Rev Enferm Atenção Saúde
2025;15(1):e20257145
DOI: 10.18554/reas.v15i1.7145
http://seer.uftm.edu.br/revistaeletronica/index.php/enfer

ORIGINAL ARTICLE

Impacts of inspired oxygen fraction and the clinical outcome of COVID-19 patients on mechanical ventilation

Impactos da fração inspirada de oxigênio e o desfecho clínico de pacientes COVID-19 em ventilação mecânica

Impacto de la fracción inspirada de oxígeno y resultado clínico de los pacientes COVID-19 en ventilación mecánica

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How to cite this article: Impacts of inspired oxygen fraction and the clinical outcome of COVID-19 patients on mechanical ventilation. Rev Enferm Atenção Saúde [Internet]. 2025 [access:____]; 15(1): e20257145. DOI: https://doi.org/10.18554/reas.v15i1.7145

Abstract

Objective: to evaluate the correlation between the average FiO2 and the outcome of these patients admitted to the Covid-19 ICU, as well as to analyze the time spent on ventilation, gender, age and days of hospitalization. **Method:** Retrospective, quantitative cohort, with patients with Covid-19 admitted to the intensive care unit of a University Hospital in Paraná-Brazil, from April 2020 to April 2021. **Results:** From the total sample (n=625), the prevalence of deaths was 73.12%, mean age 61.18 years. The average time on mechanical ventilation was 11.97 days and the average FiO2 was 52.53%. FiO2 > 60% was associated with a higher risk of death (52%). Age over 45 years was associated with a higher risk of death. A lower risk of death was identified for prolonged days of hospitalization and MV. **Conclusion:** Excessive use of oxygen is a risk factor for worse outcomes. Age was not a predictor of higher FiO2 and effective weaning was shown to be a protective factor against high oxygen concentrations.

Descriptors: Covid-19; Ventilator-Induced Lung Injury; Oxygen Inhalation Therapy; Respiration, Artificial.

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Resumo

Objetivo: avaliar a correlação entre a média de FiO2 e os desfechos de pacientes internados em UTI devido à Covid-19, analisando também o tempo de ventilação mecânica, sexo, idade e dias de internação. **Método**: Coorte retrospectiva, quantitativa, em pacientes com Covid-19 internados em UTI de um Hospital Universitário do Paraná-Brasil, de abril de 2020 a abril de 2021. **Resultados**: prevalência de óbitos foi de 73,12%, média de idade de 61,18 anos. O tempo médio de ventilação mecânica de 11,97 dias e a média de FiO2 de 52,53%. A FiO2 superior a 60% esteve associada a maior risco de óbito (52%). Idade acima de 45 anos também aumentou o risco de mortalidade. O tempo prolongado de internação e ventilação mecânica foi associado a menor risco de óbito. **Conclusão**: o uso excessivo de oxigênio é um fator de risco para piores desfechos, e o desmame eficaz protege contra altas concentrações de FiO2.

Descritores: Covid-19; Lesão Pulmonar por Ventilação Mecânica; Oxigenoterapia; respiração Artificial.

Resumen

Objetivo: evaluar la correlación entre la FiO2 promedio y el resultado de pacientes ingresados en la UCI Covid-19, así como analizar el tiempo dedicado a la ventilación, el sexo, la edad y los días de hospitalización. **Método:** Cohorte, cuantitativa y retrospectiva, con pacientes con Covid-19 ingresados en la UCI de un Hospital Universitario de Paraná-Brasil, de abril de 2020 a abril de 2021. **Resultados:** De la muestra total (n=625), se determinó la prevalencia de las defunciones fueron 73,12%, edad media 61,18 años. El tiempo promedio de ventilación mecánica fue de 11,97 días y la FiO2 promedio fue de 52,53%. FiO2 > 60% se asoció con un mayor riesgo de muerte (52%). La edad mayor de 45 años se asoció con un mayor riesgo de muerte. Se identificó un menor riesgo de muerte para días prolongados de hospitalización y VM. **Conclusión:** El uso excesivo de oxígeno es un factor de riesgo para peores resultados. La edad no fue un predictor de una mayor FiO2 y se demostró que el destete efectivo era un factor protector contra las altas concentraciones de oxígeno.

Descriptores: Covid-19; Lesión Pulmonar Inducida por Ventilación Mecánica; Terapia por Inhalación de Oxígeno; Respiración Artificial.

INTRODUCTION

During the course of the pandemic caused by the viral disease caused by SARS-Cov-2 and its variants in the world, a total of 768,187,096 cases and 6,945,714 deaths were reported by the WHO until the beginning of July 2023.[1] It is known that the pulmonary pathophysiology of COVID-19 occurs in the immunological bases and their responses. When infecting the host's target cells, the humoral immune response acts to release several pro-inflammatory chemical mediators. Therefore, the irregular response of the immune system to the virus leads to a chain of events that culminates in the destruction of pulmonary structures through cell lysis, increasing vascular permeability and the presence of interalveolar protein exudate, providing the critically ill patient with a picture of pulmonary edema and the formation of fibrotic tissue[2], which may trigger the need to apply mechanical ventilation methods.

During the use of invasive mechanical ventilation, there are different ventilatory parameters to be adopted, such as the fraction of inspired oxygen (FiO2), tidal volume, positive end-expiratory pressure (PEEP), plateau pressure and others.[3] However, most patients affected by COVID-19 disease require higher FiO2 values, with medians of up to 60 to 80%,[4]This is an alarming fact, especially due to the association between excessive use of oxygen and its deleterious effects. Furthermore, prolonged time on invasive mechanical ventilation is also associated with the outcome, with those who remain on mechanical ventilation with FiO2 greater than 60% for periods longer than 24 hours being considered at risk, especially in view of mortality and longer hospital stays.[5]

Excessive use of oxygen, defined as FiO2 >60% through the induction of hyperoxia[6] is directly related to greater toxicity of the gas, which is responsible for damage to the lung parenchyma. Damage to the lung parenchyma by Reactive Oxygen Species (ROS) causes a pathological increase in the inflammatory response, leading to cell apoptosis.[7]

Other pathological pathways to the lung parenchyma from this risk exposure are: absorptive atelectasis; direct damage to the airways; mucociliary changes and increased hypercapnia, especially in COPD patients. Systemic events may also result from elevated FiO2, such as cardiac effects secondary to coronary vasoconstriction and neurological disorders.[5]

Taking these considerations into account, the aim of this study is to evaluate the correlation between the average FiO2 and the outcome of these patients admitted to the Covid-19 ICU, as well as to analyze the time in the ventilatory regime, sex, age and days of hospitalization.

METHOD

This is an observational cohort, retrospectively identifying patients confirmed with the disease caused by COVID-19 and who required invasive mechanical ventilation (MV), during the period from April 2020 to April 2021 at a University Hospital in Paraná - Brazil.

The initial sample included 1179 patients admitted to the ICU.The inclusion criteria for the study were age over 18 years, having a positive diagnosis for COVID and having remained on invasive mechanical ventilation for at least 24 hours. On the other hand, the exclusion criteria adopted were medical records with outdated or incomplete information, in addition to those patients who were transferred to another institution.

After these criteria, the final sample consisted of 625 patients, from whom the following information was collected: sex, age, presence of comorbidity, days of hospitalization, clinical outcome, days of mechanical ventilation and the mean fraction of inspired oxygen. The codata collection was carried out using the records present in the GSUS platform®.

The mean fraction of inspired O2 was assessed during the entire invasive ventilatory regimen. FiO2 was collected from the patients' electronic medical records, and values were collected once per day of MV. The ratio between the total value of the sum of daily FiO2 and the days of mechanical ventilation was defined as the mean FiO2.

In this study, the dependent variable was the outcome of patients during the period of mechanical ventilation. The exposure variables were classified as follows: a) Patient profile - Age (up to 30, 30-45 years, 45-60, 60-80 and > 80 years) and sex (female or male); b) Related to hospitalization - Days of hospitalization (up to 5, 5-15, 15-30, 30-60 and > 60 days); days of mechanical ventilation (up to 5, 5-15, 15-30, 30-60, and > 60 days) and mean FiO2 (up to 60%, 60-80% and > 80%);

Once the data were collected, they were properly organized in a spreadsheet using the Microsoft Excel® platform. Epi Info® was used for data analysis. Statistical analysis was performed using different types of tests, including the ANOVA test, the non-parametric Kruskal-Wallis test, the Bonferroni Comparison for bivariate analysis, and linear regression, where the statistical significance value adopted will be for a p-value less than 0.05. For interpretation, categorical variables were presented in absolute and relative frequencies, bivariate analysis in relative risk (RR) and confidence intervals (95%CI), while continuous variables were presented in means and standard error.

The study was approved by the Human Research Ethics Committee (CEP) (CAAE: 31524820.9.0000.0105).

RESULTS

Of the total number of patients in this sample (n=625), 73.12% died (n=457), while 26.88% were discharged from hospital (n=168). The mean age was 61.18 years (SD±14.95), ranging from 21 to 98 years. In addition, 57.8% of this group were men (n=355) and 43.2% (n=270) were women.

Clinically, the mean number of days of hospitalization was 13.87 days (SD±10.02), ranging from 1 to 94 days, while the mean length of stay on mechanical

ventilation was 11.97 days (SD±9.23), ranging from 1 to 69 days. Regarding FiO2, the mean found among all patients was 52.53% (SD±16.63), ranging from 25 to 100%.

Table 1- Analysis of the means of continuous variables related to the clinical condition of COVID-19 positive patients undergoing MV in an ICU of a University Hospital in Paraná. Brazil, 2020 to 2021.

VARIABLES	OUTCOME				TOTAL	DP	p-value
	DEATH		HIGH				
	average	DP	Average	DP			
HOSPITALIZATION DAYS	13.01	±9.29	16.22	±11.50	13.87	±10.2	**<0.01**
AGE	63.33	±14.43	55.30	±14.78	61.18	±14.94	**0.01**
VM DAYS	11.46	±8.79	13.36	±10.22	11.97	±9.23	**0.025**
AVERAGE FiO2	56.48	±17.15	41.77	±8.39	52,53	±16.63	**<0.01**

Source: authors, 2023.

In the bivariate analysis performed with the cohort, the following groups presented a statistically significant association with the outcome of death: age over 45 years; presence of comorbidities; days of hospitalization; days of mechanical ventilation; and mean FiO2. These variables will be individually discussed below.

The mean age among those who died was 63.33 years (SD±14.43) and among those who were discharged, it was 55.3 years (SD±14.78) (p=0.01). Compared to the group up to 30 years old, the other age groups presented an increasing risk proportional to the increase in age, with the risk of death doubling for the group over 80 years old. Statistical significance was not found only for the group between 30 and 45 years old.

In the variables related to individuals, men presented a higher risk of worse outcomes; however, even representing 58.64% of deaths, there was no statistical association.

The average length of hospital stay among deaths was 13.01 days (SD±9.29) and among discharges it was 16.22 days (SD±11.5) (p<0.01). In bivariate analysis, there was an inversion of mortality risk over time, with longer hospital stays presenting lower risks of progression to death. However, even with a statistical difference,

to interpret the results presented above, one must consider the high mortality rate during the first 5 days of hospital stay, where the prevalence of deaths in this group was 91.4%.

The mean number of days on mechanical ventilation for patients who died was 11.46 days (SD±8.79) and for those who were discharged, it was 13.36 (SD±10.22) (p=0.025). Similarly to the days of hospitalization, when comparing the days in which these patients remained on mechanical ventilation, the risk of death was inversely proportional to the time on MV.

The overall mean fraction of inspired oxygen for this study was 52.53% (SD±16.63), with the mean FiO2 among deaths being 56.48% (SD±17.15) and among discharges being 41.77% (SD±8.39) (p<0.01). In the bivariate analysis of the mean FiO2, fractions of inspired oxygen above 60% had a higher risk of death, and this result was statistically significant.

Table 2- Bivariate analysis of variables associated with the hospitalization of COVID-19 patients admitted under MV in an ICU of a University Hospital in Paraná. Brazil, 2020 to 2021.

VARIABLES	OUTCOME				RR	95%CI	p-value
	DEATH		HIGH				
	n	%	n	%			
AGE							
Up to 30 years	8	44.4	10	55.6	1.0	-	-
Between 30 and 45 years old	40	56.3	31	43.7	1.26	[0.73 – 2.21]	0.365
Between 45 and 60 years old	122	70.1	52	29.9	1.57	[0.93 – 2.67]	**0.026**
Between 60 and 80 years old	232	76.8	70	23.2	1.73	[1.02 – 2.91]	**<0.01**
Over 80 years old	56	91.8	5	8.2	2.06	[1.22 – 3.48]	**<0.01**
SEX							
Feminine	189	70	81	30	1.0	-	-
Masculine	268	75.5	87	24.5	1.08	[0.97 – 1.19]	0.125
HOSPITALIZATION DAYS							
Up to 5 days	74	91.4	7	8.6	1.0	-	-
Between 5 and 15 days	227	73.7	81	26.3	0.81	[0.73 – 0.88]	**<0.01**

Between 15 and 30 days	130	66	67	34	0.72	[0.64 – 0.81]	<**0.01**
Between 30 and 60 days	26	70.3	11	29.7	0.77	[0.61 – 0.95]	<**0.01**
More than 60 days	1	33.3	2	6.7	0.36	[0.07 – 1.81]	**0.03**
VM DAYS							
Up to 5 days	103	83.7	20	16.3	1.0	-	-
Between 5 and 15 days	214	70	92	30	0.83	[0.75 – 0.93]	<**0.01**
Between 15 and 30 days	121	72.9	45	27.1	0.87	[0.77 – 0.98]	**0.03**
Between 30 and 60 days	20	66.7	10	33.3	0.80	[0.61 – 1.03]	**0.03**
More than 60 days	0	0	1	100	-	-	-
AVERAGE FIO2							
Up to 60%	294	64.3	163	35.7	1.0	-	-
Between 60 and 80%	115	96.6	4	3.4	1.5	[1.39 – 1.62]	<**0.01**
Greater than 80%	49	98	1	2	1.52	[1.40 – 1.64]	<**0.01**

Source: The authors, 2023.

DISCUSSION

Comparing the results obtained in hospital-based studies is a complex task and requires extensive research, especially when dealing with studies related to the Sars-Cov-2 pandemic. However, due to the great academic and research contribution, this discussion becomes richer and more in-depth.

Other studies addressing the theme of Covid-19 present very clear and concise data on the epidemiological profile of this disease, including differences between the sexes. In the present study, a higher prevalence of males was identified; however, the progression to a worse outcome among men was not identified with statistical significance (p=0.125). It is likely that the aforementioned result is in line with sampling issues.

In literature, related to the most severe condition, there are almost three times more chances of men being admitted to an intensive care unit, and almost 40% more chances of developing worse outcomes when compared to the female population.[8]In another study of 5,700 patients, the percentage of men hospitalized for COVID-19 was around 60%, consistent with the present study.[9]It is believed that this fact is linked to the greater expression of angiotensin-converting enzyme

receptors, which is important for the pathophysiology of the viral disease, in addition to ineffective care of health conditions.[10]

Regarding age, all age groups are susceptible to acquiring SARS-COV-2 infection; however, middle-aged and elderly adults are at higher risk for severe forms of the disease and consequently worse prognoses. In this study, age over 45 years was shown to be a statistically significant factor for worse outcomes in the overall comparison (p=0.01). In other words, there was a large increase in the risk of fatality in the group between 60 and 80 years old, and this increase was even greater for the group over 80 years old.

In another study, the fatality rates among the 70-79 and over-80 age groups were 8 and 15% respectively, while the overall fatality rate for the study was 2.3%.[11]It has even been found that there is a 20 times greater risk of death in patients over 80 years of age when compared to individuals aged 50 to 59 years.[12] This greater risk conferred to the elderly population is currently related to the effects of senescence on the immune system, increasing morbidity and mortality related to infections in elderly patients, in addition to the greater prevalence of comorbidities in this population.[13]

The average length of ICU stay found in the sample was 13.87 days (SD±10.02), contrasting with other Brazilian studies in which the variation in this average was nine[14] up to twenty-two days.[15] The analysis showed a reduction in the risk of mortality for patients with longer periods of hospitalization in the intensive care unit. This fact was related by the researchers to the high mortality rate of patients in the comparison group (up to 5 days), causing the relative risk of death to decrease when compared to the length of hospitalization.

In most cases, several days of invasive ventilation are required for severe conditions to improve. In this study, the mean number of days on ventilation for fatal cases was 11.46 days (SD±8.79), while for those who were discharged it was 13.36 (SD±10.22) (p=0.025). In another Brazilian study with 1,296 patients, a mean of 9 and 17 days was observed for survivors and non-survivors, respectively.[16] In the present sample, there was a reduction in the risk of mortality for patients with longer periods on MV, and as with days of hospitalization, it was related to the higher mortality rate in the compared group – up to 5 days on MV, in addition to the ventilatory improvement achieved in survivors.

When trying to correlate the days of MV with the mean FiO2, an inversely

proportional relationship was observed, this being a result linked to ventilatory weaning, which includes the gradual reduction of the oxygen fraction, in addition to the clinical-ventilatory improvement of these patients. Even if this variable alone does not explain the variability of FiO2, a lower exposure to high fractions of inspired oxygen during the ventilatory weaning process can be considered.

The correlation between the fraction of inspired oxygen and mortality in patients with severe acute respiratory syndrome (SARS) has already been studied. However, assessing the specific magnitude of the damage caused to the lung parenchyma by its excessive use is a complex activity, since other factors can confuse the analysis, such as comorbidities, special conditions, other injuries and especially the severity of SARS.

In the present study, patients who received high FiO2 during hospitalization had an approximately 51% higher risk of death when compared to the group that received up to 60%. Another relevant data is the difference between the standard deviation of the mean FiO2 of discharges (SD± 8.39) and deaths (SD±17.15), demonstrating greater uniformity between the use of oxygen for survivors. A study addressed the presence of hyperoxemia between the first and second day of MV in COVID-19 patients, denoting its presence in approximately 68% and 63% of patients on the first and second day of MV, respectively.[6]

The result obtained was attributed to two main events: the severity of SARS, which requires higher FiO2 and presents worse outcomes; and the deleterious effects of oxygen when administered in high concentrations, such as damage to the parenchyma by ROS, absorptive atelectasis, increased hypercapnia, coronary vasoconstriction and neurological effects.[5]

The results obtained are directly related to the daily routine of intensive care units and are of interest for research as well as clinical practice. All those involved in the multidisciplinary team must be aware of the predictors of worse outcomes and risk factors. Among these, nursing professionals stand out, as they are responsible for direct nursing care for critically ill patients at risk of death.[17] The nurse's in-depth knowledge of the subject allows them to develop critical skills for decision-making, since it is their responsibility to handle MV parameters, as long as it is under medical coordination.[18]

Caring for a critically ill patient with Covid-19 required the application of actions aimed at the physiological and human needs

of each patient, as well as the operationalization of the entire ICU (with human, structural, psychological and material resources) in matters of advanced support for these patients. However, given all the difficulties faced in these three years of pandemic, it is known that health professionals were able to provide a significant contribution to patients.[19]

In this way, knowledge and guidance about the potential risk of high concentrations of oxygen gas, and the importance of ventilatory weaning, guarantee safety and reduce unnecessary harm to patients.

CONCLUSION

The fraction of inspired oxygen at a concentration greater than 60% was significantly associated with worse outcomes, which may be related to more severe clinical conditions and the deleterious effects of oxygen. The result mentioned above demonstrates the effective association between the use of oxygen in high fractions and the worst clinical outcome, and this information is of utmost importance for care aimed at reducing the deleterious effects of this therapy. In contrast, age and time spent on mechanical ventilation were not directly associated with higher FiO2.

Age over 45 years and the presence of comorbidities were associated with a higher risk of mortality. Furthermore, prolonged hospitalization and mechanical ventilation days were associated with better outcomes; however, this may be attributed to a confounding factor related to sampling and analysis issues, resulting in a spurious association.

In this context, it is necessary to review and implement clinical practices aimed at reducing the excessive use of FiO2, especially given the increased risk of mortality among these patients. Finally, ensuring effective and early ventilatory weaning was attributed as a partially predictive factor of lower exposure to excessive inspired oxygen fractions.

The current study has limitations, including those related to the retrospective nature of the cohort and the large reduction in the initial sample, with 46.98% of patients being discarded by the exclusion criteria, in particular, the lack of complete information in the electronic medical record. Furthermore, clearly delimiting the effects of excessive oxygen use alone is a complex task, since other factors play a pathological role in these patients.

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RECEIVED: 11/07/24
APPROVED: 05/0205/25
PUBLISHED: 05/2025