Significance of Interstitial Lung Disease on Outcomes Following Cardiac Surgery

Sameer A. Hirji, MD, MPH[a], Fernando Ramirez-Del Val, MD[a], Julius I. Ejiofor, MD, MPH[a], Jiyae Lee, BS[a], Anthony V. Norman, BS[a], Siobhan McGurk, BS[a], Marc P. Pelletier, MD, MSc[a], Sary Aranki, MD[a], James Rawn, MD[a], Prem S. Shekar, MD[a], Gary M. Hunninghake, MD[b], and Tsuyoshi Kaneko, MD[a,*]

Interstitial lung disease (ILD) is a known risk factor for noncardiac surgery due to acute pulmonary exacerbations but its impact after cardiac surgery is not known. We examined perioperative outcomes and risk factors for long-term survival in ILD patients who underwent cardiac surgery. From January 2002 to June 2017, 294 cardiac surgery patients with a previous ILD diagnosis, including 75 patients with idiopathic pulmonary fibrosis (IPF), were identified. A comparison cohort of 1,481 non-ILD patients was selected based on a priori variables. Long-term survival was evaluated using Cox proportional hazard modeling. Median follow-up was 6.4 years. ILD patients had higher postoperative mortality, reintubation rates, longer intensive care unit stay, and higher 30-day readmission rates (all p <0.05). Kaplan-Meier estimates of survival at 1, 5, and 10 years were 89%, 62%, and 37% for the non-IPF ILD cohort, 89%, 50%, and 13% for the IPF cohort, and 95%, 82%, and 67% for the comparison cohort, respectively (overall p <0.001). These significant differences in survival persisted in our risk-adjusted survival analysis. Adjusted survival analysis identified IPF (hazard ratio 3.04) and ILD (non-IPF; hazard ratio 1.78) as significant contributors to all-cause mortality. However, there were no changes in pulmonary function tests after 48 months postprocedure. In conclusion, ILD patients who underwent cardiac surgery have increased operative mortality, reintubation rates, longer intensive care unit, and higher 30-day readmissions compared with non-ILD patients. Moreover, severity of ILD, especially in IPF, appears to be associated with shorter long-term survival. In these patients, pulmonary risk stratification and multidisciplinary team approach are crucial. **(Am J Cardiol 2019;124:1133−1139)**

Interstitial lung disease (ILD) encompasses a diverse group of parenchymal lung pathologies with varying clinical presentations and etiologies.[1] ILD patients who undergo surgery are considered very high-risk especially given their substantial burden of co-morbidities, the clinical progression of their underlying disease, and increasing vulnerability for postoperative acute exacerbations (PAE), all of which contribute toward their increased morality.[2−4] Although poor outcomes in ILD patients have been reported after noncardiac surgery,[3,4] the literature on postcardiac surgery outcomes in ILD patients are scarce. With improvements in surgical techniques and perioperative care, a significant proportion of high-risk patients, including those with existing chronic lung disease (CLD) undergo cardiac surgery.[5,6] With a growing prevalence of severe CLD patients (which include ILD and idiopathic pulmonary fibrosis [IPF] patients) being offered cardiac surgery, and the fact that observed clinical outcomes remain favorable in this population, there is growing interest in clinicians to examine perioperative outcomes in this unique patient population for purposes of benchmarking clinical performance against emerging transcatheter technologies. This study examines perioperative outcomes in ILD patients who underwent cardiac surgery, and identifies risk factors for long-term survival.

Methods

With approval from our institutional review board, we retrospectively reviewed all adult patients who underwent cardiac surgery from 2002 to June 2017. Patients who underwent isolated coronary artery bypass grafting (CABG), isolated valve (aortic, mitral, or tricuspid valve) repair or replacement, previous cardiac surgery, and concomitant CABG and valve procedures were included (see CONSORT diagram in Supplement Figure e1). Informed consent was waived.

The Partners Healthcare Research Patient Data Registry (RPDR) was queried for the preoperative presence of ILD diagnosis. This internal clinical data registry contains data from all institutions in the Partners HealthCare System; storing clinical information on ~10 million patients and containing more than ~2 billion data points. The International Classification of Disease (ICD)-9 codes included were 516 (other alveolar pneumonopathies), 516.3 (idiopathic fibrosing alveolitis/IPF), 515 (postinflammatory pulmonary fibrosis), and 508.1 (long-term and other pulmonary manifestations

[a]Division of Cardiac Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; and [b]Division of Pulmonary Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Manuscript received February 14, 2019; revised manuscript received and accepted June 13, 2019.

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*Corresponding author: Tel: (617) 732-7678; fax: (617) 732-6559.
E-mail address: tkaneko2@partners.org (T. Kaneko).

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due to radiation); ICD 10 codes included were J84.0 to J84.9. Potential subjects were then chart reviewed to verify they met ILD clinical criteria by 2 independent reviewers. The final cohort (n = 294 patients), included all subjects with ILD findings on imaging confirmed by a pulmonologist, and adjudicated with biopsies.

To isolate the risks of operative mortality conferred by ILD, we sought a comparison cohort from among the remaining adult cardiac surgery patients who met study inclusion criteria and were documented as having no CLD in the Society for Thoracic Surgeons (STS) database and no documentation of the above ICD codes in their electronic medical record (EMR) (Supplement Figure e1). Of the remaining 6210 patients, we further identified a subset with similar distributions of age, gender, surgical procedures, surgery year, and STS PROM scores. A logistic regression was constructed using these a priori characteristics to calculate a probability score for each patient's operative mortality. Any subject with a resulting score in excess of within a 0.05 caliper was excluded, and up to 7 qualifying controls were selected per individual case, resulting in a comparison cohort of 1,481 non-ILD patients.

Patient demographics, preoperative characteristics, and operative and in-hospital outcomes were obtained from the STS Adult Cardiac Surgery database coded to version 2.52 specifications, individual chart review or RPDR query. Chronic kidney disease was defined a priori as a preoperative creatinine ≥2.0 mm/dl or most recent clinical documentation of renal disease. Survival data were obtained from routine patient follow-up, RPDR query which includes data from the National Death index, the Social Security Death Index, and our state's Department of Public Health and Registry of Vital Statistics. Combining all methods, there was 99% follow-up for patient survival. For patients lost to follow-up, observation time was censored at the point of last known clinical contact. Follow-up time was calculated in months from the date of surgery to either death date or study close, December 30, 2017. Median follow-up time was 6.4 years ([interquartile range 3.5, 6.5]; range 0 to 15.2 years) for a total of 11,931 patient-years of data.

Primary outcomes of interest were operative mortality and long-term survival. Secondary outcomes included length of stay (LOS) and postoperative morbidity. Operative mortality was any death occurring in-house or within 30 days of the index surgery if discharged. Prolonged mechanical ventilation was defined as the continuous or intermittent accumulation of more than 24 hours of mechanical ventilation during the hospitalization.

All statistical analyses were conducted using IBM SPSS Statistics version 23.0 (IBM Corporation, Armonk, New York) with p ≤0.05 as the criterion for significance. Normally distributed variables are expressed as a mean with standard deviation, and compared using Student's *t* tests with Levene's test for homogeneity of variance. Nonnormally distributed variables are expressed as a median and interquartile range, and compared using Mann-Whitney *U* tests. Categorical variables are presented as number and percentages, and were compared using chi-square or Fisher's exact tests. Unadjusted survival was assessed using Kaplan-Meier methods. Adjusted survival was evaluated using a forward, stepwise Cox proportional hazard model. We included variables in the model based on previous knowledge or if they differed significantly between the groups, or were deemed clinically meaningful confounding sources. Interaction terms between lung disease diagnosis and age, gender, and procedure type were examined. Temporal trends in pulmonary function tests (PFTs) were assessed using longitudinal analysis.

Results

Preoperative characteristics are listed in Supplement Table e1. All other preoperative characteristics, including age, were similar between the 2 groups except for a higher prevalence of chronic kidney disease (9.2% vs 4.2%), and PVD (18% vs 9%) in the ILD group. Perioperative outcomes are shown in Table 1. ILD patients had higher

Table 1
Perioperative outcomes of ILD and comparison cohort

Variable	Comparison cohort (n = 1,481)	ILD (n = 294)	p ≤
Operative outcomes			
Perfusion time (min)	129 (93, 179)	114 (86, 149)	*0.001
Cross-clamp time (min)	91 (63, 103)	83 (64, 114)	*0.008
Procedures			0.370
Isolated CABG	472 (32%)	107 (36%)	
Iso AVR	458 (31%)	61 (21%)	
Iso MVR	142 (9.6%)	25 (8.8%)	
Iso TVR	5 (0.3%)	2 (0.7%)	
Multiple†	64 (4.3%)	31 (10%)	
AVR + CABG	253 (17%)	41 (15%)	
MVR + CABG	69 (4.7%)	17 (6.7%)	
Misc‡	17 (1.1%)	10 (3.5%)	
Transfused with pRBC	421 (28%)	112 (38%)	*0.001
Postoperative outcomes			
Reoperation for bleed	24 (1.6%)	8 (2.7%)	0.230
Stroke	44 (3%)	9 (3.1%)	0.850
New onset renal impairment	40 (2.7%)	17 (5.7%)	*0.010
Transfused with pRBC	475 (32%)	129 (43.9%)	*0.001
Ventilation time (hrs)	8 (4, 15)	7.3 (5, 127)	0.120
Required reintubation	24 (1.6%)	17 (5.8%)	*0.001
Vent > 24 hr	127 (8.6%)	34 (12%)	0.120
Total ICU time (hrs)	60 (31, 110)	62 (32, 115)	*0.001
LOS (days)	8 (6, 13)	8 (6, 12)	*0.001
30-day readmissions	187 (13%)	53 (18%)	*0.015
Operative mortality	36 (2.4%)	15 (5.1%)	*0.020
Cause of death			* 0.001
Cardiac	16 (44%)	3 (20%)	
Respiratory	3 (8%)	12 (80%)	
Renal Failure	4 (11%)	0	
Bleeding	2 (6%)	0	
Stroke	7 (20%)	0	
Other	4 (11%)	0	

Abbreviations as follows: AVR = aortic valve replacement; CABG = coronary artery bypass grafting; ICU = intensive care unit; ILD = interstitial lung disease; LOS = length of stay; MVR = mitral valve replacement; pRBC = packed red blood cells; TVR = tricuspid valve replacement; Vent = ventilator requirement.

-Continuous variables are presented as mean (SD) unless otherwise noted as median (IQR); categorical variables are summarized as n (%).

-All variables were coded according to the Society for Thoracic Surgeons (STS) Adult Cardiac Surgery database (version 2.52).

* p Value ≤0.05 was considered statistically significant.

† Multiple − implied multiple combination of valves.

‡ Misc implied multiple combinations of valves with other aortic procedure ± CABG.

Table 2
Perioperative outcomes of IPF and non-IPF patients in patients with ILD

Variable	Non-IPF (n = 219)	IPF (n = 75)	p ≤
Operative outcomes			
Perfusion time (min)	129 (93, 178)	109 (84, 163)	*0.001
Cross-clamp time (min)	90 (67, 126)	80 (60, 115)	*0.007
Procedures			*0.014
Isolated CABG	69 (32%)	38 (51%)	
Isolated AVR	44 (20%)	17 (23%)	
Iso MVR	17 (7.8%)	8 (11%)	
Iso TVR	2 (0.9%)	0	
Multiple†	29 (13%)	2 (2.6%)	
AVR + CABG	33 (18%)	8 (11%)	
MVR + CABG	15 (6.8%)	2 (2.6%)	
Misc‡	10 (4.6%)	0	
Postoperative outcomes			
Reoperation for bleed	2.3 (2.3%)	3 (4%)	0.425
Stroke	8 (3.7%)	1 (1.3%)	0.456
New onset renal impairment	13 (5.9%)	4 (5.3%)	1.000
Ventilation time (hrs)	7.9 (4.6, 14.6)	8.4 (5.0, 13.7)	0.206
Required reintubation	14 (6.4%)	3 (4%)	0.574
Vent > 24 hr	26 (12%)	8 (11)	1.000
Total ICU time (hrs)	60 (32, 115)	66 (31, 114)	*0.001
LOS (days)	8 (6, 13)	9 (6, 12)	*0.001
Operative mortality	11 (5%)	4 (5.3%)	1.000
30-day readmissions	38 (17%)	15 (20%)	0.605

Abbreviations as follows: AVR = aortic valve replacement; CABG = coronary artery bypass grafting; ICU = intensive care unit; ILD = interstitial lung disease; IPF = interstitial pulmonary fibrosis; LOS = length of stay; MVR = mitral valve replacement; TVR = tricuspid valve replacement; Vent = ventilator requirement.

-Continuous variables are presented as mean (SD) unless otherwise noted as median (IQR); categorical variables are summarized as n (%).

-All variables were coded according to the Society for Thoracic Surgeons (STS) Adult Cardiac Surgery database (version 2.52).

* p Value ≤0.05 was considered statistically significant.

† Multiple − implied multiple combination of valves.

‡ Misc implied multiple combinations of valves with other aortic procedure ± CABG.

operative mortality, higher reintubation rates, longer intensive care unit (ICU) stay, and higher 30-day readmission rates (all p <0.05). The most common cause of death was respiratory failure (80%) in the ILD cohort and cardiac-related causes (44%) in the comparison cohort.

In the ILD patients, 75 patients had preexisting IPF. Baseline characteristics, including age and PFTs, between the 2 groups were also generally similar (Supplement Table e2). Although IPF patients had significantly shorter perfusion and cross-clamp times, and longer ICU stay and overall LOS compared with non-IPF patients (all p <0.05), operative mortality, reintubation rates, and 30-day readmissions were not statistically different (Table 2).

There were 476 deaths during the study period. Kaplan-Meier estimates of unadjusted survival at 1, 5, and 10 years were 89%, 62%, and 37% for the non-IPF ILD cohort, and 89%, 50%, and 13% for the IPF cohort, and 95%, 82%, and 67% for the comparison cohort, respectively (overall p <0.001; Figure 1). These significant differences in survival persisted in our risk-adjusted survival analysis (p <0.001; Figure 1). Similar findings were observed after

Table 3
Cox proportional hazards modeling of all-cause mortality

	Hazard ratio	p ≤	95% Confidence interval	
			Lower	Upper
Contributory risk factors				
Lung diagnosis		0.001		
IPF	3.04	0.000	2.42	3.80
ILD, non-IPF	1.78	0.004	1.20	2.64
Chronic kidney disease	2.57	0.001	1.87	3.56
Non-Caucasian race	2.59	0.003	1.38	4.88
Arrhythmia	1.36	0.025	1.04	1.78
NYHA Class III/IV	1.48	0.001	1.21	1.80
Peripheral vascular disease	1.32	0.036	1.03	1.72
Congestive heart failure	1.31	0.008	1.07	1.59
Diabetes	1.10	0.046	1.002	1.42
Age (years)	1.05	0.001	1.04	1.06
Body mass index	0.98	0.003	0.99	0.96

Abbreviations: ILD = interstitial lung disease; IPF = interstitial pulmonary fibrosis.

Noncontributory variables include cerebrovascular disease, gender, myocardial infarction, reoperation, procedure group, emergent status, and smoker, procedure year.

stratifying our cohort by procedure types into isolated CABG (Supplement Figure e2), isolated valve (Supplement Figure e3), and concomitant valve and CABG procedure (Supplement Figure e4).

On Cox proportional hazards modeling, IPF (hazard ratio 3.04) and ILD (non-IPF; hazard ratio 1.78) were significant contributors to all-cause mortality (Table 3). On longitudinal analysis, expected forced expiratory volume in 1 second (FEV1) in IPF and non-IPF patients remained relatively unchanged from baseline over the 48-month duration after cardiac surgery (Figure 2). Similar findings were observed for forced vital capacity (FVC; Figure 2) and diffusing capacity of lung for carbon monoxide (DLCO; Figure 2).

Discussion

To our knowledge, this retrospective cohort study is the first to examine the clinical outcomes of ILD patients who underwent cardiac surgery. With an extensive follow-up of 15 years, this present study had several important findings. First, it highlighted that ILD patients who underwent cardiac surgery had increased 30-day mortality, higher reintubation rates, and longer ICU stay. These patients also had decreased long-term survival compared with non-ILD (comparison cohort) patients. Second, because IPF patients had longer ICU and hospital LOS compared with non-IPF patients, operative mortality, reintubation rates, and 30-day readmissions were not statistically significant. Finally, there were no changes in FEV1, FVC, and DLCO between the IPF and non-IPF patients after 48 months following cardiac surgery. Together these findings emphasize the importance of pulmonary risk stratification and a multidisciplinary team approach for patient management.

For cardiac surgery, a few studies have shown adverse outcomes in severe CLD patients but outcomes specific to

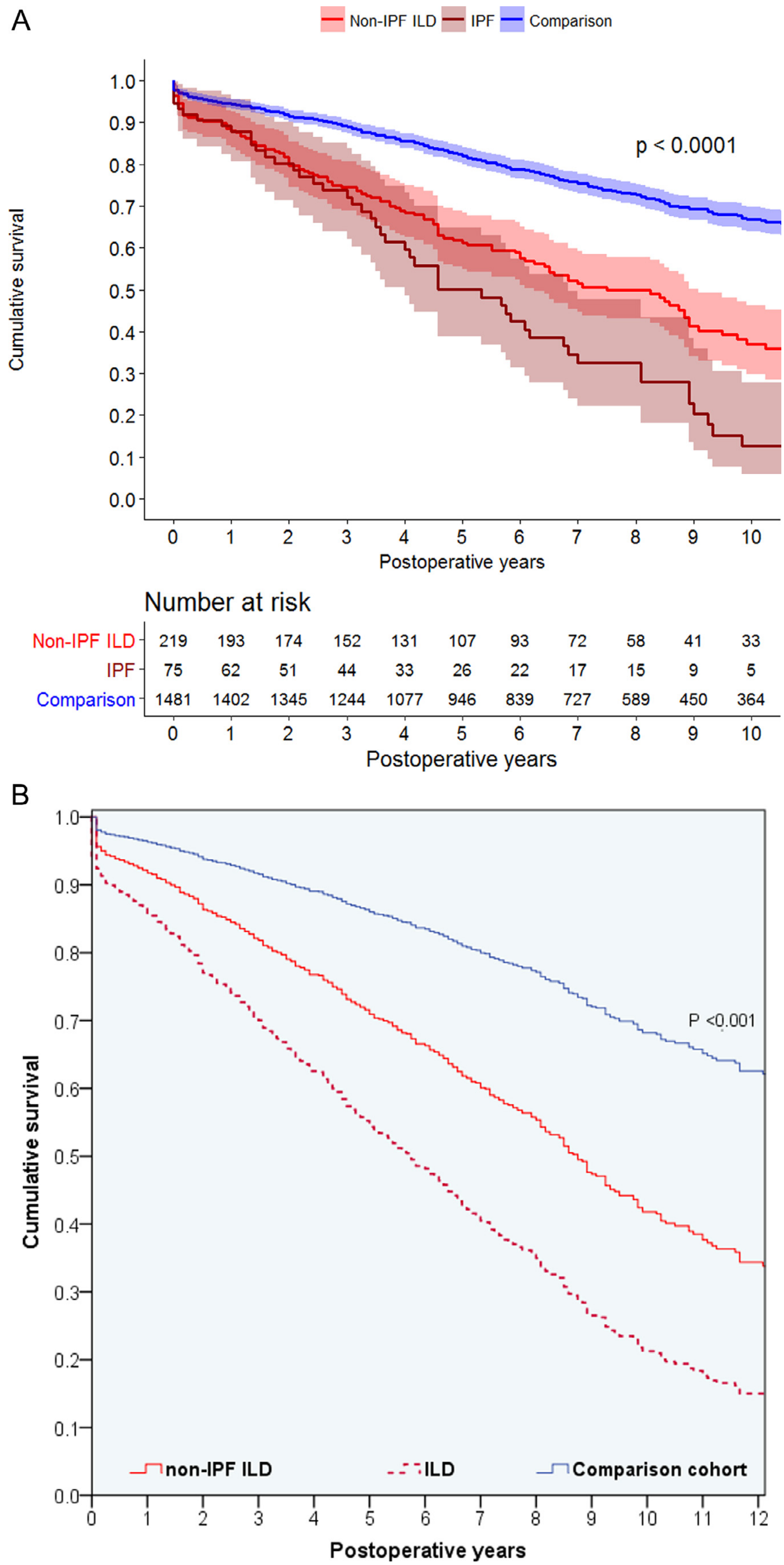

Figure 1. (*A*) Unadjusted Kaplan-Meier survival curves. (*B*) Adjusted survival curves derived from Cox proportional hazards model for patients with non-IPF ILD, IPF, and Comparison Cohort. ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis.

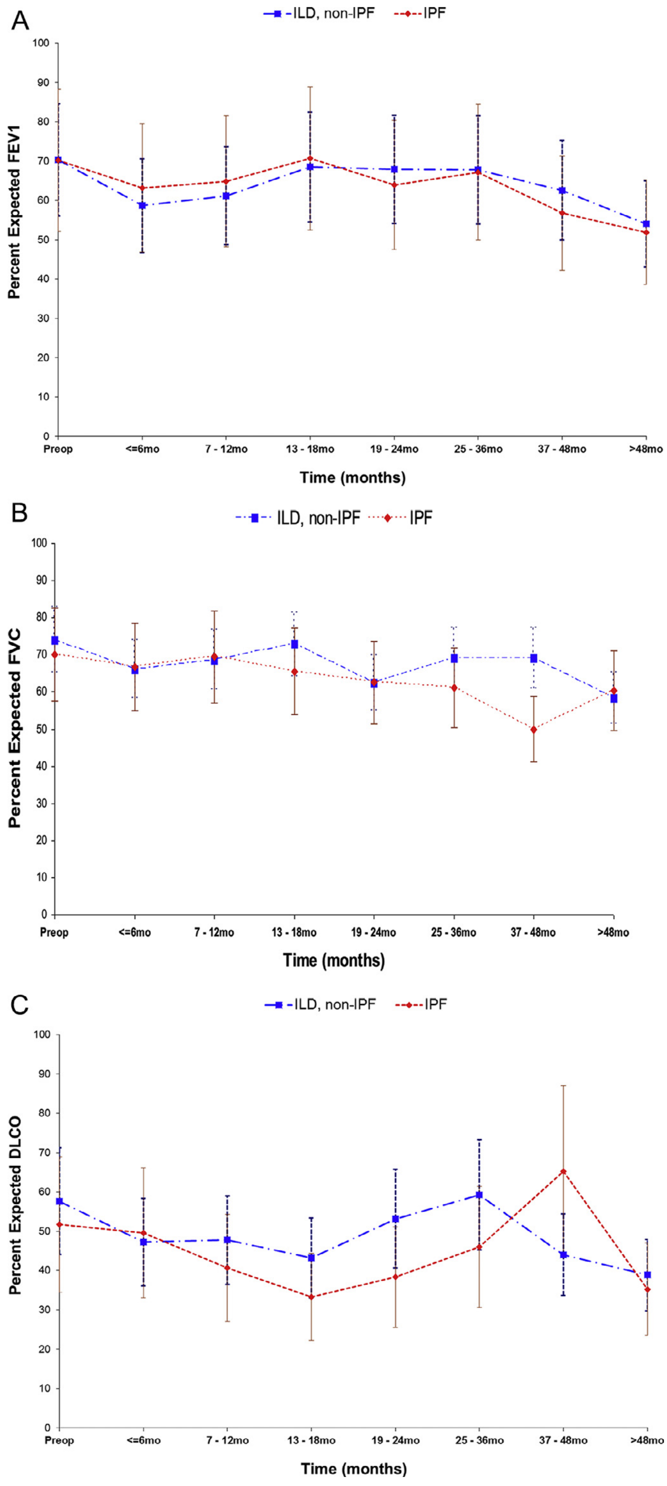

Figure 2. Temporal trends in postoperative PFTs in IPF and non-IPF patients who underwent cardiac surgery from baseline. (*A*) Percent expected forced expiratory volume in 1 second, (*B*) percent expected forced vital capacity, and (*C*) percent diffusing capacity of lung for carbon monoxide. IPF = idiopathic pulmonary fibrosis; PFT = pulmonary function test.

ILD patients have not been well reported.[5,7] In one single-center study of 7,060 patients who underwent a CABG procedure, severe CLD was associated with increased 30-day mortality (odds ratio [OR] 3.7), nonhome discharge (OR 3.6), reintubation rates (OR 3.4), and prolonged ventilation (OR 4.6).[7] Since ILD patients represent a much higher-risk cohort in the severe CLD group, but with comparable operative mortality as shown in our study, our findings challenge existing reservations that many surgeons may have on operating on ILD patients. The estimated median survival between ILD and non-ILD patients was also not much clinically different (8.5 vs 9.2 years). Thus, whereas cardiac surgery in ILD patients is high risk, it may perhaps not be completely contraindicated.

Previous studies in noncardiac surgery have reported increased operative mortality for IPF patients.[4,8] These patients are also increasingly vulnerable to developing postoperative pulmonary complications, which account for substantial morbidity, and are a subject of considerable interest.[9] Furthermore, surgical interventions, in the context of prolonged cardiopulmonary bypass duration and thoracic mechanical alterations secondary to sternotomy or thoracotomies, are considered a trigger for the development of PAE, resulting in an 80% to100% mortality in some series.[3,10,11] Thus, if respiratory failure and subsequent PAE can be avoided, IPF is not a contraindication for surgery. This fact, we believe, was likely the driving force behind the observed shorter perfusion and clamp times compared with non-IPF patients, in an effort to minimize postoperative morbidity. In the present study, IPF was a significant risk factor for long-term survival after cardiac surgery, although operative mortality was not statistically different from non-IPF. The longer ICU and hospital stays observed in these patients suggest the need for further rehabilitative services for further recovery.[9,12] These findings are also important in the context of high-risk patients in whom minimally invasive strategies such as transcatheter therapies may be potentially considered.

In this study, we explored temporal trends in PFT after ILD cardiac surgery. Preoperative PFT has been previously shown to predict mortality after SAVR and TAVR.[13] In ILD and IPF patients, taking into account their disease profile, one would expect that PFTs would worsen over time. This is because lungs with preexisting interstitial disease have less elastic tissue and could therefore be more susceptible to volutrauma and barotrauma during surgery.[14] Surprisingly however, we found that FEV1, FVC, and DLCO in IPF and non-IPF, ILD patients remained relatively unchanged from baseline over the duration of 48 months after surgery. This has important clinical implications which include optimization of preoperative care for those at risk, smoking cessation, and pulmonary hygiene.[5]

A careful multidisciplinary approach should be employed to improve patient selection and perioperative management in ILD patients. Likewise, practices to reduce pulmonary complications should be instituted since respiratory failure, which our study also highlighted, accounts for the majority of operative mortality. From a technical perspective, the management of ILD is heavily dependent on their preoperative FEV1. Thus, for patients with severely reduced FEV1s, there is a consensus practice at our institution to favor total intravenous anesthesia over inhalational anesthesia due to more reliable pharmacokinetics. Although controversial, we have also routinely utilized a strategy of low-tidal volume ventilation (tidal volume targets of 6 to 8 ml/kg predicted body weight) in the perioperative setting to provide adequate oxygenation and ventilation to limit barotrauma and subsequent lung injury.[15] Other strategies include perioperative fluid restriction, aggressive postoperative pulmonary toilet, and early mobilization to minimize postoperative pulmonary complication, with some patients requiring further postoperative cardiac rehabilitation for complete recovery. In terms of preoperative assessment, we also recommend that ILD patients should likely undergo a comprehensive prehabilitation program, although our institution currently does not have a protocol in place for the preoperative clinic to follow.

Several limitations must be noted to accurately interpret our key findings. First, given the retrospective nature of our study, our findings may not be generalizable to other populations. This was not a randomized trial and relevant residual confounders might persist despite risk adjustment. Although we accounted for year of surgery in our cox model and matching algorithm, implications of an ILD diagnosis may not be quite so pronounced in the current period given advances in respiratory care over the years. Additionally, an extensive analysis of perioperative PFTs of ILD patients was not possible since PFTs were not available on all patients. It is possible for ILD patients who underwent cardiac surgery to be subjected to both survival and selection bias, resulting in longer median survival compared with previous epidemiologic studies. We were also unable to assess the degree of selection bias around those not eligible for cardiac surgery based on PFTs.

In conclusion, utilizing our extensive 15-year experience and robust follow-up, we examined the impact of ILD in one of the largest cohorts of ILD patients who underwent cardiac surgery. Importantly, we found that patients with ILD who underwent cardiac surgery have increased operative mortality, reintubation rates, longer ICU and hospital stay, higher 30-day readmissions, and shorter long-term survivals. Moreover, severity of ILD, especially in IPF, appears to be associated with adverse long-term outcomes. In these patients, pulmonary risk stratification and multidisciplinary team approach is crucial to help guide decision making and resource planning.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.06.031.

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