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RESEARCH ARTICLE

Multistate modeling for estimating clinical outcomes of COVID-19 patients

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Abstract

The severity of COVID-19 is often associated with severe pneumonia requiring intensive care unit (ICU) without ventilation and ICU with ventilation. Clinical outcomes depend on the length of the ICU and the duration of the states. It is difficult to estimate how many people will experience each of these outcomes (discharge, death) due to the time dependence of the data and the potential for multiple events. Because of their time dependence, potential multiple events, and competing, terminal events of discharge, alive and death, estimating these quantities statistically is challenging. The main objective of this paper is to study the time-dependent progress of COVID-19 patients through the multistate approach with hazard rates and transition probabilities. The methodology allows for the analysis of active instances by accommodating censoring and the probability plots offer comprehensive information in a straightforward manner that can be easily shared with decision-makers in healthcare capacity planning.

Keywords: Multistate model, TPM, Stacked Probability plot, Competing risks, Intensive care unit, COVID-19.

Introduction

Critically ill patients frequently require intensive care unit (ICU) care and complex management, which has put a strain on healthcare systems around the world as a result of the COVID-19 pandemic. However, the disease course of COVID-19 is complex and patients frequently move between different clinical states over time which makes it difficult to analyze and predict outcomes. To date, there have been limited studies on the long-term clinical outcomes of COVID-19 patients who have survived ICU admission. There is a growing interest in the use of a multistate model to analyze the time-dependent progression of COVID-19 patients.

In a joint analysis employing a multistate approach, several steps are involved. These steps encompass defining the desired states, specifying transition probabilities, and estimating model parameters using statistical methods. The estimated model can then be used to make predictions and evaluate interventions. A Markov model is a method commonly employed for conducting such analyses. It operates on the assumption that the transition probability solely relies on the current state, independent of the past. This allows for a simplified and efficient analysis of the data. Multistate modeling is a promising statistical technique that can provide valuable insights into the disease course and clinical outcome of a patient by modeling transitions through multiple clinical states over time.

This approach considers that patients can move between different clinical states over time and these transitions can be modeled and analyzed through the estimation of hazard rate and transition probabilities. This information can provide valuable insight into the time-dependent progression of patients and can be used to predict the likelihood of transitioning to a specific clinical state.

Multistate models have found applications in various fields which include health research, epidemiology, and social sciences. They enable the analysis of multiple outcomes simultaneously like disease diagnosis, treatment, and mortality which offer a flexible and powerful approach to handle complex data structures. Multistate models provide insight into the dynamics of different outcomes over time which leads to a more comprehensive understanding of the system under study. They can answer various research questions such as assessing the effectiveness of an intervention, predicting the risk of a particular event or

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identifying factors that influence the transition between states. There is currently limited research on the multistate models to analyze the clinical course of critically ill COVID-19 patients. Previous studies have indicated that multistate models have the potential to predict clinical outcomes of critically ill patients which include those with COVID-19. Neumann, *et al.*, (2022) presented a multistate model which analyzed the healthcare transitions of older adults. They identified several potential risk factors for poor health outcomes and highlighted the importance of considering multiple health states when analyzing clinical trial data.

Another study by Önen Dumlu *et al.*, (2022) analyzed the optimal screening policies for preclinical Alzheimer's disease by a partially observable Markov model which allows the incorporation of multiple states of disease progression. The authors presented how the multistate approach allows different screening strategies to impact disease progression over time.

Zins, *et al.*, (2017) used a multistate model and compared the relationship between body mass index (BMI) and health between ages 50 and 75 and estimated the transitions between different states for the competing risks of morbidity and mortality. Wan, *et al.*, (2016) compared multi-state models and explored the advantages and limitations of different multistate modeling approaches and also discussed a comprehensive analysis of the performance of each model in capturing disease progression and transitions between different health states.

Lange *et al.* (2015) utilized a multistate model and performed a joint analysis of multistate disease processes, considering random informative observation times within electronic medical records data. Moghaddass *et al.* (2015) introduced a predictive analytics approach to analyze inspection data. They employed a nonhomogeneous semi-Markov model to investigate the transitions between different states. Alafchi, *et al.*, (2021) analysed multivariate longitudinal and multistate in renal transplantation data through simulation studies and a real data analysis. Eleuteri, *et al.*, (2018) evaluated the effectiveness of different treatment strategies for preventing metastatic death using transition probabilities between different health states. Woods *et al.* (2018) conducted estimations regarding the long-term survival and cost-effectiveness associated with the incorporation of docetaxel into long-term hormone therapy for patients with prostate cancer and incorporated different health states and transitions using a multistate model and simulated the outcomes of different treatment options over time. Kasajima *et al.* (2021) utilized a multistate transition model to project the future health and functional status of older individuals. They estimated the probabilities of transitioning between different health states. Sutradhar and Barbera (2021) explored the progression of reported cancer symptoms in individuals using multistate models. Their findings suggested that other than traditional methods the approach provides more accurate estimates of symptom progression. Pawlowski (2021) examined a large multi-state health system to explore the potential connection between cerebral venous sinus thrombosis (CVST) and COVID-19 vaccines, as well as non-COVID vaccines. The study aimed to investigate any possible association between these vaccines and CVST. Stewart, *et al.*, (2021) analyzed the impact of healthcare-associated infections (HAIs) on length of hospital stay using a multistate model which allowed for the modeling of transitions between different health states accounting for the competing risks of HAI, hospitalization, and discharge.

Chaou, *et al.*, (2020) examined the dynamic flow of emergency patient management with a multistate model. Their study provided insights into the length of stay of patients and the time spent in different stages of ED management. Cranmer, *et al.*, (2020) compared survival analysis and multi-state approach to analyse oncology data. The authors found that multi-state modeling provides additional insights into the disease progression and highlighted the potential benefits of using multi-state modeling in oncology research. Brumm, *et al.*, (2020) found that patients with sickle cell disease had higher odds of morbidity and readmissions as well as longer hospital stays and higher hospitalization costs. Lorenti, *et al.*, (2020) estimated the probabilities of transitioning between states of work, disability and death by using a multistate life table model. Zhang, *et al.*, (2020) analyzed interval-censored event-history data for neurocysticercosis research using a multistate model. Their approach allowed for the modeling of transitions between different disease states. Vermuntt, *et al.*, (2019) estimated the duration of the various clinical stages using a multistate model and discussed the importance of considering multiple stages in disease modeling. Jawad, *et al.*, (2019) analyzed the outcomes of different types of hip arthroplasty for hip fractures, including transitions between different states such as in-hospital mortality, discharge to rehabilitation, and readmission using a multistate model. Bluhmki, *et al.*, (2019) used a multistate methodology to improve risk assessment under time-varying drug intake for pregnancy outcomes and made a clear understanding of the risks and transitions between different health states over time. Wang, *et al.*, (2019) estimated disease progression among individuals with human immunodeficiency virus (HIV) using a multistate modeling approach and provided a comprehensive understanding of the complex dynamics of HIV treatment and disease progression over time. Farewell, *et al.*, (2019) analyzed a prolonged disease state using multistate modeling and estimated the probabilities of disease progression, and recovery as well as the associated time to each event. Tapak, *et al.*, (2018) analyzed time-to-event data on acquired immune deficiency syndrome (AIDS) and mortality post-HIV infection and identified prognostic factors and developed predictive models for survival outcomes by using multistate recursively imputed survival trees. Leva, *et al.*, (2017) analyzed patients with heart failure and allowed for the modeling of transitions between different health states for the competing risks of states by using a multistate model.

Stephens-Shields, *et al.*, (2017) investigated the transitions between different CKD states. They used a multistate model and analyzed the relationship between blood pressure (BP) and chronic kidney disease. Mitchell, *et al.*, (2016) applied a multistate model and analyzed the relationship between length of stay, mortality and healthcare-associated urinary tract infections also investigated the competing risks of hospitalization and mortality.

Piccarreta & Studer (2019) discussed the methodological challenges in the holistic analysis of the life course using a multistate model which allows to the modeling of transitions between different life course states. Martinot, *et al.*, (2018) have incorporated time-dependent covariates and transitions between different health states to assess the effect of PIM on frailty over time. Longué, *et al.*, (2018) analyzed treatment administration and toxicity associated with targeted therapies by using a multistate model which allows for a more comprehensive understanding and risks of the treatment. Cnudde, *et al.*, (2018) investigated the risk of surgery and mortality, also estimated the multiple possible health states and transitions over time by using multistate analysis. The motivation for using a multistate model in this work is to develop a comprehensive and accurate approach to estimate the clinical outcomes of critically ill COVID-19 patients. This model has the potential to offer a more precise forecast of patient outcomes which can assist healthcare professionals in making informed clinical decisions and allocate resources efficiently. The aim of this study is to estimate the time-dependent probabilities of transition between different health states and evaluate the hazard rates associated with COVID-19 patient clinical outcomes using multistate models and examine the transitions between different clinical states including ICU admission, ventilation, and impact of these transitions on patient outcomes including mortality, hospital length of stay, and functional status at ICU discharge. This study will build upon the existing literature on multistate modeling and also provide a comprehensive analysis of the clinical outcomes of COVID-19 patients. The insights gained from this study could also help in the development of predictive models to identify patients at high risk of adverse outcomes and target interventions to improve patient outcomes. This study provides a more accurate and comprehensive analysis of the disease and clinical outcomes of critically ill COVID-19 patients, building upon the promising results of previous studies in this area.

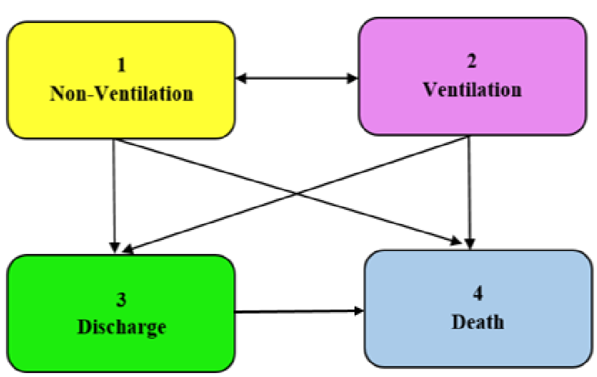

Figure 1: Multistate model

Methodology

A multistate model consists of boxes representing different states and arrows representing transitions between them. This model typically includes two types of states: initial or transient states from which individuals can enter and exit and absorbing states from which individuals cannot exit once they enter.

Multistate Markov models are used to estimate various parameter such as transition probabilities, sojourn times, and transition hazards for each state and transition between states. These models are useful for analysing complex event data and can provide insights into the probability and timing of transition between different states (Figure 1). This model has three initial states: State 1 represents patients in the ICU without ventilation (Non-Ventilation), state 2 represents patients in the ICU with ventilation (Ventilation) and state 3 represents the patients who are discharged alive from the ICU. Patients can enter the study in either of these three initial states and these states are referred to as transient states. The multistate model used to study the ICU stays in diseased patients include absorbing state: State 4 where patients die from the ICU or even after patient discharged (Death). Once patients enter an absorbing state there are no more transitions for them that is, they can no longer move to any other state. Depend on the patient health status they may receive ventilation be discharged alive or die while in state 1 (Non-Ventilation). Similarly, patients in state 2 (Ventilation) may also be discharged alive or die while receiving ventilation. Patients can transition back and forth between states 1 and 2 (ventilation and Non-ventilation) multiple times during their ICU stay.

The patient ICU stay can be described using a time homogeneous Markov chain {X(t), t} with a finite state space S={1,2,3,4} and follow-up time denoted as τ. This chain is used to model the patient transitions between the different states (1, 2, 3 or 4) at different points in time during their stay in the ICU. In the context of a multi-state model X(t) refers to the time at which a patient occupies a certain state during their stay in the ICU. The model begins by defining the probabilities of transitioning between the different states (i.e., ICU, mortality and discharge probabilities) which allows for the calculation of the likelihood of a patient moving from one state to another at any given point in time.

Transition probabilities can be used to represent the likelihood of transitions from one state (l) to another state (m) during the ICU stay in a Markov Multi-state model which is represented as

$P_{lm}(s,t)$ = P(X(t) = m| X(s) = l),

with l,m ϵ s, l≠m and 0≤s<t≤ τ.

The expression P(X(t) = m| X(s) = l) represents the probability that a patient will transition from state l to state m during their stay in the ICU given that they were in state l at time s and in state 'm' at the time 't'. Therefore, $P_{lm}(s,t)$ provide the likelihood of a patient moving from state l to state m within a specific period. The Markov property state that this probability only depends on the current time 's' and the state occupied at that time and not on any past events. This transition probability is calculated based on the observed number of i→j transitions at time t divided by the number of individuals who were at risk in state i just before time t. If state i represents the non-ventilated state and state j represents the ventilated state then Âij(t) would indicate the likelihood of transitioning from the non-ventilated to the ventilated state at time t. By estimating these transition probabilities, the study provides insights into the clinical outcomes of critically ill COVID-19 patients in the ICU and identifies potential risk factors that may influence transitions between different states. By estimating these transition probabilities, the study provides insights into the clinical course and outcome of critically ill COVID-19 patients in the ICU and identifies potential risk factors that may influence transitions between different states.

Multistate Markov Model

After being admitted to the hospital following COVID-19, a patient traverses the discrete state space S= {1, 2, 3, 4}. Let X(t)=r represents the patient's state at any given time t. The intensity, denoted as λ_{rs}(t), describes the rate at which the patient transitions to state S during the interval (t, t+Δt). Formally, it is defined as:

λ_{rs}(t) = $\lim_{\Delta t \to 0} \frac{P(X(t+\Delta t) = s \,/\, X(t) = r)}{\Delta t}$ r,s = 1,2,…,4

where r and s belong to the set {1, 2, 3, 4}

The underlying assumption here is that the multistate model is Markovian, implying that the likelihood of transitioning to a future state relies solely on the present state and not on the historical states. The transition intensity matrix, denoted as Q=$[q_{rs}]_{4\times4}$, possesses the following characteristics:

(i) $\sum s \in S\ \lambda_{rs} = 0$ for all r, indicating that the sum of intensities for all transitions from state r to any other state is equal to zero. (ii) λ_{rr}=-$\sum r \neq s\,\lambda_{rs}$. signifying that the intensity of transitioning from state r back to itself (autotransition) is the negative sum of intensities for transitioning to other states from state r. The estimation of transition intensities can be achieved using maximum likelihood estimation procedures. By utilizing the estimated transition intensities, one can calculate the transition probability matrix P(t) = $[P_{rs}(t)]_{4\times4}$, wherein where P_{rs}(t) represents the probability of a COVID-19 patient being in state *S* at time *(t+u)*, given that the patient was in state *r* at time *t*.

$P_{rs}(t)$ = P(X(t+u) = s / X(t) = r)

The transition probability matrix, expressed in terms of the intensity matrix, is acquired as P(t) = e^{tQ} .

Mean Sojourn Time and Total Length of Stay

The mean sojourn time represents the average duration of a single stay in each transient state before transitioning to any other state. This can be estimated by taking the reciprocal of the diagonal entry -1/q_{rr} in the estimated transition intensity matrix. In other words, the mean sojourn time is estimated as by -1/q_{rr} where q_{rr} corresponds to the intensity of transition to the same state r. Additionally, it is of interest to estimate the total length of stay in each transient state, as discussed in the work by Grover *et al.* (2013).

Results and Discussion

Data was gathered from hospital-based records of patients who were admitted for COVID-19 treatment. The dataset comprises 68 critically ill individuals who required admission to the ICU. The patient data were obtained during a follow-up period of one month. The states of the dataset represent the different clinical states or conditions that a patient can be in during the course of the disease or treatment. These states are often defined based on specific clinical criteria such as state 0 being denoted as censored, state 1 being denoted as ICU without Ventilation, state 2 being denoted as ICU with Ventilation, state 3 being denoted as discharge and state 4 being denoted as death. The dataset includes individual patient information such as the length of time they were on ventilation and their outcome (whether they were discharged alive or died).

Table 1 shows the number of transitions that occurred among COVID-19 patients in different states (ventilation, non-ventilation, discharged, or deceased) over the course of their treatment. This table provides information on the movement of patients between different treatment states

Table 1: Transitions counts matrix for COVID-19 patients

	Censored	*Ventilation*	*Non-ventilation*	*Discharge*	*Death*	*Total*
Ventilation	6	0	12	7	23	48
Non-Ventilation	8	14	0	13	16	51
Discharge	0	8	14	0	5	27
Total	14	22	26	20	44	126

Table 2: Transitions probability matrix for COVID-19 patients

	Ventilation	*Non-ventilation*	*Discharge*	*Death*
Ventilation	0.0000000	0.2857143	0.1666667	0.5476190
Non-ventilation	0.3255814	0.0000000	0.3023256	0.3720930
Discharge	0.2962963	0.5185185	0.0000000	0.1851852
Death	0.0000000	0.0000000	0.0000000	1.0000000

and their outcomes. The starting state of the patient is depicted by the rows, while the ending state is represented by the columns. The cells of the table indicate the number of patients who transitioned from the starting state to the ending state. A total of 14 patients in the "Censored" state which means they were lost to follow-up. 6 patients who were initially on ventilation were removed from ventilation and moved to non-ventilation, while 12 patients who were initially in non-ventilation required ventilation during their treatment. There were 22 patients who ended up on ventilation at some point during their treatment, and 44 patients in total died during the course of the study.

Table 2 shows the transition probabilities between different states (ventilation, non-ventilation, discharge, and death) for COVID-19 patients. The cells of the table indicate the probability of a patient transitioning from the starting state to the ending state. The sum of the probabilities of transitioning to ventilation, non-ventilation, discharge, and death is 1, which means that all patients who started in the ventilation state eventually transitioned to one of these four states. The probability for a patient to moves from a ventilation state to a non-ventilation state is 0.2857143, which means that approximately 28.6% of patients on ventilation transitioned to non-ventilation during their treatment. The probability of transitioning from ventilation to discharge is 0.1666667, which means that approximately 16.7% of patients on ventilation are discharged, and the probability of transitioning from ventilation to death is 0.5476190, which means that approximately 54.8% of patients on ventilation die.

The probability of transitioning from non-ventilation to discharge is 0.3023256, which means that approximately 30.2% of patients not on ventilation are discharged, and the probability of transitioning from non-ventilation to death is 0.3720930, which means that approximately 37.2% of patients not on ventilation die. Overall, this table provides information on the likelihood of patients transitioning between different treatment states and outcomes, which could be useful for predicting the prognosis of COVID-19 patients and evaluating the effectiveness of different treatment strategies.

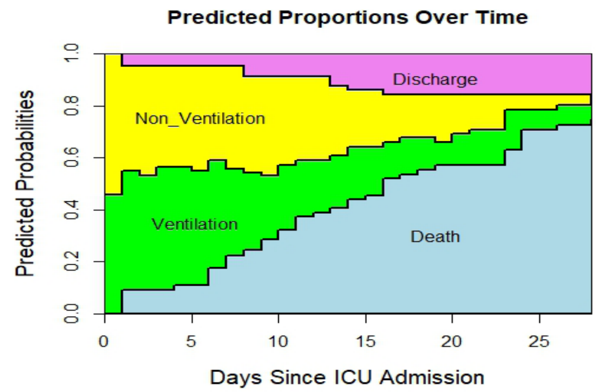

Figure 2: Stacked probability plot for the entire follow-up period

The cohort Figure 2 provides information on the expected duration of patient stays in different states. To visualize the predicted probabilities of each state over the entire follow-up period a stacked probability plot is used. This plot is generated by multiplying the transition matrix by the initial distribution and graphically represents the probability of each state at different time points. On the 21st day after admission to the ICU 25.5% of patients experienced mortality. Of the remaining patients 33.5% had already been discharged from the ICU while 26% did not require ventilation and 15% of patients were identified as needing ventilation. The predicted probabilities suggest that patients who stay in the ICU for a longer duration and require mechanical ventilation, especially for an extended period have a higher risk of mortality rate.

Table 3 displays the expected duration of stay and mortality of a group of 66 critically ill COVID-19 patients as observed during a 28-day follow-up period. The table provides information about the expected duration of stay for the patients in this cohort. Here if a patient did not require ventilation at the beginning of their ICU stay they would be expected to stay for about 13.97 days followed by an additional 3.43 days of ventilation. In total their ICU stay would last about 17.4 days and they would have a 42% risk of dying. If a patient starts non-ventilation at the beginning of their ICU stay they are expected to have a shorter duration of ventilation compared to those who did not require ventilation. Likewise, patients who begin at ventilation

Table 3: Estimated study of the expected time spent in the different states and mortality rate

	68 Critically ill COVID-19 patients results at the month end			
	Non-ventilation duration in days	*Ventilation duration in days*	*Total length of ICU stay in days*	*Death risk*
Start non-ventilation	10.19 (6.58, 14.06)	1.62 (0.30, 3.34)	11.81 (6.88, 17.4)	64% (7.5)
Start ventilation	3.57 (1.83, 5.78)	12.55 (9.44, 15.31)	19.33 (11.27, 21.09)	35% (6.7)
Full cohort	7.15 (3.18, 6.88)	6.63 (5.31, 9.86)	18.43 (8.49, 16.74)	39% (7.1)

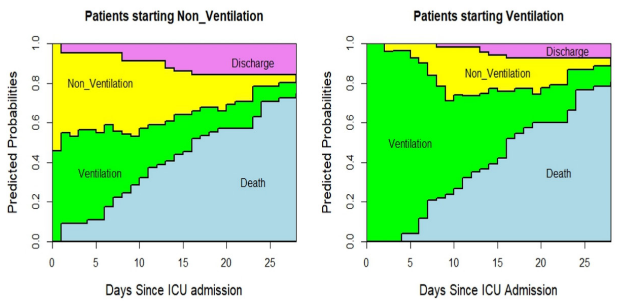

Figure 3: Stacked probability plot for non-ventilation and ventilation states

at the onset of their ICU stay are anticipated to require a longer duration of ventilation (14.05 days). These patients have a mortality rate of 58% (Confidence Intervals obtained via bootstrapping). Compared to patients who start Non-Ventilation at the beginning of their ICU stay patients who start ventilation have a higher risk of death.

The study created a stacked probability plot (Figure 3) using a multistate model which was divided based on how long the patient had been in the ICU since admission. This plot compared the clinical progress of patients who started in the two initial states non-ventilation and ventilation to illustrate the findings. The larger size of the sample enables us to make visual comparisons. According to the results on the 21st day of the 28th-day follow-up patients who started in non-ventilation had a greater likelihood of being discharged alive (30 vs 21%) and a lower chance of dying (26 vs 35.2%). Initially, Ventilation patients have a higher probability of dying which results in a shorter ICU duration while, non-ventilation patients have a higher probability of being discharged alive which also results in a shorter ICU duration. This suggests that there are differences in the ventilator needs between patients who are initially admitted without ventilation compared to those who require ventilation upon admission.

Conclusion

The findings revealed that adopting a multistate approach offers significant insights into the progression of COVID-19 patients, especially regarding metrics such as ventilation duration, length of ICU stay, and mortality within the 28-day follow-up period. The plots concisely provide extensive information and are easy to read. Comparisons were made among the clinical progression of the patients starting in ICU without ventilation and ICU with ventilation. The findings could inform clinical decision-making, and resource allocation and improve patient care for critically ill COVID-19 patients. The insights gained from this study could also help in the development of predictive models to identify patients at high risk of adverse outcomes and target interventions to improve patient outcomes. The study will build upon the existing literature on multistate modeling for COVID-19 patients and provide a comprehensive analysis of the disease and outcomes of critically ill COVID-19 patients.

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