

Factors associated with increased risk of death from COVID-19: a survival analysis based on confirmed cases

Fatores associados a maior risco de ocorrência de óbito por COVID-19: análise de sobrevivência com base em casos confirmados

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ABSTRACT: *Objective:* To perform a survival analysis of individuals diagnosed with COVID-19 identified by health information systems, analyzing the factors associated with the highest risk of death. *Methods:* Survival analysis of individuals notified with COVID-19 in Rio Grande do Norte State using data from the Health Information Systems for the surveillance of cases of and deaths from COVID-19. The dependent variable was the period until the outcome occurrence. The independent variables were sex, self-reported skin color, age group, residence in the capital, and the presence of comorbidities. For data analysis the Kaplan-Meier method and Cox-time-dependent Regression Model for multivariate analysis were used, with the covariable “period since the event notification recorded in days”. *Results:* Highest risk of death were observed in individuals aged 80 or older (HR = 8.06; $p < 0.001$), male (HR = 1.45, $p < 0.001$), non-white skin color (HR = 1.13; $p < 0.033$) or with no information (HR = 1.29; $p < 0.001$), with comorbidities (HR = 10.44; $p < 0.001$) or presence of comorbidities not reported (HR = 10.87; $p < 0.001$). *Conclusion:* The highest risk of occurrence of deaths from COVID-19 was observed in older adults, especially those over 80, patients who have comorbidities, men, and of non-white skin color. From the identification of the profile of patients with a higher risk of death with the identification by the health system, specific strategies of health care must be taken to prevent the evolution to death in these cases.

Keywords: Epidemiology. Survival analysis. Coronavirus infections.

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RESUMO: *Objetivo:* Realizar uma análise de sobrevivência de indivíduos diagnosticados com COVID-19 identificados pelos sistemas de informação em saúde, analisando os fatores associados ao maior risco de ocorrência de óbitos. *Métodos:* Análise de sobrevivência de indivíduos notificados por COVID-19 no estado do Rio Grande do Norte até o dia 24 de agosto de 2020, utilizando dados dos sistemas de informação em saúde. A variável dependente foi o tempo até a ocorrência do desfecho. As variáveis independentes foram sexo, cor da pele, faixa etária, residir ou não na capital e presença de comorbidades. Para análise de dados, utilizou-se o método de Kaplan-Meier e, na análise multivariada, utilizou-se o modelo de regressão de Cox tempo-dependente, utilizando a covariável “tempo desde a notificação do evento em dias”. *Resultados:* Apresentaram maiores riscos de ocorrência de óbitos por COVID-19 os indivíduos com 80 anos ou mais de idade (HR = 8,06; $p < 0,001$), do sexo masculino (HR = 1,45; $p < 0,001$), com cor de pele não branca (HR = 1,13; $p < 0,033$) ou sem informação (HR = 1,29; $p < 0,001$), que tinham comorbidades (HR = 10,44; $p < 0,001$) ou que a presença de comorbidades não foi informada (HR = 10,87; $p < 0,001$). *Conclusão:* O maior risco de ocorrência de óbitos por COVID-19 foi observado em indivíduos idosos, sobretudo os com idade acima de 80 anos, pacientes com comorbidades, homens e com cor de pele não branca. Com base na identificação desse perfil, estratégias e linhas de cuidado específicas devem ser tomadas para prevenir a evolução ao óbito nesses casos pela identificação desses indivíduos no sistema de saúde.

Palavras-chave: Epidemiologia. Análise de sobrevida. Infecções por coronavírus.

INTRODUCTION

In December 2019, Wuhan City, China, reported an outbreak of pneumonia of unknown cause that quickly spread across the country. The pathogen causing the disease has been identified as the novel coronavirus, SARS-CoV-2, or coronavirus of severe acute respiratory syndrome-2. The World Health Organization (WHO) named the disease caused by the new COVID-19 virus (coronavirus disease, year 2019), which was declared a public health emergency of international importance on January 30, 2020; on March 11, 2020, it was declared a pandemic.¹ Since then, a global effort is being made towards the production of information to unravel the clinical, epidemiological, and prognostic factors of the disease.

On January 22, 2020, the Health Surveillance Secretariat of the Brazilian Ministry of Health released the first measures to control infection by the hitherto novel coronavirus, with its signs and symptoms, the criteria for defining suspected cases and the flow of notification, which initially took place by the National Health Surveillance Strategic Information Center, migrating to a virtual platform and, later, by the Notification Registration System of the Ministry of Health (*e-SUS Notifica*), with immediate notification of suspected, probable, and confirmed cases of COVID-19.²

After eight months, according to WHO data from August 25, 2020, more than 23 million were confirmed cases, besides 810,492 deaths from the disease worldwide. Brazil is the second country with the highest number of cases and deaths from the disease in the world, with more than 3.5 million confirmed cases and 115,309 deaths.³ Rio Grande do

Norte State, the setting for present research, had its first case confirmed on March 12, 2020, and totals 60,161 confirmed cases and 2,192 deaths.⁴

As to risk factors for the worsening of the disease, a review showed that the most severe cases of the disease that progressed to pneumonia were more likely to occur in older patients, male, and with comorbidities, compared to milder cases. However, further studies were recommended to clarify the epidemiological characteristics of COVID-19, as well as to identify the risk factors and prognosis of patients infected with SARS-CoV-2.¹

Most of the studies developed to date have come from international settings and the clinical-hospital context.⁵ Thus, the importance of producing information that demonstrates the epidemiological characteristics of the disease in the Brazilian context is emphasized, using, for this purpose, the data produced by health information systems. Seen that, the present article aims to perform a survival analysis of individuals diagnosed with COVID-19 identified by health information systems, analyzing the factors associated with a higher risk of death.

METHODS

This study is a survival analysis of individuals diagnosed with COVID-19 in Rio Grande do Norte State, Northeastern region of Brazil, using secondary data. The source consisted of consolidated data from health information systems for the surveillance of cases and deaths by COVID-19 at the state level. The State Secretariat of Public Health of Rio Grande do Norte (SESAP-RN) composes its COVID-19 database basically by the combination of different systems, notified until August 24, 2020 (<https://portalcovid19.saude.rn.gov.br/#dados>):

- e-SUS Epidemiological Surveillance (e-SUS-VE);
- Influenza Surveillance Information System (SIVEP-Gripe);
- Management System of Laboratory Environment (GAL).

The study was conducted with information available in the public domain, with a set of data, thus not requiring ethical approval.

The dependent variable consisted of the observation time in days until the outcome occurred (death by COVID-19) from the detection of this patient in the information systems for epidemiological surveillance of the disease. The maximum observation time was 165 days and is equivalent to the time since the identification of the first case of COVID-19 in the state.

For the composition of the dependent variable, the “consolidated date of the first symptoms” was considered as the date of entry into the study, which is the date of detection of the first symptoms of COVID-19 by the health system, and the “date of closure”, which represents the date of death or the end of the observation period. The time elapsed until the outcome was measured in days until the event.

The inclusion criteria were confirmed cases notified in the information systems until the August 10, considering 14-day period prior to the final observation period. The criterion was adopted to eliminate the cases contained in the period of instability of data for the investigation of the death outcome. Deaths which occurred until August 24 for cases notified up to the defined period were included, considering the established observation time. As to the criteria for confirming cases, only the cases of COVID-19 confirmed with a diagnostic test of RT-PCR type, a rapid test to detect IgM and IgG antibodies or immunoassay were included.

Exclusion criteria for the survival analysis were attributed to cases registered with a death certificate only, in which the notification of death occurred on the day or after the detection of the individual's first symptoms by the health system. The observation of cases took place with passive follow-up.⁶

In order to identify risk factors and prognostic factors for the occurrence of deaths from COVID-19, survival time was modeled based on the independent variables:

- age group (up to 59, 60 to 79, 80 or more);
- skin color (white, non-white, or not declared);
- sex (male, female);
- presence of comorbidities (yes, no, or with no information);
- residence in the capital or in municipalities in the inner part of the state.

For data analysis, the Kaplan-Meyer method was used, using the log-rank test to compare survival curves between two groups; and the Breslow test to compare survival curves between three groups. After assessing the proportionality of competing risks by evaluating Schoenfeld residuals, the absence of proportionality of risks was observed during the observation period and, consequently, the inadequacy of the conventional Cox regression model for analysis. Thus, for the multivariate analysis of the effect, Cox time-dependent regression model was used, using a time-dependent covariate "time since the event notification in days", in addition to the dependent variable. This variable represents the different moments of the epidemic in the state, shown to be statistically significant for estimating the gross and adjusted hazard ratio (HR) in the final model, according to interest groups. The variables that presented a 5% statistical significance with Wald test were established as a parameter for permanence in the final model.

RESULTS

During the follow-up period, 52,607 cases and 1,842 deaths from COVID-19 were reported in the state. Most cases occurred in individuals up to 59 years old (81.0%), of non-white skin color (59.5%), female (52.8%), living in cities in the inner part of the state (61.7%), and who had no comorbidities (75.7%). As to deaths, most cases occurred in individuals from 60 to 79 years old (43.2%), of non-white skin color (50.9%), male (55.4%), living in cities in the inner part of the state (54.6%), and who had no comorbidities (69.4%). Higher lethality

was observed in older adults aged 80 or older (27.6%), in individuals with comorbidities (12.4%), and with no information about the presence of comorbidities (13.5%) (Table 1).

When evaluating the survival curves during the observation period of 165 days of the epidemic, considering the death of COVID-19 as an event of interest, the probability of survival of individuals without comorbidities at the end of the observation period was 99.4%, whereas of individuals with comorbidities, it was 86.4%. When considering the age group, the probability of cumulative survival of individuals up to 59 years old was 98.7%, whereas it was 69.7% among individuals aged 80 or older. In white and non-white individuals, the probability of accumulated survival was 96.7%, and in individuals with no information regarding their skin color, it was 91.3%. Female individuals had a 96.8% probability of survival, higher than that of male (95.5%), at the end of the observation period. As to the place of residence, individuals who lived in the capital had a lower probability of accumulated survival (95.5%) than individuals who lived in cities in the inner part of the state (96.6%). For all variables evaluated, statistically significant differences were observed between survival curves between the groups ($p < 0.001$) (Supplementary Material 1, 2, and 3).

Table 1. Absolute and relative frequencies of cases, deaths, and lethality due to COVID-19 in Rio Grande do Norte State, on August 10, 2020 (Brazil, 2020).

	COVID-19 cases		Deaths from COVID-19		Lethality
	n	%	n	%	%
Total	52,607	100.0	1,842	100.0	3.5
Age range					
Until 59	42,634	81.0	520	28.2	1.2
60 to 79	8,061	15.4	795	43.2	9.9
80 or more	1,912	3.6	527	28.6	27.6
Skin color					
White	15,746	29.9	446	24.2	2.8
Non-white	31,271	59.5	938	50.9	3.0
Not reported	5,590	10.6	458	24.9	8.2
Sex					
Female	27,797	52.8	822	44.6	3.0
Male	24,810	47.2	1,020	55.4	4.1
Place of residence					
Capital	20,147	38.3	837	45.4	4.2
Inner part of the state	32,460	61.7	1,005	54.6	3.1
Presence of Comorbidities					
No	39,830	75.7	234	12.7	0.6
Yes	10,333	19.6	1,278	69.4	12.4
Not reported	2,444	4.6	330	17.9	13.5

In the unadjusted analysis, the effect of all independent variables was significant to explain the risk of deaths from COVID-19. After adjusted analysis, the variables age, sex, skin color, and the presence of comorbidities remained significant to explain the risk of death. Individuals aged 80 or older (HR = 8.06; $p < 0.001$), male (HR = 1.45; $p < 0.001$), with non-white skin color (HR = 1.13; $p < 0.033$) or with no information regarding it (HR = 1.29; $p < 0.001$), with comorbidities (HR = 10.44; $p < 0.001$) or presence of comorbidities not informed (HR = 10.87; $p < 0.001$) presented higher occurrence of death from COVID-19 (Table 2).

Table 2. Survival analysis of COVID-19 cases in Rio Grande do Norte State. Adjustment made with multiple Cox regression with the variable time dependent (Brazil, 2020).

	Analysis not adjusted		Analysis adjusted	
	p-value	HR (95%CI)	p-value	HR (95%CI)
Age range				
Until 59		1		1
60 to 79	< 0.001	7.43 (6.65 – 8.31)	< 0.001	3.87 (3.45 – 4.34)
80 or more	< 0.001	18.41 (16.28 – 20.82)	< 0.001	8.06 (7.08 – 9.16)
Skin color				
White		1		1
Non-white	0.046	1.12 (1.01 – 1.26)	0.033	1.13 (1.01 – 1.27)
Not reported	< 0.001	1.99 (1.71 – 2.30)	< 0.001	1.29 (1.12 – 1.48)
Sex				
Female		1		1
Male	< 0.001	1.49 (1.35 – 1.63)	< 0.001	1.45 (1.32 – 1.59)
Place of residence				
Capital		1	-	-
Inner part of the state	< 0.001	0.66 (0.60 – 0.72)	-	-
Presence of Comorbidities				
No		1		1
Yes	< 0.001	19.60 (17.03 – 22.56)	< 0.001	10.44 (9.01 – 12.09)
Not reported	< 0.001	14.30 (12.61 – 17.68)	< 0.001	10.87 (9.16 – 12.90)
Covariable Time*	< 0.001	1.00	< 0.001	1.00

*Survival time (days) × time since notification (days). Omnibus Test of model significance: $\chi^2 = 12240.9$; $p < 0.001$; HR: hazard ratio; 95%CI: 95% confidence interval.

DISCUSSION

The present study results revealed the main factors that are associated with a higher risk of death from COVID-19, among the factors evaluated, bringing important subsidies for clinical and political decision-making, since they allow the recognition of the associated factors the prognosis of the disease at the time of identification of the case by the health system.

As to the age group, there was a dose-response effect, in which older adults between 60 and 79 years old presented a risk of 2.87, and those aged 80 years old or more had a 7.06 times greater risk of dying from COVID-19 than individuals up to 59 years old. The association between advanced age and severe symptoms of COVID-19 was found in several clinical studies.^{1,5,7} When comparing patients who developed severe acute respiratory syndrome (SARS) due to COVID-19 with patients without SARS, those who developed more severe symptoms were older adults, and most of them had comorbidities. In addition, high mortality rates were noted in patients with moderate or severe SARS.⁷

In Brazil, since the first months of the pandemic, older adults represent the highest percentage among deaths from COVID-19. Besides that, they have accumulated mortality rates higher than those found in the general population. The influence of contextual sociodemographic factors related to skin color and income on mortality rates due to COVID-19 in older adults was also verified.⁸

The presence of comorbidities proved to be the factor with the greatest effect for the occurrence of deaths from COVID-19. The presence of comorbidities increases the risk of death by 9.44 times compared to individuals with no comorbidities. Although the lethality rate for COVID-19 is lower than that observed in epidemics of diseases caused by other coronaviruses, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), increased mortality is observed in specific groups. When evaluating only deaths from COVID-19, a study showed that 31.5% of cases were individuals aged over 60 or with comorbidities.⁵

Thus, the population of older adults deserves special attention because it is also more vulnerable to developing comorbidities, such as cardiovascular and cerebrovascular diseases, cancer and mental disorders, which may increase the risk of deaths from COVID-19. Developing specific preventive protocols is needed in view of the heterogeneity of the population of older adults, with a focus on those with both a higher age range and comorbidities.⁹

Being male was a factor associated with a higher risk of dying from COVID-19. Men had a lower probability of accumulated survival than women, as well as a risk of death 45% higher than that of women. A systematic review, with a meta-analysis including nine studies, showed that men represent 60% of patients with COVID-19, suggesting greater susceptibility to infection by the virus in this population.⁵ However, in the present study, the highest proportion of cases observed was in the female population.

This finding, in addition to having clinical relevance as to the disease prognosis, is also relevant to health policy, given that the men historically have less access to health services. Moreover, the higher probability of death in the male population can be explained by the fact that they seek health services in more severe cases.¹⁰

Despite the clinical importance of the variable presence of comorbidities for the prognosis, such information is absent in 4.6% of the reported cases, with a higher percentage of omission in cases that resulted in death. The omission of information in cases of death is evident when checking the lethality rate of 13.5% of cases and the risk of death occurring 9.87 times higher in this group, compared to cases with no comorbidities.

The presence of uninformed data was also observed for the skin color variable, with 10.6% of cases not presenting information as to it. This shows the inadequate filling of the skin-color field in health information systems, which undermines the assessment of health conditions considering ethnic aspects.¹¹ Despite the percentage of lack of information on this variable, data without such information was kept to express the reality of health information systems for disease surveillance.

Despite the presence of cases with no information as to skin color, having non-white skin color increased the risk of death from COVID-19 by 13%, compared to white-skinned individuals. The effect of ethnicity/skin color on the risk of death from COVID-19 was also noted in a UK survival analysis of confirmed cases of COVID-19. Even after adjusting for the variables of sex, age, poverty, and region, individuals with non-white skin color had a risk of death up to twice that of white individuals. However, the effect of having comorbidities was not included, which may have interfered with the study's findings.¹²

Another study conducted in the United Kingdom, using data from patients with COVID-19 admitted to hospital, found a higher admission of black individuals and minority ethnic groups compared to white individuals, in relation to the proportion of these groups in the population. When assessing the survival of these patients after 30 days, black individuals and minority ethnic groups had the same or greater probability of survival than white individuals. In addition, there was no association between ethnicity and survival in patients hospitalized for COVID-19, after adjustments for other factors including the presence of comorbidities.¹³

In the present study, the maintenance of the skin color effect for the prediction of risk of death from COVID-19 was observed after adjusting the other variables, including the variable presence of comorbidities. Thus, research on mortality due to COVID-19 should consider biological and social factors, in order to identify ethnic disparities related to the disease.¹⁴

During the pandemic, several public health interventions were needed. Among these measures, travel and lockdown restrictions were adopted in many locations to flatten the pandemic curve. The essential subsidy for decision-making in public health was the data produced, allowing the emergence of the so-called "precision public health".¹⁵

Given this scenario, the importance of health information systems for epidemiological surveillance became more evident in order to provide updated information on mortality and morbidity due to the new disease in an agile and reliable way to support prevention

and control actions for the spread of COVID-19, as well as structuring the health care network to receive new cases.

An important aspect of the quality of health information systems is the adequate completion of each variable in the system. However, the completeness of data is not always observed, with a logic of relevance in filling in information, based on the assumption of the importance attributed to such information for the health sector. Thus, some relevant information is not collected or is said to be “ignored”. In this process, some variables such as sex and age are prioritized, and others such as ethnicity / skin color and education are ignored.¹⁶ This phenomenon is influenced especially by the adopted health concept, which, in many situations, is unrelated to the concept of social determinants of health and more focused on the biomedical model.¹⁷

The present study has the potential to produce survival data by COVID-19 using local data. The study limitations are related to the use of secondary data, which are likely to suffer the effect of information bias, although this is the most common data source for studies with survival analysis.^{6,13} One of the methodological strategies used to reduce bias was the exclusion of cases notified in the last two weeks of the observation period, which is considered the period necessary for cases stability. In addition, the time since notification based on the time-dependent regression model was included to control the time-concurrent bias during the various stages of the epidemic.

The highest risk of deaths from COVID-19 was observed in older adults, especially those over 80, patients with comorbidities, men, and those with non-white skin color. After adjustment for the other variables, there was no effect of living in municipalities in the inner part of the state on the risk of death from COVID-19 in the present study. Currently, effective infection control is the only way to prevent the spread of SARS-CoV-2.¹ However, when knowing the populations with the highest risk of worsening and death from the disease, therapeutic strategies that prevent the disease from worsening in these populations can be adopted. In addition, it contributes to the preparation of the hospital care network, from the moment of the recognition of the epidemiological profile of diagnosed cases, anticipating the demand for the use of hospital beds and deaths from the disease.

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