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Early non-invasive ventilation treatment for severe influenza pneumonia

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Abstract

The role of non-invasive ventilation (NIV) in acute respiratory failure caused by viral pneumonia remains controversial. Our objective was to evaluate the use of NIV in a cohort of (H1N1)v pneumonia. Usefulness and success of NIV were assessed in a prospective, observational registry of patients with influenza A (H1N1) virus pneumonia in 148 Spanish intensive care units (ICUs) in 2009–10. Significant variables for NIV success were included in a multivariate analysis. In all, 685 patients with confirmed influenza A (H1N1)v viral pneumonia were admitted to participating ICUs; 489 were ventilated, 177 with NIV. The NIV was successful in 72 patients (40.7%), the rest required intubation. Low Acute Physiology and Chronic Health Evaluation (APACHE) II, low Sequential Organ Failure Assessment (SOFA) and absence of renal failure were associated with NIV success. Success of NIV was independently associated with fewer than two chest X-ray quadrant opacities (OR 3.5) and no vasopressor requirement (OR 8.1). However, among patients with two or more quadrant opacities, a SOFA score ≤ 7 presented a higher success rate than those with SOFA score > 7 (OR 10.7). Patients in whom NIV was successful required shorter ventilation time, shorter ICU stay and hospital stay than NIV failure. In patients in whom NIV failed, the delay in intubation did not increase mortality (26.5% versus 24.2%). Clinicians used NIV in 25.8% of influenza A (H1N1)v viral pneumonia admitted to ICU, and treatment was effective in 40.6% of them. NIV success was associated with shorter hospital stay and mortality similar to non-ventilated patients. NIV failure was associated with a mortality similar to those who were intubated from the start.

Keywords: Influenza A (H1N1), non-invasive ventilation, prognosis, respiratory failure, viral pneumonia

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Introduction

In the last decade, two viral pandemics have had a significant impact on worldwide health, resulting mainly in severe acute respiratory failure (ARF). The first was the Severe Acute Respiratory Syndrome (or SARS) in 2003 [1], a virulent clinical entity with a high mortality rate; the second was influenza A (H1N1)v [2–6] in 2009, which, according to the WHO

report, caused more than 18 000 deaths within the first season.

The use of non-invasive ventilation (NIV) in adults has proved effective in treating chronic obstructive pulmonary disease exacerbation, cardiogenic pulmonary oedema, and ARF in immunocompromised patients [7]. In these patients, NIV has achieved significant reductions in the rate of endotracheal intubation and ventilator-associated complications, and has improved survival rates. Nevertheless, some meta-analyses argue against the use of NIV in ARF, because it offers no advantages over conventional ventilation [7,8]; moreover, delaying intubation in hypoxaemic intubated patients with pneumonia may increase the risk of complications [9,10].

Early use of NIV in ARDS caused by viral pneumonia is controversial. We tried to assess when clinicians used this technique and whether it was successful, performing a secondary

analysis of the GTEI/SEMICYUC (Grupo de Trabajo de Enfermedades Infecciosas/Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias) Registry, a large cohort of patients admitted to intensive care units (ICUs) for respiratory failure caused by 2009 pandemic influenza A (H1N1)v pneumonia. Secondary objectives were to assess if NIV use might increase mortality if intubation was subsequently required and if in some patients NIV could be predicted to be more successful. We hypothesized that the use of NIV in patients with ARF because of pandemic viral pneumonia might be effective in some cases and might avoid the need for invasive mechanical ventilation.

Material and Methods

Data for this study were obtained from a voluntary registry created by node 18 (Director: Jordi Rello) of CIBERES (PCI Neumonia) and recruited by investigators of the GTEI/SEMICYUC Study Group (Coordinator: Rafael Zaragoza), in 2009–10. Inclusion criteria were: adult viral pneumonia patients aged over 18 years, febrile ($>38^{\circ}\text{C}$) acute illness; respiratory symptoms such as cough, sore throat, myalgia or influenza-like illness; ARF (conventional oxygen therapy ≥ 0.5 to maintain $\text{SpO}_2 \geq 92\%$) requiring ICU admission; and microbiological confirmation of 2009 pandemic influenza A (H1N1)v by real-time PCR. Data were reported by the attending physician reviewing medical charts and radiological and laboratory records within the first 12 h after ICU admission. Patients with exacerbations of chronic obstructive pulmonary disease, acute pulmonary oedema, acute asthma and those already intubated at ICU admission or using NIV for palliative use or rescue therapy were excluded from the analysis [11]. The study was approved [11] by the institutional review board of Joan XXIII University Hospital, Tarragona (Spain). Patient identification remained anonymous and the requirement for informed consent was waived because of the observational nature of the study. The ICU admission criteria and treatment decisions for all patients, including determination of the need for intubation and type of antibiotic and antiviral therapy administered, were not standardized and were made by the attending physician.

Nasopharyngeal-swab specimens were collected at admission and respiratory secretions were also obtained in intubated patients. Reverse transcription-PCR testing was performed in accordance with the CDC protocol (<http://www.cdc.gov/h1n1flu/guidance>). H1N1 testing was performed at each institution, or centralized in a reference laboratory when not available. A 'confirmed case' was defined as an acute respiratory illness with laboratory-confirmed pan-

demic H1N1 virus infection by real-time reverse transcription-PCR or viral culture [12]. Only 'confirmed cases' were included in the current study.

The following information was recorded: demographic data, comorbidities, times of illness onset and hospital admission, time to first dose of antiviral delivery, microbiological findings and chest X-ray findings at ICU admission. Intubation and mechanical ventilation requirements (invasive and non-invasive), medical complications during ICU stay and laboratory findings at ICU admission were also recorded. Chronic obstructive pulmonary disease was defined as a disease state characterized by the presence of airflow limitation because of chronic bronchitis or emphysema. The airflow obstruction could be accompanied by airway hyper-reactivity and could be partially reversible [13]. To determine the severity of illness, the Acute Physiology and Chronic Health Evaluation (APACHE) II score [14] was recorded in all patients within 24 h of ICU admission. In addition, organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) scoring system [15].

Definition of community-acquired pneumonia was based on current American Thoracic Society and Infectious Disease Society of America guidelines [16]. Primary viral pneumonia was defined in patients in the acute phase of influenza virus illness who presented with acute respiratory distress and unequivocal alveolar opacities with negative respiratory and blood bacterial cultures. Secondary bacterial pneumonia was considered in patients with confirmation of influenza virus infection who showed recurrence of fever, increase in cough and production of purulent sputum plus positive bacterial respiratory or blood cultures [17]. Respiratory cultures were based on tracheal aspirates obtained immediately after intubation. Acute renal failure was defined as the need for renal replacement therapy, in accordance with the International Consensus Conference criteria [18].

We have defined comorbidities as the pathological antecedents of each patient, and antiviral gap as time of delay between the onset of symptoms and the start of antiviral treatment. Multiple organ dysfunction syndrome (MODS) and shock were defined following international criteria [15,19]. NIV was always used for ARF at an early stage. Failure of NIV was defined if the patient was intubated and invasively ventilated after an NIV trial (when $\text{SpO}_2 < 92\%$ or important respiratory work appeared).

Data were analysed using SPSS 18.0 software (Chicago, IL, USA). Data are expressed as frequency (percentage) or median (25th–75th interquartile range). For univariate analysis of the qualitative variables, the Chi-squared and Fisher tests were used. Quantitative variables were analysed by comparison of means with the Student's *t* test. Stepwise multivariate analysis

was performed with logistic regression taking the variables which had p values <0.20 in the univariate analysis, or others with a special clinical interest (chronic obstructive pulmonary disease or heart failure), as dependent variables. A p value of 0.05 or less was considered to be statistically significant.

Results

In all, 685 adults with 2009 pandemic influenza A viral pneumonia were admitted to the ICUs. Fig. 1 shows the distribution of the study population depending on the ventilation provided. Baseline characteristics of 177 non-invasively ventilated patients, compared with other subgroups, are briefly described in Table 1. Compared with non-ventilated subjects, patients with successful NIV presented more comorbidities (70.8 versus 57%; $p < 0.05$), a higher lactate dehydrogenase (758 versus 523 U/L; $p < 0.05$) and creatine kinase (307 versus 133 U/L; $p < 0.05$) levels, as well as longer ICU stay (6 versus 4 days; $p < 0.05$) (Table 1). An NIV trial was successful in 72 patients (40.7%), but failed in 105 (59.3%), who required intubation and invasive mechanical ventilation. Hence, of the 417 patients who underwent intubation, 312

(74.8%) were intubated and ventilated from the beginning, and 105 (25.2%) were intubated and ventilated after NIV failure. Therefore, 14.7% of ventilated patients admitted to the ICU for influenza A (H1N1)v pneumonia benefited from NIV.

Lower APACHE II score (median 10 versus 14, $p < 0.001$), lower SOFA score (median 3.5 versus 6, $p < 0.001$), the presence of fewer than two chest X-ray quadrant opacities, haemodynamic stability (analysed as the absence of the need for vasopressors) and the absence of acute renal failure or MODS were associated with NIV success (Table 2). These patients required shorter mechanical ventilation time (median 3 versus 12 days, $p < 0.001$), shorter ICU stay (6 versus 15 days, $p < 0.001$) and shorter hospital stay (11.5 versus 20.5 days, $p < 0.001$) than patients with NIV failure. Multivariate analysis (Table 2) demonstrated that NIV success was associated with the presence of fewer than two chest X-ray quadrant opacities (OR 3.59) and no vasopressor requirement (OR 8.18). Moreover, when we compared the subset of non-invasively ventilated patients with two or more quadrant opacities for those with a SOFA score >7 versus those with a SOFA ≤ 7 , the success rate increased from 5.9% to 40% (OR 10.7, 95% CI 1.3–88.6), whereas when the SOFA score was ≤ 3 , the success rate became 71% (95% CI 58–84%).

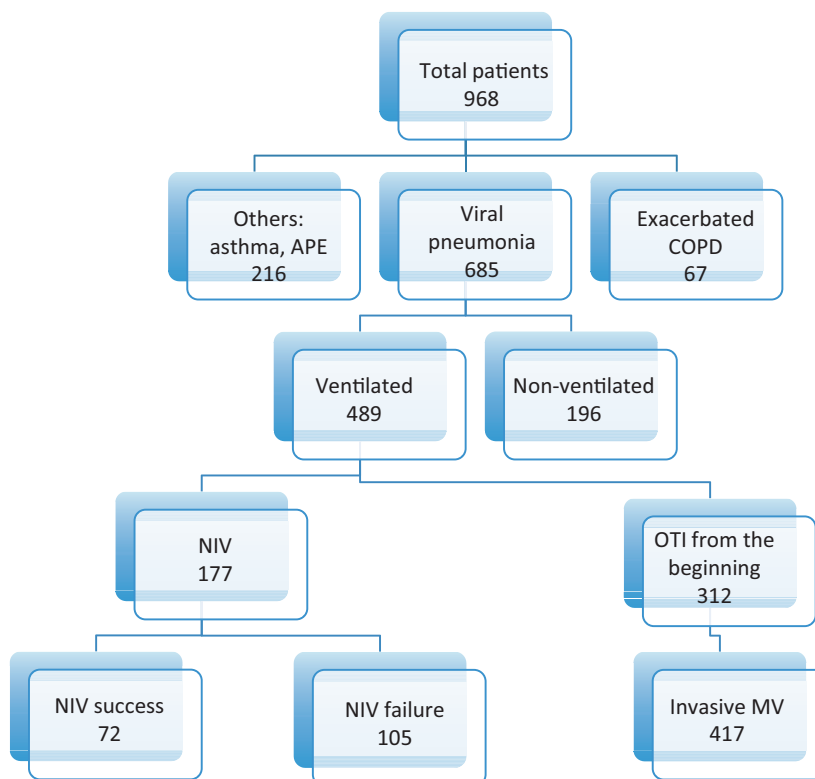


FIG. 1. Patients with influenza A (H1N1) virus infection admitted to intensive care units. APE, acute pulmonary oedema; COPD, chronic obstructive pulmonary disease; MV, mechanical ventilation; NIV, non-invasive ventilation; OTI, orotracheal intubation.

TABLE 1. Baseline characteristics of the patients admitted to intensive care units because of 2009 influenza A (H1N1)v pneumonia, comparing non-ventilated with all the groups of ventilated patients

Variables	Non-ventilated (n = 196)	Non-invasive ventilation			Initially intubated (n = 312)
		All (n = 177)	Successful (n = 72)	Failed (n = 105)	
Gender (male) (%)	56.2	56.5	56.9	56.2	53.4
Age (years)	41 (32–52)	44 (33–53)	45 (34–53)	44 (32–53)	43 (32–52)
APACHE II	9 (6–13)	12 (9–16)	10 (8–14)	14 (10–18.2)*	15 (10–19)
SOFA score	3 (2–4)	4 (3–7)	4 (3–4)	6 (4–8)*	6 (4–9)
Comorbidities (%)	57	74.6	70.8*	77.1	71.2
MODS (%)	29.1	61	27.8	83.8*	82.7
CXRqo <2 (%)	34.6	46.2	38.8	35.3**	43.2
Shock (%)	8.4	45.2	13.9	66.7*	65.8
Obesity >30% BMI (%)	17.9	31.6	38.9	26.7	21.7
Chronic renal failure (%)	4.2	5.6	2.8	7.6	5.2
Asthma (%)	11.1	10.2	13.9	7.6	8.4
COPD (%)	5.8	13.6	13.9	13.3	11.7
Heart failure (%)	3.2	6.2	8.3	4.8	4.9
Leucocyte count (per mm ³)	6250 (3450–10 650)	5400 (3500–8770)	5000 (4000–7975)	6000 (3475–9175)	6215 (3775–10 200)
Platelet count (1000/mm ³)	161.5 (117.5–228.3)	156 (121.5–226.5)	158 (115.8–2350)	155 (124–217)	150 (110–201.5)
LDH (U/L)	523 (313–829)	781 (441–1116)	758 (441–1006)*	835 (438–1249)	787 (458–1136)
CK (U/L)	133 (53–365)	265 (102–580)	307 (105–618)*	251 (100–572)	22 (95–636)
Serum creatinine (mg/dL)	0.84 (0.6–1)	0.88 (0.61–1.12)	0.8 (0.6–1)	0.9 (0.7–1.2)	0.9 (0.7–1.3)
Antiviral gap (days)	5 (3–7)	4 (2–6)	4 (2–6)	4 (2–6)	5 (3–6)
Oseltamivir treatment (days)	7 (5–10)	10 (7–12.2)	7 (7–10)	10 (7–14)**	11 (10–14)
Steroid treatment (%)	32.3	43.5	36.7	48.5	41.4
Days from symptom onset to hospital admission	5 (3–6)	4 (3–5)	4 (2–5)	5 (3–6)	4 (3–6)
Days from hospital to ICU admission	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)
MV days		7 (3–14)	3 (2–6)	12 (5–18.5)*	13 (8–23)
VAP (%)		11.1	0	11.1***	19.2
ICU days	4 (3–6)	9 (5–17)	6 (3–9)	15 (8–25)*	17 (10–28.2)
Hospital days	9 (7–13)	16 (10–24.2)	11.5 (7–15)*	20.5 (13.7–32.7)*	24 (15–37.5)
In-hospital mortality (%)	2.2	17.3	4.2	26.5*	24.2

Data are expressed as medians (25th–75th interquartile range), or percentage.

APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment scoring at ICU admission; MODS, multiple organ dysfunction syndrome; CXRqo, chest X-ray quadrants opacities; BMI, body mass index; COPD, chronic obstructive pulmonary disease; LDH, lactate dehydrogenase; CK, creatine kinase; MV, mechanical ventilation; VAP, ventilation-associated pneumonia; ICU, intensive care unit.

Comorbidities included obesity >30% BMI, chronic renal failure, asthma, COPD and heart failure, and calculated as the percentage of patients having at least one comorbidity.

All the laboratory parameters are at ICU admission. Antiviral gap: time from symptom onset to start antiviral treatment. Hospital days: from hospital admission to discharge.

*p <0.05 comparing successful NIV with non-ventilated H1N1 pneumonia patients; *p <0.001 (NIV failure versus NIV success); **p <0.01 (NIV failure versus NIV success);

***p <0.05 (NIV failure versus NIV success).

TABLE 2. Univariate and multivariate analysis of the comorbidities and parameters associated with non-invasive ventilation success (Total of 177 patients)

	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Comorbidities						
Asthma	0.51	0.19–1.36	0.18			
COPD	0.95	0.39–2.28	0.91			
Heart failure	0.55	0.16–1.87	0.34			
Non-chronic renal failure	2.88	0.59–14.01	0.18			
Pregnancy	3.28	0.68–15.65	0.13			
BMI <30%	0.57	0.30–1.08	0.08			
APACHE <15	2.94	1.26–6.87	<0.05			
SOFA <7	15.90	3.51–72.06	<0.01			
CXRqo <2	2.89	1.35–6.19	<0.01	3.59	1.15–11.19	<0.05
Haemodynamic stability	12.4	5.67–27.09	<0.01	8.18	2.07–32.30	<0.01
No MODS	13.45	6.47–27.97	<0.01			
Normal renal function	8.42	1.86–38.09	<0.01			

COPD, chronic obstructive pulmonary disease; BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment scoring at intensive care unit admission; CXRqo, chest X-ray quadrant opacities; MODS, multiple organ dysfunction syndrome. Haemodynamic stability analysed as absence of vasopressor requirement.

No differences were found comparing invasively ventilated patients after NIV failure with those initially submitted to orotracheal intubation and invasively ventilated, with regard to APACHE II and SOFA scores, radiographic infiltrates, proportion of shock or ventilator-associated pneumonia, ICU and hospital stay or mortality.

To study the possible association of complications with delay in intubation in NIV failure patients, we compared these patients intubated because of NIV failure with those intubated at ICU admission but they did not show significantly different rates of ventilator-associated pneumonia (19.2 versus 11.1%). Over two-thirds of the ventilator-associated pneumonia episodes (68.8%) were caused by *Pseudomonas aeruginosa* (31.1%), *Acinetobacter baumannii* (24.4%) or methicillin-resistant *Staphylococcus aureus* (13.3%). Mortality rates in ICU were similar in patients who failed NIV (26.5%) and in those who were intubated and invasively ventilated from the beginning (24.2%) (OR 1.12; 95% CI 0.67–1.88; p 0.64). Lengths of ICU stay and of hospital stay were also similar in both groups.

Discussion

This is the first large multicentre cohort study to suggest that ARF in some patients with viral 2009 influenza A (H1N1) pneumonia may respond to NIV therapy. Patients with only one radiological quadrant opacity, haemodynamic stability plus a SOFA score <8, were more likely to have a positive response to this treatment. Moreover, in patients with NIV failure, delayed intubation because of a trial of non-invasive mechanical ventilation did not increase mortality.

The use of NIV by clinicians in this large cohort of patients with severe acute respiratory infection is provocative, contrasting with the recommendations in many guidelines. Probably based on a previous study during the severe acute respiratory syndrome pandemic [20], the European Society of Intensive Care Medicine (ESICM) [21], the British Thoracic Society and WHO [22] include NIV as a high-risk procedure for disease transmission in ARF caused by influenza A (H1N1)v, although it has been shown that intubation is associated with a higher risk of viral particle transmission during severe acute respiratory syndrome [23]. Nonetheless, some reports suggest that NIV can be used in the management of some specific clinical cases of respiratory failure [24,25].

In this cohort, clinicians used NIV in 36.1% of ventilated patients, corresponding to 25.8% of all patients admitted to ICUs with influenza A (H1N1)v pneumonia. These values are comparable to other series with an average of reported cases of around 25% [4,5,26,27] ranging from 19% [27] to 40.7% [4] of all ventilated patients, with and without pneumonia. Overall, these reports include a total of 158 NIV patients. Only three of these series [4,5,26], with a total of 94 patients, assessed the efficacy of NIV, reporting it to be around 25% (ranging from 14.6% [5] to 58.8% [26]). None of these studies was designed with the purpose of studying only the role of NIV, so heterogeneity and lack of standardized criteria to start NIV is obviously a weakness.

Treatment decisions were not standardized and were made by the attending physician. NIV was performed in several patients despite possible contra-indications, i.e. haemodynamic instability and MODS (61% of patients). Indeed, the multivariate analysis identified haemodynamic stability and presentation with chest X-ray opacities in fewer than two quadrants as independent factors associated with NIV success. Although, vasopressor use per se is not an absolute contra-indication for NIV, data on vasopressor dosage and lactate levels could have better clarified this aspect. Based on the severity of illness of several patients undergoing NIV, one of the main messages of the present study could be that

NIV should not be offered to critically ill patients with acute respiratory failure complicating H1N1 viral pneumonia and other severe acute organ failures.

However, a key question is what happens to patients who fail NIV and must be intubated and invasively ventilated, and whether the delay is really detrimental to their clinical outcome. Some studies have reported an increasing risk of complications and worse prognosis in hypoxaemic patients intubated after NIV failure [9,10,28,29]. In our series, our comparison of invasively ventilated patients after NIV failure with those initially intubated and invasively ventilated presented a similar mortality. We found no differences between the two populations.

The main limitation of this study was its observational design. It is a secondary study of a database in which NIV was not implemented with a standardized protocol. First, no data were provided on the severity of acute respiratory failure in the patients included in the study (for instance: respiratory rate, $\text{PaO}_2/\text{FiO}_2$, PaCO_2 , pH). It is different to use NIV at an early stage of respiratory failure (for instance when the $\text{PaO}_2/\text{FiO}_2$ ratio is <250) or a late stage of ARF in patients presenting with intubation criteria. The lack of these data does not allow comparison of this study with previous studies dealing with hypoxaemic respiratory failure. Moreover, ICU admission and intubation criteria were not standardized. Delay time of intubation after NIV failure was not recorded. For the same reasons, NIV techniques and ventilation protocols are not reported. Again, comparison with previous studies is not possible. In addition, we cannot exclude that the lack of statistical difference in incidence of ventilator-associated pneumonia between patients intubated from the beginning (19.2%) and those intubated after NIV failure (11.1%) is the result of a lack of power of the current sample size. In patients at risk of failure with NIV, methods used to optimize NIV are not reported. Another limitation is the self-reporting by sites, which introduces the risk of selection bias. Healthcare workers were not prospectively assessed with follow-up serologies and the safety of the procedure should be investigated. Although no official notification of nosocomially transmitted cases has been reported using this therapy, the technique must be applied using the security measures recommended by the CDC guidelines and many scientific societies. In spite of recommendations against its use and these limitations, clinicians used NIV in nearly half of this large multicentre cohort, and in a significant proportion it was successful, suggesting that patients with severe acute respiratory infection can take benefit from early non-invasive oxygenation techniques. A randomized clinical trial is warranted to determine which patients may benefit from these techniques, to improve prognosis and to help reduce healthcare costs.

In conclusion, clinicians used NIV in 25.8% of patients with influenza A (H1N1)v viral pneumonia admitted to ICU and treatment was effective in 40.6% of them. NIV was successful in patients who presented with fewer than two chest X-ray opacities with haemodynamic stability and SOFA score ≤ 7 . NIV failure was associated with a mortality similar to that in patients who were intubated from the start.

Author Contributions

Drs Masclans and Rello contributed to the conception and design of this study, acquisition of data, analysis and interpretation of data, and manuscript preparation. Both are guarantors of the paper, taking responsibility for the integrity of the work as a whole. Drs Pérez, Socías, Marques, Vidaur, Lorente and Almirall contributed to the acquisition of data, analysis and interpretation of data, and manuscript preparation. Investigators from 148 ICUs of GTEI/SEMYCIUC contributed to the acquisition of data, and are listed in the Appendix. In addition, Dr Perez was specifically responsible for statistical analysis.

Transparency Declaration

The authors have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. Administrative support, logistics and storage of data were funded by resources assigned to node 18 (Director: Jordi Rello) of CIBERES (Centro de Investigación Respiratoria en Red en Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain), being part of PCI Neumonia-CIBERES and its own research group. Indeed, the generous dedication of Thiago Lisboa, Sandra Treffer, Mireia Llauro and Rosi Luque (salary funded by node 18 of CIBERES) and Alejandro Rodriguez (salary funded by Institut Català de la Salut) during the peak of the pandemic is greatly appreciated.

Appendix I

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