Determination of PaO2/FiO2 after 24 hours of invasive mechanical ventilation and ΔPaO2/FiO2 at 24 hours as predictors of survival in patients diagnosed with ARDS due to COVID-19

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Introduction: Acute respiratory distress syndrome (ARDS) due to Coronavirus disease 2019 (COVID-19) causes high mortality. The objective of this study is to determine whether the arterial pressure of oxygen/inspiratory fraction of oxygen (PaO2/FiO2) 24 hours after invasive mechanical ventilation (IMV) and the difference between PaO2/FiO2 at 24 hours after IMV and PaO2/FiO2 before admission to IMV (ΔPaO2/FiO2 24h) are predictors of survival in patients with ARDS due to COVID-19. Methods: A retrospective cohort study was conducted that included patients with ARDS due to COVID-19 in IMV admitted to the intensive care unit (ICU) of a hospital in southern Peru from April 2020 to April 2021. The ROC curves and the Youden index were used to establish the cut-off point for PaO2/FiO2 at 24h of IMV and ΔPaO2/FiO2 at 24h associated with mortality. The association with mortality was determined by Cox regression, calculating the crude (cHR) and adjusted (aHR) risk ratios, with their respective 95% confidence intervals (95%CI). Results: Two hundred patients were analyzed. The average age was 54.29 years, 79% were men, and 25.5% (n=51) died. The cut-off point calculated for PaO2/FiO2 24h after IMV and ΔPaO2/FiO2 24h was 222.5 and 109.5, respectively. Those participants with a value below the cut-off point of ΔPaO2/FiO2 24h and PaO2/FiO2 24h after IMV had higher mortality, aHR=3.32 (CI95%: 1.82-6.07) and aHR=2.87 (CI95%: 1.48-5.57) respectively. Conclusion: PaO2/FiO2 24 hours after IMV and ΔPaO2/FiO2 24h in patients diagnosed with ARDS due to COVID-19 on IMV were associated with higher hospital mortality. These findings are helpful

to identify those patients with a higher risk of dying on admission to the ICU.

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2 **ΔPaO2/FiO2 at 24 hours as predictors of survival in patients diagnosed with ards due to**
3 **COVID-19**

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ABSTRACT

Introduction: Acute respiratory distress syndrome (ARDS) due to Coronavirus disease 2019 (COVID-19) causes high mortality. The objective of this study is to determine whether the arterial pressure of oxygen/inspiratory fraction of oxygen (PaO2/FiO2) 24 hours after invasive mechanical ventilation (IMV) and the difference between PaO2/FiO2 at 24 hours after IMV and PaO2/FiO2 before admission to IMV (ΔPaO2/FiO2 24h) are predictors of survival in patients with ARDS due to COVID-19.

Methods: A retrospective cohort study was conducted that included patients with ARDS due to COVID-19 in IMV admitted to the intensive care unit (ICU) of a hospital in southern Peru from April 2020 to April 2021. The ROC curves and the Youden index were used to establish the cut-off point for PaO2/FiO2 at 24h of IMV and ΔPaO2/FiO2 at 24h associated with mortality. The association with mortality was determined by Cox regression, calculating the crude (cHR) and adjusted (aHR) risk ratios, with their respective 95% confidence intervals (95%CI).

Results: Two hundred patients were analyzed. The average age was 54.29 years, 79% were men, and 25.5% (n=51) died. The cut-off point calculated for PaO2/FiO2 24h after IMV and ΔPaO2/FiO2 24h was 222.5 and 109.5, respectively. Those participants with a value below the cut-off point of ΔPaO2/FiO2 24h and PaO2/FiO2 24h after IMV had higher mortality, aHR=3.32 (CI95%: 1.82-6.07) and aHR=2.87 (CI95%: 1.48-5.57) respectively.

Conclusion: PaO2/FiO2 24 hours after IMV and ΔPaO2/FiO2 24h in patients diagnosed with ARDS due to COVID-19 on IMV were associated with higher hospital mortality. These findings are helpful to identify those patients with a higher risk of dying on admission to the ICU.

Keywords: COVID-19; SARS-CoV-2; respiratory distress syndrome, respiration, artificial; mortality; hospital mortality; critical care; Peru. (MeSH)

INTRODUCTION

A significant percentage of patients with Coronavirus disease 2019 (COVID-19) develop severe disease with respiratory failure, and some of the progress to acute respiratory distress syndrome (ARDS), requiring admission to invasive mechanical ventilation (IMV) in an intensive care unit (ICU) (1,2). The lethality in these patients can vary from 28.6% to 60.4%. (3–5)

ARDS is characterized by severe hypoxemia, reduced lung compliance, and bilateral pulmonary infiltrates on chest radiography (6). Because the diagnosis is based on different parameters, in 2012, the Berlin criteria were proposed (7), which use the relationship arterial oxygen partial pressure/inspired oxygen fraction (PaO2/FiO2) to classify the severity of the condition.

Currently, there is evidence that hypoxemia is associated with an increase in mortality in patients diagnosed with COVID-19; multiple studies have determined an association between a lower PaO2/FiO2 or oxygen pulse oximetry at hospital admission with an increase in-hospital mortality in patients with COVID-19, which can be up to 7 times higher than in patients without hypoxemia. (8–10). However, the variation in PaO2/FiO2 that would impact after 24 hours of admission to IMV on hospital outcomes is still unknown. In this context, we aimed to know if the difference between PaO2/FiO2 at 24 hours after IMV and PaO2/FiO2 before admission to IMV (ΔPaO2/FiO2 24h) is associated with mortality. In addition, we evaluate whether the increase or decrease of the PAO2/FIO2 24 hours after the VMI was associated with greater or lesser mortality in patients diagnosed with ARDS by COVID-19.

MATERIALS AND METHODS

Study design and site

A retrospective cohort study was conducted using physical and electronic medical records of patients diagnosed with ARDS due to COVID-19. The study was carried out at Hospital III Daniel Alcides Carrión, located in the district of Calana in Tacna, in southern Peru. This third-level referral hospital belongs to the Tacna Social Security Health Care Network (EsSalud). It has a capacity of 28 beds in intensive care units (ICU) (11). The study period

82   was from April 2020 to April 2021. The writing of the manuscript was carried out following

83   the recommendations of STROBE to inform observational studies. (12)

84   **Study population**

85   The study population included critically ill adult patients (≥18 years) diagnosed with ARDS

86   due to COVID-19 on IMV and hospitalized in the ICU. Diagnosis of COVID-19 was made

87   by real-time polymerase chain reaction (RT-PCR) or positive nasopharyngeal swab

88   antigenic rapid test. The diagnosis of ARDS was made according to what was proposed in

89   the Berlin criteria (13). The patients who could not confirm the diagnosis of COVID-19,

90   who were still in the ICU during data collection, and in whom complete data were not

91   available in their medical record records were excluded. The sample included all patients

92   who met the eligibility criteria within the study period.

93   **Hospital management**

94   As part of the institutional protocol for critical patient ventilatory management in our

95   hospital, all patients admitted to IMV underwent initial programming with the following

96   parameters in pressure-controlled mode: a) tidal volume 6-8ml/kg of ideal weight, b)

97   Positive end-expiratory pressure (PEEP): 8-12 cmH2O, c) Respiratory rate (RR) for Carbon

98   dioxide arterial pressure (PaCO2) between 35 and 50 mmHg and or pH >7.2 and d) FiO2

99   for pulse oximetry saturation (SatO2) between 92-96%. Additionally, all patients were

100 placed in the prone position for 48 to 72 continuous hours, which was suspended when

101 PaO2/FiO2 was ≥200 mmHg with PEEP ≤10 and FiO2 ≤40%. Likewise, all patients

102 received sufficient analgesia to allow the coupling to the IMV, associated with

103 neuromuscular blockade during the prone period. On the other hand, those patients who,

104 after coming out of pronation, presented a PaO2/FiO2 <150 or a 20% decrease in

105 PaO2/FiO2 with respect to PaO2/FiO2 in prone (with or without posterior dense pulmonary

106 infiltrates evidenced in the multicut computerized tomography) were subjected again to

107 another cycle of prone.

108 We decided to evaluate all the patients who underwent MV and were admitted to the ICU

109 and met the inclusion criteria. We calculated the statistical power of the collected sample

110 (200 patients) based on the study by Michiel T.U. Schuijt et al. (5), who reported mortality

111 at 28 days in patients with severe ARDS on the second day after admission to IMV of 44.3%

112 and 28.6% in patients with mild ARDS, also reported a ratio of unexposed to exposed of

113 6.21 (764/123). With a confidence level of 95% and 200 participants in the study sample

114 and a non-exposed/exposed ratio of 3, calculated the statistical power was at 53.5%.

115 **Data collection**

116 After reviewing all physical and digital medical records, patients were evaluated from

117 hospital admission to outcome (medical discharge or death). Sociodemographic, clinical,

118 ventilatory (before access to the IMV and 24 hours later), laboratory and imaging

119 characteristics that the radiologists reported at the time of admission to the IMV were

120 collected, the calculation of the extent of parenchymal involvement was performed by a

121 semi-quantitative scoring used in previous studies (33,34). To calculate lung damage, the

122 average percentage of lung damage reported for each lobe was used (from 0 to 100%).

123 Complications and therapies administered during the ICU stay were also evaluated.

124 Two researchers conducted data collection; Each one entered the data independently; A

125 third researcher supervised and compared the data collected; when he found any error, the

126 third researcher reviewed the medical history and corrected the error. The coded data

127 collection forms were entered into the Microsoft Excel v.2016 program and performed the

128 statistical analysis with the STATA V17.0 (Stata Corp. 2019) and Prism 9 (GraphPad

129 corporation, 2021) software.

130 **Analyzed variables**

131 Result variable

132 The outcome variable was hospital mortality, this data was collected from the medical

133 records of the patients included in the study, and the data were compared with the national

134 death registry of Peru.

135 Exposure variables

136 *Clinical characteristics and treatment*

137 The clinical characteristics were sex, age, comorbidities (obesity, DM2, hypertension, heart

138 failure, asthma, chronic kidney disease, and immunosuppression), the number of

139 comorbidities and date you entered the emergency room (2020/2021). The treatment

140 administered was antibiotics, corticosteroids, colchicine, tocilizumab, and renal

141 replacement therapy; these data were obtained from digital medical records.

142 *Ventilatory and laboratory characteristics*

143 The ventilatory characteristics were obtained from the analysis of arterial gases that were

144 brought before the patient entered mechanical ventilation; the rest of the parameters were

145 obtained from the report given by the mechanical ventilator and collected by the ICU

146 nursing staff.

147 The laboratory characteristics were obtained from the record given in the digital medical

148 records.

149 *Complications during ICU stay*

150 The most important complication was ARDS, defined according to the Berlin criteria (13).

151 The rest of the complications were: nosocomial infection, sepsis, septic shock, acute kidney

152 injury, and arrhythmias. All were diagnosed according to international criteria (2,14-16).

153 **Statistical analysis**

154 Categorical variables were described as absolute and relative frequency, and quantitative

155 variables as mean/standard deviation or median/interquartile range depending on whether

156 their distribution was normal or not. The Chi-square or Fisher's exact statistical tests were

157 used for the bivariate analysis between the categorical variables and the results. For the

158 quantitative variables, the Student's t-test was used if the assumptions were fulfilled or,

159 failing that, the Mann–Whitney U test. For the comparison with the degrees of severity of

160 ARDS, the ANOVA or Kruskal Wallis statistical tests were used according to the normality

161 of the variables.

162 We investigated the predictive capacity of ΔPaO2/FiO2 24h and PaO2/FiO2 24 hours after

163 IMV as a predictor of survival in patients with ARDS due to COVID-19. First, we calculated

164 the ROC (Receiver Operating Characteristic) curves, the ROC curve (AUC) area, and the

165 corresponding Youden indices. The highest Youden index identified the optimal cut-off

166 point. Next, the 95% CI was calculated by bootstrapping a thousand repetitions, thereby

167 generating dichotomous exposure variables for ΔPaO2/FiO2 24h and PaO2/FiO2 24 hours

168 after IMV. Then, we calculated the sensitivity, specificity, and odds ratio with their

169 respective 95% CI of the established cut-off points to predict survival. In addition, the

170 differences between the ROC curves were tested using the Chi-square test (17).

171 Finally, to answer our hypothesis, we used Cox proportional hazards models to find the

172 crude and adjusted hazard ratios (aHR) and their respective 95% confidence intervals

173 (95%CI). The variables ΔPaO2/FiO2 24h, PaO2/FiO2 24h of IMV, and ARDS severity

174 before IMV and after 24 h of IMV, as they were not independent of each other, were
175 analyzed individually in different adjusted regressions (one for each variable). In the
176 adjusted model, we included the variables: age, sex, number of comorbidities, septic shock,
177 acute renal failure, positive end-expiratory pressure, plateau pressure, driving pressure, and
178 date of admission. These variables were selected for clinical plausibility as they could
179 influence the outcome. The proportionality of the multivariate model had a value of
180 p=0.452.

181 **Ethical aspects**

182 This research followed the international guidelines of the Declaration of Helsinki. The
183 research protocol was evaluated and approved by the ethics committee of the Faculty of
184 Health Sciences of the Private University of Tacna (Identification code: N391-2021-
185 UPT/FACSA-D). Due to the retrospective observational nature of the study, they did not
186 request informed consent. All information was coded to maintain the anonymity of the
187 participants, and only the researchers had access to the data.

188 **RESULTS**

189 **Characteristics of the study population**

190 Of the 235 medical records examined, 35 did not meet our inclusion criteria (25 were still
191 hospitalized and 10 had incomplete data), so a total of 200 medical records of patients with
192 ARDS secondary to COVID-19 undergoing IMV and who were admitted to the ICU; of
193 these the 79% (n=158) were male, and the mean age was 54.29 (SD: 12.19) years. 78% (n=
194 159) of those admitted had at least one comorbidity, and the most frequent were obesity
195 (59%), hypertension (26.5%), and diabetes mellitus type 2 (21.50%). The median length of
196 hospital stays, time in the ICU, and time in IMV was 20 (IQR: 14-28) days, 10 (IQR: 5.5-
197 16) days, and 10 (IQR: 6-16) days, respectively **(Table 1).**

198 At the time of hospital admission, the median SatO2 and PaO2/FiO2 were 88% (IQR: 84.5-
199 90) and 245.5 (IQR: 165.5-297), respectively, and the mean extent of pulmonary
200 involvement on chest tomography was 61.34% (SD: 14.02). At the time of admission to
201 IMV, the median PaO2/FiO2 was 91.5 (IQR: 70-129.5); likewise, 58.5% of patients were

admitted to IMV with a diagnosis of severe ARDS, and the median SOFA score at admission was 4 (IQR: 3-5) points. Regarding the laboratory data, the median of lymphocytes, procalcitonin, and lactate dehydrogenase were 675.65 (IQR: 480-1070.4) cells/mm3, 0.14 (IQR: 0.06-0.37) ng/mL, and 757.5 (IQR: 587.5-990.5) IU/L, respectively **(Table 1).**

At 24 hours after admission to IMV, the median PaO2/FiO2 was 240 (IQR: 200-301.5), and the 24h ΔPaO2/FiO2 was 141 (105-193). Concerning ventilatory parameters, the median values for PEEP, plateau pressure, and driving pressure were 12 (IQR: 10.5-14), 28 (IQR: 26-31), and 16 (IQR: 15-18), respectively. Likewise, 74.5% of patients admitted to IMV were classified as having mild ARDS at 24 hours **(Table 1).**

During the ICU stay, 29% (n= 58) of the patients presented a nosocomial infection, with pneumonia associated with IMV being the most frequent (75.86%); however, 98.5% of the patients' received antibiotics. Furthermore, 14.5% of the patients developed acute renal failure, and 51% required renal replacement therapy. Finally, 51 patients (25.5%) of those admitted to IMV died **(Table 2).**

Bivariate analysis according to the severity of ARDS

Significant differences were observed concerning greater severity of ARDS after 24 hours in IMV in elderly patients, a greater number of comorbidities. The most frequent in this group were heart failure, chronic kidney disease, and immunosuppression. The clinical and ventilatory characteristics associated with greater severity of ARDS were, entering the emergency room with minor oxygen saturation, requiring vasopressors, a higher percentage of lung damage, and a higher SOFA score **(Supplementary Table 1).**

Bivariate analysis according to death

In the bivariate analysis, statistically significant differences were observed concerning mortality in patients with older age, with the presence of 1 or more comorbidities, and among them, mainly type 2 diabetes mellitus, heart failure, and chronic kidney disease. It was also observed that those who died had a more extended stay in the ICU (median: 14

229   days vs nine days) and IMV (median: 15 days vs eight days), lower SatO2, lower

230   PaO2/FiO2 at hospital admission, a greater pulmonary involvement in the chest tomography

231   and a higher score in the SOFA score. Likewise, the patients who died presented a lower

232   PaO2/FiO2 before entering IMV (median: 68 vs 95; p<0.001) and in the same way, at 24

233   hours after IMV, PaO2/FiO2 and ΔPaO2/ FiO2 24h were lower in the deceased with a

234   median of 190 vs 260 (p<0.001) and a median of 106 vs. 152.2 (p<0.001), respectively, than

235   in the survivors (Figure 1). At 24 hours, the proportion of patients with mild ARDS was

236   84.56% in the survivors and 45% in the deceased (p<0.001). (Table 1). It was also observed

237   that deceased patients presented higher plateau pressure, driving pressure, and higher PEEP

238   values at 24 hours of IMV and a higher incidence of ventilator-associated pneumonia, septic

239   shock, arrhythmias, and acute renal failure **(Table 2).**

240   **Determination of predictive value of PaO2/FiO2 24h after IMV and ΔPaO2/FiO2 24h**

241   PaO2/FiO2 24h after IMV has an AUC ROC of 0.75 (95% CI: 0.66 – 0.83), with 222.5

242   (95% CI: 175.85 – 269.14) being the best cut-off point to determine survival, with a

243   sensitivity and specificity of 74.5% (IC95% 66.7-81.3) and 68.6% (IC95% 54.1-80.9),

244   respectively. Similarly, the AUC ROC of ΔPaO2/FiO2 24h was 0.70 (95% CI: 0.61 – 0.78),

245   with a cut-off point of 109.5 (95% CI: 85.43–133.56), whose sensitivity and specificity were

246   81.2% (IC95% 74-87.1) and 56.9% (42.2-70.7), respectively. Although the AUC ROC of

247   PaO2/FiO2 24h after IMV was higher than ΔPaO2/FiO2 24h, no statistically significant

248   differences were observed between both curves (p=0.054). **(Figure 2, Table 3).**

249   **Multivariable model**

250   In the crude Cox regression analysis, the variables associated with mortality were moderate

251   ARDS (cHR: 2.68, 95% CI: 1.49-4.83) and severe ARDS (cHR: 13.98, 95% CI: 5.59-34-

252   93) at 24 hours of IMV, ΔPaO2/FiO2 24h <109.5 (HRc: 3.70, CI95%: 2.12-6.46),

253   PaO2/FiO2 24h after IMV <222.5 (HRc: 3.41, CI95%: 1.88-6.19).

254   In the adjusted model, an aHR 3.32 (95% CI 1.87-6.07) was obtained for ΔPaO2/FiO2 24h

255   <109.5, an aHR 2.87 (95% CI: 1.48-5.57) for PaO2/FiO2 24h <222.5 after IMV and an

256 aHR: 2.18 (CI95%: 1.13-4.12) and aHR: 9.81 (CI95%: 3.43-28.04) for moderate and severe

257 ARDS after 24 hours of IMV, respectively. **(Table 4).**

258 **DISCUSSION**

259 In the present retrospective cohort study in patients diagnosed with ARDS and critical

260 COVID-19 undergoing IMV and admitted to the ICU, overall hospital mortality of 25.5%

261 was observed. Our findings show that those patients who responded with a significant

262 increase in oxygenation and classified as having mild ARDS after 24 hours of IMV had

263 lower hospital mortality than those with moderate ARDS and severe ARDS. Likewise, we

264 identified the capacity of ΔPaO2/FiO2 24h and PaO2/FiO2 24h after IMV as predictors of

265 survival in patients with ARDS and critical COVID-19.

266 In our study, the proportion of patients admitted to IMV with severe ARDS was

267 approximately double that reported in other cohorts in France (18), the Netherlands (5.19),

268 the United Kingdom (20), and Spain (21). However, hospital mortality in our cohort was

269 like that observed in these studies. Non-invasive ventilation and high-flow oxygen are used

270 in many hospitals to reduce the number of patients who ultimately require admission to

271 IMV; Unfortunately, in our hospital, we did not have these therapeutic measures, which

272 could have influenced the high number of patients who were finally admitted to IMV.

273 We also observed that VMI entry with a diagnosis of severe ARDS was not a factor

274 associated with statistically significant mortality in the adjusted model of our study. These

275 findings could suggest that the severity of the ARDS would not be a determining forecast

276 factor in mortality, especially compared to the seriousness of the ARDS 24 hours after

277 entering VMI. But more similar studies are necessary to support these results.

278 Those patients who suffered from severe ARDS after 24 hours of IMV had a higher risk of

279 death. These findings are like those reported by the PRoVENT study in patients with ARDS

280 due to COVID-19, where they observed that patients with severe ARDS on day 2 had higher

281 mortality than patients with mild or moderate ARDS (5). Similar findings were observed in

282 the pre-COVID-19 era in the LUNG SAFE study (22). In this study, they reported that

283 patients with severe ARDS at day 2 had a substantially higher risk of death than those with

284   mild and moderate ARDS and "resolved ARDS," a term that refers to those patients who no

285   longer met the definition of ARDS. The ARDS at 24 hours of IMV occurred in up to 24%

286   of those admitted to this study. Some authors propose that these patients could constitute

287   false positives for ARDS (23), who initially met the diagnostic criteria without presenting

288   the pathophysiological processes seen in classic ARDS. It is unknown if this phenomenon

289   also occurs in patients with COVID-19.

290   In our study, PaO2/FiO2 24 hours after IMV and ΔPaO2/FiO2 24h were independent factors

291   associated with mortality, not observed with PaO2/FiO2 before intubation. This coincides

292   with previous studies in the pre-COVID-19 era, where determined that oxygenation indices

293   after 24 hours of IMV are better predictors of results in patients with ARDS (24,25).

294   However, other studies in patients with critical COVID-19 observed that a lower PaO2/FiO2

295   ratio on admission to the ICU was a factor associated with higher mortality (26,27), which

296   disagrees with our findings. Although in none of these studies, it is clear what cut-off point

297   was used for this conclusion, nor the moment of its determination with respect to intubation.

298   We also found that PaO2/FiO2 24h after IMV has a higher AUC than ΔPaO2/FiO2 24h in

299   predicting survival, although at the expense of lower sensitivity. The AUC ROC of

300   PaO2/FiO2 24h after IMV observed in our study was higher than those described by other

301   authors in the pre-COVID-19 era. Lai C, et al. (28) reported that PaO2/FiO2 24h after IMV

302   presented an AUC ROC of 0.657 and was higher than that observed on day 0 of IMV (AUC

303   ROC: 0.556). Similarly, Huber W, et al. (24) reported that the AUC ROC of the Berlin

304   definition at 24 hours was 0.664 and 0.644 at 48 hours. To our knowledge, there are no

305   studies that have evaluated the AUC of PaO2/FiO2 at 24 hours after IMV or ΔPaO2/FiO2

306   at 24 hours in patients diagnosed with ARDS due to COVID-19 in IMV. An investigation

307   in patients with ARDS due to COVID-19 in IMV evaluated the mortality prognostic

308   capacity of pulse oximetry saturation/FiO2 (SatO2/FiO2) on days 1, 2, and 3 of IMV, whose

309   AUC was 0.53, 0.62, and 0.62 respectively (29), which makes it inferior as a predictive

310   metric than PaO2/FiO2 24h after IMV and ΔPaO2/FiO2 24h observed in our study.

311   Likewise, we must highlight that all the patients in our study were placed in the prone

312   position. It is likely that this intervention increased PaO2/FiO2 after IMV, as reported by

previous observational studies in intubated patients with COVID-19 (30,31) and should be considered in future research.

On the other hand, in our environment, as in most countries with limited resources, we do not have advanced strategies for the management of refractory hypoxemia such as extracorporeal circulation membrane (ECMO), high-frequency oscillatory ventilation (HFOV), or mechanical ventilators (32) with advanced modes of mechanical ventilation, which could be considered as an early alternative tool for patients with PaO2/FiO2 less than 222.5 at 24 hours of IMV and/or with ΔPaO2/FiO2 less than 109.5, in order to guarantee MV protective and prevent hypoxemia.

This research presented some limitations, including the observational and retrospective nature of the study, which did not allow the exclusion of selection bias, nor did it allow the examination of other parameters (such as mechanical power, compliance, oxygenation index, more inflammatory markers or harmful habits). Another limitation was that the study was conducted in a single health institution with a limited number of patients. Therefore, these results could not be extrapolated to the general population. Finally, it is possible that the different measures of ventilatory therapy, such as changes in PEEP and FiO2, may have influenced PaO2/FiO2 at 24 hours of IMV; even so, it was a factor associated with mortality in the adjusted model. Therefore, prospective, multicenter studies and external validation of our findings in other populations are required.

CONCLUSIONS

PaO2/FiO2 24 hours after IMV and ΔPaO2/FiO2 24h in patients diagnosed with ARDS due to COVID-19 on IMV were factors associated with higher hospital mortality. Therefore, PaO2/FiO2, 24h after IMV, and ΔPaO2/FiO2 24h are useful variables to identify those patients with a higher risk of dying in patients with ARDS due to COVID-19 in IMV.

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Demographic, clinical, ventilatory and laboratory characteristics of the study population and comparison between survivors and deceased.

* Mean and standard deviation ** Median and interquartile range [a] Student's T for equal variances [b] Chi2 [c] U-Mann Whitney [d] Fisher's exact.

DM2: Type 2 diabetes mellitus, AHT: Arterial hypertension, ICU: Intensive care unit, IMV: Invasive mechanical ventilation, SatO2: Oxygen saturation, PaO2/FiO2: the ratio between the oxygen pressure over the inspired fraction of oxygen, SOFA: sequential organ failure assessment score, CRP: C-reactive protein, LDH: Lactate dehydrogenase, CPK: Creatinine phosphokinase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

1   **Table 1:** Demographic, clinical, ventilatory and laboratory characteristics of the study population and comparison
2   between survivors and deceased.

Variable	Total (n=200)	Survivors (n=149)	Non-Survivors (n=51)	p-Value
~~Características~~ Demographic ~~demográficas~~characteristics				
Age (years)*	54.29 (±12.19)	52.14 (±11.91)	60 (±10.89)	**<0.001** [a]
- <50 years (%)	74 (37.~~00~~)	63 (~~85~~42.28~~.14~~)	11 (~~14.82~~21.576)	**0.019** [b]
- 50-59 years (%)	58 (29.~~00~~)	42 (~~7~~28.41~~8~~)	16 (~~31~~27.37~~59~~)	
- ≥60 years (%)	68 (34.~~00~~)	44 (29.54~~64.71~~)	24 (~~35~~47.29~~06~~)	
Sex				0.777 [b]
- Female (%)	42 (21.~~00~~)	32 (~~76~~21.48~~19~~)	10 (~~23.81~~9.60)	
- Male (%)	158 (79.~~00~~)	117 (7~~8~~4.0~~5~~2)	41 (~~89~~25.40~~95~~)	
Number of comorbidities **	1 (1-2)	1 (0-2)	2 (1-3)	**0.001** [c]
- No comorbidity (%)	44 (22.~~00~~)	40 (~~90.91~~26.84)	4 (~~79.09~~85)	**0.004** [b]
- Only 1 (%)	79 (39.50)	60 (~~75.95~~40.27)	19 (~~24.05~~37.25)	
- ~~More~~ Two or more~~than 2~~ (%)	77 (38.50)	49 (~~63.64~~32.89)	28 (~~36.36~~54.90)	
Comorbidities				
- Obesity (%)	118 (59.~~00~~)	88 (~~74.58~~59.06)	30 (~~25.42~~62.74)	0.976 [b]
- DM2 (%)	43 (21.50)	27 (~~62.79~~18.12)	16 (37.~~21~~.37)	**0.047** [b]
- ~~HTA~~ AHT (%)	53 (26.50)	35 (~~66.04~~23.49)	18 (3~~5~~3.29~~6~~)	0.099 [b]
- Heart failure (%)	10 (5.~~00~~)	2 (~~20~~1.34)	8 (~~80~~15.68)	**<0.001** [d]
- Asthma (%)	30 (15.~~00~~)	17 (~~56.67~~11.41)	13 (~~43.33~~25.49)	**0.015** [b]
- Chronic kidney disease (%)	8 (4.~~00~~)	1 (~~12.50~~0.67)	7 (~~87.50~~13.72)	**<0.001** [d]
- Inmunosuppressión (%)	18 (9.~~00~~)	7 (~~38.89~~4.70)	11 (~~26~~1.11~~57~~)	**0.001** [b]
Date of admission				**<0.001**[b]
- 2020	90 (45.00)	52 (43.90)	38 (74.51)	
- 2021	110 (55.00)	97 (65.10)	13 (25.49)	
Clinical and ventilatory characteristics				
- Hospital stay time (days) **	20 (14-28)	20 (14-27)	19 (14-29)	0.721 ~~0.721~~ [c]
- Time from hospitalization to IMV (days) **	2 (1-4)	2 (1-4)	2~~1~~ (1~~2~~-4)	0.949~~760~~ [c]
- Time in ICU (days) **	10 (5.5-16)	9 (5-13)	14 (10-26)	**<0.001** [c]
- Time in IMV (days) **	10 (6-16)	8 (5-12)	15 (11-26)	**<0.001** [c]
- SatO2 (%) **	88 (84.50-90)	89 (85-91)	85 (80-90)	**0.001**[c]
- PaO2/FiO2 ratio at hospital admission**	245.5 (165.50-297)	254 (179-301)	218 (128-262)	**0.008**[c]
- PaO2/FiO2 before entering IMV	91.50 (70-128)	95 (77-130)	68 (55-113)	**0.001**[c]
- Shock and need for vasopressors (%)	70 (35.~~00~~)	34 (~~48.57~~22.81)	36 (~~51.43~~70.59)	**<0.001**[b]

- PaO2/FiO2 24h after IMV **	240 (200-301.50)	260 (222-310)	190 (144-240)	**<0.001** [c]
- ΔPaO2/FiO2 24h **	141 (105-193)	152.2 (116-198)	106 (61-156)	**<0.001** [c]
- Tidal volume 24h after IMV **	460 (427.50-506.50)	460 (425-500)	474 (430-540)	0.323 [c]
- PEEP 24h after IMV **	12 (10.50-14)	12 (10-13)	13 (12-14)	**0.003** [c]
- Inspiratory pressure 24h after IMV **	15 (14-18)	15 (14-18)	15 (14-18)	0.551 [c]
- Plateau pressure 24h after IMV **	28 (26-31)	28 (26-30)	30 (28-34)	**<0.001** [c]
- Driving pressure 24h after ~~VMI~~IMV	16 (15-18)	16 (14-18)	18(15-21)~~18 (15-21)~~	**0.005** [c]~~**0.005** [e]~~
- Number of pronations				**0.001** [b]
- One	127 (63.82)	104 (69.80~~81.29~~)	23 (45.10~~18.11~~)	
- More tha one	72 (36.18)	44 (30.20~~61.11~~)	28 (54.90~~38.89~~)	
- Time in pronation				0.148 [d]
- ≤48 hours	182 (91.46~~00~~)	138 (92.62~~75.82~~)	44 (86.27~~24.18~~)	
- >48 hours	187 (98.00~~54~~)	110 (7.38~~58.82~~)	7 (13.73~~41.18~~)	
- Lung damage on CT (%)*	61.34 (±14.02)	58.12 (±12.89)	70.76 (±12.98)	**<0.001** [a]
- SOFA upon admission to ~~VMI~~IMV	4 (3-5)	4 (3-4)	5 (4-5)	**<0.001**[c]
- Severity of ARDS at 24 h of IMV				**<0.001**[d]
- Mild (%)	149 (74.50)	126 (84.56)	23 (4~~1~~5.44~~10~~)	
- Moderate (%)	45 (22.50)	23 (5~~1~~5.11~~44~~)	22 (4~~3~~8.89~~13~~)	
- Severe (%)	6 (3.00)	0 (0.00)	6 (~~100~~11.77)	
Laboratory characteristics at admission to ~~MV~~IMV				
- Leukocytes (cells/mm3) **	9920 (6950-12630)	9240 (6870-12000)	10610 (7100-16170)	0.111 [c]
- Lymphocytes (cells/mm3) **	675.65 (480-1070.40)	680 (490-1062.80)	663.2 (405.90-1078.20)	0.890 [c]
- Platelets (cells x 10^3/L) **	283 (217-354)	293 (235-366)	243 (199-305)	**0.001** [c]
- CRP (mg/dL) **	13 (6-17.40)	12.43 (5.35-17.53)	14.19 (10.31-17.07)	0.130 [c]
- Procalcitonin (ng/mL) **	0.14 (0.06-0.37)	0.12 (0.05-0.33)	0.22 (0.12-0.50)	**0.019** [c]
- LDH (U/L) **	757.50 (587.50-990.50)	727 (585-940)	886 (642-1240)	**0.016** [c]
- CPK-Total (U/L) **	129 (66-260)	120 (64-251)	161 (79-300)	0.238 [c]
- CPK-MB (U/L) **	26.25 (20-35)	26 (19.95-34)	29.2 (21.20-53)	0.084 [c]
- AST (U/L) **	51.50 (31-82)	50 (31-79)	53 (30-84)	0.997 [c]
- ALT (U/L) **	64 (39-120)	74 (42-140)	56 (34-79)	**0.004** [c]
- Total bilirubin (mg/dL) **	0.66 (0.46-0.92)	0.64 (0.45-0.90)	0.67 (0.50-1)	0.362 [c]
- Creatinine (mg/dL) **	0.84 (0.7-1.01)	0.82 (0.70-0.94)	0.95 (0.80-1.18)	**0.001** [c]

3 * Mean and standard deviation ** Median and interquartile range [a] Student's T for equal variances [b] Chi2 [c] U-Mann Whitney [d] Fisher's exact.

4 DM2: Type 2 diabetes mellitus, AHT: Arterial hypertension, ICU: Intensive care unit, IMV: Invasive mechanical ventilation, SatO2: Oxygen
5 saturation, PaO2/FiO2: the ratio between the oxygen pressure over the inspired fraction of oxygen, SOFA: sequential organ failure assessment
6 score, CRP: C-reactive protein, LDH: Lactate dehydrogenase, CPK: Creatinine phosphokinase, AST: Aspartate aminotransferase, ALT: Alanine
7 aminotransferase.

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Complications and therapy received during the ICU stay in the study population and comparison between survivors and deceased

* Median and interquartile range a Chi2 b Fisher's exact

ICU: Intensive Care Unit, MV: Mechanical Ventilation, UTI: Urinary Tract Infection.

1 **Table 2:** Complications and therapy received during the ICU stay in the study population and comparison between
2 survivors and deceased

Variable	Total (n=200)	Survivors (n=149)	Non-Survivors (n=51)	p-Value
Complications during ICU stay				
Nosocomial infection (%)	58 (29.00)	22 (~~14.93~~14.76)	36 (~~62.07~~70.58)	**<0.001** [a]
Type of superinfection				
- Pneumonia associated with MV (%)	44 (22.00)	14 (~~31.82~~9.39)	33 (6~~48.70~~18)	**<0.001** [a]
- Catheter-associated bacteremia (%)	11 (5.50)	6 (~~54.5~~502)	5 (9~~45.45~~80)	0.152 [b]
- UTI associated with catheter (%)	3 (1.50)	2 (1~~66.67~~34)	1 (3~~31.33~~96)	0.998 [b]
Sepsis (%)	143 (71.50)	99 (~~69~~66.44.~~23~~)	44 (8~~630.2~~77)	**0.007** [a]
Septic shock (%)	58 (29.00)	24 (41~~6.38~~10)	34 (5~~866.66~~2)	**<0.001** [a]
Acute kidney failure (%)	29 (14.50)	8 (~~27.5~~379)	21 (~~72~~.41.~~17~~)	**<0.001** [a]
Arrhythmia (%)	13 (6.50)	4 (~~30.77~~2.68)	9 (17.64~~69.23~~)	**0.001** [b]
Therapies received during the ICU stay				
- Antibiotics (%)	197 (98.50)	146 (~~74.11~~97.98)	51 (~~25.89~~100.00)	0.572 [b]
- Corticosteroids (%)	194 (97.49)	144 (~~74.23~~96.64)	50 (98.03~~25.77~~)	0.998 [b]
- Colchicine (%)	52 (26.00)	34 (~~65.38~~22.81)	18 (3~~54.6~~29)	0.080 [a]
- Tocilizumab (%)	26 (13.00)	14 (~~53.85~~9.39)	12 (~~46.15~~23.52)	**0.010** [a]
- Renal replacement therapy (%)	15 (7.50)	2 (1~~3.34~~3)	13 (~~86.67~~25.49)	**<0.001** [b]

3 * Median and interquartile range a Chi2 b Fisher's exact

4 ICU: Intensive Care Unit, MV: Mechanical Ventilation, UTI: Urinary Tract Infection.

Cox regression analysis to assess predictors of death in patients hospitalized for critically ill COVID-19

cHR: crude Hazard ratio, aHR: adjusted Hazard ratio, IMV: invasive mechanical ventilation, PaO2/FiO2: fraction between arterial oxygen pressure over the inspired fraction of oxygen, ΔPaO2/FiO2 24h: the difference between PaO2/FiO2 at 24 hours after IMV and PaO2/FiO2 before admission to IMV, ARDS: Acute respiratory distress syndrome.

The variables ΔPaO2/FiO2 24h, PaO2/FiO2 24h of IMV, and severity of ARDS at admission to IMV and 24 hours later, as they were not independent of each other, were analyzed individually. The variables adjusted each one: Age, sex, number of comorbidities, septic shock, acute renal failure, positive end-expiratory pressure, plateau pressure, driving pressure and date of admission.

1   **Table 3:** Cox regression analysis to assess predictors of death in patients hospitalized for critically ill COVID-19

2   cHR: crude Hazard ratio, aHR: adjusted Hazard ratio, IMV: invasive mechanical ventilation, PaO2/FiO2: fraction between arterial oxygen pressure

Variable	cHR (95% CI)	p-Value	aHR (95% CI)	p-Value	over the inspired
ΔPaO2/FiO2 24h <109.5	3.70 (2.12-6.46)	<0.001	3.32~~01~~ (1.82~~60~~-65.07~~65~~)	≤0.001	fraction of oxygen, ΔPaO2/FiO2
PaO2/FiO2 24h IMV <222.5	3.41 (1.88-6.19)	<0.001	2.87~~56~~ (1.48~~32~~-5.57~~4.96~~)	0.002~~5~~	24h: the difference between
ARDS upon admission to IMV					PaO2/FiO2 at 24 hours
Moderate	Ref		Ref		after IMV and
Severe	1.40 (0.75-2.61)	0.280	0.91~~2~~ (0.47-1.79~~3~~)	0.806~~781~~	PaO2/FiO2 before
ARDS at 24 hours of IMV					admission to IMV, ARDS:
Mild	Ref		Ref		Acute respiratory
Moderate	2.68 (1.49-4.83)	0.001	2.18~~1.95~~ (1.13~~1.03~~-4.12~~3.66~~)	0.020~~38~~	distress syndrome.
Severe	13.98 (5.59-34.93)	<0.001	9.81~~13.64~~ (3.43~~4.95~~-28.04~~37.60~~)	<0.001	The variables ΔPaO2/FiO2 24h,

PaO2/FiO2 24h of IMV, and severity of ARDS at admission to IMV and 24 hours later, as they were not independent of each other, were analyzed individually. The variables were adjusted by: Age, sex, number of comorbidities, septic shock, acute renal failure, positive end-expiratory pressure, plateau pressure, driving pressure, and date of admission. ~~The variables adjusted each one: Age, sex, number of comorbidities, septic shock, acute renal failure, positive end-expiratory pressure, plateau pressure, driving pressure.~~

Area under the ROC curve and cut-off points with the highest AUC ROC of the variables PaO2/FiO2 24h after MV and ΔPaO2/FiO2 24h to predict survival in patients hospitalized for critically ill COVID-19

AUC: area under the curve, ROC: receptor operating characteristic, PaO2/FiO2: fraction of arterial oxygen pressure over the inspired fraction of oxygen, MV: Mechanical ventilation, ΔPaO2/FiO2 24h: the difference between PaO2/FiO2 at 24 hours after MV and PaO2/FiO2 before entering MV * p=0.054

2 **Table 4:** Area under the ROC curve and cut-off points with the highest AUC ROC of the variables
3 PaO2/FiO2 24h after MV and ΔPaO2/FiO2 24h to predict survival in patients hospitalized for critically ill
4 COVID-19

	PaO2/FiO2 24h after MV (IC 95%)	ΔPaO2/FiO2 24h (IC 95%)
AUC ROC *	0.75 (0.66 – 0.83)	0.70 (0.61 – 0.78)
Cutpoint	222.5 (175.85 – 269.14)	109.5 (85.43 – 133.56)
- **Sensitivity at cutpoint %**	74.5 (66.7-81.3)	81.2 (74.0-87.1)
- **Specificity at cutpoint %**	68.6 (54.1-80.9)	56.9 (42.2-70.7)
- **AUC ROC at cutpoint**	0.72 (0.64-0.79)	0.69 (0.65-76.58)
- **Odds ratio at cutpoint**	6.39 (3.20-12.75)	5.70 (2.87-11.31)
- **Youden index**	0.431	0.381

AUC: area under the curve, ROC: receptor operating characteristic, PaO2/Fi

18 O2: fraction of arterial oxygen pressure over the inspired fraction of oxygen, MV: Mechanical ventilation, ΔPaO2/FiO2 24h: the
19 difference between PaO2/FiO2 at 24 hours after MV and PaO2/FiO2 before entering MV

20 * p=0.054

Figure 1

Difference between a) ΔPaO2/FiO2 24 hours and b) PaO2/FiO2 24 hours after IMV in patients diagnosed with ARDS due to COVID-19 between deceased and survivors

PaO2/FiO2: fraction between the arterial pressure of oxygen over the inspired fraction of oxygen, ΔPaO2/FiO2 24h: the difference between PaO2/FiO2 at 24 hours after IMV and PaO2/FiO2 before admission to IMV
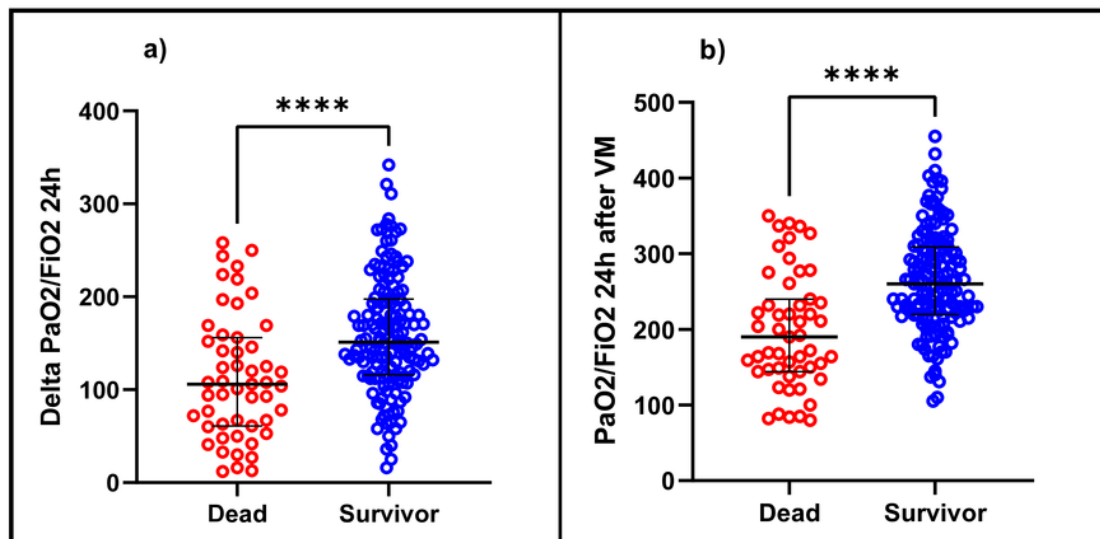
Figure 2

ROC curve and AUC ROC of PaO2/FiO2 24 hours after IMV and ΔPaO2/FiO2 24 hours to predict survival

AUC: area under the curve, ROC: receptor operating characteristic, PaO2/FiO2: fraction of arterial oxygen pressure over inspired fraction of oxygen, ΔPaO2/FiO2 24h: difference between PaO2/FiO2 at 24 hours after IMV and PaO2/FiO2 before entering IMV