Risk factors for in-hospital mortality in older patients with acute respiratory distress syndrome due to COVID-19: A retrospective cohort study

Autor

Jimmy Hadid Anzueta Duarte

Director:

David Rene Rodríguez Lima

Médico Especialista en Medicina Crítica y Cuidado Intensivo

Facultad de ciencias de la salud

Medicina Crítica y Cuidado Intensivo

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Title:

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Authors:

David Rene Rodriguez Lima [1,2*] ORCID: 0000-0002-7089-018X

Jimmy Hadid Anzueta Duarte [3,4]

Cristhian Rubio Ramos [1]

Laura Otálora González [4]

Darío Isaías Pinilla Rojas [1]

Leonardo Andrés Gómez Cortés [1]

Edith Elianna Rodríguez Aparicio[1]

Andrés Felipe Yepes Velasco [3,4]

German Devia Jaramillo [2]

Affiliations:

[1] Critical and Intensive Care Medicine, Hospital Universitario Mayor-Méderi, Bogotá, Colombia.

[2] Grupo de Investigación Clínica, Escuela de Medicina y Ciencias de la Salud, Universidad del Rosario, Bogotá, Colombia.

[3] Critical and Intensive Care Medicine, Hospital Universitario Fundación Santa Fe de Bogotá, Bogotá, Colombia.

[4] Escuela de Medicina y Ciencias de la Salud, Universidad del Rosario, Bogotá, Colombia.

*Corresponding author:

David Rene Rodriguez Lima: drrodriguezl@hotmail.com

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Abstract

Background

Advancing age is associated with an increase in mortality among patients with acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19). This study aimed to determine risk factors for in-hospital mortality in patients over 60 years old with COVID-19-related ARDS (C-ARDS).

Methods

This was an observational, analytical, retrospective study conducted on a cohort that included all patients aged 60 years or older diagnosed with COVID-ARDSwho were admitted to a high-complexity hospital in Bogotá, Colombia, between March 2020 and July 2021.

Results

A total of 1563 patients were included in the analysis, with a median age of 73 years (interquartile range [IQR]: 67-80) and 811 deaths (51.8%). Independent risk factors for in-hospital mortality were identified as follows: patients aged 71-80 [OR 1.87 (95% CI 1.33-2.64)], age > 80 [OR 8.74 (95% CI 5.34-14.31)], lactate dehydrogenase (LDH) [OR 1.009 (95% CI 1.003-1.0015)], severe C-ARDS [OR 2.16 (95% CI 1.50-3.11)], use of invasive mechanical ventilation (IMV) [OR 12.94 (95% CI 9.52-17.60)], and use of steroids [OR 1.49 (95% CI 1.09-2.03)]. In patients over 80 years of age (n=388), the primary risk factor associated with in-hospital mortality was the use of IMV (n=76) [OR 6.26 (95% CI 2.67-14.69)], resulting in an in-hospital mortality rate of 89.4% (n=68) when this therapy was implemented.

Conclusions

The primary risk factors for in-hospital mortality in patients older than 60 years were age, the use of IMV, the severity of C-ARDS, use of steroids and elevated LDH values. Among patients older than 80 years, the main risk factor for in-hospital mortality was the use of IMV. In cases of C-ARDS in older patients, the decision to initiate IMV should always be individualized; therefore, the use of alternative oxygen delivery systems as the first-line approach can be considered.

Keywords

COVID-19, mortality, acute respiratory distress syndrome, mechanical ventilation, aged, risk factors

Background

Acute respiratory distress syndrome (ARDS) was first described in 1967 as an entity secondary to a systemic inflammatory response with hypoxemia and bilateral diffuse infiltrates within the pulmonary parenchyma [1]. This disease can be caused by multiple clinical conditions, such as pancreatitis, trauma and sepsis, with viral or bacterial pneumonia being the main cause [2]. ARDS is characterized by hypoxemia, defined as the ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration (P/F) below 300, diffuse alveolar infiltrates on chest X-ray ruling out cardiogenic pulmonary edema. Additionally, there is a triggering cause in the 7 days prior to diagnosis [3]. ARDS has an incidence rate of 10% to 15% of all intensive care unit (ICU) admissions [2,4]. However, it increases during epidemics, such as the seasonal flu[5] and coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2)[6]. COVID-19 can cause death and disability through multiple mechanisms; however, the majority of deaths occur in patients with viral pneumonia who meet the diagnostic criteria for ARDS [7,8].

Patients with ARDS require ICU management, with an average stay of 7.8 days and a duration of invasive mechanical ventilation (IMV) lasting approximately 5.3 days [9]. The mortality rate varies between 27% and 43% depending upon the disease severity [2,3,10]. During the COVID-19 pandemic, the demand for IMV has been reported in 9% to 32% of hospitalized patients [11–13], with mortality rates ranging from 36% to 81%[12,14,15].

Advanced age is a key determinant of the severity of COVID-19, since patients over 65 years of age have a greater risk of dying than younger patients [16]. This is secondary to changes in the immune response typical of the aging process [17] and the greater likelihood of comorbidities that make older adults more susceptible to severe disease due to COVID-19[6,18].

Whether older patients should receive IMV is controversial [19] since there is no clear clinical benefit. In addition, the utilization of this therapeutic approach can potentially result in respiratory dysfunction and muscle weakness, with an enormous impact on the patient's general condition and complicating the rehabilitation process, alongside the high resource consumption [20,21]. During the pandemic, a large number of patients with ARDS due to COVID-19 (C-ARDS) were treated [22], many of whom were older. This study aimed to determine risk factors for in-hospital mortality in patients over 60 years old with C-ARDS.

As a secondary outcome, the risk factors for in-hospital mortality in patients over 80 years of age are described.

Methods

Study design and setting

This was an observational, analytical, retrospective study of a cohort that included all patients aged 60 years or older with a confirmed diagnosis of C-ARDS admitted to a high complexity hospital located in the city of Bogotá, Colombia, from March 2020 to July 31, 2022. Data from the electronic clinical records were reviewed and collected by members of the research group. Patients were followed-up until hospital discharge or in-hospital death.

Participants

All consecutive patients with a confirmed diagnosis of COVID-19 were included in the analysis if they met the following inclusion criteria: age ≥ 60 years, SARS-CoV-2 confirmed by polymerase chain reaction (PCR) in nasopharyngeal swabs and confirmed diagnosis of C-ARDS.

Variables

For this study, C-ARDS was defined as the presence of diffuse alveolar infiltrates in a chest image (radiography or tomography), ARDS with P/F ≤ 300, no clinical suspicion of cardiogenic pulmonary edema, and the use of positive end-expiratory pressure (PEEP) ≥ 5 cmH2O was not evaluated for the diagnosis, which was based on the definition of Kigalli[23]. Furthermore, in our clinical experience, many patients who met ARDS criteria were not treated with positive pressure administration systems, since these values, despite being low, are close to normal or not correlated with clinical outcomes given the hypobaric hypoxemia of the altitude present in the city of Bogotá, at 2640 meters above sea level (masl)[3,12]. The international management recommendations for COVID-19 were followed as the pandemic progressed, according to the evidence [24].

Demographic data were collected (age, sex, body mass index (BMI)), comorbidities (hypertension, congestive heart failure, chronic pulmonary disease, diabetes and the Charlson Index), admission laboratories (complete blood count (CBC), neutrophil/lymphocyte ratio (N/L ratio), lactate dehydrogenase (LDH), D dimer, procalcitonin and ferritin, oxygenation index (P/F at admission, at the moment of ARDS diagnosis and the lowest value during hospitalization), C-ARDS severity (evaluated based on Berlin definition: mild with P/F> 200≤ 300, moderate with P/F> 100 ≤ 200 and severe with P/F ≤100), tracheostomy realization, treatment with steroids, IMV requirement, respiratory mechanics parameters from Day 1 (tidal volume, tidal volume

adjusted by ideal weight, respiratory rate, plateau pressure, peak pressure, PEEP, driving pressure, mechanic power and prone hours per day).

The primary outcome assessed was in-hospital mortality during the C-ARDS care event.

Study size

To ensure that the study has sufficient statistical power to detect significant associations between different risk factors and mortality, based on a described mortality rate of 50% for ARDS patients in the general population and an expected mortality rate of 70% for patients with C-ARDS over 60 years old, with 95% confidence and 90% power, a sample size of 70 patients was calculated for each group (alive vs. dead).

The number of recruited patients exceeded this calculated sample size.

Statistical analysis

The qualitative variables were described by absolute and relative frequencies, and the quantitative variables were described by the mean and standard deviation or the median and its interquartile range (IQR) according to normality.

A bivariate analysis was performed with respect to the principal outcome (in-hospital mortality); furthermore, exploratory bivariate analyses were performed in relation to age categories, such as 60 to 70 years, 71 to 80 years and older than 80 years, and the use of IMV. For the qualitative variables, the statistical significance of the association was evaluated with the chi-square test, and to evaluate the statistical significance of the differences for the quantitative variables, the T test or the Mann–Whitney-Wilcoxon test was used according to normality. For the bivariate analysis of categorized age, considering there are three groups, an analysis of variance (ANOVA) or the Kruskal–Wallis test was employed based on the assumption of normality. A statistical significance level of $p < 0.05$ was considered.

To determine the risk factors for in-hospital mortality, a multivariate analysis using logistic regression was conducted. Variables with a p value < 0.05 in the bivariate analysis were included, and those with statistical significance ($p < 0.05$) in the multivariate analyses were considered independent risk factors for in-hospital mortality. This process was conducted in the whole population and in the group of patients older than 80 years. For the variables included in the multivariate analysis, odds ratios (ORs) were presented along with their respective 95% confidence intervals (CIs). All analyses were performed using R Studio version 4.1.

Results

Between March 19, 2020, and July 31, 2021, 7345 COVID-19 patients were hospitalized, with 7289 cases confirmed by pharyngeal swab PCR. Of these, 2313 met the C-ARDS criteria. After excluding 103 cases lacking P/F values at ARDS diagnosis, the final analysis included 1563 patients aged 60 or above (Figure 1).

Figure 1. Patient selection flowchart

In the final analysis, 1563 patients were included, the global mortality among this cohort was 51.8% (n=811), 64.7% (n=1012) were men, and the median age was 73 (IQR 67-80).

Table 1 presents baseline characteristics from the population and bivariate analysis by in-hospital mortality, assessing demographic and clinical characteristics, admission laboratories, oxygenation index, ARDS severity, oxygen administration system, treatment with steroids and for ventilated patients shows pulmonary mechanics parameters at day 1 which describes the protective mechanical ventilation strategy

Being male, age, a high Charlson Index, N/L ratio, LDH, procalcitonin, P/F ratio at admission, P/F ratio at the time of diagnosis, lowest P/F ratio during hospitalization, severe C-ARDS, IMV, tracheostomy, and steroid treatment were all associated with an elevated risk of in-hospital mortality (Table 1). Among ventilated patients, there were no clinically significant differences observed in pulmonary mechanics.

Table 1. Baseline characteristics and bivariate analysis by in-hospital mortality in all patients

Table 2 depicts the bivariate analysis categorized by age groups (60-70, 71-80, and >80 years). Within this cohort, patients aged 60-70 years constituted 39.5% (n=618), those aged 71-80 years accounted for 35.6% (n=557), and individuals older than 80 years constituted 24.8% (n=388). The in-hospital mortality rates were 43.8% (n=271), 51.7% (n=288), and 64.9% (n=252), respectively, for each age group. IMV was utilized in 57.9% (n=358) of patients in the 60-70 age group, while for those aged 71-80, the proportion was 52.6% (n=293), and for those over 80, it was 19.5% (n=76) (Table 2). In-hospital mortality rates among ventilated patients were 68.7% (n=246) for the 60-70 age group, 78% (n=229) for the 71-80 age group, and 89.4% (n=68) for individuals over 80 years of age (Table 4) (Supplementary Material Table 1) (Supplementary Material Table 2).

Patients over 80 years old showed lower leukocyte counts, lower hemoglobin levels, reduced LDH and ferritin levels, and higher values of D-dimer. Additionally, there was an observed increase in the Charlson Index with advancing age (Table 2).

Table 2. Bivariate analysis by categorical age (60-70, 71-80 and >80 years).

In patients over 80 years old who died, 57.9% (n=146) were males, had elevated levels of LDH and procalcitonin along with lower oxygenation indices, and IMV was employed in 26.9% (n=68) of cases (Table 3).

Table 3. Baseline characteristics and bivariate analysis by in-hospital mortality in patients older than 80 years.

The patients over 80 years of age who underwent IMV were predominantly males at 51.3% (n=39) and exhibited higher BMI, elevated LDH and procalcitonin levels, with lower oxygenation indices and greater severity of C-ARDS. (Table 4).

Table 4. Bivariate analysis by use of IMV in patients older than 80 years.

A multivariate analysis was conducted as described. The results reported that patients aged 71-80 [OR 1.87 (95% CI 1.33-2.64)], aged > 80 [OR 8.74 (95% CI 5.34-14.31)], LDH [OR 1.009 (95% CI 1.003-1.0015)], C-ARDS severe [OR 2.16 (95% CI 1.50-3.11)], IMV [OR 12.94 (95% CI 9.52-17.60)] and steroids [OR 1.49 (95% CI 1.09-2.03)] were identified as independent risk factors for in-hospital mortality in the whole population (Figure 2).

In patients older than 80 years, the following factors were identified as independent predictors for in-hospital mortality: LDH [OR 1.0027 (95% CI 1.0009-1.0045)], moderate C-ARDS [OR 1.98 (95% CI 1.16-3.37)], severe C-ARDS [OR 5.20 (95% CI 2.49-10.86)] and IMV [OR 6.26 (95% CI 2.67-14.69)] (Figure 3).

Figure 2. Multivariate analysis presenting the OR for in-hospital mortality in patients older than 60 years

Figure 3. Multivariate analysis presenting the OR for in-hospital mortality in patients older than 80 years

Discussion

In this study, the following factors were identified as independent risk factors for in-hospital mortality: age, use of IMV, severity of C-ARDS, steroid administration, and elevated levels of LDH.

Advancing age has been described as one of the main risk factors for in-hospital mortality in COVID-19, [25] [12,26,27], although there are few reports about ventilatory treatment strategies in older patients.

The overall mortality rate for this cohort was 51.8% (n = 811), and among those aged over 80 years, it was 64.9% (n = 252). However, in ventilated patients, the mortality rate increased to 66.9% (n = 543), rising further to 89.4% (n = 68) in individuals over the age of 80. Despite high rates, it is similar to that reported in older patients undergoing IMV[26], with reports of a 73-84% mortality rate at age 80[26] [28].

It was observed that 53.5% of the patients in this cohort did not receive IMV despite having ARDS, in relation to the high mortality rates observed with this therapy since the onset of the pandemic and based on the recommendations for the use of other oxygen delivery systems[29,30]. Sagoschen et al., in a cohort with more than 11000 patients in Germany with C-ARDS where 41% were treated with IMV and showed a mortality of 64.5% in patients older than 70 years, these values are similar to the ones shown in this work where 46% of patients with C-ARDS were treated with IMV and mortality in patients older than 70 years was 57.1%[27].

Few studies have demonstrated the clinical outcomes of octogenarian patients managed with IMV for COVID-19-induced ARDS. Smolin et al., in a cohort of 554 patients aged over 65 years managed with IMV, reported a mortality rate of 64.1%, which increased to 70.4% for those over 80 years and 73.8% for those over 85 years [20]. However, this study did not present oxygenation indices or compare clinical outcomes with nonventilated patients. In the current study, the mortality rate in ventilated patients with ARDS over 80 years old was 89.4%, while in nonventilated patients, it was 58.7%. It should be noted that the P/F ratio at the time of ARDS diagnosis in ventilated patients was 123.44 (IQR 84.27-180.71) compared to 180.31 (IQR 107.10-227.61) in those who were not ventilated, indicating that IMV increases mortality; however, ventilated patients had more severe hypoxemia.

Similar to previous series of non-COVID ARDS, mortality increases with the severity of this condition, indicating that low oxygenation levels are associated with higher mortality [31][32].

The RECOVERY study demonstrated that the use of dexamethasone reduced mortality at 28 days in patients receiving supplementary oxygen, including those on IMV; however, no benefit was observed in the subgroup of patients over 70 years old [34]. Jung et al., in an observational study, it was showed that the use of steroids in older patients is associated with increased mortality [35], and that there were similar findings to those obtained in this study.

Severe infections can lead to tissue damage and the release of LDH, which has been described as a marker of severity in COVID-19, including the older population [36][37].

The levels of LDH, moderate and severe C-ARDS, and the use of IMV were independent factors associated with mortality in patients over 80 years of age. These findings were consistent with those described in a previous series [27,28].

In brief, among patients aged between 60 and 80 years, the use of IMV is associated with increased mortality. However, ventilated patients experience greater hypoxemia than nonventilated patients, which inhibits the decision making process of which patients should benefit from this management strategy, but it suggests that if a patient is not clinically in respiratory failure and acceptable oxygen levels can be maintained using other oxygen delivery systems, then that should be the preferred ventilation strategy. For patients over 80 years of age, the mortality rate associated with IMV is much higher than in noninvasive ventilation strategies; therefore, the use of alternative oxygen delivery systems should be considered as the first-line approach. Thus, the decision for IMV must be made individually based on the patient's personal preferences, family input, and the treating team's experience in managing octogenarian patients.

This study has limitations. It is a cohort of a single center, the collection of patients was retrospective, and it was carried out during the COVID-19 pandemic. Therefore, it may not reflect the usual management standard in older patients with ARDS. In addition, ventilation in the prone position was offered as a therapeutic technique performed in our hospital to treat patients with respiratory failure both in IMV and alert patients; however, the record in the clinical history of the ventilation mechanism and the duration of treatment was deficient; therefore, this information was not available for analysis.

Another important limitation of this study is the absence of additional management strategies regarding ventilated and nonventilated patients, such as the need for antibiotic management due to superinfection and the relationship between the ratio of doctors and nurses per patient during the peaks of the pandemic. All these factors are related to the quality of care and clinical outcomes. However, the hospital strictly

followed institutional and national management protocols for patients with COVID-19, and hospitalized patients were monitored by geriatrics and palliative care professionals in patients who, by personal decision or medical indication, were not candidates for IMV.

The main strength of this study is the size of the sample, since in a situation other than the health emergency caused by COVID-19, it would not be possible to recruit so many older patients with ARDS not taking IMV, which clearly indicates the association between the use of IMV and increased in-hospital mortality.

Conclusion

In patients over 60 years of age, factors such as age, the use of IMV, the severity of C-ARDS, the use of steroids and elevated LDH values are the primary risk factors for in-hospital mortality. In patients over 80 years old, the primary risk factor for mortality was the use of IMV. In cases of C-ARDS in older patients, the decision to initiate IMV should always be individualized, and the use of alternative oxygen delivery systems as the first-line approach can be considered.

Abbreviations

ARDS: acute respiratory distress syndrome; COVID-19: coronavirus disease 2019; C-ARDS: acute respiratory distress syndrome secondary to COVID-19; IQR: interquartile range; LDH: lactate dehydrogenase; IMV: invasive mechanical ventilation; ICU: intensive care unit; severe acute respiratory syndrome coronavirus 2 (SARS-COV2); PCR: polymerase chain reaction; PEEP: positive end-expiratory pressure; cmH2O: water centimeters; masl: meters above sea level; BMI: body mass index; CBC: complete blood count; N/L: neutrophil/lymphocyte ratio; OR: odds ratio; CI: confidence interval; mL: millilitres; kg: kilograms; U/L: units per liter; ng/ml: nanograms per millilitre

Declarations

Ethics approval and consent to participate

This study was presented and approved by the ethics committee of the Universidad del Rosario (DVO005 2226-CV1672) and performed in line with the principles of the Declaration of Helsinki. The 1563 subjects who participated in the study signed informed consent forms for participation and publication of the results approved by the institutional ethics committee.

Consent for publication

Not applicable.

Availability of data and materials

The data used in the present study are available in Supplementary Material.

Competing interests

The authors declare no competing interests.

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Authors' contributions

DR wrote the protocol and participated in the statistical analysis and interpretation of the results. JA, CR, LO, DP, LG, ER, AY, and GD wrote the protocol and participated in the interpretation of the results.

All authors participated in the writing of the article and approved the final version of the manuscript.

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Author information

David Rene Rodriguez Lima M.D. PhD(c)

Intensivist at Hospital Universitario Mayor Méderi, Bogotá-Colombia

Doctoral candidate in clinical research

email: drrodriguezl@hotmail.com

Jimmy Hadid Anzueta Duarte M.D.

Resident of Critical Care at Universidad del Rosario, Bogotá-Colombia

email: jimmy.anzueta3@gmail.com

Cristhian Rubio Ramos M.D.

Intensivist at Hospital Universitario Mayor Méderi, Bogotá-Colombia

email: crisrubnal@gmail.com

Laura Otálora González

Medical student at Universidad del Rosario, Bogotá-Colombia

email: laura.otalorag@urosario.edu.co

Darío Isaías Pinilla Rojas M.D.

Intensivist at Hospital Universitario Mayor Méderi, Bogotá-Colombia

email: dario.pinilla@mederi.com.co

Leonardo Andrés Gómez Cortes M.D.

Intensivist at Hospital Universitario Mayor Méderi, Bogotá-Colombia

email: leoandresgomez@gmail.com

Edith Elianna Rodríguez Aparicio M.D.

Intensivist at Hospital Universitario Mayor Méderi, Bogotá-Colombia email: edith.rodriguez@urosario.edu.co

Andrés Felipe Yepes Velasco M.D.

Intensivist at Fundación Santa Fe, Bogotá-Colombia

email: yepespipe@hotmail.com

German Devia Jaramillo M. D

Emergency Medicine at Fundación Santa Fe, Bogotá-Colombia

email: germandevia@gmail.com

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Legends

Table 1. Baseline characteristics and bivariate analysis by in-hospital mortality in all patients.

IQR: interquartile range; LDH: lactate dehydrogenase; P/F: ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration; ARDS: acute respiratory distress syndrome; C-ARDS: COVID-19-related acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; ICU: intensive care unit; mL: millilitres; kg: kilograms; cmH2O: water centimeters; U/L: units per liter; ng/ml: nanograms per millilitre

Table 2. Bivariate analysis by categorical age (60-70, 71-80 and >80 years)

IQR: interquartile range; LDH: lactate dehydrogenase; P/F: ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration; ARDS: acute respiratory distress syndrome; C-ARDS: COVID-19-related acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; ICU: intensive care unit; mL: millilitres; kg: kilograms; cmH2O: water centimeters; U/L: units per liter; ng/ml: nanograms per millilitre

Table 3. Baseline characteristics and bivariate analysis by in-hospital mortality in patients older than 80 years.

IQR: interquartile range; LDH: lactate dehydrogenase; P/F: ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration; ARDS: acute respiratory distress syndrome; C-ARDS: COVID-19-related acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; ICU: intensive care unit; mL: millilitres; kg: kilograms; cmH2O: water centimeters; U/L: units per liter; ng/ml: nanograms per millilitre

Table 4: Bivariate analysis by use of IMV in patients older than 80 years.

IQR: interquartile range; LDH: lactate dehydrogenase; P/F: ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration; ARDS: acute respiratory distress syndrome; C-ARDS: COVID-19-related acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; ICU: intensive care unit; mL: millilitres; kg: kilograms; cmH2O: water centimeters; U/L: units per liter; ng/ml: nanograms per millilitre

Figure 1. Patient selection flowchart

ARDS: acute respiratory distress syndrome; P/F: ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration;

Figure 2. Multivariate analysis presenting the OR for in-hospital mortality in patients older than 60 years

BMI: body mass index; N/L ratio: neutrophil/lymphocyte ratio; LDH: lactate dehydrogenase; C-ARDS: COVID-19-related acute respiratory distress syndrome; CI: confidence interval

Figure 3. Multivariate analysis presenting the OR for in-hospital mortality in patients older than 80 years

BMI: body mass index; LDH: lactate dehydrogenase; C-ARDS: COVID-19-related acute respiratory distress syndrome; CI: confidence interval

Supplementary Material. Table 1. Bivariate analysis by use of IMV in patients from 60 to 70 years old.

IQR: interquartile range; LDH: lactate dehydrogenase; P/F: ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration; ARDS: acute respiratory distress syndrome; C-ARDS: COVID-19-related acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; ICU: intensive care unit; mL: millilitres; kg: kilograms; cmH2O: water centimeters; U/L: units per liter; ng/ml: nanograms per millilitre

Supplementary Material. Table 2. Bivariate analysis by use of IMV in patients from 71 to 80 years old.

IQR: interquartile range; LDH: lactate dehydrogenase; P/F: ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration; ARDS: acute respiratory distress syndrome; C-ARDS: COVID-19-related acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; ICU: intensive care unit; mL: millilitres; kg: kilograms; cmH2O: water centimeters; U/L: units per liter; ng/ml: nanograms per millilitre

Table 1. Baseline characteristics and bivariate analysis by in-hospital mortality in all patients

	Overall patients (n = 1563)		Alive (n = 752) (48.1%)	Death (n = 811) (51.8%)	*p value*
	Patients	missing	Patients	Patients	
Demographic					
Sex n (%)	*Female* 551(35.2%) *Male* 1012(64.7%)	0	*Female* 246(32.7%) *Male* 506(67.2%)	*Female* 305(37.6%) *Male* 506(62.3%)	**0.048**[+]
Age (years) median [IQR]	73[67-80]	0	72[66-78]	75[68-82]	**< 0.001***
Age (categorized by decades) n (%)	*60-70 years* 618(39.5%) *71-80 years* 557(35.6%) *>80 years* 388(24.8%)	0	*60-70 years* 347(46.1%) *70-80 years* 269(35.7%) *>80 years* 136(18.0%)	*60-70 years* 271 (33.4%) *70-80 years* 288(35.5%) *>80 years* 252(31.0%)	**<0.001**[+]
Body mass index median [IQR]	26.34[23.8-29.3]	0	26.17[23.8-29.05]	26.36[23.72-29.41]	0.46*
Comorbidities					
Hypertension n (%)	474(30.3%)	0	240(31.9%)	234(28.8%)	0.20[+]
Congestive heart Failure n (%)	86(5.5%)	0	36(4.7%)	50(6.1%)	0.27[+]
Chronic pulmonary disease n (%)	124(7.9%)	0	64(8.5%)	60(7.3%)	0.47[+]
Diabetes n (%)	278(17.7%)	0	140(18.6%)	138(17.0%)	0.44[+]
Charlson Index median [IQR]	3[3-4]	0	3[2-4]	4[3-4]	**<0.001***
Laboratory values median (IQR)					
White blood count (cells x 10^6/L)	8690[6370-11852]	11	8760[6705-11733]	8620[6148-11965]	0.27*
Neutrophil-lymphocyte ratio	8.84[5.22-14.59]	12	8.33[5.11-13.13]	9.25[5.39-16.40]	**0.004***
Hematocrit (%)	43.5[39.2-47.4]	10	43.7[39.8-47.3]	43.4[38.5-47.5]	0.28*
Hemoglobin (g/dl)	14.5[13.1-15.8]	10	14.6[13.3-15.8]	14.5[12.8-15.9]	0.08*

LDH (U/L)	424[331-537.5]	68	396[318-498]	455[351-595.5]	**<0.001***
D dimer (ng/ml)	1217[761-2198]	98	1168[768.5-2152]	1264 [735.5-2250.7]	0.37*
Procalcitonin (ng/ml)	0.42[0.17-1.39]	829	0.26[0.12-0.69]	0.6[0.25-1.87]	**<0.001***
Ferritin (ng/ml)	1180[732.4-2145.5]	1256	1063 [738-1551.5]	1275 [729.3-2367.7]	0.10*
Oxygenation index median [IQR]					
P/F ratio at admission	169.2[108.7-227.7]	0	193.8[134.4-241.0]	142.3[93.1-205.1]	**< 0.01***
P/F ratio at the diagnosis of ARDS	167.1[107.8-222.0]	0	191.4[134.1-237.8]	139.9 [92.2-200.4]	**< 0.01***
Lowest P/F ratio	74.1[55.5-128.2]	0	106.3[69.7-187.5]	60.49[49.5-78.9]	**< 0.01***
C-ARDS					
Mild n (%)	550(35.1%)	0	346(46.0%)	204(25.1%)	**< 0.01⁺**
Moderate n (%)	685(43.8%)	0	315(41.8%)	370(45.6%)	**< 0.01⁺**
Severe n (%)	328(20.9)	0	91(12.1%)	237(29.2%)	**< 0.01⁺**
Oxygen support strategy					
Mechanical ventilation n (%)	727(46.5%)	0	184(24.4%)	543(66.9%)	**< 0.01⁺**
Tracheostomy n (%)	66(4.2%)	0	31(16.8%)	35(6.4%)	**< 0.01⁺**
Treatment					
Any steroid n (%)	1248(79.8%)	0	574(45.9%)	674(83.1%)	**0.001⁺**
Respiratory mechanics Day 0 median [IQR]					
Tidal volume (mL)	400[370-450]	869	400[362.5-450]	400[370-450]	0.506*
Tidal volume adjusted by ideal weight (mL/kg)	7.02[6.5-7.5]	869	6.9[6.5-7.6]	7[6.5-7.5]	0.958*
Respiratory rate	18[16-18]	870	18[16-18]	18[16-19]	**0.003***
Plateau pressure (cmH_2O)	23.5[21-26]	1159	23[21-25]	24[21-26]	0.463*
Peak pressure (cmH_2O)	28[25-32]	1028	28[24-31]	28[25-32]	0.321*
PEEP (cmH_2O)	12[10-12]	868	12[10-12]	12[10-12]	0.997*
Driving pressure (cmH_2O)	12[10-14]	1161	12[10-14]	12[10-14]	0.449*
Mechanic power	15.5[12.7-18.6]	1191	14.9[11.9-18.3]	15.8[13.4-19.3]	**0.020***
Prone (hours/day)	0[0-3]	861	0[0-6]	0[0-2]	0.183*
Outcomes median [IQR]					
Duration of mechanical ventilation (days)	9[5-14]	0	9[6-16]	9[5-14]	0.09*
⁺p values were obtained using Chi-square test ***p values were obtained using the Mann–Whitney test** **Bold values indicate statistically significant p values**					

IQR: interquartile range; LDH: lactate dehydrogenase; P/F: ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration; ARDS: acute respiratory distress syndrome; C-ARDS: COVID-19-related acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; ICU: intensive care unit; mL: millilitres; kg: kilograms; cmH2O: water centimeters; U/L: units per liter; ng/ml: nanograms per millilitre

Table 2. Bivariate analysis by categorical age (60-70, 71-80 and >80 years)

	60-70 years (n=618) (39.5%)	71-80 years (n=557) (35.6%)	>80 years (n=388) (24.8%)	*p value*
	Patients	Patients	Patients	
Demographic				
Sex n (%)	*Female 211*(34.1%) *Male* 407(65.8%)	*Female* 183(32.8%) *Male* 374(67.1%)	*Female* 157(40.4%) *Male* 231(59.5%)	**0.041⁺**
Age (years) median [IQR]	65[62-68]	75[73-78]	85[82-88]	**< 0.001***
Body mass index median [IQR]	26.7[24.2-29.7]	26.5[24.0-29.3]	25.2[23.1-28.0]	**< 0.001***
Comorbidities				
Hypertension n (%)	159(25.7%)	184(33.0%)	131(33.7%)	**0.005⁺**
Congestive heart Failure n (%)	27(4.3%)	29(5.2%)	30(7.7%)	0.069⁺
Chronic pulmonary disease n (%)	24(3.8%)	52(9.3%)	48(12.3%)	**<0.001⁺**
Diabetes n (%)	129(20.8%)	98(17.5%)	51(13.1%)	**0.007⁺**
Charlson Index median [IQR]	2[2-3]	3[3-4]	4[4-5]	**<0.001***
Laboratory values median (IQR)				

White blood count (cells x 10^6/L)	9070[6855-12095]	8475[6228-11842]	8260[6070-11650]	**0.005***
Neutrophil-lymphocyte ratio	9.05[5.75-13.82]	8.57[4.82-14.65]	8.86[4.87-16.09]	0.42*
Hematocrit (%)	44.1[40.2-47.6]	44.1[39.8-47.6]	41[36.9-45.7]	**<0.001***
Hemoglobin (g/dl)	14.8[13.5-16]	14.7[13.4-15.9]	13.6[12.3-15.2]	**<0.001***
LDH (U/L)	452.5[352.2-568]	421[333-530]	381[299-497]	**<0.001***
D dimer (ng/ml)	1085[677-2024]	1204[758-2052]	1545 [899-2889]	**<0.001***
Procalcitonin (ng/ml)	0.42[0.17-1.2]	0.43[0.17-1.5]	0.39[0.11-1.37]	0.65*
Ferritin (ng/ml)	1436[863.5-2409]	978.5[604.1-1782.2]	962.9[545.7-1977]	**0.003***
Oxygenation index median [IQR]				
P/F ratio at admission	170.0[110.5-222.6]	168[108.9-232.2]	171.5[102.6-228.2]	0.7*
P/F ratio at the diagnosis of ARDS	168.7[110.2-218.1]	165.4[108.5-227.6]	165.3[99.9- 221.7]	0.47*
Lowest P/F ratio	70.1[53.4-118.4.]	72.0[54.4-121.5]	81.6[60.6-143.7]	**0.00015***
C-ARDS				
Mild n (%)	207(33.4%)	206(36.9%)	137(35.3%)	0.07+
Moderate n (%)	290(46.9%)	242(43.4%)	153(39.4%)	0.07+
Severe n (%)	121(19.5%)	109(19.5%)	98(25.2%)	0.07+
Oxygen support strategy				
Mechanical ventilation n (%)	358(57.9%)	293(52.6%)	76(19.5%)	**< 0.01+**
Tracheostomy n (%)	35(9.7%)	27(9.2%)	4(5.2%)	**< 0.01+**
Treatment				
Any steroid n (%)	491(79%)	441(79%)	316(81%)	0.659+
Respiratory mechanics Day 0 median [IQR]				
Tidal volume (mL)	410[370-450]	400[370-450]	400[360-422.5]	0.060*
Tidal volume adjusted by ideal weight (mL/kg)	7[6.5-7.5]	7[6.5-7.5]	7.1[6.6-8.1]	0.116*
Respiratory rate	18[16-18]	18[16-19]	16[16-18]	**0.008***
Plateau pressure (cmH_2O)	24[22-26]	23[21-25]	22[20-24]	**0.040***
Peak pressure (cmH_2O)	28[25-32]	28[25-32]	27[23.5-30]	0.350*
PEEP (cmH_2O)	12[10-12]	12[10-12]	10[10-12]	**0.016***
Driving pressure (cmH_2O)	12[10-14]	12[10-14]	11[9.2-13]	0.257*
Mechanic power	15.4[12.7-19.1]	15.9[13-18.6]	14.6[12.2-16.8]	0.168*
Prone (hours/day)	0[0-6]	0[0-1]	0[0-3]	0.296*
Outcomes				
Mortality	271(43.8%)	288(51.7%)	252(64.9%)	**< 0.01+**
Duration of mechanical ventilation (days) median [IQR]	10[6-15]	9[4-14]	7[3-12]	**<0.001***

+ p values were obtained using Chi-square test
***p values were obtained using the Kruskal–-Wallis test**
Bold values indicate statistically significant p values

IQR: interquartile range; LDH: lactate dehydrogenase; P/F: ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration; ARDS: acute respiratory distress syndrome; C-ARDS: COVID-19-related acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; ICU: intensive care unit; mL: millilitres; kg: kilograms; cmH2O: water centimeters; U/L: units per liter; ng/ml: nanograms per millilitre

Table 3. Baseline characteristics and bivariate analysis by in-hospital mortality in patients older than 80 years.

	Overall patients (n = 388)		Alive (n = 136) (35.1%)	Death (n = 252) (64.9%)	*p value*
	Patients	missing	Patients	Patients	
Demographic					
Sex n (%)	*Female* 157(40.4%) *Male* 231(59.5%)	0	*Female* 51(37.5%) *Male* 85(62.5%)	*Female* 106(42%) *Male* 146(57.9%)	**0.027+**
Age (years) median [IQR]	85[82-88]	0	84[82-86]	85[83-88]	**<0.001***
Body mass index median [IQR]	25.20[23.14-28.04]	0	25.24[23.43-27.57]	25.19[23.09-28-51]	0.673*
Comorbidities					
Hypertension n (%)	131(33.7%)	0	55(40.4%)	76(30.1%)	0.053+
Congestive heart Failure n (%)	30(7.7%)	0	13(9.5%)	17(6.7%)	0.429+

Chronic pulmonary disease n (%)	48(12.3%)	0	22(16.1%)	26(10.3%)	0.130[+]
Diabetes n (%)	51(13.1%)	0	18(13.2%)	33(13%)	1[+]
Charlson Index median [IQR]	4[4-5]	1	4[4-5]	4[4-5]	0.334*
Laboratory values median (IQR)					
White blood count (cells x 10^6/L)	8260[6070-11650]	1	7625[6155-10665]	8530[6055-11950]	0.258*
Neutrophil-lymphocyte ratio	8.86[4.87-16.09]	1	7.95[4.42-12.62]	9.49[5.08-17.62]	0.076*
Hematocrit (%)	41[36.9-45.7]	1	40.6[37.1-44.3]	41.4[36.9-46.1]	0.392*
Hemoglobin (g/dl)	13.6[12.3-15.2]	1	13.6[12.4-14.8]	13.7[12.3-15.4]	0.505*
LDH (U/L)	381[299-497]	27	346.5[284.2-422]	417[317-538]	**<0.001***
D dimer (ng/ml)	1545.5[899.7-2889.2]	31	1430[950-2810]	1559[865-2929.5]	0.830*
Procalcitonin (ng/ml)	0.39[0.11-1.37]	265	0.14[0.09-1.17]	0.63[0.18-1.59]	**0.015***
Ferritin (ng/ml)	962.9[545.7-1977]	457	984[643-1313.5]	962.9[501.2-2120.2]	0.813*
Oxygenation index median [IQR]					
P/F ratio at admission	171.52[102.64-228.2]	0	213.3[163.4-252.2]	139.6[85.9-207.7]	**<0.001***
P/F ratio at the diagnosis of ARDS	165.3[99.9-221.7]	0	206.1[162.4-245.7]	137.4[85.3-202.1]	**<0.001***
Lowest P/F	81.66[60.6-143.7]	0	139[79.2-206.8]	69.4[56.1-92.4]	**<0.001***
C-ARDS					
Mild n (%)	137(35.3%)	0	73(53.6%)	64(25.3%)	**<0.001**[+]
Moderate n (%)	153(39.4%)	0	49(36%)	104(41.2%)	**<0.001**[+]
Severe n (%)	98(25.2)	0	14(10.2%)	84(33.3%)	**<0.001**[+]
Oxygen support strategy					
Mechanical ventilation n (%)	76(19.5%)	0	8(5.8%)	68(26.9%)	**<0.001**[+]
Tracheostomy n (%)	4(1%)	0	1(12.5%)	3(4.4%)	0.894[+]
Treatment					
Any steroid n (%)	316(81.4%)	0	106(77.9%)	210(83.3%)	0.243[+]
Respiratory mechanics Day 0 median [IQR]					
Tidal volume (mL)	400[360-422.5]	320	435[375-455]	400[360-420]	0.133*
Tidal volume adjusted by ideal weight (mL/kg)	7.1[6.6-8.1]	320	7.8[7.4-8]	7.1[6.6-8.1]	0.125*
Respiratory rate	16[16-18]	320	17[15.5-18]	16[16-18]	0.840*
Plateau pressure (cmH_2O)	22[20-24]	350	21[20-22]	22[20-25]	0.325*
Peak pressure (cmH_2O)	27[23.5-30]	337	23[21.7-28]	27[24.5-30-5]	0.135*
PEEP (cmH_2O)	10[10-12]	320	12[10-12]	10[10-12]	0.250*
Driving pressure (cmH_2O)	11[9.2-13]	350	9[9-11]	12[10-13.5]	0.081*
Mechanic power	14.6[12.2-16.8]	352	14[11.9-16.6]	15[12.2-17]	0.857*
Prone (hours/day) [IQR]	0[0-3]	320	0[0-6.2]	0[0-1.5]	0.688*
Outcomes median [IQR]					
Duration of mechanical ventilation (days)	7[3-12]	260	9[4.7-18.5]	7[3-12]	0.281*
[+]p values were obtained using Chi-square test ***p values were obtained using the Mann–Whitney test** **Bold values indicate statistically significant p values**					

IQR: interquartile range; LDH: lactate dehydrogenase; P/F: ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration; ARDS: acute respiratory distress syndrome; C-ARDS: COVID-19-related acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; ICU: intensive care unit; mL: millilitres; kg: kilograms; cmH2O: water centimeters; U/L: units per liter; ng/ml: nanograms per millilitre

Table 4. Bivariate analysis by use of IMV in patients older than 80 years.

	Overall patients (n = 388)		Mechanical ventilation (n = 76) (19.5%)	Other oxygen support strategy (n = 312) (80.5%)	*p value*
	Patients	missing	Patients	Patients	
Demographic					
Sex n (%)	*Female* 157(40.4%) *Male* 231(59.5%)	0	*Female* 37(48.6%) *Male* 39(51.3%)	*Female* 120(38.4%) *Male* 192(61.5%)	**<0.001**[+]
Age (years) median [IQR]	85[82-88]	0	83[82-84.2]	85[83-89]	0.12*
Body mass index median [IQR]	25.20[23.14-28.04]	0	26.26[23.43-28.65]	25.1[22.9-27.87]	**0.044***

Comorbidities					
Hypertension n (%)	131(33.7%)	0	18(23.6%)	113(36.2%)	0.052[+]
Congestive heart Failure n (%)	30(7.7%)	0	4(5.2%)	26(8.3%)	0.5[+]
Chronic pulmonary disease n (%)	48(12.3%)	0	8(10.5%)	40(12.8%)	0.72[+]
Diabetes n (%)	51(13.1%)	0	7(9.2%)	44(14.1%)	0.34[+]
Charlson Index median [IQR]	4[4-5]	1	4[4-5]	4[4-5]	**0.023***
Laboratory values median [IQR]					
White blood count (cells x 10^6/L)	8475[6227-11842]	1	9010[5940-12637]	8200[6130-11260]	0.33*
Neutrophil-lymphocyte ratio	8.57[4.82-14.65]	1	9.39[5.68-18.98]	8.73[4.52-15.20]	0.17*
Hematocrit (%)	44.1[39.8-47.6]	1	41.5[37.9-45.3]	40.8[36.7-45.7]	0.64*
Hemoglobin (g/dl)	14.7[13.4-15.92]	1	14.1[12.6-15.3]	13.6[12.3-15.17]	0.3*
LDH (U/L)	421[333.25-530]	27	445[333-558]	371.5 [293-465.75]	**0.002***
D dimer (ng/ml)	1204.5[758.5-2052]	31	1220.5[789.5-2631.7]	1611 [920.5-3198.5]	0.62*
Procalcitonin (ng/ml)	0.43[0.17-1.53]	265	0.96[0.28-1.71]	0.23[0.09-0.99]	**0.005***
Ferritin (ng/ml)	978.5[604.1-1782.25]	457	1163[416.1-2555]	953.9[583.5-1619.5]	0.44*
Oxygenation index median [IQR]					
P/F ratio at admission	168.05[108.98-232.2]	0	123.44[84.27-180.71]	185.19[110.17-236.90]	**< 0.01***
P/F ratio at the diagnosis of ARDS	165.4[108.57-227.61]	0	123.44[84.27-180.71]	180.31[107.10-227.61]	**0.0003***
Lowest P/F	72.08[54.4-121.5]	0	58.23[49.87-67.85]	88.28[66.45-163.58]	**< 0.01***
C-ARDS					
Mild n (%)	137(35.3%)	0	15(19.7%)	12239.1(51.8%)	**0.0005[+]**
Moderate n (%)	153(39.4%)	0	36(47.3%)	117(37.5%)	**0.0005[+]**
Severe n (%)	98(25.2)	0	25(38.2%)	73(23.3%)	**0.0005[+]**
Other Airway management					
Tracheostomy n (%)	4(1%)	0	4(5.2%)	0	-
Treatment					
Any steroid n (%)	316(81.4%)	0	66(86.8%)	250(80.1%)	0.235[+]
Respiratory mechanics Day 0 median [IQR]					
Tidal volume (mL)	400[360-422.5]	320	400[360-422.5]	NA	-
Tidal volume adjusted by ideal weight (mL/kg)	7.1[6.6-8.1]	320	7.1[6.6-8.1]	NA	-
Respiratory rate	16[16-18]	320	16[16-18]	NA	-
Plateau pressure (cmH_2O)	22[20-24]	350	22[20-24]	NA	-
Peak pressure (cmH_2O)	27[23.5-30]	337	27[23.5-30]	NA	-
PEEP (cmH_2O)	10[10-12]	320	10[10-12]	NA	-
Driving pressure (cmH_2O)	11[9.2-13]	350	11[9.2-13]	NA	-
Mechanic power	14.6[12.2-16.8]	352	14.6[12.2-16.8]	NA	-
Prone (hours/day)	0[0-3]	320	0[0-3]	NA	-
Outcomes					
Mortality	252(64.9%)	0	68(89.4%)	184(58.7%)	**< 0.01[+]**
Duration of mechanical ventilation (days) median [IQR]	10[6-15]	260	7[3-12]	0	-

[+]p values were obtained using Chi-square test
***p values were obtained using the Mann–Whitney test**
Bold values indicate statistically significant p values

IQR: interquartile range; LDH: lactate dehydrogenase; P/F: ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration; ARDS: acute respiratory distress syndrome; C-ARDS: COVID-19-related acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; ICU: intensive care unit; mL: millilitres; kg: kilograms; cmH2O: water centimeters; U/L: units per liter; ng/ml: nanograms per millilitre