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Original Article

Outcomes and predictors of mortality in patients with severe COVID-19 and COPD admitted to ICU: A multicenter study

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ABSTRACT

Background: High mortality rates among patients with chronic obstructive pulmonary disease (COPD) admitted to intensive care units (ICUs) during the COVID-19 pandemic highlight the need for tailored clinical management strategies.

Study Design and Methods: Epidemiological, clinical, and laboratory data were collected in REDCap for 6512 patients hospitalized with COVID-19 across 55 Spanish ICUs. Patients were stratified into three groups: those with COPD, those with other chronic respiratory diseases (CRD), and those without respiratory comorbidities (No CRD). The primary outcome was to determine clinical predictors for 90-day mortality, focusing on the COPD group. A propensity score matching (PSM) method was applied to analyze the effects of respiratory support, biomarkers, and immunomarkers.

Results: Patients with COPD (n = 328) exhibited a 50% mortality rate compared to 33% of those with other chronic respiratory diseases (CRD, n = 547), and those without respiratory comorbidities (No CRD, n = 5124). Among COPD patients, 95% of whom had Acute Respiratory Distress Syndrome (ARDS) due to COVID-19, the use of a high-flow nasal cannula (HFNC) was associated with reduced 90-day mortality (hazard ratio: 0.54 (95% Confidence Interval [0.31–0.95]). At a molecular scale, lower IgG levels but higher viral load and TNF-alpha, Vascular Cell Adhesion Molecule-1 (VCAM-1), and Fas Cell Surface Death Receptor (Fas) were associated with mortality in the COPD group.

Conclusions: In COPD patients with ARDS due to COVID-19, the use of HFNC was associated with a better prognosis. The dysregulation in biomarkers and immunomarkers in COPD patients and its association with mortality highlight the need for further targeted therapeutic strategies.

List of abbreviations: COPD, Chronic Obstructive Pulmonary Disease; CRD, Chronic Respiratory Disease; ARDS, Acute Respiratory Distress Syndrome; ICUs, Intensive care units; IMV, Invasive Mechanical Ventilation; NIMV, Non-Invasive Mechanical Ventilation; HFNC, High-flow nasal cannulas; CPAP, Primarily continuous positive airway pressure; BiPAP, Bilevel positive airway pressure; SOFA, Sequential Organ Assessment Failure Score; APACHE, Acute Physiology and Chronic Health disease Classification System; Ig, Immunoglobulin; ICAM-1, Intercellular Adhesion Molecule-1; Lipocalin-2, Neutrophil Gelatinase-Associated Lipocalin; MPO, Myeloperoxidase; VCAM-1, Vascular Cell Adhesion Molecule-1; D-dimer, Fibrin Degradation Product; RANTES, Regulated on Activation, Normal T Cell Expressed and Secreted; CD27, Cluster of Differentiation 27; Fas, Fas Cell Surface Death Receptor; SPD, Surfactant Protein D; TSG-14, Tumor Necrosis Factor-Stimulated Gene-14; IL-10, Interleukin-10; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; IL-7, Interleukin-7; CXCL-10, C-X-C Motif Chemokine Ligand 10; Angiopoietin-2, Angiopoietin-2; IL-1RA, Interleukin-1 Receptor Antagonist; IL-6, Interleukin-6; CCL2, C-C Motif Chemokine Ligand 2; IL-12p70, Interleukin-12p70; IL-2, Interleukin-2; IL-4, Interleukin-4; IL-15, Interleukin-15; Granzyme B, Granzyme B; IFN-gamma, Interferon-Gamma; TNF-alpha, Tumor Necrosis Factor-Alpha; Endothelin-1, Endothelin-1; Granzyme A, Granzyme A; IL-8, Interleukin-8; CTLA-4, Cytotoxic T-Lymphocyte Antigen-4; EGF, Epidermal Growth Factor; TREM-1, Triggering Receptor Expressed on Myeloid Cells-1; UPA-1, Urokinase-Type Plasminogen Activator 1; B7-H1, Programmed Death-Ligand 1; G-CSF, Granulocyte Colony-Stimulating Factor; IFN-beta, Interferon-Beta; IL-1b, Interleukin-1 Beta; HR, Hazard Ratio; CI, Confidence Interval; PSM, Propensity Score Matching.

1. Introduction

The mortality rate among patients admitted to intensive care units (ICUs) and those requiring mechanical ventilation during the coronavirus disease 2019 (COVID-19) pandemic has been particularly high, especially in those with several comorbidities or immunocompromised status [1–3].

In some series, the incidence of chronic obstructive pulmonary disease (COPD) among hospitalized COVID-19 cases was lower than expected [3,4]. Several factors could potentially account for the lower prevalence of severe COVID-19 cases in individuals with advanced COPD. These factors include their relative isolation from the general population, potential immunity acquired from previous viral infections [5], or the role of inhaled corticosteroids [6–9]. Nevertheless, extensive datasets have consistently identified chronic respiratory diseases, particularly COPD, as an independent predictor for adverse outcomes, such as hospitalization, ICU admission, and increased mortality [8,10,11].

Thus, to guide more personalized clinical management and improve prognosis, it is highly relevant to gain a comprehensive understanding of the clinical and biological factors contributing to the increased vulnerability and poorer outcomes of patients with COPD.

In patients with COPD and severe COVID-19, the primary objective of this study was to identify clinical predictors of 90-day mortality. The secondary objectives included the identification of predictors of 28-day mortality and the assessment of immune markers and biomarkers associated with 28-day and 90-day mortality. The investigation, conducted prospectively and in a multicentre manner, generated one of the largest observational cohorts of patients with confirmed SARS-COV-2 infection admitted to Spanish ICUs under the CIBERESUCICOVID project. The research provides a comprehensive analysis of COPD, encompassing both a non-COPD respiratory group and a non-respiratory group, emphasizing the heightened vulnerability of the COPD group. Considering that a high proportion of COPD patients presented with Acute Respiratory Distress Syndrome (ARDS) during COVID-19, our findings may be useful beyond the pandemic to inform tailored management of COPD with ARDS caused by severe viral infections.

2. Methods

2.1. Study design

This observational, multicentre study finds its roots in research undertaken with the CIBERESUCICOVID cohort. The CIBERESUCICOVID is a prospectively collected and retrospectively analyzed cohort study of patients with SARS-CoV-2 infection from across 55 Spanish ICUs [12].

The study received approval from the Institutional Internal Review Board (IIRB) and followed the Strengthening the Reporting of Observational Study in Epidemiology (STROBE) guidelines for observational studies [13].

Data from the CIBERESUCICOVID study were collected from February 6th, 2020, to July 6th, 2022, which included the enrolment of consecutive, ICU-admitted patients. We anonymized data and stored it *via* the REDCap electronic database.

2.2. Study population and data collection

Inclusion criteria were 18 years old, admission to ICU, and laboratory-confirmed SARS-CoV-2 infection (confirmed by a polymerase chain reaction (PCR) test). Exclusion criteria were non-confirmation of SARS-CoV-2 infection by PCR and no data either at baseline or hospital discharge.

We collected epidemiological data, including demographics, comorbidities, clinical symptoms, disease chronology, and treatment administered at hospital and ICU admission, at the start of invasive mechanical ventilation (IMV), 72–96 h after ICU admission, and at ICU and/or hospital discharge. Finally, mean forced expiratory volume in one second (FEV_1) was reported in 122 out of 328 (37%) patients with COPD before COVID-19 admission.

2.3. Definitions

We focused on three ICU groups: 1) COPD: patients who met diagnostic criteria for COPD (*i.e.*, persistent respiratory symptoms and limitations in airflow with a history of smoking, in accordance with the gold standard [2,6,14] CRD: patients with any other chronic respiratory disease (CRD) except for COPD (*i.e.*, asthma, non-cystic fibrosis bronchiectasis, cystic fibrosis, interstitial pulmonary disease, and other conditions); 3) No CRD: patients without any of the aforementioned respiratory comorbidities.

In addition, for the COPD population, patients were divided into two groups: 1) those who received IMV during their ICU stay and 2) those who never underwent IMV but did receive non-invasive respiratory support (NIRS). The group with NIRS included patients with conventional oxygen therapy (COT), high-flow oxygen cannulas (HFNC) and non-invasive mechanical ventilation (NIMV), primarily continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP).

We considered dysregulated host response and uncontrolled viral infection in those critically ill patients who presented at 24−48 h of ICU admission with comparatively higher levels of SARS-CoV-2 nucleocapsid 1 and 2 (N1, N2) RNA in plasma, a poor antibody response and tissue and endothelial damage as previously described [15].

Acute Respiratory Distress Syndrome (ARDS) was defined according to the Berlin definition, categorized as severe ($PaO_2/FiO_2 < 100$), moderate (PaO_2/FiO_2 100–200), Mild (PaO_2/FiO_2 200–300) or No ARDS ($PaO_2/FiO_2 > = 300$) [16]. Hypercapnia, normocapnia, and hypocapnia were defined as $PaCO_2 > 45$ mmHg, $PaCO_2$ 35−45 mmHg, and $PaCO_2 < 35$ mmHg, respectively. Severe, and moderate hypoxemia were defined as $PaO_2 < 60$, $PaO_2 = 60−80$, respectively.

2.4. Primary and secondary outcomes

The primary outcome was all-cause, 90-day mortality in the COPD population. Secondary outcomes included 28-day as well as biomarkers and immune markers associated with 28-day and 90-day mortality.

2.5. Biomarker profiling

For those patients with plasma samples collected during the first 24−48 h of ICU admission (n = 921, of which 45, 87, and 789 belonged to the COPD, CRD, and No CRD, respectively) we determined the levels of 36 immune and inflammatory biomarkers following methods previously described [17]. These 36 biomarkers are reported in the supplementary data. Additionally, we quantified SARS-CoV-2 N1, N2, and human ribonuclease P (RNAse P) RNAs in plasma (Bio-Rad SARS-CoV2 ddPCR Kit), as well as antibody concentration [15].

2.6. Statistical analyses

Descriptive statistics were used for basic features of study data, whilst appropriate statistical tests were performed to compare groups: COPD, CRD, and No CRD.

We assessed differences in 28-day and 90-day mortality among groups using the Kaplan-Meier method (Gehan-Breslow-Wilcoxon test). Moreover, associations with 28-day and 90-day mortality were also tested by multivariable analyses, using a Cox regression model stratified on the center variable. Then, to identify factors independently associated with 28-day and 90-day mortality in patients with COPD, we used a Cox regression multivariable model stratified on the center variable. In addition, effect modification by factors potentially associated with patient outcomes (*i.e.*, 28-day and 90-day mortality) and hypercapnia at ICU admission ($PaCO_2 > 45$ mmHg) was assessed by an interaction term. We additionally analyzed differences between HFNC, NIMV, and IMV for the mortality outcomes in patients with COPD using the propensity score matching (PSM) method [18], and obtained the balance among baseline variables between patients with HFNC and NIMV, between HFNC and IMV, and between NIMV and IMV (Table S10A, S11A, and S12A, respectively).

Moreover, we used a mixed-effects multivariable model [19] with centers as a random effect to identify factors independently associated with IMV in patients with COPD.

We used the multiple imputation method for missing data in the covariates of the multivariable analyses [20].

For the immune biomarkers differences between COPD, CRD, and No CRD, we used the PSM method [18] and obtained the balance among baseline variables between patients with COPD and those with CRD, and between COPD and No CRD (Fig. S1).

We conducted Spearman's rank correlation tests to evaluate the strength and direction of the association between biomarkers and mortality.

The level of significance was set at 0.05 (two-tailed) and was not adjusted for multiple comparisons. All statistical analyses were performed using IBM SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

We provided supplementary material containing detailed information about the conducted analyses.

3. Results

3.1. Demographics and clinical characteristics at ICU admission

Of 5999 patients included in the analysis, 875 (15%) had a history of respiratory comorbidities, with 328 (5%) having a history of COPD and 547 (9%) having other CRD without COPD. The remaining population (5124 patients, 85%) had no respiratory comorbidities, namely No CRD (Fig. 1). Table 1 presents the demographic and baseline characteristics at ICU admission of COPD, CRD, and No CRD groups. Compared to the CRD and No CRD cohorts, those with COPD were older; had a higher incidence of comorbidities, and presented more frequently hypercapnia. When solely compared to the No CRD cohort, those with COPD had higher APACHE and SOFA scores; required earlier ICU admission since symptom onset, received NIRS more often, and had higher coinfection rates at admission. Most of the patients regardless of the study group had ARDS (COPD-95%, CRD-98%, and No CRD-95%). However, the incidence of patients with severe ARDS was higher in COPD (45%) and CRD (47%) groups compared to No CRD (41%) (Table 1). A higher proportion of hypercapnic COPD received IMV (57%) compared to CRD (39%) and No CRD (44%). Compared to No CRD, COPD, in particular those with hypercapnia, received more frequently NIMV at admission (Table 1, Fig. 1).

In terms of laboratory findings, COPD presented higher creatinine levels, lower platelets count, and, compared to CRD, higher PCT (Table S1A). Laboratory findings and the FEV_1 values prior to ICU admission of the COPD-IMV compared to COPD-NIRS are shown in (Table S1B).

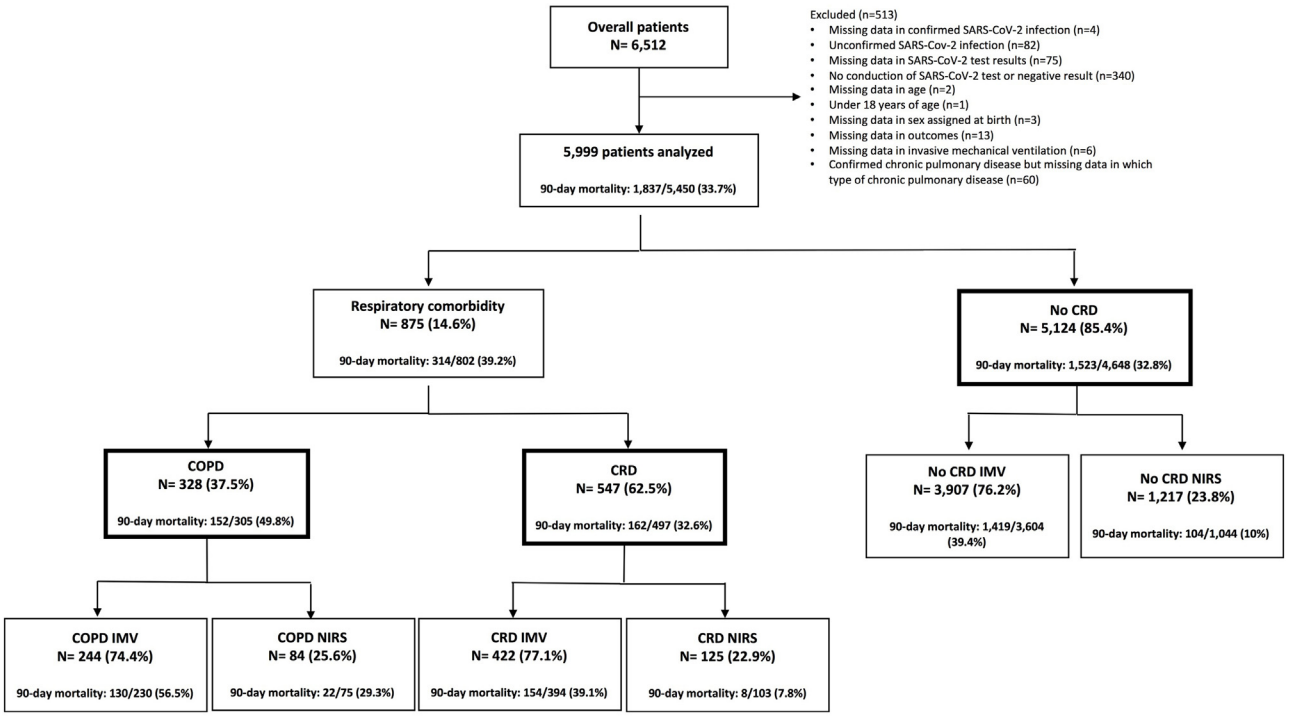

Fig. 1. Flow chart of patient screening and enrolment. The squares highlighted in bold represent the study population cohorts: COPD (n = 328), CRD (n = 547), and No CRD (n = 5124). Of the 5999 patients analyzed, 549 were lost to follow-up at 90 days. Abbreviations: CRD indicates chronic respiratory disease; COPD, chronic obstructive pulmonary disease; NIRS, non-invasive respiratory support. COPD IMV are patients with COPD who received invasive mechanical ventilation during hospitalization; COPD NIRS are patients with COPD who did not receive invasive respiratory support; however, they did receive high-flow oxygen cannulas, non-invasive ventilation, or continuous positive airway pressure (CPAP).

Table 1
Characteristics of the study population at ICU admission.

Variables	COPD (N = 328)	CRD (N = 547)	No CRD (N = 5124)	*p*-value
Age, median [Q1–Q3], years	69 [64–74]	62 [52–70]	63 [54–71]	<**0.001***†
≥60 years, n (%)	277 (84.5)	312 (57)	3120 (60.9)	<**0.001***†
Male sex, n (%)	283 (86.3)	324 (59.2)	3616 (70.6)	<**0.001***†‡
BMI, median [Q1–Q3], kg/m^2	29 [26.1–32.8]	30.4 [27–34.5]	28.7 [26–32]	<**0.001***†
Comorbidities, n (%)[a]				
Diabetes mellitus	125 (38.1)	138 (25.2)	1219 (23.8)	<**0.001***†
Hypertension	223 (68)	279 (51)	2508 (48.9)	<**0.001***†
Metabolic disease	104 (31.7)	155 (28.3)	1209 (23.6)	<**0.001**†‡
Metabolic syndrome (diabetes mellitus, hypertension and obesity)	44 (14.9)	57 (11.4)	383 (8.5)	<**0.001**†
Chronic liver disease	17 (5.2)	21 (3.8)	174 (3.4)	0.218
Chronic heart disease	90 (27.4)	85 (15.5)	588 (11.5)	<**0.001***†‡
Chronic renal failure	47 (14.3)	54 (9.9)	328 (6.4)	<**0.001**†‡
Immunosuppression	19 (5.8)	37 (6.8)	200 (3.9)	**0.003**‡
Chronic respiratory disease				
COPD	328 (100)	0 (0)	0 (0)	<**0.001***†
Asthma	22 (6.7)	337 (61.6)	0 (0)	<**0.001***†‡
Bronchiectasis	6 (1.8)	19 (3.5)	0 (0)	<**0.001**†‡
Interstitial lung disease	5 (1.5)	23 (4.2)	0 (0)	<**0.001***†‡
Sleep apnoea	14 (4.3)	40 (7.3)	0 (0)	<**0.001**†‡
Others	1 (0.3)	19 (3.5)	0 (0)	<**0.001**†‡
Toxic habits, n (%)				<**0.001**
No smoke	60 (18.9)	313 (62.9)	3136 (66.4)	<**0.001***†
Current smoking	40 (12.6)	22 (4.4)	270 (5.7)	<**0.001***†
Former smoking	218 (68.6)	163 (32.7)	1315 (27.9)	<**0.001***†
Alcohol abuse (current or former)	36 (11.8)	21 (4.3)	233 (5)	<**0.001***†
Days since initial symptoms, median [Q1–Q3]	8 [6–11]	9 [6–12]	9 [7–12]	**0.004**†
Confirmed bacterial coinfection, n (%)	15 (5.5)	14 (3.2)	95 (2.2)	**0.002**†
Treatment before admission, n (%)				
Angiotensin-converting enzyme inhibitor	87 (39.4)	97 (35.3)	962 (39)	0.479
Antibiotic therapy	40 (12.4)	104 (19.1)	643 (12.6)	<**0.001**†‡
Steroids (inhaled)	34 (10.6)	94 (17.2)	344 (6.8)	<**0.001***†‡
Statin	171 (52.6)	186 (34.1)	1501 (29.5)	<**0.001***†
Non-steroidal anti-inflammatory drug	70 (21.7)	84 (15.6)	566 (11.2)	<**0.001**†‡
Characteristics, median [Q1–Q3]				
Glasgow Coma Scale,	15 [15–15]	15 [15–15]	15 [15–15]	0.180
APACHE-II score	13 [10–17]	12 [9–16]	11 [9–15]	**0.001**†
SOFA score	5 [4–8]	5 [4–8]	5 [3–7]	**0.003**†
Temperature, ºC	36.7 [36–37.4]	36.8 [36–37.5]	36.8 [36–37.5]	0.580
Respiratory rate, bpm	25 [21–30]	25 [22–32]	25 [21–30]	0.188
Arterial blood gases, median [Q1–Q3]				
PaO_2/FiO_2	107.1 [80–155.6]	104.8 [75–156]	113.3 [80.6–165]	**0.010**‡
PaO_2/FiO_2 < 100 (severe ARDS)	131 (45.2)	224 (46.8)	1768 (40.9)	**0.022**‡
PaO_2/FiO_2 100–200 (moderate ARDS)	117 (40.3)	199 (41.5)	1834 (42.6)	0.708
PaO_2/FiO_2 200–300 (mild ARDS)	28 (9.7)	43 (9.0)	508 (11.8)	0.116
PaO_2/FiO_2 ≥ 300 (No ARDS)	14 (4.8)	13 (2.7)	204 (4.7)	0.128
PaO_2/FiO_2 ratio in ventilated patients	105.3 [79.6–153.3]	102 [74.5–149.1]	112.2 [80–162.5]	**0.005**‡
$PaCO_2$, mmHg	41 [34.5–49.2]	39 [34.1–45.9]	39 [33.8–46.8]	**0.014**†
Hypercapnia ($PaCO_2$ > 45 mmHg), n (%)	129 (39.3)	171 (31.3)	1633 (31.9)	**0.001***†
Hypercapnia ($PaCO_2$ > 45 mmHg) in ventilated patients, n (%)	127 (40.4)	160 (31.1)	1555 (32.8)	**0.013***†
HFNC[b]	20 (21.5)	25 (18.4)	224 (15.5)	0.227
NIMV[b]	12 (22.6)	10 (16.9)	107 (20.3)	0.745
IMV[b]	95 (56.5)	125 (39.2)	1224 (44.3)	**0.001***†
Respiratory support, n (%)[b]				**0.002**
COT	13 (4)	31 (5.7)	376 (7.4)	**0.030**
HFNC	93 (28.4)	136 (25)	1448 (28.3)	0.248
NIMV	53 (16.2)	59 (10.8)	526 (10.3)	**0.003**†
IMV	168 (51.4)	319 (58.5)	2764 (54)	0.075

Abbreviations: COPD indicates chronic obstructive pulmonary disease; CRD, chronic respiratory disease; ICU, intensive care unit; Q1, first quartile; Q3, third quartile; BMI, body mass index; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; COT, conventional oxygen therapy; HFNC, high-flow nasal cannula; NIMV, non-invasive mechanical ventilation; IMV, invasive mechanical ventilation. Percentages calculated on non-missing data. P-values marked in bold indicate numbers that are statistically significant on the 95% confidence limit.

* $P < 0.05$ for comparison between the COPD and CRD cohorts.

† $P < 0.05$ for comparison between the COPD and No CRD cohorts.

‡ $P < 0.05$ for comparison between the CRD and No CRD cohorts.

[a] Possibly >1 comorbidity.

[b] Possibly >1 respiratory support.

3.2. Complications, treatments, and outcomes

Of note, COPD patients exhibited a higher incidence of bacterial pneumonia compared to CRD and No CRD. Particularly, among those COPD with a history of prior corticosteroid use or previous coinfections (Table 2), even though the CRD group had a higher previous intake of corticosteroids and antimicrobials (Table 1).

In-hospital, 28-day and 90-day mortality was higher in patients with COPD (47%–50%) than in CRD (30%–33%) and No CRD (30%–33%) patients, respectively (Table 2). The Kaplan-Meier curves show that patients with COPD (compared to the CRD and No CRD cohorts [Fig. 2A]) and patients with COPD-IMV (compared to those with COPD-NIRS [Fig. 2B]) had a higher likelihood of 90-day mortality ($p < 0.001$) and worse outcomes (Table S2A). The mortality of the COPD cohort clustered by the severity of ARDS, hypercapnia, or hypoxemia, and the respiratory support is reported in Table S2B. Overall, the main causes of death were respiratory failure (45%), multiorgan failure (38%), and septic shock (7%) (data not shown).

In the multivariable analyses (Table S3), several variables were independently associated with 28-day and 90-day mortality, showing that COPD is associated with increased mortality.

3.3. Biomarkers among groups

After we matched the populations (n = 225 of which, 45, 45 and 135 belonged to COPD, CRD, and No CRD, respectively), the COPD group presented significantly lower IgM and IgG compared to the No CRD group. Furthermore, COPD compared to CRD had significantly higher levels of TNF-alpha, VCAM-1, and Fas at ICU admission (Fig. S2, Table S4A). COPD-IMV compared to COPD-NIRS

Table 2
Complications and treatments during hospitalization and outcome variables.

Variables	COPD (N = 328)	CRD (N = 547)	No CRD (N = 5124)	*p*-value
Complications, n (%)				
Nosocomial pneumonia[a]	95 (30.6)	112 (21.9)	1093 (22.9)	**0.006***†
Hospital-acquired pneumonia (HAP)	20 (6.5)	20 (3.9)	170 (3.6)	**0.034***†
Ventilator-associated pneumonia (VAP)	75 (24.2)	92 (18)	923 (19.4)	0.078
Microbiologically confirmed HAP/VAP[b]	85 (26.2)	116 (21.3)	1132 (22.2)	0.211
Previous inhaled steroids	12 (37.5)	17 (19.5)	63 (19.2)	0.050
Previous antibiotic therapy	13 (21.3)	14 (18.2)	103 (19.6)	0.900
Steroids during hospital stay	91 (34.1)	107 (23.9)	993 (24.7)	**0.002***†
Tocilizumab during hospital stay	37 (33.3)	36 (18.8)	377 (19.5)	**0.002***†
With previous bacterial coinfection	2 (22.2)	1 (11.1)	1 (2.5)	0.093
Previous inhaled steroids	4 (40)	2 (22.2)	4 (5.1)	**0.001**†
Previous antibiotic therapy	12 (37.5)	17 (19.5)	63 (19.2)	0.050
Heart failure	14 (4.3)	3 (0.5)	54 (1.1)	<**0.001***†
Cardiac ischemia	15 (4.6)	7 (1.3)	93 (1.8)	**0.001***†
Anaemia[c]	228 (69.5)	357 (65.3)	3192 (62.4)	**0.018**†
Acute renal failure[d]	155 (47.3)	173 (31.6)	1665 (32.5)	<**0.001***†
Hyperglycaemia	269 (82.3)	433 (79.2)	3774 (73.8)	<**0.001**†‡
Haemorrhage	41 (12.5)	45 (8.2)	374 (7.3)	**0.003**†
Treatment during hospitalization, n (%)				
Remdesivir	41 (12.5)	83 (15.2)	733 (14.4)	0.541
Corticoids	281 (86.5)	479 (87.9)	4317 (85.5)	0.302
Tocilizumab	117 (35.8)	205 (37.6)	2079 (40.9)	0.073
Outcomes, n (%)				
28-day mortality	117 (36.8)	120 (23.3)	1073 (22.3)	<**0.001***†
In-hospital mortality	154 (47)	165 (30.2)	1518 (29.6)	<**0.001***†
90-day mortality[e]	152 (49.8)	162 (32.6)	1523 (32.8)	<**0.001***†
LOS in ICU, median [Q1–Q3], days	14 [7–29]	13 [7–26]	14 [7–28]	0.796
Surviving patients	18 [7–37]	12.5 [7–26]	13 [7–28]	**0.029***†
LOS, median [Q1-Q3], days	24 [13–43]	24 [14–38]	24 [15–40]	0.891
Surviving patients	34.5 [20–56]	27 [16–41]	25 [16–44.5]	<**0.001***†
Ventilator-free days, median [Q1–Q3]	0 [0–1]	0 [0–16]	0 [0–16]	<**0.001***†
IMV	244 (74.4)	422 (77.1)	3907 (76.2)	0.648
IMV length, median [Q1–Q3][f]	17 [8–30]	14 [8–25]	15 [8–27]	0.353
Surviving patients	23.5 [11–38]	13 [8–25]	14 [8–27]	<**0.001***†
ICU-free days, median [Q1–Q3]	0 [0–11.5]	4 [0–19]	3 [0–19]	<**0.001***†
Tracheostomy	104 (31.7)	151 (27.7)	1540 (30.1)	0.384
Reintubation[g]	8 (5.4)	21 (8.4)	238 (10)	0.141
ECMO support	4 (1.2)	16 (2.9)	140 (2.7)	0.238

Abbreviations: COPD indicates chronic obstructive pulmonary disease; CRD, chronic respiratory disease; ICU, intensive care unit; Q1, first quartile; Q3, third quartile; ECMO, extracorporeal membrane oxygenation; LOS, length of stay; IMV, invasive mechanical ventilation. Percentages calculated on non-missing data. Other non-significant complications were (average, %): Pneumothorax (8%), pleural effusion (11%), Organizing pneumonia (5%), Tracheobronchitis (1%), Pulmonary embolism (8%), Septic shock[c] (7%), Bacteraemia (25%), Delirium (20%), Coagulation disorder[d], (31%, Disseminated intravascular coagulation 40%), Liver dysfunction (32%). P-values marked in bold indicate numbers that are statistically significant on the 95% confidence limit.

* $P < 0.05$ for comparison between the COPD and CRD cohorts.

† $P < 0.05$ for comparison between the COPD and No CRD cohorts.

‡ $P < 0.05$ for comparison between the groups CRD and No CRD cohorts.

[a] Clinically or radiologically diagnosed bacterial pneumonia managed with antimicrobials. Bacteriological confirmation was not required.

[b] Microbiologically confirmed pneumonia was defined as clinically or radiologically diagnosed bacterial pneumonia managed with antimicrobials with a positive culture of pathogenic germs in respiratory secretion samples.

[c] Haemoglobin consistently below 120 g/L for non-pregnant women and 130 g/L for men.

[d] Acute renal injury was defined as either an increase in serum creatinine by ≥0.3 mg/dL within 48 h or an increase in serum creatinine to ≥1.5 times that at baseline.

[e] Calculated only for patients with 90-day follow-up (305 in the COPD cohort, 497 in the CRD cohort, and 4648 in the NO CRD cohort).

[f] Duration of invasive mechanical ventilation was measured from initiation of ventilation until either successful extubation, successful permanent disconnection, or death.

[g] Reintubation due to extubation failure.

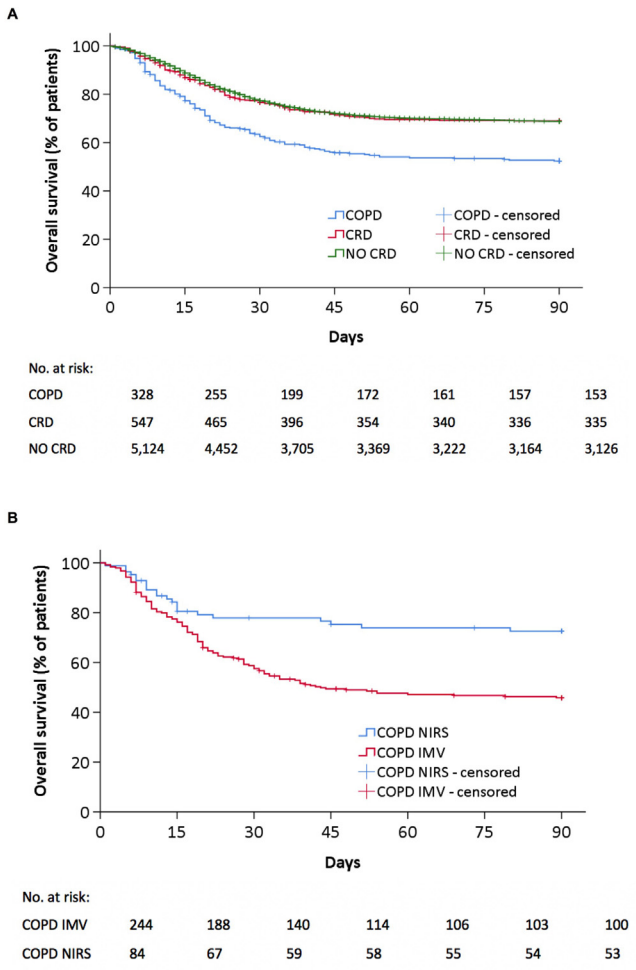

Fig. 2. Kaplan-Meier analysis of 90-day mortality among the different population cohorts. A) In the total population, separated by COPD (n = 328), CRD (n = 547), and No CRD (n = 5124) cohorts. Gehan-Breslow-Wilcoxon test indicated a significant difference among the three cohorts ($P < 0.001$). $P < 0.05$ for comparison between the COPD and CRD cohorts; $P < 0.05$ for comparison between the COPD and No CRD cohorts; $P = 0.706$ for comparison between the CRD and No CRD cohorts. B) In the COPD population, separated by the IMV and NIRS groups. Gehan-Breslow-Wilcoxon test indicated a significant difference between the two cohorts ($P = 0.001$). Abbreviations: COPD indicates chronic obstructive pulmonary disease; CRD, chronic respiratory disease; IMV, invasive mechanical ventilation; NIRS, non-invasive respiratory support.

presented higher levels of CXCL10, Angiopoietin-2, and IL-12p70 (Table S4B).

3.4. Biomarkers associated with mortality

Significant positive correlation with 28-days mortality in the COPD group was found for the following immunomarkers and biomarkers: SARS-CoV-2 plasma viral load, VCAM, endothelin-1, IL-8, Fas and TNF-alpha, being these last two also associated with 90-days mortality (Figure S3, Table S5). In contrast, IgG levels were negatively correlated with 28-days mortality in the COPD population (r = −0.303, $p = 0.043$) without statistical significance with 90-days mortality (r = −0.243, $p = 0.107$).

For the CRD population, IL-8 and CTLA-4 were associated with 28-day mortality and only CTLA-4 with 90-day mortality. For the No CRD group, SARS-CoV-2 plasma load, and endothelin-1 were associated with 28-day mortality, and SARS-CoV-2 plasma load, endothelin-1, and IL-8 with 90-day mortality (Figs. S4 and S5, Tables S6 and S7).

3.5. Clinical predictors for mortality

The 90-day mortality multivariable analysis of patients with COPD showed that creatinine levels, SOFA score, and the need for IMV were associated with an increased risk of death (37%, 7%, and 196%, respectively). In contrast, HFNC use was associated with a reduced risk of death (46%), an association not found for NIMV (Table 3). The same clinical predictors were associated with 28-day mortality (Table 3). To examine risks for particular types of patients, we explored effect modification by HFNC, NIVM, or IMV and hypercapnia at ICU admission, and no significant effects were found for the interaction terms (Tables S8A, S8B, S8C, S8D, S8E, and S8F).

3.6. Clinical predictors for IMV

A 4% rise in the odds of IMV need in the multivariable analysis of patients with COPD was found for a ten-unit increase in C-reactive protein at ICU admission (Table S9).

Propensity score matching analyses for the outcomes in COPD patients receiving HFNC *vs.* NIMV, HFNC *vs.* IMV, or NIMV *vs.* IMV are included in the Supplementary material (before matching: Table S10B, S11B, and S12B, respectively). After matching, statistically significant differences indicated increased mortality for IMV compared to HFNC (Table S11C) and compared to NIMV (Table S12C), but not comparing HFNC *vs.* NIMV (Table S10C).

4. Discussion

Our study is based on one of the largest datasets of critically ill COVID-19 patients in Spain - the CIBERESUCICOVID [12]. Among our patient population, we observed a low prevalence of COPD in the ICU (5%), yet an alarmingly high mortality rate (50%), particularly among patients with COPD requiring IMV (57%). The mortality rate was lower (33%) in patients with other non-COPD respiratory diseases or without respiratory comorbidities.

We found that HFNC use was associated with decreased odds for mortality in the COPD group, regardless of hypercapnia, whereas NIMV showed no significant association. Furthermore, prior inhaled steroid use was associated with an increased risk of bacterial pneumonia in COPD patients, highlighting the potentially harmful impact of this medication. Finally, our data on biomarkers suggest the high mortality observed in the COPD cohort was associated with a profound dysregulated immune response, indicating COPD might be a target for immunomodulatory therapies.

Patients with COPD and severe viral infection (SARS-CoV-2) are at higher risk of experiencing poor outcomes including higher odds of hospitalization, ICU admission, and mortality compared to those without COPD [1,8]. Studies conducted in South Korea and the SEMI-COVID register found a similar prevalence of ICU admission among patients with COPD (6%–7% *vs.* 5%) but a lower mortality rate compared to ours (38% *vs.* 50%) [4]. We observed similar IMV rates across groups (76%–78%). Only a higher proportion of COPD hypercapnic patients required IMV (57%) compared to the hypercapnic ones in the other study groups CRD (39%) and No CRD (44%) [4,21].

Despite the well-established benefits of non-invasive mechanical ventilation (NIVM) in acute exacerbations of COPD, there is limited literature addressing the specific beneficial effects of HFNC in COPD patients with ARDS [22–26]. The 2022 ERS task force for the non-invasive respiratory support during acute respiratory failure (ARF) suggests the use of HFNC over NIMV in ARF hypoxaemic but emphasizes the need for further trials in COPD with hypercapnic ARF [27]. In our study, HFNC was associated with

Table 3
Multivariable models assessing predictors of 28-day and 90-day mortality of the COPD population (N = 328).

	28-day mortality		90-day mortality	
Variables	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (+1 year)[a]	1.13 (0.60–2.12)	0.697	1.43 (0.80–2.55)	0.227
Female sex	1.03 (0.52–2.03)	0.926	0.99 (0.53–1.82)	0.965
Serum creatinine at ICU admission (+1 mg/dL)	1.47 (1.17–1.83)	**0.001**	1.37 (1.15–1.64)	<**0.001**
Metabolic syndrome (diabetes mellitus, hypertension and obesity)	0.91 (0.47–1.75)	0.775	0.80 (0.44–1.46)	0.460
SOFA score at ICU admission (+1)[a]	1.07 (1.00–1.15)	**0.042**	1.07 (1.01–1.14)	**0.027**
Oral steroids before admission	0.99 (0.47–2.09)	0.989	1.36 (0.74–2.49)	0.322
Hypercapnia at ICU admission ($PaCO_2$ > 45 mmHg)	1.22 (0.74–1.99)	0.436	1.26 (0.82–1.93)	0.290
High-flow nasal cannula	0.55 (0.32 to 0.96)	**0.035**	0.54 (0.31 to 0.95)	**0.034**
Non-invasive mechanical ventilation	1.05 (0.57–1.92)	0.875	1.12 (0.66–1.92)	0.678
Invasive mechanical ventilation	2.87 (1.29–6.42)	**0.010**	2.96 (1.44–6.06)	**0.003**
Bacterial coinfection	1.68 (0.75–3.74)	0.204	1.67 (0.82–3.41)	0.156
Nosocomial pneumonia		0.153		0.352
No	1.00	–	1.00	–
HAP no-VAP	0.74 (0.28–1.94)	0.537	0.87 (0.38–2.02)	0.751
VAP	0.47 (0.22–1.01)	0.053	0.64 (0.35–1.17)	0.150
Nosocomial pneumonia due to *Pseudomonas aeruginosa*	0.46 (0.15–1.46)	0.190	0.60 (0.26–1.34)	0.208
Nosocomial pneumonia due to *Staphylococcus aureus*	0.85 (0.29–2.52)	0.768	0.72 (0.30–1.72)	0.464
Prone position	0.68 (0.38–1.21)	0.187	0.79 (0.47–1.31)	0.350

Abbreviations: COPD indicates chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval; ICU, intensive care unit; SOFA, sequential organ failure assessment; $PaCO_2$, partial pressure of arterial carbon dioxide. Data are shown as estimated HRs (95% CIs) of the explanatory variables in the 28-day mortality group. Cox regression model stratified on the center variable and adjusted by COVID-19 wave. The variables included in the multivariate model were age, sex, serum creatinine at ICU admission, metabolic syndrome (diabetes mellitus, hypertension, and obesity), SOFA score at ICU admission, oral steroids before admission, hypercapnia at ICU admission (>45 mmHg), high-flow nasal cannula, non-invasive mechanical ventilation, invasive mechanical ventilation, bacterial coinfection, nosocomial pneumonia (No, HAP no-VAP, VAP), nosocomial pneumonia due to *Pseudomonas aeruginosa*, nosocomial pneumonia due to *Staphylococcus aureus*, and prone position. The *P*-value is based on the null hypothesis that all HRs relating to an explanatory variable equal unity (no effect).

[a] "+1" means a one-unit increase on the scale in the predictor variable (*i.e.*, going from 1 to 2, 2 to 3, *etc.*).

decreased odds for mortality in the COPD group regardless of hypercapnia, as opposed to NIMV (CPAP and BiPAP). Further PSM analyses confirmed the lower mortality in COPD receiving HFNC compared to IMV but not compared to NIMV.

Our findings align with those from a cross-sectional small study (n = 21) in which authors found that COPD patients treated with NIMV compared to those with HFNC had longer ICU stay, higher risk of intubation, and mortality, although significance was limited by small sample size [28]. In another study, HFNC has also been identified as protective for mortality among unselected critically ill patients with COVID-19 who did not receive IMV within 6 h of admission [29]. Notably, in our study, 28-day mortality was lower in COPD patients who received HFNC first and transitioned to IMV but not in those receiving NIVM first and then intubated (Table S2B). This could be attributed to a reduction in patient self-induced lung injury (P-SILI) associated with the use of HFNC when compared to NIMV. This reduction in P-SILI gains significance in the clinical context of severely damaged lungs often seen in cases of severe ARDS during severe COVID-19.

In contrast to the findings of Marc Garnier *et al.*, our study did not identify VAP as an independent risk factor for mortality in the COPD group. Regarding the impact of the causative pathogen on mortality, we found no association between COPD-related mortality and nosocomial pneumonia caused by *P. aeruginosa* or *S. aureus*. These findings are consistent with those of Marc Garnier *et al.*, who reported no increased risk of death when comparing *P. aeruginosa*-associated VAP to non-*P. aeruginosa* VAP [30].

Interestingly, we compared COPD patients to another group of patients with non-COPD chronic respiratory diseases (Figs. 2 and S6). The mortality rate in the non-COPD group was similar to the control group and half that of the COPD population. This result is significant, as non-pulmonology specialists often tend to group COPD and non-COPD patients together.

The heatmaps (Fig. S3, Table S5) highlight the critical association of immune and inflammatory markers with 28-day mortality among the COPD population. In our previous studies, we found that a higher viral load and lower levels of IgG and IgM at admission to the ICU were associated with an increased risk of mortality [15,17]. Notably, we found that despite both populations, COPD and CRD, had decreased levels of IgM and IgG compared to No CRD, only in COPD low IgG levels correlated significantly with 28-day mortality. Additionally, COPD patients presented a proinflammatory profile (TNF-alpha) with endothelial damage (higher VCAM-1) and cell apoptosis (higher Fas) compared to individuals of the CRD group.

The detrimental impact of prolonged immunosuppressive therapies, such as prior use of inhaled corticosteroids, is underscored within the COPD cohort. Our findings are in accordance with previous RCTs reporting a higher probability of having pneumonia among patients receiving inhaled corticosteroids compared to placebo or salmeterol alone [31]. These results collectively emphasize the vulnerability of COPD patients to infections and the profound influence of their immune dysregulation on their survival prospects in the context of severe SARS-CoV-2 infection [5–9].

Major strengths of this study include its multicentre nature, the consecutive inclusion of all patients from each ICU, thorough data quality check, and the high number of patients in each subpopulation: COPD, CRD, and No CRD.

Limitations of our study include the availability of plasma samples (n = 921, 225 after matching). However, the biomarkers and immune status analyses described important features not previously detailed in COPD series with severe SARS-CoV-2 infection. Another limitation is the partial availability (37%) of FEV_1 values before ICU admission, even though most studies in COVID-19 literature do not provide this information. We acknowledge the description of immunosuppression associated with inhaled corticosteroids (ICS) remains at a descriptive level. Finally, no adjustments were made for multiple comparisons. Despite the high patient influx during the pandemic, which led to expert ICU and new ICU setups potentially biasing COVID-19 mortality studies, previous research found no difference in mortality between them [32].

In conclusion, our study highlights the impact of severe COVID-19 on COPD patients, demonstrating significantly higher mortality rates compared to other groups. COPD patients showed increased

susceptibility to bacterial pneumonia, altered immune responses, and elevated biomarkers, complicating their clinical course. Importantly, the use of HFNC but not NIVM was associated with improved outcomes in this specific COPD group with ARDS due to severe COVID-19. These findings underscore the need for tailored management strategies in critically ill COPD patients with ARDS due to severe viral infection.

CRediT authorship contribution statement

Conception and design of the study: LFB, AT, AM, JB, FB. Data acquisition: all authors. Statistical analysis: AG. Data analysis and interpretation: LFB, AT, AM. Manuscript drafting: LFB with the participation of AT, AM, JC, AG, RLA. Critical revision for important intellectual content: all authors. Final approval of the submitted version: all authors. The CiberesUCICOVID consortium participated in data collection.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

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Declaration of competing interest

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Appendix A. Supplementary data

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