Respiratory Research

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A worldwide assessment of the mechanical ventilation in patients with acute exacerbations of chronic obstructive pulmonary disease. Analysis of the VENTILAGROUP over time. A retrospective, multicenter study

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Abstract

Background The trend over time and across different geographical areas of outcomes and management with noninvasive ventilation or invasive mechanical ventilation in patients admitted for acute exacerbations of chronic obstructive pulmonary disease and treated with ventilatory support is unknown. The purpose of this study was to describe outcomes and identify variables associated with survival for patients admitted to an intensive care unit (ICU) with acute exacerbation of chronic obstructive pulmonary disease [aeCOPD] who received noninvasive or invasive mechanical ventilation worldwide.

Methods Retrospective, multi-national, and multicenter studies, including four observational cohort studies, were carried out in 1998, 2004, 2010, and 2016 for the VENTILAGROUP following the same methodology.

Results A total of 1,848 patients from 1,253 ICUs in 38 countries admitted for aeCOPD and need of ventilatory support were identified in the four study cohorts and included in the study. The overall incidence of aeCOPD as a cause for ventilatory support at ICU admission significantly decreased over time and varied widely according to the gross national income. The mortality of patients admitted to ICU for aeCOPD and ventilatory support significantly decreased over time regardless of the geographical area and gross national income; however, there is a remarkable variability in ICU mortality according to geographical area and gross national income. The use of NPPV as the first attempt at ventilatory support has significantly increased over time, with a parallel reduction of invasive mechanical ventilation regardless of gross national income.

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Conclusion In this worldwide observational study, including four sequential cohorts of patients over 18 years from 1998 to 2016, the mortality of patients admitted to ICU for aeCOPD and ventilatory support significantly decreased regardless of the geographical area and gross national income. Future research will need to investigate the reason for the remarkable variability in ICU mortality according to the geographical area, gross national income, and methods to select patients for the appropriate ventilatory support.

Keywords Exacerbation, Chronic obstructive pulmonary disease, Mechanical ventilation, Mortality

Introduction

Chronic obstructive pulmonary disease [COPD] is a significant health burden worldwide and is currently the third leading cause of death worldwide, causing 3.23 million deaths in 2019 [1–3]. It is estimated to be the seventh and tenth leading cause of disability-adjusted life years in high-income and low- middle-income countries, respectively [4]. Globally, the COPD burden is projected to increase in the coming decades because of continued exposure to COPD risk factors and the aging of the population5.

Acute exacerbations of COPD [aeCOPD] are a major cause of morbidity and mortality, ranging between 8 to 26% in patients admitted to the intensive care unit [ICU] [4, 5]. 20% to 60% of these patients receive ventilatory support to decrease work of breathing and restore adequate gas exchange with noninvasive positive pressure ventilation [NPPV], which has been shown to reduce mortality [6] significantly and or the need for invasive mechanical ventilation [IMV].

Previous observational data have shown that among patients hospitalized for aeCOPD, the use of NPPV has increased significantly over time, and the need for IMV and in-hospital mortality has declined [7, 8]. Conversely, patients failing NPPV and transitioning to IMV have the highest in-hospital mortality and the most expensive and most extended hospitalizations [9, 10].

However, data on the use and clinical impact of NPPV and IMV in aeCOPD are from studies restricted to one country and over a short period [11–14], potentially precluding the global generalizability of the results. In addition, several aspects of the ventilatory management of critically ill patients have been shown to differ over time across ICUs and countries, leading to considerable clinical variability [15] and, therefore, raising the question of whether these differences impact patient outcomes around the world.

The International Study Group on Mechanical Ventilation [VENTILAGROUP] carried out a worldwide observational study to describe the clinical characteristics and outcomes of patients receiving IMV or NPPV in 1998, 2004, 2010, and 2016, using the same methodological approach in the four patient cohorts, which include patients with aeCOPD [16]. This is the only study that has investigated the potential change in the management and clinical outcomes of aeCOPD based on data from different countries worldwide over about two decades.

The objective of this study was to estimate whether mortality in patients with aeCOPD admitted to the ICU for respiratory support has changed over time across different countries and to identify factors associated with failure of NPPV and duration of IMV.

Methods

Database

The study design was a retrospective analysis of the observational study performed by the International Study Group on Mechanical Ventilation [VENTILAGROUP] [15]. The VENTILAGROUP performed a prospective, observational, and multi-national study every 6 years from 1998, 2004, 2010, and 2016, from a total of 1253 units in 38 countries following the same methodology for each of the four studies, which included all critically ill adults, in a 1-month period, who received at ICU admission IMV longer than 12 h or NPPV for more than 1 h. The local practice of the ICUs participating in the study decided to use NPPV and initiate IMV. All studies collected data on baseline characteristics [age, gender, and severity at admission]. National coordinators from the participating countries recruited local investigators from eligible ICUs (see the complete list of Investigators in the Electronic Supplementary Material). Only the research team members at each site knew the purpose and the precise timing of the study. Ethics Committees of each participating institution approved the protocol; according to local regulations, the investigator obtained a waiver of informed consent.

Definitions

The definition of aeCOPD was pre-defined as the worsening of dyspnea and cough and sputum in the previous 14 days [17] in patients with a previous diagnosis of COPD and development of acute respiratory failure treated with ventilatory support either in the modality of NPPV or IMV at ICU admission. Patients with a history of COPD but who did not have acute respiratory failure

due to their condition as the main reason for ICU admission were excluded.

We defined prolonged IMV as treatment with IMV for 14 days or longer [18], failure of NPPV as treatment with IMV after the delivery of respiratory support with noninvasive support [19], and lung protective ventilation strategy as tidal volume below 6 ml/kg predicted body weight or tidal volume below 8 ml/kg predicted body weight and plateau or peak inspiratory pressure less than 30 cm H2O [20].

Outcomes

The primary outcome was all-cause ICU mortality [21]. Prespecified secondary outcomes included ventilatory management during the first three days, failure of NPPV, complications during IMV up to a maximum of 28 days and only if they appeared 48 h after mechanical ventilation (barotrauma, acute respiratory distress syndrome (ARDS), ventilator-associated pneumonia (VAP), sepsis, cardiovascular dysfunction, acute renal failure, liver failure and coagulopathy), duration of ventilatory support, length of ICU stay, need of reintubation along the ICU stay, tracheotomy rate, hospital mortality and length of hospital stay.

For this study, the countries were grouped into six geographical regions: North America (Canada and the United States of America [USA], South America, Europe, Asia, Oceania (Australia and New Zealand), and Africa.

Individual countries were also classified into three income groups by their 2011 gross national income (GNI) per person, using thresholds defined by the World Bank Atlas method [22]: GNI less than US$4,045 as low and lower-middle income, $4,045–$12,535 as upper-middle income, and greater than $12,535 as high income, and then classified as follows: Low GNI countries: Bolivia, India, Morocco, Vietnam, Egypt, Tunisia; Lower-middle GNI countries: Argentina, Brazil, Mexico, Colombia, Ecuador, Guatemala, Peru, Venezuela, China, Turkey, Thailand; High GNI countries: USA, Canada, Australia, New Zealand, Spain, France, Germany, Greece, Italy, Chile, Korea, Portugal, Rusia, Uruguay, UK, Saudi Arabi, Ireland, Belgium, Denmark, Hungary, Netherlands, Panama, Poland, Puerto Rico.

Statistical analysis

The main objective of the analysis was to evaluate the inter-country variability over time of ICU mortality.

We summarized data with means and standard deviation (SD), medians and p25 and p75s, or numbers and percentages. Crude mortality rates are given as percentages with a Wald 95% confidence interval (CI). Single missing values were imputed by linear interpolation. When the first or last values are missing, carry the nearest value backward or forward.

We used the Kolmogorov–Smirnov test, histograms, and quantile–quantile plots to verify whether there were significant deviations from the normality assumption of continuous variables. We did different testing between groups with ANOVA, Kruskal–Wallis test, Student's t-test, Mann–Whitney test, χ. Test, or Fisher's exact test, as appropriate. The least significant difference testing procedure was used for pairwise comparisons.

ICU death was analyzed using multilevel logistic regression with three levels: patient, hospital, and country. We provide the results of fixed effects (measures of association) as odds ratios (OR) with their 95% CIs and the 80% interval OR. Random effects (measures of variation) measures included the variance and its standard error (SE), the proportional change in variance, and the median OR [23, 24]. We calculated the statistical significance of covariates with the Wald test.

The objectives of the analysis were to investigate the potential predictive model of three main outcomes: ICU mortality, failure of NPPV, and the need for prolonged IMV.

We performed logistic multivariable models to evaluate the prediction of failure of NPPV and ICU mortality. We evaluated the failure of NPPV only in those patients who received an initial attempt of ventilator support for a trial of NPPV at ICU admission. The variables included in this model were age, SAPS II, physiologic respiratory values (pH, $PaCO_2$, PaO_2/FiO_2 ratio), and development of cardiovascular failure on day 1, defined as an increase in Sequential Organ Failure Assessment (SOFA) score higher than 2 points [25]. The ICU mortality was analyzed in all patients and adjusted by prespecified covariates as follows: age, SAPS II, gas exchange parameters on day 1 of ventilatory support (pH, PaCO2, PaO2/FiO2 ratio), cardiovascular failure on day 1, use of lung protective ventilator strategy on day 1.

We defined the outcome of prolonged IMV in three categories: patients who do not die and have a duration of IMV of less than 14 days, patients who do not die and have a duration of IMV longer than 14 days, and patients who die before 14 days. For this outcome, we performed a multinomial logistic regression. The variables included in the model were age, SAPS II score, variables within the first 72 h at admission in the ICU (PaO_2/FiO_2 ratio, cardiovascular failure, protective ventilation, barotrauma, ARDS complication, and VAP on day 3), and initial treatment with IMV at ICU admission.

To characterize country-level variation and estimate country-specific rates of ICU mortality, we fitted a mixed-effects logistic regression with a random effect in

which the patients were nested in countries. If the patient was moved to an area with higher ICU mortality, we calculated the median odds ratio (MOR) to estimate the impact on the risk of death in the ICU [26, 27].

In all the models, we applied backward elimination of predictors from the full model with p-value < 0.05. We evaluated the discrimination of the model using the area under the curve (AUC). For the multinomial logistic model, we generate multiclass ROC curves for classification accuracy based on multinomial logistic regression using the "mlogitroc" command in Stata. We performed the analyses using Stata, version 17.0 (StataCorp LLC).

Results

Epidemiology of aeCOPD upon ICU admission

A total of 1848 patients from 1253 ICUs in 38 countries were included in the study, most commonly from Europe and South America (Table 1). This cohort represents 7% of 26,112 patients included in all four prospective cohorts from the 1998, 2004, 2010, and 2016 studies. The overall incidence of aeCOPD as a cause for artificial respiratory support at ICU admission significantly decreased over time. Figure 1 provides a graphical description of patients included in the different cohorts over time (in 1998, prevalence 10.0%, 95% confidence interval [95% CI] 9.2–10.8%; in 2004, 5.3%, 95% CI 4.7–6.0%; in 2010, 6.4%, 95% CI 5.8–6.9%; in 2016, 6.8%, 95% CI 6.3–7.4%, p < 0.001).

The incidence rates varied widely by GNI (Table 1). Indeed, the aeCOPD incidence rates were higher in ICUs from low-middle-income countries than in high-income countries (all p < 0·0001).

Table 1 shows the comparisons of baseline patient characteristics across cohorts. The age of critically ill patients admitted to ICU for aeCOPD significantly increased (p < 0.001) over time, and male is the most significant proportion found across the four sequential cohorts, with similar severity of illness at ICU admission based on SAPS II (p = 0.288). However, patients successfully treated with NPPV had a significantly lower SAPS II score at baseline compared with those who failed NPPV or those who initially received IMV (Table 2). There was a significantly higher proportion of males treated initially

Table 1 Descriptive baseline characteristics of included patients from VENTILAGROUP.,

Variable	1998 N = 522	2004 N = 267	2010 N = 524	2016 N = 535
Age, mean (SD), years	67 (10)	68 (11)	69 (11)	70 (11)
Sex, n (%)				
Male	341 (66)	169 (63)	347 (66)	339 (63)
Female	175 (34)	98 (37)	177 (34)	196 (36)
Geographical area, n (%)				
Africa	34 (6.5)	21 (8)	30 (5.7)	26 (5)
Asia	N/A	3 (1.1)	98 (18.7)	171 (32)
Australia & New Zealand	N/A	N/A	27 (5)	3 (1)
Europe	288 (55)	117 (44)	196 (37)	201 (38)
South America	74 (14)	49 (18)	88 (17)	118 (22)
USA & Canada	126 (24)	77 (29)	85 (16)	16 (3)
SAPS-II, mean (SD), points	40.83 (15)	40.80 (14)	42.43 (15.5)	41.06 (16)
Initial ventilatory support, n (%)				
Successful NPPV	63 (12)	78 (29)	188 (36)	213 (40)
Failure NPPV	22 (4)	27 (10)	59 (11)	59 (11)
Invasive mechanical Ventilation	437 (84)	162 (61)	277 (53)	263 (49)
Body mass index, mean (SD), kg/m^2	–	28 (8)	28.5 (10)	26 (8)
Arterial blood gas values at ICU admission				
pH, mean (SD)	7.38 (0.10)	7.33 (0.11)	7.30 (0.12)	7.33 (0.12)
$PaCO_2$, median [p25, p75], mmHg	53 [43–59]	56 [45–70]	60 [47–76]	53 [44–67]
Ratio PaO_2/FiO_2, median [p25, p75]	200 [156–249]	194 [149–280]	194 [140.5–262]	190 [131–284]
GNI, n (%)				
Low income	35 (7)	22 (8)	56 (11)	62 (11)
Low-medium income	63 (12)	40 (15)	120 (23)	250 (47)
High income	424 (81)	205 (77)	348 (66)	223 (42)

Abbreviations: N/A, no applicable; SAPS, Simplified Acute Physiology Score II, GNI, gross national income; SD standard deviation

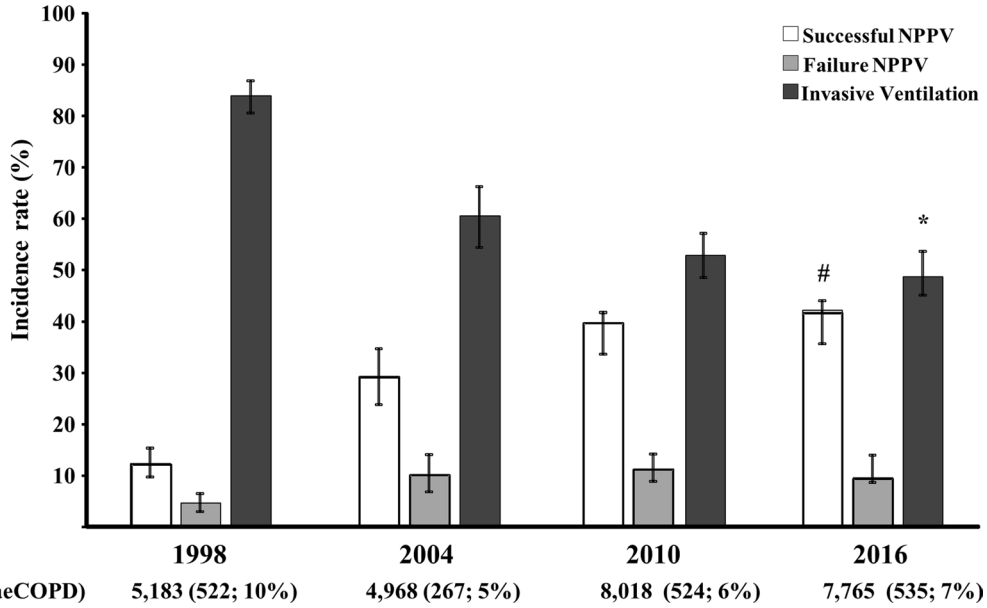

Fig. 1 Bar chart of the frequency (incidence rate) showing the first ventilatory support in aeCOPD critically ill patients at ICU admission over time. # $p < 0.001$ versus period 1998; *# $p < 0.001$ versus period 1998. Abbreviation: *NPPV*, noninvasive positive pressure ventilation (reference 28)

with IMV compared with patients who received NPPV, regardless of the year of study ($p < 0.05$).

Ventilatory management

Table 3 shows the changes in the management of ventilator support over time. The proportion of patients successfully treated with NPPV significantly increased over time, and in parallel, the proportion of patients who received IMV as initial treatment decreased ($p < 0.001$), regardless of the geographical area or the GNI of the index country. Assist-control ventilation was the most common ventilator modality on the first day in patients receiving IMV, but it significantly decreased over time ($p < 0.001$). Pressure-controlled ventilation (PCV) and synchronized intermittent mandatory ventilation plus pressure support ventilation mode (SIMV-PSV) remained the second and the third most used ventilatory modality, respectively, in the four sequential study cohorts ($p < 0.001$).

Figure 2 represents the arterial blood gas parameters during the first three days of ventilator support in all patients included in the study. There was no difference in pH, $PaCO_2$ or PaO_2/FiO_2 ratio between ventilatory support modalities. Ventilator management in aeCOPD patients did not vary during the first three days of invasive mechanical ventilation. In these patients, the median (p25, p75) tidal volume received was 7.3 mL/kg PBW (6.0, 8.8 mL/kg PBW), and the median (p25, p75) level of PEEP received was 5 cm H_2O (3, 6 cm H2O) (Table 3). The use of lung protective ventilatory strategy on the first day of invasive mechanical ventilation has significantly increased over time (38% in 1998, 51% in 2004, 53% in 2010, and 68% in 2016; $p < 0.001$). Continuous infusion of sedatives has significantly increased over time, and the administration of neuromuscular blockers in continuous infusion remained in less than 10% of the patients.

Outcomes

ICU and hospital mortality rates widely varied by geographical area (Table 4). Crude ICU and hospital mortality rates were higher in patients admitted to ICUs in upper-middle-income countries than to ICUs in low and lower-middle or high-income countries (all $p < 0.0001$). There is a relevant variability in mean ICU mortality of 20.7% (95% CI 12.0–30.6%) in all countries (Median Odds Ratio (MOR) 1.56 [95% CI 1.22; 1.90]).

Patients initially receiving NPPV had significantly lower hospital mortality than those initially treated with IMV (18% versus 35%, respectively; $p < 0.001$). Patients who failed NPPV as initial respiratory support developed a higher rate of complications during mechanical ventilation compared with patients who required IMV as initial treatment, including cardiovascular failure, sepsis, and renal failure, regardless of the year of study or the GNI of the index country ($p < 0.001$; interaction $p = 0.358$).

There is a progressively significantly higher proportion of patients over time classified as having simple weaning ($p < 0.001$). In contrast, over time, a progressively decreased number of patients reached the readiness for the liberation from IMV and were successfully extubated ($p = 0.016$, interaction $p = 0.024$), likely requiring

Table 2 Descriptive analysis according to ventilatory support including all patients during the four studies

Variable	1998 (N = 522)			2004 (N = 267)			2010 (N = 524)			2016 (N = 535)		
	Successful NPPV N = 63	Failure NPPV N = 22	Invasive Ventilation N = 437	Successful NPPV N = 78	Failure NPPV N = 27	Invasive Ventilation N = 162	Successful NPPV N = 188	Failure NPPV N = 59	Invasive Ventilation N = 277	Successful NPPV N = 213	Failure NPPV N = 59	Invasive Ventilation N = 263
Age, mean (SD), years	69 (10)	68 (7)	68 (11)	69 (11)	70 (9)	67 (11)	68 (11)	67 (10)	70 (11)	71 (11)	71 (11)	69 (12)
Sex, n (%)												
Male	40 (63.5)	15 (68)	286 (66)	51 (65)	17 (63)	101 (62)	116 (62)	34 (58)	197 (71)	125 (59)	36 (61)	178 (68)
Female	23 (36.5)	7 (32)	145 (34)	27 (35)	10 (37)	61 (38)	72 (38)	25 (42)	80 (29)	88 (41)	23 (39)	85 (32)
Geographical area, (%)												
Africa	6 (9.5)	N/A	28 (6)	9 (11.5)	3 (11)	9 (6)	13 (7)	8 (14)	9 (3)	12 (6)	6 (10)	8 (3)
Asia	N/A	N/A	N/A	N/A	N/A	3 (2)	23 (12)	9 (15)	66 (24)	63 (29)	15 (25)	93 (35)
Australia & New Zealand	N/A	N/A	N/A	N/A	N/A	N/A	16 (8.5)	2 (3)	9 (3)	1 (0.5)	1 (2)	1 (0.4)
Europe	41 (65)	18 (82)	229 (52)	42 (54)	13 (48)	62 (38)	79 (42)	24 (41)	93 (34)	95 (45)	21 (36)	85 (32)
South America	12 (19)	1 (4.5)	61 (14)	9 (11.5)	5 (18)	35 (22)	26 (14)	9 (15)	53 (19)	38 (18)	15 (25)	65 (25)
USA & Canada	4 (6)	3 (14)	119 (27)	18 (23)	6 (22)	53 (33)	31 (16.5)	7 (12)	47 (17)	4 (2)	1 (2)	11 (4)
SAPSII, mean (SD), points	38 (14)	40 (13)	44 (16)	37 (13)	39 (12)	43 (14)	36 (13)	43 (14)	47 (16)	37 (14)	37 (13)	45 (17)
BMI, mean (SD), kg/m^2	N/A	N/A	N/A	26 (6)	27 (8)	28 (8)	30 (10)	29 (8)	27 (9)	27 (8)	25 (6)	26 (8)
Arterial blood gas on day 1												
pH, mean (SD)	7.34 (0.08)	7.32 (0.12)	7.39 (0.09)	7.32 (0.08)	7.32 (0.12)	7.33 (0.11)	7.28 (0.09)	7.26 (0.10)	7.33 (0.13)	N/A	7.31 (0.12)	7.33 (0.12)
$PaCO_2$, median [p25, p75], mmHg	57.5 [53–74.5]	66.5 [53– 74]	50 [42–57]	65 [53–75]	62 [45–74]	52 [42–66]	70 [55–85]	68.5 [58–82.5]	52 [43–65]	N/A	55 [47–78]	52 [44–65]
PaO_2/FiO_2, median [p25, p75]	200 [166–222]	200 [171–278]	200 [153–252]	204 [157–260]	179 [153–304]	194 [143–299.5]	197 [147–232]	174 [101.5–218]	196 [140–289]	N/A	190 [133–290]	188 [130–280]

Abbreviations: NPPV; non-invasive positive pressure ventilation; SAPS, Simplified Acute Physiology Score; BMI, body mass index; SD, standard deviation

Table 3 Ventilatory parameters according to ventilatory support and year (TABLE 3) on day 1 of ventilator support

Variable	1998			2004			2010			2016			p-value between cohorts
	Failure NPPV N = 22	Invasive Ventilation N = 437	p-value	Failure NPPV N = 27	Invasive Ventilation N = 162	p-value	Failure NPPV N = 59	Invasive Ventilation N = 277	p-value	Failure NPPV N = 59	Invasive Ventilation N = 263	p-value	
Mechanical ventilation modalities, (%)			< 0.001			< 0.001			< 0.001			0.868	< 0.001
Assist-control	0	286 (73.5)		0	95 (58.6)		0	139 (50.2)		22 (37.3)	107 (40.7)		
Pressure support	0	18 (4.6)		0	5 (3.1)		0	17 (6.1)		4 (6.8)	17 (6.5)		
SIMV	0	21 (5.4)		0	3 (1.8)		0	15 (5.4)		1 (1.7)	15 (5.7)		
SIMV-PS	0	43 (11.1)		0	15 (9.3)		0	27 (9.7)		9 (15.2)	33 (12.5)		
PCV	0	16 (4.1)		0	14 (8.6)		0	46 (16.6)		11 (18.6)	41 (15.6)		
CVRP	0	0		0	8 (4.9)		0	15 (5.4)		3 (5.1)	14 (5.3)		
APRV/BIPAP	0	0		0	17 (10.5)		0	11 (4.0)		8 (13.6)	25 (9.5)		
Other Mode	0	5 (1.3)		0	3 (1.8)		0	3 (1.1)		0	1 (0.4)		
NPPV	21 (95.4)	0		27 (100)	2 (1.2)		59 (100)	0		0	0		
Missing	1 (4.6)	48 (11.0)		0	0		0	14 (1.4)		1 (1.7)	10 (3.8)		
Protective Ventilation, (%)			0.800			0.553			0.284			0.504	0.001
No	13 (59.1)	270 (61.8)		15 (55.6)	80 (49.4)		32 (54.2)	129 (46.6)		16 (27.1)	83 (31.6)		
Yes	9 (40.9)	167 (38.2)		12 (44.4)	82 (50.6)		27 (45.8)	148 (53.4)		43 (72.9)	180 (68.4)		
Sedation, (%)			0.125			0.036			0.475			0.414	< 0.001
No	12 (54.5)	167 (38.2)		17 (63.0)	67 (41.4)		18 (30.5)	98 (35.4)		11 (18.6)	62 (23.6)		
Yes	10 (45.5)	270 (61.8)		10 (37.0)	95 (58.6)		41 (69.5)	179 (64.6)		48 (81.4)	201 (76.4)		
Infusion of neuromuscular blockers (NMB), (%)			0.755			0.866			0.128			0.286	0.138
No	21 (95.5)	410 (93.8)		26 (96.3)	157 (96.9)		58 (98.3)	258 (93)		52 (88.1)	243 (92.4)		
Yes	1 (4.5)	27 (6)		1 (4)	5 (3)		1 (2)	19 (7)		7 (11.9)	20 (7.6)		
Ventilator parameters on day 1													
Tidal Volume, median [p25, p75], mL	585.7 [560, 600]	585.7 [500, 650]	0.506	500 [450, 550]	500 [450, 600]	0.491	495 [400, 550]	480 [406, 520.5]	0.987	430 [380, 480]	450 [400, 500]	0.018	0.590
Tidal volume, median [p25, p75], mL/kg PBW	8.2 [6.5, 9.3]	8.4 [6.9, 10.0]	0.407	7.4 [6.2, 8.7]	6.8 [5.8, 8.3]	0.264	6.3 [5.4, 8.1]	6.8 [5.8, 8.0]	0.571	6.4 [5.5, 7.5]	6.7 [5.6, 7.8]	0.508	0.502

Table 3 (continued)

Variable	1998			2004			2010			2016			p-value between cohorts
	Failure NPPV N = 22	Invasive Ventilation N = 437	p-value	Failure NPPV N = 27	Invasive Ventilation N = 162	p-value	Failure NPPV N = 59	Invasive Ventilation N = 277	p-value	Failure NPPV N = 59	Invasive Ventilation N = 263	p-value	
Applied PEEP, median [p25, p75], cm of water	3.6 [0, 5.0]	3.1 [0, 5.0]	0.315	5.0 [4.0, 6.0]	5.0 [5.0, 7.5]	0.334	5.0 [5.0, 8.0]	5.0 [5.0, 8.0]	0.245	6.0 [5.0, 8.0]	5.0 [5.0, 8.0]	0.065	0.183
Plateau pressure, median [p25, p75], cm of water	25.0 [21.9, 29.0]	21.9 [21.9, 21.9]	0.031	17.0 [14.0, 20.0]	22.0 [18.0, 26.0]	0.007	20.0 [18.5, 24.5]	20.0 [16.0, 24.0]	0.442	20.0 [15.0, 25.0]	20.0 [16.0, 25.0]	0.772	0.001
Driving pressure, median [p25, p75], cm of water	19.1 [19.1, 25.0]	19.1 [16.9, 21.9]	0.279	12.0 [10.0, 19.0]	17.0 [13.0, 21.0]	0.040	15.0 [13.0, 19.5]	13.0 [10.0, 19.0]	0.101	14.0 [10.0, 19.0]	14.0 [10.0, 19.0]	0.662	0.042

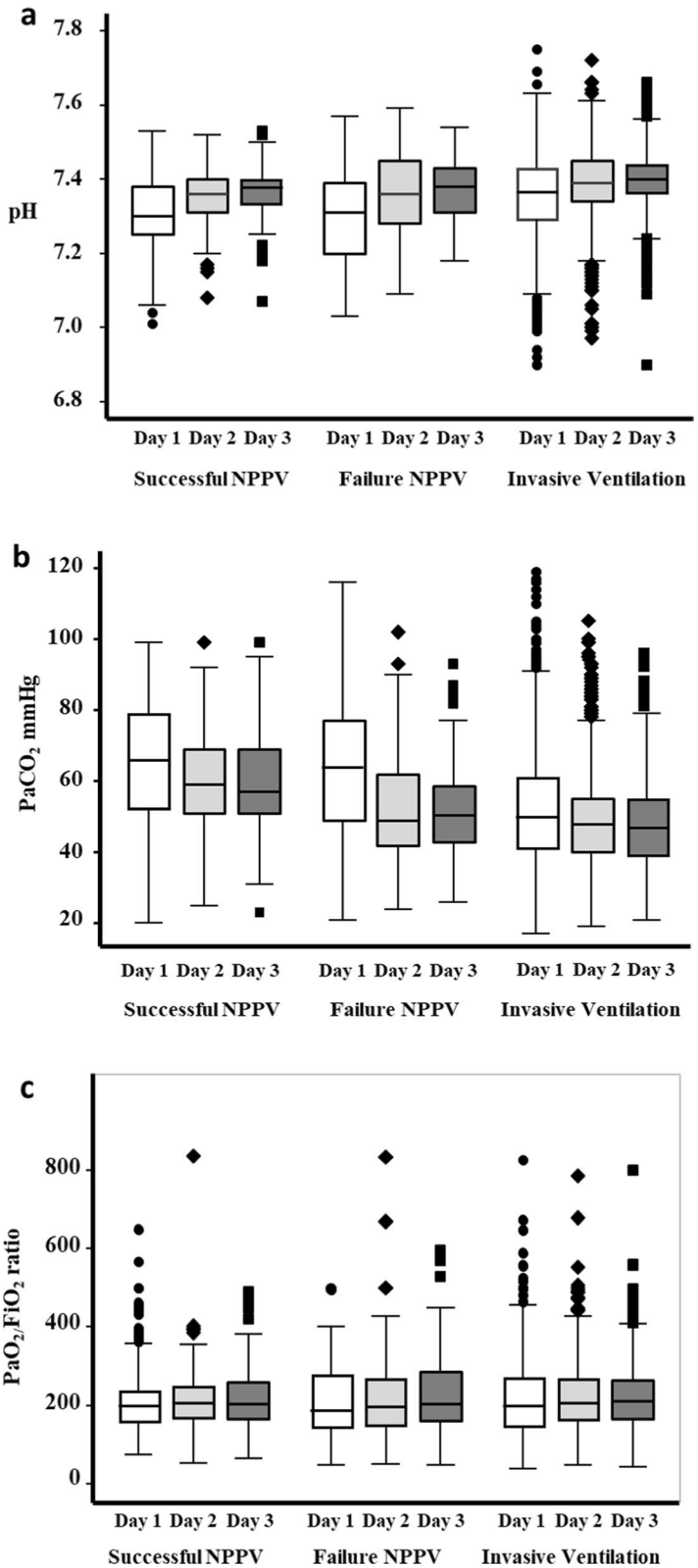

Fig. 2 Box plot panel describing the arterial blood gas parameters during the first days of ventilator support including all patients from the four studies: **a**, pH values; **b**, $PaCO_2$; **c**, PaO_2/FiO_2 ratio. In the box plot, the median (dark line inside the box), quartiles 1 and 3 (box edges), minimum and maximum (whisker ends), and outliers (points beyond 1.5 × IQR) are shown

Table 4 Complications and outcomes in COPD patients according to gross national income (GNI) and cohort

Variable	1998			2004			2010			2016		
	Low N = 35	Lower-middle N = 63	High N = 424	Low N = 22	Lower-middle N = 40	High N = 205	Low N = 56	Lower-middle N = 120	High N = 348	Low N = 62	Lower-middle N = 250	High N = 223
First Ventilation support, n (%)												
Successful NPPV	6 (17)	10 (16)	47 (11)	9 (41)	8 (20)	61 (30)	27 (48)	32 (27)	129 (37)	27 (43.5)	86 (34)	100 (45)
Failure NPPV	0	0	22 (5)	3 (14)	4 (10)	20 (10)	14 (25)	10 (8)	35 (10)	9 (14.5)	26 (10)	24 (11)
Mechanical Ventilation	29 (83)	53 (84)	355 (84)	10 (45.5)	28 (70)	124 (60)	15 (27)	78 (65)	184 (53)	26 (42)	138 (55)	99 (44)
Complications, n (%)												
Barotrauma	4 (11)	2 (3)	9 (2)	2 (9)	1 (2.5)	3 (1.5)	1 (2)	0	8 (2)	0	1 (0.4)	3 (1)
Ventilator-associated pneumonia	9 (26)	14 (22)	78 (18)	1 (4.5)	3 (7.5)	2 (1)	1 (2)	1 (1)	10 (3)	3 (5)	9 (4)	6 (3)
Sepsis	6 (17)	2 (3)	50 (12)	5 (23)	7 (17.5)	28 (14)	13 (23)	22 (18)	63 (18)	13 (21)	46 (18)	34 (15)
Acute respiratory distress syndrome	4 (11)	0	8 (2)	3 (14)	2 (5)	9 (4)	3 (5)	6 (5)	12 (3)	1 (2)	10 (4)	17 (8)
Cardiovascular failure	6 (17)	10 (16)	53 (12.5)	9 (41)	19 (47.5)	70 (34)	12 (21)	36 (30)	127 (36)	12 (19)	70 (28)	74 (33)
Renal failure	7 (20)	2 (3)	44 (10)	2 (9)	9 (22.5)	32 (16)	9 (16)	19 (16)	53 (15)	11 (18)	31 (12)	37 (17)
Hepatic failure	3 (9)	0	6 (1)	3 (14)	0	9 (4)	0	14 (12)	10 (3)	3 (5)	0	1 (0.4)
Coagulopathy	2 (6)	1 (2)	11 (3)	0	4 (10)	8 (4)	4 (7)	3 (2.5)	16 (5)	4 (6.5)	10 (4)	9 (4)
Clinical outcomes, n (%)												
Scheduled extubation, n (%)	13 (37)	41 (65)	258 (61)	5 (23)	22 (55)	93 (45)	21 (37.5)	45 (37.5)	131 (38)	16 (26)	94 (38)	78 (35)
Reintubation, n (%)	2 (15)	8 (19.5)	52 (20)	0	7 (32)	9 (10)	3 (14)	12 (27)	24 (18)	3 (19)	20 (21)	12 (15)
Tracheotomy post-extubation, n (%)	1 (8)	4 (10)	17 (7)	0	5 (23)	4 (4)	0	6 (13)	10 (8)	0	4 (4)	4 (5)
Use of NPPV postextubation, n (%)	N/A	N/A	N/A	2 (15)	1 (3)	15 (10)	4 (14)	18 (20)	26 (12)	10 (29)	36 (22)	31 (25)
Use of HFNC postextubation, n (%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3 (9)	5 (3)	7 (6)
Time to tracheotomy, days, median, [p25, p75]	10 [10–10]	7 [5–12]	12 [8–19]	N/A	13[11–21]	14[8–18]	N/A	16[12–23]	16[8–20]	N/A	15[11–19]	9[5–12]
Duration of mechanical ventilation												
Survivors, days, median, [p25, p75]	4 [3–6]	4 [3–6]	3 [2–5]	8 [7–12]	5[4–8]	5 [3–8]	5 [4–7]	5 [3–7]	4[3–6]	5 [3–9]	6[4–9]	5[3–7]
Nonsurvivors, days, median, [p25, p75]	7 [4–11]	4.5 [3–6]	5 [3–8]	7 [2–15]	8 [4–11]	6.5[3–11]	3 [2–7]	5 [3–11]	6 [3–12]	4 [2–9]	7 [4–14]	6 [3–10]
Prolonged ventilation, n (%)	1 (3)	2 (34)	17 (4.5)	4 (31)	5 (16)	18 (12.5)	2 (7)	16 (18)	22 (10)	4 (11)	24 (15)	12 (10)
ICU mortality, n (%)	16 (46)	12 (19)	88 (21)	8 (36)	11 (27.5)	36 (18)	11 (20)	35 (29)	64 (18)	6 (10)	46 (18)	39 (17.5)
Length of ICU stay												
Survivors, days, median [p25, p75]	9 [6–14]	7 [5–8]	8 [5–12]	11 [7–14]	7 [5–11]	7 [4–11]	7 [5–11]	7 [4–13]	6 [4–10]	6 [4.5–14]	8 [5–12]	7 [4–10]
NonSurvivors, days, median [p25, p75]	13 [7.5–21]	17.5 [5–27]	9 [5–17]	7 [2.5–20]	9 [4–22]	10 [6–19]	8 [3–21]	8[3–19]	9[5–19]	9 [3–17]	10 [6–17]	7[4–15]
Hospital mortality, n (%)	17 (49)	14 (24)	117 (29.5)	8 (44)	16 (41)	53 (26)	13 (23)	38 (34)	83 (24.5)	6 (10)	59 (26)	58 (27)
28-day mortality, N (%)	16 (46)	14 (22)	99 (23)	7 (32)	12 (30)	43 (21)	12 (21)	33 (27.5)	69 (20)	5 (8)	45 (18)	45 (20)

Table 4 (continued)

Variable	1998			2004			2010			2016		
	Low N = 35	Lower-middle N = 63	High N = 424	Low N = 22	Lower-middle N = 40	High N = 205	Low N = 56	Lower-middle N = 120	High N = 348	Low N = 62	Lower-middle N = 250	High N = 223
Length of hospital stay, days, median [p25, p75]	15[8–22]	13[10–24]	17[1–28]	15[9–20]	12[10–22]	17[10–27]	11[7–16]	15[8–29]	15[9–25]	11[7–21]	15[9–24]	15[8–26]

Abbreviations: NPPV, noninvasive positive pressure ventilation; HFNC, high flow oxygen nasal cannula

tracheostomy. The use of NPPV post-extubation significantly increased over time and reached up to 20% of extubated patients in 2016 ($p < 0.001$). Moreover, in the 2016 cohort, a high-flow nasal cannula was used in 8% (15/188) of extubated patients. The reintubation rate remained clinically constant regardless of the year of the study. The proportion of patients with prolonged IMV did not significantly change over time ($p = 0.790$, interaction $p = 0.206$), irrespective of the year of study or the GNI. There are no clinically significant differences in the length of ICU or hospital stays over time.

Prediction of clinical outcomes

The severity of illness and development of cardiovascular dysfunction on day 1 of ventilatory support were significantly associated with ICU mortality. The pH and PaCO2 values on day 1 of ventilatory support were associated with decreased mortality (area under the curve [AUC] 0.637 [95% CI 0.60–0.67]) (Fig. 2).

The only variable independently associated with NPPV failure, when adjusted for age, SAPS II, and gas exchange parameters (pH, $PaCO_2$, ratio PaO_2/FiO_2), was cardiovascular failure on day 1 of ventilatory support (Odds Ratio [OR] 2.81; 95% confidence interval (CI) 1.52, 5.19, $p = 0.001$) AUC 0.61; 95% CI 0.57; 0.65; Fig. 3). The predictors independently associated with prolonged IMV were severity of critical illness at ICU admission (SAPS II, relative risk ratio [RRR] 1.02; 95% CI 1.01, 1.03) and cardiovascular failure (RRR 1.48; 95% CI 1.11, 1.98; AUC = 0.64 [95% CI 0.60–0.67).

Discussion

The main results of this study are the following: the overall incidence of aeCOPD as a cause for ventilatory support as ICU admission significantly decreased over time; incidence of aeCOPD as cause for ventilatory support varied widely according to GNI, being higher in ICUs of low-middle income countries than in ICUs of high-income countries; mortality of aeCOPD patients admitted to ICU and ventilatory support significantly decreased over time regardless of geographical area and GNI; a remarkable variability in ICU mortality according to geographical location and GNI exists and changed over time. Our study shows a dramatic shift toward NPPV use for treating respiratory failure from aeCOPD overall. These findings were consistent with the results reported by investigators in smaller studies, describing increased use of NIPPV among their patients hospitalized with acute exacerbations. A variety of factors have likely contributed to this trend. First, since 1993, an extensive body of research has consistently reported that NPPV is efficacious in reducing the need for IMV and in-hospital mortality. Second, healthcare providers are becoming more confident with using NPPV, and even patients acutely decompensating with an acute exacerbation in the ICU should be given a trial of NIPPV first [28]. Last, unlike IMV, NPPV can be provided outside the ICU, which is advantageous because of the chronic shortage of ICU beds at many hospitals and different GNI countries. Some hospitals have, therefore, created special Respiratory High-dependency Care Units, commonly located next to the ICU, to facilitate NPPV use [29, 30] with different levels of care depending on the amount of resources, the severity of ARF and the complexity of interventions performed. The tremendous increase in NPPV use nationwide highlights the importance of training healthcare providers on the correct use of NPPV, which requires different expertise and equipment compared with traditional invasive mechanical ventilation.

Cardiovascular dysfunction diagnosed on day 1 of ventilatory support is independently associated with ICU mortality, failure of NPPV, and prolonged mechanical ventilation. Our findings are consistent with published research. Indeed, in a generalizable population of patients hospitalized with aeCOPD, acute heart failure was expected, and mortality was substantially higher [31]. The potential use of cardiac biomarkers such as NT-proBNP could play a role in screening for acute heart failure in aeCOPD. There is a clinical need for further research in this area, including the clinical impact of structured cardiovascular assessment with optimization of treatment in patients hospitalized with aeCOPD [30].

The use of NPPV as the first attempt of ventilatory support has significantly increased over time, with a parallel reduction of invasive mechanical ventilation regardless of GNI; patients who failed NPPV had worse clinical outcomes and a higher rate of complications during their ICU stay compared with those who were treated with invasive mechanical ventilation as the first strategy of ventilatory support.

To our knowledge, this is the first study describing the change over the span of 18 years in the outcome and management of critically ill patients with aeCOPD admitted to the ICU and treated with ventilatory support in different geographical areas worldwide. Our study is also the first to assess over-time trends in morbidity and mortality in critically ill patients with aeCOPD.

Our finding of improving prognosis over time concurs with the recently observed mortality reduction reported in stable patients with COPD [32, 33]. These outcomes may be due to improved outpatient inhaled medications, a focus on rehabilitation among severe COPD patients, and other interventions. These changes may have also affected the incidence of aeCOPD requiring ICU admission for ventilatory support.

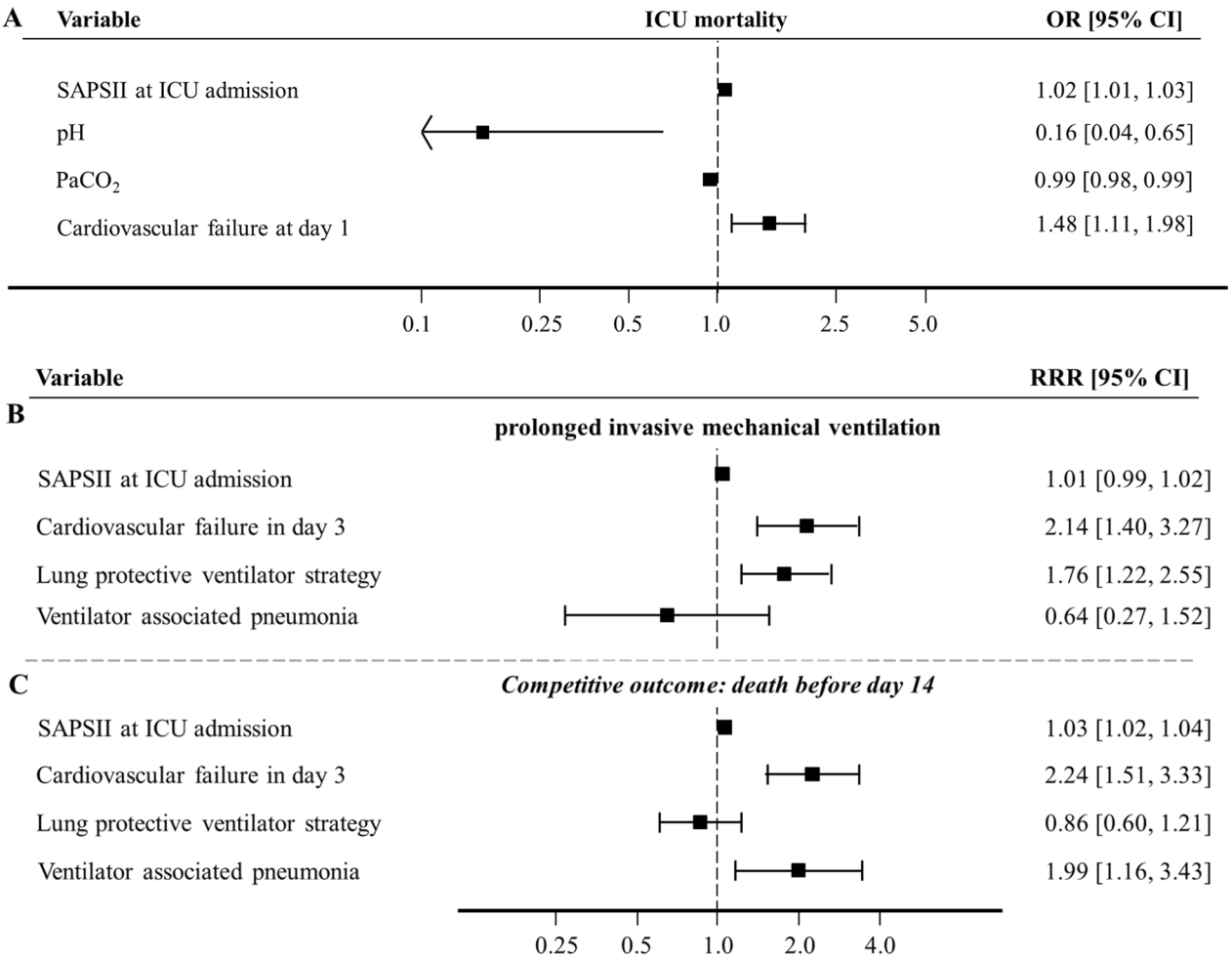

Fig. 3 Forest plot for the prediction of poor outcomes in aeCOPD patients. **A** ICU mortality; **B** prolonged invasive mechanical ventilation on day 3; **C** mortality in patients receiving invasive mechanical ventilation as competitive outcome for patients with prolonged invasive mechanical ventilacion (longer or equal to 14 days). Abbreviations: *SAPSII*: Simplified Acute Physiology Score. X-axes are represented in a logarithmic scale

Several longitudinal studies have demonstrated that COPD patients who require mechanical ventilation have an inferior prognosis. However, the mortality rates recorded over time in this study are at the lower end of the ranges quoted from previous studies, with ICU mortality reported between 6 and 28% [34–36] and hospital mortality ranging from 11 to 48% [37]. These findings are likely related to improved standards of acute in-patient COPD care in recent years and improved management of co-existing chronic illnesses. Notably, after adjustment for possible confounders in a multivariable analysis, there was a stepwise increase in the risk of ICU mortality according to decreasing GNI. Our study's hospital and ICU mortality compares favorably to the other studies reporting hospital and ICU mortality for this patient group. However, we have found a notable variability in mortality worldwide, meaning that, on average, the risk of dying in the ICU increases by 56% if a patient with aeCOPD moves randomly to an area with a higher risk.

Our study has similar findings to those reported by the observational study of Chandra et al. [8]. They described a progressive increase in the use of NPPV and a parallel decline in the initial use of IMV in patients with aeCOPD in the United States over the decade between 1998 and 2008. They also show a reduction in mortality in these patients over time. However, the study of Chandra et al. was limited to high-income countries, such as the United States, and over one decade. Our findings demonstrated that the trend of improvement in outcome occurred over time regardless of the geographical area and GNI, suggesting that the causes of these improvements may not be related to the applications of selected and technologically advanced treatment strategies. Our results confirmed the findings of Chandra et al. of significantly higher mortality in the group of aeCOPD that failed the

initial treatment with NPPV. In their study, Chandra et al. found that the mortality rate of this group of patients was increasing over time. However, in our study, the mortality rate of patients who failed NPPV increased in the study cohorts of 2004 compared to the one in 1998. Still, it progressively decreased afterward in the years 2010 and 2016 cohorts. Our study showed that cardiovascular dysfunction, defined as a worsening of the SOFA score by > 2 points on day 1 of ventilatory support, was independently associated with failure of NPPV and increased ICU mortality. Other observational studies showed that SAPSII was independently associated with NPPV failure in patients with aeCOPD [38]. These data suggest that the selection of patients for NPPV vs. IMV may be the cause of the increased mortality in patients failing NPPV, rather than end-of-life decisions or death before the start of mechanical ventilation.

We need to acknowledge several limitations of this study. The diagnosis of aeCOPD used in this study was based on previous history and clinical findings. Poor details on the etiology of COPD exacerbations and comorbidities were available and would have potentially improved the analysis of poor outcome prediction. In addition, the study of poor outcome prediction has been limited by the need for more data on patients' pulmonary function tests and end-of-life decision-making. Indications of NPPV and IMV have not been analyzed, as data on gas exchange before the start of ventilatory support in the ICU, pulmonary function test, and cause of exacerbation were not available. Furthermore, given the retrospective nature of this study, data collection was limited, and some unmeasured confounders were not included in our analysis.

Conclusions

aeCOPD remains a significant public health problem for the foreseeable future. Several clinical questions remain open regarding the weaning of patients with aeCOPD and the application of other interventions that may improve clinical outcomes. Patients with aeCOPD have an undeservedly negative reputation, and their critical care remains a challenging field of clinical research.

Abbreviations

aeCOPD	Acute exacerbations of chronic obstructive pulmonary disease
ARDS	Acute respiratory distress syndrome
AUC	Area under the curve.
BMI	Body mass index.
CI	Confidence interval.
COPD	Chronic obstructive pulmonary disease
HFNC	High flow nasal cannula
GNI	Gross national income
NPPV	Noninvasive positive pressure ventilation
ICU	Intensive care Unit
IMV	Invasive mechanical ventilation
MOR	Median odds ratio
OR	Odds ratio
PBW	Predicted body weight
PEEP	Positive end-expiratory pressure
SAPSII	Simplified Acute Physiology Score
SD	Standard deviation
SE	Standard error
SOFA	Sequential Organ Failure Assessment
VAP	Ventilator-associated pneumonia
USA	United States of A

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-024-03037-0.

Additional file 1.

Acknowledgements

The authors would like to thank the following local investigators for completing the VENTILAGROUP analysis listed in the supplementary material.

Author contributions

OP, FFV, LdCA, AM, and AE had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: OP, LdS, LMQ, AzA, FFV and AA. Acquisition, analysis, or interpretation of data: OP, LdCA, AM, NN, AT, BD, BP, FR, MCM, SM, KR, MG, AB, PA, NC, GYS, FA, MJ, DM, AzA, YS, AE, and LdS. Drafting of the manuscript: OP, LdS, LdCA, AE, and FFV. Critical revision of the manuscript for important intellectual content: OP, LdCA, AM, LMQ, AA, AzA, FFV, and LdS. Statistical analysis and data verification: OP, LdCA, AM, and FFV. Obtained funding: Not applicable. Administrative, technical, or material support: OP, LdCA, AM, FFV. Supervision: OP, LdS, AM, FFV, LdS, AE, and AzA. All authors read and approved the final manuscript.

Funding

No additional funding was received for this analysis.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to approval

The creation of the pooled database did not require additional ethical approval. The pooled studies had individual approval from the local Hospital Universitario de Getafe, Spain Institutional Review Board (PY16/14).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 15 August 2024 Accepted: 10 November 2024
Published online: 18 December 2024

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