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Life Expectancy of COVID-19 Vaccination Recipients with Comorbidities

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Abstract
One of the biggest and longest-lasting viral pandemics in history, COVID-19, caused by the SARS-CoV-2 virus, has left millions of individuals throughout the world with serious health issues. However, there was a sense of hope that successful vaccination campaigns would result from the development of vaccines by scientists and pharmaceutical companies. Despite this development, misconceptions about the composition, applications, allergic reactions, and effectiveness of COVID-19 vaccinations continue to exist, causing some people to be hesitant while others eagerly seek vaccination. Numerous studies have shown that the COVID-19 mortality rate is highly influenced by characteristics like male gender, advanced age, smoking, and comorbidities including diabetes, hypertension, cardiovascular illnesses, cerebrovascular disorders, and respiratory ailments. Surprisingly, there hasn't been much study done on COVID-19 vaccination recipients' long-term survival. the analysis will then be done by using Cox PH regression model and the significant of the variables is presented. The significance value obtained is smaller than 0.05, which implies the result of this analysis.

Keywords: Cox PH regression; hazard ratio; survival function; COVID-19 vaccine; survival rate

1. Introduction

The discovery of the SARS-CoV-2 gene sequence in 2020 [1] prompted significant global research and development efforts to develop a vaccine. The pandemic's economic impact led to the evaluation of next-generation vaccine technology platforms, with the first COVID-19 vaccine candidate entering human clinical testing on March 16, 2020 [2]. COVID-19 vaccines come in various forms, including mRNA-based, viral vector-based, protein subunit, and inactivated vaccines. mRNA-based vaccines contain messenger RNA, a small amount of the virus's genetic material, which initiates an immune response. Viral vector-based vaccines use a harmless virus as a vector to transport the spike protein genetic material into cells, triggering an immunological response. Protein subunit vaccines use purified components of the virus, while inactivated vaccines inactivate the virus using heat, chemicals, or radiation. As more people become fully vaccinated, some still become infected or hospitalized with COVID-19. The CDC has been tracking the frequency of breakthrough infections, which are defined as SARS-CoV-2 detection in a respiratory specimen 14 days or more after receiving all recommended vaccination doses [3]. Despite the need for a vaccine, some people are skeptical about its effectiveness, as mortality still occurs after complete vaccination. Further research is needed to provide sufficient evidence that the COVID-19 vaccination is not a lifesaver.

The COVID-19 pandemic has significantly impacted global health and economic consequences, with comorbidities at a higher risk of severe disease and death. The COVID-19 vaccine has been developed to reduce virus spread and lower mortality rates. However, there is a gap in knowledge about its impact on mortality rates, especially among pre-existing health conditions. This study aims to investigate the long-term effects of COVID-19 vaccinations on life expectancy and death rates in vaccinated adults with underlying health issues. The findings will guide public health policies and facilitate targeted interventions to protect vulnerable populations with comorbidities during the pandemic. This research aims to analyze COVID-19 vaccination survival and compare life expectancy among recipients with comorbidities.

This research analyzes COVID-19 deaths from January 2021 up to December 2022 using a public repository and Cox Proportional Hazard model. Results show vaccination does not improve comorbidity survival for patients with comorbidities. Survival analysis is a crucial statistical method in medical research to evaluate the survival rate of vaccinated patients. The Cox PH model can help examine COVID-19 vaccine recipients' survival rates with comorbidities. This helps clinicians estimate survival rates and reduce mortality risks, potentially saving lives.

2. Methodology

Survival analysis examines the interval between an individual's observation and the occurrence of an event [4], known as survival time. It can be measured in days, weeks, months, or years. The events studied include death, adverse reactions, relapse, and new disease entities. However, waiting until the event occurs for all subjects is not practical, and censored observations occur when extensive information is not available. Censoring occurs when not all individuals had the opportunity to experience the event [5], leading to unknown survival times. Survival analysis can also be applied in engineering applications, such as military equipment reliability. Most statistical research for engineering applications focused on parametric models, but with the growth in clinical trials, nonparametric approaches have become more important. Survival analysis relies on the survival function, $S(t)$, which provides summary data for different t values [6]. Estimating this non-decreasing function is crucial [7], but estimating conditional or covariate survival functions remains challenging. A semi-parametric method [8]combines baseline hazard estimate with Cox PH model.

The Cox PH model is a widely used semi-parametric regression model for analyzing the relationship between independent factors and data on survival time. It is commonly used in economics, business, and medical research [9]. The final model produces a linearity equation model, with dependent variables [10] representing risk factors and independent variables representing event incidence rates. Time-independent independent variables are required for the extended Cox model. Başar (2017) [11] studied the length of delivery processes in 95 mothers in Central Java using a Cox proportional hazard regression model. Brembilla (2018) [12] assessed the risk of death in 601 individuals with lung cancer surgery using a multivariate Cox model. Ihwah (2015) [13] analyzed consumer purchasing risk and independent variables like education, employment, and income.

The Kaplan-Meier approach computes the survival rate using the survival function, which is non-parametric and does not assume a distribution of survival times. The survival function is the number of people who survived at least t time periods divided by the study population. The survival probability is determined using the formula,

$$S(t) = \frac{\text{(Number of subjects living at the start-Number of subjects died)}}{\text{(Number of subjects living at the start)}}$$

A hazard function represents the probability of an event occurring for an individual at time t, while a survival function is concerned with the event not occurring. It provides insight into conditional failure rates and helps define a survival model. The log rank test is a Chi-square test used to compare the distribution of time until an event of interest among independent groups. It examines the survival experience between groups and determines if there are statistical differences between groups' survival estimates. The null hypothesis is similar event time distributions, and the test examines whether survival curves are similar or overlapping. When the risk of an occurrence is continuously higher for one group, the test is more likely to find a difference. To calculate a p-value for the log-rank test, tables of the Chi-square distribution are used. For example, a study in Ethiopia [14] found a statistically significant difference in mortality risk among breast cancer patients between educational status, treatment, pathology type, and domicile.

COVID-19 data from January to December 2022 was sourced from a public repository, analyzed in Microsoft Excel, and sorted in Johor for 24 months was used to do this study. SPSS is a useful tool for analyzing survival studies, including Cox regression. For this study, it gathers data on COVID-19 patients, including days until death, vaccination doses, comorbidities, and death events. All variables are entered as numerical values, labelled in the variable view.

Click on "Analyze, then "Survival, then "Cox Regression Analysis" to begin doing Cox Regression in SPSS. Insert the status in the "event" space. A question mark appears next to the event as soon as a status is entered in this section. It serves as an indicator to inform software what numerical value qualifies as an event. As a result, click "define event" and then enter the value that is considered to be an event. Enter the covariates that should be taken into account as impacting the chance of survival in the field marked "covariates." By selecting the categorical option, the type of covariate must be defined as either categorical or continuous. If necessary, SPSS provides the ability to plot graphs.

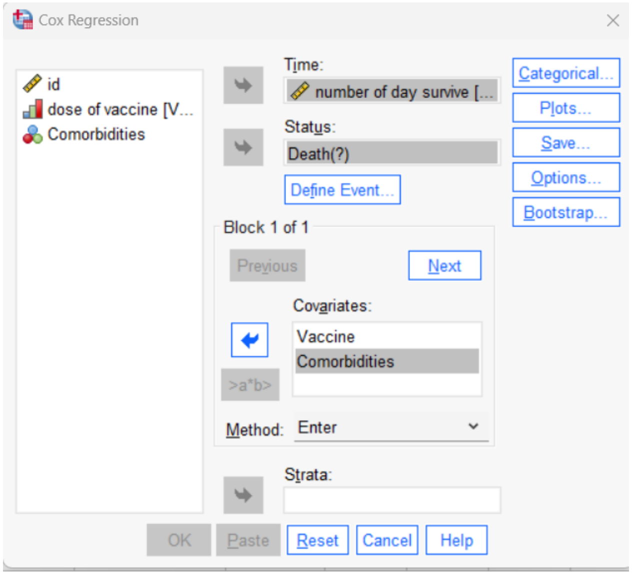

Figure 1 Cox regression window in SPSS "Define event" is the section to tell SPSS what number defines an event. Death is indicated by 1 in this study.

Click the "option" button. Next, choose the button on the 95% confidence interval (CI) of the exp(B) and select continue. Finally, click OK on the main panel to view the SPSS result.

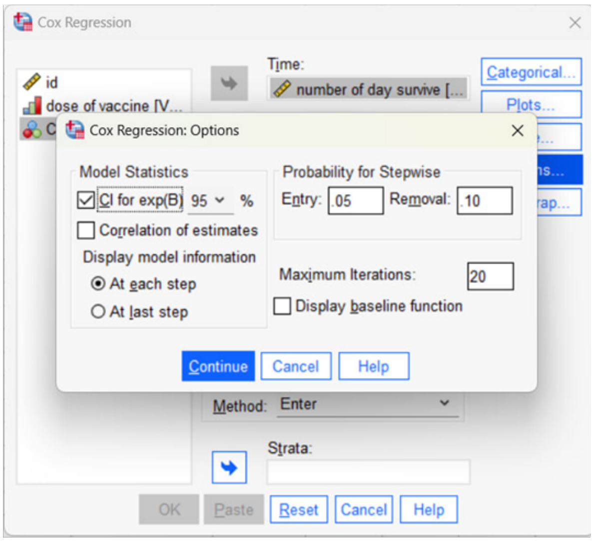

Figure 2 The window seen after clicking the options button. The red mark shows where a click has to be placed to obtain 95% CI for hazard.

3. Results and discussion

The study involved 4649 individuals diagnosed with COVID-19, including those who received vaccines. 84.79% died, while 15.21% were missing or alive. Over half did not receive any vaccines, while 17.68% received one dose, 22.58% received two, and 3.98% received three. The majority had comorbidities, with 3257 patients with 82.62% and 685 without. The criteria and variables listed below were used to set up the analysis.

Table 1: Criteria and variables used in this study

Criteria	**Variable**
Comorbidities	x_1
One dose of vaccine	x_2
Two doses of vaccine	x_3
Three doses of vaccine	x_4

In the Kaplan-Meier plot, which includes comorbidities and at least one vaccination, cumulative survival functions are shown for several groupings of variables. By showing the cumulative survival proportion versus time for each group, this helps in interpreting and analyzing the data.

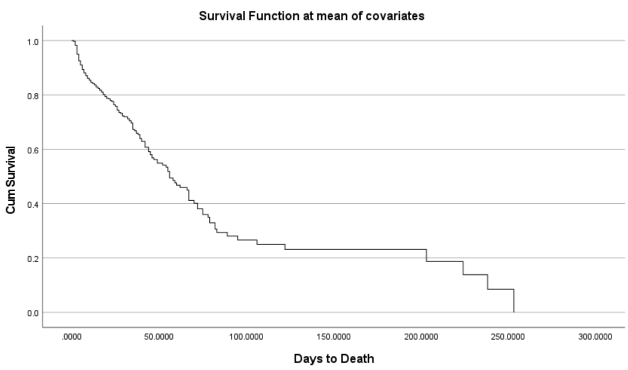

Figure 3 Survival function plot for this study. The fast decline in survival rate as $t \to \infty$ The probability of surviving past $t = 150$ days is 0.21. Only 21% of subjects, in other words, live for longer than 150 days. Additionally, the patients' survival rate declines with increasing time.

Construct the following regression coefficients hypothesis, β_i, to start the significant parameter test.

$$H_0: \beta_i = 0 \qquad \text{vs} \qquad H_1: \beta_i \neq 0$$

Table 2: Result summary obtained from SPSS

	B	SE	Wald	df	Sig.	Exp (B)	95% CI for Exp(B)	
							Lower	Upper
Comorbidities	-0.8581	0.0801	114.6751	1	0	0.4240	0.3623	0.4961
Vaccine (1)	-0.4087	0.1229	11.0517	1	0	0.6645	0.5222	0.8456
Vaccine (2)	0.2110	0.0936	5.0705	1	0.0243	1.2349	1.0277	1.4838
Vaccine (3)	0.9471	0.1530	38.3297	1	0	2.5783	1.9103	3.4797

The p-value for the patients having comorbidities and who had one and three doses of vaccination is 0.0000, as shown in Table 2, but the p-value for patients with two doses of vaccine is 0.02434. With a 95% confidence interval, all of the p-values are less than 0.05. As a result, H_0 is rejected. This indicates that comorbidities and vaccination dosage have an effect on the survival time of COVID-19 patients.

The hazard ratio is denoted by the abbreviation Exp(B), which is the exponential of B. The hazard ratio is defined as the expected change in hazard for each unit increment in the predictor. The factors that affect survival times vary in terms of significance according to the interpretation of the hazard ratio. This implies that having comorbidities and receiving just one dose of vaccination are protective prognostic indications (0 < HR < 1), but receiving two or three doses of vaccine is worse prognostic indications (HR > 1). Other than that, Wald test was used for evaluating whether variables in the Cox PH model were significant. Table 3 shows the significance of the Wald test statistic for each variable in the Cox PH model.

Table 3: Significance of the Wald test statistic for Cox PH model

Variable		$\lvert z \rvert$	Significance
Comorbidities	x_1	114.6751	> 1.96
Vaccine (1)	x_2	11.0517	> 1.96
Vaccine (2)	x_3	5.0705	> 1.96
Vaccine (3)	x_4	38.3297	> 1.96

The absolute values of the Wald test statistics for all variables are more than the crucial value of 1.96 at a significance level of 5%, as shown in Table 3 above. The findings show that |z| > 1.96 and is significant in the model, rejecting the null hypothesis for these variables. Consequently, the model's variables are significant.

Additionally, the parameter-estimated Wald test p-values for each variable were reported. The null hypothesis is strongly supported by the fact that the p-value for the 95% confidence interval is less than 0.05.

Conclusion

Survival analysis and Cox regression are crucial in medical industry, evaluating COVID-19 patients with comorbidities who received vaccinations. The analysis considers variables like vaccines and comorbidities, affecting the participants' survival time. Cox PH model reveals comorbidities and vaccination status significantly impact COVID-19 patients' life expectancy, with p-values below 0.05 for 95% confidence interval. The correlation between components in COVID-19 vaccines can be established through analysis. mRNA vaccines, viral vector-based vaccines, and inactivated virus vaccines are all essential in mitigating the risk of contracting the virus. However, comorbidities, such as heart disease, diabetes, respiratory problems, or weakened immune systems, can increase the risk of severe symptoms and complications. Those with comorbidities need extra care, such as following public health rules, maintaining cleanliness, and seeking medical assistance, to effectively treat their underlying health disorders.

References

[1] H. Wang *et al.*, “The genetic sequence, origin, and diagnosis of SARS-CoV-2”, doi: 10.1007/s10096-020-03899-4/Published.

[2] J. Mellet and M. S. Pepper, “A covid-19 vaccine: Big strides come with big challenges,” *Vaccines*, vol. 9, no. 1. MDPI AG, pp. 1–14, Jan. 01, 2021. doi: 10.3390/vaccines9010039.

[3] M. Birhane *et al.*, “COVID-19 Vaccine Breakthrough Infections Reported to CDC — United States, January 1–April 30, 2021,” *MMWR Morb Mortal Wkly Rep*, vol. 70, no. 21, pp. 792–793, May 2021, doi: 10.15585/MMWR.MM7021E3.

[4] F. Emmert-Streib and M. Dehmer, “Introduction to Survival Analysis in Practice,” *Mach Learn Knowl Extr*, vol. 1, no. 3, pp. 1013–1038, Sep. 2019, doi: 10.3390/make1030058.

[5] K.-M. Leung, R. M. Elashoff, and A. A. Afifi, “CENSORING ISSUES IN SURVIVAL ANALYSIS,” 1997. [Online]. Available: www.annualreviews.org

[6] T. G. Clark, M. J. Bradburn, S. B. Love, and D. G. Altman, “Survival Analysis Part I: Basic concepts and first analyses,” *British Journal of Cancer*, vol. 89, no. 2. pp. 232–238, Jul. 21, 2003. doi: 10.1038/sj.bjc.6601118.

[7] A. Bienvenüe and D. Rullière, “Iterative adjustment of survival functions by composed probability distortions,” *GENEVA Risk and Insurance Review*, vol. 37, no. 2, pp. 156–179, Sep. 2012, doi: 10.1057/GRIR.2011.7/TABLES/2.

[8] A. Wey, J. Connett, and K. Rudser, “Combining parametric, semi-parametric, and non-parametric survival models with stacked survival models,” *Biostatistics*, vol. 16, no. 3, pp. 537–549, Jul. 2015, doi: 10.1093/biostatistics/kxv001.

[9] R. Singh and K. Mukhopadhyay, “Survival analysis in clinical trials: Basics and must know areas,” *Perspect Clin Res*, vol. 2, no. 4, p. 145, 2011, doi: 10.4103/2229-3485.86872.

[10] S. Abd Elhafeez, G. D’Arrigo, D. Leonardis, M. Fusaro, G. Tripepi, and S. Roumeliotis, “Methods to Analyze Time-to-Event Data: The Cox Regression Analysis,” *Oxid Med Cell Longev*, vol. 2021, 2021, doi: 10.1155/2021/1302811.

[11] E. Başar, “Aalen’s Additive, Cox Proportional Hazards and The Cox-Aalen Model: Application to Kidney Transplant Data (Aditif Aalen, Bahaya Berkadaran Cox dan Model Cox-Aalen: Penggunaan ke atas Data Pemindahan Buah Pinggang),” *Sains Malays*, vol. 46, no. 3, pp. 469–476, 2017, doi: 10.17576/jsm-2017-4603-15.

[12] A. Brembilla, A. Olland, M. Puyraveau, G. Massard, F. Mauny, and P. E. Falcoz, “Use of the Cox regression analysis in thoracic surgical research,” *J Thorac Dis*, vol. 10, no. 6, p. 3891, Jun. 2018, doi: 10.21037/JTD.2018.06.15.

[13] A. Ihwah, “The Use of Cox Regression Model to Analyze the Factors that Influence Consumer Purchase Decision on a Product,” *Agriculture and Agricultural Science Procedia*, vol. 3, pp. 78–83, Jan. 2015, doi: 10.1016/J.AASPRO.2015.01.017.

[14] B. Feleke, L. M. Tesfaw, and A. A. Mitku, “Survival analysis of women breast cancer patients in Northwest Amhara, Ethiopia,” *Front Oncol*, vol. 12, Dec. 2022, doi: 10.3389/FONC.2022.1041245.