ANALYSIS OF THE IMPACT OF COMORBIDITIES ON THE MORTALITY OF PATIENTS HOSPITALIZED WITH COVID-19

Ana Teresa Sobreira Lima Verde[1], Ana Vitória Magalhães Chaves[1], Yara Ceres e Silva Ferreira Lima[1], Yuri Lopes Nassar[1], Marília de Oliveira Bringel[1], Fernando Barroso Duarte[1]

1 Hospital Universitário Walter Cantídio

Correspondence to: Ana Teresa Sobreira Lima Verde (anateresa.sobreira@gmail.com)

ABSTRACT

Introduction: SARS-CoV-2 has resulted in a pandemic since March 2020. The knowledge of the impact of risk factors is fundamental for its adequate treatment. This study aims to analyze the impact of comorbidities and transplant of solid organs and tissues in patients who were hospitalized because of Covid-19. Methods: There were collected data from 457 patients that had been diagnosed with Covid-19 who were hospitalized in a ward or in an intensive care unit (ICU) at a university hospital. All the patients were sorted for history of transplant of solid organs and tissues. The laboratory results of admission, place of hospitalization and outcome were compared among the group of transplanted and non-transplanted patients. Results: In total, there were collected 457 patient's data that had been diagnosed with Covid-19. The lethality in our service was 17,94%. The mortality of patients hospitalized in ICUs was 57,14%. The patients that presented hypertension (48,36%) showed a mortality level of 23,53% versus 12,71% who did not. Differently from the previous comorbidity, DM-2 showed no statistical significance. Transplanted patients had 2,13 more chances of being hospitalized in the ICU than in the ward. Also, transplanted patients had 2,21 more chances of death. The mortality in kidney transplant patients was 35.29%, liver transplant was 23.08% and allogenic bone marrow transplant 33.33%. Conclusion: In our sample of patients that had been hospitalized with COVID-19, the prior diagnosis of hypertension and transplant showed higher levels of mortality, mainly kidney transplantated patients (35.29%).

INTRODUCTION

The disease caused by SARS-CoV-2 has resulted in a pandemic since March 2020, and many studies have been done in order to understand the broad spectrum of the seriousness of this disease. The knowledge of the impact of risk factors is fundamental for its adequate treatment. We, hereby, present the analysis of 457 patients that were hospitalized with COVID-19, at the University Hospital Walter Cantídio, in Fortaleza, Ceará, Brazil.

OBJECTIVES

This study aims to analyze the impact of transplant in solid organs and tissues, in patients who were hospitalized because of Covid-19. As a secondary objective, we studied the impact of comorbidities (hypertension, diabetes and chronic renal disease) in patients' mortality.

METHODS

There were collected data from 457 patients that had been diagnosed with Covid-19 who were hospital-

ized in a ward or in an intensive care unit (ICU) at the University Hospital Walter Cantídio. There were only included patients with confirmed diagnosis through RT-PCR or a fast molecular test for COVID-19.

All the patients were sorted for history of transplant of solid organs and tissues (renal, hepatic and of bone marrow, as well as comorbidities as systemic arterial hypertension (SAH), diabetes mellitus type 2 (DM-2) and chronic kidney disease (CKD). The laboratory results of admission, including inflammatory marker, place of hospitalization and outcome, were compared among the group of transplanted and non-transplanted patients. All data were extracted from an electronic record.

The Mann-Whitney test was used to compare central trends of two independent samples, and the Chi – Square Test of Independence, in order to analyze the joint distribution of two variables, being used as a significant, p<0,05.

The statistical analyses were held with the support of software Microsoft Excel 2019 and R version 4.1.0. This paper was previously approved by the Institutional Review Board by Universidade Federal do Ceará (Hospital Universitário Walter Cantidio) by the number 4.023.458, CAAE: 31511620.6.0000.5045.

RESULTS

In total, there were collected 457 patients that had been diagnosed with Covid-19 and were hospitalized in wards or ICUs, being that 73,96% were in wards, and the other ones - 26,04% - in ICUs.

Among these patients, 57,33% were males. Regarding the presence of the main comorbidities, 48,36% had previous diagnosis of hypertension, 33,26% DM-2 and 12,47% CKD. In total, 8,53% of patients had undergone a certain type of transplant, being that: 3,72% kidney transplant, 2,84% liver transplant and 1,97% allogeneic bone marrow transplant.

Patients' mean age was 57 years old; with quartile deviation of 22 years [18 -103 years old]. The mean body mass index (BMI) was 26,9 kg/m², with deviation of 8,35.

Of all, 17,94% progressed to death. Regarding the mortality of patients hospitalized in ICUs, the percentage was 57,14%. In order to understand the patients' risks of death, and their associations with other factors, a cross tabulation was done between the studied variables and outcomes.

Firstly, on Table 1, it is shown the outcome associations, with the main socio-demographic variables. It is noticed that:

The percentage of deaths in male patients was 19,47%, while that in women this percentage was a little lower, 15,9%. Despite the difference, there wasn't statistical significance among the sexes.

The patients that presented SAH (48,36%) showed mortality level of 23,53%, and the ones who didn't, showed mortality level of 12,71%, with statistical significance. The patients with SAH showed 2,11 more chances of death.

Differently from the previous comorbidity, DM-2 didn't show significant value in the chi-square test, p value = 0,335 > 0,05. Out of the patients with DM-2, 20,39% died versus 16,72% of those without DM-2. Out of the patients without DM-2, 24,9% needed a bed in the ICU, versus 29,86% of diabetic patients, also without statistical significance.

The proportion of death of patients with CKD was 26,32%, and patients without CKD was 16,75%. Despite this difference, the obtained p value was 0,078 > 0,05.

We can see the association of the holding of any kind of transplant with the place of hospitalization, the outcome and the values of some laboratory variables.

The number of patients that did any type of transplants was 39, which corresponds to 8,53% of the total of analyzed patients, being that 3,72% was kidney transplant, 2,84% liver transplant and 1,97% bone marrow transplant.

On Table 2, it is presented the laboratory variables, according to the groups that had or had not done a transplant. We concluded that the values of white blood cells (WBC), neutrophils, segmented neutrophils, lymphocytes, monocytes and platelets were lower in the groups of transplanted patients, with statistical significance. The amount of band neutrophils, although higher in the group of non-transplanted patients, did not show any statistical significance.

Beyond the laboratory variables, it was also crossed with the holding of transplant, the place of hospitalization – ward or ICU- and the outcomes of death or cure, which follows:

There were hospitalized in the ward, a total of 338 patients, and in the ICU, 119 patients, being that out

of the total number of patients that had been hospitalized in the ward, 6,8% had done a certain type of transplant, and regarding the patients who were in the ICU, 13,45% of them had done a transplant.

The percentage of transplanted patients is higher in the ones in the ICU than in a ward, with statistical significance.

With the aim of quantifying the identified association, it calculated the odds ratio considering the chances of a transplanted patient in the ICU, by the chances of transplanted patients in the ward, and the obtained result was 2,13, with confidence interval of 95% between 1,08 and 4,18. We conclude there are 2,13 more chances of transplanted patients being hospitalized in the ICU, than in the ward and 2,21 more chances of death in the transplanted patients group.

ASSOCIATION BETWEEN LABORATORY VARIABLES AND OUTCOME, IN THE TRANSPLANT GROUP

With the purpose of knowing if the holding of a transplant influences the patient's risk of death, it was done the analysis of the crossing between the outcome and the laboratory variables, for each group of patients, the ones that had done a transplant and the ones who had not.

Table 3 shows the mean values and the interquartile deviation, together with the p value for each comparison between the variable and the outcome, for each transplant group.

Out of the people who **did** any kind of transplant, the amount of lymphocytes statistically differ, with 95% confidence interval, between the ones that died and the ones who were cured.

And among the patients who **did not** do a transplant, the amount of lymphocytes was also significantly different among the ones who died and the ones who were cured, the amount of lymphocytes was also higher in the group of patients who were cured.

DISCUSSION

In this study, we analyzed the data of 457 patients who were hospitalized with COVID-19 in a tertiary hospital in Fortaleza, Ceará, Brazil. The mean age was 57 years old, and there was a higher prevalence of the male sex, in a consensus with other cohorts[1,2,3]. The mortality rate in our service was 17,94%.

Among the total of hospitalized patients, 48,36% had the previous diagnosis of SAH. It was observed 2,11

more chances of death than in patients who did not show this disease, in consensus with what was found by M. Salazar et al., they considered as possible causal nexus the myocardial damage and myocardial dysfunction supported by frequent findings of high levels of troponin and electrocardiographic anomalies[4].

Huang et al, in a meta-analysis of 6452 patients, found that DM-2 is associated with mortality, severity of COVID-19 and respiratory distress syndrome[5]. However, in our sample, although the number of diabetic patients that died and had needed an ICU was higher, in relation to the non-diabetic patients, there was not a statistical significance.

A meta-analysis with 15017 patients, identified that CKD was associated with the severity of COVID-19[6], in contrast to what had been found in our sample.

The divergences that were found in literature may be due to the absence of a previous diagnosis and appropriate treatment of the underlying disease.

The immune response of the organ receptors, particularly the immune response of T cells, is suppressed because of the prolonged use of immunosuppressive agents. In addition, transplanted patients showed higher prevalence of comorbidities, such as hypertension, DM-2 and CKD, which increase the severity and mortality. We identified that transplanted patients showed 2,21 more chances of death than non-transplanted patients. According to Guangyu et al, the innate and adaptive immunity can be altered in receptors of transplant of solid organs who make use of immunosuppressive drugs for a prolonged period, causing a risk of infection. Moreover, the use of immunosuppression makes these patients more susceptible to viral respiratory infections and they are more prone to develop bacterial and fungal co-infections[7].

CONCLUSION

We conclude that the prior diagnosis of arterial hypertension and transplant of solid organs and tissues, showed higher levels of mortality, if compared to the population who did not show these co-morbidities in patients with COVID-19.

REFERENCES

1. Guan WJ, NiZ Y, Hu Y, et al; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.

2. Richardson S, Hirsch JS, Narasimhan M, et al; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323(20):2052-9.

3. Docherty AB, Harrison EM, Green CA, et al; ISARIC4C investigators. Features of 20 133 UK patients in hospital with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369:m1985.

4. Salazar M, Barochiner J, Espeche W, et al. COVID-19, hipertensión y enfermedad cardiovascular [COVID-19 and its relationship with hypertension and cardiovascular disease]. Hipertens Riesgo Vasc. 2020;37(4):176-180. Spanish.

5. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - A systematic review, meta-analysis, and meta- regression. Diabetes Metab Syndr. 2020;14(4):395-403.

6. Singh J, Malik P, Patel N, et al. Kidney disease and COVID-19 disease severity-systematic review and meta-analysis. Clin Exp Med. 2022;22(1):125-135.

6. Ao G, Wang Y, Qi X, et al. The association between severe or death COVID-19 and solid organ transplantation: A systematic review and meta-analysis. Transplant Rev (Orlando). 2021;35(3):100628.

TABLE 1 – Frequency of sociodemographic characteristics by hospitalization outcome.

Variables	Outcome		Total	Value p[a]	RC (CI 95%)
	Death (%)	Cure (%)			
Sex					
Female	31 (15,9%)	164 (84,1%)	195 (100%)	0,325	
Male	51 (19,47%)	211 (80,53%)	262 (100%)		
Place of Hospitalization					
Ward	14 (4,14%)	324 (95,86%)	338 (100%)	<0,001	
ICU	68 (57,14%)	51 (42,86%)	119 (100%)		30,86 (16,16-58,91)
Previous Hospitalization due to Other Reasons					
No	64 (16,62%)	321 (83,38%)	385(100%)	0,089	
Yes	18 (25%)	54 (75%)	72(100%)		
Diagnosis Means					
Fast Test	10 (19,61%)	41 (80,39%)	51 (100%)	0,003	
PCR	12 (17,73%)	334 (82,27%)	406(100%)		2,11(1,29-3,46)
Presence of DM-2					
No	51 (16,72%)	254 (83,28%)	305 (100%)	0,335	
Yes	31 (20,39%)	121 (79,61%)	152 (100%)		
Presence of CKD					
No	67 (16,75%)	333(83,25%)	400(100%)	0,078	
Yes	15 (26,32%)	42 (73,68%)	57(100%)		
Transplant					
Renal	6 (35,29%)	11 (64,71%)	17 (100%)	0,843[b]	
Hepatic	3 (23.08%)	10 (76,92%)	13 (100%)		
Bone Marrow	3 (33,33%)	6 (66,67%)	9 (100%)		
Nor applicable ⱶ	70 (16,75%)	348 (83,25%)	418 (100%)		
Total	829 (17,94%)	375 (82,06%)	457(100%)		

Chi Square Test of Independence; b. Fisher's Exact Test; c. Category is not considered in the significance test.

TABLE 2 – **Descriptive statistics of laboratory variables**

Variables	Transplant	Mean	IQI	Minimum	Maximum	p Value
White blood cells	No	9129	4961,75	23,55	214500	< 0,001
	Yes	4997	4884,5	104	28270	
	Total	8919	5239,5	23,55	214500	
Neutrophils	No	7189	4783,5	0	47636	< 0,001
	Yes	3780	4348	0	25725	
	Total	6953	4918,5	0	47637	
Band Neutrophils	No	204,5	308,5	8	3928	0,173
	Yes	770,5	1142,75	186	1400	
	Total	212,5	332,5	8	3928	
Segmented Neutrophils	No	7197	4537	0	40761	< 0,001
	Yes	3780	4442	39	29594	
	Total	7011	4821	0	40761	
Lymphocyte	No	1036	874,25	0	13370	0,015
	Yes	730	1024,5	38	2450	
	Total	1005	876	0	13370	
Monocyte	No	504,5	428,75	0	3189	0,002
	Yes	356	381,5	2	1960	
	Total	487	431,5	0	3189	
Platelet	No	245250	156725	7660	673300	< 0,001
	Yes	110400	127230	8847	465200	
	Total	237900	155100	7660	673300	
PT (INR)	No	1,01	0,18	0,8	2,28	< 0,001
	Yes	1,09	0,23	0,89	1,62	
	Total	1,02	0,19	0,8	2,28	
APTT	No	1	0,3	0,03	7	< 0,001
	Yes	1,2	0,36	0,72	2,57	
	Total	1,01	0,32	0,03	7	
D-Dimer	No	1134,5	1673,5	0,03	113023	0,039
	Yes	4,26	1325,75	0,72	42104	
	Total	1069	1612	0,03	113023	
Fibrinogen	No	478	173	1,45	848	0,478
	Yes	484	284	231	875	
	Total	481	212	1,45	875	
PCR	No	5,3	9,85	0,01	23,2	0,261
	Yes	6,07	11,09	0,04	20,61	
	Total	5,34	9,93	0,01	23,2	
Ferritin	No	852,5	380,25	44	14351	0,026
	Yes	1309,5	1400	73,6	5667	
	Total	886	944,5	44	14351	
LDH	No	678,5	395,75	248	7060	0,736
	Yes	701	404	284	5282	
	Total	681	398	248	7060	

TABLE 3 – **Association between laboratory variables and outcome**

Variables	Did Transplant		p value	Did not do Transplant		p value
	Death	Cure		Death	Cure	
White blood Cells	5546 (6933,5)	4997 (3870)	0,642	11270 (7490)	8905 (4524)	< 0,001
Neutrophils	5086 (6222,75)	3659 (3249,5)	0,191	9916 (6731)	6782(4180,5)	< 0,001
Band Neutrophils	1330 (607)	211 (0)	1	463,5 (496,5)	174,5 (227)	0, 075
Segmented Neutrophils	5086 (6231,5)	3659 (3249,5)	0,224	9570 (6731)	6937 (4068)	< 0,001
Lymphocytes	445 (639,5)	907 (840,5)	0,045	907 (735)	1071 (845)	0,01
Monocytes	158,5 (365,25)	405 (287,5)	0,132	509 (551)	494 (399)	0,646
Platelets	102960(108967,5)	129100(127685)	0,578	1,14 (0,2)	0,99 (0,14)	< 0,001
PT	1,13 (0,23)	1,08 (0,22)	0,129	1,14 (0,2)	0,99 (0,14)	< 0,001
APPT	1,29 (0,66)	1,18 (0,3)	0,75	1,18 (0,48)	0,97 (0,25)	< 0,001
D DIMER	706,13(11578,47)	4 (974,25)	0,527	1462 (3891)	1049(1558)	0,161
Fibrinogen	577,5(284,25)	484 (284)	0,8825	414 (151,5)	493,5(209,75)	0,306
PCR	14,93 (4,58)	4,8 (7,43)	< 0,001	11,56 (8,88)	4,36 (8,84)	< 0,001
Ferritin	109,75(1446,75)	1432,5(1281,75)	0,792	999 (1218,62)	814 (835,75)	0,128
LDH	787,5 (235,5)	566 (418)	0,031	768 (501,25)	658,5 (372,25)	0,047