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ORIGINAL RESEARCH

Risk Factors of Readmission in COVID-19 Patients; a Retrospective 6-Month Cohort Study

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Abstract: **Introduction:** The available literature regarding the rate of readmission of COVID-19 patients after discharge is rather scarce. Thus, the aim in the current study was to evaluate the readmission rate of COVID-19 patients and the components affecting it, including clinical symptoms and relevant laboratory findings. **Methods:** In this retrospective cohort study, COVID-19 patients who were discharged from Imam Hossein hospital, Tehran, Iran, were followed for six months. Data regarding their readmission status were collected through phone calls with COVID-19 patients or their relatives, as well as hospital registry systems. Eventually, the relationship between demographic and clinical characteristics and readmission rate was assessed. **Results:** 614 patients were entered to the present study (mean age 58.7±27.2 years; 51.5% male). 53 patients were readmitted (8.6%), of which 47 patients (7.6%) had a readmission during the first 30 days after discharge. The reasons for readmission were relapse of COVID-19 symptoms and its pulmonary complications in 40 patients (6.5%), COVID-19 related cardiovascular complications in eight patients (1.3%), and non-COVID-19 related causes in five patients (0.8%). Older age (OR=1.04; 95% CI: 1.01, 1.06; p=0.002) and increased mean arterial pressure during the first admission (OR=1.04; 95% CI: 1.01, 1.08; p=0.022) were found to be independent prognostic factors for the readmission of COVID-19 patients. **Conclusion:** Readmission is relatively frequent in COVID-19 patients. Lack of adequate hospital space may be the reason behind the early discharge of COVID-19 patients. Hence, to reduce readmission rate, extra care should be directed towards the discharge of older or hypertensive patients.

Keywords: Patient readmission; prognosis; follow-up studies; COVID-19

1. Introduction

Since December 2019 and the emergence of the "Severe Acute Respiratory Syndrome Coronavirus 2", a novel virus from the family of coronaviruses, in Wuhan, China, until January 29, 2021, more than 102 million people have been infected, worldwide, and over 2.2 million people have died due to the disease caused by it. World Health Organization (WHO) has named the disease COVID-19, and its pandemic

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continues to this day (1, 2). The most common organs involved in this disease are the lungs, and the most prevalent clinical signs are fever, cough, body aches, fatigue, and shortness of breath. However, signs of the involvement of other organs, such as neurological, cardiovascular and renal signs, have also been reported (3, 4). The incidence of severe clinical signs and the severe form of the disease is higher in older people and patients with an underlying disease, compared to other patients. Death is also more frequent in these people. Hypertension due to diabetes and cardiovascular diseases have been reported to be the most common underlying diseases corresponding to disease severity and mortality due to COVID-19 (5-8).

Considering the increasing number of COVID-19 patients, worldwide, the shortage in the number hospital beds and the crushing pressure on the health care systems are becoming a global crisis. In these circumstances, doctors may be prompted into early discharge of the patients, which could cause readmission of the discharged patients and eventually increase the pressure on the health care systems, even more. Moreover, several studies exist that have reported cases of readmission among COVID-19 patients (9, 10). On that account, knowing the exact probability of readmission due to COVID-19 and the factors affecting it would be of great importance in aiding patients' management and anticipating the treatment results. The most important reasons for readmission in COVID-19 patients are the reoccurrence of respiratory symptoms or the occurrence of non-pulmonary complications of COVID-19, such as cardiovascular, central nervous system, and renal complications. In this regard, few studies exist, reporting a readmission rate of two to 19 percent (11-14). This versatility in the reporting rates, in addition to the limited existing evidence, presents the need for further research in this field.

Since the probability of readmission due to COVID-19 in the current crisis situation should be assessed precisely, our aim in the present study is to investigate the rate of readmission in COVID-19 patients and the affecting factors, including clinical symptoms and related laboratory findings.

2. Methods

2.1. Study design and setting

The present study is a retrospective cohort study, conducted on patients admitted to Imam Hossein Hospital, Tehran, Iran, between February 18, 2020 and July 20, 2020. COVID-19 infection was confirmed based on RT-PCR test. The study protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (code: IR.SBMU.RETECH.REC.1399.680), and the researchers adhered to the principles of Helsinki declaration throughout the study.

2.2. Participants

In the present study, confirmed COVID-19 patients admitted to Imam Hossein hospital, who were recovered from the disease and discharged, were recruited. Exclusion criteria was insufficient clinical and laboratory data, patients' death during the first admission, and not being able to contact the patient after discharge.

2.3. Data gathering

In the present study, data from all COVID-19 patients, admitted to Imam Hossein hospital, were gathered through hospital registry databases. Then, mortality cases were eliminated. Next, based on their admission code and Iranian National Code, patients who were readmitted to Imam Hossein Hospital were identified. The data extracted from patients' records included demographic data, history of cardiovascular disease, history of other comorbidities, clinical symptoms at the time of admission, mean arterial pressure during their hospital stay, laboratory and imaging findings, and the patients' status at the time of discharge.

Later on, a nurse, familiar with the data collecting process, contacted all the included patients through phone call, to ask about the readmission cases in other hospitals. In cases of no answer, a second call was made within 24 hours. If no one answered, other phone numbers in the patient's hospital profile were reached. If again no one answered the call, another phone call was made, one week later, to minimize the missing data. It is worth to mention that the least follow up period was six months, whereas the longest follow up timeframe was nine months. Also, the assessed outcome in our study was readmission. In the assessment of the underlying causes of readmission (either from the patients' profile or phone call), the causes were divided into three groups: readmission due to the COVID-19 disease or respiratory complications, readmission due to cardiovascular complications, and readmission due to other causes. Readmission was defined as the rehospitalization of COVID-19 patients who had previously recovered from COVID-19 within 2 weeks after discharge (15).

2.4. Statistical analysis

All analyses were performed using SPSS 22.0 statistical program. Quantitative data were presented as mean and standard deviation (SD) or median and interquartile range, and qualitative data were reported as frequency and percentage. Patients were classified into two groups of readmission and non-readmission. Next, the relationship of demographic characteristics and clinical symptoms or laboratory findings with readmission was investigated. For the comparison of quantitative variables, t-test or Mann-Whitney equivalent was used. Also, for the comparison of qualitative variables, Chi-square or Fisher's exact tests were applied. Fur-
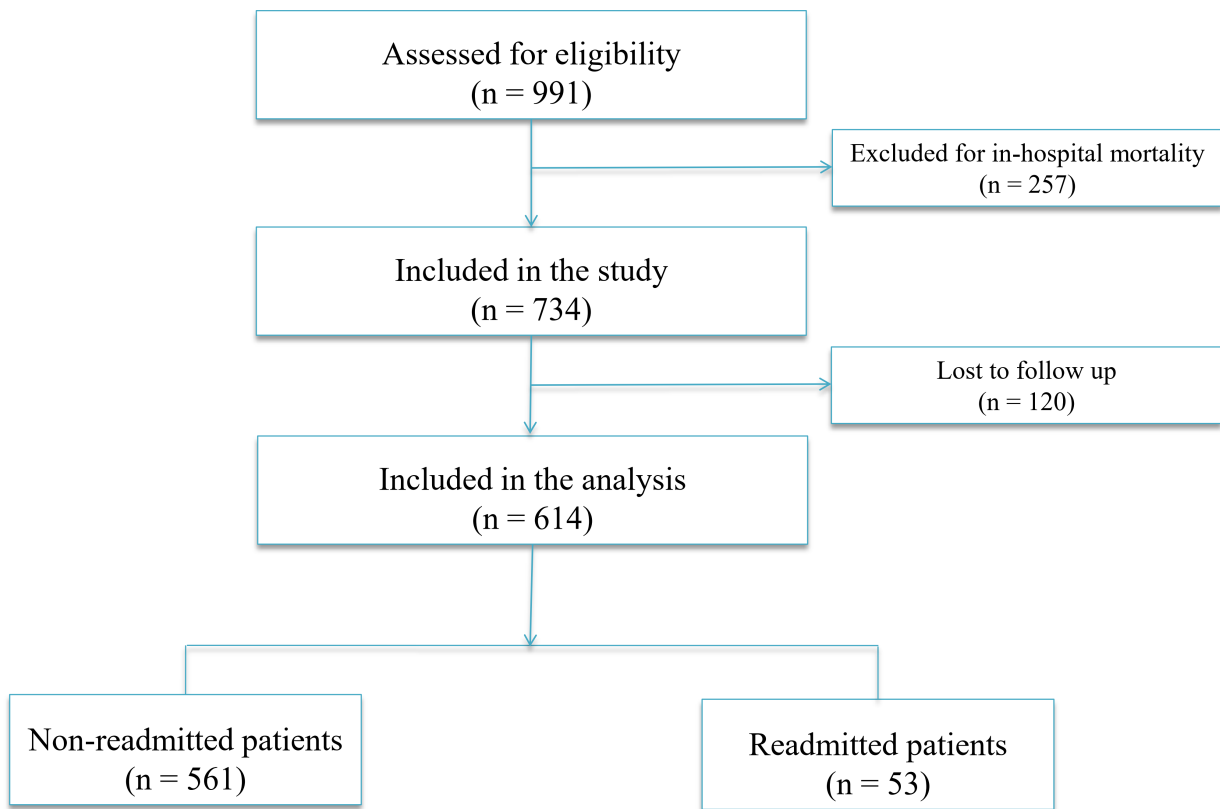
Figure 1: Flow diagram of the present study.

thermore, the relationship between the confounding factors was assessed fitting a stepwise multivariate logistic regression model to investigate the relationship between demographic variables, clinical symptoms or laboratory findings and readmission. In all analyses, a p value less than 0.05 was considered significant. The prevalence of readmission was 19.9% in the study with the longest follow up design, which was two months of follow up (11). Therefore, considering the 95% confidence interval (CI) and 5% error, the minimum required sample size was calculated to be 246 patients for the entire study.

3. Results

During the study period, data from 991 patients had become available. Of these, 257 patients died during their hospitalization and 734 patients were discharged. Throughout the follow up, 120 patients (16.3%) did not answer the phone call, so 614 patients entered the present study (Figure 1). The mean age of these patients was 58.7±27.2 years and 51.5% of them were male. Of these 614 patients, 53 patients were readmitted (8.6%), out of which 47 patients' readmission (7.6%) had occurred within the first 30 days following their discharge. The median time frame between discharge and

readmission was 6.5 days (with a range of 1 to 240 days). The reasons for readmission were relapse of COVID-19 symptoms and its pulmonary complications in 40 patients (6.5%), COVID-19 related cardiovascular complications in eight patients (1.3%), and non-COVID-19 related causes in five patients (0.8%) (Figure 2).

Univariate analyses showed that the mean age of the readmitted patients (66.6±16.5 years) was lower than the mean age of the non-readmitted group (57.9±16.5 years) (p<0.001). Also, possible prognostic factors for the readmission of COVID-19 patients in univariate analyses included a history of coronary artery diseases (p=0.013), mean arterial pressure during hospitalization (p=0.028), white blood cells count in the blood (p<0.001), lymphocyte count in the blood (p=0.004), neutrophil count in the blood (p=0.034), and the occurrence of cardiovascular accidents during hospitalization (p=0.041) (Table 1 and 2).

The multivariate logistic regression model depicted that older age (OR=1.04; 95% CI: 1.01, 1.06; p=0.002) and increased mean arterial pressure during the first hospitalization (OR=1.04; 95% CI: 1.01, 1.08; p=0.022) were independent prognostic factors for the readmission of COVID-19 patients (table 3).

Table 1: Baseline characteristics of COVID-19 patients based on readmission status

Variable	Readmitted		Total (n=614)	P
	No (n=561)	Yes (n=53)		
Age (year)	57.9±16.5	66.6±16.5	58.7±27.2	<0.001
Gender				
Female	272 (48.5)	26 (49.1)	298 (48.5)	0.937
Male	289 (51.5)	27 (50.9)	316 (51.5)	
BMI (kg/m2)	—-	26.92±6.0	27.2±4.9	
History of coronary artery disease				
No	408 (72.70)	30 (56.60)	438 (71.30)	0.013
Yes	153 (27.30)	23 (43.40)	176 (28.70)	
Length of stay	—-	7.0±8.1	7.4±5.5	0.055
Vital sign				
Body temperature	37.0 (36.8, 37.3)	37.0 (36.9, 37.3)	37.0 (36.8, 37.3)	0.351
Heart rate (beat/min)	83.3 (79.3, 89.0)	82.7 (78.8, 89.2)	83.3 (79.3, 89.0)	0.942
SpO2 (%)	91.7 (89.7, 94.0)	91.3 (88.7, 93.8)	91.7 (89.7, 94.0)	0.393
Respiratory rate (per min)	18.7 (17.3, 21.3)	19.3 (18.0, 22.7)	18.7 (17.7, 21.6)	0.104
Mean arterial pressure (mmHg)	86.7 (81.1, 91.1)	90.0 (82.2, 95.0)	86.7 (81.1, 91.1)	0.028
Laboratory				
PvO2 (mmHg)	29.0 (23.3, 39.7)	30.6 (22.7, 47.1)	29.2 (23.2, 40.1)	0.531
PvCO2 (mmHg)	42.2 (37.6, 46.4)	41.7 (35.6, 45.8)	42.1 (37.5, 46.3)	0.445
WBC count	6.5 (4.9, 8.6)	8.1 (6.1, 11.7)	6.6 (5.0, 8.8)	<0.001
Lymphocyte (%)	20.0 (13.1, 27.0)	16.0 (10.3, 21.4)	20.0 (13.0, 26.7)	0.004
Neutrophil (%)	73.1 (65.5, 80.0)	74.7 (69.5, 83.1)	73.3 (65.6, 80.3)	0.034
CRP (mg/L)	45.1 (19.4, 72.0)	42.1 (18.6, 66.1)	44.6 (19.2, 72.0)	0.349
Hb (gr/dL)	12.6 (11.4, 13.7)	12.2 (11.2, 13.3)	12.6 (11.4, 13.7)	0.334
RBC count	4.5 (4.1, 4.9)	4.5 (4.0, 4.8)	4.5 (4.1, 4.9)	0.646
Cr (mg/dL)	1.1 (1.0, 1.4)	1.2 (1.0, 1.7)	1.2 (1.0, 1.4)	0.135
Hematocrit (%)	37.5 (34.2, 40.5)	36.8 (33.9, 40.8)	37.5 (34.2, 40.5)	0.643
CPK (U/L)	104.0 (58.0, 222.5)	90.0 (55.8, 240.5)	103.0 (58.0, 222.0)	0.752
Cardiac dysrhythmia				
No	264 (52.40)	24 (49.00)	288 (52.10)	0.649
Yes	240 (47.60)	25 (51.00)	265 (47.90)	
Cardiac complication during hospitalization				
No	527 (93.90)	45 (84.90)	572 (93.20)	0.041
Yes	34 (6.10)	8 (15.10)	42 (6.80)	

Data are presented as mean ± standard deviation, median (percentile 25- percentile 75) and frequency (%). WBC: White blood cell; RBC: Red blood cell; CRP: C-reactive protein; Hb: Hemoglobin; Cr: Creatinine; CPK: Creatine phosphokinase.

Table 2: Comparing the readmission rate based on the COVID-19 treatment protocol

Treatment protocol	Readmitted		Total (n=614)	P
	No (n=561)	Yes (n=53)		
Corticosteroid + interferon + remdesivir	10 (1.80)	1 (1.90)	11 (1.80)	
Corticosteroid + interferon + favipiravir	13 (2.30)	0 (0.00)	13 (2.10)	
Corticosteroid + interferon + kaletra + HCQ	48 (8.60)	6 (11.30)	54 (8.80)	
Corticosteroid + interferon + kaletra	32 (5.70)	0 (0.00)	32 (5.20)	
interferon + kaletra + HCQ	42 (7.50)	5 (9.40)	47 (7.70)	0.290
Interferon + kaletra	27 (4.80)	3 (5.70)	30 (4.90)	
Kaletra + HCQ	86 (15.30)	6 (11.30)	92 (15.00)	
HCQ	163 (29.10)	12 (22.60)	175 (28.50)	
Others	140 (25.00)	20 (37.70)	160 (26.10)	

Data are presented as frequency (%). HCQ: hydroxychloroquine.

4. Discussion

For the first time, the present study aimed to follow COVID-19 patients for a period of six months to conclude that 8.6% of the patients discharged alive will be admitted to the hospital, again. Of these, 75.5% of the readmission cases were due to the recurrence of the COVID-19 symptoms or its respira-

Table 3: Multiple logistic regression for prediction of readmission of COVID-19 patients

Variable	Odds ratio	95% CI	P
Older age	1.04	(1.01, 1.06)	0.002
Cardiac complication during hospitalization	2.32	(0.86, 6.25)	0.095
Increase in lymphocyte (continuous)	0.96	(0.93, 1.00)	0.051
Increase in mean arterial pressure (continuous)	1.04	(1.01, 1.08)	0.022

CI: confidence interval.

tory complications, and cardiovascular complications were the cause in 15.1% of the readmitted patients. The most paramount prognostic factors for readmission were older age and increased mean arterial pressure during the first hospital stay.

The findings of the current study demonstrated that 67.9% of the readmissions occur during the first week following discharge. Hence, it seems that the impetuosity of health care directors in patients' discharge could have been the primary reason behind the readmissions. This matter can be attributed to the lack in the resources, such as hospital beds, human resources, and equipment, during the peak of the pandemic, which could have been the leading cause behind the early discharge of the patients, showing relative resolution of their symptoms without complete recovery or having a negative PCR test. As a result, the primary cause of the readmissions should be considered the lack of resources, rather than medical errors.

As shown in preceding studies, a great number of COVID-19 patients develop cardiovascular complications (16). Therefore, 15.1% of the readmission cases may be related to the cardiovascular complications following COVID-19. Since we showed that a history of cardiovascular comorbidities was unrelated to readmission, the cardiovascular complications that led to readmission may be due to the infection itself.

The available evidence indicate that older age is an independent factor for the severity of the disease and its pertaining mortality (5, 6, 17, 18). In the present study, it was depicted that age is an independent risk factor for the readmission of COVID-19 patients as well, indicating the role of older age in the development of severe clinical symptoms and prolonged course of the disease. On the contrary, Donnelly et al., who performed a two-month follow up on COVID-19 patients and presented a 19.9% readmission rate, did not find a relationship between older age and readmission (11). This difference between the results of the present study and that of Donnelly et al.'s may be because of the differences between the ages of the included patients. In the current study, 22.4% of the patients were under 45 years old, while in that study, only 3.2% of the patients were under 45 years of age. Since Donnelly et al.'s study was conducted in a much narrower range of age and their patients group consisted of a larger group of old patients, their nonsignificant results for the relationship of readmission and older age may be attributed to these two reasons.

In another study by Yeo et al. the 30-day readmission rate of COVID-19 patients was evaluated (14). In this study, it was concluded that 4.5% of the patients may be readmitted during the mentioned timeframe. Meanwhile, this rate was calculated to be 8.6% in the present study. This difference between the two rates may be attributed to the follow up strategy adopted in their study and that of ours. In Yeo et al 's study, the follow up timeframe was decided to be 30 days, while in our study this timeframe was six months. More importantly, in Yeo et al.'s study, readmission to other hospitals was not assessed. In other words, readmissions to a single center was evaluated in their study. Consequently, the actual rate of readmission may be underestimated in their study, because a number of the patients may be admitted to other hospitals. In the present study, this bias was prevented by contacting the patients or their relatives through phone calls, in addition to reviewing profiles of patients who were readmitted to Imam Hossein hospital, to include readmissions to other medical centers, as well. In addition, there are studies reporting a readmission rate of about 2% for COVID-19. However, their results were limited to much shorter follow up timeframes, and their results are not comparable to that of our study (12, 13).

In the univariate analyses performed in Yeo et al.'s study, age and hypertension, were significantly related to the readmission of COVID-19 patients, but in their multivariate analysis model, these two variables became non-significant in relation to readmission (14). In their study, stepwise models were not utilized to identify independent prognostic factors for readmission. As a result, if they would have used stepwise models, which is a more precise multivariate analysis method for identifying prognostic factors, different results would/could have been obtained. In line with the findings of the present study, Woo-Hwi et al. also concluded that older age is a risk factor for the readmission of COVID-19 patients (9).

The increase in mean arterial pressure during the first admission was concluded to be one of the factors contributing to readmission. Likewise, Ramirez et al. concluded that hypertension is associated with a greater probability of readmission (10). Moreover, a significant relationship was observed

between hypertension and readmission in Atalla et al.'s study (19). Hypertension or higher blood pressure, is a risk factor for the severe form of COVID-19. Hence, the status of the hypertensive patients is more critical than that of other patients, and their prompt discharge may result in increased chances of their readmission.

5. Limitations

One of the limitations of the present study was the loss of the 120 patients during our follow up period. Nonetheless, this 16.3% loss is still lower than the 20% cut-off mentioned in the guidelines of the quality control of observational studies (20). Subsequently, the effects of this loss are rather inconsiderable. Furthermore, the cause of readmission in 15.1% of the patients was cardiovascular accidents. Although cardiovascular complications are one of the prevalent complications of COVID-19, but the mentioned cardiovascular accidents may not be completely attributable to COVID-19. Eventually, the retrospective design of the present study, limited the researchers' ability to investigate all of the probable risk factors and prognostic factors affecting readmission.

6. Conclusion

Readmission is a relatively common phenomenon in COVID-19 patients. The six-month follow up preformed revealed an overall readmission rate of 8.6% in COVID-19 patients, the risk of which may increase with older age and with an elevated mean arterial pressure. It seems that the lack of resources may be the underlying factor for the early discharge of COVID-19 patients in the peak of the pandemic, leading to the increase in readmission probability. Therefore, it is recommended that older or hypertensive patients' discharge be performed cautiously to reduce their readmission.

7. Declarations

7.1. Acknowledgments

The authors kindly appreciate all staff members of Imam Hossein Hospital who helped us to collect the data and perform this study.

7.2. Data availability

The data is at the disposal of the corresponding author of the article and it it can be made available to the researchers upon request.

7.3. Authors' contributions

Study design: MHA, MY
Collecting and cleaning the data: All authors
Analysis and interpretation of results: AP, AT, AMN
Drafting: MY, AT, AMN

Revising: All authors

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7.5. Conflict of interest

There is no conflict of interest.

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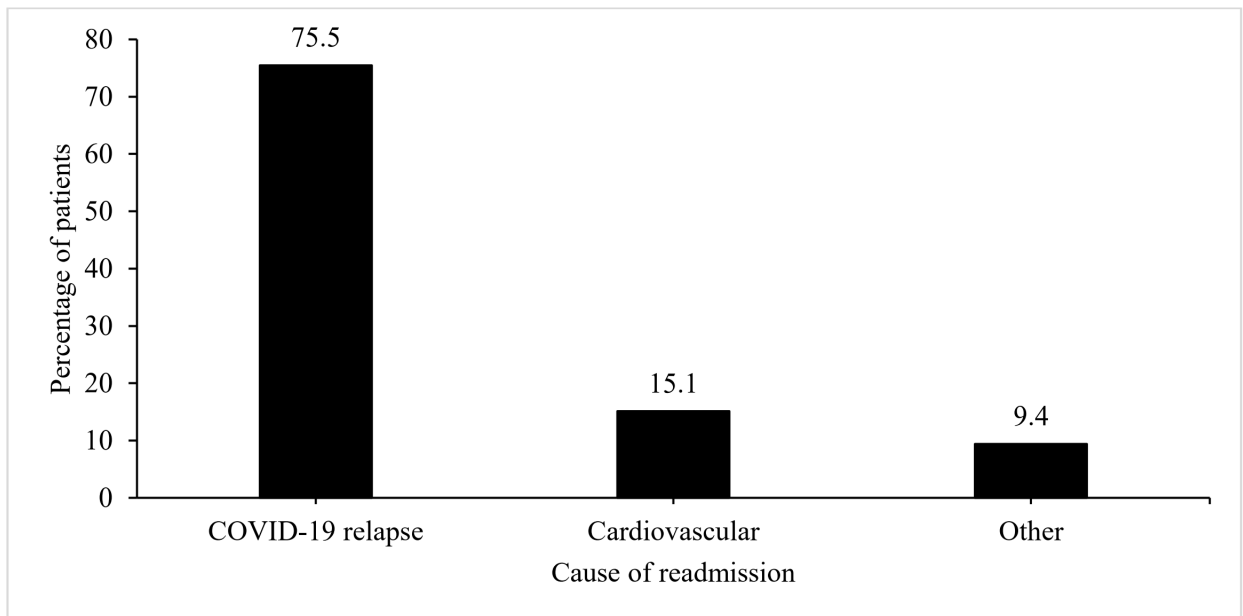
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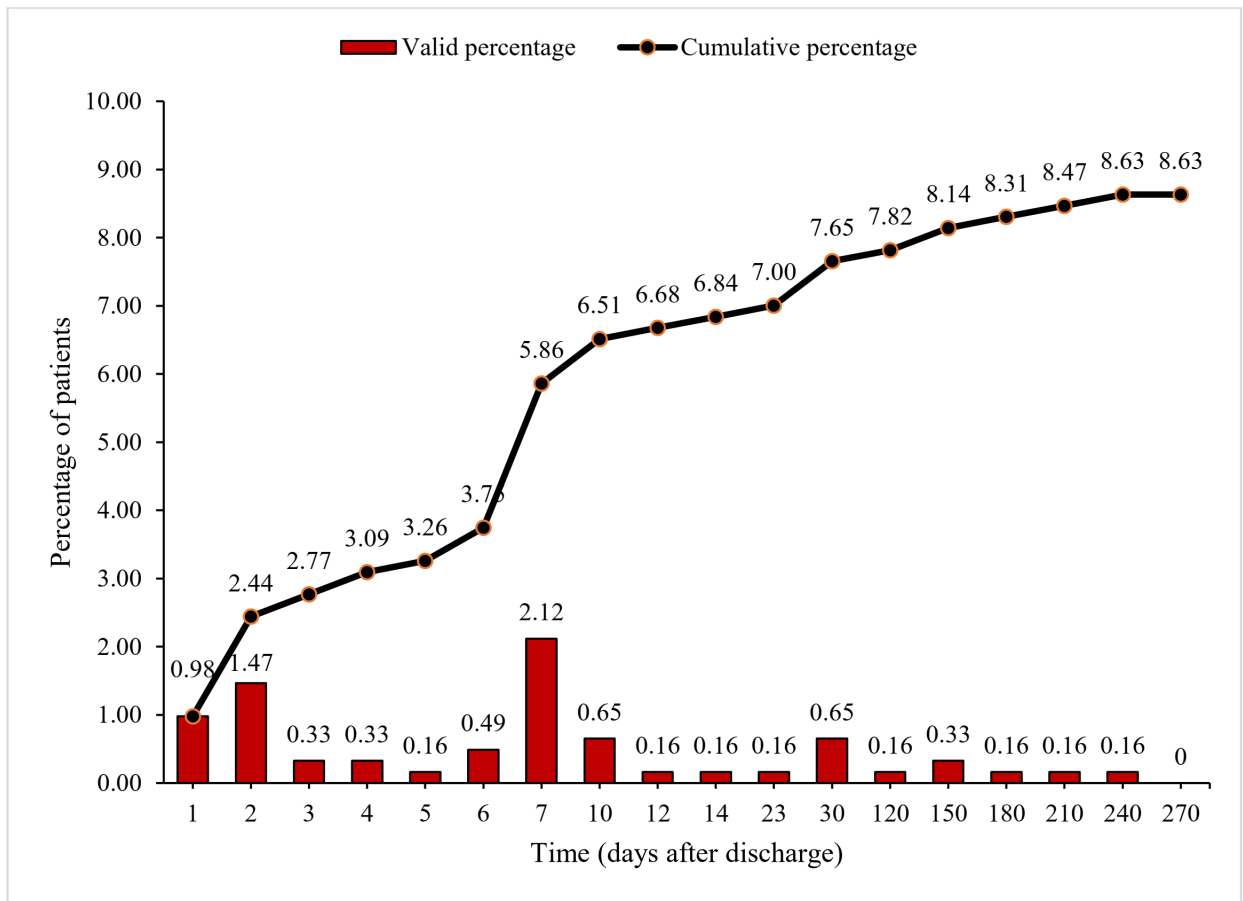
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Figure 2: Readmission rate among COVID-19 patients based on the time of readmission (A) and cause of readmission (B). COVID-19 relapse: Relapse of COVID-19-related symptoms or its respiratory complication.