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Acute respiratory failure due to diffuse parenchymal lung diseases in a respiratory intensive care unit of North India

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Abstract. *Background:* Acute respiratory failure (ARF) due to diffuse parenchymal lung diseases (DPLDs) is associated with high mortality. Whether ARF due to acute interstitial pneumonia (AIP), idiopathic pulmonary fibrosis (IPF) and non-IPF DPLDs behaves differently remains unclear. *Methods:* A retrospective analysis of consecutive DPLD subjects with ARF admitted to respiratory intensive care unit (RICU). The baseline clinical, demographic characteristics, cause of ARF and mortality were compared between the groups. *Results:* 145 (5.8% of RICU admission) subjects (mean [SD] age, 51.6 [14.7] years, 406% males) with DPLD-related ARF (17 AIP; 32 IPF; 96 non-IPF DPLD) were admitted. Common causes of ARF were acute exacerbation of the underlying DPLD (n=59, 40.4%) followed by infections (n=48, 37.5%). There was no difference in the peak, plateau and driving pressures across groups. The mortality rate was 45.5% (66/145) and was highest in AIP (82%) followed by IPF (59%) and non-IPF DPLD (34%). On multivariate logistic regression analysis, baseline APACHE II score, PaO_2:FiO_2 ratio, delta SOFA, and the use of invasive mechanical ventilation were independent predictors of mortality. The type of underlying DPLD however, did not affect survival. *Conclusions:* DPLD-related ARF is an uncommon cause of admission even in a RICU, and is associated with a high mortality. *(Sarcoidosis Vasc Diffuse Lung Dis 2018; 35: 363-370)*

Key words: respiratory failure, sarcoidosis; interstitial lung disease, acute interstitial pneumonia, connective tissue disease

Introduction

Diffuse parenchymal lung diseases (DPLDs) or interstitial lung diseases (ILDs) are a heterogeneous group of progressive lung disorders that are characterized by varying degrees of inflammation and fibrosis of the lung parenchyma. Depending on the etiology and clinicoradiological characteristics, DPLDs are categorized as idiopathic interstitial pneumonias, and other DPLDs from known and unknown causes (1-3). Idiopathic interstitial pneumonias include idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia, acute interstitial pneumonia (AIP) and others (1-4). The DPLDs from known causes include hypersensitivity pneumonitis, drug-induced ILD, and radiation-induced ILD while DPLD from unknown cause include sarcoidosis and others (3). DPLD can also complicate the course of connective tissue diseases such as rheumatoid arthritis, dermatomyositis/polymyositis, systemic sclerosis and systemic lupus erythematosus (5).

Most DPLDs present with chronic symptoms that are interspersed with acute worsening due to

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known (infections, disease progression) and unknown (idiopathic) causes. Acute respiratory failure (ARF) due to diffuse parenchymal lung disease (DPLD) forms an uncommon indication for intensive care unit (ICU) admission (6, 7). Several studies comprising of subjects with idiopathic pulmonary fibrosis (IPF) have demonstrated a high ICU mortality (6, 8-11). Many factors have been attributed to high mortality in IPF including high baseline ICU severity scores, severe hypoxemia, need for mechanical ventilation, and others (12, 13). Similar trends of mortality have also been reported in acute interstitial pneumonia (AIP).(14) On the other hand, hospitalization due to ARF in non-IPF DPLDs such as connective tissue disease (CTD) related DPLD, hypersensitivity pneumonitis (HP) and sarcoidosis has been shown to have better outcomes (7, 15-18). Previous studies have focused on AIP, IPF, and non-IPF DPLD separately (17, 19, 20). However, there is no head-to-head comparison of outcomes in subjects with ARF due to AIP, IPF and non-IPF DPLDs in same set of cohort. Herein, we compare the outcomes between ARF due to AIP, IPF and non-IPF DPLD requiring ICU care.

Methods

This was a retrospective study conducted in the respiratory intensive care unit (RICU) of this Institute between 1st February 2001 and 30th June 2017. The study protocol was approved by the Institute Ethics Committee. A consent waiver was allowed as the study involved the use of anonymized retrospective patient data. The patient data was entered prospectively using a specifically designed computer software, as previously described (21, 22). Briefly, data was recorded at the time of RICU admission and thereafter every 24 hours. The worst value for each variable during the 24-hour period was recorded. The time interval from RICU admission to 8:00 AM the next day was defined as day 0. Values on day 0 were used to calculate the baseline acute physiology and chronic health evaluation (APACHE II) scores and sequential organ failure assessment (SOFA) scores. Subsequent days were calendar days timed from 8:00 AM to 8:00 AM of the next day. Delta SOFA was calculated by subtracting the baseline SOFA score from the maximum SOFA score during the RICU stay (23).

Subjects with a diagnosis of DPLD or suspected to have DPLD admitted to RICU with ARF were eligible for inclusion into the study. The following information was retrieved on a data abstraction form: (a) demographic profile; (b) type of DPLD; (c) etiology of ARF; (d) baseline APACHE II and SOFA scores; (e) daily SOFA score including the maximum SOFA score attained during RICU stay; (f) nature of respiratory support (oxygen supplementation, non-invasive ventilation [NIV] or invasive mechanical ventilation [IMV]); (g) worst values of the following physiologic and ventilator parameters recorded daily (Pa_{O2}/Fi_{O2} ratio, positive end-expiratory pressure [PEEP], plateau pressure [Pplat], driving pressure (Pplat minus PEEP) and peak inspiratory pressure [Ppeak]); (h) ICU length of stay (LOS), and; (i) final outcome (death or discharge).

Definitions: The diagnosis of DPLDs was made on the basis of standard guidelines (1-5, 14, 24). Briefly, the diagnosis of DPLD was made on an outpatient basis after a consensus between the pulmonologist, radiologist and the histopathologist (25). The diagnosis of DPLD at RICU admission was made after discussions between the intensivists (ISS, RA) and an ILD expert (SD) in subjects in whom the diagnosis of DPLD was not made previously. The DPLDs were categorized as AIP, IPF, and non-IPF DPLD (all DPLDs except IPF and AIP).

Assessment of cause of acute worsening: Acute respiratory failure (ARF) was defined as an acute and rapid clinical worsening within four weeks, associated with hypoxemia with or without hypercarbia ($PaCO_2$ ≥45 mmHg) (26). Reasons for ARF were classified as progression of underlying DPLD, idiopathic (acute exacerbation of underlying DPLD), infection, cardiovascular disorders, pulmonary thromboembolism, and others (spontaneous pneumothorax, post-surgical lung biopsy). These assessments were determined with the help of clinical, hemodynamic, radiological, microbiological, and pathology results in the medical records for each subject by a multi-disciplinary team (pulmonologist, histopathologist and a radiologist). Pneumonia was clinically diagnosed by the radiographic presence of new or progressive radiological infiltrates, with fever, peripheral blood leukocytosis, purulent respiratory secretions, and/or documented microbiological results (27).

Treatment protocol: All the subjects who were diagnosed to have acute exacerbation of DPLD, AIP or disease progression received intravenous pulses of high dose methylprednisolone (15-20 mg/kg body weight; not exceeding 1 gram/day) for three days followed by oral prednisolone (1 mg/kg body weight). Subjects who were diagnosed with AIP or who had CTD-related ILD were additionally treated with intravenous cyclophosphamide (375 mg/m^2; maximum 1 gram/day). Subjects found to have specific infective causes (bacterial pneumonia, *Pneumocystis jirovecii* pneumonia, *Mycobacterium tuberculosis*, *Cytomegalovirus* pneumonia and others) of exacerbation were treated with specific agents.

All subjects requiring mechanical ventilation were managed with low tidal volumes as per the ARDSnet strategy (28). All subjects received sedation and neuromuscular blocking agents during the initial 48-72 hours to facilitate mechanical ventilation. They also received stress ulcer and deep venous thrombosis prophylaxis as per the ICU protocol. Patients were given enteral nutrition using a nasogastric tube.

Statistical analysis: The statistical analysis was performed using a commercial statistical software package (SPSS for MS-Windows, version 22.0; IBM SPSS Inc; Chicago IL). Data are presented as mean (standard deviation, SD) or number with percentages. Differences between the categorical and continuous variables were compared using the Chi square test and the Kruskal-Wallis ANOVA tests, respectively. Multivariate logistic regression analysis was performed to identify factors affecting survival. Survival curves were constructed to study the effect of different DPLDs on ICU mortality for the RICU stay using Kaplan-Meier curves. Differences between the survival curves were analyzed using log-rank test. A post hoc analysis of survival between groups (AIP vs IPF; AIP vs non-IPF DPLD; IPF vs non-IPF DPLD) was assessed by pairwise stratification. A p-value less than 0.05 was considered statistically significant.

Results

During the study period 2,491 subjects were admitted to the RICU of which 145 (5.8%) subjects were admitted with ARF due to DPLD. The mean (SD) age of the study population (40.6% males) was 51.6 (14.5) years. The baseline mean (SD) APACHE II score of the study population was 13.7 (7.9) with a predicted mortality of 24% (Table 1). The most common type of DPLD requiring ICU admission was CTD-related DPLD (n=36, 24.7%) followed by IPF (n=32, 21.9%) and NSIP (n=32, 21.9%). Seventeen (11.6%) subjects were diagnosed with AIP. Other DPLDs included sarcoidosis (n=26, 17.8%), hypersensitivity pneumonitis (n=3, 2.1%), pulmonary alveolar proteinosis (n=5, 3.4%), idiopathic pulmonary hemosiderosis (n=2, 1.4%), cryptogenic organizing pneumonia (n=2, 1.4%) and cystic ILD (n=1, 0.7%). Amongst CTD-related DPLDs, the underlying connective tissue diseases included rheumatoid arthritis (n=11, 30.6%), dermatomyositis (n=8, 22.2%), undifferentiated CTD (n=7, 19.4%), systemic sclerosis (n=6, 16.7%), mixed connective tissue disease (n=2, 5.6%) and systemic lupus erythematosus (n=2, 5.6%).

The most common reason for admission was acute exacerbation of underlying DPLD (n=56, 43.8%) followed by lower respiratory tract infections (n=48, 37.5%) and progression of the underlying ILD (n=16, 12.5%). Other causes of ARF included pulmonary embolism (n=4, 3.1%), pneumothorax (n=2, 1.6%) and heart failure (n=2, 1.6%). In four subjects, acute exacerbation was attributed to lung biopsy (surgical lung biopsy, n=3; cryo-lung biopsy, n=1). A majority of the study subjects (n=133, 91.7%) required some form of positive airway pressure (21 NIV and 112 IMV); all required oxygen supplementation. The mean (SD) peak airway pressure, plateau pressure, driving pressure and PEEP at baseline were 24.7 (9.1), 17.9 (7.9), 6.9 (4.7), and 5.9 (2.1) cm H_2O, respectively. The most common organisms isolated from respiratory secretions were *Pseudomonas aeruginosa* (n=9, 6.2%), *Klebsiella pneumoniae* (n=6, 4.1%), *Mycobacterium tuberculosis* (n=4, 2.7%), *Staphylococcus aureus* (n=2, 1.4%) and *Aspergillus fumigatus* (n=2, 1.4%). The organisms isolated in peripheral blood included *Staphylococcus aureus* (n=3, 2.1%), *Enterococcus* (n=2, 1.4%), *Streptococcus* (n=1, 0.7%) and *Candida* (n=1, 0.7%). Ventilator-associated pneumonia (n=10) and central line-associated blood stream infection (n=1) were the common form of hospital-acquired infection (*Acinetobacter baumanii* in all events).

Subjects with IPF-related ARF were significantly older than the subjects with non-IPF DPLD and AIP (Table 1). Subjects with AIP and IPF were pre-

Table 1. Comparison of clinical and outcome parameters between IPF, AIP and non-IPF DPLD

Parameters	AIP (n=17)	IPF (n=32)	Non-IPF DPLD (n=96)	Total (n=145)	P value
Baseline demography					
Age, years	44.2±14.7	61.7±9.6	48.3±14.4	51.6±14.5	<0.0001
Male gender, n (%)	12 (70.6)	24 (75)	28 (29.2)	52 (40.6)	<0.0001
ICU severity scoring					
APACHE II score	18.5±7.1	14.1±6.9	13.6±8.3	13.7±7.9	0.022
Delta SOFA score	4.4±4.4	2±2.9	1.9±2.6	1.9±2.6	0.016
Cause for worsening*, n (%)					<0.0001
Acute exacerbation of DPLD	-	18 (56.3)	38 (39.6)	56 (43.8)	
Progression of underlying DPLD	-	2 (6.3)	14 (14.6)	16 (12.5)	
Infective exacerbation	-	11 (34.4)	37 (38.5)	48 (37.5)	
Pulmonary embolism	-	1 (3.1)	3 (3.1)	4 (3.1)	
Pneumothorax	-	0	2 (2.1)	2 (1.6)	
Heart failure	-	0	2 (2.1)	2 (1.6)	
Physiological variables					
PaO_2:FiO_2 ratio	132±63.1	172.5±72.2	218.1±103.7	206.7±98.5	<0.0001
pH	7.36±0.07	7.37±0.08	7.38±0.08	7.38±0.08	0.244
$PaCO_2$, mmHg	51.6±15.9	47.9±13.3	43±14.6	44.3±14.4	0.022
Type of respiratory support, n (%)					0.098
Oxygen supplementation	1 (5.9)	1(3.1)	10 (10.4)	12 (8.3)	
NIV	1 (5.9)	9 (28.1)	11 (11.5)	21 (14.5)	
IMV	15 (88.2)	22 (68.8)	75 (78.1)	112 (77.2)	
Ventilatory parameters					
Peak pressure, cm H_2O	29.2±9.4	25.3±10.6	24.5±8.8	24.7±9.1	0.136
Pplat, cm H_2O	21.5±8.7	19.4±9.9	17.5±7.4	17.9±7.9	0.217
PEEP, cm H_2O	7±3.7	5.9±1.7	6±2.2	5.9±2.1	0.754
P_{drive}, cm H_2O	7.7±6.6	5.9±2.9	7.3±4.9	6.9±4.7	0.709
Outcomes					
ICU length of stay, days	9.8±9.6	8.5±9.7	8.5±9.9	8.5±9.9	0.295
Mortality, n (%)	14 (82.4)	19 (59.4)	33 (34.4)	66 (45.5)	<0.0001

*17 cases of AIP excluded from this analysis.
All values are mean ± standard deviation, unless otherwise specified
APACHE II: acute physiological and chronic health evaluation II score; AIP: acute interstitial pneumonia; DPLD: diffuse parenchymal lung disease; FiO_2: fraction of oxygen in inspired air; ICU: intensive care unit; IMV: invasive mechanical ventilation; IPF: idiopathic pulmonary fibrosis; NIV: noninvasive ventilation; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; P_{drive}: driving pressure; PEEP: positive end expiatory pressure; Pplat: plateau pressure; SOFA: sequential organ failure assessment score

dominantly males in comparison to non-IPF DPLD. The etiology of respiratory failure was also significantly different between IPF and non-IPF DPLD, with acute exacerbation of underlying DPLD being more common than infective exacerbation in IPF. Subjects with AIP had the most severe hypoxemia when compared to those with IPF and non-IPF DPLD. Most (n=15, 88%) subjects with AIP required invasive mechanical ventilation. There was no difference in the Ppeak, Pplat and the driving pressures between AIP, IPF and non-IPF related ARF.

The overall mortality in the study population was 45.5% (66/145). The mortality was highest in AIP followed by IPF and non-IPF DPLD. The time to mortality was significantly lower in the AIP and IPF-related ARF compared to non-IPF DPLD (Figure 1). Subjects with AIP had higher baseline APACHE II score and delta SOFA score compared to those with IPF-related ARF. However, there was no difference in the mortality and ICU length of stay between AIP (82.4%) and IPF-related (59.4%) ARF (p=0.123 & 0.673, respectively). The non-survivors had lower PaO_2:FiO_2 ratio at admission, higher baseline APACHE II score, delta SOFA, and higher PEEP requirement when compared to survivors (Table 2). There was no difference in the driving pressures between survivors and non-survivors. The use of IMV was associated with a significantly higher

Table 2. Univariate and multivariate logistic regression analysis comparing factors affecting outcomes in acute respiratory failure related to diffuse parenchymal lung diseases (DPLDs)

Parameters	Survivors (n=79)	Non-survivors (n=66)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Demographic factors				
Age, years	49.1±15.1	52.7±13.9	1.0 (0.9-1.0)	1 (0.9-1.1)
Male gender, n (%)	30 (38)	34 (51.5)	0.6 (0.3-1.1)	0.6 (0.2-2.7)
ICU severity score				
APACHE II score	10.8±5.7	18.6±8.2*	1.2 (1.1-1.3)#	1.1 (1-1.2)*
Delta SOFA score	1.1±1.7	3.6±3.6*	1.5 (1.2-1.8)#	1.4 (1.1-1.9)*
Physiological variables				
PaO_2:FiO_2 ratio	236.1±99.3	151.5±73.8*	0.9 (0.9-0.99)#	0.98 (0.97-0.99)*
$PaCO_2$, mmHg	42.9±13.4	47.9±15.8	1.0 (1-1.04)*	1 (0.9-1)
P_{drive}, cm H_2O	5.1±6.3	6.1±8.3	1.0 (0.9-1.1)	1 (0.9-1.2)
PEEP, cm H_2O	5.4±1.1	6.8±3*	1.4 (1.1-1.9)*	1.4 (0.9-2.3)
Ventilatory support				
Non-invasive support^	27 (34.2)	6 (9)*	Ref	Ref
IMV	52 (65.8)	61 (91)*	5.2 (2-13.6)*	11.1 (1-129.7)*
Type of DPLD				
Non-IPF, n (%)	63 (79.7)	33 (50)#	Ref	Ref
AIP, n (%)	3 (3.8)	14 (21.2)#	8.9 (2.4-33.2)*	3.9 (0.4-39.9)
IPF, n (%)	13 (16.5)	19 (28.8)#	2.7 (1.2-6.3)*	2.9 (0.3-25.4)

*p<0.05; #p<0.0001
^this includes non-invasive ventilation and oxygen supplementation
All values are mean ± standard deviation, unless otherwise specified
APACHE II: acute physiological and chronic health evaluation II score; AIP: acute interstitial pneumonia; FiO_2: fraction of oxygen in inspired air; ICU: intensive care unit; IMV: invasive mechanical ventilation; IPF: idiopathic pulmonary fibrosis; OR: odds ratio; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; PEEP: positive end-expiratory pressure; P_{drive}: driving pressure; SOFA: sequential organ failure assessment score

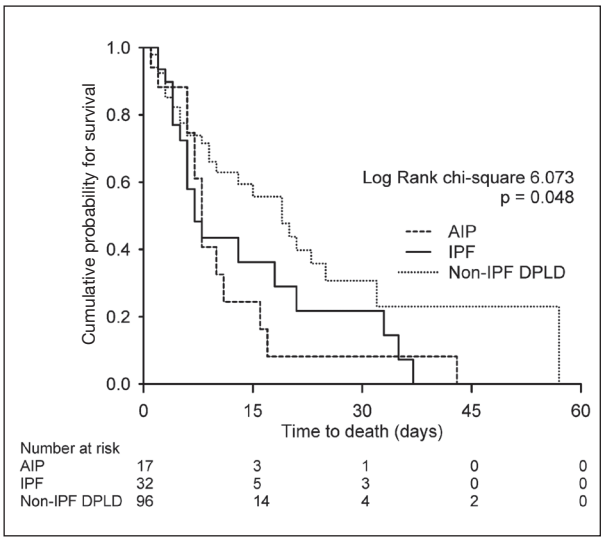

Fig. 1. Kaplan Meier survival curves comparing cumulative probability of mortality in acute interstitial pneumonia (AIP), idiopathic pulmonary fibrosis (IPF) and non-IPF diffuse parenchymal lung disease (DPLD) during intensive care unit stay

mortality. On multivariate logistic regression analysis, higher baseline APACHE II score, high delta SOFA score, lower PaO_2:FiO_2 ratio at admission, and the use of IMV were associated with higher odds of death (Table 2). The type of underlying DPLD however, did not affect the survival in the multivariate logistic regression analysis.

Discussion

The results of this study suggest that ARF due to DPLD is an uncommon indication (5.8%) for admission even in a respiratory ICU; however, it is associated with a high mortality (45.5%). CTD-related DPLD was the commonest form of DPLD requiring ICU admission. The most common cause of ARF was acute exacerbation of the underlying ILD. The mortality was highest amongst subjects with AIP compared to non-IPF DPLD and IPF. A higher baseline APACHE II score, high delta SOFA score, lower PaO_2:FiO_2 ratio at admission, and the

need for IMV were independent variables associated with mortality. Interestingly, the mortality was not influenced by the type of DPLD.

DPLDs are chronic lung disorders of the lung parenchyma; their clinical course is interspersed with acute worsening due to known and unknown causes. The outcomes of ARF due to disease progression, in some DPLDs such as IPF are rather poor thereby discouraging a more aggressive form of therapy (6, 29, 30). However, not all DPLD subjects with ARF have outcomes similar to that of IPF, and a subset of DPLD subjects may have better or worse outcomes. This was highlighted in our study where the outcomes were worst in AIP and IPF while the mortality in non-IPF DPLD was the least. The difference in mortality between IPF and non-IPF DPLD may be explained by the etiology of ARF. In IPF, ARF was primarily due to acute exacerbation or progression of IPF, while ARF in non-IPF DPLDs was most commonly due to infections, and thus reversible. The higher incidence of infections in non-IPF DPLD is probably due to the use of immunosuppressive agents required for its management; in contrast immunosuppression is contraindicated in IPF (31). The overall mortality was 45%, while the mortality estimated using the baseline APACHE II score was 24%. This suggests that the ICU severity scores such as APACHE II and SOFA may underestimate the risk of mortality in subjects with DPLD (20).

In this study, DPLD secondary to CTD was the most common form of DPLD. This may represent a selection bias as CTD-related DPLDs occur in young patients and are believed to have a better prognosis; thus, they are likely to be preferably admitted to the ICU. Also, subjects with IPF do not opt for a more aggressive treatment due to known dismal outcomes. Another important finding in our study was that subjects with AIP who require ICU admission had the worst prognosis. This is despite the fact that the subjects were young, had no comorbid illness and were managed aggressively with a combination of immunosuppression and IMV. Although the physiology of respiratory failure in AIP is similar to that of ARDS, there is a rapid progression to organized stage of diffuse alveolar damage (14). Thus, the use of recruitment maneuvers and application of high PEEP may not be beneficial in AIP or fibrotic DPLDs (32). Infact, application of higher PEEP in ARF due to DPLD has been associated with increased mortality (33, 34).

Although, mortality was not associated by the type of underlying DPLD in a multivariate analysis, this could be attributed to a small sample size and unequal distribution of subjects across the three groups. A higher baseline APACHE II score, poor oxygenation and the need for invasive mechanical ventilation were independent predictors of mortality, similar to previous studies (12, 20, 30, 35).

Finally, our study has a few limitations. This was a retrospective analysis from a single center of subjects with DPLD and the long-term outcomes of subjects after hospital discharge are not available. However, we meticulously collected daily data prospectively in a dedicated ICU software. It is likely that some of the patients in the current study could have been misclassified as per the current guidelines; however, the diagnosis of DPLD at our center is made after a consensus amongst the histopathologist, pulmonologist and a radiologist (25). We classified the patients as IPF, non-IPF and AIP and reported the outcomes in these groups. It would have been interesting to study the outcomes in the histological category of UIP versus non-UIP, irrespectively of the etiology. This would have provided the outcomes in patients with histological pattern of UIP, including those with connective tissue disease-related UIP pattern. Unfortunately, we do not routinely perform lung biopsy in subjects with HRCT chest findings consistent with IPF or in those with connective tissue related ILDs. Thus, the outcomes in histological variety of UIP cannot be ascertained from our study. Although the pulmonary function tests were not available for our study population, it has not been shown to affect the outcomes (19). The strength of the study is a large sample size and a heterogeneous group of subjects with unselected DPLD.

In conclusion, ARF due to DPLD is an uncommon cause of admission to ICU and has a high mortality. ARF due to AIP is associated with the worst outcomes when compared to IPF and non-IPD DPLDs.

Author contributions:

ISS- conceived the idea, performed statistical analysis, drafted and revised the manuscript

RA- provided intellectual content to the manuscript, drafted and revised the manuscript

SD- drafted and revised the manuscript
KTP- drafted and revised the manuscript
ANA- performed statistical analysis, drafted and revised the manuscript
DB- drafted and revised the manuscript

ISS: guarantor of the paper, takes responsibility for the integrity of the work as a whole, from inception to published article

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