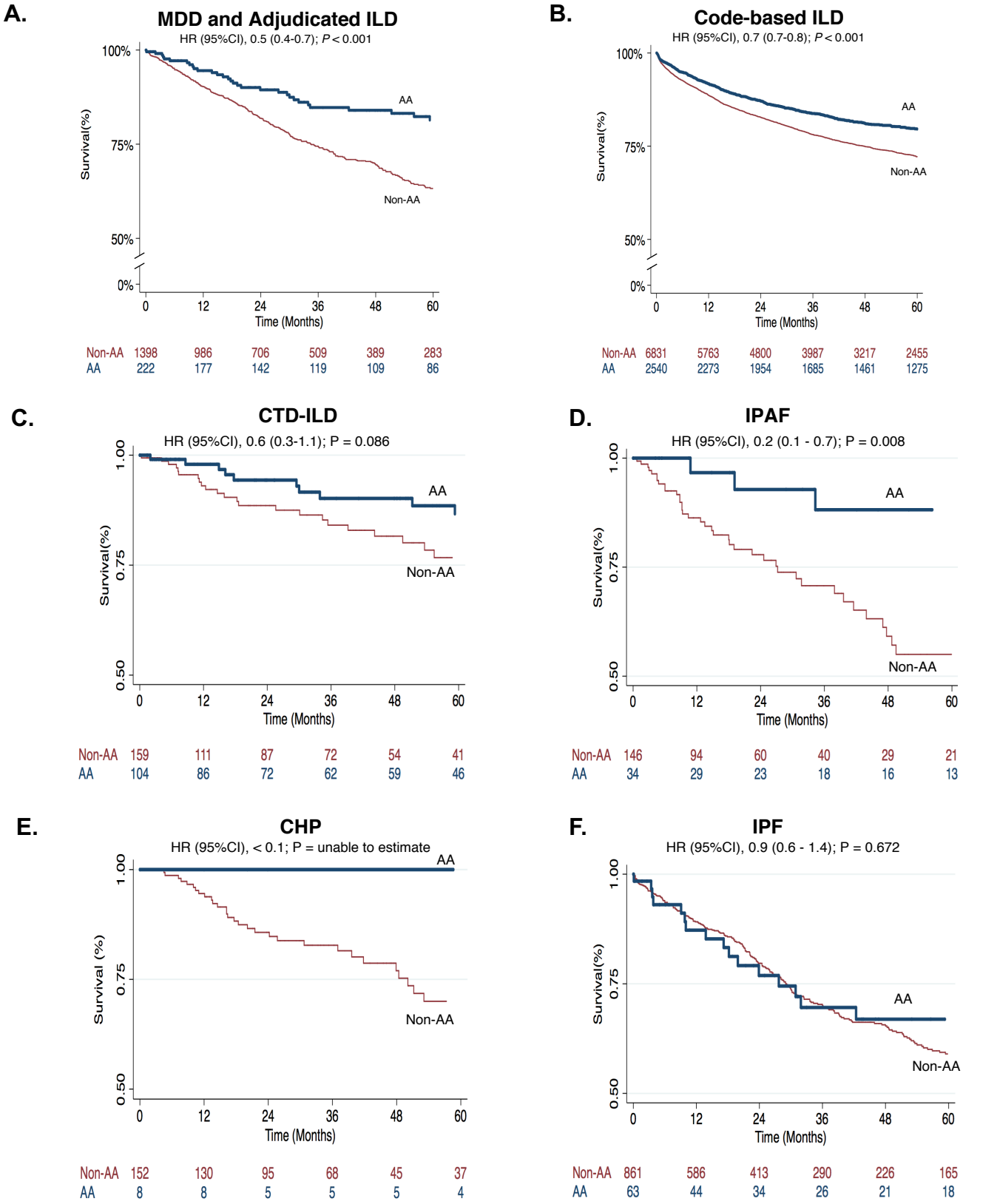


Figure 2. Survival stratified by race among patients with (a) multidisciplinary (MDD) and adjudicated diagnosis of ILD; (b) Code-based ILD diagnosis (consists of subjects with ICD-9 based ILD diagnosis codes, excluding all patients with multidisciplinary or adjudicated ILD diagnosis); (c) connective tissue disease-associated ILD (CTD-ILD); (d) interstitial pneumonia with autoimmune features (IPAF); (e) chronic hypersensitivity pneumonitis (CHP); (f) idiopathic pulmonary fibrosis (IPF); patients with unclassifiable diagnosis included in IPF category. AA=African-Americans; ILD=interstitial lung disease. Time zero (0) = initial ILD evaluation at study center.

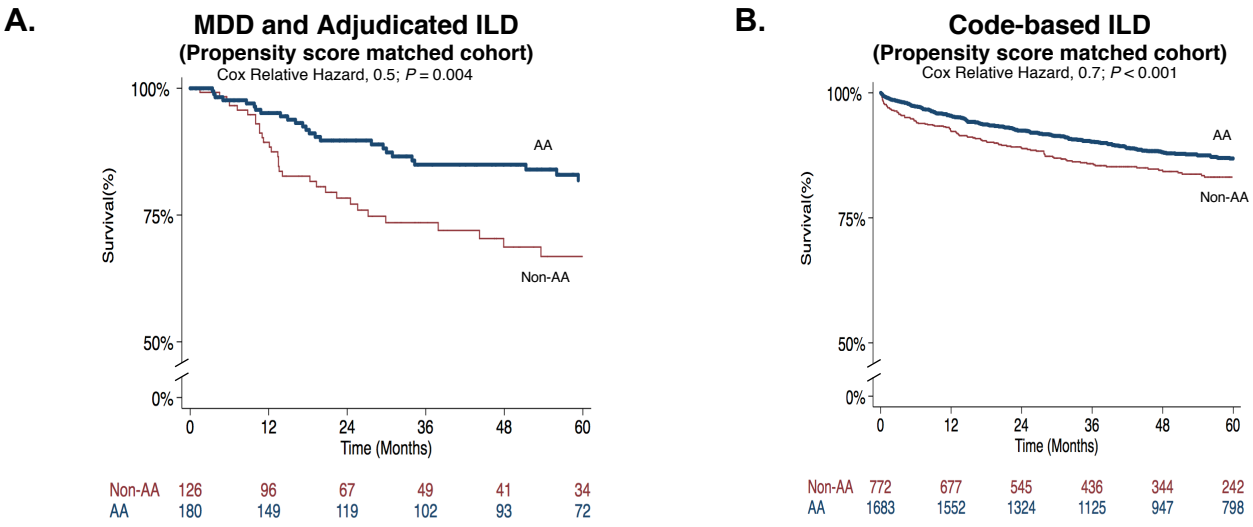
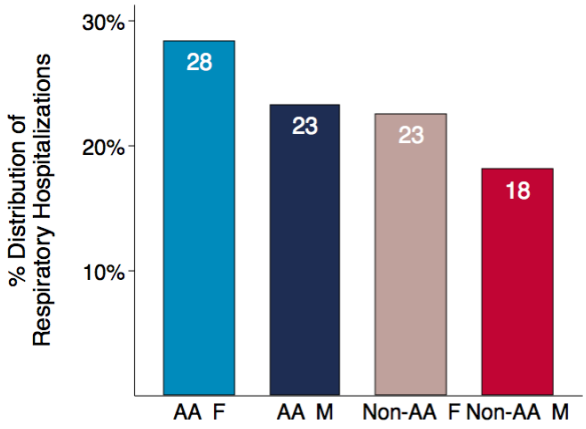
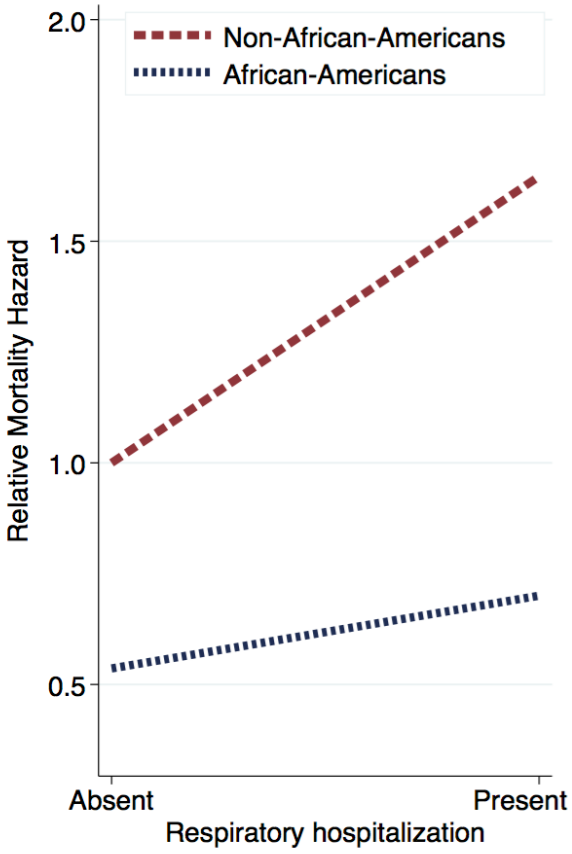


Figure 3. Survival stratified by race among the propensity matched cohorts with (a) multidisciplinary (MDD) and adjudicated diagnosis of ILD; and (b) Code-based ILD diagnosis (consists of subjects with ICD-9 based ILD diagnosis codes, excluding all patients with multidisciplinary or adjudicated ILD diagnosis). AA=African-Americans; ILD=interstitial lung disease. Time zero (0) = initial ILD evaluation at study center.

A.



B.



	Predictive Margin Model		
Independent variables	**HR**	**95% CI**	***P* value**
African-American race	0.54	0.32 - 0.75	< 0.001
Respiratory hospitalization	1.65	1.29 - 2.00	< 0.001
Interaction	0.70	0.33 - 1.07	< 0.001

Figure 4 (a) Percentage distribution of respiratory hospitalizations in multidisciplinary and adjudicated ILD cohort stratified by race and gender. (b) Predictive margin interaction model demonstrating the relative mortality hazard in patients with multidisciplinary and adjudicated ILD diagnosis and respiratory hospitalization; (n=1640). AA=African-American; ILD=interstitial lung disease; GAP=gender, age, physiology. *P<0.05. *P<0.0005 .

E-supplement

Table E1. Criteria for Independent Adjudication of ILD diagnosed at non-tertiary centers.*#

	Frequency
Thoracic CT scan report noting honeycombing or traction bronchiectasis	245
Thoracic CT scan report noting reticulation and ground glass opacities	96
Thoracic CT scan report noting reticulation; and patient requires supplemental oxygen	43
Thoracic CT scan report noting reticulation; and pulmonary crackles on physical examination	104
Thoracic CT scan report noting ground glass opacities, pulmonary crackles on examination and moderate to severe restrictive PFT pattern	107
Thoracic CT scan report noting ground glass opacities, patient requires supplemental oxygen and has moderate to severe restrictive PFT pattern	55
Thoracic CT scan report noting ground glass opacities, and DLCO below 50% predicted	109
Pulmonary crackles on examination and moderate or severe restrictive PFT pattern	244
Moderate or severe restrictive PFT pattern and DLCO below 70%	317
Pulmonary crackles, patient requires supplemental oxygen and DLCO below 50%	72

*All patients performed Chest-CT scan, pulmonary function tests, and were subsequently diagnosed with ILD after pulmonologist evaluation at the non-tertiary center
#Participants were eligible for more than one criterion

Table E2. Unadjusted and Adjusted Odds Ratio of ILD sub-category diagnosis Among African-American Patients with Multidisciplinary (MDD) and adjudicated diagnosis of ILD

Characteristics	Tertiary Referral Medical Center (n=1,152)			Non-Tertiary Academic Medical Centers (n=488)			Pooled Population (n=1,640)		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Univariate Logistic Regression									
IPF	0.23	0.14 – 0.36	<0.001	0.20	0.08 – 0.48	<0.001	0.18	0.12 – 0.28	<0.001
CHP	0.27	0.13 – 0.57	<0.001	--	--	--	0.34	0.17 – 0.71	0.004
IPAF	1.19	0.78 – 1.80	0.414	2.49	0.30 – 21.04	0.401	1.56	1.04 – 2.34	0.030
CTD-ILD	5.57	4.01 – 7.75	<0.001	8.73	2.50 – 30.49	0.001	6.88	5.04 – 9.39	<0.001
Unclassifiable/Others	0.76	0.51 – 1.14	0.187	2.90	1.32 – 6.35	0.008	0.87	0.62 – 1.23	0.430
*Multivariable Logistic Regression**									
IPF	0.29	0.17 – 0.50	<0.001	0.19	0.08 – 0.48	<0.001	0.21	0.13 – 0.32	<0.001
CHP**	0.19	0.09 – 0.43	<0.001	--	--	--	0.28	0.12 – 0.62	0.002
IPAF	1.15	0.73.- 1.83	0.540	1.22	0.11 – 13.27	0.871	1.66	1.07 – 2.58	0.023
CTD-ILD	4.48	2.97 – 6.76	<0.001	6.59	1.63 – 26.70	0.008	6.28	4.32 – 9.12	<0.001
Unclassifiable/Others	0.98	0.41 – 2.31	0.961	1.68	0.71 – 3.99	0.238	0.86	0.52 – 1.42	0.556

*Adjusted for age, gender, body mass index, smoking status, co-morbid diseases and referral status

**Regression estimates incalculable due to decreased subgroup numbers at the non-tertiary medical centers

Table E3. Sensitivity Analysis Evaluating Association between African-American Race, Mortality, All-Cause Hospitalizations, and Respiratory Hospitalizations in Patients with Code-based ILD (n=9,503)

Characteristics	Tertiary Referral Medical Center			Non-Tertiary Academic Medical Centers			Pooled Population		
	AA patients	Non-AA Patients	*P* value	AA patients	Non-AA patients	*P* Value	AA patients	Non-AA patients	*P* value
ICD-9 code diagnosis of ILD, n (%)	2297(44.2)	2895 (55.8)	--	251 (5.8)	4060 (94.2)	--	2548 (26.8)	6955 (73.2)	--
Mean survival time, (95% CI), months	102 (100 – 104)	101 (100 – 103)	0.466	104 (97 – 111)	88 (86 – 90)	<0.001	102 (100 – 104)	95 (94 – 96)	<0.001
Mortality, No. (%)	527 (22.9)	660 (22.8)	0.923	43 (17.0)	1276 (31.4)	<0.001	570 (22.3)	1936 (27.8)	<0.001
Lung transplantation, No. (%)	13 (0.6)	38 (1.3)	0.007	0 (0.4)	2 (0.05)	0.725	13 (0.5)	40 (0.6)	0.707
***Propensity Score Models*#**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* value**
Unadjusted model	0.76	0.60-0.97	0.025	0.66	0.42-1.06	0.084	0.72	0.55-0.82	0.002
Adjusted model*	0.63	0.44-0.91	0.013	0.88	0.50-1.56	0.674	0.60	0.44-0.81	0.001
Plus referral status	0.63	0.44-0.91	0.014	0.91	0.51-1.62	0.081	0.59	0.43-0.80	0.001
Plus immunosuppressive therapy	0.64	0.45-0.92	0.017	0.89	0.50-1.59	0.697	0.59	0.43-0.81	0.001
Plus income level	0.67	0.46-0.98	0.037	0.87	0.47-1.59	0.647	0.60	0.43-0.83	0.002
Plus insurance type	0.68	0.46-0.99	0.044	0.90	0.49-1.64	0.724	0.59	0.43-0.83	0.002
All-Cause Hospitalizations	**AA patients**	**Non-AA Patients**	***P* value**	**AA patients**	**Non-AA patients**	***P* Value**	**AA patients**	**Non-AA patients**	***P* value**
Number of hospitalized patients, n (%)	986 (42.9)	804 (27.8)	<0.001	240 (95.6)	3611 (88.9)	<0.001	1226 (48.1)	4415 (63.5)	<0.001
Risk of hospitalization, OR	1.96	--	<0.001	2.71	--	<0.001	0.53	--	<0.001
Hospitalizations per patient**, IRR (SE)	1.20	--	0.001	0.71	--	<0.001	0.95	--	0.231

* adjusted for baseline demographic characteristics - age, gender, body mass index, smoking status, co-morbid diseases (coronary artery disease, gastroesophageal reflux, diabetes mellitus), geographical residence, and ILD subtype.

after propensity score matching, n=2471 in pooled population; tertiary medical center, n=2039 (AA=1480, non-AA=559); non-tertiary medical center, n=432 (AA=210, non-AA=222)

ILD=interstitial lung disease; GAP=gender, age, physiology; OR=log odds ratio; IRR=incidence rate ratio; IQR=interquartile range; SE=standard error

**evaluated among hospitalized patients

Table E4. Sensitivity Analysis Adjusting Propensity Score for Co-morbid diseases, Use of Antifibrotic, ANA seropositivity, Total Lung Capacity, Six-minute Walk Distance, and Radiologic Honeycomb Fibrosis in Patients with Multidisciplinary and adjudicated ILD

	Tertiary Referral Medical Center			Non-Tertiary Academic Medical Centers			Pooled Population		
Propensity Score Models#	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* value**
Unadjusted model	0.48	0.30-0.78	0.003	0.67	0.15-2.92	0.593	0.51	0.32-0.80	0.004
Adjusted model*	0.43	0.25-0.72	0.002	0.43	0.09-2.16	0.305	0.48	0.29-0.79	0.004
Plus referral status	0.43	0.25-0.73	0.002	0.43	0.09-2.16	0.305	0.48	0.29-0.79	0.004
Plus immunosuppressive therapy	0.43	0.25-0.73	0.002	0.42	0.08-2.17	0.303	0.48	0.29-0.79	0.004
Plus income level	0.43	0.25-0.73	0.002	0.36	0.07-1.95	0.238	0.47	0.29-0.78	0.003
Plus insurance type	0.43	0.25-0.73	0.002	0.32	0.07-1.61	0.168	0.46	0.28-0.77	0.003
Plus antifibrotic therapy	0.43	0.25-0.74	0.002	0.19	0.02-1.65	0.133	0.45	0.27-0.74	0.002
Plus ANA seropositivity	0.35	0.19-0.65	0.001	--	--	--	0.34	0.19-0.60	<0.001
Plus total lung capacity	0.34	0.18-0.64	0.001	--	--	--	0.32	0.18-0.57	<0.001
Plus six-minute walk distance	0.28	0.15-0.54	<0.001	--	--	--	0.29	0.15-0.5	<0.001
Plus honeycomb fibrosis	0.31	0.17-0.58	<0.001	--	--	--	0.32	0.18-0.60	<0.001

* adjusted for baseline demographic characteristics – body mass index, age, gender, percent predicted forced vital capacity, percent predicted diffusing capacity of the lung for carbon monoxide, and ILD subtype; GAP-ILD score.
# after propensity score matching, after propensity score matching, n=306 in pooled population; tertiary medical center, n=262 (AA=156, non-AA=106); non-tertiary medical center, n=44 (AA=24, non-AA=20). ILD=interstitial lung disease; OR=log odds ratio; IRR=incidence rate ratio; IQR=interquartile range; SE=standard error

Table E5. Causes of Respiratory-related Hospitalizations among patients with Multidisciplinary (MDD) and adjudicated ILD diagnosis.[#]

	Frequency
Other respiratory worsening	
Increased dyspnea	331
Hypoxia	237
Respiratory distress	242
Other unclassifiable acute respiratory worsening	104
Respiratory-tract infection or pneumonia	115
Respiratory failure (requiring mechanical ventilation)	86
COPD exacerbation	31
Elective admission for lung biopsy*	128
Acute exacerbation of ILD (physician diagnosed)	139
Pneumothorax	9
Aspiration event	6
Pulmonary embolism	16
Elective admission for lung transplantation*	33
Pulmonary hypertension	20

*Not included in respiratory hospitalization
[#]Participants were eligible for more than one criterion

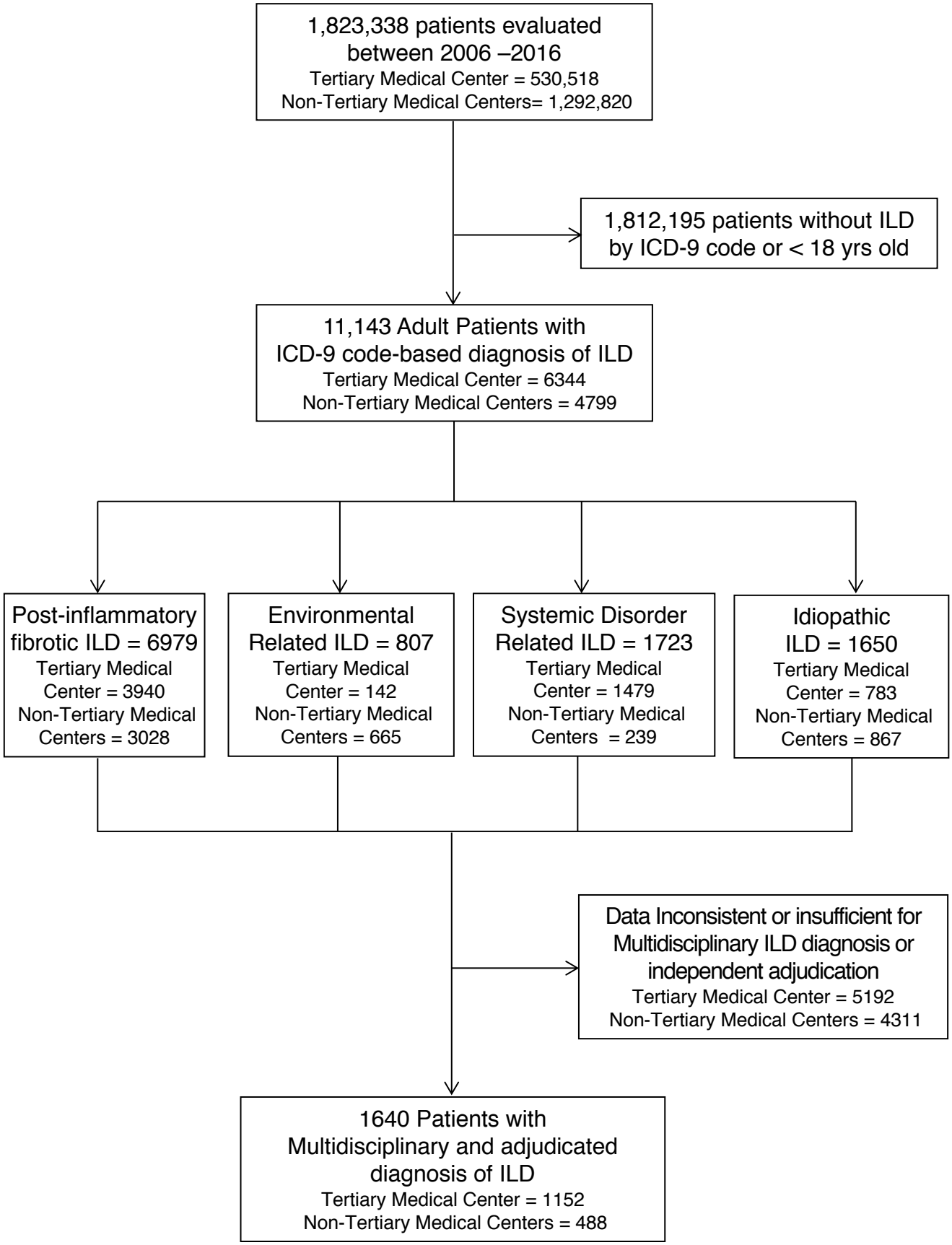


Figure E1. CONSORT diagram

A.

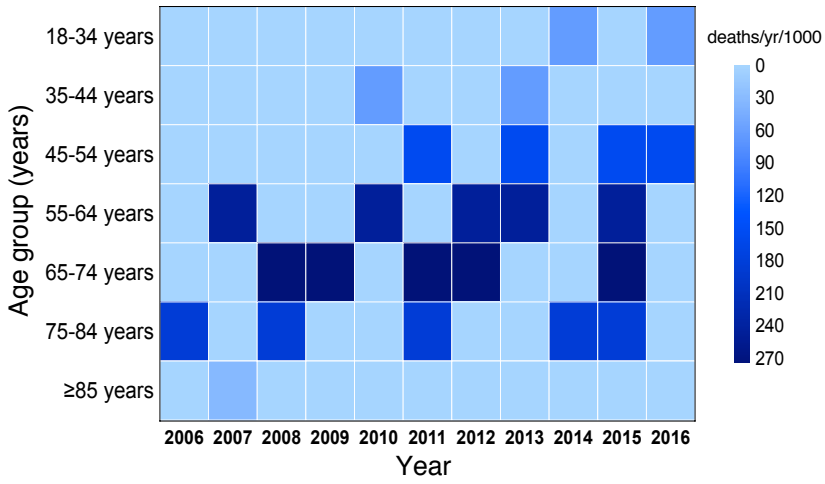


Figure E2. Age-standardized annual mortality rates (AMR) among African-American patients with multidisciplinary (MDD) and adjudicated diagnosis of ILD stratified by age group; population AMR depicted per thousand patients with ILD.

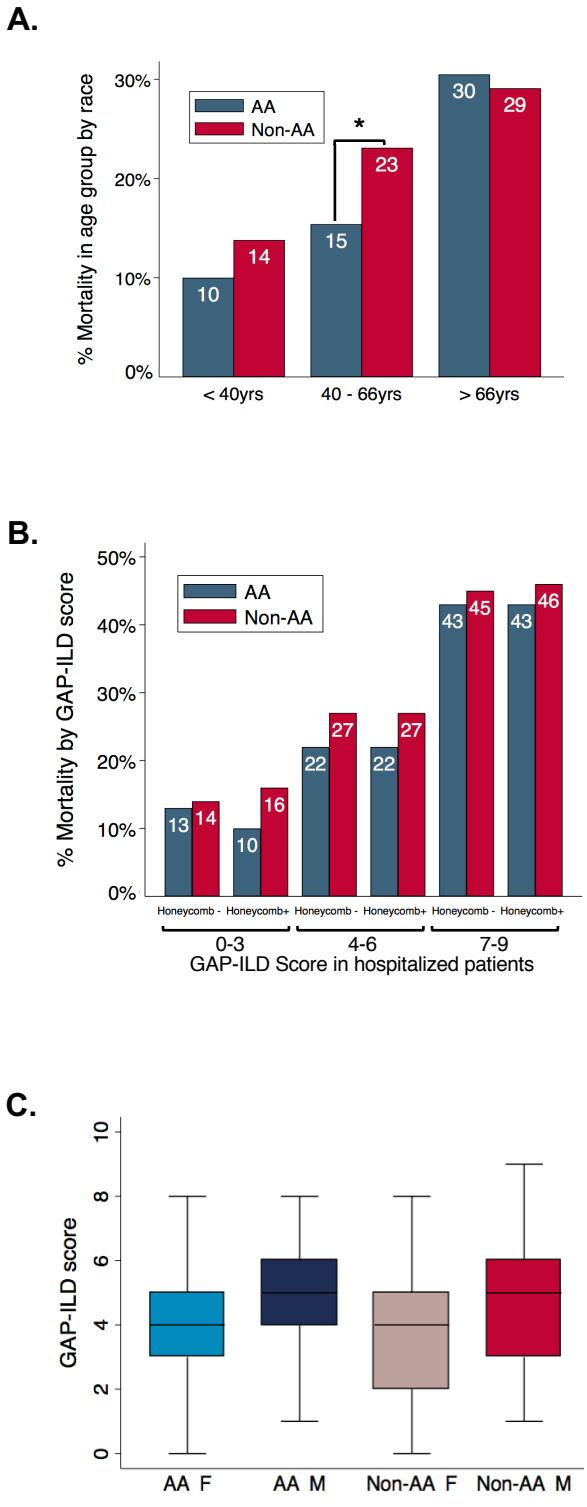


Figure E3 (a) Percentage distribution of mortality in multidisciplinary (MDD) and adjudicated ILD cohort stratified by age group and race. Percentage distribution of **(b)** mortality in MDD and adjudicated ILD cohort substratified by race, radiographic honeycombing and GAP-ILD score; and **(c)** distribution of GAP-ILD score stratified by race and gender. AA=African-American; ILD=interstitial lung disease; GAP=gender, age, physiology. *P<0.05.