

## Supplemental material

### Pooled analysis on mortality rates associated with IMV and NIMV in mixed-ILD

e-Table 2 describes the number of patients who received NIMV and IMV and the associated mortality rates. Thirteen studies included 631 patients with mixed-ILD (IPF, CTD-ILD, HP, IIP, among other ILDs) but only 508 had available information on mortality with IMV.[12, 14-18, 20-23, 26-28] Forty-nine percent of these patients received NIMV (including patients who failed NIMV and were intubated) and 23% received NIMV alone, with a mortality rate of 52% and 22%, respectively. The rate of failure of NIMV was 52%. IMV-associated mortality was 67% when including patients who were intubated on admission and 71% when including those who failed NIMV. These data suggest that intubation was prevented in a fifth of patients when they were given NIMV. The selection of these patients is important because the mortality is slightly higher for those who ended up failing NIMV and subsequently required to be intubated. Alternatively, the lower mortality in NIMV versus IMV can also represent an indicator of less severity, as patients who were offered NIMV could have been those with only mild or moderate disease.

Strategies for IMV have changed significantly in the past five to ten years. Therefore, we stratified the studies according to the year of publication by using an equal time period (group A: 2001-2009 and group B: 2010-2017). The mortality rate of NIMV decreased from 77% to 48% and the NIMV failure (patients who had to be intubated) rate dropped from 100% to 44% (e-Table 3). However, the IMV-associated mortality increased from 67% to 74%. Notably, this is not consistent with the hypothesis that using low volumes has improved outcomes in patients with ILD. This phenomenon might be related to the

increased use of NIMV in ILD, thus only the sickest patients may be ultimately intubated. For instance, the number of patients who received NIMV increased two-fold over time (27% in group A and 57% in group B) and the number of patients who received NIMV alone increased from 0% to 32%. Identifying the patients who will benefit from intubation requires further investigation.

### **Pooled analysis on mortality rates associated with IMV and NIMV in IPF.**

Out of 495 IPF patients from 15 studies reported in the literature, information on IMV outcomes was available in 467 patients.[30-33, 35-45] Eighty-four patients received NIMV and 51% failed this intervention and were transitioned to IMV. The calculated mortality for patients who were on NIMV alone was 46%. This number increased to 71% when including all patients who received NIMV (those who failed therapy and were intubated). The mortality for patients who were intubated without prior NIMV was 77% and increased to 79% when including those patients who failed NIMV.

In IPF studies, there is a significant difference in both IMV and NIMV associated mortality when separating studies according to the year of publication (e-Table 3). By using an equal time period (group A: 1993 to 2004 and group B: 2005-2017), the mortality for patients who underwent NIMV alone was 50% in group A and decreased to 45% in group B although the number of patients was small (eight in group A and 33 in group B). In IMV, the mortality rate dropped from 88% in group A to 76% in group B, which is consistent with our hypothesis that low tidal volumes have been improving outcomes in patients with ILD. The failure rate of NIMV remained around 50% in both groups, and the mortality rate for all patients who underwent NIMV increased from 63% in group A to 74% in group B. Nevertheless, one limitation is that only 16 patients received NIMV in group A and 68 in group B so the apparent increased mortality might

be explained by the small number of patients in group A. Notably, when changing the periods of time, the NIMV mortality rate and NIMV failure rate down-trended over time, especially after 2010 (e-Table 3), and only 7-9% received NIMV alone in both groups.

e-Table 1. Search strategy run on 11/21/2017.

Database	Key words	Results
PubMed	(“Lung Diseases, Interstitial”[Mesh] OR “Idiopathic Interstitial Pneumonias”[Mesh] OR “interstitial lung disease”[tw] OR “interstitial lung diseases”[tw] OR “Idiopathic Pulmonary Fibrosis”[Mesh] OR “idiopathic pulmonary fibrosis”[tw] OR “idiopathic pulmonary fibroses”[tw] OR “IPF”[tw] OR “ILD”[tw] OR “interstitial pneumonia”[tw]) AND (“Critical Care Outcomes”[Mesh] OR “survival rate”[mesh] OR “Treatment Outcome”[Mesh] OR “outcome”[tw] OR “outcomes”[tw] OR “Mortality”[Mesh] OR “mortality”[tw] OR “death rate”[tw] OR “death rates”[tw] OR “fatality”[tw] OR “fatalities”[tw] OR “survival”[tw]) AND (“intensive care units”[mesh] OR “Critical Care”[Mesh] OR “intensive care”[tw] OR “ICU”[tw] OR “critical care”[tw] OR “acute care”[tw]) NOT (animals [mh] NOT humans [mh]).	150
Cochrane	([mh “Lung Diseases, Interstitial”] OR [mh “Idiopathic Interstitial Pneumonias”]) OR “interstitial lung disease”:ti,ab,kw OR “interstitial lung diseases”:ti,ab,kw OR [mh “Idiopathic Pulmonary Fibrosis”] OR “idiopathic pulmonary fibrosis”:ti,ab,kw OR “idiopathic pulmonary fibroses”:ti,ab,kw OR “IPF”:ti,ab,kw OR “ILD”:ti,ab,kw OR “interstitial pneumonia”:ti,ab,kw) AND ([mh “Critical Care Outcomes”] OR [mh “survival rate”] OR [mh “Treatment Outcome”] OR “outcome”:ti,ab,kw OR “outcomes”:ti,ab,kw OR [mh “Mortality”] OR “mortality”:ti,ab,kw OR “death rate”:ti,ab,kw OR “death rates”:ti,ab,kw OR “fatality”:ti,ab,kw OR “fatalities”:ti,ab,kw OR “survival”:ti,ab,kw) AND ([mh “intensive care units”] OR [mh “Critical Care”] OR “intensive care”:ti,ab,kw OR “ICU”:ti,ab,kw OR “critical care”:ti,ab,kw OR “acute care”:ti,ab,kw).	3
Embase	(‘interstitial lung disease’/exp OR ‘interstitial pneumonia’/exp OR ‘interstitial lung disease’:ti,ab,de OR ‘interstitial lung diseases’:ti,ab,de OR ‘idiopathic pulmonary fibrosis’:ti,ab,de OR ‘idiopathic pulmonary fibroses’:ti,ab,de OR ‘IPF’:ti,ab,de OR ‘ILD’:ti,ab,de OR ‘interstitial pneumonia’:ti,ab,de)	242

	<p>AND  ('Critical Care Outcome'/exp OR 'survival rate'/exp OR  'Treatment Outcome'/exp OR 'outcome':ti,ab,de OR  'outcomes':ti,ab,de OR 'Mortality'/exp OR  'mortality':ti,ab,de OR 'death rate':ti,ab,de OR 'death  rates':ti,ab,de OR 'fatality':ti,ab,de OR 'fatalities':ti,ab,de  OR 'survival':ti,ab,de)</p> <p>AND  ('intensive care unit'/exp OR 'intensive care':ti,ab,de OR  'ICU':ti,ab,de OR 'critical care':ti,ab,de OR 'acute  care':ti,ab,de)</p> <p>Limits: English, Spanish, Article, Article in Press</p>	
<b>Scopus</b>	TITLE-ABS-KEY("interstitial lung disease" OR "interstitial lung diseases" OR "idiopathic pulmonary fibrosis" OR "idiopathic pulmonary fibroses" OR "IPF" OR "ILD" OR "interstitial pneumonia") AND TITLE-ABS- KEY("outcome" OR "outcomes" OR "mortality" OR "death rate" OR "death rates" OR "fatality" OR "fatalities" OR "survival") AND TITLE-ABS-KEY("intensive care" OR "ICU" OR "critical care" OR "acute care").	206
<b>SCIELO</b>	("interstitial lung disease" OR "interstitial lung diseases" OR "idiopathic pulmonary fibrosis" OR "idiopathic pulmonary fibroses" OR "IPF" OR "ILD" OR "interstitial pneumonia") AND ("outcome" OR "outcomes" OR "mortality" OR "death rate" OR "death rates" OR "fatality" OR "fatalities" OR "survival") AND ("intensive care" OR "ICU" OR "critical care" OR "acute care").	1
<b>WHO</b>	("interstitial lung disease" OR "interstitial lung diseases" OR "idiopathic pulmonary fibrosis" OR "idiopathic pulmonary fibroses" OR "IPF" OR "ILD" OR "interstitial pneumonia") AND ("outcome" OR "outcomes" OR "mortality" OR "death rate" OR "death rates" OR "fatality" OR "fatalities" OR "survival") AND ("intensive care" OR "ICU" OR "critical care" OR "acute care").	121
<b>Total</b>		<b>723</b>
	<i>Duplicates removed by reference software.</i>	379*
	<i>Duplicates manually removed.</i>	15*
<b>Other sources</b>	Additional references cited in the articles that were included in the study.	19 <sup>†</sup>
<b>Final total</b>		<b>348</b>

\*Number of articles subtracted from 723.

† Number of articles added to 723.

**e-Table 2. Mortality in mixed-ILD and IPF patients who received NIMV and IM**

	Study	N, total	N, included	NIMV, N	NIMV to IMV, N	IMV, N	NIMV Mortality, N (%)	NIMV to IMV Mortality, N (%)	IMV Mortality, N (%)
<b>Mixed-ILD</b>	Churg[13] (2007)	12	ni	nr	nr	nr	nr	nr	nr
	Fernandez-Perez [14](2008)*	94	94	.	21	73	.	13 (62)	37 (51)
	Fumeaux[15] (2001)	11	11	.	11	.	.	11 (100)	.
	Gaudry[16] (2014)*	27	27	.	19	8	.	15(79)	6 (86)
	Goncalves[17] (2016)	33	33	.	9	24	.	5 (56)	18 (75)

Gungor[18] (2013)	116	116	48	27	41	10 (21)	22 (81)	39 (95)
Huie[12] (2010) <sup>†</sup>	20	15	ni (5)	nr	15	nr	Nr	14 (93)
Martinez[19] (2015) <sup>‡</sup>	36	ni	nr	nr	nr	nr	nr	nr
Molina[20] (2003) <sup>*, §</sup>	17	17	.	3	14	.	3 (100)	14 (100)
Olson[21] (2008) <sup>  </sup>	4	4	.	.	4	.	.	4 (100)
Osman[22] (2017)	14	14	.	.	14	.	.	4 (29)
Park[23] (2007)	6	6	.	.	6	.	.	6 (100)
Tachikawa[24] (2012) <sup>†</sup>	37	ni	ni (28)	ni (2)	ni (7)	nr	nr	nr

	Tomii[25] (2010) <sup>†</sup>	33	ni	ni(5)	ni	ni (9)	nr	nr	nr
	Vial-Dupuy[26] (2013)	50	50	12	27	11	0 (0)	27 (100)	3 (27)
	Yokoyama[27] (2012) <sup>¶</sup>	38	38	26	12	.	10 (38)	8 (67)	.
	Zafrani[28] (2014)	83	83	33	.	50	6 (18)	.	28 (56)
	<b>Total</b>	<b>631</b>	<b>508</b>	<b>119</b>	<b>129</b>	<b>260</b>	<b>26</b>	<b>104</b>	<b>173</b>
<b>IPF</b>	Akira[29] (1997)	17	0	nr	nr	nr	nr	nr	nr
	Al- Hameed[30] (2004)	24	24	3	.	21	3 (100)	.	20 (95)
	Ambrosini[31] (2003)	2	2	1	0	1	0 (0)	0 (0)	1 (100)



Blivet[32] (2001)	15	15	3	2	10	1 (33)	2 (100)	8 (80)
Kim[33] (2006)	9	9	.	.	9	.	.	9 (100)
Kondoh[34] (1993)	3	0	.	.	.	.	.	.
Mollica[35] (2010)	34	34	14	5	15	9 (64)	5 (100)	15 (100)
Nava[36] (1999)**	7	7	.	.	7	.	.	6 (86)
Oda[37] (2016)	209	209	.	.	209	.	.	138 (66)
Papiris[38] (2015) <sup>†</sup>	8	0	ni(2)	nr	ni(6)	nr	nr	nr
Parambil[39] (2005)*	7	7	.	3	4	.	3 (100)	3 (75)
Rangappa[40]	23	23	4	13	6	3 (75)	13 (100)	6 (100)

(2009)									
Saydain[41] (2002)*	20	20	1	6	13	0 (0)	4 (67)	9 (69)	
Song[42] (2011)	65	65	.	.	65	.	.	56 (86)	
Stern[43] (2001) <sup>  </sup>	23	23	.	.	23	.	.	23 (100)	
Vianello[44] (2014) <sup>  </sup>	18	18	8	10	.	1 (13)	10 (100)	.	
Yokoyama[45] (2010)	11	11	7	4	.	2 (29)	4 (100)	.	
<b>Total</b>	<b>495</b>	<b>467</b>	<b>41</b>	<b>43</b>	<b>383</b>	<b>19</b>	<b>41</b>	<b>294</b>	

\* Authors only report the total number of deaths; thus, the values were estimated proportionally to the number of patients who were exposed (Fernandez-Perez: 50 deaths, Gaudry: 20 deaths and 1 transplant, Moline: 17 deaths, Parambil: 6 deaths, and Saydain: 13 deaths).

† As no information on outcome was available for some patients, they were not included in the analysis (only 5 were excluded in Huie et al.)

‡ Author only reports that 27 patients received NIMV and 20 IMV.

§ Seventeen patients were intubated: 6 on admission; 11 later (3 received NIMV). We are assuming these 3 patients died as the remaining 8 were only on reservoir bag or venture mask).

|| Lung transplants (Olson: 1 in IMV group, Stern: 1 in IMV group, and Vianello: 1 in NIMV group).

¶ Twenty patients failed NIMV but only 12 were intubated.

\*\* Authors do not comment on the outcome of 1 patient who was extubated and transitioned to NIMV.

nr: not reported; ni: not included in the analysis.

ILD: interstitial lung disease, IPF: idiopathic pulmonary fibrosis, IMV: invasive mechanical ventilation, NIMV: non-invasive mechanical ventilation, N: number of patients.

e-Table 3. Mortality in IPF and Mixed-ILD patients who received NIMV and IMV according to the year of publication.

		NIMV alone mortality, %	All NIMV mortality (includes NIMV failure), %	NIMV failure rate, %	IMV mortality, %	All IMV mortality (includes NIMV failure), %	All NIMV /total, %	NIMV alone/total, %	Mean overall mortality, %
<b>Mixed-ILD</b>	2001-2009	.	77	100	63	67	27	.	62
	2001-2010	.	77	100	67	69	24	.	62
	<b>2001-2017</b>	<b>22</b>	<b>52</b>	<b>52</b>	<b>67</b>	<b>71</b>	<b>49</b>	<b>23</b>	<b>51</b>
	2010-2017	22	48	44	69	74	57	32	48

	2011-2017	22	48	44	67	73	59	33	48
IPF	1993-2004	50	63	50	89	88	18	9	79
	1993-2006	50	68	58	90	89	18	7	78
	1993-2009	58	81	67	90	91	28	9	80
	<b>1993-2017</b>	<b>46</b>	<b>71</b>	<b>51</b>	<b>77</b>	<b>79</b>	<b>18</b>	<b>9</b>	<b>68</b>
	2005-2017	45	74	51	74	76	18	9	65
	2009-2017	45	72	49	73	76	18	9	65
	2010-2017	41	65	40	72	74	14	9	65

ILD: interstitial lung disease, IPF: idiopathic pulmonary fibrosis, IMV: invasive mechanical ventilation, NIMV: non-invasive mechanical ventilation, N: number of patients.

**e-Table 4. Mean overall mortality in Mixed-ILD and IPF patients according to the year of publication.**

	<b>Period</b>	<b>Mortality rate, %</b>	<b>N of studies</b>	<b>N of patients</b>
<b>Mixed-ILD</b>	2001-2009	62	6	154
	2001-2010	62	7	181
	2001-2012	61	8	219
	<b>2001-2017</b>	<b>51</b>	<b>15</b>	<b>685</b>
	2010-2017	48	9	531
	2012-2017	48	8	504
	2013-2017	48	7	466
<b>IPF</b>	1993-1999	60	2	10
	1993-2004	79	7	116
	1993-2006	78	9	134
	1993-2009	80	10	158
	1993-2011	71	12	282
	<b>1993-2017</b>	<b>68</b>	<b>15</b>	<b>526</b>
	2001-2011	72	10	272
	2005-2017	65	8	421
	2009-2016	65	6	392
	2010-2016	65	5	368
	2014-2016	65	3	244

ILD: interstitial lung disease, IPF: idiopathic pulmonary fibrosis, N: number.

**e-Table 5. Overall mortality in mixed-ILD and IPF patients according to geographic regions.**

	<b>Continent</b>	<b>Mortality rate, %</b>	<b>N, studies</b>	<b>N, patients</b>
<b>Mixed-ILD</b>	Africa	9.90%	1	91
	America	52.87%	4	137
	Asia	58.67%	3	168
	Europe	58.09%	6	253
	Oceania	69.00%	1	36
<b>IPF</b>	America	75.97%	3	70
	Asia	60.66%	4	313
	Europe	79.53%	7	119
	Oceania	91.70%	1	24

ILD: interstitial lung disease, IPF: idiopathic pulmonary fibrosis, N: number.