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Covid-19 And Endocrine Status: Characteristics Of Patients Who Survived Intensive Care In Campina Grande

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Abstract:
Objective: *To evaluate the endocrine-metabolic status of patients who survived severe Covid-19 after hospitalization in intensive care units in Campina Grande-Paraíba, Brazil.*
Materials and Methods: *The study was observational, prospective and analytical. Data were collected from the patients' records who were followed in 2021 and 2022 at the Endocrinology outpatient department. Adequate statistic tests were used, and $p \leq 0.05$ was accepted for the rejection of a null hypothesis. This project was approved by the Committee for Ethics in Research under the number of: 4,478,650. All individuals who agreed to participate in the research signed the Consent Form.*
Results*: It was recruited 45 patients. Most were men (n=25; 55.6%), with a mean of 52.0 ± 12.3 years. The most prevalent comorbidity was obesity (n=25; 55.6%), followed by hypertension (n=18; 40.0%). The predominant pulmonary involvement observed through computer tomography (CT scan) of the chest ranged from 25 to 50% (n=20; 44.4%). The variants with statistic significance were the association between ventilatory support and CT scan findings (p = 0.033), as well as hospitalization time (p = 0.011). In the follow-up phase, new diagnosis of hypertension was made for 8 (17.8%) patients, pre-diabetes in 8 (17.8%), diabetes in 5 (11.1%), and dyslipidemias in 4 (8.9%).*
Conclusion: *Endocrine-metabolic status was worse in the patient sample and new diseases arose in survivors of severe covid-19 in the city of Campina Grande.*
Key Word*: Coronavirus infections. Diseases of the endocrine system. Metabolic diseases. Survivors.*

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I. Introduction

Late in 2019, infections by a new beta coronavirus, the SARS-CoV-2, were reported in people exposed to a seafood market in the city of Wuhan, in China. From there, the virus spread rapidly and resulted in an epidemic in the whole of China, followed by a rising number of cases in other countries. In February 2020, the World Health Organization (WHO) named the disease caused by the SARS-CoV-2 as Covid-19. In March 2020, the WHO declared it a pandemic[1-4].

In the first years of the pandemic, in the absence of herd immunity and of effective vaccines, countries all over the world witnessed an unprecedented strain on their health systems and in their economies[5-6].

Infection by covid-19 manifests in many different ways, ranging from asymptomatic disease to symptomatic disease from mild to critical. Among hospitalized patients, the rate of critical or fatal disease is higher. The rate of severe or fatal cases may vary from place to place[6].

More advanced age and the presence of comorbidities are associated to a more severe course of the disease. The most prevalent metabolic comorbidities are hypertension, cardiovascular diseases, obesity, and diabetes. These are significant predictive factors of morbidity and mortality in patients with Covid-19[7].

Patients with metabolic diseases present a state of metabolic inflammation that predisposes them to the exacerbated release of cytokines. In Covid-19, a tempest of cytokines has been implicated in the multiple organ failure reported in patients with severe disease. Metabolic inflammation also compromises the immune system, reducing the body's ability to fight the infection and jeopardizing the healing process, extending the recovery process. Therefore, even though Covid-19 is not a primarily metabolic disease, the metabolic control of glucose, of lipid levels and of blood pressure is crucial in these patients, in order to reduce local inflammatory response and lower the risk of death[8,9].

It is believed that the SARS-CoV-2 binds to the receptors of angiotensin converting enzyme 2 (ACE 2), which are expressed in the main metabolic organs and tissues, including beta pancreatic cells, adipose tissue, small intestine, and kidneys. It is, therefore, plausible that SARS-CoV-2 can cause pleotropic alterations in glucose metabolism that may further complicate the physiopathology of pre-existing diabetes or lead to new cases of the disease[10,11]. All patients without diabetes and, in particular, those at a high risk of metabolic disease who contracted the viral infection must be monitored for a new diabetes[11].

Just like the SARS virus (SARS-CoV-1), it is possible that the SARS-CoV-2 can induce long-term metabolic alterations in patients infected by the virus. Therefore, careful cardiometabolic monitoring of patients who have survived severe Covid-19 may be necessary[12]. In this sense, research on the clinical effects of the virus and follow-up of recovered patients is a priority, taking into account the potential for countless effects on endocrine organs[13].

This study is justified by the hypothesis that the prevalence of endocrine conditions in patients who survived severe forms of Covid-19 would be higher than before they were affected by the viral disease, evidence which has not been fully proven in literature. In addition, it is supposed that pre-existing endocrine-metabolic conditions would be more difficult to control after having Covid-19.

The general objective of the study was to evaluate the endocrine and metabolic status of patients who survived severed Covid-19 after hospitalization in intensive care units in the city of Campina Grande.

Secondary objectives were: to describe sociodemographic and clinical data of participants in the study; to verify the main endocrine-metabolic risk factors that predict the occurrence of severe forms of Covid-19; to determine whether there is a relation between patient age and length of hospital stay due to severe covid-19; to verify whether there is an association between patient gender and the level of pulmonary involvement in CT scans, the type of ventilator support required, and length of hospital stay due to Covid-19; to define whether there is an association between the type of ventilator support used by hospitalized patients and the level of pulmonary involvement and with length of hospital stay; to establish whether the presence of endocrine metabolic comorbidities is associated to the degree of pulmonary involvement observed in CT scans, to the type of ventilator support required during hospitalization, and with length of hospital stay due to Covid-19; to evaluate whether the body mass index (BMI) and age of patients is associated to the ventilator support used during hospitalization.

II. Material And Methods

Study Design: The study was observational, prospective and analytical.

Population and sample size: It was recruited a sample of 45 patients who recovered from severe forms of Covid-19 after hospitalization in intensive care units.

Place of study: The study was carried out in the city of Campina Grande, in the state of Paraíba – Brazil. The patients were referred from the following hospitals: Pedro I Municipal Hospital and the Alcides Carneiro University Hospital. Patients were followed at the Endocrinology Ambulatory of the Teaching Hospital and Research Laboratory (HELP, in the Brazilian Portuguese acronym).

Procedures

Technical procedures

The study involved an active search for patients who had recovered from Covid-19. They were informed of the methodology and objectives of the study. Those who were willing to participate were examined in the HELP's specialized Endocrinology Outpatient Department, led by the main researcher All recruited patients signed the Informed Consent Form (TCLE in the Brazilian Portuguese acronym – Annex II). Additional information was collected from the patients included in the investigation (clinical data, hospitalization history, diet, need for ventilator support, use of corticoids, antibiotics, insulin and antihypertensive drugs during hospitalization, and need for hemodialysis. (Appendix I).

The initial interview took place at HELP's Endocrinology Outpatient Department, after a first contact with the patient, after signing the TCLE. Identification, sociodemographic data, time and place of hospital admission due to Covid-19, comorbidities, use of medications, life habits were recorded as baseline data.

The questionnaire (Appendix II) was applied at the Outpatient Department in an individual fashion, and all the data were fed into an electronic tool. Physical examination results were also recorded. Anthropometric data (body weight, height and BMI), mean blood pressure and laboratory tests were equally recorded.

All the next visits took place at HELP's Endocrinology Outpatient Department, through 2021 and 2022. During these visits, exam and test results were recorded and compared with the physical examination parameters collected at the initial interview.

Analytical procedures

The data were entered into an Excel file and analyzed through SPSS, version 26.0. The statistical data were the result of a descriptive analysis of the qualitative variables, through the absolute and relative frequencies of the data. For quantitative variables, measures of central tendency and dispersion were taken. An inferential analysis was also carried out by means of association tests (Pearson's chi-squared test; Fisher's exact test), correlation tests (Spearman's rank correlation coefficient), and comparison tests (ANOVA comparison test; Kruskal-Wallis test).

Fisher's exact test was used in the cases in which the number of cells with a frequency below 5 was 20%. Non-parametric tests were used in situations in which the result of the Kolmogorov-Smirnov test showed a data distribution result tending towards non-normalcy. For all other analysis a level of significance of 5% was used (p-value < 0.05).

In addition, the variable length of hospital stay was dichotomized through a median cut and was therefore divided in up to 10 days and more than 10 days.

Ethical procedures

The project was approved by UNIFACISA's Committee for Ethics in Research on Human Beings, under the number 4,478,650. All individuals who agreed to participate in the research signed the TCLE.

The researchers signed a Term of Agreement with the Research project and a Responsible Researcher's Term of Commitment, agreeing to respect the CNS Resolution 466/2012.

III. Result

Forty-five patients were recruited, with at least 2 visits to the Endocrinology Outpatient Department. Sociodemographic, clinical data including previous comorbidities and post Covid-19 diseases, oxygen use, habits, physical activity and lung image CT scan are reported in table 1.

Table 1. Distribution of sociodemographic and clinical data of the participants.

Variables	**n**	**%**
Sex		
Male	25	55.6
Female	20	44.4
Previous comorbidities		
None	10	22.2
Obesity	25	55.6
Hypertension	18	40.0
Diabetes mellitus	8	17.8
Pre-diabetes	3	6.7
Dyslipidemia, on medication	1	2.2
Hypertension + obesity	8	17.8
Diabetes mellitus + hypertension	1	2.2
Hypertension + diabetes mellitus	1	2.2
Diabetes mellitus + hypertension + obesity	5	11.1
Hypertension + obesity + dyslipidemia	1	2.2
Subjects with hypertension		
Patients on 1 antihypertensive	6	33.3
Patients on 2 antihypertensives	4	22.2
Patients on 3 or more antihypertensives	8	44.5
Subjects with diabetes mellitus		
Patients on 1 antidiabetic drug	2	25.0
Patients on 2 antidiabetic drugs	2	25.0
Patients on 3 antidiabetic drugs	1	12.5
Patients on insulin	3	37.5
Diet		
Oral	33	73.3
Enteral	12	26.7
Parenteral	0	0.0
Ventilatory support		
Oxygen through nasal cannula	16	35.6
Oxygen through mask	19	42.2
Mechanical ventilation	10	22.2
Use of corticoids during hospital stay		
Yes	45	100.0
No	0	0.0
Use of antibiotics during hospital stay		
Yes	45	100.0
No	0	0.0
Use of basal insulin during hospital stay		
Yes	18	40.0
No	27	60.0
Use of antihypertensive during hospital stay		
Yes	29	64.4

No	16	35.6
Need for hemodialysis		
Yes	0	0.0
No	45	100.0
CT scan findings		
Pulmonary involvement, up to 25%	6	13.3
Pulmonary involvement, from 25 to 50%	20	44.5
Pulmonary involvement >50%	19	42.2
Diseases diagnosed after covid-19		
Hypertension	8	17.8
Pre-diabetes	8	17.8
Subclinical hypothyroidism	6	13.3
Diabetes mellitus	5	11.1
Dyslipidemia, on medication	4	8.9
Deep vein thrombosis	3	6.7
Pulmonary mycosis	1	2.2
Anemia	1	2.2
Physical activity prior to covid-19		
Yes	9	20.0
No	36	80.0
Alcohol consumption		
Yes	2	4.4
No	43	95.6
Smoking		
Yes	1	2,2
No	44	97.8

Note: COPD: Chronic Obstructive Pulmonary Disease.

The means age, weight, height, BMI, length hospital stay, time on mechanical ventilation (MV), laboratory tests and the mean of blood pressure are reported in table 2.

Table 2 – Measures of central tendency and dispersion of sociodemographic and clinical data of the participants.

Variables		
Age (years)		
Mean ± standard deviation	52.8 ± 13.3	
Minimum - maximum	22 – 86	
Length of hospital stay (days)		
Mean ± standard deviation	16.1 ± 11.9	
Minimum - maximum	2 – 45	
Days on mechanical ventilation		
Mean ± standard deviation	4.1 ± 8.6	
Minimum - maximum	0 - 34	
Weight (kg)		
Mean ± standard deviation	86.8 ± 17.3	
Minimum - maximum	47 – 120	
Height (cm)		
Mean ± standard deviation	164.2 ± 9.5	
Minimum - maximum	143.0 – 183.0	
BMI (kg/m²)		
Mean ± standard deviation	32.1 ± 5.8	
Minimum - maximum	18.3 – 45.8	
O25 OH D (ng/dl)		
Mean ± standard deviation	27.0 ± 6.9	
Minimum - maximum	15.3 - 49.7	
HbA1C (%)		
Mean ± standard deviation	6.5 ± 1.9	
Minimum - maximum	4.0 – 12.4	
Fasting glycemia (mg/dl)		
Mean ± standard deviation	113.1 ± 56.2	
Minimum - maximum	66.0 – 425.0	
Triglycerides (mg/dl)		
Mean ± standard deviation	188.7 ± 171.2	
Minimum - maximum	66.0 – 425.0	
Total cholesterol (mg/dl)		
Mean ± standard deviation	203.4 ± 52.6	
Minimum - maximum	109.0 – 318.0	
HDL (mg/dl)		
Mean ± standard deviation	47.0 ± 11.1	

Minimum - maximum	26.0 – 73.0	
LDL (mg/dl)		
Mean ± standard deviation	123.1 ± 38.7	
Minimum - maximum	53.0 – 221.0	
TSH (um/L)		
Mean ± standard deviation	3.2 ± 1.9	
Minimum - maximum	0.7 – 7.8	
T4L (ng/dl)		
Mean ± standard deviation	0.9 ± 0.1	
Minimum - maximum	0.6 – 1.2	
PAS (mmHg)		
Mean ± standard deviation	130.7 ± 20.1	
Minimum - maximum	100.0 – 180.0	
PAD (mmHg)		
Mean ± standard deviation	83.6 ± 10.5	
Minimum - maximum	60.0 – 100.0	

Note: BMI: Body Mass Index; HbA1C: glycated hemoglobin; SAP: Systolic Arterial Pressure; DAP: Diastolic Arterial Pressure.

There was no correlation between age and length of hospital stay (Spearman's correlation coefficient – p = 0.670).
There was no association between sex and CT scan findings, ventilator support and hospitalization time. Table 3.

Table 3 – Association between sex and tomography findings, ventilatory support, and length of hospital stay amongst the participants.

Variables	**Sex**		**p-value**	**RR CI (95%)**
	Male n (%)	**Female n (%)**		
CT scan findings				
Pulmonary involvement, up to 25%	3 (50.0)	3 (50.0)		
Pulmonary involvement, from 25 to 50%	10 (50.0)	10 (50.0)	0.707[b]	-
Pulmonary involvement >50%	12 (63.2)	7 (36.8)		
Ventilatory support				
Oxygen, nasal cannula	10 (62.5)	6 (37.5)		
Oxygen, mask	11 (57.9)	8 (42.1)	0.513[b]	-
Mechanical ventilation	4 (40.0)	6 (60.0)		
Length of hospital stay				
Up to 10 days	11 (47.8)	12 (52.2)	0.286[a]	1.435 (0.729 – 2.824)
More than 10 days	14 (63.6)	8 (36.4)		

Note: [a]Pearson's chi-squared test; [b]Fisher's exact test; (-) No data available.

When it was analyzed the association between ventilator support, CT scan findings and length of hospital stay, it was identified a statistically significant association with pulmonary involvement (p=0.033) and length of hospital stay (p-value=0.011), in which mechanical ventilation (MV) was predominant among those with a longer hospital stay and with pulmonary involvement > 50%. Table 4.

Table 4 – Association between ventilatory support and tomography findings and length of hospital stay among the participants.

Variables	**Ventilatory support**			**p-value**	**RR IC (95%)**
	Oxygen, nasal cannula n (%)	**Oxygen, mask n (%)**	**Mechanical ventilation n (%)**		
CT scan findings					
Pulmonary involvement, up to 25%	5 (83.3)	0 (0.0)	1 (16.7)		
Pulmonary involvement, 25-50%	8 (40.0)	8 (40.0)	4 (20.0)	**0.033**[b]	-
Pulmonary involvement, >50%	3 (15.8)	11 (57.9)	5 (26.3)		
Length of hospital stay					
Up to 10 days	11 (47.8)	11 (47.8)	1 (4.3)	**0.011**[a]	-
More than 10 days	5 (22.7)	8 (36.4)	9 (40.9)		

Note: [a]Pearson's chi-squared test; [b]Fisher's exact test; (-) No data available.

Table 5 shows that the association between having endocrine metabolic comorbidities and the variables chest CT scan findings, ventilator support and length of hospital stay did not show statistical significance. However, the predominance among those with comorbidities was that of pulmonary involvement between 25 and 50% in the CT scan, use of oxygen (mask), and length of hospital stay higher than 10 days.

Table 5 – Association between endocrine-metabolic comorbidities and tomography findings, ventilatory support, and length of hospital stay among the participants.

Variables	Endocrine-metabolic comorbidities			RR CI (95%)
	Yes n (%)	No n (%)	p-value	
CT scan findings				
Pulmonary involvement, up to 25%	5 (83.3)	1 (16.7)		
Pulmonary involvement, 25-50%	14 (70.0)	6 (30.0)	0.907[b]	
Pulmonary involvement >50%	13 (68.4)	6 (31.6)		
Ventilatory support				
Oxygen, nasal cannula	11 (68.8)	5 (31.3)		
Oxygen, mask	13 (68.4)	6 (31.6)	0.835[b]	-
Mechanical ventilation	8 (80.0)	2 (20.0)		
Length of hospital stay				
Up to 10 days	16 (69.6)	7 (30.4)	0.815[a]	1.116 (0.444 – 2.802)
More than 10 days	16 (72.7)	6 (27.3)		

Note: [a]Pearson's chi-squared test; [b]Fisher's exact test; (-) No data available.

In the association of the variables development of endocrine metabolic diseases post-covid-19 and chest CT scan findings, ventilator support and length of hospital stay, it was not found a statistically significant association between the variables. However, the predominance of those who developed disease showed that most had pulmonary involvement of 25-50%, used oxygen through a mask, and stayed in hospital for up to 10 days. Table 6.

Table 6 – Association between the variable developed of endocrine metabolic diseases and tomography findings, ventilatory support, and length of hospital stay among the participants.

Variables	Developed endocrine metabolic diseases			RR CI (95%)
	Yes n (%)	No n (%)	p-value	
CT scan findings				
Pulmonary involvement, up to 25%	1 (16.7)	5 (83.3)		
Pulmonary involvement, 25-50%	12 (60.0)	8 (40.0)	0.098[b]	-
Pulmonary involvement >50%	6 (31.6)	13 (68.4)		
Ventilatory support				
Oxygen, nasal cannula	6 (37.5)	10 (62.5)		
Oxygen, mask	9 (47.4)	10 (52.6)	0.830[a]	-
Mechanical ventilation	4 (40.0)	6 (60.0)		
Length of hospital stay				
Up to 10 days	10 (43.5)	13 (56.5)	0.862[a]	0.957 (0.581 – 1.576)
More than 10 days	9 (40.9)	13 (59.1)		

Note: [a]Pearson's chi-squared test; [b]Fisher's exact test; (-) No data available.

When it was compared the data between mean BMI and ventilator support (oxygen through nasal cannula/oxygen through mask/mechanical ventilation), using the ANOVA comparison test, it was observed no statistically significant difference between the groups (p=0.821).

When comparing age and ventilator support (oxygen through nasal cannula/oxygen through mask/mechanical ventilation) using the Kruskal-Wallis comparison test, it was observed no statistically significant association between the variables (p=0.571).

IV. Discussion

Covid-19 and endocrinology have been associated in various contexts during the pandemic. Endocrine issues, including obesity and diabetes, are some of the risk factors for severe diseases. Endocrine organs, such as pancreas, suprarenal glands and testicles, have been identified as potential targets for the SARS-CoV-2[13-16]. Recent onset endocrine issues related to covid-19 have also been reported. Knowing whether hormonal dysfunctions will be among the long-term effects of the disease is something that is yet to be better clarified[17,18].

Although there is an abundance of hypothesis on the physiopathological pathways connecting endocrine issues and covid-19 results, there is not enough research testing these possibilities. It was in this scenario that the current study was developed, with the goal of amplifying the relation between endocrine issues and covid-19: whether covid-19 worsens pre-existing problems and whether it is related to the appearance of endocrine diseases in the long run. In addition, we attempted to get to know the sociodemographic characteristics of the patients in the city of Campina Grande, where the study was held, with the goal of achieving more focused treatment and long-term surveillance.

Main clinical findings

Patients in this study were admitted to intensive care units (ICUs), which means they all had severe forms of covid-19. Most participants were male, which is in conformity with the literature, showing that male patients are almost three times more likely to require admission to an ICU and have a higher chance of death[2,14,19]. This higher need for admission to an ICU and higher severity of covid-19 among male patients can be attributed to differences in the sexual hormones involved in the inflammatory processes, in the expression levels of ACE2 and TMPRSS2, as well as to differences in lifestyle[19].

As for the mean age of the patients in this study, we observed that the mean age of covid-19 patients who were severely ill was lower than in other studies[2,20]. In most of those, age above 59 years was associated to a more severe disease and higher risk of death[1]. It is believed that this discrepancy regarding available literature can be justified by the fact that although our patients were younger, they had comorbidities that are known to be associated to a more severe course of the disease caused by covid-19[20,21].

The most prevalent comorbidities were metabolic, especially obesity, as referred in other papers[14,15,22]. French data on people admitted to hospital with covid-19 show that patients with severe obesity (BMI ≥ 35 kg/m²) require invasive mechanical ventilation more frequently than thin patients, regardless of age, sex, diabetes or blood pressure[23]. Similarly, an American study showed a significant association between obesity and the need for hospitalization and patients' critical status (intensive therapy, mechanical ventilation and/or death), independently from other comorbidities[24]. A recent revision also confirmed the association between obesity and high risk of death by covid-19[25].

In addition to obesity, other comorbidities commonly found in the current study were hypertension and diabetes mellitus. In most studies, hypertension and diabetes are also pointed as risk factors for severe pneumonia, worse clinical evolution, and higher mortality, when compared with individuals that do not have these diseases[4,16,26]. Another point that should be highlighted is the fact that in this study patients with metabolic comorbidities stayed in hospital for longer (> 10 days), when compared with those who did not have those comorbidities.

Of the patients in the study, whether they were known to have hypertension or not, most of them needed antihypertensive drugs, suggesting high blood pressure levels during admission and already expected for severe patients. According to a Chinese study[27], high average systolic arterial pressure and high variability of systolic/diastolic arterial pressure during hospital stay were independently associated to intra-hospital mortality, ICU admission, and heart failure. The study also observed[27] that intra-hospital hyperglycemia was a predictive factor for adverse outcomes, such as need to be admitted to an ICU and need for mechanical ventilation. In the present study, 40% of patients needed basal insulin during their stay in hospital, an indication of hyperglycemia during hospitalization.

Another factor evaluated as risk factor for severity in covid-19 patients was a higher level of pulmonary involvement observed in CT scans of the chest. Chest tomographies in both hospitals involved in the study were examined and described according to the percentage of pulmonary involvement: < 25% involvement, involvement of 26-50% of the lung, > 50% involvement. All patients in the study had pulmonary involvement, most with at least > 25%, in line with studies that showed that the number of pulmonary lobes affected was higher in severe patients than in non-severe patients[27,28].

Smoking described as risk factor for severe covid-19 was not observed in this study. A meta-analysis discovered that 25.6% of patients hospitalized with covid-19 had a history of smoking. Current smokers had a significantly higher risk of severe covid-19 (RR: 1.80; CI 95%: 1.14−2.85) and severe or critical covid-19 (RR: 1.98; CI 95%: 1.16−3.38)[29]. In the sample of the present study, only 1 patient (2.2%) was a smoker. It is believed that the limited number of the sample may have influenced this result, but we should also consider that in the city of Campina Grande the Basic Health Units make great efforts to implement programs that stimulate their users to quit smoking, and there had also been an anti-smoking program running up until the pandemic in one of the hospitals involved in this research (Alcides Carneiro University Hospital).

Of the complications that arose during hospital stay, also unlike what has been reported in many studies[30,31], no patient required renal replacement therapy (RRT) due to acute kidney injury (AKI). In a study on covid-19 patients admitted to hospital in the city of New York, most patients under mechanical ventilation developed AKI (86.9%), and 23.2% of intubated patients required RRT[31]. We believe this non-concordance with the literature is caused by the small sample size of the present study.

As for ventilatory support, it was observed that most were given oxygen through a mask. The predominance of those in mechanical ventilation was seen among those with pulmonary involvement > 50%. The need for invasive mechanical ventilation in this sample of patients under study was lower than in a Brazilian study in which invasive mechanical ventilation was necessary for 65% of patients[32]. A higher need for invasive mechanical ventilation was also observed in another study[33]. We believe that the profile of younger patients found in the present study contributed to lower rates of mechanical ventilation, in addition to the low frequency of respiratory diseases and smoking, factors that are knowingly considered adverse for an unfavorable evolution of covid-19.

We also observed that the variables ventilatory support and length of hospital stay showed a significant association, in which mechanical ventilation was predominant among individuals who were admitted for longer, a fact observed in literature[32,33].

Regarding the analysis of laboratory tests collected at the Endocrinology Ambulatory, we observed an alteration of the average of main laboratory metabolic markers (fasting glycemia, glycated hemoglobin, and lipid panel), which may suggest a deregulation of the endocrine system after infection by the coronavirus[13]. Authors have reported that patients with hyperglycemia and patients with normal blood glucose all showed insulin resistance; glycemic abnormalities may last for up to 2 months after recovery. Dyslipidemia was also frequently observed in covid-19[34].

On the other hand, no significant alterations were observed in thyroid function. This was expected, as thyroid hormones undergo alterations during severe disease (euthyroid sick syndrome or nonthyroidal illness syndrome), tending to normalize a few weeks after hospital discharge[10,13,17]. Slight alterations (compatible with subclinical hypothyroidism) found in some patients may also reflect the recovery phase from euthyroid sick syndrome and should not be treated.

During the patients' ambulatory follow-up, new diagnosis of cardio-metabolic diseases were observed, such as hypertension, pre-diabetes, diabetes mellitus, and dyslipidemias. However, the development of these conditions had no statistical association with other variables under study (CT findings, ventilation support, and length of hospital stay).

Cardiovascular complications were described during the acute phase of covid-19, but it already known that the risk of incident cardiovascular disease extends way beyond the acute phase of the disease. Long-term follow-up shows higher incidence of arrhythmia, heart failure, acute coronary syndrome, right ventricular dysfunction, myocardial fibrosis, hypertension, and diabetes[35-37].

As for the onset of diabetes mellitus, several studies have shown a higher rate of recent onset diabetes during the pandemic[34,38,39,40]. In the present study, patients were found to have the biochemical criteria for diabetes and pre-diabetes. A Chinese study reported recent onset diabetes in 3.3% of 1,733 people, 6 months after their hospital discharge due to covid-19[37]. A systematic review of four cohort studies with a follow-up of 3 months observed that of the 698 patients with hospital hyperglycemia, 131 (18.8%) had recently diagnosed diabetes[39]. An English study with 47,780 subjects who had been discharged from hospital after being admitted due to covid-19 showed that 4.9% had developed diabetes, in an average follow-up of 140 days[40].

People with stress-induced hyperglycemia can revert to normal blood glucose levels after recovering from an acute disease, and therefore cannot be classified as having diabetes or in need of any drugs to lower their blood glucose. These patients require following to confirm the recent onset diabetes is really permanent. There are limited data available on the follow-up of patients recently diagnosed with covid-19. Considering the many uncertainties on the direct and indirect effects of covid-19, people with diabetes must be followed from up close. More studies are necessary with this aim in mind[40].

Study limitations and strengths

The present study is a groundbreaking investigation in the Northeast Region of Brazil. It makes it possible to carry out a longitudinal follow-up of the patients not only retrospectively, but also prospectively. Due to the scarcity of prospective studies in this field, the impact of Covid-19 on the endocrine system is little known. It was observed in the present investigation the effects of the coronavirus on the endocrine system in the long term, helping to understand the metabolic alterations induced by the virus in the post-acute phase of the disease.

Among the limitations of the study, the reduced size of the sample may have limited the acknowledgement of new endocrine conditions associated to severe covid-19. At the same time, it made it impossible to describe possible variables associated to the onset of post-covid-19 endocrine diseases. In addition, patients with normal test results presented at the second medical visit did not return to continue their follow-up. Similarly, the time in which patients were recruited for the investigation was not recorded in terms of amplitude during data collection, making it impossible to establish a relation between post-covid time and the onset of endocrine conditions.

Another limitation of the study was the absence of laboratory data (glycated hemoglobin upon admission, peptide C) considered important to attempt to define the mechanism behind hyperglycemia associated to covid-19. These tests were not carried out due to limited resources.

V. Conclusion

The metabolic study of patients who survived severe Covid-19 was characterized by the appearance of new cases of hypertension, pre-diabetes, diabetes mellitus, and dyslipidemias.

We observed that most patients were male, varying in age from 22 to 86 years old, and BMI ranging from 18.3 to 45.8 kg/m^2. The most prevalent comorbidities were obesity and hypertension. The predominant level of pulmonary involvement as seen on CT scan of the chest was in the range between 25 and 50%.

The variables that showed statistical significance were the association between ventilatory support and pulmonary involvement ($p = 0.033$) and length of hospital stay ($p = 0.011$), in which mechanical ventilation was predominant among individuals with a longer hospital stay and who had pulmonary involvement levels > 50%.

After being discharged from the hospital, during ambulatory follow-up, it was observed alterations of the average of the main laboratory metabolic markers (fasting glycemia, glycated hemoglobin, and lipid panel) on the patients being followed.

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