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ARTICLE

A competing risk survival analysis of the sociodemographic factors of COVID-19 in-hospital mortality in Ecuador

Un análisis de supervivencia de riesgos competitivos de los factores sociodemográficos de la mortalidad intrahospitalaria por COVID-19 en Ecuador

Uma análise concorrente de sobrevida de risco dos fatores sociodemográficos da mortalidade intra-hospitalar por COVID-19 no Equador

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Abstract

This study aimed to analyze the effect of sociodemographic characteristics on COVID-19 in-hospital mortality in Ecuador from March 1 to December 31, 2020. This retrospective longitudinal study was performed with data from publicly accessible registries of the Ecuadorian National Institute of Statistics and Censuses (INEC). Data underwent a competing risk analysis with estimates of the cumulative incidence function (CIF). The effect of covariates on CIFs was estimated using the Fine-Gray model and results were expressed as adjusted subdistribution hazard ratios (SHR). The analysis included 30,991 confirmed COVID-19 patients with a mean age of 56.57±18.53 years; 60.7% (n = 18,816) were men and 39.3% (n = 12,175) were women. Being of advanced age, especially older than or equal to 75 years (SHR = 17.97; 95%CI: 13.08-24.69), being a man (SHR = 1.29; 95%CI: 1.22-1.36), living in rural areas (SHR = 1.18; 95%CI: 1.10-1.26), and receiving care in a public health center (SHR = 1.64; 95%CI: 1.51-1.78) were factors that increased the incidence of death from COVID-19, while living at an elevation higher than 2,500 meters above sea level (SHR = 0.69; 95%CI: 0.66-0.73) decreased this incidence. Since the incidence of death for individuals living in rural areas and who received medical care from the public sector was higher, income and poverty are important factors in the final outcome of this disease.

COVID-19; Hospital Mortality; Survival Analysis

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Introduction

Since its onset in Wuhan, China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is associated with coronavirus disease 2019 (COVID-19), has become one of the biggest health problems worldwide, causing significant morbidity and mortality [1,2].

The clinical characteristics of COVID-19 vary from asymptomatic to symptomatic [3]. Asymptomatic patients generally improve over time and do not require specialized medical care; however, a significant proportion of COVID-19 cases develop pneumonia, severe acute respiratory failure, and even multiple organ failure [3]. In these cases, patients often require hospitalization, admission to intensive care units, and intubation, leading to a substantial increase in in-hospital mortality [3]. The first confirmed case of COVID-19 in Ecuador occurred in the city of Guayaquil at the end of February 2020 [4]. Despite the efforts and the strict government containment measures implemented to control its spread, SARS-CoV-2 invaded and collapsed the weakened Ecuadorian health system [5]. The situation was devastating during the first months of the pandemic, with overcrowded hospitals and high mortality rates, turning the country into an "epicenter" of the pandemic in Latin America [6]. By the end of 2020, Ecuador had 212,512 confirmed cases and 14,034 deaths from COVID-19 [7].

To date, most survival analyses with COVID-19 in-hospital mortality as the event of interest used conventional statistical methods, such as the Kaplan-Meier estimator, in which recovery events are considered right-censored and not competing risks. A competing risk is an event that prevents the occurrence of the event of interest [8,9]. COVID-19 death and recovery are mutually exclusive events, thus, in this case, survival data must undergo a competing risk analysis. In the presence of competing risks, a regression model must be used: (1) for etiological reasons, and (2) to address questions about incidence and prognosis [8,9]. This study did not aim to assess an etiological link, but to evaluate the incidence of the event. The cumulative incidence function (CIF) is better to evaluate the incidence of an event in the setting of competing risks. According to some studies, the cause-specific hazard model is more appropriate for etiological questions while the Fine-Gray model is better for questions about incidence and prognosis [8,9]. The Fine-Gray model must be more useful to estimate the absolute event rate in the setting of competing risks, as it allows the estimation of the effect of covariates on CIF [8,9].

Several survival studies in Latin American countries have been published [3,10,11,12], however, to the best of our knowledge, no study considers recovery a competing risk. Not considering competing risks leads to biased mortality estimates and an overestimation of survival curves. Therefore, the analysis of mortality data is more accurate when using a competing risk approach [8,9].

COVID-19 in-hospital mortality varies greatly both within a country and between countries. This heterogeneity is probably due to demographic differences and socioeconomic inequalities regarding access to adequate medical care, the presence of comorbidities, among other factors [10,13,14,15]. The analysis of the sociodemographic characteristics of COVID-19 deaths would provide valuable information on barriers to accessibility and the response capacity of the health system. Therefore, this study aimed to analyze the effect of sociodemographic characteristics on COVID-19 in-hospital mortality in Ecuador using a competing risk approach.

Methods

Study design

This retrospective longitudinal study was performed with Ecuadorian hospitalized patients with a diagnosis of "U07.1 COVID-19, virus identified", according to the 10th revision of the International Classification of Diseases (ICD-10). Data were obtained from the Statistical Registry of Hospital Beds and Discharges of the Ecuadorian National Institute of Statistics and Censuses (INEC), which is available on a publicly accessible website (https://www.ecuadorencifras.gob.ec/camas-y-egresos-hospitalarios/) [16].

Study location

The study was performed in Ecuador, a country located in South America and bordered by Colombia in the north, Peru in the south/east, and the Pacific Ocean in the west. Ecuador is divided into four geographical regions – Pacific Coast (Costa), Highlands (Sierra), Amazon Basin (Oriente), and the Galápagos Islands (Insular) – and administratively and politically subdivided into 24 provinces, 221 cantons, and parishes, which are classified as urban or rural. In 2020, Ecuador had about 17,510,643 inhabitants [17].

Study population

This study included patients with a confirmed diagnosis of COVID-19 hospitalized in all public and private health centers in Ecuador from March 1 to December 31, 2020, with a length of hospital stay of up to 60 days. The original dataset included 31,117 patients, of which five were admitted prior to the date on which the first case of COVID-19 was officially reported in Ecuador and 123 were hospitalized for more than 60 days. These patients were not included in the analyses.

Variables

Age, sex, area of residence (urban or rural), and health sector (private or public) were independent variables while length of hospital stay and the patient's condition at the time of hospital discharge (alive or dead) were dependent variables. The dataset has complete information on admission and discharge dates, which allowed data collection for the variable "lengh of hospital stay". The variables "region of residence" (Coast, Highlands, Amazon Basin and Galápagos Islands) and "elevation of residence" (high: > 2,500 meters above sea level [masl]; low: ≤ 2,500masl) were created from data on the canton of residence of patients in the INEC dataset. Cantons were classified based on the geographical region where they are located and their elevation was obtained from the Digital Elevation Model of Ecuador, which is available on a publicly accessible website (http://geoportal.agricultura.gob.ec). For survival analysis, patients were divided into four age groups (< 25, 25-49, 50-74, and ≥ 75).

Statistical analysis

Descriptive analyses of the continuous and categorical variables were expressed as mean and standard deviation (SD) and frequency or percentage (%), respectively. Population pyramids were used to represent the age and sex distribution of hospitalized patients with COVID-19 in all geographical regions of Ecuador. The Kolmogorov-Smirnov goodness-of-fit test was used to evaluate the normality of the variable "age," since its distribution was normal. Student's t-test was used to compare individuals who died and who survived. The association between categorical variables was analyzed using the χ^2 test. In-hospital death and recovery were evaluated by a competing risk analysis and the result was tested in relation to the length of hospital stay (the time from patients' hospital admission and their date of recovery or death). In the competing risk analysis, the cumulative incidence function (CIF) was estimated and Gray's test was used to compare CIF curves. The effect of covariates on CIF for in-hospital death and recovery were estimated by a Fine-Gray proportional subdistribution hazard model and the covariates of interest with statistically different CIF curves were included in this model. Results are presented in adjusted subdistribution hazard ratios (SHR) and their 95% confidence intervals (95%CI). All p-values < 0.05 were statistically significant. Data were analyzed using the SPSS statistical program version 25.0 for Windows (https://www.ibm.com/) and EZR version 1.54 for Windows (https://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/windowsEN.html) [18].

Ethical considerations

According to local and international regulations, this study did not require ethical approval. All data from secondary registries are available in the public domain, without any sensitive or confidential information that might violate the rights to the protection of personal data. Although this study did not require approval, the authors were ethically committed to data handling, analysis, and publication.

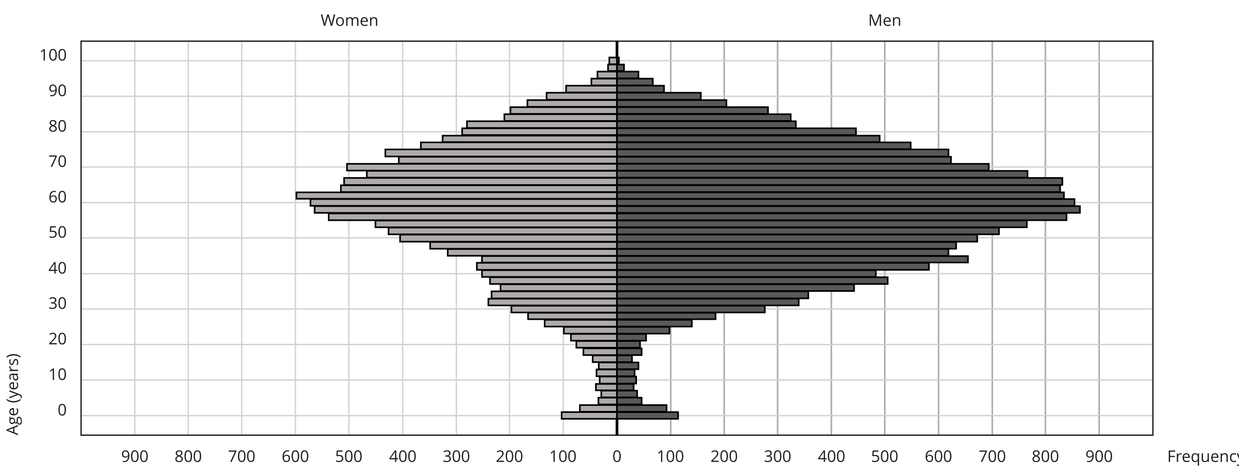
Results

The INEC Statistical Registry of Hospital Beds and Discharges shows that from March 1 to December 31, 2020, 31,112 patients were hospitalized with a diagnosis of "U07.1 COVID-19, virus identified", of which 30,991 were hospitalized for 60 days or less. The mean age of patients was 56.57±18.53 years and 60.7% (n = 18,816) were men. The sex and age distribution pattern was similar in all regions of Ecuador, but most patients were men and aged 40 to 80 years (Figure 1).

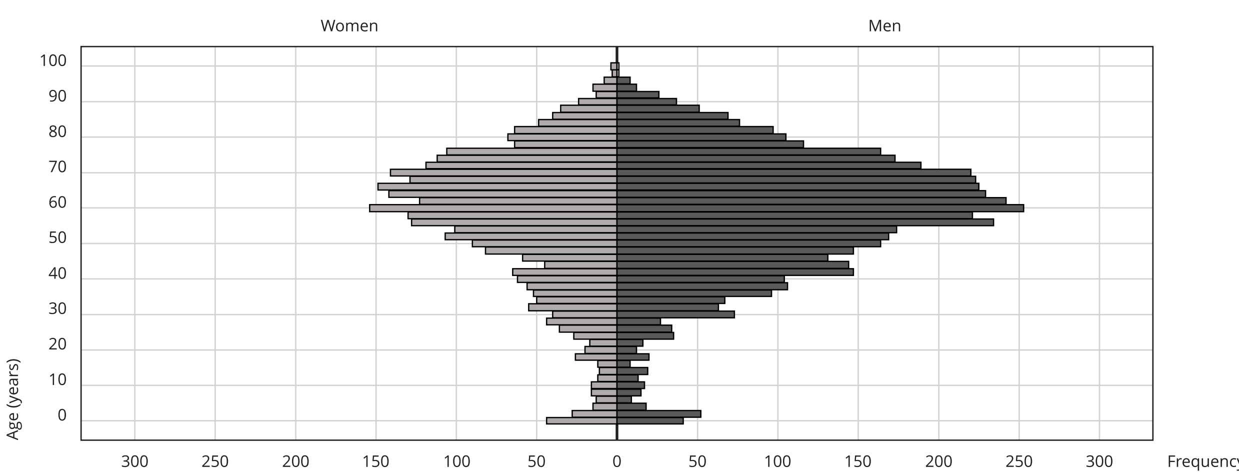
Figure 1

Population pyramids for hospitalized patients with confirmed COVID-19 in Ecuador.

1a) Total study population



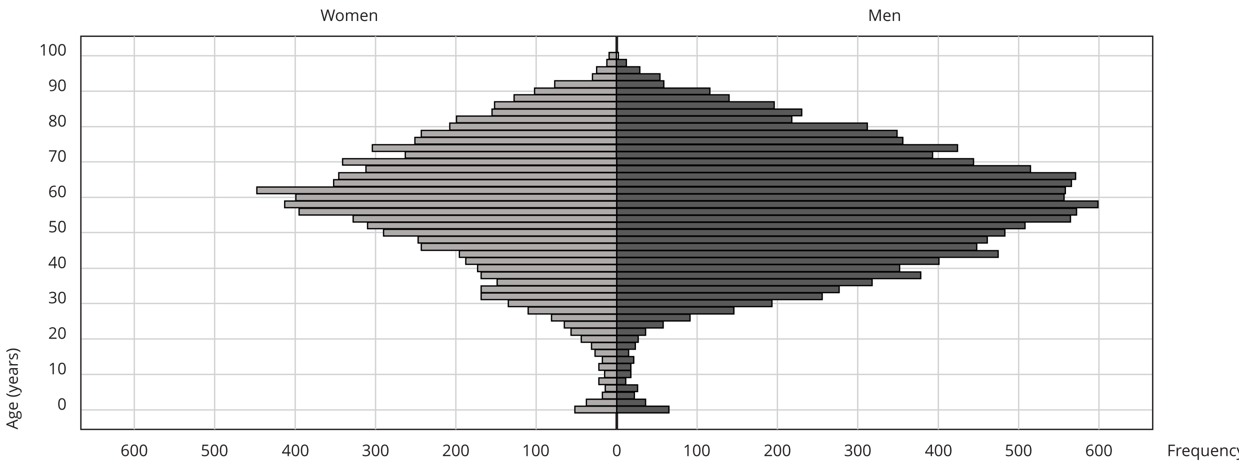
1b) Coast region



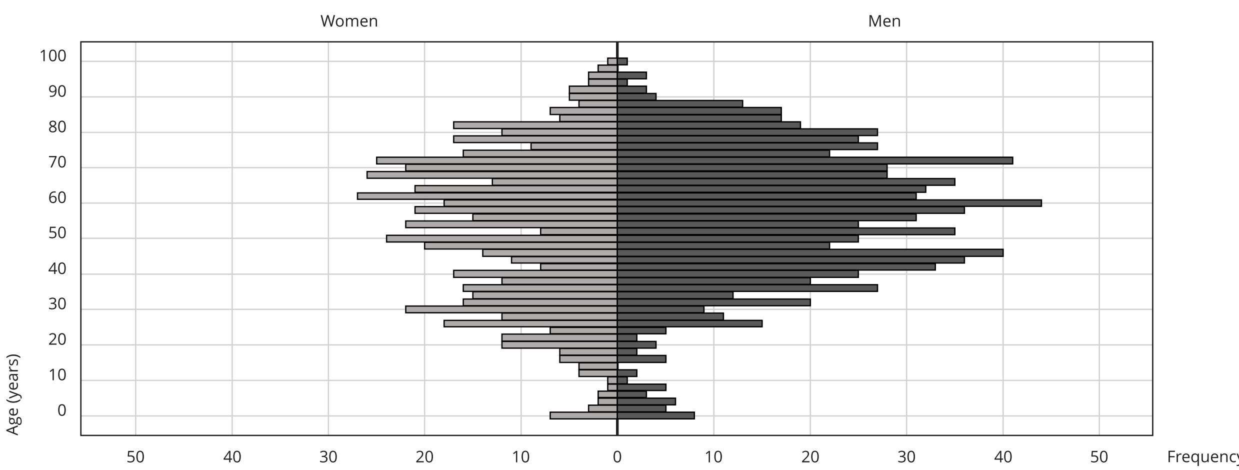
(continues)

Figure 1 (continued)

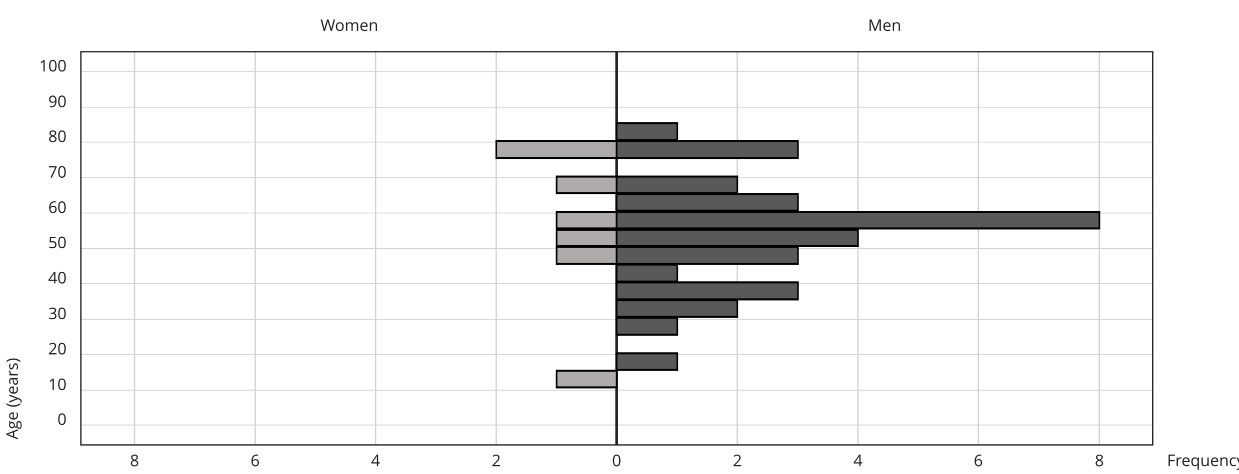
1c) Highlands region



1d) Amazon Basin region



1e) Galápagos Islands region



In total, 18.8% (n = 5,821) of patients with COVID-19 died. Compared with patients who survived, they were significantly older (67.48±14.62 years old) and mainly men (65.76%) ($p < 0.001$). Moreover, 83.5% of them were hospitalized in public health centers ($p < 0.001$). Regarding the area of residence, 85.8% of patients lived in urban areas, however, the proportion of deaths was higher in rural areas ($p < 0.001$). Higlands was the geographical region of Ecuador with most hospitalizations for COVID-19 (69.5%), however, it had the lowest proportion of deaths (16.8%) compared with Coast, which had the highest proportion of deaths (23.1%). A total of 60% of hospitalized patients lived at an elevation higher than 2,500masl, however, the proportion of patients who died was higher in cantons at an elevation lower than or equal to 2,500masl (22.9%) (Table 1).

Table 1

General characteristics of hospitalized patients with confirmed COVID-19.

Characteristics	Total n (%) [n = 30,991]	Recovery n (%) [n = 25,170]	Death n (%) [n = 5,821]	p-value *
Age (years)				< 0.001
Mean±SD	56.57±18.53	54±18.42	67.48±14.62	
0-9	635 (2.0)	628 (98.9)	7 (1.1)	
10-19	406 (1.3)	389 (95.8)	17 (4.2)	
20-29	1,270 (4.1)	1,217 (95.8)	53 (4.2)	
30-39	3,150 (10.2)	2,990 (94.9)	160 (5.1)	
40-49	4,595 (14.8)	4,167 (90.7)	428 (9.3)	
50-59	6,417 (20.7)	5,534 (86.2)	883 (13.8)	
60-69	6,659 (21.5)	5,138 (77.2)	1,521 (22.8)	
70-79	4,792 (15.5)	3,275 (68.3)	1,517 (31.7)	
80-89	2,498 (8.1)	1,516 (60.7)	982 (39.3)	
≥ 90	596 (1.8)	316 (55.5)	253 (44.5)	
Sex				< 0.001
Man	18,816 (60.7)	14,988 (79.7)	3,828 (20.3)	
Woman	12,175 (39.3)	10,182 (83.6)	1,993 (16.4)	
Health sector				< 0.001
Public	25,869 (83.5)	20,686 (80.0)	5,183 (20.0)	
Private	5,122 (16.5)	4,484 (87.5)	638 (12.5)	
Area of residence				< 0.001
Urban	26,599 (85.8)	21,681 (81.5)	4,918 (18.5)	
Rural	4,392 (14.2)	3,489 (79.4)	903 (20.6)	
Region of residence				< 0.001
Coast	7,917 (25.5)	6,078 (76.8)	1,839 (23.2)	
Highlands	21,549 (69.5)	17,920 (83.2)	3,629 (16.8)	
Amazon Basin	1,486 (4.8)	1,142 (76.9)	344 (23.1)	
Galápagos Islands	39 (0.1)	30 (77.8)	9 (22.2)	
Elevation of residence (masl)				< 0.001
≤ 2,500	12,032 (38.8)	9,277 (77.1)	2,755 (22.9)	
> 2,500	18,959 (61.2)	15,893 (83.8)	3,066 (16.2)	

masl: meters above sea level; SD: standard deviation.

* The χ^2 test for categorical variables and Student's t-test for continuous variables were used to determine statistically significant differences.

The survival analysis included 30,991 patients, of which 5,821 died. When evaluating CIF, we found differences both between death and recovery curves of the variables "age" ($p < 0.001$), "sex" ($p < 0.001$), "health sector" ($p < 0.001$), "area of residence" ($p < 0.001$), and "elevation of residence" ($p < 0.001$) (Figure 2). The cumulative incidence of death for the first, second, and third weeks of hospitalization was 8.88% (95%CI: 8.6-9.2), 13.97% (95%CI: 13.6-14.4), and 16.72% (95%CI: 16.3-17.1), respectively. The cumulative incidence of recovery for the first, second, and third weeks of hospitalization was 43.94% (95%CI: 43.4-44.5), 67.78% (95%CI: 67.3-68.3), and 75.26% (95%CI: 74.8-75.7), respectively (Supplementary Material: http://cadernos.ensp.fiocruz.br/static//arquivo/suppl-csp-2947-21_8403.pdf).

In the multivariate regression model, we included all variables with significant differences in CIF curves, except for geographical region of residence, due to the imbalance between the number of patients in Galápagos Islands and other regions of Ecuador. The incidence of in-hospital death was significantly higher for patients aged 75 or older (SHR = 17.97; 95%CI: 13.08-24.69), whose incidence of recovery was significantly reduced (SHR = 0.29, 95%CI: 0.27-0.31) when compared with younger patients. Men had a higher incidence of death (SHR = 1.29; 95%CI: 1.22-1.36) when compared with women, whose incidence of recovery was significantly reduced (SHR = 0.82; 95%CI: 0.80-0.84). The incidence of death increased and the incidence of recovery decreased among patients hospitalized in public health centers and living in rural areas. On the other hand, living at an elevation higher than 2,500masl resulted in a lower incidence of death and an increase in the incidence of in-hospital recovery (Table 2).

Discussion

Our findings showed that older patients, men, patients living in rural areas, and patients hospitalized in public health centers were more likely to die from COVID-19. These factors were also associated with a lower probability of recovery. However, patients living at elevations higher than 2,500masl had a lower probability of death and a higher probability of recovery.

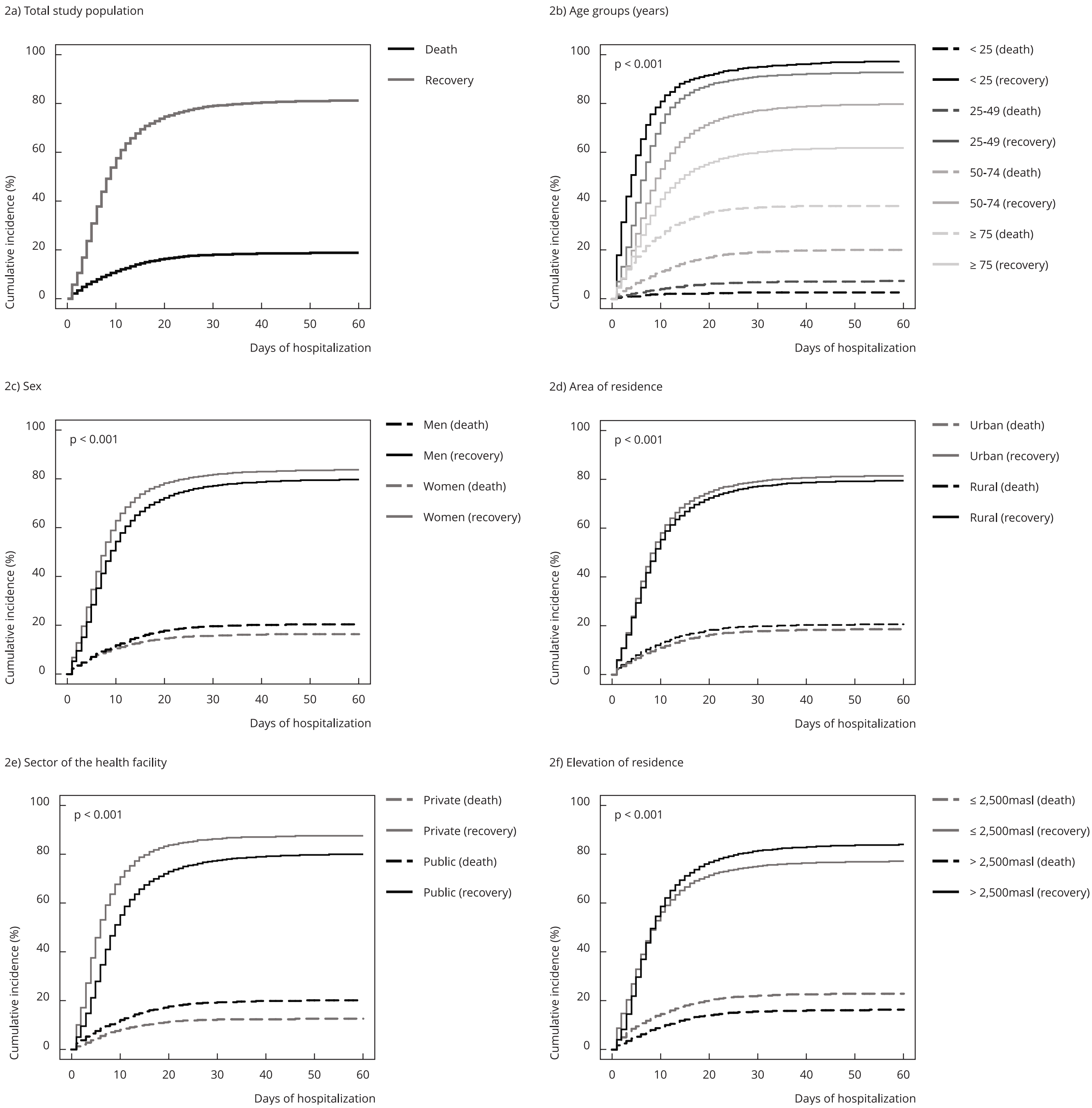
Several studies show that the risk of dying from COVID-19 increases with age and is higher among men [19,20,21,22]. This is similar to the results of other survival analyses [10,13,23] and our study. Aging leads to several changes in the immune system, which can be broadly classified as immunosenescence and is associated with the age of the immune system and a reduced ability to fight new infections. Moreover, immunosenescence can contribute to the development of a chronic state of inflammation called inflammatory aging [24].

The role of angiotensin-converting enzyme 2 (ACE2) has been discussed. Besides allowing the entry of SARS-CoV-2, this enzyme also plays an important anti-inflammatory role [24,25]. When the levels of ACE2 or its activity are low, the risk of the SARS-CoV-2 infection having a worse outcome is higher [25] and aging promotes a downregulation in the expression of ACE2 [26,27,28,29]. Moreover, lethality exponentially decreases in the presence of higher levels of the ACE2 receptor [30]. The association between an increased viral receptor and a lower severity of the disease can be paradoxical, however, evidence shows that in certain circumstances, higher levels of a viral receptor slow down the spread of the virus in the infected organism [31].

Men and women respond differently to COVID-19 due to multiple factors, such as biological differences, the immune response, or underlying comorbidities for each sex [32,33]. The levels of ACE2 are usually higher in women than in men, which can be partially due to the effect of estrogens on the activity of ACE2 and could explain the higher frequency of severe cases among men [25]. Current evidence suggests that high estrogen levels in women lead to a stronger response against SARS-CoV-2 [32]. Although social factors may contribute to differences between men and women regarding the severity of the disease, evidence points to biological differences as determinants of risk [33].

Figure 2

Cumulative incidence function curves for death and recovery of hospitalized patients with confirmed COVID-19.



masl: meters above sea level.

Table 2

Adjusted subdistribution hazard ratios (SHR) of death and recovery of hospitalized patients with confirmed COVID-19.

Characteristics	Death		Recovery	
	SHR * (95%CI)	p-value	SHR * (95%CI)	p-value
Age (years)				
< 25	1.00 (reference)		1.00 (reference)	
25-49	2.80 (2.03-3.88)	< 0.001	0.72 (0.68-0.76)	< 0.001
50-74	8.31 (6.06-11.40)	< 0.001	0.44 (0.42-0.47)	< 0.001
≥ 75	17.97 (13.08-24.69)	< 0.001	0.29 (0.27-0.31)	< 0.001
Sex				
Woman	1.00 (reference)		1.00 (reference)	
Man	1.29 (1.22-1.36)	< 0.001	0.82 (0.80-0.84)	< 0.001
Area of residence				
Urban	1.00 (reference)		1.00 (reference)	
Rural	1.18 (1.10-1.26)	< 0.001	0.94 (0.90-0.97)	< 0.001
Health sector				
Private	1.00 (reference)		1.00 (reference)	
Public	1.64 (1.51-1.78)	< 0.001	0.69 (0.67-0.72)	< 0.001
Elevation of residence (masl)				
≤ 2,500	1.00 (reference)		1.00 (reference)	
> 2,500	0.69 (0.66-0.73)	< 0.001	1.10 (1.07-1.13)	< 0.001

95%CI: 95% confidence intervals; masl: meters above sea level.

* Adjusted for age groups, sex, area of residence, health sector, and elevation of residence.

The severity of the disease was lower and less deaths occurred among patients with COVID-19 living at high elevations [34,35,36,37,38]. In our study, the incidence of death was lower among patients living at elevations higher than 2,500masl. Several factors, such as ethnic and genetic differences, environmental factors related to viral transmission, differences in social structure, transportation, and containment measures, among others, could influence these findings [39]. Moreover, the percentage of beds available in health centers was lower in Coast than in Highlands [40]. The pathophysiological reason for this relationship in unknown, however, the chronic hypoxia experienced at high elevations is particularly relevant due to the expression of ACE2 mediated by hypoxia. Experimental studies observed a positive regulation of ACE2 in the presence of hypoxia [41,42,43] and this increase in ACE2 could represent better results in the case of a SARS-CoV-2 infection. However, to date, no evidence in either humans or animals characterizes the expression of ACE2 in the epithelium of the respiratory tract in chronic hypoxia conditions or show the genetic adaptations of the expression of ACE2 in patients living at high elevations [39].

The largest cities worldwide have been reporting a higher rate of COVID-19 cases possibly due to their connectivity to a greater number of cities [44]. In 2020, the contagion was greater in the Ecuadorian municipalities with the highest number of inhabitants [5]. Similarly, in this study, the number of infected individuals was higher in urban areas. However, patients living in rural areas were more likely to die. Evidence shows health differences between urban and rural areas and patients living in rural areas have worse health outcomes and a higher overall mortality [45,46]. Moreover, rural minority populations usually experience poverty and have a low schooling level and a higher prevalence of comorbidities, which, along with the lack of resources, increases the risk of mortality [45,46]. In December 2020, the incidence of poverty in Ecuador was 25.1% in urban areas and 47.9% in rural areas while the incidence of extreme poverty was 9% in urban areas and 27.5 % in rural areas [5,47].

The higher risk of death for patients hospitalized in the public sector is consistent with the findings of previous studies in the Latin America region [10,14,23], which attributed this higher risk to the greater number of COVID-19 cases admitted to public health centers, leading to a high probability of overcrowding [10], and unequal access to health services for individuals with lower incomes [14,15]. In Ecuador, the public health system collapsed [5] and the deficit in public health was evident. The public health budget decreased considerably from 2017 to 2019, which caused the reduction of health personnel and a decrease in medical supplies, leaving the country defenseless in the face of the pandemic [48]. Moreover, the corruption in 2020 diverted the resources aimed at medical supplies and devices, medicines, and infrastructure, which severely affected the performance and credibility of the public health system [5].

The large multicenter population and the survival analysis performed using a competing risk approach, which provides more accurate mortality estimates compared with using a conventional survival analysis, were strengths of our study. However, the use of a secondary dataset, which limits the analysis of the already registered data, was its main limitation. Therefore, we could not obtain specific information regarding the exact time of the onset of symptoms, the severity of the disease, the evolution of patients, the need for referral to the intensive care unit, and the presence and type of comorbidities. The lack of these key characteristics may affect our results, thus, more research on this topic is needed. Not knowing the admission criteria and the specific cause of death was another limitation of our study, as the dataset only included the condition of discharge (alive or dead). However, using the diagnosis of "U07.1 COVID-19, virus identified" as the cause of admission for all patients included was a strength.

This study considered the first stages of the COVID-19 pandemic, thus, the results could be affected by different pandemic phases, including periods of overcrowded hospitals. However, since overcrowding occured mainly in public health centers, our analyses included this health sector as a variable for adjustment in the multivariate analyses. This study did not aim to present survival probability from the onset of symptoms, thus, it was estimated from the date of hospital admission to the date of recovery or death. Our results show probabilities of hospital stay survival. However, patients attended to health centers when presenting severe symptoms and were sometimes admitted after several days of waiting, which could lead to records of one day of hospitalization and affect the estimation of survival probabilities. Moreover, considering only confirmed deaths from COVID-19 that occurred after hospital admission could have led to an underestimation of the true mortality effect of the pandemic. Therefore, deaths related to COVID-19 outside the hospital could have different properties compared with this study.

The interaction between the pandemic and its social environment may have led to an unequal burden, with a worse result for more disadvantaged individuals in society. The higher incidence of death among patients living in rural areas and who received medical care in the public sector suggests that income and poverty are important factors in the final outcome of this disease. These findings highlight the importance of an equitable distribution of public health in developing countries such as Ecuador.

Contributors

G. J. Lapo-Talledo contributed with the study conception, methodology, data curation and analysis, writing and review of the article, and approved the final version to be published. J. A. Talledo-Delgado contributed with the study conception, data curation, writing and review of the article, and approved the final version to be published. L. S. Fernández-Aballí contributed with the study conception, methodology, data analysis, writing and review of the article, and approved the final version to be published.

Additional information

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References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382:727-33.
2. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579:270-3.
3. Sousa GJB, Garces TS, Cestari VRF, Florêncio RS, Moreira TMM, Pereira MLD. Mortality and survival of COVID-19. Epidemiol Infect 2020; 148:e123.
4. Ortiz-Prado E, Simbaña-Rivera K, Barreno LG, Diaz AM, Barreto A, Moyano C, et al. Epidemiological, socio-demographic and clinical features of the early phase of the COVID-19 epidemic in Ecuador. PLoS Negl Trop Dis 2021; 15:e0008958.
5. Gobierno de Ecuador. Evaluación socieconómica. PDNA Covid-19, Ecuador. Marzo-diciembre, 2020. https://www.planificacion.gob.ec/wp-content/uploads/downloads/2021/06/INFORME_PDNA_COVID-19_ECUADOR_WEB.pdf (accessed 20/Sep/2021).
6. Zibell M. Coronavirus in Ecuador: the drama of Guayaquil, which has more deaths from covid-19 than entire countries and fights against the clock to give them a dignified burial. BBC News 2020; 1 Apr. https://www.bbc.com/mundo/noticias-america-latina-52116100.
7. Comité de Operaciones de Emergencia Nacional. Informe de situación COVID-19 Ecuador. https://www.gestionderiesgos.gob.ec/wp-content/uploads/2020/12/Informe-de-Situacion-No067-Casos-Coronavirus-Ecuador-31122020.pdf (accessed on 20/Sep/2021).
8. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016; 133:601-9.
9. Schuster NA, Hoogendijk EO, Kok AAL, Twisk JWR, Heymans MW. Ignoring competing events in the analysis of survival data may lead to biased results: a nonmathematical illustration of competing risk analysis. J Clin Epidemiol 2020; 122:42-8.
10. Salinas-Escudero G, Carrillo-Vega MF, Granados-García V, Martínez-Valverde S, Toledano-Toledano F, Garduño-Espinosa J. A survival analysis of COVID-19 in the Mexican population. BMC Public Health 2020; 20:1616.
11. Galvão MHR, Roncalli AG. Factors associated with increased risk of death from covid-19: a survival analysis based on confirmed cases. Rev Bras Epidemiol 2021; 23:e200106.
12. Malagón-Rojas J, Ibáñez E, Parra EL, Toloza-Perez YG, Álvarez S, Mercado M. Analysis of COVID-19 mortality and survival in Colombia: a prospective cohort study. Infectio 2021; 25:176-81.
13. Drefahl S, Wallace M, Mussino E, Aradhya S, Kolk M, Brandén M, et al. A population-based cohort study of socio-demographic risk factors for COVID-19 deaths in Sweden. Nat Commun 2020; 11:5097.

14. Li SL, Pereira RHM, Prete Jr CA, Zarebski AE, Emanuel L, Alves PJH, et al. Higher risk of death from COVID-19 in low-income and non-white populations of São Paulo, Brazil. BMJ Glob Health 2021; 6:e004959.
15. Karmakar M, Lantz PM, Tipirneni R. Association of social and demographic factors with COVID-19 incidence and death rates in the US. JAMA Netw Open 2021; 4:e2036462.
16. Instituto Nacional de Estadística y Censos. Registro estadístico de camas y egresos hospitalarios. https://www.ecuadorencifras.gob.ec/camas-y-egresos-hospitalarios/ (accessed on 20/Sep/2021).
17. Instituto Nacional de Estadística y Censos. Proyecciones poblacionales. https://www.ecuadorencifras.gob.ec/proyecciones-poblacionales/ (accessed on 20/Sep/2021).
18. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013; 48:452-8.
19. Nasiri MJ, Haddadi S, Tahvildari A, Farsi Y, Arbabi M, Hasanzadeh S, et al. COVID-19 clinical characteristics, and sex-specific risk of mortality: systematic review and meta-analysis. Front Med 2020; 7:459.
20. Ahrenfeldt LJ, Otavova M, Christensen K, Lindahl-Jacobsen R. Sex and age differences in COVID-19 mortality in Europe. Wien Klin Wochenschr 2021; 133:393-8.
21. Gundogan K, Akbudak IH, Hanci P, Halacli B, Temel S, Gullu Z, et al. Clinical outcomes and independent risk factors for 90-day mortality in critically ill patients with respiratory failure infected with SARS-CoV-2: a multicenter study in Turkish intensive care units. Balkan Med J 2021; 38:296-303.
22. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020; 323:1775-6.
23. Márquez-González H, Méndez-Galván JF, Reyes-López A, Klünder-Klünder M, Jiménez-Juárez R, Garduño-Espinosa J, et al. Coronavirus disease-2019 survival in Mexico: a cohort study on the interaction of the associated factors. Front Public Health 2021; 9:660114.
24. Bajaj V, Gadi N, Spihlman AP, Wu SC, Choi CH, Moulton VR. Aging, immunity, and COVID-19: how age influences the host immune response to coronavirus infections? Front Physiol 2021; 11:571416.
25. Pagliaro P, Penna C. ACE/ACE2 ratio: a key also in 2019 coronavirus disease (Covid-19)? Front Med (Lausanne) 2020; 7:335.
26. Booeshaghi AS, Pachter L. Decrease in ACE2 mRNA expression in aged mouse lung. bioRxiv 2020; 5 Apr. https://www.biorxiv.org/content/10.1101/2020.04.02.021451v1.
27. Chen J, Jiang Q, Xia X, Liu K, Yu Z, Tao W, et al. Individual variation of the SARS-CoV-2 receptor ACE2 gene expression and regulation. Aging Cell 2020; 19:e13168.
28. Zhang Z, Guo L, Huang L, Zhang C, Luo R, Zeng L, et al. Distinct disease severity between children and older adults with COVID-19: impacts of ACE2 expression, distribution, and lung progenitor cells. Clin Infect Dis 2021; 73:e4154-65.
29. Ortiz ME, Thurman A, Pezzulo AA, Leidinger MR, Klesney-Tait JA, Karp PH, et al. Heterogeneous expression of the SARS-coronavirus-2 receptor ACE2 in the human respiratory tract. EBioMedicine 2020; 60:102976.
30. Bastolla U. Mathematical model of SARS-Cov-2 propagation versus ACE2 fits COVID-19 lethality across age and sex and predicts that of SARS. Front Mol Biosci 2021; 8:706122.
31. Ortega-Cejas V, Fort J, Méndez V, Campos D. Approximate solution to the speed of spreading viruses. Phys Rev E Stat Nonlin Soft Matter Phys 2004; 69(3 Pt 1):031909.
32. Wehbe Z, Hammoud SH, Yassine HM, Fardoun M, El-Yazbi AF, Eid AH. Molecular and biological mechanisms underlying gender differences in COVID-19 severity and mortality. Front Immunol 2021; 12:659339.
33. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol 2020; 20:442-7.
34. Fernandes JSC, Silva RS, Silva AC, Villela DC, Mendonça VA, Lacerda ACR. Altitude conditions seem to determine the evolution of COVID-19 in Brazil. Sci Rep 2021; 11:4402.
35. Arias-Reyes C, Carvajal-Rodriguez F, Poma-Machicao L, Aliaga-Raduán F, Marques DA, Zubieta-DeUrioste N, et al. Decreased incidence, virus transmission capacity, and severity of COVID-19 at altitude on the American continent. PLoS One 2021; 16:e0237294.
36. Stephens KE, Chernyavskiy P, Bruns DR. Impact of altitude on COVID-19 infection and death in the United States: a modeling and observational study. PLoS One 2021; 16:e0245055.
37. Chen H, Qin L, Wu S, Xu W, Gao R, Zhang X. Clinical characteristics and laboratory features of COVID-19 in high altitude areas: a retrospective cohort study. PLoS One 2021; 16:e0249964.
38. Jaramillo PRM, Simbaña-Rivera K, Silva JVV, Gómez-Barreno L, Campoverde ABV, Cevallos JFN, et al. High-altitude is associated with better short-term survival in critically ill COVID-19 patients admitted to the ICU. medRxiv 2021; 25 Jan. https://www.medrxiv.org/content/10.1101/2021.01.22.21249811v1.
39. Pun M, Turner R, Strapazzon G, Brugger H, Swenson ER. Lower incidence of COVID-19 at high altitude: facts and confounders. High Alt Med Biol 2020; 21:217-22.
40. Chauca R. La covid-19 en Ecuador: fragilidad política y precariedad de la salud pública. Hist Ciênc Saúde-Manguinhos 2021; 28:587-91.

41. Clarke NE, Belyaev ND, Lambert DW, Turner AJ. Epigenetic regulation of angiotensin-converting enzyme 2 (ACE2) by SIRT1 under conditions of cell energy stress. Clin Sci (Lond) 2014; 126:507-16.
42. Joshi S, Wollenzien H, Leclerc E, Jarajapu YP. Hypoxic regulation of angiotensin-converting enzyme 2 and Mas receptor in human CD34+ cells. J Cell Physiol 2019; 234:20420-31.
43. Hampl V, Herget J, Bíbová J, Baňasová A, Husková Z, Vaňourková Z, et al. Intrapulmonary activation of the angiotensin-converting enzyme type 2/angiotensin 1-7/G-protein-coupled Mas receptor axis attenuates pulmonary hypertension in Ren-2 transgenic rats exposed to chronic hypoxia. Physiol Res 2015; 64:25-38.
44. United Nations Human Settlements Programme. Cities and pandemics: towards a more just, green and healthy future. https://unhabitat.org/sites/default/files/2021/03/cities_and_pandemics-towards_a_more_just_green_and_healthy_future_un-habitat_2021.pdf (accessed on 20/Sep/2021).
45. Anderson TJ, Saman DM, Lipsky MS, Lutfiyya MN. A cross-sectional study on health differences between rural and non-rural U.S. counties using the county health rankings. BMC Health Serv Res 2015; 15:441.
46. Probst JC, Zahnd WE, Hung P, Eberth JM, Crouch EL, Merrell MA. Rural-urban mortality disparities: variations across causes of death and race/ethnicity, 2013-2017. Am J Public Health 2020; 110:1325-7.
47. Instituto Nacional de Estadística y Censos. Boletín técnico nº 02-2021-ENEMDU. Encuesta Nacional de Empleo, Desempleo y Subempleo (ENEMDU), diciembre 2020. Pobreza y desigualdad. https://www.ecuadorencifras.gob.ec/documentos/web-inec/POBREZA/2020/Diciembre-2020/Boletin tecnico pobreza diciembre 2020.pdf (accessed 20/Sep/2020).
48. Iturralde PJ. Ecuador, Covid-19 y deuda. https://www.eurodad.org/ecuador_covid_19_y_deuda (accessed on 14/Sep/2021).

Resumen

Este estudio tuvo como objetivo analizar el efecto de las características sociodemográficas en la mortalidad intrahospitalaria de los pacientes con COVID-19 confirmado en Ecuador entre el 1 de marzo y el 31 de diciembre de 2020. Se trató de un estudio longitudinal retrospectivo realizado con datos extraídos de registros de acceso público reportados por el Instituto Nacional de Estadística y Censos (INEC) de Ecuador. Los datos se analizaron empleando un enfoque de riesgo competitivo, utilizando estimaciones de la función de incidencia acumulada (FIA). El efecto de las covariables sobre las FIA se estimó mediante el modelo de Fine-Gray, y los resultados se expresaron como cocientes de riesgos de subdistribución (CRS) ajustados. El análisis incluyó 30.991 casos confirmados de COVID-19 con una edad media de 56,57±18,53 años; el 60,7% (n = 18.816) eran hombres y el 39,3% (n = 12.175) mujeres. Los factores que aumentaron la incidencia de muerte por COVID-19 fueron una edad avanzada, con mayor riesgo para los mayores o iguales a 75 años (CRS = 17,97; IC95%: 13,08-24,69); ser hombre (CRS = 1,29; IC95%: 1,22-1,36); residir en zonas rurales (CRS = 1,18; IC95%: 1,10-1,26); y recibir atención en un centro sanitario público (CRS = 1,64; IC95%: 1,51-1,78); mientras que un factor que disminuyó la incidencia de muerte fue residir en altitudes superiores a los 2.500 metros sobre el nivel del mar (CRS = 0,69; IC95%: 0,66-0,73). La mayor incidencia de muerte entre los que residían en zonas rurales y los que recibían atención médica del sector público sugiere que los ingresos y la pobreza son factores importantes en el desenlace final de esta enfermedad.

COVID-19; Mortalidad Hospitalaria; Análisis de Supervivencia

Resumo

O objetivo deste estudo foi analisar o efeito de características sociodemográficas sobre a mortalidade intra-hospitalar de pacientes com COVID-19 confirmada no Equador, entre 1º de março e 31 de dezembro de 2020. Este é um estudo longitudinal e retrospectivo desenvolvido com dados extraídos de registros de acesso público declarados pelo Instituto Nacional de Estatística e Censos do Equador (INEC). Os dados foram analisados usando uma abordagem de risco concorrente com estimativas da função de incidência cumulativa (FIC). O efeito das covariáveis sobre as FICs foi estimado pelo modelo de Fine-Gray e os resultados expressos em índices de risco de subdistribuição (IRS) ajustados. A análise incluiu 30.991 casos confirmados da COVID-19 em pacientes com idade média de 56,57±18,53 anos; sendo 60,7% (n = 18.816) do sexo masculino e 39,3% (n = 12.175) do sexo feminino. Os fatores que aumentaram a incidência de óbitos por COVID-19 foram idade avançada, com maior risco para aqueles com 75 anos ou mais (IRS = 17,97; IC95%: 13,08-24,69); ser do sexo masculino (IRS = 1,29; IC95%: 1,22-1,36); residir em áreas rurais (IRS = 1,18; IC95%: 1,10-1,26); e receber atendimento em unidade pública de saúde (IRS = 1,64; IC95%: 1,51-1,78); ao passo que um fator que diminuiu a incidência de óbitos foi residir em altitudes superiores a 2.500 metros acima do nível do mar (IRS = 0,69; IC95%: 0,66-0,73). A maior incidência de óbitos naqueles que residiam em áreas rurais e que receberam atendimento médico do setor público sugere que a renda e a pobreza são fatores importantes no desfecho dessa doença.

COVID-19; Mortalidade Hospitalar; Análise de Sobrevida

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