Mortality Incidence for SARS-CoV-2 Non-Survivor Infected in Colombia: A Potential Vaccination Priority Guide Based on Comorbidities

Milton Soto-Ferrari
Department of Marketing and Operations
Indiana State University
Terre Haute IN 47807, USA
milton.soto-ferrari@indstate.edu

Odette Chams-Anturi
Department of Economic Science
Universidad de la Costa
Barranquilla, Colombia
ochams@cuc.edu.co

Juan P. Escorcia-Caballero
Department of Entrepreneurship and Management
Universidad del Norte
Barranquilla, Colombia
juane@uninorte.edu.co

Daniel Romero-Rodriguez
Department of Industrial Engineering
Universidad del Norte
Barranquilla, Colombia
hromero@uninorte.edu.co

Julio Daza-Escorcia
Department of Industrial Engineering
Fundación Universidad de América
Bogotá, Colombia
julio.daza@profesores.uamerica.edu.co

Blas Ferrari-Padilla
Department of Clinical Medicine
Universidad Cooperativa de Colombia
Santa Marta, Colombia
blas.ferrari@campusucc.edu.co

Abstract

The SARS-CoV-2 vaccination plan development in Colombia, set to begin in February 2021, included a comprehensive assessment of the spread to set population priorities in rank-ordered phases. In Phase 3 of the plan, populations between 16 and 59 years with a set of specific comorbidities will be vaccinated. Our study aims to evaluate the comorbidities incidence in the survival probability to assess the population at most risk if infected and assist in the assignation on this phase. In this study, multivariate Cox regression and Kaplan-Meier curves were performed to determine risk predictors of mortality for 610 reports of up to 15-day decay non-survivor SARS-CoV-2 infected in Colombia. After implementation, higher hazard ratios were associated with diabetes. Kaplan-Meier curves indicate that patients with diabetes that have an older age and hypertension are at a higher risk of earlier death.

Keywords
SARS-CoV-2, Cox regression, Kaplan-Meier, Patient comorbidities

1. Introduction

The novel coronavirus SARS-CoV-2 (also know as COVID-19) is a type of acute respiratory infectious disease of person-to-person transmission (Centers for Disease, Control, and Prevention, 2020). The virus has caused thousands of deaths worldwide—patients with SARS-CoV-2 present fever, fatigue, and dry cough as initial symptoms primarily. Although most patients are expected to have a favorable prognosis, older patients and those with underlying comorbidities may have a more extended recovery period and worse outcomes (Zhou et al., 2020). Reported clinical studies of SARS-CoV-2 had shown that comorbidities significantly impact mortality rates (Li et al., 2020; Wang et al., 2020; Zhou et al., 2020). Underlying comorbidities directly affects recovery even when healthcare is provided on time (Ji et al., 2020). Diabetes, hypertension, respiratory illnesses, cancer, and coronary or cardiovascular diseases are the most common underlying comorbidities among SARS-CoV-2 infected with a higher risk of an adverse prognosis (Li et al., 2020; Zhou et al., 2020). In addition to age and comorbidities in-development countries, conditions related to life quality (e.g., malnutrition, smoking) might also play a significant role in SARS-CoV-2 mortality.

Nations are currently developing vaccination plans worldwide to reduce the spread of the SARS-CoV-2 outbreak. In Colombia, the vaccination plan will begin in February 2021 (Ministerio de Salud, 2021). The program will divide vaccination priorities into five rank-ordered phases; in phase 1, all populations older or equal to 80 years old, medical personnel, and staff in the first line of the outbreak's response will receive the vaccination; this includes professionals performing the immunization. Phase 2 consists of the population between 60 and 79 years old and all other medical personals not in phase 1. Phase 3 includes the population between 16 and 59 years old with the comorbidities of hypertension, diabetes, renal diseases, human immunodeficiency viruses (HIV), cancer, tuberculosis, chronic obstructive pulmonary disease (COPD), asthma, obesity, or patients in the organ transplantation list. This phase also includes all personal related to serving older adults or children and security forces in formation. Phase 4 and Phase 5 have all security forces not included in other phases and the population's remainder but establishing priorities based on age.

While in Colombia, the vaccination plan development included a comprehensive assessment of the SARS-CoV-2 spread (Ministerio de Salud, 2021). Our focus is to evaluate the comorbidities incidence in the probability of survival for SARS-CoV-2 infected in Colombia; since Phase 3 of the plan contemplates a considerable number of comorbidities, we will assess their incidence for non-survivor patients. We realize that information is continuously changing given that the outbreak remains active and that SARS-CoV-2 variants such as the Brazilian are present in the country (Ministerio de Salud, 2021); however, our objective is to propose an approach to evaluate comorbidities incidence on patient survival within the context of the vaccination plan.

This study evaluated medical reports of non-survivor confirmed SARS-CoV-2 infected in Colombia from the year 2020. Local hospitals reported the data through the national institute of health in Colombia, which releases periodical reports of cases and deaths in the country (Instituto Nacional de Salud, 2020). Information includes demographic data, medical history, and underlying comorbidities. The focus is non-survivor patients with up to 15-day decay before death. The date of disease onset is the day when symptoms are first noticed. The dataset consists of 610 patients and includes the underlying comorbidities of diabetes, hypertension, cancer, renal disease, cardiovascular disease, chronic obstructive pulmonary disease (COPD), obesity, and the reported life quality conditions of malnutrition and smoking. We implemented a Multivariate Cox proportional hazards regression model to determine higher hazard ratios for patients with significance set at $P< 0.05$, and we further extended the analysis using Kaplan-Meier curves.

2. Methodological framework

This section will introduce the methods used in this article's data analysis, including survival curves and multivariate cox proportional hazards regression.

2.1 Survival curves

The survival curves reference an event that defines a course's conclusion, which can be favorable or unfavorable. When analyzing data, there will be cases or observations that have already reached the event of interest and others that have not, which are denoted as incomplete observations. In most statistical models, not having reached the event of interest is called "survival" (Fox and Weisberg, 2011). The survival rate (percentage of cases that have not reached the event of interest) can be estimated at each period of the studied process. Its graphic representation is the survival curve, which shows a time unit in the horizontal axis in contrast with the survival rate. Additionally, the Kaplan-Meier method is traditionally used to estimate the survival curve (Jager et al., 2008). It involves the computation of probabilities of occurrence of the events at each period. Then, these probabilities are multiplied to obtain an event estimation. The survival probability at any particular period is given by:

$$\hat{S}(t) = \prod_{t_i<t} \frac{n_i - d_i}{n_i}$$

Where:

- d_i, denotes the number of subjects that have reached the event at t_i
- n_i, denotes the number of subjects at "risk" before t_i.

Accordingly, to the previous formula, the survival probability computation is based on the number of subjects surviving divided by the number of subjects at risk.

2.2 Multivariate proportional hazards cox regression

The proportional hazard cox regression is frequently used to test whether several factors are related to an event's time. It consists of analyzing the survival probability at each time, taking into account the effect of different explanatory factors(Katz and Hauck, 1993). In a cox regression models, the hazard (h) for a subject is given by the following formulation:

$$h = h(t, X) = h_0(t)e^{\Sigma\beta ixi}$$

Where *h(t)* represents the underlying hazard at time *t*, *xi* is the particular subject's values for the covariates, and *Bi* is the regression coefficients. Therefore, the risk function, *h = h(t)*, assumes that the risk rate depends on time but also depends on other explanatory variables *xi*, which can be included in the model.

3. Results

We proceed to develop survival curves and multivariate cox proportional hazards regression with assessed information of un-identified non-survivor patients with up to 15-day decay before death in Colombia. The information included the baseline characteristics of age, sex, city, starting date of symptoms, date of the positive test, date of death, and underlying comorbidities. We evaluated a total of 610 patients with obesity as the most common comorbidity, as presented in Table 1.

Multivariate Cox proportional hazards regression was applied using the underlying comorbidities, age, and sex as predictors. The risk factor for diabetes indicates that non-diabetes patients reduce hazards by an estimated factor of 1.22 (95% CI [1.01-1.50]). No other comorbidities nor quality life conditions were found significant in the study (see Table 1). The survival probability curves of diabetes as presented in Figure 1A show that the probability of dying increases significantly after day ten for patients with diabetes. Patients with diabetes display a lower survival probability along the curve since day one after the starting day of symptoms.

Our results support the relationship of diabetes with death in SARS-CoV-2 cases by providing new evidence about the influence of diabetes on 15-day decay non-survivor patients. As previous research has supported age, hypertension, and diabetes as primary drivers of SARS-CoV-2 prognosis (Leung, 2020; Lippi et al., 2020; Shi et al., 2020).

Table 1. Baseline Characteristics of Non-survivor Patients with Cox Model Results

	No. (%) Total (n = 610)	**Beta**	**No. (95% CI) Hazard Ratio**	***P* value[b]**
Age (median ,(IQR), CV)	70 (20) 0.2	-0.0006	1.00 (0.99-1.01)	0.841
Sex		-0.0263	0.97 (0.82-1.15)	0.760
Female	227 (37.2)			
Male	383 (62.8)			
Infected				
Decay days (median ,(IQR), CV)	12 (3.8) 0.3			
Comorbidities as reported[a]				
Cancer	42 (6.9)	-0.2337	0.79 (0.57-1.10)	0.164
Malnutrition	16 (2.6)	-0.0027	1.00 (0.60-1.66)	0.992
Diabetes	170 (27.9)	0.1950	1.22 (1.01-1.50)	0.037
Cardiovascular	76 (12.5)	-0.1123	0.89 (0.70-1.14)	0.371
COPD	107 (17.5)	0.1530	1.17 (0.93-1.46)	0.186
Smoking	30 (4.9)	-0.1852	0.83 (0.56-1.22)	0.347
Hypertension	97 (15.9)	-0.1644	0.85 (0.67-1.08)	0.185
Obesity	314 (51.5)	-0.0136	0.99 (0.82-1.18)	0.884
Renal	83 (13.6)	-0.0079	0.99 (0.78-1.27)	0.950

[a] Patient may have more than one comorbidity reported.
[b] *P* values were calculated from a multivariate Cox regression with a $P < 0.05$ threshold for significance.
Abbreviations: COPD, chronic obstructive pulmonary disease.

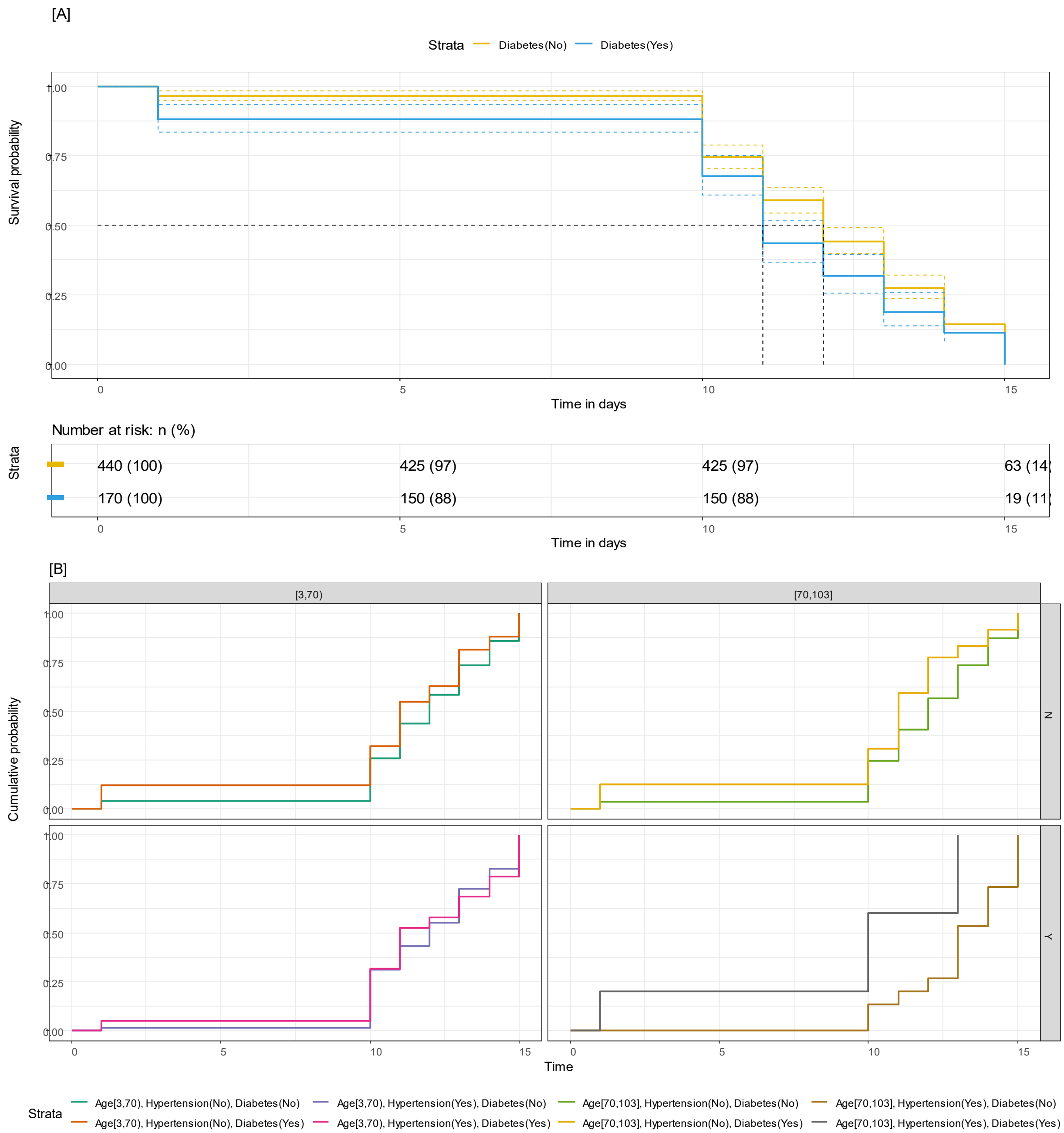

Figure 1. Survival and Kaplan-Meier Curves for Diabetes

4. Conclusions

We further extended the analysis by applying Kaplan-Meier curves to evaluate age, hypertension, and diabetes as presented in Figure 1B. This assessment showed that all patients (100%) in the study with age range [70-103], hypertension, and diabetes died before (day thirteen) when compared to other patients that present different combinations of age and hypertension. These results indicate that those SARS-CoV-2 infected with diabetes, older age, and hypertension are at a higher risk of earlier death.

Given that Colombia is currently starting its SARS-CoV-2 vaccination plan and the healthcare system, due to the outbreak, reaches high occupation levels, the developed evaluations provide a substantial reference of the underlying patients' comorbidities that are likely to increase the severity of the infection. Our findings could support clinical initiatives to assess the population at most risk if infected, including a priority not solely based on age on Phase 3 of the vaccination plan. Still, it might also consider the comorbidities that most affect SARS-CoV-2 infected survival rates in the country.

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6. Biographies

Milton Soto-Ferrari is an assistant professor in the Department of Marketing and Operations at Indiana State University. His research interests include business and healthcare analytics, supply chain management, and logistics. His recent publications are related to healthcare analytics and forecasting policies.

Odette Chams Anturi is a professor at the Science Economics Department, Universidad de la Costa (Colombia). Her research interests are Supply Chain Management, Organizational Learning, Innovation, and Ambidexterity. She has worked in public and private companies of mass consumption and healthcare entities. She is currently part of a research project about Quality Management and Ambidexterity in the Organic Agro-Food Industry.

Juan P. Escorcia Caballero is a professor at the Entrepreneurship and Management Department, Business School, Universidad del Norte (Colombia). His research interests are Supply Chain Quality Management, Innovation, and Ambidexterity. He has published several journal and conference papers. He has participated in three research projects funded by the Administrative Department of Science, Technology, and Innovation of Colombia. He is currently part of a research project about Quality Management and Ambidexterity in the Organic Agro-Food Industry.

Daniel Romero-Rodriguez is an assistant professor at Universidad del Norte in Barranquilla, Colombia (2018-present). He completed a Ph.D. in Industrial Engineering at the University of South Florida in 2018. His research interests include Resilience Measurement, Social Systems Resilience, and Supply Chain Risk Management. He is a researcher of the project "Voluntarily redistribution of immigrants in Colombia" in collaboration with the Immigration Policy Lab from Stanford University.

Julio Daza-Escorcia is an assistant professor in the Department of Industrial Engineering of the Fundación Universidad de América (Colombia). His research interests are in supply chain management and operations research. He has worked in food and beverage companies, mass consumption, and entities in the health area.

Blas Ferrari-Padilla is a medical physician from Universidad Metropolitana (Colombia). He has been a general doctor of the ISS's emergency service in Colombia, the Julio Mendez Barreneche hospital (Colombia), and the Clínica Marr Caribe emergency service (Colombia). Alternatively, he is a professor in the clinic of the Universidad Cooperativa de Colombia.