The PANDORA Study: Prevalence and Outcome of Acute Hypoxemic Respiratory Failure in the Pre-COVID-19 Era

OBJECTIVES: To establish the epidemiological characteristics, ventilator management, and outcomes in patients with acute hypoxemic respiratory failure (AHRF), with or without acute respiratory distress syndrome (ARDS), in the era of lung-protective mechanical ventilation (MV).

DESIGN: A 6-month prospective, epidemiological, observational study.

SETTING: A network of 22 multidisciplinary ICUs in Spain.

PATIENTS: Consecutive mechanically ventilated patients with AHRF (defined as $Pao_2/Fio_2 \leq 300$ mm Hg on positive end-expiratory pressure [PEEP] ≥ 5 cm H_2O and $Fio_2 \geq 0.3$) and followed-up until hospital discharge.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Primary outcomes were prevalence of AHRF and ICU mortality. Secondary outcomes included prevalence of ARDS, ventilatory management, and use of adjunctive therapies. During the study period, 9,803 patients were admitted: 4,456 (45.5%) received MV, 1,271 (13%) met AHRF criteria (1,241 were included into the study: 333 [26.8%] met Berlin ARDS criteria and 908 [73.2%] did not). At baseline, tidal volume was 6.9 ± 1.1 mL/kg predicted body weight, PEEP 8.4 ± 3.1 cm H_2O, Fio_2 0.63 ± 0.22, and plateau pressure 21.5 ± 5.4 cm H_2O. ARDS patients received higher Fio_2 and PEEP than non-ARDS (0.75 ± 0.22 vs 0.59 ± 0.20 cm H_2O and 10.3 ± 3.4 vs 7.7 ± 2.6 cm H_2O, respectively [$p < 0.0001$]). Adjunctive therapies were rarely used in non-ARDS patients. Patients without ARDS had higher ventilator-free days than ARDS (12.2 ± 11.6 vs 9.3 ± 9.7 d; $p < 0.001$). All-cause ICU mortality was similar in AHRF with or without ARDS (34.8% [95% CI, 29.7–40.2] vs 35.5% [95% CI, 32.3–38.7]; $p = 0.837$).

CONCLUSIONS: AHRF without ARDS is a very common syndrome in the ICU with a high mortality that requires specific studies into its epidemiology and ventilatory management. We found that the prevalence of ARDS was much lower than reported in recent observational studies.

KEY WORDS: acute hypoxemic respiratory failure; acute respiratory distress syndrome; epidemiology; lung-protective ventilation; outcome; positive end-expiratory pressure

Jesús Villar, MD, PhD, FCCM[1–3]

Juan M. Mora-Ordoñez, MD[4]

Juan A. Soler, MD, PhD[5]

Fernando Mosteiro, MD, PhD[6]

Anxela Vidal, MD[7]

Alfonso Ambrós, MD, PhD[8]

Lorena Fernández, MD[9]

Isabel Murcia, MD[10]

Belén Civantos, MD[11]

Miguel A. Romera, MD[12]

Adrián Mira, MD[13]

Francisco J. Díaz-Domínguez, MD[14]

Dácil Parrilla, MD[15]

J. Francisco Martínez-Carmona, MD[4]

Domingo Martínez, MD[5]

Lidia Pita-García, MD[6]

Denis Robaglia, MD[7]

Ana Bueno-González, MD[8]

Jesús Sánchez-Ballesteros, MD[9]

Ángel E. Pereyra, MD[10]

Mónica Hernández, MD[11]

Mechanical ventilation (MV) is ubiquitous in the ICU setting. Worldwide, more than 300 million patients/yr are ventilated, mostly in the operating room, with approximately 10 million ventilated annually in ICUs (1, 2). A recent population-based study revealed that about 310 people per 100,000 adult population undergo MV annually for nonsurgical indications (3). Main goals of MV include relief of excessive work of breathing and improvement of gas exchange, without impairing hemodynamics, or subjecting patients to iatrogenic injury from ventilator-induced lung injury.

Limiting tidal volume (VT) and inspiratory pressures while providing sufficient positive end-expiratory pressure (PEEP) to minimize lung collapse is the underlying principle lung-protective MV (4).

Hypoxemia is common in mechanically ventilated ICU patients. Approximately 1 million patients worldwide develop acute hypoxemic respiratory failure (AHRF), although epidemiological data on the exact prevalence and outcomes vary substantially (5–12). The acute respiratory distress syndrome (ARDS), considered a severe form of AHRF, has been studied widely. However, there are relatively few studies in the current era of lung-protective ventilation addressing epidemiological characteristics, patterns of ventilation, and clinical outcomes in AHRF patients without ARDS. Recent retrospective surveys using administrative databases have substantial limitations since they did not include specific hypoxemic conditions (13–15) or were focused on ARDS mortality (16, 17). A 1-day point prevalence study conducted in 2016 in France (18) in hypoxemic ICU patients had a number of limitations, including the fact that arterial blood gases were not analyzed in 31% of patients on the study day.

The goal of the present study was to establish the epidemiological characteristics, ventilator management, and clinical outcomes in invasively mechanically ventilated patients with AHRF (defined as $Pao_2/Fio_2 \leq 300$ mm Hg on PEEP ≥ 5 cm H_2O and $Fio_2 \geq 0.3$) admitted to a network of hospitals in Spain. The methodology of this study has been piloted in a smaller study in Wales (19). We postulated that these data would be valuable in understanding how recent recommendations on lung-protective ventilation have affected patient care and outcomes in AHRF patients with and without ARDS.

Carlos Chamorro-Jambrina, MD[12]

Pilar Cobeta, MD[13]

Raúl I. González-Luengo, MD[14]

Raquel Montiel, MD[15]

Leonor Nogales, MD[16]

M. Mar Fernández, MD, PhD[17]

Blanca Arocas, MD[18]

Álvaro Valverde-Montoro, MD[4]

Ana M. del Saz-Ortiz, MD[5]

Victoria Olea-Jiménez, MD[4]

José M. Añón, MD, PhD[1,11]

Pedro Rodríguez-Suárez, MD[19]

Rosa L. Fernández, MSc[1,2]

Cristina Fernández, MSc[2]

Tamas Szakmany, MD, PhD[20,21]

Jesús M. González-Martín, PhD[2]

Carlos Ferrando, MD, PhD[1,22]

Robert M. Kacmarek, PhD, RTT[23, †]

Arthur S. Slutsky, MD[3,24]

for the Prevalence AND Outcome of acute hypoxemic Respiratory fAilure (PANDORA) Network

METHODS

This study was approved by the Ethics Committees of Hospital Universitario La Paz, Madrid (#PI-2694) and Valladolid-Este (#PI17-594), Spain, and adopted by all participating centers, as required by Spanish legislation. The study was considered an audit, with waived informed consent, except in two sites (**Supplemental File,** http://links.lww.com/CCX/A978). The study followed "Strengthening the Reporting of Observational Studies in Epidemiology" guidelines (20) and was registered with ClinicalTrials.gov (NCT03145974).

Patients, Study Design, and Oversight

This was a 6-month, multicenter, prospective, observational study conducted in 22 ICUs in 14 geographical areas of Spain under the acronym Prevalence AND Outcome of acute hypoxemic Respiratory fAilure (details in Supplemental File, http://links.lww.com/CCX/A978). Patients were enrolled during three periods of two consecutive months (May 1, 2017–June 30, 2017, October 1, 2017–November 30, 2017, February 1, 2018–March 31, 2018), covering several seasons. During study periods, all consecutive patients were screened daily and included if they fulfilled the following criteria: 1) age greater than or equal to 18 years, 2) underwent endotracheal intubation and MV, although patients could have been on noninvasive respiratory support before intubation, and 3) Pao_2/Fio_2 less than or equal to 300 mm Hg with PEEP greater than or equal to 5 cm

H_2O and FIO_2 greater than or equal to 0.3. We did not use oxygen saturation as measured by pulse oximetry (SpO_2) as a surrogate for PaO_2 for enrolling patients. Clinicians only considered qualifying blood gases while patients were clinically stable and did not consider transient falls in PaO_2/FIO_2 resulting from acute events unrelated to the disease process (Supplemental File, http://links.lww.com/CCX/A978). Chest imaging was mandatory by protocol to assess pulmonary abnormalities at study inclusion.

No ICU patients meeting these criteria were excluded regardless of age, gender, underlying disease, life expectancy, or duration of MV.

Data Collection and Outcomes

Day 0 was defined as the day that AHRF criteria were satisfied. We collected data on patient demographics, ICU admission diagnosis, etiology of ARDS, chest imaging, physiologic and laboratory results, management, and complications during ICU stay. We recorded duration of MV and calculated ventilator-free days (VFDs) from the day of study inclusion to day 28 (Supplemental File, http://links.lww.com/CCX/A978). MV, Sequential Organ Failure Assessment (SOFA) score (21), and general data were collected on days 0, 1, 3, 7, and the last day of MV (details in Supplemental File, http://links.lww.com/CCX/A978). Acute Physiology and Chronic Health Evaluation II score (22) was obtained during the first 24 hours of AHRF diagnosis. In the context of MV patients, ARDS was deemed to exist if patients fulfilled the Berlin criteria (23): an initiating clinical condition developed within 1 week of a known clinical insult, bilateral pulmonary infiltrates on chest imaging not explained by cardiac failure or fluid overload, and hypoxemia ($PaO_2/FIO_2 \leq 300$ on PEEP ≥ 5) (details in Supplemental File, http://links.lww.com/CCX/A978). Patients were followed until hospital discharge.

Standard good clinical practice according to established evidence-based guidelines was encouraged. In particular, physicians were encouraged to follow recommendations for lung-protective MV (24, 25) in all patients, which included: VT 4–8 mL/kg predicted body weight (PBW), ventilatory rate to maintain $PaCO_2$ 35–50 mm Hg, plateau pressure (Pplat) less than 30 cm H_2O, and PEEP/FIO_2 combinations to maintain PaO_2 greater than 60 mm Hg or SpO_2 greater than 90%. Clinicians were also encouraged to follow usual critical care management, including antibiotic therapy and hemodynamic support, among others (details in Supplemental File, http://links.lww.com/CCX/A978). Data were collected and stored at each center and then sent de-identified to study coordinators. Demographics, physiologic and laboratory data, and severity scores were checked against standardized ranges at the coordinating center (details in Supplemental File, http://links.lww.com/CCX/A978); inconsistencies were corrected after discussion with site principal investigators.

The primary outcome was the prevalence of AHRF requiring MV. We calculated prevalence rates using three approaches: 1) per total ICU admissions, 2) per total mechanically ventilated patients, and 3) per ICU bed (details in Supplemental File, http://links.lww.com/CCX/A978). Secondary outcomes included prevalence of ARDS, ventilator management, all-cause ICU mortality, and use of adjunctive therapies (e.g., prone positioning and recruitment maneuvers).

Statistical Analysis

Since this was an observational study with no benefit/harm, we had no predefined sample size. Based on previous epidemiological studies by our group (5, 26, 27), we hoped to enroll at least 1,100 patients with AHRF (including $\geq$ 300 ARDS patients). With an estimated maximum screening rate of 15% of the total number of admitted ICU patients, we estimated that an average of 50 AHRF patients would be included in each ICU.

We used descriptive statistics to summarize binary (number and percentage) and continuous (mean and SD, median and P_{25}–P_{75}) variables. Kolmogorov-Smirnov test was used to check normality. We compared variables across groups using Student t test or Mann-Whitney U test for numerical variables and Fisher exact test for categorical variables. We report between-group differences and 95% CIs. The 95% CI for the difference between medians was estimated using a bootstrap procedure (10,000 replications). We assessed probability of cumulative survival to day 30 during hospitalization after study entry using the Kaplan-Meier method, analyzed with the log-rank test. Patients discharged alive from hospital before day 30 were censored. All time to events were defined from day of AHRF diagnosis. Missing data were not imputed. For all comparisons, a two-sided p value of less than or equal to 0.001 was considered a real effect

size to keep a false discovery rate less than 5% (28). Analyses were performed using R software, Version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Centers verified that during study periods, they screened every ICU patient for AHRF. There were 9,803 ICU admissions; 4,456 of them received MV. A total of 3,185 patients (71%) on MV had Pao_2/Fio_2 greater than 300 mm Hg during their ICU stay, 1,271 patients (13.0% of ICU admissions) met criteria for AHRF; 30 patients were excluded and 1,241 patients were enrolled (**Fig. 1**) representing an average of 3.3 AHRF patients/ICU bed. A total of 333 mechanically ventilated patients met Berlin ARDS criteria, representing 3.4% of ICU admissions, and 7.5% of patients who received MV. Median age was 65 years (P_{25}–P_{75} 54–74 yr); 67.2% were male. Main reasons for intubation and MV were cerebral pathology (head trauma, stroke, or coma), postoperative ventilation, pneumonia, and sepsis (**Table 1**; **Table S1**, http://links.lww.com/CCX/A978; and Fig. 1). Patients with postoperative ventilation and neurologic insults had other disorders (e.g., fluid overload, pneumonia, atelectasis, aspiration) as major mechanisms for hypoxemia.

Median days from ICU admission to AHRF diagnosis were 0 days (0–1 d). Mean values at AHRF diagnosis (day 0) for all patients were: Pao_2/Fio_2 170.5±64.1 mm Hg, Vt 6.9±1.1 mL/kg PBW, Pplat 21.5±5.4 cm H_2O, and PEEP 8.3±3.0 cm H_2O (Table 1). At study entry, Vt was less than or equal to 8 mL/kg PBW in 86.1% (1,068/1,241), PEEP was greater than or equal to 8 cm H_2O in 59.4% (737/1,241), and Fio_2 was less than or equal to 0.7 in 71.4% (886/1,241) of patients. Clinicians largely chose ventilator strategies with low Vt (4–8 mL/kg PBW, PEEP 8–12 cm H_2O, Pplat < 30 cm H_2O, and avoided high Fio_2 [≥ 0.7] within the first 24 hr) (**Fig. 2**; and **Table S2**, http://links.lww.com/CCX/A978).

From 971 patients (78.2%) with recorded Pplat within the first 24 hours, only four patients (0.41%) were ventilated with Vt greater than 8 mL/kg PBW and Pplat greater than or equal to 30 cm H_2O (**Table S3**, http://links.lww.com/CCX/A978). Most ARDS patients (282/333, 84.7%) received PEEP greater than or equal to 10 cm H_2O (median, 12 cm H_2O; P_{25}–P_{75}, 10–14) within the first 24 hours of ARDS diagnosis.
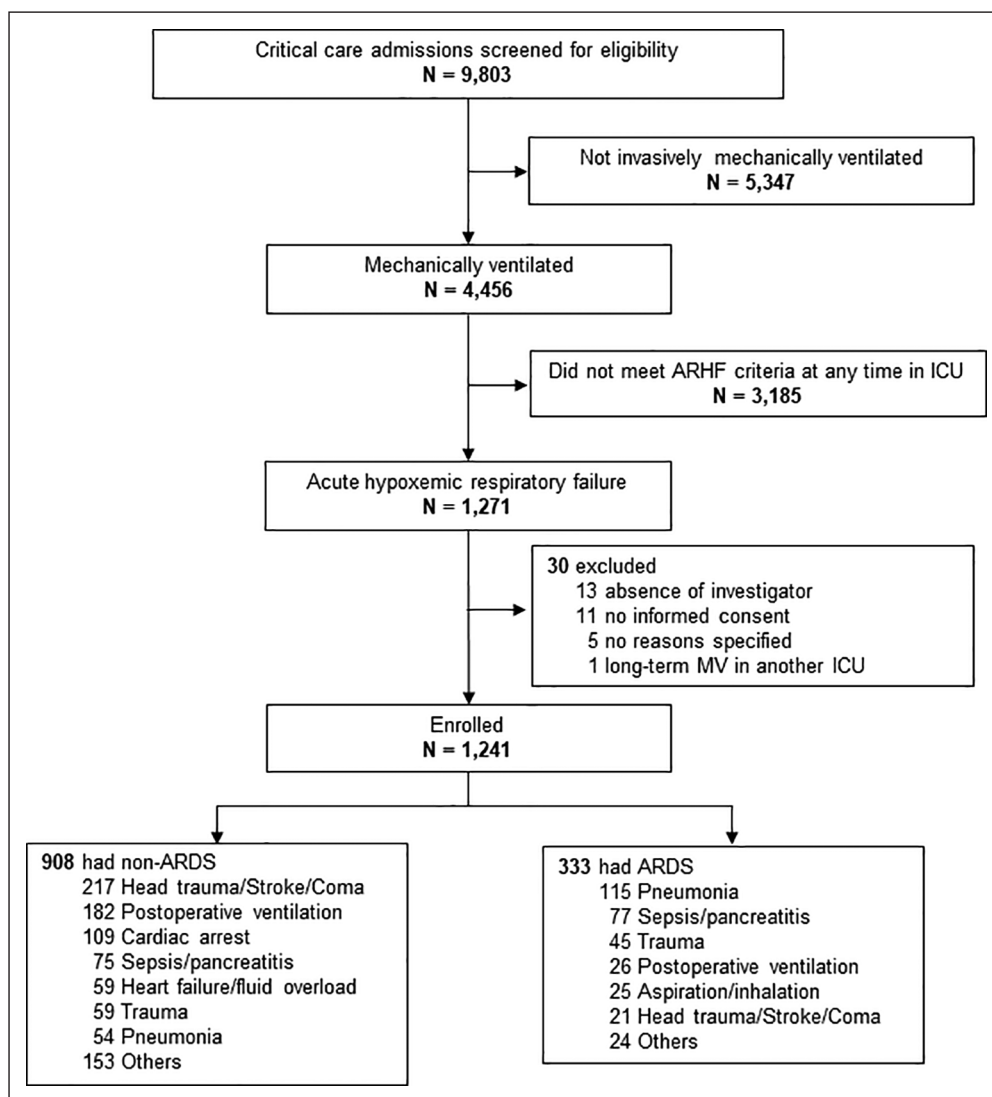

Figure 1. Flow chart of patient screening and enrollment. ARDS = acute respiratory distress syndrome, AHRF = acute hypoxemic respiratory failure, MV = mechanical ventilation.

TABLE 1.

Baseline Characteristics and Outcome Data of 1,241 Patients With Acute Hypoxemic Respiratory Failure

Variables	Total Patients, $n = 1,241$	AHRF Without ARDS ($n = 908$)	AHRF With ARDS ($n = 333$)	Absolute Difference (95% CI)[a]	p[a]
Age, yr, mean ± SD	62.8±14.3	64.5±13.8	58.0±14.6	6.5 (4.7–8.2)	< 0.001
Sex, n (%)					
Men	834 (67.2)	591 (65.1)	243 (73.0)	7.0 (1.9–12.1)	0.009
Women	407 (32.8)	317 (34.9)	90 (27.0)		
Reason for invasive MV, n (%)					< 0.001
Head trauma/stroke/coma	238 (19.2)	217 (23.9)	21 (6.3)		
Postoperative ventilation	208 (16.8)	182 (20.0)	26 (7.8)		
Pneumonia	169 (13.6)	54 (5.9)	115 (34.5)		
Sepsis/pancreatitis	152 (12.2)	75 (8.3)	77 (23.1)		
Cardiac arrest	117 (9.4)	109 (12.0)	8 (2.4)		
Trauma	104 (8.4)	59 (6.5)	45 (13.5)		
Heart failure/fluid overload	62 (5.0)	59 (6.5)	3 (0.9)		
Aspiration/inhalation	49 (3.9)	24 (2.6)	25 (7.5)		
Others	142 (11.4)	129 (14.2)	13 (3.9)		
Acute Physiology and Chronic Health Evaluation II score, mean ± SD	21.0±8.0	21.1±8.1	20.9±7.7	0.2 (−0.8 to 1.2)	0.737
Sequential Organ Failure Assessment score, mean ± SD	8.9±3.5	8.6±3.4	9.6±3.5	1.00 (0.6–1.4)	< 0.001
Pao_2/Fio_2, mm Hg, mean ± SD	170.5±64.1	182.6±61.4	137.7±59.9	44.9 (37.2–52.5)	< 0.001
Fio_2, mean ± SD	0.63±0.22	0.59±0.20	0.75±0.22	0.17 (0.14–0.19)	< 0.001
Pao_2, mm Hg, mean ± SD	98.9±34.5	100.3±33.9	95.3±36.1	5.0 (0.7–9.3)	0.023
$Paco_2$, mm Hg, mean ± SD	46.1±12.4	44.8±11.7	49.8±13.5	5.0 (3.4–6.7	< 0.001
pH, mean ± SD	7.32±0.11	7.33±0.11	7.28±0.11	0.05 (0.04–0.06)	< 0.001
Tidal volume, mL/kg predicted body weight, mean ± SD	6.91±1.12	6.95±1.12	6.80±1.12	0.15 (0.01–0.29)	0.032
Set respiratory rate, cycles/min, mean ± SD	19.8±4.4	19.2±4.2	21.3±4.6	2.1 (1.6–2.7)	< 0.001
Minute ventilation, L/min, mean ± SD	8.6±2.1	8.4±2.0	9.2±2.0	0.8 (0.6–1.1)	< 0.001
Positive end-expiratory pressure, cm H_2O, mean ± SD	8.3±3.0	7.7±2.6	10.1±3.4	2.4 (2.0–2.8)	< 0.001
Peak inspiratory pressure, cm H_2O, mean	27.3±7.4	26.4±7.3	29.8±7.1	3.4 (2.5–4.3)	< 0.001
Plateau pressure, cm H_2O, mean ± SD[b]	21.5±5.4	20.5±5.1	24.0±5.3	3.5 (2.8–4.1)	< 0.001
Driving pressure, cm H_2O, mean ± SD[b]	13.1±4.7	12.8±4.6	13.9±4.9	1.1 (0.5–1.7)	< 0.001
Number of extrapulmonary organ failure, median (P_{25}–P_{75})	2 (1–2)	2 (1–2)	2 (1–2)	0 (−1 to 1)	0.094
Length of ICU stay, d, median (P_{25}–P_{75})	10 (4–21)	8 (4–19)	16 (8–27)	8 (5–10)	< 0.001
Duration MV from inclusion, median (P_{25}–P_{75})	6 (2–14)	4 (2–11)	10 (5–18)	6 (4–7)	< 0.001
Ventilator-free days from study inclusion, d, mean ± SD	11.4±11.2	12.2±11.6	9.3±9.7	2.9 (1.5–4.3)	< 0.001
Days from ICU admission to AHRF onset	0 (0–1)	0 (0–1)	0 (0–2)	0 (−1 to 0)	0.015
All-cause ICU mortality, n (%) (95% CI)	438 (35.3) (32.6–37.9)	322 (35.5) (32.3–38.6)	116 (34.8) (29.7–39.9)	0.6 (−5.4 to 6.5)	0.837
All-cause hospital mortality, n (%) (95% CI)	514 (41.4) (38.7–44.2)	385 (42.4) (39.2–45.6)	129 (38.7) (33.5–44.0)	3.7 (−2.5 to 9.7)	0.246

AHRF = acute hypoxemic respiratory failure, ARDS = acute respiratory distress syndrome, MV = mechanical ventilation.

[a]Absolute difference and p represent comparisons between AHRF without ARDS and with ARDS for each variable.

[b]Plateau pressure was not reported at baseline in 169 patients (149 in AHRF without ARDS and 20 in AHRF with ARDS).
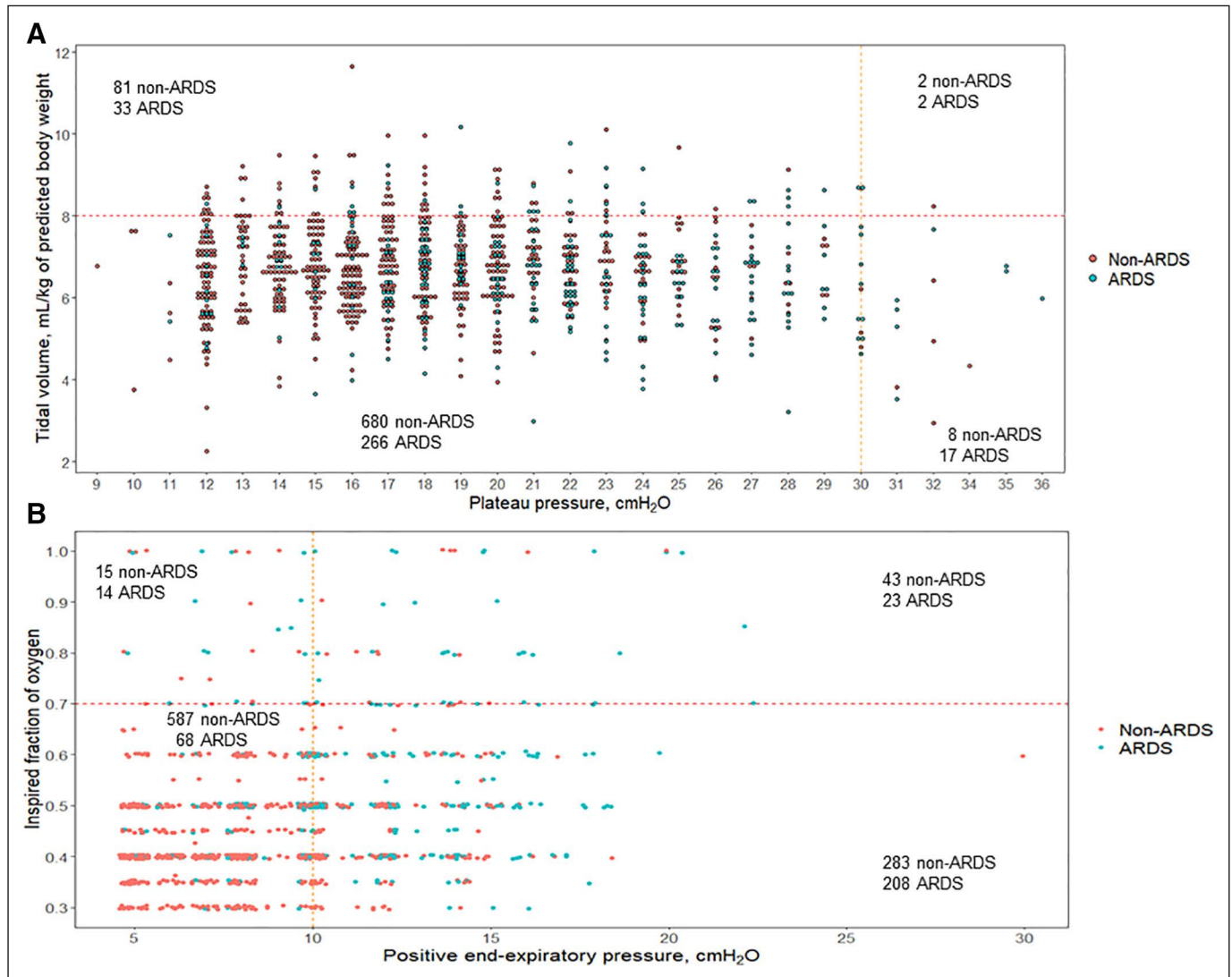
Figure 2. Ventilation parameters in 1,241 patients with acute hypoxemic respiratory failure within the first 24 hr of enrollment into the study. **A**, Distribution of tidal volume versus plateau pressure for each patient. Most patients ($n = 946$) fell within the limits of protective ventilation, defined as plateau pressure less than 30 cm H_2O and tidal volume less than or equal to 8 mL/kg of predicted body weight. **B**, Distribution of positive end-expiratory pressure (PEEP) versus F_{IO_2}. Most patients were ventilated with a PEEP in the range of 8–12 cm H_2O ($n = 662$, 53.3%) and F_{IO_2} less than 0.7 ($n = 1,146$, 92.3%). ARDS = acute respiratory distress syndrome.

The degree of V_T variability (< 6, 6–8, > 8 mL/kg PBW) was not associated with ICU mortality: 39.7% (119/300), 33.9% (271/800), and 34.0% (48/141), respectively ($p = 0.1911$). Variability of PEEP (5–8, 9–12, > 12 cm H_2O) was not associated with ICU mortality: 34.2% (223/653), 35.1% (148/422), and 40.4% (67/166), respectively ($p = 0.3247$). In general, AHRF patients with and without ARDS had different values at baseline, overall the trajectory of these values over the first week was similar in both groups (lower SOFA, similar V_T and PEEP, lower F_{IO_2}, improvement in Pao_2/F_{IO_2}, and normalization of $Paco_2$ and pH) (**Table S4**, http://links.lww.com/CCX/A978).

Prior to study enrollment, 17.8% (221/1,241) were treated with noninvasive respiratory support. Patients received a number of interventions and adjunctive therapies (prone positioning, extracorporeal assist) (**Table 2**); these therapies were rarely used in non-ARDS patients. A total of 82 ARDS patients (24.6%) received prone ventilation; this represented 81.2% of patients ($n = 101$) with Pao_2/F_{IO_2} less than 150 mm Hg in the first 48 hours of ARDS onset.

A high proportion of patients developed respiratory and systemic complications (**Table S5**, http://links.lww.com/CCX/A978). Most patients had comorbidities

TABLE 2.

Summary of Management and Intervention Modalities in 1,241 Patients With Acute Hypoxemic Respiratory Failure While in the ICU

Management and Intervention[a]	AHRF Without ARDS, $n = 908$	AHRF With ARDS, $n = 333$	Absolute Difference (95% CI)	p
Pulmonary artery catheter	33 (3.6)	7 (2.1)	1.5 (−0.9 to 3.3)	0.176
Blood transfusion (> 1 U)	231 (25.4)	119 (35.7)	10.3 (4.5−16.2)	< 0.001
Neuromuscular blockade	105 (11.6)	126 (37.8)	26.3 (20.7−31.9)	< 0.001
Corticosteroids	225 (24.8)	136 (40.8)	16.1 (10.1−22.1)	< 0.001
Vasopressor use	682 (75.1)	299 (89.8)	14.7 (10.1−18.7)	< 0.001
Systemic vasodilator use	111 (12.2)	14 (4.2)	8.0 (4.6−10.9)	< 0.001
Tracheostomy	176 (19.4)	92 (27.6)	8.2 (3.0−13.8)	0.002
Renal replacement therapy	146 (16.1)	109 (32.7)	16.6 (11.2−22.3)	< 0.001
Adjunctive therapies				
High-frequency ventilation	0	0	0	NA
Nitric oxide	7 (0.8)	8 (2.4)	1.6 (0.2−3.9)	0.020
Recruitment maneuvers	84 (9.2)	120 (36.0)	26.8 (21.4−32.3)	< 0.001
Prone positioning	14 (1.5)	82[b] (24.6)	23.1 (18.6−28.0)	< 0.001
Extracorporeal assist	4 (0.4)	20 (6.0)	5.6 (3.4−8.7)	< 0.001
None of the above	808 (89.0)	173 (51.9)	37.0 (31.3−42.7)	< 0.001
Noninvasive respiratory support before intubation	127 (14.0)	94 (28.2)	14.2 (9.1−19.7)	< 0.001
Noninvasive respiratory support after extubation	84 (9.2)	36 (10.8)	1.6 (−2.0 to 5.7)	0.410

AHRF = acute hypoxemic respiratory failure, ARDS = acute respiratory distress syndrome, NA = not applicable.

[a]Total is greater than 100% in each group because patients could have more than one intervention.

[b]This figure represented the 81.2% of 101 patients with a $Pao_2/Fio_2 < 150$ mm Hg within 48 hr of ARDS onset.

Data are reported as n (%).

prior to ICU admission (**Table S6**, http://links.lww.com/CCX/A978). All-cause ICU mortality was 35.3% (438/1,241) and was similar in patients with ARDS (116/333, 34.8% [95% CI, 29.7–40.2%]) or without ARDS (322/908, 35.5% [95% CI, 32.3–38.7%]) ($p = 0.837$) (Table 1). Cumulative 30-day survival was somewhat lower in patients with non-ARDS than in ARDS (58.1% vs 65.5%; $p = 0.029$) (**Fig. 3**). There were no significant differences in ICU mortality (89/241, 36.9%) in patients diagnosed with ARDS at study entry (241/333) compared with mortality (27/92, 29.3%) of patients in whom ARDS was diagnosed during their ICU stay (92/333) (ICU mortality difference, 7.6%; 95% CI, –3.98% to 17.99%) ($p = 0.195$).

Pneumonia and sepsis were the most common causes of ARDS (details in **Supplementary Results**, http://links.lww.com/CCX/A978) (**Tables S7** and **S8**, http://links.lww.com/CCX/A978). ICU mortality increased with severity defined by Pao_2/Fio_2 at time of ARDS diagnosis: mild 13.3% (95% CI, 3.8–30.7%), moderate 32.7% (95% CI, 26.1–39.7%), and severe 44.9% (95% CI, 35.2–54.8%) (Table S8, http://links.lww.com/CCX/A978). Patients without ARDS had higher VFDs than ARDS patients (12.2 ± 11.6 vs 9.3 ± 9.7 d; $p < 0.001$) (Table 1). In non-ARDS patients at study entry, ICU mortality varied with Pao_2/Fio_2 ratio (≤ 100 mm Hg [43/87, 49.4%]; Pao_2/Fio_2 101–200 mm Hg [161/474, 34.0%]; or Pao_2/Fio_2 201–300 mm Hg [118/347, 34.0%] [$p = 0.017$]). Presence of pulmonary infiltrates/opacities on chest imaging at study entry was not associated with outcome whether or not ARDS criteria were met (**Table S9**, http://links.lww.com/CCX/A978). The most frequent cause of death was multisystem organ failure, commonly associated with limitation of therapeutic efforts (**Table S10**, http://links.lww.com/CCX/A978).

DISCUSSION

The main findings of this epidemiological study are: 1) about 12% of ICU admissions and 25% of MV patients
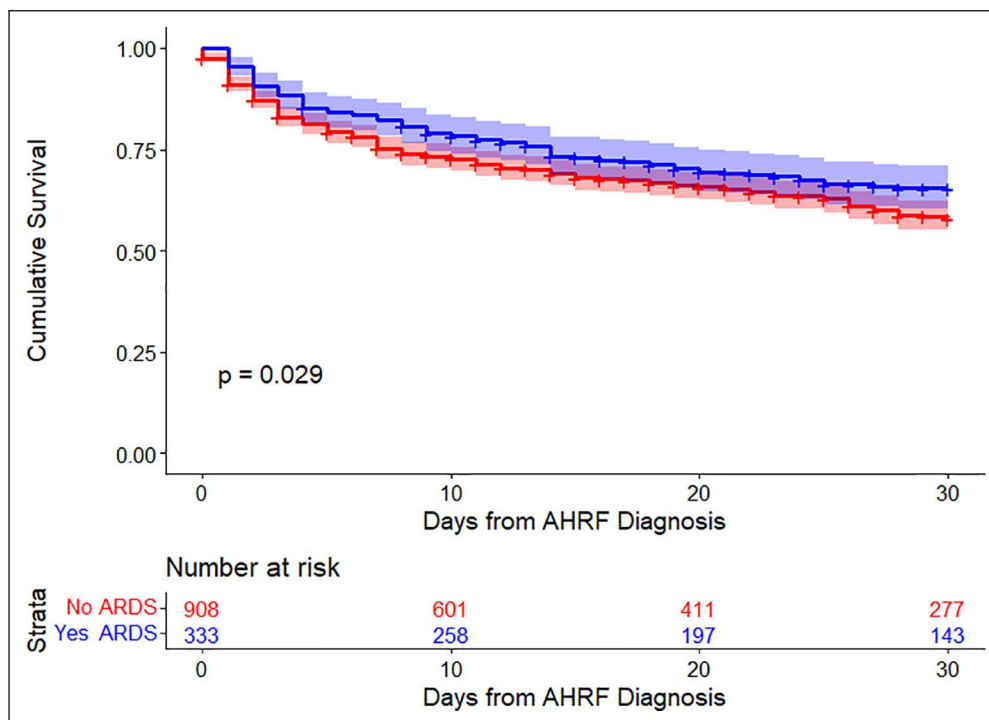
Figure 3. Probability of cumulative survival to day 30 (± 95% CI) in 1,241 patients with acute hypoxemic respiratory failure (AHRF) stratified by not having (n = 908) or having (n = 333) acute respiratory distress syndrome (ARDS).

possible reasons for this including the seasonality of data collection in LUNG-SAFE (only in winter), the experience of centers (expertise in data collection not required), and low adherence to lung-protective ventilation strategies (7). Another major reason is the different definitions for AHRF used in the two studies. The LUNG-SAFE study required the presence of new parenchymal abnormalities on chest imaging for diagnosis of AHRF, whereas our study did not mandate radiographic entry criteria. This would lead to a higher ARDS/AHRF ratio in the LUNG-SAFE study since their denominator was smaller and would

had AHRF; 2) there were almost three times as many patients without ARDS than those with ARDS; 3) all-cause ICU and hospital mortality were similar in both groups; and 4) the use of lung-protective ventilation was similarly applied in AHRF patients without or with ARDS. At the time this study was designed, the focus of lung-protective MV strategies was to target V_T, although recent data suggest that targeting driving pressure or mechanical power may be more effective in mechanically ventilated patients (29, 30).

Previous prospective observational studies in patients with acute respiratory failure (**Table S11**, http://links.lww.com/CCX/A978) had large variability in the definitions and in the description of baseline characteristics and had a lack of clinically relevant information on management and complications (5–8, 10–12, 19, 31–36) (Table S11, http://links.lww.com/CCX/A978). Our prevalence of ARDS (3% of ICU admissions and 7% of MV patients) was similar to that reported in other studies (5, 12, 33) but much lower than reported in the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG-SAFE) study (10% of ICU admissions, 23% of MV patients) using the same ARDS definition (7). There are a number of

likely lead to a lower percentage of non-ARDS patients because there were fewer patients in the numerator (see *Discussion* in Supplemental File, http://links.lww.com/CCX/A978). There are well-documented issues of clinicians' ability to recognize ARDS (7). We monitored this by contacting site investigators and through discussion in regular meetings after each study period. In order to avoid confirmation bias, we opted not to use the raw data in the case report form for ARDS identification.

We found that clinicians generally chose MV strategies compatible with lung-protective ventilation, independent of the reason for intubation and MV, perhaps because lung-protective ventilation has been shown to also be beneficial for patients with healthy lungs (37, 38). In our study, most patients with AHRF were ventilated according to the ARDS Network and international societies' criteria (24, 25). This differs from the LUNG-SAFE study in which more than half of patients did not receive proven or recommended approaches to lung-protective MV and adjunctive therapies (7).

There are a number of key findings in our study. First, about 25% of ventilated ICU patients had AHRF and only about a quarter of these patients had ARDS. Interestingly, all-cause mortality of patients with or

without ARDS was almost identical, despite a number of baseline demographic differences and diverse reasons for initiating MV. Other outcomes were different, with ARDS patients having longer duration of MV and ICU length of stay than non-ARDS patients. Our outcome data are in accord with Luhr et al (6) from 25 years ago, but their study differed in that they studied patients with acute respiratory failure, not just those with AHRF, and it was published before the modern era of lung-protective MV; thus, their patients were ventilated with higher V_T (applied as actual body weight) and much lower PEEP (Table S11, http://links.lww.com/CCX/A978). In a recent update of the LUNG-SAFE study (39), investigators reported that the overall hospital mortality of 4,499 mechanically ventilated patients with AHRF was 38.6%, but the definition of AHRF in that study excluded patients without parenchymal abnormalities.

Second, both ARDS and non-ARDS patients were ventilated with similar strategies (low V_T and low Pplat), suggesting that the diagnosis of ARDS does not affect the selection of specific ventilatory settings, despite the fact that there are very few specific RCTs aimed at non-ARDS patients (40). It is possible that clinicians opted for specific strategies for underlying physiologic reasons in non-ARDS patients or simply they opted to follow lung-protective ventilation strategies in the majority of patients with hypoxemia. There were differences in other interventions (recruitment maneuvers, prone position, neuromuscular blockade, noninvasive respiratory support prior to intubation) between groups. Although it is plausible that non-ARDS patients could benefit from some adjunctive therapies applied to ARDS patients, AHRF encompasses such a diversity of disorders that each requires specific or even personalized management.

Given the scarcity of studies addressing ventilatory strategies in non-ARDS patients, we suggest that the ICU community should increase research in those patients. We envision that in the future, there will be biomarkers in lung lavage, serum, expired gas or a combination, to better characterize and stratify AHRF patients, as well as to provide personalized therapy (41). In future studies, it would also be interesting to examine post-acute sequela and functional outcomes in survivors of mechanically ventilated non-ARDS AHRF patients (42).

Our study has several strengths. First, it is a prospective study addressing the national prevalence and outcome of AHRF patients during the lung-protective era. Second, it is comprehensive providing data on: 1) patients with and without ARDS; mild ARDS, moderate ARDS, and severe ARDS, 2) ventilatory management (V_T, PEEP, F_{IO_2}, Pplat, and use of adjunctive therapies), and 3) clinical outcomes (including pulmonary and systemic complications, ICU/hospital mortality, and causes of death). There are, however, some limitations. First, our findings may not be generalizable to all countries since local ICU policies and regional patient demographics would influence clinicians' performance. Encouragingly, a small pilot study conducted in Wales, employing the same methodology, found similar results (19). Second, this study focused on the acute phase of AHRF and data analysis was largely restricted to the first day of MV (as currently performed in most prevalence and outcome studies), although we did obtain outcome data until ICU/hospital discharge. Third, we only enrolled intubated and mechanically ventilated patients and excluded patients with hypoxemic respiratory failure treated with conventional oxygen therapy, high-flow nasal oxygen therapy, or noninvasive ventilation. We are confident, however, that no patients were excluded if they required intubation and MV during the study periods, despite being treated with noninvasive respiratory support prior to MV. Finally, we do not have detailed data on compliance by clinicians to lung-protective MV during the entire ICU stay, although our data on V_T, PEEP, and Pplat over the first 7 days of MV do not suggest that clinicians changed the practice of applying lung-protective MV from the time of intubation.

In summary, in this epidemiological study reporting adherence to lung-protective MV principles, we found that about 25% of mechanically ventilated patients had AHRF and about 75% of these patients did not have ARDS. Lung-protective ventilation was used in ARDS and non-ARDS patients, and overall mortality was essentially the same in both groups. Our data suggest that AHRF without ARDS is a common syndrome with a high mortality that requires specific studies into its epidemiology and ventilatory management.

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1 CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain.

2   Research Unit, Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Spain.

3   Li Ka Shing Knowledge Institute at St. Michael's Hospital, Toronto, ON, Canada.

4   Intensive Care Unit, Hospital Universitario Regional Carlos Haya, Málaga, Spain.

5   Intensive Care Unit, Hospital Universitario Virgen de Arrixaca, Murcia, Spain.

6   Intensive Care Unit, Hospital Universitario de A Coruña, La Coruña, Spain.

7   Intensive Care Unit, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain.

8   Intensive Care Unit, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain.

9   Intensive Care Unit, Hospital Universitario Río Hortega, Valladolid, Spain.

10 Intensive Care Unit, Complejo Hospitalario Universitario de Albacete, Albacete, Spain.

11 Intensive Care Unit, Hospital Universitario La Paz, IdiPaz, Madrid, Spain.

12 Intensive Care Unit, Hospital Universitario Puerta de Hierro, Madrid, Spain.

13 Department of Anesthesia, Hospital Universitario Ramón y Cajal, Madrid, Spain.

14 Intensive Care Unit, Complejo Asistencial Universitario de León, León, Spain.

15 Intensive Care Unit, Hospital Universitario N.S. de Candelaria, Santa Cruz de Tenerife, Spain.

16 Intensive Care Unit, Hospital Clínico Universitario de Valladolid, Valladolid, Spain.

17 Intensive Care Unit, Hospital Universitario Mutua Terrassa, Terrassa, Barcelona, Spain.

18 Surgical Intensive Care Unit, Department of Anesthesia, Hospital Clínico de Valencia, Valencia, Spain.

19 Department of Thoracic Surgery, Hospital Universitario Dr. Negrín, Las Palmas de Gran Canaria, Spain.

20 Intensive Care Medicine & Anaesthesia, Aneurin Bevan UHB, Newport, United Kingdom.

21 Department of Anaesthesia, Intensive Care and Pain Medicine, Cardiff University, Cardiff, United Kingdom.

22 Surgical Intensive Care Unit, Department of Anesthesia, Hospital Clinic, IDIBAPS, Barcelona, Spain.

23 Department of Respiratory Care, Massachusetts General Hospital, Boston, MA.

24 Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada.

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APPENDIX

All members of the PANDORA network are listed below: Hospital Universitario de La Paz, Paseo de la Castellana 261, 28046 Madrid, Spain: José M. Añón, Belén Civantos, Mónica Hernández; Hospital Virgen de La Luz, Hermanos Donantes de Sangre 1, 16002 Cuenca, Spain: Elena González, Rosario Solano; Complejo Asistencial Universitario de León, Altos de Nava s/n, 24001 León, Spain: F. Javier Díaz-Domínguez, Demetrio Carriedo, Raul I. González Luengo; Hospital Clínico Universitario de Valencia, Blasco Ibañez 17, 46010 Valencia, Spain: Carlos Ferrando, Blanca Arocas, Javier Belda, Marina Soro, Gerardo Aguilar, Ernesto Pastor; Hospital Universitario Río Hortega, Dulzaina 2, 47012 Valladolid, Spain: Lorena Fernández, Jesús Sánchez-Ballesteros, Arturo Muriel, Pablo Blanco-Schweizer, José Ángel de Ayala, Jesús Blanco, César Aldecoa, Alba Pérez, Jesús Rico-Feijoo; Hospital Clínico Universitario de Valladolid, Avda. Ramón y Cajal 3, 47003 Valladolid, Spain: Leonor Nogales, David Andaluz, Laura Parra; Hospital Universitario Virgen de Arrixaca, Ctra. Madrid-Cartagena s/n, 30120 El Palmar, Murcia, Spain: Juan A. Soler, Domingo Martínez, Ana M. del Saz-Ortiz; Hospital General Universitario de Ciudad Real, Obispo Rafael Torija s/n, 13005 Ciudad Real, Spain: Alfonso Ambrós, Ana Bueno-González, Carmen Hornos-López; Hospital Universitario NS de Candelaria, Ctra. del Rosario 145, 38010 Santa Cruz de Tenerife, Spain: Raquel Montiel, Dácil Parrilla, Eduardo Peinado; Hospital Universitario 12 de Octubre, Avda. de Córdoba s/n, 28041 Madrid, Spain: Isidro Prieto, Mario Chico; Hospital Universitario Puerta de Hierro, Manuel de Falla 1, 28222 Majadahonda, Madrid, Spain: Miguel A. Romera, Carlos Chamorro-Jambrina; Hospital Universitario Regional Carlos Haya, Carlos Haya s/n, 29010 Málaga, Spain: Juan M. Mora-Ordoñez, J. Francisco Martínez-Carmona, Álvaro Valverde-Montoro, Victoria Olea-Jiménez; Hospital NS del Prado, Ctra. Madrid Km 114, 45600 Talavera de la Reina, Toledo, Spain: Paco Alba, Ruth Corpas; Hospital Universitario de A Coruña, As Xubias 84, 15006 A Coruña, Spain: Fernando Mosteiro, Lidia Pita-García; Hospital El Bierzo, Médicos sin Fronteras 7, 24404 Ponferrada, León, Spain: Eleuterio Merayo, Chanel Martínez, Ángeles de Célis-Álvarez; Hospital La Mancha Centro, Avda. Constitución 3, 13600 Alcázar de San Juan, Ciudad Real, Spain: Carmen Martín-Delgado; Hospital Universitario Ramón y Cajal, Ctra. Colmenar Viejo Km 9.1, 28034 Madrid, Spain: Adrián Mira, Pilar Cobeta, David Pestaña; Hospital Universitario Mutua Terrassa, Plaça del Dr. Robert 5, 08221 Terrassa, Barcelona, Spain: María del Mar Fernández; Hospital Virgen de la Concha, Avda. Requejo 35, 49022 Zamora, Spain: Concepción Tarancón, Silvia Cortés-Díaz; Hospital Fundación Jiménez Díaz, Avda. Reyes Católicos 2, 28040 Madrid, Spain: Anxela Vidal, Denis Robaglia, César Pérez; Hospital Universitario de Albacete, Hermanos Falcó 37, 02006 Albacete, Spain: Isabel Murcia, Ángel E. Pereyra-Pache; Cardiff University, Cardiff CF14 4XN, United Kingdom: Tamas Szakmany; Hospital Universitario Dr. Negrín, Barranco de la Ballena s/n, 35019 Las Palmas de Gran Canaria, Spain: Jesús Villar, Rosa L. Fernández, Cristina Fernández, Pedro Rodríguez-Pérez, Jesús M. González-Martín; Massachusetts General Hospital, 55 Fruit St, Warren 1225, Boston, MA 01460: Robert M. Kacmarek (deceased); Li Ka Shing Knowledge Institute, St. Michael's Hospital, 2009 Victoria St, Toronto, ON M5B 1T8, Canada: Arthur S. Slutsky.