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RELATIONSHIP BETWEEN THE PRESENCE OF COMORBIDITIES AND RISK OF DEATH IN OBESE PATIENTS DIAGNOSED WITH COVID-19

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Abstract: Introduction: Obesity is a risk factor for mortality in COVID-19. Comorbidities present in these patients may be related to a worse outcome of COVID-19. **Objective:** to investigate in obese patients with COVID-19 the association between cardiovascular, hematological, neurological, hepatic, pulmonary, renal, diabetes, bronchial asthma and immunosuppression with death. **Method:** A total of 4,243 cases were evaluated through a retrospective cohort study, with obese patients diagnosed with COVID-19. Data were obtained from the "COVID-19 Surveillance Database for Severe Acute Respiratory Syndrome Surveillance", available at Open DATASUS, 2020. Overall mortality was evaluated and stratified according to comorbidities, focusing on the risk association with death.
Results: Overall mortality was 33.8%, increased among patients aged ≥60 years, non-white, with a lower level of education and from rural areas. Comorbidities related to the risk of death were cardiovascular disease (41.39%; RR 1.53; CI95 1.40-1.67), diabetes mellitus (42.83%; RR 1.48; CI95 1.36-1.61), chronic lung diseases (56.07%; RR 1.71; CI95 1.51-1.95), immunosuppression (53.7%; RR 1.61; CI95 1.34-1.93), disease renal (58.67%; RR 1.79; CI95 1.58-2.03) and neurological (mortality 47.01%; RR 1.40; CI95 1.17-1.69).**Conclusion:** The presence of chronic kidney disease, chronic lung disease, immunosuppression, cardiovascular disease and diabetes mellitus were associated with a higher risk of death in obese patients with COVID-19.
Keywords: coronavirus; obesity; comorbidity; risk factors, mortality.

INTRODUCTION

COVID-19 is a disease of viral origin first identified in December 2019, in the city of Wuhan, China, and is an imminent threat to global health [1]. From its appearance, the spread was rapid, until March 2020, approximately 185 countries had already detected cases of the disease. In that same year, according to the director general of the World Health Organization (WHO) it was characterized as a pandemic. [2]. The virus responsible for the infection is part of the coronavirus family, known since 1937, consisting of alpha coronavirus HCoV-NL63, alpha coronavirus HCoV-229E, beta coronavirus HCoV-OC43, beta coronavirus HCoV-HKU1, SARS-CoV, MERS-CoV, and the most modern discovered, SARSCoV-2[2]. The disease caused by SARS-CoV-2, associated with severe acute respiratory syndrome, has as one of its main characteristics the high rate of contagion, being responsible for more than 115 million cases and resulting in almost 2.7 million deaths by March 2021[2,3].

Its symptomatology is variable, often starting as a flu-like illness, evolving into mild, moderate and severe forms, where Severe Acute Respiratory Syndrome (SARS) is present. [4]. Greater lethality is related to severe forms, especially in elderly patients and patients with certain chronic diseases (comorbidities)[4]. Questions have been raised in order to understand the reasons for certain subgroups to present a more serious and potentially fatal clinical condition. Following this perspective, there is an association between the severity of the infection and its clinical and laboratory manifestations with immunological markers, corroborating the thesis of an exacerbated inflammatory response in patients with comorbidities that affect the immune system [5].

Since the first months of the pandemic, it was initially observed empirically and later through epidemiological studies, that obese patients have a worse prognosis of the disease. [6]. A recently published meta-analysis, which included 14 studies, concludes that obesity is a risk factor for mortality in COVID-19[7]. Obesity per se is another global pandemic, responsible for a high mortality rate around the world. Defined as the excessive accumulation of adipose tissue in an amount that constitutes a detriment to health and BMI greater than or equal to 30 kg/m2 or the 97th percentile in children, it is present in more than 650 million people around the world, with increasing numbers in recent decades [8].

In Brazil, until September 2021, approximately 21 million cases of COVID-19 were registered, with 585 thousand deaths [9]. In turn, regarding obesity, data from 2019 indicate that six out of ten Brazilians are overweight and 26.8% of the adult population is obese [10]. It is known that, among obese patients, the existence of other associated chronic diseases is common. Thus, it would be particularly interesting to know which would be the main comorbidities present in obese patients related to the worst outcome of COVID-19. Such data are extremely important for the management of health strategies in our environment, considering that there are still many doubts regarding the behavior of the epidemic over the next few years. Based on this, the present study aims to investigate in obese patients with COVID-19, attended by the public health network (SUS) in the state of Mato Grosso between January 1, 2020 and March 31, 2021, the existing association between different comorbidities chronic diseases (cardiovascular, hematological, neurological, hepatic, pulmonary, renal, diabetes, bronchial asthma and immunosuppression) and the occurrence of death in the course of the disease.

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METHOD

Retrospective cohort study, based on data collected from patients diagnosed with COVID-19, present in the “Database of COVID-19 in the surveillance of Severe Acute Respiratory Syndrome (SRAG)”, publicly available on Open DATASUS, 2020 (Sistema Único de Saúde, Brazil). It is a publicly accessible database, available at: https://opendatasus.saude.gov.br/, access was made on 03/26/2021. Obese patients were selected who presented compatible clinical features and positive laboratory test for COVID-19 (detected through nasopharyngeal secretion, bronchoalveolar lavage, post-mortem tissue or cerebrospinal fluid), between March 19, 2020 and March 3, 2021, of both sexes and aged between 18 and 99 years. Pregnant women at the time of diagnosis were excluded, as this could lead to confusion in the measurement of body mass index (BMI).

The sociodemographic characteristics of the studied population were determined (age, sex, race/ethnicity, area of residence – rural or urban – and schooling), as well as the presence of comorbidities (cardiovascular, hematological, neurological, hepatic, pulmonary, renal diseases, in addition to diabetes, bronchial asthma and immunosuppression), length of hospital stay, presence of respiratory distress (oxygen saturation below 95%), need for ventilatory support (non-invasive or invasive), hospitalization in an intensive care unit and the occurrence of death.

Obesity was defined according to the definition of the Ministry of Health [12], based on a body mass index (BMI) greater than 30kg/m2. General and categorized mortality was determined, focusing on the risk of death according to: age, gender, ethnicity, education, area of origin and presence of chronic comorbidities including cardiovascular disease, liver disease, asthma, diabetes mellitus, pneumopathies, kidney disease, haematological disease, neurological disease and immunosuppression. Categorical variables were expressed as absolute numbers, percentages and 95% confidence intervals (95%CI). All the dependent variables analyzed were arranged in the form of binary variables (dichotomized). The impact of the presence of the different investigated covariates on mortality (primary outcome) was determined, expressed through the Relative Risk (RR) measure, with the respective 95% confidence interval (95% CI). The analysis between the different binary subgroups was performed using the chi-square test or Fisher’s exact test, when the expected values in any of the cells were less than 5. The value of $p<0.05$ was adopted as the level of statistical significance. The database was initially generated in the form of an Excel table, in order to allow filtering of data to be evaluated individually or grouped. Subsequently, for the analysis of categorical variables, descriptive statistics were used, the results of which were presented in absolute (n) and relative (%) frequency tables in the EPI-INFO 7.2 program (EpiInfo TM, GA, USA). In order to carry out this study, it was not necessary to use the Informed Consent Form (Res. CNS 466\2 in its chapter IV.8), as it is a public database analysis with free access without exposing data personal. According to resolution 510\2016, Law 12.527\2011, it was not necessary to submit the work to the CEP-CONEP System.

RESULTS

A total of 4,243 obese patients with a confirmed diagnosis of COVID-19 were selected. Of these, 2085 (49.14%) were female patients and 2158 (50.86%) were male. The largest proportion of this population was of white ethnicity (66.56%) and aged less than 60 years (62.36%). With regard to education, 78.88% had elementary 1st, 2nd or high school level; 17.72% had higher education and 3.39%

were illiterate. The majority (95.9%) were patients from urban areas. Table 1 presents the general characteristics of the studied sample.

Overall mortality was 33.82% (95CI 32.41%-35.26%), corresponding to 1435 cases. A total of 1828 patients (43.08%) required intensive care unit (ICU) treatment. Hospital stay longer than six days occurred in 62.17% of the cases, with 76.97% presenting oxygen saturation below 95% on admission. Non-invasive ventilatory support was required in 55.72% of patients while 25.19% required invasive ventilatory support.

Cardiac comorbidities were the most prevalent with 2015 cases. Diabetes mellitus was present in 1499 cases. Next, in order, the most common comorbidities were bronchial asthma (270), chronic lung disease (214), chronic kidney disease (196), neurological disease (134), immunosuppression (108), chronic liver disease (49) and hematologic disease chronic (43). Figure 1 shows the distribution of comorbidities presented according to their frequency in percentage of prevalence.

Mortality was higher in individuals aged over 60 years (48.47%) compared to individuals aged between 18 and 59 years (24.98%). There were no differences in mortality by gender (32.04% in women versus 35.54% in men, p>0.01). Regarding ethnicity, lower mortality was observed in whites (31.76%) when compared to non-whites (37.91%). Patients with complete higher education had a mortality rate of 21.94%, significantly lower compared to individuals with complete secondary education (29.02%), complete elementary education (44.96%) and illiterates (47.22%). Regarding the area of residence, mortality in patients from urban areas was lower than that of patients from rural areas (33.55% versus 40.37%; p<0.001). Table 2 presents the percentage of deaths stratified according to the studied sociodemographic variables and chronic comorbidities.

As shown in Table 3, there was a relationship with a higher risk of death in obese patients with COVID-19 the presence of cardiovascular disease (41.39%; RR 1.53; CI95 1.40-1.67), diabetes mellitus (42.83%; RR 1.48; CI95 1.36-1.61), chronic lung diseases (56.07%; RR 1.71; CI95 1.51-1.95), immunosuppression (53.7%; RR 1.61; CI95 1.34-1.93), kidney disease (58.67%; RR 1.79; CI95 1.58-2.03) and neurological disease (47.01% mortality; RR 1.40 ; IC95 1.17-1.69). Bronchial asthma, chronic liver disease and hematological disease were not associated with the occurrence of deaths. Figure 2 shows mortality stratified according to the presence of comorbidities in the sample.

DISCUSSION

The present study presents data about the clinical outcome of obese patients admitted to the public health network in the state of Mato Grosso (SUS-Brazil), particularly investigating the relationship between the presence of chronic comorbidities in these patients and the occurrence of death. In this series, there was higher mortality in obese patients with chronic kidney disease (1.79x higher risk compared to patients without kidney disease), chronic lung disease (1.71x higher risk compared to patients without this comorbidity) and immunodepression (risk 1.69x higher). A recent meta-analysis 11 including 73 studies evaluating the association between multiorgan dysfunction and the outcome of COVID-19 revealed that patients with chronic kidney disease were more likely to develop the severe form of SARS-CoV-2 infection (OR 1.84 [95%CI 1.47-2.30]). As an explanation for such an association, it is proposed that since, from a pathophysiological perspective, COVID-19, especially in severe forms, is characterized by an overproduction of inflammatory components due to the cytokine storm triggered by viral infection, leading to systemic inflammation and to a prothrombotic state, several organ complications are observed in patients with SARS-CoV-2 infection, including kidney damage, such as acute kidney injury (AKI) 12. COVID-19 infection deserves close attention by the medical team.

It is also worth remembering that obesity, present in the patients in this study, also promotes a state of generalized inflammation, which may further enhance the emergence of complications. In such a metabolic condition there is production of pro-inflammatory adipokines (IL-6, IL-8, IL6, IL-8, monocyte chemoattractant protein-1, leptin and plasminogen activator inhibitor-1), and to a lesser extent, anti -inflammatory (adiponectin and IL10), contributing to a picture of immunological imbalance, with a recruitment of macrophages that produce more inflammatory cytokines, formalizing a cycle, leading to a chronic inflammatory picture [13]. This fact becomes even more evident in the case of SARS-CoV-2, with a strong association between such conditions, making obesity a risk factor for death in infected patients, especially children and adolescents, age groups that in non-obese individuals, they have milder clinical features and a lower mortality rate when compared to adult individuals. Furthermore, obesity is largely associated with the lack of physical activity, resulting in hyperinsulinism due to insulin resistance, causing the high level of insulin to impair the immune response. [8,14].

Following this perspective, according to Souza ARL, this comorbidity was responsible for a significant increase in the mortality rate (OR=2.06; p<0.001)15. Still according to Silveira et al..[16], this virus is responsible for the destruction of the lung parenchyma, causing interstitial inflammation and extensive consolidation. Individuals affected by this disease have severe pathophysiological changes in the pulmonary interstitium and possibly defective cortical processing of respiratory signals. Therefore, as it is a disease that acts mainly on the lung parenchyma, it is understandable that chronic lung diseases are a risk factor with a significant association with mortality16.

Although immunosuppression is considered among the conditions that aggravate the chances of worse evolution, the current medical literature still does not have a significant amount of data on the behavior of SARS-CoV-2 infection in individuals with this condition. Furthermore, various conditions can lead to different forms of immunosuppression and may be associated with different degrees of risk. Individuals undergoing organ transplants are intentionally immunosuppressed with the intention of preventing the recipient's immune system from rejecting the transplanted organ. The degree of immunosuppression varies according to the type of transplant, the time elapsed from the surgical procedure and the drugs administered, which makes it more difficult to design studies to understand the role of immunosuppression in the development of COVID-19. However, the studies found in the literature present results compatible with those found in our research, according to Pereira et al.[17], a study that analyzed patients receiving transplanted organs concluded that of the 90 patients analyzed, 27 evolved to the severe form of the disease, that is, 30% of the patients, which represents a rate considerably higher than that found in the general population [17].

In our study, the occurrence of cardiovascular disease (RR 1.53; CI95 1.40-1.67) and diabetes mellitus (RR 1.48; CI95 1.36-1.61) also showed an association with mortality, which deserve special consideration. Published data on cardiovascular disease and

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COVID-19 point to a direct relationship between cardiovascular disease and negative outcomes. According to Cavalcante IS, et al 18, patients with cardiac pathologies have a higher risk of serious evolution and death when infected with SARS-CoV-2, compared to the group without heart disease, possibly associated with the presence and action of angiotensin-converting enzyme receptors. For the authors, the pathophysiological aspects of SARS-COV-2 infection demonstrate the role of the angiotensin-converting enzyme 2 in the internalization of the virus by human cells, with emphasis on myocardial cells, evidencing the relationship of COVID-19 with mechanisms of cardiac injury and the possible manifestations resulting from it [21]. With regard to diabetes mellitus, there is abundant published evidence regarding the influence of this comorbidity in the face of SARS-CoV-2 infection, for example, a study conducted in China with a total of 44,672 cases of COVID-19 pointed out that diabetes mellitus was the second disease most associated with death [19]. Chronic liver diseases and asthma did not show statistically significant associations. In fact, in the researched literature, no publications were found that relate liver diseases and asthma to mortality or to the unfavorable evolution of infection by the new coronavirus. However, we must consider that the present study has potential limitations. Although this analysis was not carried out concurrently, where hospitalizations are monitored concomitantly during the follow-up period, the use of secondary data from the Severe Acute Respiratory Syndrome (SARS) surveillance database of Open Datasus allowed the calculation of estimates of relative risks of the various predictor variables analyzed. A possible limitation of this study is that the database does not contain information about the treatment of each patient, as well as other procedures performed during hospitalization, thus preventing the evaluation of important intervention variables for a better estimation of the risk of death. The lack of information about the clinical course and severity of the patient with COVID-19 at the time of admission must also be considered. Furthermore, the continental size of Brazil must not be disregarded in relation to its quality of hospital care, varying between regions, with differences between the supply of ward beds and ICU beds, a variable that is not measured according to municipalities due to the lack of availability of these beds. data. It is known that both the supply of beds and the level of professional qualification are not equitable when comparing different Brazilian regions and states, as well as between state health macro-regions.

Despite its limitations, this study has the importance of being one of the first to assess factors associated with the risk of death among obese patients during the COVID-19 pandemic in Brazil. It is important to interpret the prognostic factors as well as their limitations, hospital demand and deaths from COVID-19.

Considering the COVID-19 pandemic, epidemiological studies are crucial for providing data that allow characterizing the disease and also making associations with the transmission profile. This information can guide the ways of acting and the measures to be taken. The acquisition of information about obese patients with COVID-19 made it possible to describe the population in question and raise potential risk factors for death, also of a sociodemographic order. Among the main ones are age over 60 years, patients with a lower level of education, non-white ethnicities and living in a rural area. This shows the strong social impact of the disease. North American and British series have observed a large percentage of obese patients hospitalized for COVID-19 who are black, Hispanic and from other minority ethnic backgrounds20. These groups have a higher prevalence of obesity and its associated complications (arterial hypertension, diabetes mellitus or chronic kidney disease) than whites 20,21. Furthermore, they typically come from more socially depressed and economically disadvantaged urban areas, with a low level of education, where less attention is paid to health and where social distancing measures are more difficult to maintain. Globally, these circumstances favor the spread of infection and result in higher admission rates due to COVID-1922.

Finally, the association between obesity, COVID-19 and the aforementioned risk factors increased the risk of death, proving to be potential predictors for the increase in the fatality rate. Monitoring and greater assistance before, during and after infection to these patients must be carried out in order to optimize the prognosis and modify the outcome of these cases.

CONCLUSION

The overall mortality of obese patients with COVID-19 treated in Brazil between January 1, 2020 and March 31, 2021 was considerably higher when compared to the non-obese population. Among these patients, the presence of chronic kidney disease, chronic lung disease, immunosuppression, chronic cardiovascular disease and diabetes mellitus were associated with an increased risk of death when compared to patients without the comorbidity, respectively. Bronchial asthma, chronic liver disease and hematological disease had no risk association with the occurrence of deaths.

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	N=4234	%	IC95 (%)	IC95 (%)
Gender				
Female	2085	49,14	47,64	50,64
Male	2158	50,86	49,36	52,36
Ethnicity				
Black	2824	66,56	65,12	67,96
White	291	6,86	6,14	7,66
Yellow	29	0,68	0,48	0,98
Brown	1094	25,78	24,49	27,12
Indian	5	0,12	0,05	0,28
Age				
<60 years	2646	62,36	60,89	63,81
≥60 years	1597	37,64	36,19	39,11
Education				
Illiterate	144	3,39	2,89	3,98
Elementary 1	1021	24,06	22,80	25,37
Elementary 2	820	19,33	18,17	20,54
High school	1506	35,49	34,07	36,95
Superior	752	17,72	16,60	18,90
Living Area				
Countryside	174	4,10	3,54	4,74
Urban	4069	95,90	95,26	96,46
Length of hospital stay				
<6 days	1588	37,83	36,37	39,31
≥6 days	2610	62,17	60,69	63,63
Breathing difficulty				
Saturation 0_2 <95%	3266	76,97	75,68	78,22
Ventilatory support				
Without necessity	810	19,09	17,94	20,30
Non-invasive	2364	55,72	54,22	57,20
Invasive	1069	25,19	23,91	26,52
ICU treatment	1828	43,08	41,60	44,58
Death	1435	33,82	32,41	35,26

Table 1 - General characteristics of the studied sample.

Source: COVID-19 surveillance database in Severe Acute Respiratory Syndrome (SARS) surveillance made available at Open DataSUS, 2020.

Co-variable	% deaths	RR	Confidence Interval (IC95)	p
Age ≥60 years	48,47	1,94	1,78 – 2,10	< 0,001
Gender				
Female	32.63			
Male	33.83	1.03	1.00 – 1.06	> 0,01
Ethnicity				
White	31,76	0,83	0,76 – 0,91	< 0,001
Not white	37,91			<0,001
Education				
University level	21,94			
High school	29,02	1,32	1.30 – 1.35	<0,001
Elementary School	44,96	2,04	2,0 – 2,06	<0,001
No schooling	47,22	2,15	2,13 – 2,18	<0,001

Table 2 – Mortality (% deaths) stratified according to sociodemographic variables and bivariate analysis in relation to the risk of death.

Source: COVID-19 surveillance database in Severe Acute Respiratory Syndrome (SARS) surveillance available on Open DataSUS,2020.

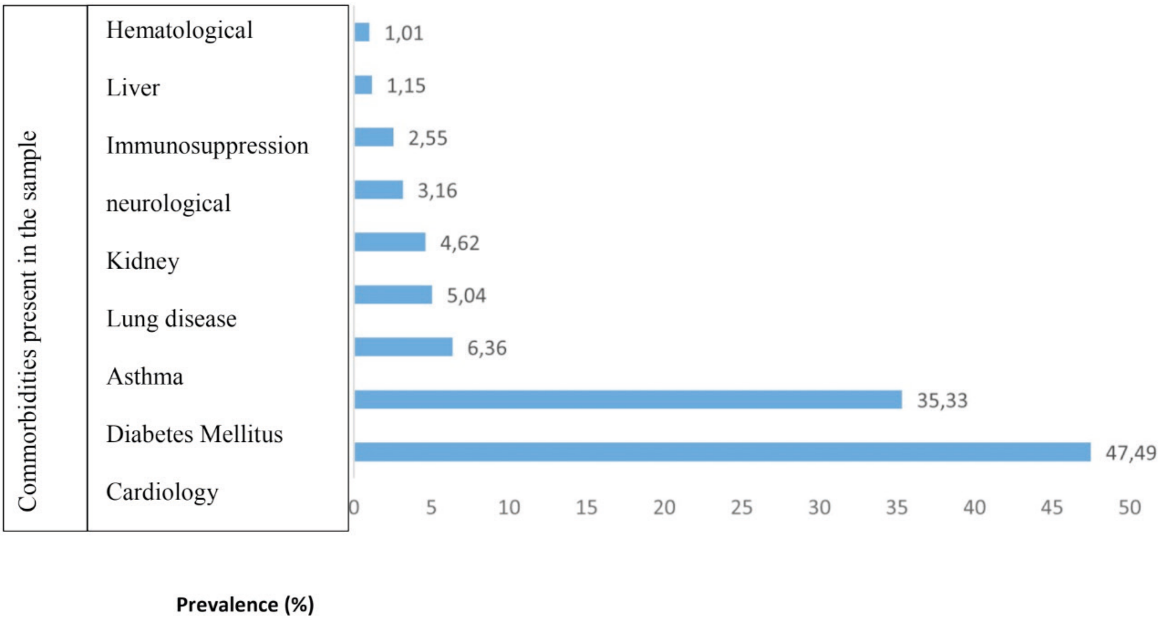

Figure 1 – Prevalence of comorbidities in the studied sample in percentage

Prevalence (%)

Source: COVID-19 surveillance database in Severe Acute Respiratory Syndrome (SARS) surveillance available on Open DataSUS,2020.

Co-variable	% deaths	RR	Confidence Interval (IC95)	p
Kidney				
Yes	58,67	1,79	1,58 – 2,03	<0,001
No	32,62	0,61	0,51 – 0,72	<0,001
Chronic lung disease				
Yes	56,07	1,71	1,51 – 1,95	<0,001
No	32,64	0,65	0,55 – 0,75	<0,001
Immunosuppression				
Yes	53,7	1,61	1,34 – 1,93	<0,001
No	33,30	0,69	0,56 – 0,85	<0,001
Neurologic				
Yes	47,01	1,4	1,17 – 1,69	<0,001
No	33,39	0,79	0,67 – 0,93	<0,001
Diabetes Mellitus				
Yes	42,83	1,48	1,36 – 1,61	<0,001
No	28,90	0,80	0,76 – 0,84	<0,001
Cardiovascular				
Yes	41,39	1,53	1,40 – 1,67	<0,001
No	26,97	0,80	0,76 – 0,83	<0,001
Hepatic				
Yes	36,73	1,08	0,75 – 1,57	>0,001
No	33,79	0,95	0,77 – 1,18	>0,001
Hematological				
Yes	34,88	1,03	0,68 –1,55	>0,001
No	33,81	0,98	0,78 –1,22	>0,001
Asthma				
Yes	33,93	1,02	0,94 – 1,11	>0,001
No	33,93	1,02	0,94 – 1,11	>0,001

Table 3 – Mortality (% deaths) stratified according to the presence and absence of comorbidities and bivariate analysis in relation to the risk of death.

Source: COVID-19 surveillance database in Severe Acute Respiratory Syndrome (SARS) surveillance available on Open DataSUS,2020.

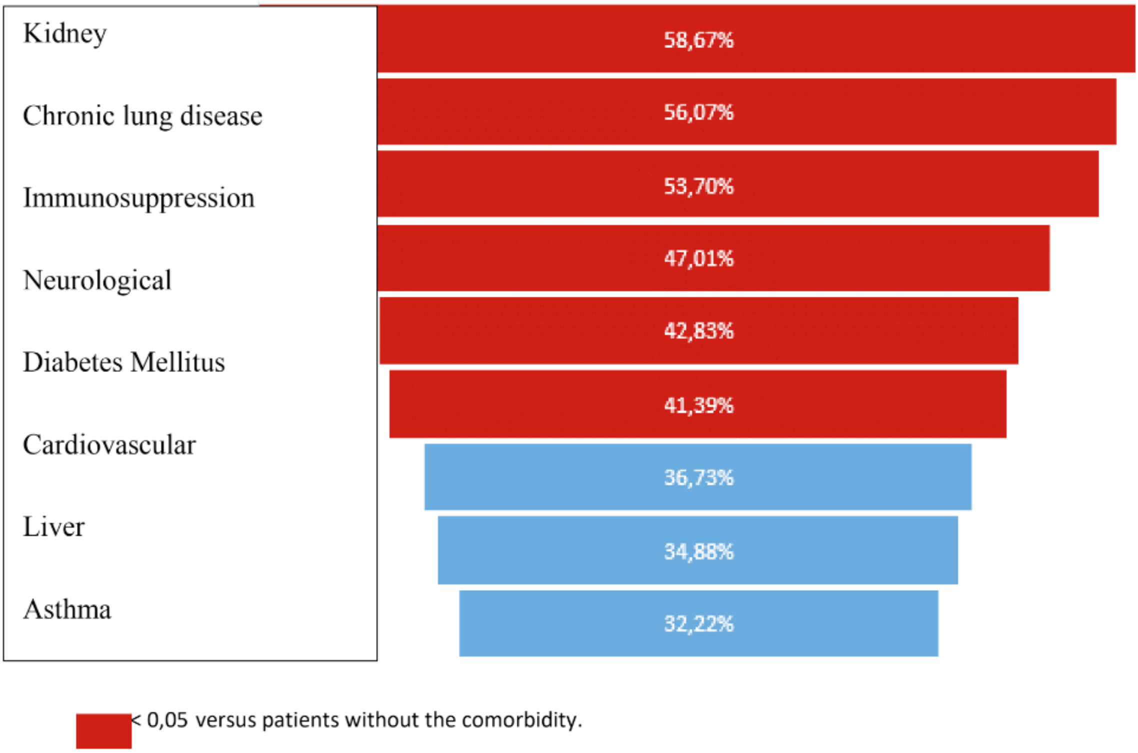

Figure 2 – Mortality stratified according to the presence of comorbiditie

p< 0,05 versus patients without the comorbidity.

Source: COVID-19 surveillance database in Severe Acute Respiratory Syndrome (SARS) surveillance available on Open DataSUS,2020.