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ARTIGO ORIGINAL

Clinical and epidemiological characteristics and factors associated with mortality in adult patients admitted by COVID -19 in intensive care

Características clínicas, epidemiológicas e fatores associados à mortalidade em pacientes adultos internados por COVID -19 em unidade de terapia intensiva

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Abstract

Objectives: We conducted a retrospective, observational, case-control type study to define the clinical and epidemiological characteristics and factors associated with death in the intensive care of these patients. **Methodology**: We reviewed the medical records and examinations of 72 patients with confirmed diagnosis of SARS-CoV-2 infection in our intensive care unit (ICU). **Results**: In the review, 20 patients died during hospitalization, and 52 were discharged from the ICU. Associated with mortality, we verified, after analysis, that age, male gender, smoking, troponin levels, creatinine, lymphocytes, bilirubin, and respiratory compliance were statistically significant. SOFA, APACHE 2, and SAPS 2 scores were good predictors of ICU mortality in this population. **Conclusion**: Despite several limitations, our study was able to demonstrate a series of clinical and laboratory factors associated with ICU death by COVID-19, compatible with international and multicenter case series.

Keywords: Coronavirus. Adult Respiratory Discomfort Syndrome. Critical Care

Resumo

Objetivo: Realizamos um estudo retrospectivo, observacional, tipo caso-controle com o objetivo de definir as características clínicas, epidemiológicas e fatores associados à morte em terapia intensiva desses pacientes. **Metodologia:** Revisamos os prontuários e exames de 72 pacientes com diagnóstico confirmado de infecção por SARS-CoV-2 em nossa unidade de terapia intensiva (UTI), realizando uma análise de fatores associados a óbito em terapia intensiva em nossa população. **Resultados**: Em nosso centro, 20 pacientes morreram durante o internamento, e 52 tiveram alta da UTI. Associado à mortalidade, verificamos, após análise, que idade, sexo masculino, tabagismo, níveis de troponina, creatinina, linfócitos, bilirrubinas e complacência respiratória tiveram significância estatística. Os escores SOFA, APACHE 3 e SAPS 2 foram bons preditores de mortalidade em UTI nessa população em nosso meio. **Conclusão:** Apesar das várias limitações, nosso estudo conseguiu demostrar uma série de fatores clínicos e laboratoriais associados a óbito em UTI por COVID-19, compatível com séries de casos internacionais e multicêntricas.

Palavras-chave: Coronavírus. Síndrome do Desconforto Respiratório do Adulto. Cuidados Críticos.

INTRODUCTION

At the end of 2019, a new coronavirus was identified as the cause of a set of pneumonia cases in Hubei province, China, resulting in an epidemic throughout the country, followed by an increasing number of cases in other countries in the world[1]. In February 2020, the World Health Organization named the disease COVID-19, the virus that causes COVID-19 is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In Brazil, we have about 4 million cases and 120,000 deaths reported so far, 200,000 of these patients in the state of Ceará, having around 8,000 deaths.

The full spectrum of Covid-19 ranges from mild, self-limited disease of the respiratory tract to severe progressive pneumonia, multi-organ failure and death[2]. In China, factors associated with mortality were age, presence of comorbidities, smoking, immunosuppression. Laboratory data such as lymphopenia, d-dimer and ferritin also correlated with severity[3].

In intensive care, mortality is estimated to vary from 40 - 100 %, depending on local variables[4]. It is suggested that the exhaustion of intensive care capacity, such as lack of life support devices and medical teams may contribute to the high mortality of these patients[2, 5-8].

Data on the clinical characteristics and outcomes of critical patients with SARS-CoV-2 infection are scarce in our population, but of paramount importance for the understanding of the disease in our environment and for the reduction of mortality. Our study evaluated patients severely ill with laboratory confirmed SARS-CoV-2 pneumonia who were admitted to São

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Carlos Hospital.

METHODOLOGY

The study was approved by the research ethics committee of Hospital São Carlos, with a favorable opinion number of 4,168,585, in accordance with Resolution 466/12 of the National Health Council.

We perfomed an analytical, observational and retrospective study in which we evaluated adult patients severely ill with SARS-CoV-2 pneumonia who were admitted to the intensive care unit (ICU) of the São Carlos hospital (Fortaleza, Brazil) between March 2020 and July 2020.

The study was case-control type, having as a group of cases patients with PCR (polymerase chain reaction) positive for SARS - CoV 2 in nasal swab collection, pharyngeal or bronchoalveolar lavage that evolved to death and, in the control group, patients with PCR positive survivors 28 days after admission.

The admission records of 72 patients were retrospectively reviewed in the period between March and July 2020 at Hospital São Carlos. Clinical data, including initial symptoms, past medical history, date of hospitalization, treatment, radiological and laboratory changes were obtained directly through the institutional electronic patient database. Patients with were included:

1. COVID-19 confirmed by nasal, oropharyngeal or tracheal sample PCR.
2. Documented outcome in 30 days (hospital discharge or death).

All patients were treated according to local and national guidelines[9], including oxygen support for saturation <94%, early intubation in case of clinical deterioration, hemodynamic support, high-dose anticoagulant (40 mg enoxaparin twice a day or equivalent), broad spectrum antibiotics, 80 mg prednisone or equivalent corticoid, neuromuscular blockade and prone position in refractory cases, according to protocols[10-12].

The categorical quantitative results were presented in the form of percentages and counts and the numerical results in the form of central tendency measures. Kolmogorov-Smirnov normality tests were performed for the numerical variables. For categorical variables, the chi-square test was used to verify association between categorical variables and Mann-Whitney or Kruskall-Wallis for non-parametric numerical variables. Significant p values below 0.05 were considered. The data obtained in the collection were tabulated and analyzed by IBM SPSS Statistics for Windows, Version 23.0 software. Armonk, NY: IBM Corp. IBM Corp. Released 2015

RESULTS

We evaluated 72 adult patients hospitalized at Hospital São Carlos with diagnosis of SARS-COV2 pneumonia, confirmed by detection of RNA SARS-CoV-2 year between March and June 2020. In the final analysis, 20 patients died during hospitalization and 52 were discharged from the ICU. The mean age of the patients was 72 years, ranging from 28 years to 92 years, and most were male (table 1). Comorbidities were present in almost half of the patients, with hypertension (49 patients or 69.0%) being the most common comorbidity, followed by diabetes, obesity and coronary diseases (table 1). Regarding smoking, 7 patients (9.7%) were active smokers. The most common symptoms at admission were fever (57 patients or 82.6%), dyspnea (58 or 84.1%) and cough (45 patients or 65.2%), followed by adynamia, coryza and diarrhea (table 1).

Table 1. Clinical and epidemiological characteristics

Clinical and epidemiological characteristics	Survivors (n =52)	Deaths (n = 20)	Total (n = 72)	P-value
Age (years)	69.5 (38.0-92.0)	79.0 (28.0-90.0)	72.0 (28.0-92.0)	0.0020
Sex	-	-	-	0.0407
F	21 (40.4%)	3 (15.0%)	24 (33.3%)	
M	31 (59.6%)	17 (85.0%)	48 (66.7%)	
Hospitalization time (days)	14.0 (3.0-126.0)	27.5 (2.0-90.0)	15.5 (2.0-126.0)	0.0365
APACHE 2	13 (3-27)	20 (13-32)	14 (3-32)	<.0001
SOFA	7.5 (2.0-15.0)	12.5 (3.0-33.0)	8.0 (2.0-33.0)	0.001
SAPS	33.0 (8.0-70.0)	57.5 (28.0-84.0)	40.0 (8.0-84.0)	<.00011
Smoking	2 (3.8%)	5 (25.0%)	7 (9.7%)	0.00672
Etilism	2 (3.8%)	3 (15.0%)	5 (6.9%)	0.09542
Dyslipidemia	2 (3.8%)	2 (10.5%)	4 (5.6%)	0.27982
Diabetes Mellitus	19 (36.5%)	10 (52.6%)	29 (40.8%)	0.22202
Hypertension	36 (69.2%)	13 (68.4%)	49 (69.0%)	0.94792

Clinical and epidemiological characteristics	Survivors (n =52)	Deaths (n = 20)	Total (n = 72)	P-value
Obesity	7 (13.5%)	0 (0.0%)	7 (9.9%)	0.09212
Coronary Arterial Disease	3 (5.8%)	3 (15.8%)	6 (8.5%)	0.17902
Chronic Renal Disease	2 (3.8%)	1 (5.3%)	3 (4.2%)	0.79272
Heart Failure	3 (5.8%)	3 (15.8%)	6 (8.5%)	0.17902
Asthma	2 (3.8%)	0 (0.0%)	2 (2.8%)	0.38592
Cardiopathy	1 (1.9%)	0 (0.0%)	1 (1.4%)	0.54272
Dementia	1 (1.9%)	2 (10.5%)	3 (4.2%)	0.11062
Travel	3 (6.0%)	1 (5.6%)	4 (5.9%)	0.94522
Known contact with COVID	22 (46.8%)	4 (23.5%)	26 (40.6%)	0.09402
Cough	35 (68.6%)	10 (55.6%)	45 (65.2%)	0.31682
Mialgia	14 (27.5%)	4 (22.2%)	18 (26.1%)	0.66402
Fever	45 (88.2%)	12 (66.7%)	57 (82.6%)	0.05722
Coriza	12 (23.5%)	7 (38.9%)	19 (27.5%)	0.20982
Dispnea	44 (86.3%)	14 (77.8%)	58 (84.1%)	0.39722
Diarrhea	6 (11.8%)	3 (16.7%)	9 (13.0%)	0.59552
Adinamia	6 (11.8%)	6 (33.3%)	12 (17.4%)	0.03792
Odinofagia	5 (9.8%)	2 (11.1%)	7 (10.1%)	0.87452
Thoracic pain	1 (2.0%)	0 (0.0%)	1 (1.4%)	0.54952
Lowering the level of consciousness	3 (5.9%)	1 (5.6%)	4 (5.8%)	0.95932
Oxygen therapy	51 (100.0%)	20 (100.0%)	71 (100.0%)	
Mechanical Ventilation	40 (76.9%)	18 (94.7%)	58 (81.7%)	0.08582
Orotracheal Intubation Days	14.0 (3.0-60.0)	21.0 (3.0-60.0)	14.0 (3.0, 60.0)	0.22201
Tracheostomy	12 (25.5%)	6 (31.6%)	18 (27.3%)	0.61752
Lower Oxygenation Index (PAO2 / Wire2)	140.0 (69.0-227.0)	135.0 (80.0-250.0)	140.0 (69.0-250.0)	0.49151
Plateau Pressure (worst mechanical)	25.0 (18.0-35.0)	25.0 (15.0-35.0)	25.0 (15.0-35.0)	0.12471
Complacency	40.0 (15.0-55.0)	30.0 (10.0-50.0)	36.0 (10.0-55.0)	0.01761
Neuromuscular Blockade	25 (54.3%)	10 (50.0%)	35 (53.0%)	0.74502
Use of vasopressor	32 (62.7%)	16 (84.2%)	48 (68.6%)	0.08542
Prona Position	7 (14.9%)	3 (15.0%)	10 (14.9%)	0.99112

The mean time of ICU stay was 15.5 days, and 58 patients (81.7%) needed invasive ventilatory support for an average time of 14 days, with no significant difference in the mechanical ventilation rate between groups. Tracheostomy was necessary in 18 patients (27.3%). The oxygenation index varied between 69.0-250.0, with a mean of 140. In terms of ventilatory mechanics, the mean plateau pressure was 25 mmHg (ranging from 15.0-35.0) and static compliance varied from 10 to 55 ml/cmH2O, with a mean of 36 ml/cmH2O. According to national protocols, 10 patients (14.9%) were proned for at least 16 hours and 35 patients (53.0%) used neuromuscular blocker, mostly cisatracurium, for at least 48 hours. All patients in our ICU used oxygen support.

Regarding complications, 48 patients (68.6%) required vasopressor use, 37 (51.4%) evolved with hospital pneumonia, 7 (9.7%) with bloodstream infection and 21 (29.2%) with CAM-ICU diagnosed delirium. Acute kidney injury requiring hemodialysis occurred in 24 patients (33%). Pulmonary embolism was documented in 4 (5.6%).

The average percentage of tomographic involvement of patients was 50% from visual estimates. The lymphocytic count at admission was 779 cells mm3, ranging from 182 - 2850. The mean dimer-D levels were 2.0 milligrams per deciliter, ranging from 0.5 to 20.0.

In univariate analysis, the probabilities of intra-hospital death were higher in male patients (p = 0.04), active smokers (0.0067), and patients with lower respiratory compliance (p=0.0176)

(table 1). Age was also associated with higher mortality (p = 0.020). In the admission laboratory tests, high lymphopenia, aspartate aminotranferase (AST), serum bilirubin, creatinine levels and cardiac troponin levels were associated with mortality.

Serum d-dimer levels and visual estimation of tomographic involvement were more pronounced in patients who evolved to death, but this difference had no statistical significance (table 2). The most used severity scores in intensive care unit Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health disease Classification System II (APACHE 2) and Simplified Acute Physiology Score (SAPS 2) were good predictors of in-hospital mortality at admission.

Table 2. Laboratory tests and image and relation with mortality.

Laboratory and imaging examinations	Survivors (n =52)	Deaths (n = 20)	Total (n = 72)	P-value
Quantitative troponin	14.0 (0.0-1000.0)	70.0 (10.0-1499.0)	22.0 (0.0-1499.0)	0.00041
Troponin > 6x	16 (32.0%)	14 (73.7%)	30 (43.5%)	0.00182
Quantitative D-dimer	1.8 (0.0-20.0)	2.9 (0.5-20.0)	2.0 (0.0-20.0)	0.10101
D-dimer changed > 6x	13 (25.0%)	8 (44.4%)	21 (30.0%)	0.12082
Creatinine	1.1 (0.3-9.0)	1.9 (0.0-5.9)	1.3 (0.0-9.0)	0.0080
Lymphocytes	918.0 (335.0-2850.0)	497.5 (182.0-1250.0)	779.0 (182.0-2850.0)	<.0001
AST	45.0 (15.0-2010.0)	68.0 (11.0-745.0)	50.0 (11.0-2010.0)	0.0242
ALT	47.0 (13.0-1352.0)	52.0 (20.0-1618.0)	49.0 (13.0-1618.0)	0.3235
Bilirubina	0.3 (0.1-11.0)	0.8 (0.2-76.0)	0.4 (0.1-76.0)	0.0006
Chest CT (% involvement)	50.0 (25.0-100.0)	75.0 (25.0-100.0)	50 (25.0-100.0)	0.28711

There were 5 cases of pumonary thromboembolism (4 embolism and 1 peripheral thrombosis) documented and 1 case of stroke. Two patients using SGLT-2 inhibitors for diabetes were admitted with diabetic ketoacidosis (table 3).

Table 3. Complications during hospital stay.

Complications	Survivors (n =52)	Deaths (n = 20)	Total (n = 72)	P-value
Cerebral Vascular Accident	0 (0.0%)	1 (5.3%)	1 (1.4%)	0.09572
Peripheral Venous Thrombosis	0 (0.0%)	1 (5.3%)	1 (1.4%)	0.09572
Pneumonia	28 (53.8%)	9 (45.0%)	37 (51.4%)	0.50122
Bloodstream infection	5 (9.6%)	2 (10.0%)	7 (9.7%)	0.96062
Delirium	19 (36.5%)	2 (10.0%)	21 (29.2%)	0.02652
Pulmonary thromboembolism	2 (3.8%)	2 (10.0%)	4 (5.6%)	0.30722
Cetoacidosis	2 (3.8%)	0 (0.0%)	2 (2.8%)	0.37372

DISCUSSION

This retrospective study identified several risk factors for death in adults in Fortaleza. In correspondence with previous studies, older male patients, with a mean age of 79.0 years, were more prone to poor outcomes related to COVID-19. SOFA, APACHE 2 and SAPS 2 high scores were associated with higher probability of hospital death.

So far, some previous studies have indicated multiple risk factors associated with poor prognosis, such as impaired respiratory status, advanced age, male gender, lymphocytopenia, high score of Sequential Assessment of Organ Failure and high levels of c-reactive protein, lactate dehydrogenase, d-dimer[2, 4-7,13-22]. Our study corroborates a good part of these markers of poor prognosis, helping in the validation of these parameters at regional level.

The initial ventilatory parameters such as plateau pressure and oxygenation index were similar in both groups. We know that there is great pulmonary heterogeneity in patients with this pathology. Although the pulmonary pattern of severe patients with COVID-19 has been defined as acute respiratory distress syndrome (ARDS), it does not always represent or resemble ARDS[23]. In our study, patients with low static compliance after intubation had higher mortality, possibly because they behaved like classical ARDS.

The increase in d-dimer, a product of fibrin degradation, is reported as a factor associated with higher mortality[24-26], a

fact not found in our study. Due to the fact that we routinely use high doses of anticoagulant in our service, the impact of thrombosis was potentially reduced, not reaching statistical significance. This fact is corroborated by the low incidence of documented thrombotic and ischemic events in our patients. A patient who evolved to death opened the picture with a cerebral ischemic event associated with COVID-19, a condition previously described in several studies[27, 28].

High levels of transaminases and bilirubin were associated with a worse prognosis with a median AST of 68.0 u/L (ranging from 11.0-745.0) and bilirubin 0.8 mg/dl (ranging from 0.2-76.0) in patients with a lethal outcome. We found a high rate of liver damage in our critical patients with COVID- 19, similar to previous studies[29, 30]. Liver damage may be associated with the organ-specific immune response to coronavirus or secondary to hypoxemia, systemic inflammatory response and drugs. Our study indicates that these parameters should be monitored during admission and hospitalization.

The Creatinine level was significantly higher at the admission of patients with COVID-19, since out of a total of 72 patients, 24 evolved to dialysis renal failure, demonstrating the need to monitor renal function in these patients[31].

Our study has several limitations. Firstly, due to the retrospective conception of the study, not all laboratory tests were performed on all patients. Secondly, for data analysis the laboratory dosages of the admission were considered, which may underestimate the risk of death associated with these data. Some patients did not have daily documentation of pulmonary mechanics, which may lead to error in the correct interpretation of these data and their impact. We do not have long-term follow-up data for outpatients and those discharged; therefore, the clinical result observed may not reflect the true result. The study was restricted by the heterogeneity of treatments based on the disease situation over time, which was practically impossible to summarize in this compilation.

CONCLUSION

Despite several limitations, our study was able to demonstrate a series of clinical and laboratory factors associated with ICU death by COVID-19, compatible with international and multicenter case series.

SOFA, APACHE 2 and SAPS 2 scores were good predictors of hospital mortality by COVID-19 and can be a useful tool for screening patients with high risk of death.

Highlights

Usual ICU scores and simple lab tests (creatinine, bilirubin, troponins, Liver enzymes) can predict mortality in critical patients with COVID 19 .

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