Interstitial Lung Disease Associated Acute Respiratory Failure Requiring Invasive Mechanical Ventilation: A Retrospective Analysis

Cyrus A. Vahdatpour (cyrus.vahdatpour@pennmedicine.upenn.edu)
University of Pennsylvania Perelman School of Medicine https://orcid.org/0000-0002-8917-2807
Alexander Pichler
Medizinische Universitat Wien Universitatsbibliothek
Harold I Palevsky
University of Pennsylvania Perelman School of Medicine
Michael J Kallan
University of Pennsylvania Perelman School of Medicine
Namrata B Patel
University of Pennsylvania Perelman School of Medicine
Paul A Kinniry
University of Pennsylvania Perelman School of Medicine

Research

Keywords: Critical Care, Acute respiratory failure, Interstitial lung disease, Mechanical ventilation

Posted Date: February 25th, 2020

DOI: https://doi.org/10.21203/rs.2.24446/v1

Version of Record: A version of this preprint was published at The Open Respiratory Medicine Journal on December 18th, 2020. See the published version at https://doi.org/10.2174/1874306402014010067.

Abstract

Background Interstitial lung disease (ILD) patients requiring invasive mechanical ventilation (IMV) for acute respiratory failure (ARF) are known to have a poor prognosis. Few studies have investigated determinants of outcomes and the utility of trialing non-invasive positive pressure ventilation (NIPPV) prior to IMV to see if there are any effect(s) on mortality or morbidity.

Methods We designed a retrospective study using patients at four different intensive care units within one health care system. Our primary objective was to determine if there are differences in outcomes for in-hospital and one-year mortality between patients who undergo NIPPV prior to IMV and those who receive only IMV. A secondary objective was to identify potential determinants of outcomes.

Results Of 54 ILD patients with ARF treated with IMV, 20 (37.0%) survived to hospital discharge and 10 (18.5%) were alive at one-year. There was no significant mortality difference between patients trialed on NIPPV prior to IMV and those receiving only IMV. Several key determinants of outcomes were identified with higher mortality, including: higher ventilatory support, idiopathic pulmonary fibrosis (IPF) subtype, high dose steroids, use of vasopressors, supraventricular tachycardias (SVTs), and higher body mass index.

Conclusions Considering that patients trialed on NIPPV prior to IMV was associated with no mortality disadvantage to patients treated with only IMV, trialing patients on NIPPV may identify responders and avoid complications associated with IMV. Increased ventilator support, need of vasopressors, SVTs, and high dose steroids reflect higher mortality and palliative care involvement should be considered as early as possible if lung transplant is not an option.

Background

Interstitial lung disease (ILD) patients can be subject to episodes of acute respiratory failure (ARF) and rapid decline during their disease course. Patients with ILD experiencing ARF have known poor outcomes once invasive mechanical ventilation (IMV) is initiated. Retrospective studies have reported in-hospital mortality ranging from 51–100% in ILD patients with ARF requiring ICU level of care(1–6). IMV may be required in ILD associated ARF (ILD-ARF), although its benefit is unclear unless used as a bridge to lung transplantation (LTx).

ARF from an ILD exacerbation is defined by: a subjective worsening of dyspnea within the month prior to presentation; new ground glass opacities or consolidation by chest imaging; hypoxemia with > 10 mmHg decline in PaO2; and no evidence of PE, CHF, lung infection, or pneumothorax(7,8). This definition has been modified for the acute exacerbation of idiopathic pulmonary fibrosis (IPF) to now include pulmonary infection as an etiology, but this modification has not been incorporated into the other ILD subtypes(9).

IMV can initiate and exacerbate lung injury, termed ventilator-induced lung injury (VILI), increasing mortality and morbidity(6). Noninvasive positive pressure ventilation (NIPPV) may offer some benefits of

IMV, by improving oxygenation and reducing the work of breathing, and minimize risk for VILI. The effectiveness of NIPPV in avoiding IMV in patients with ILD-ARF has not been well studied. Whether or not trialing NIPPV, and potentially delaying IMV, increases mortality is also unclear.

There are no guidelines on how to select ILD-ARF patients to place on IMV. Gungor et al (2013) proposed that physicians should be guarded about the use of IMV in ILD-ARF patients that are not suitable for lung transplantation (LTx), especially in patients requiring continuous NIPPV(5). There are several studies looking at IPF patients who require IMV, revealing high in-hospital mortality. Although IPF is the most common idiopathic interstitial pneumonia, it represents a fraction of patient with ILD who have ARF(7). The outcomes of ILD patients as a whole has been less frequently reported. While there are individuals who survive IMV, there is limited data to differentiate these individuals from those who do not. As a result, this limits the ability to have informed goals of care discussions for critically ill patients.

The primary objective of this study was to investigate mortality outcomes between two cohorts of ILD-ARF patients: (1) those who are trialed on NIPPV prior to receiving IMV and (2) those receiving only IMV. The secondary objective was to identify the determinants of outcomes within the entire study population and within each stated cohort.

Methods

Study population

From January 2014 to October 2018, 54 patients with ILD-ARF underwent IMV in 4 different hospitals within the University of Pennsylvania Health System. Patients were identified by using the International Classification of Diseases (ICD) codes to search within our institution's electronic medical record (EMR). Institutional review board (IRB) approval was obtained prior to the review of medical records.

Patient's records were reviewed if they were previously diagnosed with ILD and if ARF was experienced during their admission. Only the first presentation of ARF requiring IMV was used in this study in cases of patients with repeat admissions for ARF. Their ARF had to require any form of positive pressure ventilation (PPV) initially and ultimately required IMV for 24 hours (6).

ILD diagnosis based on American Thoracic Society criteria was limited in assessment based on EMR review. To improve the accuracy of the ILD diagnosis we created major and minor criteria for patient eligibility. Major criteria included: an available CT scan read by a radiologist that was suggestive of ILD and either co-existing restrictive PFTs or pulmonologist documentation that confirmed ILD as a clinical diagnosis; available tissue biopsy confirming diagnosis; or documented proof of lung transplant screening due to an ILD. Minor criteria included: either stated ILD in prior and/or current physician encounter, a CT scan referencing ILD, a pulmonary function test (PFT) with restrictive profile, an ICD code for ILD in the EMR, and a pulmonary provider documentation noting ILD in current encounter. A patient required either one major criteria or three minor criteria to be included in our study.

Patients were excluded if they: had a chronic tracheostomy, were surgical patients experiencing ARF within 48 hours after being extubated for a surgical procedure, had no ARF during their encounter, were intubated for reasons that were unrelated to ARF, or had a history of having undergone LTx.

We defined ARF based on the British Medical Journal best practice guidelines(10). Once a patient met criteria of ARF, we required evidence of supplemental oxygenation use that ultimately needed to be escalated to PPV for respiratory support. For patients already on home oxygen, we defined ARF as an increased oxygen requirement from their home requirement. All patients included in this study eventually required IMV support for greater than 24 hours for ARF.

PH diagnosis was based on prior ICD coding or defined in patients with recent echocardiography report within 6 months of encounter or during encounter with an sPAP ³ 45mmHg(11).

Pulse dose steroids were defined as 1g of methylprednisolone for a minimum of 3 days(12). Stress dose steroids were defined as a documented administration at no more than 300mg of hydrocortisone (or equivalent) in a 24 hour time period(13,14) for the duration of shock physiology or death. Observed stress dose steroid regimens were 50mg of hydrocortisone every 6 hours or 100mg of hydrocortisone every 8 hours.

Data Collection

Primary study outcomes were survival to hospital discharge and at one-year in patients trialed on NIPPV prior to IMV and in patients only treated with IMV. As a secondary outcome, we investigated possible determinants of the primary outcomes including: demographic data, baseline patient characteristics, ILD subtype, ventilator settings, echocardiography and ICU level interventions. We also stratified patients based on the presence or absence of pulmonary hypertension to see if this had any impact on primary or secondary outcomes. Cardiothoracic imaging, PFTs, lung histopathology, lab values, ventilator settings, and patient history were collected from EMR. Mechanical ventilation settings were recorded at the end of a 24-hour time interval from its first initiation during their hospital admission. For patients transferred from another institution, mechanical ventilator settings were recorded from: (1) their documented ventilator settings prior to transfer that was closest to the 24 hour time interval from its first initiation, or (2) ventilator settings on arrival to our institution provided they were on IMV for greater than 24 hours and had no ventilator settings available prior to transfer.

Statistical analysis

Results are presented as median and interquartile range (IQR) for quantitative variables and frequencies and percentages for qualitative variables. Fisher's exact tests were used for binominal variables and variables with more than two labels as appropriate. One-year survival was determined from the date of onset from ARF. The Kaplan-Meier survival curves were plotted for survival data with statistical evaluation through Mantel-Cox log- rank statistics. Threshold for statistical significance was $p < 0.05$.

Results

We identified 106 potential ILD patients who were admitted to our health system between January 2014 and October 2018, with ARF and who required IMV. Fifty-two patients were excluded: 33 patients did not have enough data to support the ILD diagnosis; 16 patients were previously LTx recipients; 2 patients had chronic tracheostomies; and 1 patient had experienced a surgical related ARF. The remaining 54 patients fulfilled inclusion criteria and were included in the analysis (Figure 1).

General Baseline Characteristics

Table 1 and 2 provides a detailed description of patient characteristics. The mean age of patients was 65 years and males represented 55.6% of the total cohort. An ILD diagnosis for greater than 1 year was seen in 55.6% of patients. Connective tissue disease (CTD) was the most commonly identified cause of the ILD diagnosis, representing 31.5% of the patients and idiopathic pulmonary fibrosis (IPF) was the second most common diagnosis, representing 14.8% of the patients. Chronic steroid use was found in 56% of the patients and 40% of the patients were on other chronic immunosuppressants. 55.6% of patients were transferred from another institution. Home oxygen supplementation was used in 46.3% of patients.

Admission Characteristics

The average duration of hospital admission was 22 days and the average duration of ICU admission was 18 days. The average duration on IMV was 13.6 days and the average of duration on any form of PPV was 14.3 days. Pulse dose steroids were administered to 25% of patients and 21% were treated with stress dose steroids. Super ventricular tachycardia (SVT) complicated 90% of patients during their hospital course. Vasopressors were used in 85% of patients during their hospital course.

Assist control/volume control ventilation was the most commonly used ventilation mode. Norepinephrine was the most common first vasopressor utilized in patients with shock physiology. Tracheostomy was performed in 18.5% of patients, which was equally balanced in both cohorts. LTx was documented to be considered in 11 (22%) patients, 2 of whom received LTx and were both alive at one year. 6 patients were supported with ECMO: two died, two were weaned off and ultimately discharged, and two were the recipients of LTx. Palliative care consultation was performed in 48.8% of patients.

Mortality and determinants

Of the 54 ILD patients with ARF treated with IMV, 20 (37%) survived to hospital discharge and 10 (18.5%) were alive at one-year (Table 3). No mortality difference was observed in patients who were trialed on NIPPV prior to IMV versus those only treated with IMV. Significant increases of in-hospital mortality were found in patients with a higher BMI, the IPF subtype, vasopressor use, and stress or pulse steroids administration. Patients already on supplemental oxygenation at home and with known ILD diagnosis of greater than one year were found to have lower inpatient mortality. Analysis of mechanical ventilation parameters impacting in-hospital mortality is demonstrated in Table 4. Ventilator parameters with increased PEEP and FiO2 settings and higher documented average airway pressures were associated

with higher in-hospital mortality. Figure 2 demonstrates the significant mortality differences between these ventilator parameters using day of intubation as the starting point.

Significantly increased one-year mortality was found in patients with: the IPF subtype, no past medical history of CTD, presence of SVT, and vasopressor use (Table 5). In patients in the NIPPV prior to IMV cohort, an age greater than 65 years was associated with increased one-year mortality in comparison to those treated with only IMV. In the NIPPV prior to IMV cohort, those without pulmonary hypertension had higher one-year mortality.

When splitting the patient cohort based on the presence or absence of PH, there was no significant mortality difference (see supplemental data-Table 6).

Discussion

This retrospective study describes the clinical course, ICU management, and outcome of 54 ILD patients requiring IMV for ARF at a tertiary-referral institution. Both in-hospital and one -year mortality was high, and no difference was found in the primary outcome. Higher ventilator support requirements, vasopressor use, high dose steroids, and the IPF subtype were associated with worse in hospital mortality. The IPF subtype, ILD exacerbation as cause of ARF, no past history of CTDs, presence of SVT, vasopressor use were independent predictors of one-year mortality.

One prior study has described the in-hospital and one-year mortality of ILD patients experiencing ARF, requiring IMV, as 53% and 59%, respectively(6). Our study demonstrated a 63% in-hospital mortality and 82.5% one-year mortality. Differences in mortality rates are likely in part to the fact that our study had a large percentage of patients that were transferred from an outside hospital; which may reflect patients with worse prognosis having failed to respond to initial medical care prior to transfer. NIPPV trialed prior to IMV was found to have higher mortality in the study by Fernandez-Perez(6). Others have suggested that patients receiving an NIPPV trial prior to IMV have worse clinical outcomes(15). Patients trialed on NIPPV prior to IMV is not a standardized intervention and there is no recognized definition of what time duration of NIPPV trial is needed before it can be considered as failure. Our study found no significant difference for in-hospital mortality and one-year mortality in general between the two cohorts. With the exception of sarcoidosis patients with ILD-ARF, in-patient mortality was high and more studies are needed to validate this finding regarding sarcoid patients experiencing ARF. An age of 65 years or older had a worse one-year mortality in patients trialed on NIPPV prior to IMV in comparison to those undergoing only IMV. This proposes an ethical dilemma for critical care physicians because, in general, mortality is high for ILD-ARF patients who fail a NIPPV trial and it is unclear if IMV is even worthwhile after NIPPV failure. IMV is often an intervention that has been considered futile if transplantation is not an option for patients with advanced underlying ILD; this has most commonly been discussed in IPF patients (6,16–18). However, NIPPV trial prior to IMV initiation may identify a subset of patients who are responders and avoid need for IMV altogether.

Fernandez-Perez described that the ventilator settings which correlated with increased mortality were higher PEEP, lower tidal volume, and higher FiO2(6). They also found higher documented mean, plateau, and peak airway pressures and lower PaO2/FiO2 ratios were associated with increased mortality. Our study supported that higher PEEP settings and higher FiO2 were associated with increased in-hospital mortality. These findings were also associated with decreased one-year survival starting from day of intubation. This suggests that ARF-ILD patients requiring IMV are subject to increased risks of barotrauma, volutrauma, and cellular injury related to hyperoxia/free radical damage. Statistical differences in tidal volume settings, recorded peak airway pressures, and recorded PaO2/FiO2 ratios between our study and the Fernandez-Perez study is likely related to power. Additionally, lower tidal volume requirements to maintain plateau pressures suggests higher disease burden and poor compliance that is prognostically concerning. It is reasonable for physicians caring for ILD-ARF patients requiring IMV to adopt mechanical ventilator strategies from ARDS protocols that incorporate using the lowest possible tidal volumes and PEEP settings (19–21). FiO2 should also be aggressively titrated to the lowest possible setting to avoid hyperoxic acute lung injury(22).

PH and its effect on the primary study outcome was unclear. Our study did not support that PH impacts mortality or morbidity in ILD-ARF. Saydain et al also found no difference in systolic pulmonary artery pressures between survivors and non-survivors(17). Zafrani et al did find that PH was a determinant for in-hospital and one year mortality(7). IMV in patients with severe PH should be avoided if possible due to potential complications of hemodynamic instability(23). Right heart catheterization (RHC) remains the diagnostic modality for PH and is not commonly done in this cohort of patients. No study has evaluated IMV outcomes of ILD patients with PH diagnosed by RHC.

Zafrani et al found that corticosteroid therapy was potentially of benefit during ILD-ARF in patients admitted to the ICU(7). About 41% of our cohort received high dose steroids during their ICU course compared with 65% in the Zafrani et al study. In their study, patients with less fibrosis on chest CT scan were noted to have better response to steroids and earlier treatment with corticosteroids was associated with an improved mortality. Our study found that high dose corticosteroid therapy (pulse or stress dosing) was associated with increased mortality. The reason for differences in these findings were difficult to determine as it was unclear what the different subtypes of ARF were in their cohort. Our cohort had ARF primarily from pneumonia/sepsis and ILD exacerbations and all of our patients underwent IMV, whereas Zafrani et al had only 61% of patients treated with IMV during their ICU course(7). It is difficult to compare their cohort with ours as all our patients required IMV for respiratory support, implying that our cohort had higher all-cause disease burden. Fernandez-Perez found that high dose corticosteroid therapy had no significant effect on ILD-ARF patients requiring IMV(6). It remains unclear what the effect of high dose corticosteroid therapy is in patients ILD-ARF requiring IMV.

SVT, aside from sinus tachycardia, was associated with higher in-hospital ($p= 0.06$) and one-year mortality ($p=0.037$). There is limited data on the epidemiology of AAs in ILD patients. Studies in IPF have demonstrated that SVTs are common(24,25). SVT can be difficult to manage in ILD-ARF because: (1)

there is no standardized approach to management in this cohort and (2) it is difficult to assess if SVT is the primary cause of ARF or if the SVT is secondary to the underlying etiology of ARF.

Limitations

Our study has several limitations that could have influenced our findings. Our study is limited in its retrospective study design and by low power, thus necessitating the need for further investigations to validate our discovered associations. Due to reliance of the diagnosis of ILD and ARF from ICD coding and EMR investigation, it is possible that we missed patients who were not coded properly. Additionally, EMR charting was not always reliable for data extraction and some patients had missing values when analyzing potential determinants of mortality which could have impacted statistical significance. Our conclusions cannot be generalized to all ILD patients, because our study does not include ILD-ARF patients who may have not received IMV due to either the decision for palliative care interventions, death while on NIPPV, or improvement with NIPPV trial. Using cutoffs of patients on IMV for ³24 hours may have missed ILD patients that were too ill for inclusion. Our strict inclusion criteria may have also contributed to lower power. Finally, our study is only representative of one health system and may be subject to limitations related to individualized institutional cultural practices.

Conclusion

Our study has several important clinical findings that support previous findings in prior studies. ILD-ARF requiring IMV has a poor prognosis. We found no difference in outcome between patients trialed on NIPPV prior to IMV versus patients treated with only IMV for their ARF. Lowest possible PEEP and FiO2 settings should be utilized in patients requiring IMV. PH was not found to influence mortality in ILD-ARF patients requiring IMV. Use of high dose corticosteroids is unclear in ILD-ARF patients requiring IMV. The presence of SVT was associated with increased mortality and more studies are needed to define best management strategies.

Abbreviations

ARF: Acute Respiratory Failure

BMI: Body Mass Index

CTD: Connective Tissue Disease

DLCO: Diffusing Capacity for Carbon Monoxide

ECG: Electrocardiography

ECMO: Extracorporeal Membrane Oxygenation

ED: Emergency Department

EMR: Electronic Medical Record

FEV1/FVC: Ratio of Forced Expiratory Volume in the First Second to Forced Vital Capacity

ICD: International Classification of Diseases

ICU: Intensive Care Unit

ILD: Interstitial Lung Disease

ILD-ARF: Interstitial Lung Disease associated Acute Respiratory Failure

IMV: Invasive Mechanical Ventilation

IPF: Idiopathic Pulmonary Fibrosis

IRB: Institutional review board

LTx: Lung Transplantation

NIPPV: Noninvasive Positive Pressure Ventilation

OSH: Outside Hospital

PEEP: Positive End Expiratory Pressure

PFT: Pulmonary Function Test

PH: Pulmonary Hypertension

PPV: Positive Pressure Ventilation

RHC: Right Heart Catheterization

SIMV: Synchronized Intermittent Mandatory Ventilation

sPAP: Systolic Pulmonary Artery Pressure

SVT: Supraventricular Tachycardia

TLC: Total Lung Capacity

VILI: Ventilator Induced Lung Injury

Declarations

Ethics approval and consent to participate: IRB approval was obtained through the University of Pennsylvania prior to conducting this study

Consent for publication: All authors have provided consent to publish this manuscript in accordance with our IRB approval

Competing interests: None of the authors have any competing interests that could have impacted the study design and drafting of this manuscript

Funding: None of the authors have any financial disclosures to reveal that could have impacted the study design and drafting of this manuscript

Author Contributions: All authors contributed to the study design and drafting of this manuscript. CV lead the study design, data collection, and drafting of the manuscript. CV and MK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects.

Acknowledgements: None

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Mollica C, Paone G, Conti V, Ceccarelli D, Schmid G, Mattia P, et al. Mechanical Ventilation in Patients with End-Stage Idiopathic Pulmonary Fibrosis. Respiration. 2010;79(3):209–15.
2. Mooney JJ, Raimundo K, Chang E, Broder MS. Mechanical ventilation in idiopathic pulmonary fibrosis: a nationwide analysis of ventilator use, outcomes, and resource burden. BMC Pulm Med [Internet]. 2017 Dec [cited 2018 Jun 7];17(1). Available from: http://bmcpulmmed.biomedcentral.com/articles/10.1186/s12890-017-0426-2
3. Rush B, Wiskar K, Berger L, Griesdale D. The use of mechanical ventilation in patients with idiopathic pulmonary fibrosis in the United States: A nationwide retrospective cohort analysis. Respir Med. 2016 Feb;111:72–6.
4. Gaudry S, Vincent F, Rabbat A, Nunes H, Crestani B, Naccache JM, et al. Invasive mechanical ventilation in patients with fibrosing interstitial pneumonia. J Thorac Cardiovasc Surg. 2014 Jan;147(1):47–53.
5. Gungor G, Tatar D, Salturk C, Cimen P, Karakurt Z, Kirakli C, et al. Why Do Patients With Interstitial Lung Diseases Fail in the ICU? A 2-Center Cohort Study. Respir Care. 2013 Mar 1;58(3):525–31.
6. Fernández-Pérez ER, Yilmaz M, Jenad H, Daniels CE, Ryu JH, Hubmayr RD, et al. Ventilator Settings and Outcome of Respiratory Failure in Chronic Interstitial Lung Disease. Chest. 2008

May;133(5):1113–9.

7. Zafrani L, Lemiale V, Lapidus N, Lorillon G, Schlemmer B, Azoulay E. Acute Respiratory Failure in Critically Ill Patients with Interstitial Lung Disease. Assassi S, editor. PLoS ONE. 2014 Aug 12;9(8):e104897.
8. Akira M, Hamada H, Sakatani M, Kobayashi C, Nishioka M, Yamamoto S. CT findings during phase of accelerated deterioration in patients with idiopathic pulmonary fibrosis. AJR Am J Roentgenol. 1997 Jan;168(1):79–83.
9. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. Am J Respir Crit Care Med. 2016 01;194(3):265–75.
10. Acute respiratory failure - Symptoms, diagnosis and treatment | BMJ Best Practice [Internet]. [cited 2019 Sep 2]. Available from: http://bestpractice.bmj.com/topics/en-us/853
11. Arcasoy SM, Christie JD, Ferrari VA, Sutton MStJ, Zisman DA, Blumenthal NP, et al. Echocardiographic Assessment of Pulmonary Hypertension in Patients with Advanced Lung Disease. Am J Respir Crit Care Med. 2003 Mar;167(5):735–40.
12. Franchin G, Diamond B. Pulse steroids: how much is enough? Autoimmun Rev. 2006 Feb;5(2):111–3.
13. MacLaren R, Jung R. Stress-dose corticosteroid therapy for sepsis and acute lung injury or acute respiratory distress syndrome in critically ill adults. Pharmacotherapy. 2002 Sep;22(9):1140–56.
14. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008 Jan;36(1):296–327.
15. Mosier JM, Sakles JC, Whitmore SP, Hypes CD, Hallett DK, Hawbaker KE, et al. Failed noninvasive positive-pressure ventilation is associated with an increased risk of intubation-related complications. Ann Intensive Care [Internet]. 2015 Dec [cited 2019 Aug 28];5(1). Available from: http://www.annalsofintensivecare.com/content/5/1/4
16. Al-Hameed FM, Sharma S. Outcome of patients admitted to the intensive care unit for acute exacerbation of idiopathic pulmonary fibrosis. Can Respir J. 2004 Mar;11(2):117–22.
17. Saydain G, Islam A, Afessa B, Ryu JH, Scott JP, Peters SG. Outcome of Patients with Idiopathic Pulmonary Fibrosis Admitted to the Intensive Care Unit. Am J Respir Crit Care Med. 2002 Sep 15;166(6):839–42.
18. Stern JB, Mal H, Groussard O, Brugière O, Marceau A, Jebrak G, et al. Prognosis of patients with advanced idiopathic pulmonary fibrosis requiring mechanical ventilation for acute respiratory failure. Chest. 2001 Jul;120(1):213–9.
19. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000 04;342(18):1301–8.

20. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators, Cavalcanti AB, Suzumura ÉA, Laranjeira LN, Paisani D de M, Damiani LP, et al. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA. 2017 Oct 10;318(14):1335.
21. Walkey AJ, Del Sorbo L, Hodgson CL, Adhikari NKJ, Wunsch H, Meade MO, et al. Higher PEEP versus Lower PEEP Strategies for Patients with Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2017 Oct;14(Supplement_4):S297–303.
22. Kallet RH, Matthay MA. Hyperoxic acute lung injury. Respir Care. 2013 Jan;58(1):123–41.
23. Hoeper MM, Granton J. Intensive Care Unit Management of Patients with Severe Pulmonary Hypertension and Right Heart Failure. Am J Respir Crit Care Med. 2011 Nov 15;184(10):1114–24.
24. Fernández Pérez ER, Daniels CE, St. Sauver J, Hartman TE, Bartholmai BJ, Yi ES, et al. Incidence, Prevalence, and Clinical Course of Idiopathic Pulmonary Fibrosis. Chest. 2010 Jan;137(1):129–37.
25. Hyldgaard C, Hilberg O, Bendstrup E. How does comorbidity influence survival in idiopathic pulmonary fibrosis? Respir Med. 2014 Apr;108(4):647–53.

Tables

Table 1. General Patient Characteristics

	Total			NIPPV prior to IMV			Only IMV		
Variable	n	Out of	%	n	Out of	%	n	Out of	%
All Patients	54	54	100.0%	27	27	100.0%	27	27	100.0%
Race		54			27			27	
Asian	3		5.6%	0		0.0%	3		11.1%
Black	13		24.1%	7		25.9%	6		22.2%
Hispanic	3		5.6%	0		0.0%	3		11.1%
Other	3		5.6%	2		7.4%	1		3.7%
Unknown	2		3.7%	2		7.4%	0		0.0%
White	30		55.6%	16		59.3%	14		51.9%
Female	24	54	44.4%	13	27	48.1%	11	27	40.7%
Smoking History		54			27			27	
Current	1		1.9%	1		3.7%	0		0.0%
Never	18		33.3%	9		33.3%	9		33.3%
Prior Use	32		59.3%	16		59.3%	16		59.3%
Unknown	3		5.6%	1		3.7%	2		7.4%
Duration of Years with ILD		54			27			27	
< 1 Year									
1 to < 3 Years	24		44.4%	11		40.7%	13		48.1%
3 to < 5 Years	12		22.2%	5		18.5%	7		25.9%
5+ Years	7		13.0%	5		18.5%	2		7.4%
	11		20.4%	6		22.2%	5		18.5%
On Home Oxygen	25	54	46.3%	15	27	55.6%	10	27	37.0%
ILD Subtype		54			27			27	
IPF	8		14.8%	2		7.4%	6		22.2%
CTDs	17		31.5%	8		29.6%	9		33.3%
Sarcoidosis	7		13.0%	4		14.8%	3		11.1%
Other	22		40.7%	13		48.1%	9		33.3%
Known Histological Classification		54			27			27	
Yes									
No	15		27.8%	7		25.9%	8		29.6%
Unknown	34		63.0%	17		63.0%	17		63.0%
	5		9.3%	3		11.1%	2		7.4%

Group	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Age (Years)	54	65.2 (12.3)	27	65.3 (11.8)	27	65.0 (13.0)
BMI	54	27.2 (6.2)	27	28.1 (5.9)	27	26.4 (6.5)
TLC	21	59.7 (17.2)	12	60.8 (20.9)	9	58.1 (11.7)
FEV1/FVC	34	91.2 (21.3)	16	89.5 (19.3)	18	92.8 (23.3)
DLCO	24	38.6 (16.7)	13	37.9 (19.6)	11	39.5 (13.3)

Legend: BMI, Body Mass Index; CTDs, Connective Tissue Diseases; DLCO; Diffusing Capacity for Carbon Monoxide % predicted; FEV1/FVC, ratio of Forced Expiratory Volume in the First Second to Forced Vital Capacity; ILD, Interstitial Lung Disease; IPF, Idiopathic Pulmonary Fibrosis; SD, Standard Deviation; TLC; Total Lung Capacity % predicted

Table 2. General Admission Characteristics

	Total			NIPPV prior to IMV			Only IMV		
Variable	n	Out of	%	n	Out of	%	n	Out of	%
All Patients	54	54	100.0%	27	27	100.0%	27	27	100.0%
How Patients Presented		54			27			27	
ED									
OSH Transfer	22		40.7%	11		40.7%	11		40.7%
Another Provider	30		55.6%	15		55.6%	15		55.6%
	2		3.7%	1		3.7%	1		3.7%
Ventilation Mode		41			20			21	
Volume Control	24		58.5%	11		55.0%	13		61.9%
Pressure Control	2		4.9%	1		5.0%	1		4.8%
SIMV	1		2.4%	0		0.0%	1		4.8%
Other	14		34.1%	8		40.0%	6		28.6%
Re-intubation(s)		50			26			24	
0	42		84.0%	23		88.5%	19		79.2%
1	7		14.0%	3		11.5%	4		16.7%
2+	1		2.0%	0		0.0%	1		4.2%
Tracheostomy	10	54	18.5%	5	27	18.5%	5	27	18.5%
Palliative Care Consultation	21	43	48.8%	11	21	52.4%	10	22	45.5%
Consideration for Lung Transplant	11	51	21.6%	6	25	24.0%	5	26	19.2%
Group	n	Mean (SD)		n	Mean (SD)		n	Mean (SD)	
Initial pH	54	7.38 (0.1)		27	7.40 (0.1)		27	7.34 (0.1)	
Initial pO2	54	128.4 (108.1)		27	116.7 (90.3)		27	140.2 (124.0)	
Initial pCO2	54	49.8 (17.2)		27	47.9 (16.6)		27	51.8 (17.8)	
Initial PaO2/FiO2	42	224.8 (114.7)		21	231.5 (162.2)		21	218.2 (128.5)	

Legend: ED, Emergency Department; OSH, Outside Hospital; SD, Standard Deviation; SIMV, Synchronized Intermittent Mandatory Ventilation

Table 3. Determinants of In-Hospital Mortality

Variables	Total	p-value	NIPPV prior to IMV	Only IMV	p-value
All Patients	N=54 Deaths 34 (63.0%)		N=27 Deaths 17 (63.0%)	N=27 Deaths 17 (63.0%)	1.00
	Deaths/n		Deaths/n	Deaths/n	
BMI		**0.047**			
<26.9	13/27 (48.1%)		5/12 (41.7%)	8/15 (53.3%)	0.70
26.9+	21/27 (77.8%)		12/15 (80.0%)	9/12 (75.0%)	1.00
Age		0.15			
<65	11/22 (50.0%)		3/9 (33.3%)	8/13 (61.5%)	0.39
65+	23/32 (71.9%)		14/18 (77.8%)	9/14 (64.3%)	0.45
Gender		1.00			
Female	15/24 (62.5%)		9/13 (69.2%)	6/11 (54.5%)	0.68
Male	19/30 (63.3%)		8/14 (57.1%)	11/16 (68.8%)	0.71
ILD Subtype		**0.027**			
IPF	7/8 (87.5%)		1/2 (50.0%)	6/6 (100.0%)	0.25
CTDs	12/17 (70.6%)		5/8 (62.5%)	7/9 (77.8%)	0.62
Sarcoidosis	1/7 (14.3%)		1/4 (25.0%)	0/3 (0.0%)	1.00
Other	14/22 (63.6%)		10/13 (76.9%)	4/9 (44.4%)	0.19
ILD Duration		**0.046**			
ILD <1 year	19/24 (79.2%)		10/11 (90.9%)	9/13 (69.2%)	0.33
ILD ≥1 year	15/30 (50.0%)		7/16 (43.8%)	8/14 (57.1%)	0.72
Supplemental O2		**0.049**			
Prescribed	12/25 (48.0%)		8/15 (53.3%)	4/10 (40.0%)	0.69
Not prescribed	22/29 (75.9%)		9/12 (75.0%)	13/17(76.5%)	1.00
Pulmonary Hypertension		1.00			
Present					
Not Present	18/28 (64.3%)		7/14 (50.0%)	11/14 (78.6%)	0.24
	16/26 (61.5%)		10/13 (76.9%)	6/13 (46.2%)	0.23
History of CTD		0.78			
Present	16/27 (59.3%)		8/14 (57.1%)	8/13 (61.5%)	1.00
Not Present	18/27 (66.7%)		9/13 (69.2%)	9/14 (64.3%)	1.00
Cause of ARF		0.45			
Pneumonia/Sepsis	21/33 (63.6%)		9/17 (52.9%)	12/16 (75.0%)	0.28
ILD Exacerbation	7/9 (77.8%)		5/6 (83.3%)	2/3 (66.7%)	1.00
All others	6/12 (50.0%)		3/4 (75.0%)	3/8 (37.5%)	0.55
SVTs		0.06			
Sinus Tachycardia	11/21 (52.4%)		4/7 (57.1%)	7/14 (50.0%)	1.00
All Other SVTs	20/25 (80.0%)		12/15 (80.0%)	8/10 (80.0%)	1.00
Vasopressor		**0.043**			
Used	30/44 (68.2%)		15/22 (68.2%)	15/22 (68.2%)	1.00
Not used	2/8 (25.0%)		0/3 (0.0%)	2/5 (40.0%)	0.46
Pulmonary Vasodilator		0.25			
Used					
Not Used	15/22 (68.2%)		5/8 (62.5%)	10/14 (71.4%)	1.00
	13/26 (50.0%)		8/15 (53.3%)	5/11 (45.5%)	1.00
Steroid Use		**0.001**			
Pulse/Stress Dose	19/22 (86.4%)		11/13 (84.6%)	8/9 (88.9%)	1.00
Other Dose	10/26 (38.5%)		6/14 (42.9%)	4/12 (33.3%)	0.70

Legend: Column 3 represents p-value for the mortality of the total number of patients as a comparison of death rate prior to cohort stratification. Column 6 represents p-values for mortality of patients compared within each strata of both NIPPV prior to IMV and Only IMV.

Table 4. Mechanical Ventilation Settings and In-Hospital Mortality

Variables	Total	p-value	NIPPV prior to IMV	Only IMV	p-value
All Patients	N=54 Deaths 34 (63.0%)		N=27 Deaths 17 (63.0%)	N=27 Deaths 17 (63.0%)	1.00
	Deaths/n		Deaths/n	Deaths/n	
Set Respiratory Rate		0.21			
<25					
25+	9/14 (64.3%)		6/8 (75.0%)	3/6 (50.0%)	0.58
	13/15 (86.7%)		6/7 (85.7%)	7/8(87.5%)	1.00
Set Tidal Volume		1.00			
<400	10/14 (71.4%)		4/6 (66.7%)	6/8 (75.0%)	1.00
400+	9/12 (75.0%)		5/6 (83.3%)	4/6 (66.7%)	1.00
Set PEEP		**0.003**			
<10	15/29 (51.7%)		9/16 (56.3%)	6/13 (46.2%)	0.72
10+	12/12 (100.0%)		4/4 (100.0%)	8/8 (100.0%)	1.00
Set FiO2		**0.046**			
<50	11/22 (50.0%)		6/11 (54.5%)	5/11 (45.5%)	1.00
50+	16/19 (84.2%)		7/9 (77.8%)	9/10 (90.0%)	0.58
Peak Airway Pressure		0.18			
<30					
30+	8/16 (50%)		3/7 (42.9%)	5/9 (55.6%)	1.00
	15/16 (93.8%)		8/11 (72.7%)	6/8 (75.0%)	1.00
Average Airway Pressure		**0.002**			
<15					
15+	9/21 (42.9%)		5/12 (41.7%)	4/9 (44.4%)	1.00
	15/16 (93.8%)		7/7 (100.0%)	8/9 (88.9%)	1.00
PaO2/FiO2		0.10			
<150	13/16 (81.3%)		7/8 (87.5%)	6/8 (75.0%)	1.00
150+	14/26 (53.8%)		6/13 (46.2)	8/13 (61.5%)	0.70

Legend: Column 3 represents p-value for the mortality of the total number of patients as a comparison of death rate prior to cohort stratification. Column 6 represents p-values for mortality of patients compared within each strata of both NIPPV prior to IMV and Only IMV.

Table 5. Determinants of One-Year Mortality

Variables	Total	p-value	NIPPV prior to IMV	Only IMV	p-value
All Patients	N=54 Deaths 44 (81.5%)		N=27 Deaths 23 (85.2%)	N=27 Deaths 21 (77.8%)	0.73
	Deaths/n		Deaths/n	Deaths/n	
BMI		0.29			
<26.9	20/27 (74.1%)		9/12 (75.0%)	11/15 (73.3%)	1.00
26.9+	24/27 (88.9%)		14/15 (93.3%)	10/12 (83.3%)	0.57
Age		0.28			
<65	16/22 (72.7%)		5/9 (55.6%)	11/13 (84.6%)	0.18
65+	28/32 (87.5%)		18/18 (100.0%)	10/14 (71.4%)	**0.028**
Gender		0.74			
Female	19/24 (79.2%)		11/13 (84.6%)	8/11 (72.7%)	0.63
Male	25/30 (83.3%)		12/14 (85.7%)	13/16 (81.3%)	1.00
ILD Subtype		**0.001**			
IPF	8/8 (100%)		2/2 (100.0%)	6/6 (100.0%)	1.00
CTD	13/17 (76.5%)		6/8 (75.0%)	7/9 (77.8%)	1.00
Sarcoidosis	2/7 (28.6%)		2/4 (50.0%)	0/3 (0.0%)	0.43
Other	21/22 (95.5%)		13/13 (100.0%)	8/9 (88.9%)	0.41
ILD Presence		0.16			
<1 year	22/24 (91.7%)		11/11 (100.0%)	11/13 (84.6%)	0.48
1 year	22/30 (73.3%)		12/16 (75.0%)	10/14 (71.4%)	1.00
Pulmonary Hypertension		1.00			
Present					
Not Present	23/28 (82.1%) 21/26 (80.8%)		10/14 (71.4%) 13/13 (100.0%)	13/14 (92.9%) 8/13 (61.5)	0.33 0.039
History of Connective Tissue Disease		**0.011**			
Present					
Not Present	18/27 (66.7%) 26/27 (96.3%)		10/14 (71.4%) 13/13 (100.0%)	8/13 (61.5) 13/14(92.9%)	0.69 1.00
Cause of ARF		0.45			
Pneumonia/Sepsis	28/33 (84.8%)		14/17 (82.4%)	14/16 (87.5%)	1.00
ILD Exacerbation	9/9 (100.0%)		6/6 (100.0%)	3/3 (100.0%)	1.00
All others	7/12 (58.3%)		3/4 (75%)	4/8 (50.0%)	0.58
SVTs		**0.037**			
Sinus Tachycardia	15/21 (71.4%)		6/7 (85.7%)	9/14 (64.3%)	0.61
All Other SVTs	24/25 (96.0%)		14/15 (93.3%)	10/10 (100.0%)	1.00
Vasopressor		**0.035**			
Used	38/44 (86.4%)		19/22 (86.4%)	19/22 (86.4%)	1.00
Not used	4/8 (50.0%)		2/3 (66.7%)	2/5 (40.0%)	1.00
Pulmonary Vasodilator		0.31			
Used					
Not Used	19/22 (86.4%) 19/26 (73.1%)		6/8 (75.0%) 13/15 (86.7%)	13/14 (92.9%) 6/11 (54.5%)	0.53 0.09
Steroid Use		0.08			
Pulse/Stress Dose	20/22 (90.9%)		12/13 (92.3%)	8/9 (88.9%)	1.00
Other Dose	18/26 (69.2%)		11/14 (78.6%)	7/12 (58.3%)	0.40

Legend: Column 3 represents p-value for the mortality of the total number of patients as a comparison of death rate prior to cohort stratification. Column 6 represents p-values for mortality of patients compared within each strata of both NIPPV prior to IMV and Only IMV.

Figures

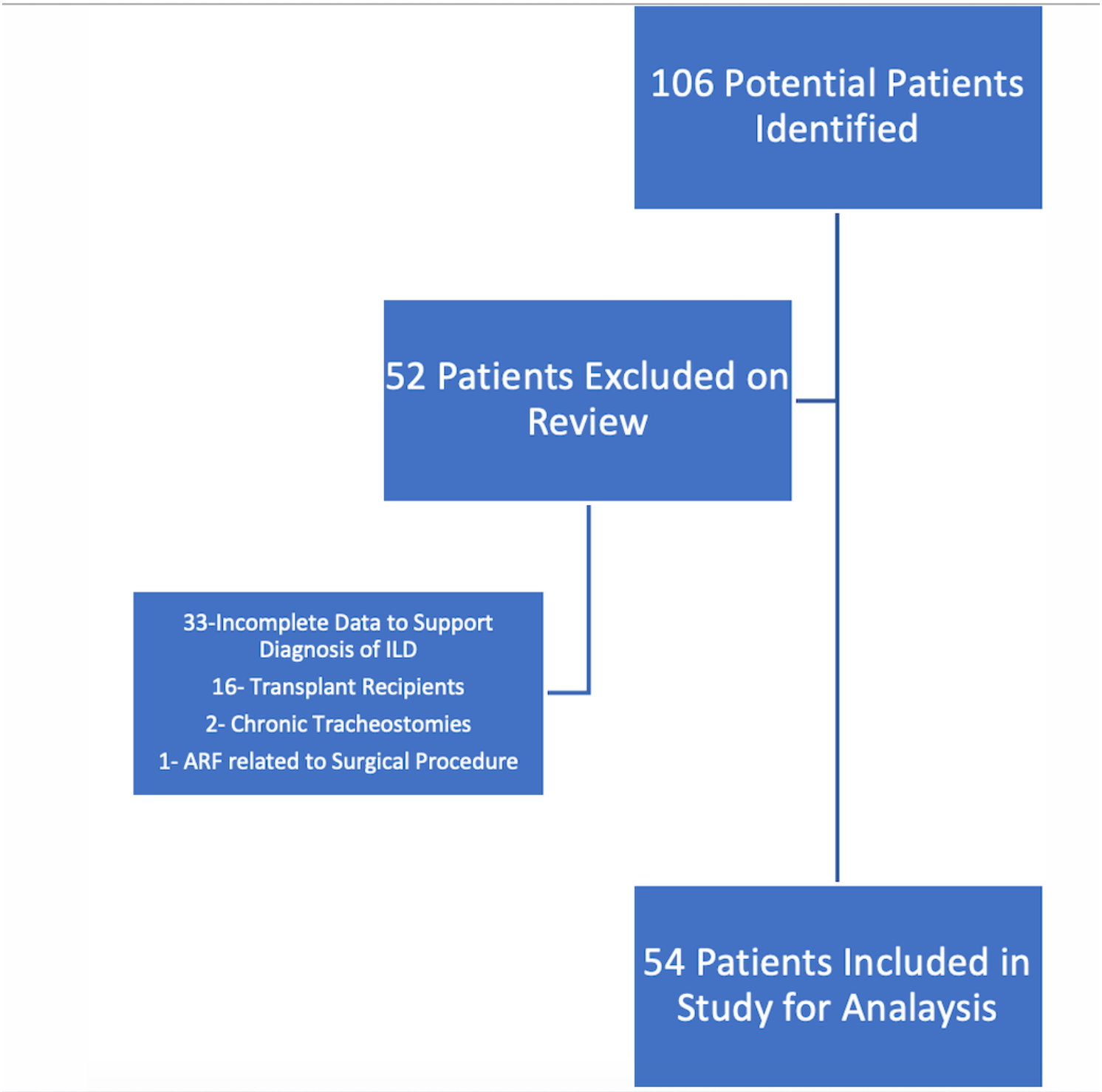

Figure 2

Graphical Representation of Patients Meeting Inclusion Criteria

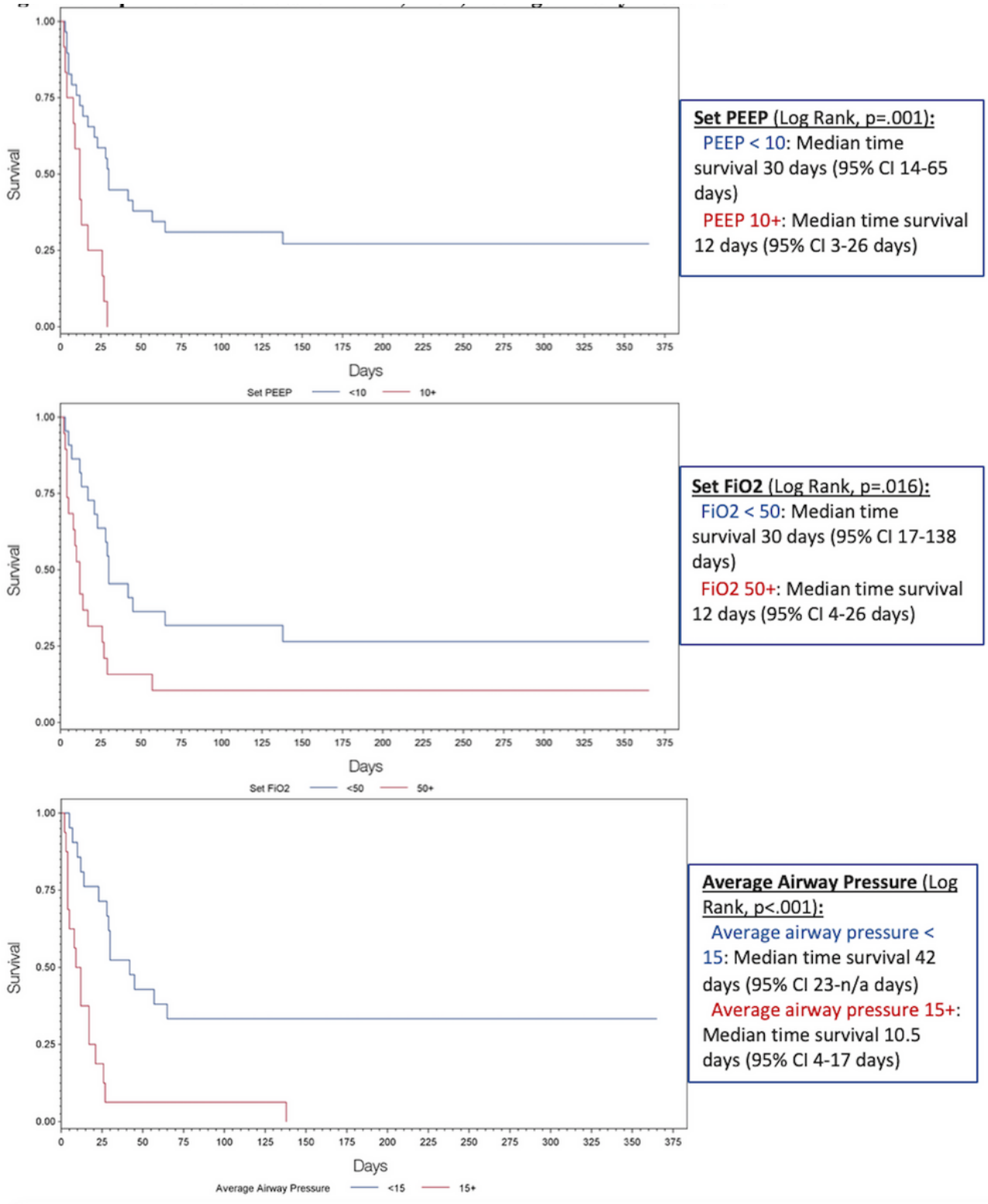

Figure 3

Kaplan-Meier Curves for PEEP, FiO2, Average Airway Pressures

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalDataforRR.docx
- SupplementalDataforRR.docx