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Original Article

Diabetes mellitus and severity by COVID-19 in hospitalized Brazilians

Diabetes mellitus e gravidade por COVID-19 em brasileiros hospitalizados

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ABSTRACT

Objective: to estimate the prevalence of severity of hospitalized cases of COVID-19 and its association with diabetes mellitus. **Methods**: a cross-sectional study, which used secondary data from the Influenza Epidemiological Surveillance Information System, totaling 405,294 confirmed cases. To verify the association of diabetes and severity in hospitalized patients with COVID-19, Poisson regression models with robust variance estimator were used. Initially, the association of disease with outcome was verified; next, several adjustments for potential confounders were performed. **Results**: the prevalence of diabetes in the 405,294 hospitalized and positive cases was 25.7% (Confidence Interval: 25.5% - 25.8%). After adjustments, diabetes was found to increase the severity of COVID-19 by 19% (Confidence Interval: 1.17 - 2.21). **Conclusion**: a significant association of diabetes mellitus with severe cases of COVID-19 infection has been identified. **Contributions to practice**: the evidence generated by the study guides the risk stratification of patients and directs clinical management.

Descriptors: Diabetes Mellitus; Coronavirus Infections; Hospitalization; Severity of Illness Index; Cross-Sectional Studies.

RESUMO

Objetivo: estimar a prevalência de gravidade de casos hospitalizados de COVID-19 e sua associação com o diabetes mellitus. **Métodos**: estudo transversal, que utilizou base de dados secundários do Sistema de Informação de Vigilância Epidemiológica da Gripe, totalizando 405.294 casos confirmados. Para verificar a associação do diabetes e a gravidade em pacientes com COVID-19 hospitalizados, foram usados modelos de regressão de Poisson com estimador de variância robusta. Inicialmente, verificou-se a associação da doença com o desfecho; em seguida, foram realizados diversos ajustes para os potenciais confundidores. **Resultados**: a prevalência de diabetes nos 405.294 casos hospitalizados e positivos foi de 25,7% (Intervalo de Confiança: 25,5% - 25,8%). Após ajustes, observou-se que a diabetes aumentou a gravidade da COVID-19 em 19% (Intervalo de Confiança: 1,17 – 2,21). **Conclusão**: identificou-se associação importante do diabetes mellitus com casos graves de infecção pela COVID-19. **Contribuições para a prática**: a evidência gerada pelo estudo guia a estratificação de risco de pacientes e direciona o manejo clínico.

Descritores: Diabetes Mellitus; Infecções por Coronavírus; Hospitalização; Índice de Gravidade de Doença; Estudos Transversais.

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Introduction

Diabetes Mellitus (DM) is a chronic disease of high prevalence worldwide, constituting a public health problem in continuous rise[1]. In the pandemic context of COVID-19, diabetic patients are more likely to experience symptoms of severity[2], similar to other viral pandemics, such as Severe Acute Respiratory Syndrome (SARS) in 2003, Influenza (H1N1) in 2009, and Middle East Respiratory Syndrome in 2012[3].

Allied to this, international studies point out that DM can influence the worsening of the clinical condition of hospitalized patients[2], accelerating their mortality. These findings reflect the relevance of preventive actions and measures of social distancing and isolation, since, with the increase of cases, patients with DM will comprise a disproportionately larger number of these admissions and, once hospitalized, tend to develop greater severity of the disease[4].

Therefore, it is pertinent to evaluate how the presence of DM can impact the clinical evolution and prognosis of COVID-19 in Brazilian patients, since this is one of the countries of the American continent most affected by the pandemic of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus. Moreover, preventing unfavorable outcomes of COVID-19 infection and helping to define the profile of patients prone to greater severity enables the provision of qualified and directed care, benefiting patients, professionals, managers and the healthcare system.

Although the evidence available so far points to a possible relationship between DM and severity, we emphasize the existence of gaps in knowledge on the subject in the Brazilian context, which justifies this research. It is noteworthy that the Brazilian scenario has peculiarities related to the discontinuity of treatment of patients with DM in primary care, making them more susceptible to complications.

Thus, the study aimed to estimate the prevalence of severity of hospitalized cases of COVID-19 and its association with diabetes mellitus.

Methods

Cross-sectional, analytical, confirmatory study, reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), a tool used for reporting observational studies. In this research, secondary data from the Influenza Epidemiological Surveillance Information System (*Sistema de Informação de Vigilância Epidemiológica da Gripe*/SIVEP-Gripe) database, reported in the months of January to October 2020, were the corpus of analysis.

During the period that the research was delimited, SIVEP-Gripe housed epidemiological data on 757,658 suspected and confirmed cases of influenza disease, including COVID-19, throughout the Brazilian territory, including information related to socio-demographic, clinical and laboratory variables, comorbidities and hospitalization.

Brazil corresponds to a continental sized country, divided into 5,570 municipalities, 27 states and five large regions, equivalent to an area of 8,510,820.623 km^2, which houses a population of 210,147,125 people, comprising a density of 22.43 inhabitants/km^2[5].

For this study, we included all cases with flu-like symptoms who had undergone Reverse Transcription-Polymerase Chain Reaction (RT-PCR) testing for SARS-CoV-2, tested positive, and were hospitalized, for a total of 405,294 confirmed cases.

For the purposes of this research, the outcome was considered to be the severity of the patient with COVID-19, i.e., hospitalization and admission to Intensive Care Units (ICU). The main independent variable was defined as the comorbidity Diabetes Mellitus (yes/no). This condition was defined by self-report during the admission interview or laboratory confirmation during the hospitalization process.

Covariates related to socio-demographic characteristics (age, sex, education), clinical picture (vomiting, diarrhea, anosmia, dyspnea, fever, and saturation less than 95%), other comorbidities (pneumopathies, obesity, neurological diseases, liver

diseases, heart diseases, kidney diseases, immune-depression), and hospitalization conditions (nosocomial infection) were also used.

Descriptive statistics were used to characterize the variables, as well as bivariate analysis to associate socio-demographic and clinical data, especially DM, with the outcome severity. Quantitative variables were expressed by medians and interquartile range, with association verified by the Mann-Whitney test; this option was chosen due to the non-adherence to normal distribution of these variables, according to the application of the Shapiro-Wilk test. The categorical variables were expressed by simple and relative frequencies and associated with the outcomes through the Chi-square test. In both cases it was considered significant when $p<0.05$.

To test the hypothesis, Poisson regression models with robust variance estimator were applied. In the initial model, only the effect of DM on the outcome was verified (crude model); next, several adjustments were made for covariates, which may indicate confounding or effect modification, in the following order: socio-demographic characteristics (age, sex, education), signs and symptoms (vomiting, diarrhea, anosmia, dyspnea, fever, and saturation less than 95%), comorbidities (pneumopathies, obesity, neurological diseases, liver diseases, heart diseases, kidney diseases, immune-depression), and hospitalization conditions (nosocomial infection). The final model included all the previous adjustments. The strength of association in all models was measured using the Prevalence Ratio (PR) and 95% Confidence Interval (95%CI), considering significant the associations that presented $p<0.05$. All analyses were performed in Stata 13 (StataCorp LP, College Station, TX, USA).

Regarding ethical aspects, this study did not require prior approval from the Research Ethics Committee, since the data on COVID-19 are freely available on the Internet by the Brazilian Ministry of Health. It is noteworthy that there is no participant identification data. Even so, the ethical responsibility of the researchers was maintained in the manipulation of the data, the analysis, and the publication of the information in line with Resolution 466/2012 and 510/2016 of the National Health Council.

Results

A total of 405,294 hospitalized cases positive for COVID-19 were analyzed, with a median age of 58 years (1st quartile 44 years, 3rd quartile 72 years; interquartile range 28 years); 228,159 (43.7%) were female and 166,680 (41.1%) with 2nd Elementary School education. The prevalence of DM was 25.7% (95% CI: 25.5% - 25.8%). Moreover, the prevalence of severe cases of the disease was 16.1% (95% CI: 16% - 16.2%). In the group with DM, the prevalence of severity as a result of COVID-19 was 20.3%. It is noteworthy that obesity, however statistically significant, had 219,005 (54%) missing data. Thus, it was only described and not used in regression analyses.

Table 1 shows general characteristics of cases of COVID-19 associated with disease severity.

Table 1 – Severity by COVID-19 in Brazilian diabetic patients (n=405,294). Fortaleza, CE, Brazil, 2021

Variables	Total (%)	Severity		p-value	PR	95%CI
		Yes (%)	No (%)			
Age (median)	58 (44-72)	62 (48 – 73)	58 (43 – 71)	<0.001*	1.009	1.008 –1.01
Sex						
Female	228,159 (43.7)	38,531 (16.9)	189,628 (83.1)	–	1	–
Male	177,048 (56.3)	26,831 (15.1)	150,217 (84.9)	<0.001†	0.90	0.88 – 0.91
Education						
Illiterate	131,578 (32.5)	18,618 (14.1)	112,960 (85.8)	–	1	–
Elementary School	38,866 (9.6)	7,100 (18.3)	31,766 (81.7)	<0.001†	1.29	1.25 – 1.32
Middle School	166,680 (41.1)	28,629 (17.2)	138,051 (82.8)	<0.001†	1.21	1.19 – 1.23
Highschool	43,923 (10.8)	6,807 (15.5)	37,116 (84.5)	<0.001†	1.09	1.06 – 1.12
Higher education	21,012 (5.2)	3,872 (18.4)	17,140 (81.6)	<0.001†	1.30	1.26 – 1.34

(the Table 1 continue in the next page...)

Variables	Total (%)	Severity		p-value	PR	95%CI
		Yes (%)	No (%)			
Vomit						
Yes	32,841 (8.1)	4,700 (14.3)	28,141 (85.7)	<0.001†	0.87	0.86 – 0.90
No	372,452 (91.9)	60,677 (16.3)	311,785 (83.7)	–	1	–
Diarrhea						
Yes	55,299 (13.6)	7,989 (14.4)	47,310 (85.6)	<0.001†	0.88	0.86 – 0.90
No	349,994 (86.4)	57,378 (16.4)	292,616 (83.6)	–	1	–
Anosmia						
Yes	16,128 (4.0)	21,85 (13.5)	13,943 (86.4)	<0.001†	0.83	0.80 – 0.88
No	389,166 (96.0)	63,182 (16.2)	325,984 (83.8)	–	1	–
Dyspnea						
Yes	286,688 (70.7)	51,328 (17.9)	23,5360 (82.1)	<0.001†	1.51	1.48 – 1.53
No	118,606 (29.3)	14,039 (11.8)	104,567 (88.2)	–	1	–
Fever						
Yes	263,193 (69.9)	41,583 (15.8)	221,610 (84.2)	<0.001†	0.94	0.93 – 0.96
No	142,101 (35.1)	23,784 (16.7)	11,8317 (83.3)	–	1	–
Pneumopathies						
Yes	15,196 (3.7)	39.26 (25.8)	11,270 (74.2)	<0.001†	1.64	1.59 – 1.69
No	390,097 (96.3)	61,441 (15.7)	328,656 (84.3)	–	1	–
Obesity						
Yes	20,164 (10.8)	5,407 (26.8)	14,757 (73.2)	<0.001†	1.52	1.48 – 1.55
No	166,125 (89.2)	29,392 (17.7)	136,733 (82.3)	–	1	–
Neurological diseases						
Yes	16,065 (4.0)	3,627 (22.6)	12,438 (77.4)	<0.001†	1.42	1.38 – 1.64
No	389,229 (96.0)	61,740 (15.9)	237,489 (84.1)	–	1	–
Asthma						
Yes	10,827 (2.7)	1,947 (18.0)	8,880 (82.0)	<0.001†	1.11	1.07 – 1.16
No	394,467 (97.3)	63,420 (16.1)	331,047 (83.9)	–	1	–
Liver disease						
Yes	3,715 (0.9)	931 (25.1)	2,784 (74.9)	<0.001†	1.56	1.48 – 1.65
No	401,579 (99.1)	64,436 (16.0)	337,143 (84.0)	–	1	–
Cardiopathies						
Yes	137,654 (34.0)	27,089 (20.2)	10,9845 (79.8)	<0.001†	1.44	1.42 – 1.46
No	267,640 (66.0)	37,558 (14.0)	23,002 (86.0)	–	1	–
Kidney dysfunction						
Yes	12,217 (4.2)	4,488 (26.1)	12,729 (73.9)	<0.001†	1.66	1.62 – 1.70
No	388,077 (95.8)	60,879 (15.7)	327,198 (84.3)	–	1	–
Immunodepression						
Yes	11,037 (2.7)	2,572 (23.3)	8,465 (76.7)	<0.001†	1.46	1.41 – 1.51
No	394,257 (97.3)	62,795 (15.9)	331,462 (84.1)	–	1	–
Nosocomial infection						
Yes	8,529 (2.1)	2,035 (23.9)	6,494 (76.1)	<0.001†	1.49	1.44 – 1.55
No	396,765 (97.9)	63,332 (16.0)	333,433 (84.0)	–	1	–
Saturation <95%						
Yes	233,758 (57.7)	45,173 (19.3)	188,585 (80.1)	<0.001†	1.64	1.61 – 1.67
No	171,536 (42.3)	20,194 (11.8)	151,342 (88.2)	–	1	–
Diabetes						
Yes	104,058 (25.7)	21,101 (20.3)	82,957 (79.7)	<0.001†	1.38	1.36 – 1.40
No	301,235 (74.3)	44,266 (14.7)	256,969 (85.3)	–	1	–

*p-value for Mann-Whitney U-value; †p-value for Chi-square; PR: Prevalence Ratio; CI: Confidence Interval

In the crude analysis, it was possible to observe the association of DM in severe cases of the disease (PR=1.38; 95%CI: 1.36 - 1.40). There was a small reduction in the prevalence ratio to 1.30 (95%CI: 1.28 - 1.32) after adjustment for socio-demographic covariates (Model 2), then to 1.26 (95%CI: 1.24 - 1.28) when adjusted for symptoms (Model 3), and to 1.19 (95%CI: 1.17 - 2.21) when adjustment considered comorbidities (Model 4). When adjusted for nosocomial infection (Model 5), there was no difference in the effect when compared to the previous one. Thus, after adjustments it was observed that there is an increase in the prevalence of severity by 19% when hospitalized patients with COVID-19 have diabetes mellitus (Table 2).

Table 2 – Multivariate statistical analysis for severity in patients hospitalized for COVID-19 (n=405,294). Fortaleza, CE, Brazil, 2021

Model	Severity		
	PR	CI 95%	p-value
Model 1 (crude)*	1.38	1.36 – 1.40	<0.001
Model 2†	1.30	1.28 – 1.32	<0.001
Model 3‡	1.26	1.24 – 1.28	<0.001
Model 4§	1.19	1.17 – 1.21	<0.001
Model 5‖	1.19	1.17 – 2.21	<0.001

*Model 1: diabetes; †Model 2: Model 1 + age + sex + education; ‡Model 3: Model 2 + vomiting + diarrhea + fever + dyspnea + anosmia + saturation <95%; §Model 4: Model 3 + pneumopathies + neurological disease + asthma + liver disease + renal dysfunction + immune-depression + heart disease; ‖Model 5: Model 4 + nosocomial infection; PR: Prevalence Ratio; CI: Confidence Interval

Discussion

The evidence presented points to DM as a factor associated with the severity of Covid-19 infection in hospitalized patients. It is relevant to note that diabetes affects about 3% of the world's population, and when analyzing the deaths related to the new coronavirus, almost one-third occurred in people with DM[6], which raises the importance of researching this issue in the current scenario[2].

A continental analysis of COVID-19 cases, performed together with socio-demographic factors associated with mortality rates, revealed that DM represents a significant risk factor for severity on different continents[7]. The effects of diabetes in patients with COVID-19 are associated with severe outcomes such as hospitalization, ICU admission, and death[8].

A meta-analysis with 33 studies and 16,003 participants showed that patients with DM and COVID-19 have a higher risk of developing clinical severity, an odds ratio of 2.75 (95% CI: 2.09 and 3.62; p<0.01) compared to those with COVID-19 and without DM[9]. In another study, a twofold risk in terms of mortality, severity, and progression to acute respiratory distress syndrome was highlighted in patients with diabetes affected by COVID-19[10]. In this scope, many potential mechanisms of adverse outcomes in patients with diabetes and COVID-19 infection have been hypothesized[11]. However, the pathological link remains unclear.

In this study, the prevalence of diabetes in patients with COVID-19 was similar to the findings in Italy[12], but lower than the results of a systematic review of 1,885 patients with the virus[13] and in a cross-sectional study conducted in Brazil[14]. The aging population, the rising prevalence of an unhealthy lifestyle, and the processes of urbanization and globalization figure as factors responsible for the increasing incidence and prevalence of DM worldwide[13]. When associated with the new coronavirus, it has increased social and financial costs to patients and the healthcare system.

The severity was also significantly associated with all covariates included in the regression model. The prognostic severity of the association between DM and COVID-19 has several explanations: because it is a chronic condition that alters metabolic functions, the diabetic patient has an ineffective immune response against infections, making the body unable to protect itself against physiological[15], in addition, diabetes increases the risk of pulmonary fibrosis and decreases respiratory function[16], being considered a promoter of cardiovascular vulnerability[17].

Other evidence suggests that coronavirus infec-

tion exacerbates the underlying effects of hyperglycemic state and potentiates direct viral toxicity in metabolically relevant tissues, including pancreatic beta cells and targets of insulin action[18]. It is also worth noting that the severity of COVID-19 among people with diabetes must include poor glycemic control, the pharmacodynamics of some medications commonly used in the treatment of diabetes, and limited access to medications[19].

Add to these factors the various prevention and control measures related to COVID-19, including social distancing and quarantine practices, which can result in decreased daily physical activity, poor dietary diversity, psychological distress, as well as delays in seeking health-related care due to fear of exposure[20]. These measures are associated with increased anxiety levels, which can lead mainly to emotional eating rich in simple carbohydrates[21]. Thus, there is higher caloric intake, lower energy expenditure and instability of the metabolic profile[22].

Clinical variables such as symptoms, comorbidities, and hospitalization conditions can determine the severity of patients with diabetes and COVID-19. DM is a complex chronic condition that, when decompensated, can bring negative consequences to several systems of the body, in addition to causing dehydration and respiratory complications. It is usually associated with other comorbidities that, when coupled with the new coronavirus infection, can lead to both reversible and irreversible damage in the short and long term[23].

In all analyses, diabetes showed a significant association with severity in hospitalized patients with COVID-19. These data are relevant and subsidize the reinforcement of preventive measures, such as wearing masks, social isolation, and avoiding crowds. Moreover, actions for the maintenance of practices for self-care in health, such as maintaining daily physical activity, balanced diet, sleep hygiene, and stress control.

About the high prevalence of diabetes in people with COVID-19 in Brazil, it is emphasized that routine diabetes care was interrupted during the pandemic in the Brazilian context[24]. Moreover, the pandemic scenario also increases stress levels, makes it difficult to maintain a healthy diet and reduces the maintenance of routine physical activity, which contributes to worse outcomes during and after the pandemic. Thus, it is considered the need to emphasize that health services need to reorganize themselves to maintain the follow-up of patients with DM even in public health emergencies, especially in primary care, where higher levels of discontinuity were evidenced.

Study limitations

This study has limitations. The first one lies in the use of secondary data, because they are susceptible to mis-registration and, sometimes, missing data can interfere in the results. However, it is noteworthy that, with the exception of obesity, all variables had less than 1% of missing data. Finally, the study of hospitalized cases may have potentiated the association of DM on severity by COVID-19, since the hospitalization of the case, in many moments of the pandemic, was done for presenting moderate to severe condition. However, the adjustment of the multiple statistical models aimed to correct this latter limitation.

Contributions to practice

The association of DM with severe cases of COVID-19 infection, evidenced in the present study, was high. This was an important finding that deserves to be highlighted in future investigations, given the uniqueness of the disease and the evidence available so far. Given this scenario, it was essential to specify the strength of the association between the prognosis of COVID-19, which may help to create more effective prevention strategies in the population and to enhance the procedures for adherence to treatment of diabetes and its control.

Conclusion

A high prevalence of diabetes mellitus was identified in people with COVID-19 in Brazil, in addition to its association with severe cases of the virus infection, even after constant adjustments for potential confounders. The results evidenced in this research point to a worrisome public health problem worldwide when facing the real burden of chronic non-communicable diseases, especially diabetes mellitus. The evidence generated by the study guides the risk stratification of aggravation of DM patients affected by COVID-19, and may direct clinical management.

Authors' contribution

Conception, data design and analysis, manuscript writing, critical review, final approval of the version to be published, and responsibility for all aspects of the text. Garces TS, Sousa GJB, Cestari VRF, Mattos SM, Florêncio RS, Pereira MLD, Moreira TMM.

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