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The effect of antiviral treatment on SARS-CoV-2 infectious disease progression: A comparison of the multi-state models

Nihan Potas*
Dept. of Healthcare Management, Ankara Hacı Bayram Veli University, Turkey
**Corresponding author: nihan_potas@hotmail.com*

Abstract

Combating SARS-CoV-2 is the first concern and goal of the whole world faced with the global health crisis. Since 2019, the SARS-CoV-2 infection (COVID-19) and even mutated infection cases have been increasing rapidly. From 2019 through 27 August 2021, a total of 214,468,601 individuals were confirmed cases of SARS-CoV-2, including 4,470,969 death toll. Some of these individuals were able to access treatment and some could not, but for a while there was complete uncertainty. It was not known whether those who accessed treatment were lucky, but treatment was based on trial and error because of this uncertainty around the world until data was collected. Therefore, the aim of this study was to model SARS-CoV-2 infectious disease progression from the date of polymerase chain reaction (PCR) test to the date of negative outcome via Bayesian multi-state model approaches considering risk factors such as gender, age, and antiviral treatment. Data from 746 inpatients were collected from August 1st until the December 1st, 2020. For the multi-state model, five various discrete states were selected according to the Republic of Turkey Ministery of Health treatment algorithm. The results showed that Bayesian multi-state models with the Weibull distributed baseline hazard function were more appropriate models in the presence of risk factors and antiviral treatment.

Keywords: Bayesian multi-state modeling; continuous-time Markov process; antiviral treatment; baseline hazard function, SARS-CoV-2 infectious disease progression

1. Introduction

Longitudinal failure time data and also the occurrence of subsequential medical events are widely described and investigated by complex models such as multi-state modeling and competing risks models (Beyersmann *et al.*, 2012). Modeling, estimating and predicting transition probabilities of being in the state (having disease or not), and between states are common for evaluating progression of chronic and non-chronic diseases and events (death) in practice and epidemiology. Infectious diseases are included in non-chronic diseases in spite of the fact that the transitions of times are shorter. It was observed that complex situations in chronic diseases are also experienced in infectious disease progression with the effect of potential risk factors (Crowther and Lambert, 2017). The complexity of multi-state data depends on the number of states, risk factors (covariates), and the transitions between the states. However, as complex as it is, multi-state modeling can be estimated by parametric, semiparametric, and non-parametric inferences with both frequentist and bayesian approaches.

Some of the most important studies about Bayesian approaches to disease multi-state modeling include, but are not restricted to prostate cancer data analyzed based on surgery and radiotherapy outcomes, with the Bayesian multi-state modeling (Beesley *et al.*, 2019). A proposed hierarchical Bayesian multi-state model was investigated by multiple capture-recapture ecological data (Calvert *et al.*, 2009). Using a new Bayesian multi-state model, radio-telemetry, band-resight, and dead recovery data for reintroduced individuals were analyzed based on survival and breeding state transitions (Converse *et al.*, 2012). The

breast cancer tumor progression for women was modeled with Bayesian multi-state analysis, considering the risk factor of tumor history in the family (Hui-Min Wu *et al.*, 2008). When in attempt to determine the risk factors and transitions between the smoking states in a Bayesian multi-state model, the expectation-maximization variable selection method was proposed (Koslovsky *et al.*, 2018). HIV disease progression in Zimbabwe was investigated with the Bayesian multi-state model according to patients receiving antiretroviral therapy (Matsena Zingoni *et al.*, 2019). A Bayesian multi-state modeling approach was presented for periodic cancer screening data (Shen *et al.*, 2017). The Bayesian approach was used to identify and explore the relationship between occasion-specific cognitive function and stroke (van den Hout *et al.*, 2015).

Since 2019, the SARS-CoV-2 infectious disease (COVID-19) caused health concerns around the world, and multi-state modeling studies for patients are scarce (El Zowalaty and Järhult, 2020; Wang *et al.*, 2020). This is due to the use of data that requires longitudinal follow-up in the nature of the modeling.

In spite of advancements in treatment and vaccination, SARS-CoV-2 disease has affected 2 billion people worldwide and still poses to be a global threat (Ursino *et al.*, 2021). Despite the fact that some patients are asymptomatic, SARS-CoV-2 infectious disease led to around 20% of patients being admitted to the intensive care unit (ICU), and 70% of inpatients being intubated (Luo *et al.*, 2020; Petrilli *et al.*, 2020). However, in clinical studies and the experience of many physicians, very contradictory results emerged regarding patients who were admitted to the intensive care unit, were intubated, and given antiviral treatments (Çelik and Çora, 2020; Elavarasi *et al.*, 2020; Ghazy *et al.*, 2020; Kılıç *et al.*, 2021; Ladapo *et al.*, 2020; Meng *et al.*, 2020; Nadaroglu, 2020; Zhou *et al.*, 2020). Countries followed various or similar treatment algorithms; still, the risk factors impacting the clinical states of patients have yet to be completely understood. The issue of mortality is still being debated. While few studies about multi-state modeling related to the SARS-CoV-2 disease all around the world were done (Ursino *et al.*, 2021; Zuhairoh *et al.*, 2020), a unique study has not been performed using a Bayesian approach for multi-state modeling.

The aim of this study was to model SARS-CoV-2 infectious disease progression from the date of testing with a PCR test to the date of being negative via Bayesian multi-state model approaches considering risk factors such as gender, age, and antiviral treatment. Subsequently, using a mean sojourn time, how fast a disease progresses from one state to another was determined with the influence of risk factors. Also, the performances were compared based on Bayesian multi-state model approaches.

In Section 2, SARS-CoV-2 infectious disease progression using Bayesian and frequentist approaches in a continuous-time discrete-state Markov model is examined. The SARS-CoV-2 infectious disease dataset was described and the data collection process was explained. The theoretical formulations of the continuous-time discrete-state Markov model-based Bayesian approach are presented. Section 3, summarizes the results and compares the performance of the approaches for a five-state Markov model considering risk factors such as gender, age, and antiviral treatment. Finally, in Section 4, the advantages and limitations of the models are discussed.

2. Material and methods

The data were collected from Edirne Sultan 1st Murat state hospital patients who were diagnosed with SARS-CoV-2 infectious disease and hospitalized for the study. Due to the intensity and difficulty of the treatment of the screened patients, it was decided that it would be appropriate to study the patients after they were discharged. All patients were evaluated in terms of a PCR test to detect SARS-CoV-2. For inclusion into study, the following criteria were used; diagnosed with SARS-CoV-2 infectious disease, hospitalized and treated in Edirne Sultan 1st Murat state hospital, willingness to participate in the study, and having enough education to understand the aim of the study. The surviving inpatients who did not fully complete the online survey or gave un-realistic answers were excluded. Therefore, twenty-one of the online surveys were eliminated based on exclusion criteria.

The study was approved by Edirne Provincial Health Directorate Scientific Research Committee. Also data was collected from August 1st until the December 1st, 2020 after ethics committee approval

from Ankara Hacı Bayram Veli University (2020-65).

A semi-structured information form was designed to obtain time-to-event data regarding the ages, gender, and antiviral treatment. To determine the sequence of states of progression of SARS-CoV-2 information was obtained as follows: date of PCR test, date of being positive for SARS-CoV-2, date of admission to ICU, date of intubation, and date of being negative for SARS-CoV-2. The survival time, which was defined as the number of days between the date at which the inpatient's initial state was recorded and the date at which the inpatient entered another state until death/recovery. The descriptive statistics for variables and results of test statistics are presented in Table 1 .

	Categories	**Survivors** ($n = 702$)	**Non-survivors** ($n = 44$)	$p - value$
Gender	*Male*	397 (56.6%)	22 (50.0%)	0.488^a
	Female	305 (43.4%)	22 (50.0%)	
Age		50.6 ± 22.1	72.1 ± 12.9	p^b<.001**
Antiviral Treatment	*Control*	259 (36.9%)	8 (18.2%)	p^a<.001**
	Treatment	443 (63.1%)	36 (81.8%)	
Intensivecare unit	*No*	655 (93.3%)	6 (13.6%)	p^a<.001**
	Yes	47 (6.7%)	38 (86.4%)	
Intubation	*No*	687 (97.9%)	13 (29.5%)	p^a<.001**
	Yes	15 (2.1%)	31 (70.5%)	
Survival Time (day)		7.8 ± 11.7	18.7 ± 17.0	
Favipiravir	*No*	643 (91.6%)	23 (52.3%)	p^a<.001**
	Yes	59 (8.4%)	21 (47.7%)	
Azitro||Azax	*No*	409 (58.3%)	35 (79.5%)	0.008^a*
	Yes	293 (41.7%)	9 (20.5%)	
Plaquenil	*No*	404 (57.5%)	29 (65.9%)	0.351^a
	Yes	298 (42.5%)	15 (34.1%)	
Hydroxychloroquine||Chloroquine	*No*	640 (91.2%)	43 (97.7%)	0.216^c
	Yes	62 (8.8%)	1 (2.3%)	
Other	*No*	390 (55.6%)	14 (31.8%)	0.004^a*
	Yes	312 (44.4%)	30 (68.2%)	

Table 1. Results of Descriptive Statistics ($n = 746$; p<.05*, p<.001**, " || " = or; a: Chi-Square test, b: Independent Sample t-test, c: Fisher's Exact test)

2.1 Continuous-time discrete-state transition probabilities

The phenomenon of SARS-CoV-2 infectious disease progression is still an issue for the entire world. Considering the unique characteristics of the data, different multi-state model approaches were proposed with the inclusion of risk factors for SARS-CoV-2-specific outcomes. The multi-state models, in particular, were able to reduce or eliminate bias caused by antiviral treatment allocation and potentially provide a more valid antiviral treatment comparison (Calvert *et al.*, 2009). The multi-state models are an exclusive form of illness-death model; where the individuals start healthy and then may become infected, then admitted and even die. In theory, patients who suffer from illness can recover and become healthy (Andersen *et al.*, 2002). In fact, even intubated inpatients recover from SARS-CoV-2 infectious disease and regain health. To understand the overall survival of SARS-CoV-2 infectious disease, the univariate and multivariate Cox proportional hazard model was used, which describes the effect of covariates on the survival of SARS-CoV-2 inpatients.

According to the Republic of Turkey Ministery of Health treatment algorithm, five discrete states were selected for the multi-state model in Figure 1 (Ministry of Health, 2020), event-free and SARS-CoV-2 infectious disease-negative (State 0), alive and SARS-CoV-2 infectious disease-positive (State 1),

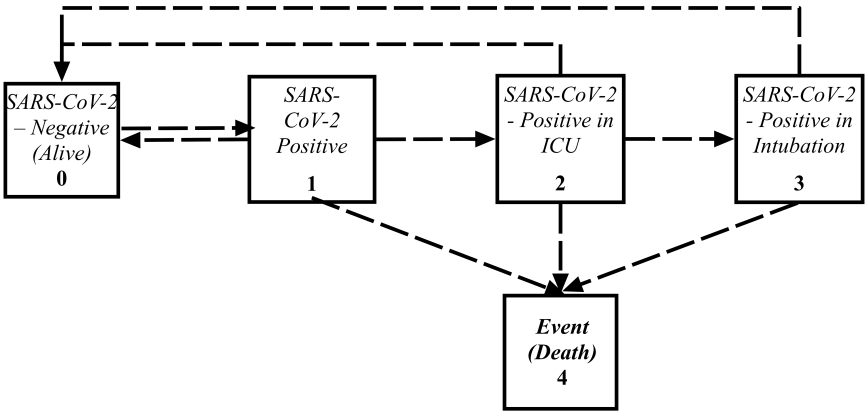

Fig. 1. Diagram of SARS-CoV-2 Infectious disease progression (multi-state model).

alive and SARS-CoV-2 infectious disease-positive in the ICU (State 2), alive and SARS-CoV-2 infectious disease-positive intubated (State 3) and absorb-state and death (State 4).

Transitions are not possible from SARS-CoV-2 infectious disease-positive intubated (State 3) to the ICU (State 2) or from SARS-CoV-2 infectious disease-positive in ICU (State 2) to SARS-CoV-2 infectious disease-positive (State 1) for the inpatients.

As stated by the Ministry of Health, older than 65 years of age was evaluated as a risk. However, it was concluded that the cut-off point in the dataset should be reconsidered since the age variable was not significant in multi-state models. Maximally Selected Rank Statistics via conditional Monte-Carlo was used to determine the cut-off point for the risk group (Lausen and Schumacher, 1992). Figure 2 demonstrates the results ($M = 4.21$; $p < 0.01$).

Let $(Y(t),\ t \in \mathcal{T})$ with a descrete finite states space $S = \{0,\ 1,\ 2,\ 3,\ 4\}$ be known as a continuous-time Markov process. Let k and $l,\ k \neq l$ denote one of the five states of SARS-CoV-2 infectious disease, where $k,\ l \in \{0,\ 1,\ 2,\ 3,\ 4\}$. Consider, $Y(t)$ represents inpatients with SARS-CoV-2 infectious disease in state S at a given time t. For a continuous time, the transition intensity is defined by

$$\lambda_{kl}(t) = \lim_{\Delta t \to 0^+} P_{kl}\left(Y(t+\Delta t) = k \,|Y(t) = l, Z(t)\right)/\Delta t\ ,\ \ k \neq l$$

$$\lambda_{ll}(t) = -\sum_{k \neq l} \lambda_{kl}(t)\ ,\ \ k,\ l = 0,\ 1,\ 2,\ 3,\ 4$$

where $p_{kl}(\Delta t) = P_{kl}\left(Y(t+\Delta t) = l \,|Y(t) = k,\ Z(t)\right)$, is the probability of transition from state $k \to l$ during time period Δt with time dependent covariate vector $Z(t)$ (Andersen and Keiding, 2002; Jackson *et al.*, 2003; Régis and Artes, 2015). Transition intensities will be modeled as a function of age, gender, and antiviral treatments (favipiravir, azitro||azax, plaquenil, hydroxychloroquine||chloroquine and other) as previously stated. Specifically, each of the 9 non-zero transition intensities seen in Figure 1 is denoted by λ_{kl} for $k,\ l \in S$,

$$\begin{aligned}\log(\lambda_{kl}) \ = \beta_{kl,0} + \beta_{kl,1} \times age + \beta_{kl,2} \ \times female + \beta_{kl,3} \times Favipiravir \\ +\beta_{kl,4} \times Azitro||Azax \ + \beta_{kl,5} \times Plaquenil \\ +\beta_{kl,6} \times Hydroxychloroquine||Chloroquine + \beta_{kl,7} \times Other.\end{aligned} \tag{1}$$

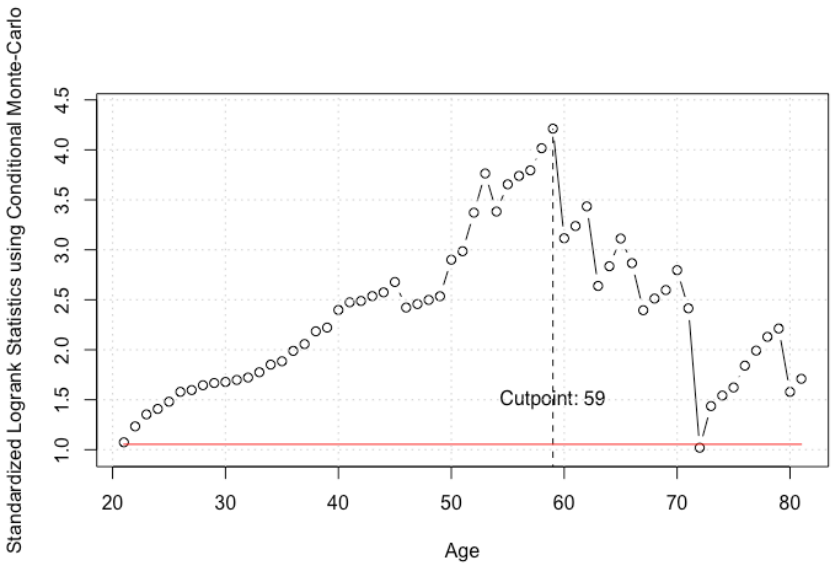

Fig. 2. Results of the standardized logrank statistics using conditional Monte-Carlo (Replication Number = 10^5).

where *age* is an indicator of inpatients who are less than or equal to 59 years of age, with older than 59 years as the baseline. The variable *male* is an also indicator of the gender of patients, where *female* inpatients are the baseline. The antiviral treatment covariates are considered the same; *Favipiravir* is the indicator for *not treated with favipivavir* where *treated with favipivavir* is the baseline. For a continuous-time Markov process with 5-states in Figure 1, the Markov transition intensity matrix $Q(\boldsymbol{\lambda})$ is

$$\begin{pmatrix} \lambda_{00} = -\lambda_{01} & \lambda_{01} & 0 & 0 & 0 \\ \lambda_{10} & \lambda_{11} = -(\lambda_{10} + \lambda_{12} + \lambda_{14}) & \lambda_{12} & 0 & \lambda_{14} \\ \lambda_{20} & 0 & \lambda_{22} = -(\lambda_{20} + \lambda_{23} + \lambda_{24}) & \lambda_{23} & \lambda_{24} \\ \lambda_{30} & 0 & 0 & \lambda_{33} = -(\lambda_{30} + \lambda_{34}) & \lambda_{34} \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

where the diagonal of Q matrix defined as $\lambda_{ll} = -\sum_{k \neq l} \lambda_{kl}$, which is exceptional for any model in the absorb-state $\lambda_{ll} = 0$, let $\boldsymbol{\lambda}$ be the vector of transition intensity with a length of 25 (Jackson *et al.*, 2003). The Chapman–Kolmogorov forward and backward differential equations, using the transition intensities, are computed as $dP_{kl}(t)/dt = \sum_{\forall u} P_{ku}(t)\lambda_{ku}, \quad \forall k, l$. The solution to the differential equations, to obtain transition probabilities $p_{kl}(\Delta t)$ are from $P(\Delta t) = \exp(Q\Delta t)$ (Cox and Miller, 1965).

The forward or backward equations in selection and computation problems arise for complex models. Some methods are satisfied by both backward and forward equations such as using the Taylor expansion of $\exp(Q\Delta t)$ (Reddy, 2011). Kulkarni (2011) has demonstrated, however, the accuracy of using the Taylor expansion method is numerically unstable. The uniformization algorithm for $P(t)$ was proposed to implement an easier solution.

The algorithm was computed by using the following steps (Kulkarni, 2011):

Step 1: Given Q, t, where approximation error $0 < \epsilon < 1$.

Step 2: Compute λ_{max} by using $\sum_l^4 \lambda_{kl} = \lambda_k$ and $\lambda_{max} \geq \max_{1 \leq u \leq k}(\lambda_u)$.

Step 3: Compute $\hat{P}$ by using $\hat{P} = [\hat{p}_{kl}]$ as $(1 - \sum \lambda_k/\lambda_{max})$ if $k = l$ or $(\lambda_{kl}/\lambda_{max})$ if $k \neq l$.

Step 4: $A = \hat{P}$; $B = \exp -(\lambda_{max} t)\, I$; $c = \exp -(\lambda_{max} t)$; $sum = c$; $k = 1$.

Step 5: While $sum < 1 - \epsilon$, do:

i. $c = c \times (\lambda_{max} t)/k$

ii. $B = B + cA$

iii. $\mathrm{A} = \mathrm{A}\hat{P}$

iv. $sum = sum + c$

v. $k = k + 1$

end.

Step 6: B is within ϵ of $P(t)$.

After that, for inpatients i and observation time t_{ij}, $j = 1, \cdots, m_i$, is recorded over n_i discrete time points until the sample of n inpatients is complete. In the corresponding states for inpatients i, observed at a particular time period t_{ij}, $t_{i(j-1)}$ can be defined as $\delta_{ij} = t_{ij} - t_{i(j-1)}$.

Let N_k be the total observed inpatients in state k and $O_{kl}(\delta_{ij})$ is the observed inpatients from state $j \rightarrow k$ during time period δ_{ij}. For the likelihood function of SARS-CoV-2 infectious data, assuming that the observed transitions from the starting state k during time period δ_{ij} can be modelled, the multinomial distribution is as follows:

$$(O_{k0}(\delta_{ij}), \ldots, O_{k4}(\delta_{ij})) \sim Multinomial\,(P_{k0}(\delta_{ij}), \ldots, P_{k4}(\delta_{ij}); N_k(\delta_{ij}))\,.$$

The likelihood function is defined by considering the risk factors as follows:

$$L(\boldsymbol{\lambda}, \boldsymbol{\beta}|\, Y) = \prod_{i=1}^{n} \prod_{j=1}^{m_i} \prod_{k=0}^{4} \frac{N_k(\delta_{ij})!}{\prod_{l=0}^{4} O_{kl}(\delta_{ij})!} \prod_{l=0}^{4} P_{kl}(\delta_{ij}; Z|\boldsymbol{\lambda}, \boldsymbol{\beta})^{O_{kl}(\delta_{ij})}.$$

The product of transition probabilities between observed states, inpatients i, $i = 1$, ..., n, at a given time $t_{i,1}, \ldots, t_{i,m_i}$ where observation times j which are observed k times (Kalbfleisch and Lawless, 1985).

2.2 Illness-death with recovery model representation including risk factors

Multi-state model parameters can be estimated using maximum likelihood or Bayesian approaches. In this study, Bayesian Multi-State Models (BMSM) with different distributed baseline hazard functions were applied to consider the risk factors. Bayesian estimations, where parameters are iteratively drawn in a Markov chain Monte Carlo algorithm, were used in an attempt to focus on comparing the maximum likelihood estimation. The key benefit of utilizing a Bayesian approach is that it provides a flexible way for estimating posterior transitions based on both the likelihood of SARS-CoV-2 infectious disease progression data and also additional prior information for unknown parameters (Rashid and Chand, 2019).

In the study, it is assumed that each transition of the illness-death and recovery model is represented by a Cox proportional hazards model. Accordingly, the transition intensities are defined as follows using this formula:

$$\lambda_{kl}(t) = \lambda_{kl,0}(t) \exp\left(\beta_{kl}^{T} Z(t)\right) \tag{2}$$

where $\lambda_{kl,0}$ is the baseline hazard function for transition $k \rightarrow l$ and β_{kl} is a vector of coefficients associated with time dependent covariate vector $Z(t)$ (Marshall and Jones, 1995; Putter *et al.*, 2006).

In the Bayesian multi-state model, a prior distribution is applied to the baseline hazards functions and the model coefficients. In this analysis of the SARS-CoV-2 infectious disease data using the proposed Bayesian approach, $\lambda_{kl,0}$ is assumed to have a parametric-prior distribution as follows:

$$\lambda_{kl,0} \sim Exp\left(a_{kl}^{e}\right), \;\; k,\, l \in S, \tag{3}$$

$$\lambda_{kl,0} \sim Weibull\left(a_{kl}^{w}, b_{kl}^{w}\right), \;\; k,\, l \in S, \tag{4}$$

$$\lambda_{kl,0} \sim Gamma\left(a_{kl}^{g}, b_{kl}^{g}\right), \;\; k,\, l \in S. \tag{5}$$

For all 9 transitions, a Cox proportional hazards model structure was utilized, with Gaussian, Weibull and gamma baseline hazard function (Beesley *et al.*, 2019; Beesley and Taylor, 2021; Casellas, 2007; Kern *et al.*, 2016). In Bayesian inference, it is common to investigate the effects of the different prior distributions (Koc and Cengiz, 2020; Ulas and Karaman, 2018). The eight parameters were stated in equation 1, intercept $(\beta_{kl,0})$ and the model coefficients $(\beta_{kl,1}, \ldots, \beta_{kl,7})$, respectively.

Within Bayesian models, the choice of prior distribution is a significant decision. Non-informative priors were chosen as only limited or very little and vague information is known clearly about the parameters of SARS-CoV-2 infectious disease progression (Saberi and Ganjali, 2013). Each of the prior distributions for regression coefficients is taken as a Gaussian $\beta_{kl} \sim Normal\left(0, \tau_{kl}^{2}\right)$. The posterior distribution of parameters $\lambda_{kl,0}$ and β_{kl}, $\pi\left(\boldsymbol{\lambda}, \boldsymbol{\beta}|Y\right)$ is obtained by using Bayes' theorem $\pi\left(\boldsymbol{\lambda}, \boldsymbol{\beta}|Y\right) \propto L\left(\boldsymbol{\lambda}, \boldsymbol{\beta}|Y\right)\pi\left(\boldsymbol{\lambda}\right)\pi\left(\boldsymbol{\beta}\right)$ where $\pi\left(\boldsymbol{\lambda}\right)$ and $\pi\left(\boldsymbol{\beta}\right)$ are prior distributions (Ibrahim *et al.*, 2001). Random effect variance parameters are frequently given conjugate inverse-gamma priors that appear to be weakly informative (Rashid and Chand, 2019; Röver *et al.*, 2021). Also, choosing the random effect variance parameters within proper intervals did not change any of the results of the analysis. In common practice, non-informative priors are assigned either uniform or diffuse normal priors with large variances. However, a generative Bayesian model can be defined with prior predictive simulation to eliminate the vague information (Wesner and Pomeranz, 2021). The prior distributions (iid) involved are: $a_{kl}^{e}, a_{kl}^{w}, a_{kl}^{g} \sim Normal\left(0, 4\right)$, $b_{kl}^{w}, b_{kl}^{g} \sim Gamma\left(2.5, 0.4\right)$,$\tau_{kl}^{2} \sim Inv-Gamma\left(0.1,\ 10\right)$. The values in computations are suggested according to prior predictive simulation.

To complete the analysis in WinBUGS and R version 4.0.2 software, the likelihood function was combined with the prior information. For Bayesian estimation, all the parameters were run for 30000 iterations with a burn-in of 9000 iterations to provide draws from the posterior distributions in a Markov chain Monte Carlo (MCMC) algorithm. In practice, the various posterior distributions can be complex, and parameters can be estimated using Metropolis-Hastings within Gibbs sampling algorithm. In general Gibbs sampling assume that the target distribution is $\pi\left(\boldsymbol{\lambda}\right)$ where $\boldsymbol{\lambda} = \left(\lambda_1, \ldots, \lambda_d\right)$ and that the full conditional distributions $\pi\left(\lambda_i\right) = \pi\left(\lambda_i|\boldsymbol{\lambda}_{-i}\right)$, $i,\ i = 1,\ ...,\ d$ are available. The steps are generated from $\pi\left(\boldsymbol{\lambda}\right)$. However, sometimes $\pi\left(\lambda_i|\boldsymbol{\lambda}_{-i}\right)$ cannot be sampled directly because of the instability in the posterior estimates of noninformative priors, Metropolis-Hastings steps can be generated as a substitute. All the convergence results for Metropolis-Hastings within the Gibbs sampling algorithm still hold (Beesley and Taylor, 2021; Ghirmai, 2015; Ibrahim *et al.*, 2001). Figure 3 demonstrated Bayesian approach estimates of the hazard ratio for baseline risk factors and antiviral treatments in each of the 9 transitions from equation 1. In addition, to compare with the multi-state models, univariate and multivariate maximum likelihood estimates of the hazard ratio and 95% CIs from standard Cox proportional hazards models are presented in Table 2.

In the literature, there are several types of variable and model selection methods for multi-state modelling. In the study, the known method for model comparison and the recent method for variables selection were used. For Bayesian model comparison and selection of adequate models, the Deviance Information Criterion (DIC) is extensively utilized in the literature (Ando, 2010; Plummer, 2008; Rossi *et al.*, 2021). For the variable selection, the expectation-maximization method for Bayesian multi-state Markov models was proposed with supplementary documents (Koslovsky *et al.*, 2018).

3. Results

According to the survival status of 746 inpatients, there was an overwhelming significant difference in the risk factors of age, antiviral treatment, being in the ICU, being intubated, and treated with favipiravir ($p < .001$). In Table 1, there was a more significant difference in the risk factors of treated with

azitro||azax and others ($p < .05$). The other treatments (such as immunoglobulin and oseltamivir) were combined as other treatments due to the low frequencies among inpatients.

	Categories	$HRs_{univariable}$ (95%CIs)	$HRs_{multivariable}$ (95%CIs)
Gender	*Male*	-	-
	Female	1.22	0.74
		(0.67, 2.21)	(0.39, 1.40)
Age		1.03**	1.04**
		(1.01, 1.05)	(1.02, 1.06)
Antiviral Treatment	*Control*	-	-
	Treatment	0.68	-
		(0.36, 1.29)	-
Favipiravir	*No*	-	-
	Yes	2.91**	2.38*
		(1.55, 5.44)	(1.17, 4.84)
Azitro||Azax	*No*	-	-
	Yes	0.59	0.65
		(0.28, 1.28)	(0.26, 1.60)
Plaquenil	*No*	-	-
	Yes	1.10	1.96
		(0.57, 2.12)	(0.86, 4.48)
Hydroxychloroquine|| Chloroquine	*No*	-	-
	Yes	0.33	0.56
		(0.05, 2.45)	(0.08, 4.85)
Other	*No*	-	-
	Yes	2.20*	1.66
		(1.17, 4.17)	(0.81,3.41)
Likelihood ratio test			30.34**
Wald test			24.53**
Score (logrank) test			26.96**
AIC			405.80
Concordance Index			0.80

Table 2. Results of univariate and multivariate Cox proportional hazard model ($n = 746$; $p<.05$*,$p<.001$**; " || " = or; *HRs*: Hazard Ratios, CIs: Confidence Intervals)

Regarding Table 2, age (*HR* 1.03, 95% CI: 1.01–1.05), treated with favipiravir (*HR* 2.91, 95% CI: 1.55–5.44) and other treatments (*HR* 2.2, 95% CI: 1.17–4.17) were significantly associated with overall survival in univariate analysis.

Briefly; age and being treated with favipiravir were associated with the overall survival in the models. Interestingly, being treated with favipiravir did not decrease the risk of death (*HR* 2.38, 95% CI: 1.17–4.84), and similar to the literature, age increased the risk of death (*HR* 1.04, 95% CI: 1.02–1.06). However, the antiviral treatments were not clear according to Cox hazard proportional models, this increased the need for more complex analysis and models. Antiviral treatments should be investigated for whether they increase or decrease the risk of entering the next state. Therefore, the results will be effective for the treatment of infected patients and inpatients.

Transitions		*to*				
from		***SARS-CoV-2 -Negative***	***SARS-CoV-2 -Positive***	***SARS-CoV-2 -Positive in ICU***	***SARS-CoV-2 - Positive in Intubation***	***Event (Death)***
	State	***0***	***1***	***2***	***3***	***4***
SARS-CoV-2 -Negative	***0***	0	746	0	0	0
SARS-CoV-2 -Positive	***1***	655	0	85	0	6
SARS-CoV-2 -Positive in ICU	***2***	32	0	0	46	7
SARS-CoV-2 -Positive in Intubation	***3***	15	0	0	0	31

Table 3. Number of the total inpatients' transitions between states.

The number of inpatients entering these states is summarized in Table 3. These 746 inpatients were defined as going from SARS-CoV-2-Negative (0) to SARS-CoV-2-Positive (1) in the multi-state model.

The highest contribution of the transitions came from 655 (87.8%) of inpatients who went from SARS-CoV-2-Positive (1) to SARS-CoV-2-Negative (0). This means that most of the inpatients recovered. The highest contribution to the death state came from 31 (75%) intubated inpatients; while contrarily, the lowest contribution to the SARS-CoV-2-Negative state came from 15 intubated inpatients. The posterior mean estimates for hazard ratios with 95% confidence intervals in the Bayesian multi-state models are presented in Table 4. The results show that multi-state models can be used to determine which risk factors are relevant for which transitions. The results reveal the expected tendencies of the SARS-CoV-2 disease.

The baseline risk factors were not associated with the transition from initial SARS-CoV-2-Negative to SARS-CoV-2-Positive in all multi-state models.

For the transition from SARS-CoV-2-Positive to SARS-CoV-2-Positive in ICU, there was an association with age, azitro||azax, plaquenil and other treatments in all univariate multi-state models. Patients treated with azitro||azax, (EBMSM-*HR* 0.17, 95% CI: 0.06–0.45; WBMSM-*HR* 0.24, 95% CI: 0.10–0.41; GBMSM-*HR* 0.32, 95% CI: 0.11–0.98, respectively) and plaquenil (EBMSM -*HR* 0.11, 95% CI: 0.06–0.21; WBMSM-*HR* 0.28, 95% CI: 0.13–0.62; GBMSM-*HR* 0.11, 95% CI: 0.06–0.19, respectively) and other treatments (EBMSM -*HR* 0.37, 95% CI: 0.19–0.72; WBMSM-*HR* 0.52, 95% CI: 0.26–0.99; GBMSM-*HR* 0.32, 95% CI: 0.16–0.63, respectively) had significantly reduced the risk of admission to the ICU. Older age excessively increased the transition rate for the same transitions.

In exponential and Weibull-bayesian multi-state models, the favipiravir-treated intubated inpatients had decreased risk of death; however, interestingly GBMSM results were not significant. Favipiravir treatment showed promising results for SARS-CoV-2 in the literature and the same results are observed in our univariate study (Coomes and Haghbayan, 2020).

An expected result was that female inpatients and hydroxychloroquine||chloroquine treated inpatients had no significant association with transition to another state in the univariate models. Another interesting result was that SARS-CoV-2-Positive inpatients in ICU treated with plaquenil had decreased the risk of being intubated (EBMSM -*HR* 0.41, 95% CI: 0.17–0.97; WBMSM-*HR* 0.32, 95% CI: 0.20–0.84; GBMSM-*HR* 0.35, 95% CI: 0.15–0.84, respectively).

When considering the recovery transitions, older age was associated with a reduction in transitions from SARS-CoV-2-Positive to SARS-CoV-2-Negative. Favipiravir (just in EBMSM), plaquenil, and other treatments reduced the transition rate from SARS-CoV-2-Positive in ICU to SARS-CoV-2-Negative; and also favipiravir (just in EBMSM) and plaquenil reduced the transition rate from SARS-CoV-2-Positive intubated to SARS-CoV-2 -Negative. According to the DIC criteria of the univariate models, the lowest DIC was derivated from the Weibull Bayesian multi-state models.

Figure 3 demonstrates the hazard ratio for baseline risk factors and antiviral treatment in each of the 9 transitions in the multivariate multi-state models

In the multivariate multi-state models, there was an association between azitro||azax and plaquenil-

Transitions	Model	Covariates $mean\ estimates\ HRs^{a,b,c}$ $(95\%\ Credible\ Interval)^{a,b,c}$						
		Gender **Female**	**Age** **≥59**	**Favipiravir** **Treatment**	**Azitro||Azax** **Treatment**	**Plaquenil** **Treatment**	**Hydroxychloroquine||** **Chloroquine** **Treatment**	**Other** **Treatment**
0 → 1	a	0.870	0.500	0.789	1.503	1.586	1.074	1.011
		(0.473, 1.60)	(0.210, 1.191)	(0.336, 1.851)	(0.629, 3.593)	(0.668, 3.765)	(0.496, 2.33)	(0.538, 1.899)
	b	0.914	0.665	0.848	1.235	1.245	0.982	0.962
		(0.431, 1.934)	(0.355, 1.242)	(0.319, 2.255)	(0.641, 2.381)	(0.606, 2.559)	(0.288, 3.341)	(0.513, 1.802)
	c	0.909	0.615	0.873	1.084	1.651	0.976	0.991
		(0.424, 1.949)	(0.328, 1.153)	(0.317, 2.402)	(0.455, 2.577)	(0.659, 4.134)	(0.275, 3.462)	(0.511, 1.946)
1 → 2	a	1.521	17.440	0.997	0.170	0.113	0.780	0.373
		(0.764, 3.03)	(7.691, 39.546)	(0.431, 3.307)	(0.064, 0.447)	(0.062, 0.207)	(0.277, 2.19)	(0.191, 0.728)
	b	1.225	6.851	0.934	0.288	0.288	0.476	0.515
		(0.618, 2.427)	(2.321, 20.213)	(0.476, 2.476)	(0.098, 0.414)	(0.134, 0.618)	(0.161, 1.408)	(0.263, 0.991)
	c	1.226	7.947	1.514	0.323	0.107	0.478	0.321
		(0.614, 2.448)	(2.843, 22.221)	(0.658, 3.478)	(0.107, 0.979)	(0.059, 0.192)	(0.161, 1.420)	(0.163, 0.634)
1 → 4	a	1.058	1.354	0.977	0.750	0.897	0.816	0.889
		(0.007, 15.96)	(0.006, 28.32)	(0.00, 24.94)	(0.005, 9.592)	(0.00, 8.158)	(0.002, 26.94)	(0.007, 14.411)
	b	1.036	1.238	0.931	0.837	0.931	0.865	0.911
		(0.037, 2.863)	(0.012, 1.408)	(0.003, 2.285)	(0.014, 4.917)	(0.030, 2.845)	(0.013, 5.401)	(0.035, 2.375)
	c	1.041	1.249	0.940	0.847	0.904	0.863	0.848
		(0.035, 3.076)	(0.006, 2.289)	(0.001, 5.277)	(0.020, 3.579)	(0.000, 9.898)	(0.013, 5.728)	(0.01, 1.181)
2 → 3	a	1.028	1.471	0.695	0.700	0.405	0.729	1.912
		(0.466, 2.269)	(0.528, 4.095)	(0.286, 1.689)	(0.236, 2.075)	(0.168, 0.973)	(0.137, 3.86)	(0.857, 4.265)
	b	1.002	1.111	1.271	0.791	0.317	0.772	1.801
		(0.460, 2.181)	(0.392, 3.143)	(0.493, 3.377)	(0.277, 2.259)	(0.197, 0.837)	(0.122, 1.486)	(0.802, 2.042)
	c	0.993	1.087	1.245	0.786	0.352	0.772	1.853
		(0.456, 2.160)	(0.384, 3.067)	(0.482, 3.210)	(0.264, 2.338)	(0.148, 0.838)	(0.127, 4.672)	(0.825, 4.162)
2 → 4	a	1.237	0.883	0.403	1.230	1.63	0.845	1.049
		(0.056, 26.96)	(0.014, 5.550)	(0.003, 5.131)	(0.007, 2.038)	(0.040, 6.644)	(0.021, 33.93)	(0.050, 21.799)
	b	1.092	0.933	0.586	1.151	1.147	0.981	1.002
		(0.172, 6.925)	(0.070, 1.243)	(0.050, 2.804)	(0.064, 2.057)	(0.095, 2.380)	(0.072, 1.330)	(0.103, 1.976)
	c	1.077	0.925	0.586	1.096	2.836	0.984	1.247
		(0.168, 6.905)	(0.052, 1.659)	(0.048, 7.117)	(0.087, 3.706)	(0.060, 3.349)	(0.072, 2.350)	(0.015, 2.057)
3 → 4	a	1.208	2.799	0.457	1.699	0.501	0.905	1.048
		(0.521, 2.799)	(1.072, 7.308)	(0.212, 0.988)	(0.594, 4.861)	(0.213, 1.178)	(0.086, 9.47)	(0.426, 2.582)
	b	1.027	1.622	0.555	1.459	0.977	0.811	1.165
		(0.458, 2.303)	(0.602, 4.374)	(0.315, 0.820)	(0.474, 2.493)	(0.381, 2.095)	(0.057, 1.114)	(0.432, 1.314)
	c	1.037	1.797	0.834	1.177	0.478	0.813	0.907
		(0.468, 2.301)	(0.659, 4.896)	(0.317, 2.191)	(0.382, 3.628)	(0.209, 1.089)	(0.060, 1.987)	(0.377, 2.197)
1 → 0	a	0.836	0.389	0.609	1.710	1.711	1.155	1.001
		(0.444, 1.572)	(0.159, 0.948)	(0.250, 1.483)	(0.706, 4.143)	(0.712, 4.115)	(0.519, 2.57)	(0.521, 1.922)
	b	0.882	0.511	0.704	1.342	1.286	1.032	0.955
		(0.407, 1.908)	(0.265, 0.987)	(0.253, 1.964)	(0.684, 1.263)	(0.615, 2.268)	(0.296, 3.601)	(0.498, 1.831)
	c	0.861	0.493	0.724	1.199	1.825	1.045	0.997
		(0.392, 1.887)	(0.255, 0.951)	(0.251, 2.086)	(0.495, 2.909)	(0.659, 4.134)	(0.287, 3.797)	(0.511, 1.945)
2 → 0	a	1.446	2.452	0.217	0.664	0.061	2.892	0.214
		(0.636, 3.285)	(0.634, 9.469)	(0.059, 0.796)	(0.186, 2.360)	(0.010, 0.357)	(1.122, 7.45)	(0.083, 0.551)
	b	1.418	0.867	0.362	1.113	0.386	2.245	0.348
		(0.513, 2.537)	(0.209, 3.586)	(0.115, 1.142)	(0.301, 1.410)	(0.105, 1.412)	(0.865, 4.584)	(0.142, 0.856)
	c	1.145	0.992	0.353	1.315	0.035	2.216	0.166
		(0.511, 2.563)	(0.246, 3.996)	(0.108, 1.154)	(0.375, 4.602)	(0.004, 0.315)	(0.852, 5.763)	(0.060, 0.456)
3 → 0	a	1.396	7.346	0.084	0.210	0.056	6.104	0.537
		(0.411, 4.732)	(1.906, 28.304)	(0.018, 0.386)	(0.023, 1.881)	(0.018, 0.171)	(1.401, 26.58)	(0.159, 1.808)
	b	1.122	1.993	0.367	0.580	0.416	1.614	0.676
		(0.331, 3.810)	(0.541, 7.339)	(0.068, 1.977)	(0.108, 1.107)	(0.063, 0.731)	(0.021, 3.364)	(0.195, 1.235)
	c	1.126	2.521	0.353	0.765	0.046	1.595	0.456
		(0.327, 3.876)	(0.699, 9.085)	(0.064, 1.950)	(0.157, 3.730)	(0.014, 0.765)	(0.025, 3.781)	(0.139, 1.489)
-2Log-likelihood	a	1705.239	1650.527	1673.928	1684.143	1677.912	1693.88	1694.377
DIC		3446.478	3337.053	3383.857	3404.286	3491.823	3423.76	3424.75
-2Log-likelihood	b	1705.143	1650.172	1673.521	1683.242	1677.521	1693.8	1694.312
DIC		3446.287	3336.344	3446.287	3402.483	3402.483	3423.01	3424.24
-2Log-likelihood	c	1707.178	1652.41	1673.754	1685.876	1679.393	1695.781	1696.438
DIC		3450.357	3340.821	3383.509	3407.752	3394.786	3427.562	3428.875

Table 4. Results of univariate Bayesian multi-state models across transitions (a: Exponential- Bayesian multi-state model (EBMSM), b:Weibull-Bayesian multi-state model (WBMSM), c:gamma-Bayesian multi-state model(GBMSM).

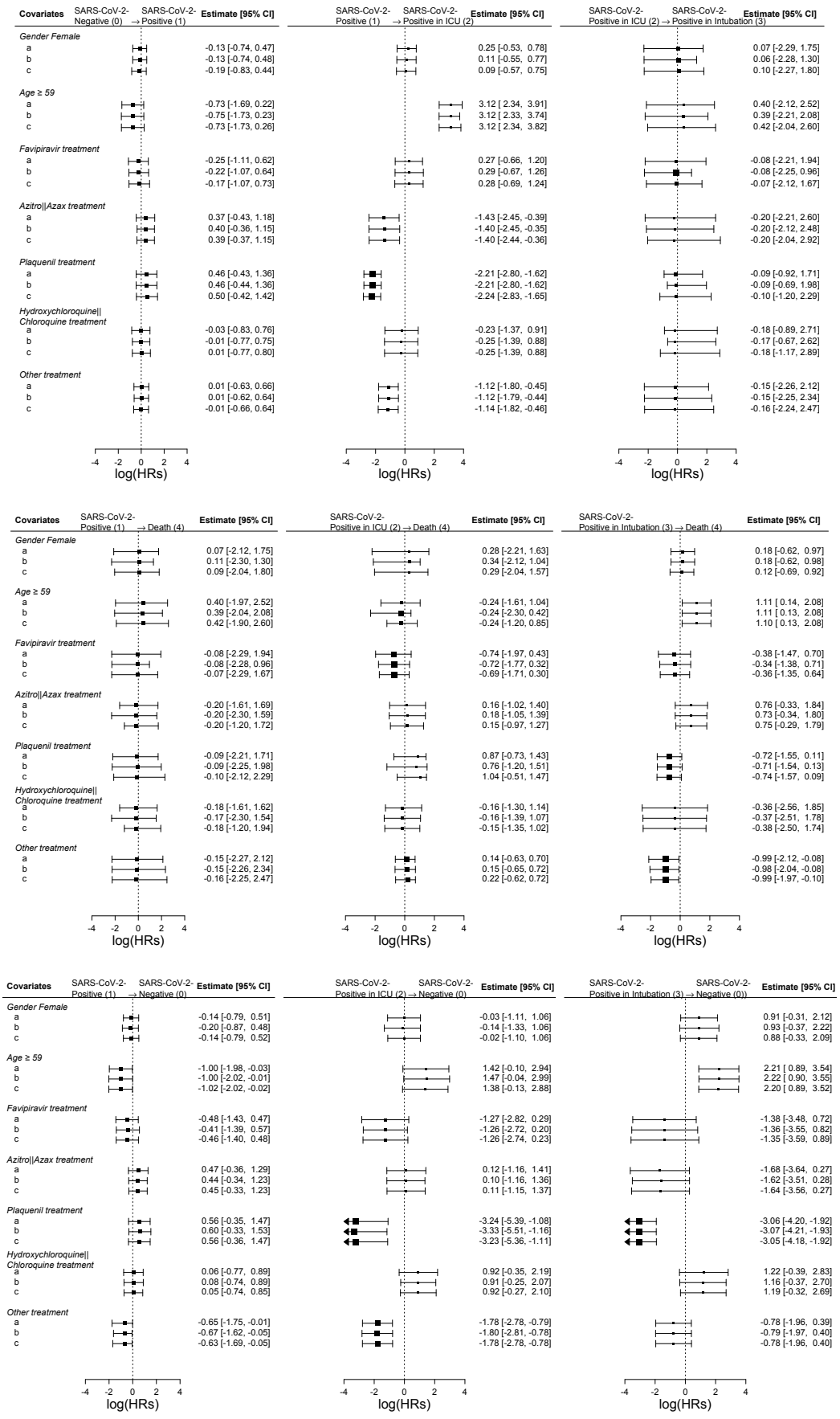

Fig. 3. Results of multivariate Bayesian multi-state models across transitions (a: Exponential- Bayesian multi-state model (EBMSM), b:Weibull-Bayesian multi-state model (WBMSM), c:gamma-Bayesian multi-state model(GBMSM).

treated older inpatients and the transition from SARS-CoV-2-Positive to SARS-CoV-2-Positive in ICU; both treatments significantly reduced the risk of being in the ICU but age increased the risk. In all multivariate Bayesian multi-state models, there was an association between older inpatients with other treatments and the transition from SARS-CoV-2-Positive intubated to Death; other treatments reduced the risk of death in older inpatients. In the recovery transitions, older inpatients with other treatments had increased transitions rate from SARS-CoV-2-Positive to Negative; however, the transitions rate decreased because of age. The multivariate Weibull bayesian multi-state model had the lowest DIC compared to the other models (EBMSM *-2Log-likelihood* 1644.631, *DIC*: 3361.262; WBMSM-*2Log-likelihood* 1648.318, *DIC*: 3350.637; GBMSM-*2Log-likelihood* 1649.858, *DIC*: 3353.716, respectively).

Hydroxychloroquine||chloroquine treatments were statistically significant in the multivariate and univariate models in many studies but both worst and best scenarios for inpatients (Elavarasi *et al.*, 2020; Lahouati *et al.*, 2020; Ursino *et al.*, 2021). In our study in both univariate and multivariate cases there were no associations between hydroxychloroquine||chloroquine and any transitions.

Considering the Cox proportional hazard model, the results showed that favipiravir (in both univariate and multivariate cases) and other treatments (in univariate cases) increased the risk of death, but the results reversed considering the multi-state modeling. In this kind of pandemic, evaluating each transition is valuable with multi-state models. The comprehensive statistical models used enabled us to derive clinically meaningful results that would not have been attainable using less complex methods.

4. Conclusion

The study was based on data obtained from a single-center city and possible unobservable confounders. A limitation of study is the unobservable transitions in the model. By making different assumptions about the baseline hazard function, several proportional hazard models can be created. Generally, in the literature of the proportional hazard model baseline hazard function is defined as the exponential family. The reason for that; assuming the baseline hazard is constant, the risk is doubled or tripled, which causes the new risk to be constant even though it is high over time. Furthermore, it can be useful to model monotonic upward or downward trends over time with Weibull and Gompertz, which include the properties of the exponential family as a special case.

In the literature of example of baseline function, the gamma-distributed baseline hazard function was used to analysis of cancer trajectories of palliative care patients for the Bayesian joint model (Lesperance *et al.*, 2015). For the different states, Weibull and piecewise- exponential-distributed baseline hazard functions were taken to model the outcome of the surgery and radiotherapy in Prostate Cancer (Beesley *et al.*, 2019). A piecewise Weibull baseline hazard function was used to model the animal survival data (Casellas, 2007). In order not to spoil the general framework, one special case, and two exponential family distributions were taken in Bayesian multi-state models.

The results showed that the estimated marginal posterior distributions substantially covered the true values of parameters in the simulation data. The true values of the parameter were defined as:
$\beta_{0\to1} = \left[0.9, 0.7, 0.8, 1.1, 1.6, 1.0, 1.0\right]$, $\beta_{1\to2} = \left[1.2, 6.9, 1.0, 0.3, 0.2, 0.5, 0.5\right]$,
$\beta_{1\to4} = \left[1.0, 1.2, 0.9, 0.8, 0.9, 0.9, 0.9\right]$, $\beta_{2\to3} = \left[1.0, 1.1, 1.2, 0.8, 0.4, 0.8, 1.9\right]$,
$\beta_{2\to4} = \left[1.1, 0.9, 0.6, 1.1, 1.1, 1.0, 1.0\right]$, $\beta_{3\to4} = \left[1.0, 1.6, 0.5, 1.5, 1.0, 0.8, 1.1\right]$,
$\beta_{1\to0} = \left[0.9, 0.5, 0.7, 1.3, 1.3, 1.0, 1.0\right]$, $\beta_{2\to0} = \left[1.4, 0.9, 0.3, 1.1, 0.3, 2.3, 0.3\right]$,
$\beta_{3\to0} = \left[1.1, 2.0, 0.3, 0.5, 0.4, 1.6, 0.5\right]$.

In this study, statistical testing was confined to the evaluation of HR posterior means estimates and 95% CIs for all Bayesian multi-state model fits. The Weibull-Bayesian multi-state model was more consistent based on the results in the literature, and the DIC was the lowest. In Bayesian models, 95% confidence intervals had more accurate and consistent results.

The baseline hazards functions are important because of represent the hazard when all risk factors and antiviral treatments are equal to zero. In this study, it was concluded that SARS-CoV-2 time-to-event data were more in consistent with the Weibull distribution. It is known that a Weibull baseline hazard function is restricted to monotonous behavior. This shows that without risk factors and antiviral treatments, the hazard of SARS-CoV-2 inpatients has a monotonically increase, decrease, or constant

trend over time.

Observation of the time-dependent conditions of SARS-CoV-2 inpatients is important in identifying risk factors and antiviral treatment methods.When compared to estimation based on the Cox proportional hazard model applied to overall survival data, the intervals calculated using Bayesian multi-state estimations tend to be narrower and it can reveal situations that may be misleading with antiviral treatment and risk factors. In the models were observed that the simultaneous use of antiviral treatments does not create a very good situation and that even single-use antiviral treatment has different effects in each state. The chance to observe that the situation would differ even in distributions with different but similar structures was shown. In addition, it was also investigated whether the distribution of the baseline risk can be differentiated through the disease progresses.

This study also demonstrates the benefits of Bayesian multi-state modeling in identifying risk factors and antiviral treatments related to SARS-CoV-2.The simultaneous and single-use effects of antiviral treatments on the states in the progress of the disease will make a serious contribution to the literature. By the distribution information in this study, it is thought that it will help to take other than non-informative priors. Thus researchers who want to model using SARS-CoV-2 patient data using Bayesian approaches will be given different perspectives.

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