Original Article

Journal of Iranian Medical Council, Volume 7, Issue no. 3
http://dx.doi.org/10.18502/jimc.v7i3.15727

Hospital Readmission in Patients with COVID-19

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Received: 14 Mar 2023
Accepted: 29 Nov 2023

Citation to this article
Rahimian N, Heidari M, Hashemi-Madani N, Tavakoli N, Khamseh ME. Hospital Readmission in Patients with COVID-19. *J Iran Med Counc.* 2024;7(3):504-10.

Abstract

Background: During the Coronavirus Disease 2019 (COVID-19) pandemic, the demand for hospital beds has exceeded substantially. Thus, we aimed to conduct this study to identify factors associated with the risk of readmission in order to introduce the best discharge plan for patients with high risk of hospital readmission.

Methods: This is a multicenter, case-control study including 1357 patients hospitalized with COVID-19 infection. Age-sex-matched case and control groups were paired at 1:2 ratios, and COVID-19 readmission rate was assessed. Moreover, the logistic regression analysis was applied to determine the factors associated with readmission.

Results: Of the 1357 patients, 99 (7.29%) subjects were readmitted. The most common cause of readmission was respiratory distress. The median (interquartile) of the interval between hospital discharge and the second admission was 5 (2-16) days. Upon adjusting with the main risk factors, having at least one underlying disease and being treated with the corticosteroid were significantly associated with a higher rate of readmission (OR: 2.76, 95%CI: 1.30- 5.87) and (OR: 8.24, 95%CI: 3.72-18.22), respectively.

Conclusion: Identification of risk factors of COVID 19 readmission will improve resource utilization and patient care.

Keywords: Adrenal cortex hormones, COVID-19, Hospitals, Patient readmission, Respiratory Distress Syndrome

Introduction

Coronavirus Disease 2019 (COVID-19) is a complex health crisis caused by a new corona virus, named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2) (1). The virus was initiated at late 2019 in Hubei, China and spread rapidly all over the world and became a pandemic in January 30, 2020 (2).

COVID-19 hospitalization rate is over 70 *per* 100,000 patients, and 1 in 10 cases is readmitted after receiving inpatient care (3). Readmissions represent a significant burden on healthcare delivery systems (4). As the progression of COVID-19 remains unclear, hospital readmission becomes an emerging and costly public health concern (5). Understanding the clinical course of COVID-19 in patients readmitted after discharge has crucial implications for policy-makers to optimize healthcare resource utilization (6). To our best knowledge, there are a few studies focusing on COVID-19 readmission. Chen *et al* found that 7.6% of the COVID-19 patients in China, were readmitted (7). Moreover, Jeon *et al* reported that out of the 2864 COVID-19 patients admitted to hospitals, 103 patients were readmitted after discharge mainly due to high comorbidity score (3).

Although a little is known about risk factors for re-hospitalization of patients with COVID-19, respiratory complications are found to be the main reason for readmission (8). Moreover, another study concluded that readmission within the first 12 days after discharge is more likely to be directly related to the COVID-19 while at the later time, it is due to other reasons such as psychiatric problems (9). However, there is still a knowledge gap on post-hospitalization outcomes in patients with COVID-19. Therefore, we aimed to conduct a study to identify the risk factors associated with readmission in order to introduce the best discharge plan for patients with high risk of hospital readmission.

Previous studies showed that virus subtype, immunodeficiency, underlying diseases, sex, age and Body Mass Index (BMI) affect the risk Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2) reinfection. Also, a theory has been raised that SARS-COV-2 can remain in host cells and reactivate in some conditions. It concluded that host baseline characteristics play an important role in risk of virus reactivation (10).

Materials and Methods

Setting

This multicenter case-control study was performed in 5 academic hospitals affiliated to Iran University of Medical Sciences (IUMS) in Tehran. The study was approved by the ethics committee of the IUMS. All hospitalized patients with positive oropharyngeal or nasopharyngeal Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) for SARS-CoV-2 were considered as COVID-19. Moreover, those without laboratory confirmation for COVID-19 who presented the clinical manifestations of COVID-19 along with typical chest CT findings were also regarded as having COVID-19. All patients admitted to these hospitals received standard medical treatment and respiratory support according to the national protocol of Iran Ministry of Health (11).

Study design and data collection

We retrospectively analyzed data from COVID-19 patients admitted to five IUMS-affiliated hospitals between March 2020 and September 2020. Hospital readmission was identified using the electronic medical records. Readmission was defined as the hospital admission due to COVID-19-related symptoms at least 24 *hr* after the date of discharge. For each patient who was re-admitted, two sex- and age-matched individuals with history of one admission for COVID-19 infection and discharged alive were included as the control group. Applying the propensity score matching, a 2-1 sample was extracted from the single-admitted patients. Demographic and clinical characteristics of the patients were extracted from the hospital medical records. In the readmitted patients, data on the first admission were included for the final analysis. Patients with incomplete information were excluded from the study.

Data on demographic characteristics (age and gender), habitual history (smoking and opium addiction), underlying diseases, clinical features (vital signs at the time of admission), chest Computed Tomography (CT) imaging, medications used during the hospitalization (Hydroxychloroquine (HCQ), Lopinavir/Ritonavir (Kaletra), Sofosbuvir, and Glucocorticoid (GC), hospital course features

(length of hospital stay, Intensive Care Unit (ICU) admission, and type of ventilation (invasive *vs.* non-invasive), as well as associated comorbidities including Hypertension (HTN), Diabetes (DM), Coronary Artery Disease (CAD), Heart Failure (HF), Chronic Kidney Disease (CKD), Chronic Obstructive Pulmonary Disease (COPD), asthma, liver disease, Cerebrovascular Accident (CVA), cancer, and Tuberculosis (TB) were extracted from the records.

Statistical analysis

Continuous and categorical variables are presented as median [Interquartile Range (IQR)] and number (percentage), respectively. Logistic regression analysis was applied to determine the factors associated with readmission due to COVID-19. The outcome of interest was readmission and the explanatory variables were age, sex, smoking status, opium use, underlying disease, vital signs at the time of admission, lung involvement documented by CT images, hospital course, and medication received during the hospitalization. Statistical analyses were performed applying Stata software (version 13). All the tests of significance were two-tailed (with 95% confidence interval), and values of $p<0.05$ were considered statistically significant.

Results

1357 patients with COVID-19 infection were admitted between March 2020 and September 2020, and 99 (7.29%) subjects were readmitted to the hospitals. The median (IQR) of the interval between the first discharge and the second admission was 5 (2-16) days.

Characteristics of the readmitted patients

Out of 99 readmitted patients, 12 patients were readmitted two times and the others were readmitted one time. The most common cause of readmission was respiratory distress (70.7%).

Demographic and clinical characteristics of the patients are presented in table 1. Smoking and opium use were significantly associated with higher rates of readmission (18.0 *vs.* 4.1%, p=0.001) and (15.3 *vs.* 4.0%, p=0.002), respectively. HTN (49.0 *vs.* 33.8%, p=0.012), CAD (42.9 *vs.* 7.5%, p<0.001), CKD (10.3 *vs.* 3.5%, p=0.019), COPD (8.3 *vs.* 1.5%, p=0.007), CVA (13.4 *vs.* 4%, p=0.003), and cancer (11.3 *vs.* 4.6%, p=0.029) were associated with significantly higher rates of readmission. Moreover, those with at least one underlying disease were more likely to be readmitted compared to those without any underlying disease (77.8 *vs.* 58.1%, p=0.001). Furthermore, the readmission rate was significantly higher in patients who received GC (38.8 *vs.* 9.3%, p<0.001), while those who received Kaletra (46.4% *vs.* 63.1%, p<0.006), HCQ (52.5 *vs.* 90.4%, p<0.001), and sofosbuvir (12.4 *vs.* 38.9%, p<0.001) had negative association.

Results of Logistic Regression

Results of univariate analysis on the COVID-19 readmission patients are presented in table 2. In terms of habitual histories and underlying comorbidities, current smoking (OR: 5.20, 95%CI: 1.98-13.63), opium user (OR: 4.28, 95%CI: 1.57-11.67), HTN (OR: 1.88, 95%CI: 1.14-3.08), CAD (OR: 9.10, 95% CI: 4.69-17.65), CKD (OR: 3.14, 95%CI: 1.15-8.53), COPD (OR: 3.14, 95%CI: 1.15-8.53), CVA (OR: 3.68, 95%CI: 1.47-9.21), and cancer (OR: 2.69, 95%CI: 1.07-6.73) were associated with a significant risk of COVID-19 readmission. Moreover, patients who had at least one associated comorbidity were readmitted 2.53 times more than those with no associated comorbidity (OR: 2.53, 95%CI: 1.45, 4.39). Patients who received GC at first admission were more likely to be readmitted (OR:6.19, 95%CI: 3.29-11.67). Also, patients who received Kaletra, HCQ, and sofosbuvir were less likely to be readmitted (OR:0.51, 95%CI: 0.31-0.83), (OR:0.12, 95%CI: 0.06-0.22), and (OR: 0.22, 95%CI: 0.11-0.43), respectively.

Upon adjusting with the main risk factors, having at least one underlying disease and being treated with the GC were significantly related to a higher rate of readmission (OR: 2.76, 95%CI: 1.30-5.87) and (OR: 8.24, 95%CI: 3.72-18.22), respectively. The results are presented in table 3.

Discussion

This multicenter study indicated that from the 1357 COVID-19 patients survived from the first admission, 99 individuals (7.29%) were readmitted. The number of underling diseases and being treated with GC during hospitalization were associated with

Table 1. Baseline characteristics of the study population

Characteristics	Non-readmission		Readmission		p-value
	N	198	N	99	
Age (yr)	198	67(55-76)	99	68(55-78)	0.774
Sex (% male)	198	125(63.1%)	99	65(65.7%)	0.669
Ever Smokers (% yes)	197	8(4.1%)	61	11(18.0%)	**0.001**
Opium use (%)	198	8(4.0%)	59	9(15.3%)	**0.002**
HTN (%)	198	67(33.8%)	98	48(49.0%)	**0.012**
DM (%)	198	57(28.8%)	99	38(38.4%)	0.095
CAD (%)	197	15(7.6%)	98	42(42.9%)	**<0.001**
HF (%)	196	8(4.1%)	98	6(6.1%)	0.439
CKD (%)	198	7(3.5%)	97	10(10.3%)	**0.019**
COPD (%)	198	3(1.5%)	97	8(8.3%)	**0.007**
Asthma (%)	197	4(2.0%)	97	5(5.2%)	0.162
Liver disease (%)	198	4(2.0%)	97	1(1.0%)	0.536
CVA (%)	198	8(4.0%)	97	13(13.4%)	**0.003**
Cancer (%)	198	9(4.6%)	97	11(11.3%)	**0.029**
TB (%)	198	2(1.0%)	97	0(0.0%)	0.450
HIV (%)	134	0(0.0%)	99	0(0.0%)	-
Number of underlying diseases (% ≥1)	198	115(58.1%)	99	77(77.8%)	**0.001**
O2 saturation on admission (%)	198	93(90-95)	85	92(89-95)	0.556
T on admission (C^0)	195	37(36.8-37.5)	90	37(36.9-37.7)	0.995
RR on admission (breath/min)	198	18(16-20)	84	18(16-20)	0.833
Duration of hospital stay (day)	197	6(3-9)	99	6(4-11)	0.211
Chest CT infiltration (%)	198	173(87.4%)	95	82(86.3%)	0.801
GC (%)	194	18(9.3%)	98	38(38.8%)	**<0.001**
Kaletra (%)	198	125(63.1%)	97	45(46.4%)	**0.006**
HCQ (%)	198	179(90.4%)	99	52(52.5%)	**<0.001**
Sofosbuvir (%)	198	77(38.9%)	97	12(12.4%)	**<0.001**
ICU-admission (%)	198	49(24.8%)	97	28(28.9%)	0.449
Non-invasive ventilation (%)	198	25(12.6%)	86	5(5.8%)	0.096
Invasive ventilation (%)	196	1(0.51%)	85	3(3.5%)	0.084

a significantly higher rate of readmission.

Rate of readmission in this study was comparable with that of the studies from the other countries (3,12). Some diseases such as HTN, CAD, CKD, COPD, CVA, and cancer increased the rate of readmission; however, their effects vanished after the multivariate adjustment. Adjustment was done for the main contributing factors smoking, opium use, the number of underlying diseases, ICU admission, and chest CT infiltration. After the multivariate adjustment, GC therapy and the number of underlying disease (>=1) were associated with an increase in the rate of readmission.

The association between COVID-19 readmission

Table 2. Univariate logistic regression results for readmission of COVID-19 patients

Characteristics	Unadjusted OR (95%CI)	p-value
Ever Smokers (yes)	5.20(1.98,13.63)	0.001
Opium use (yes)	4.28(1.57,11.67)	0.005
HTN (yes)	1.88(1.14,3.08)	0.013
CAD (yes)	9.10(4.69,17.65)	<0.001
CKD (yes)	3.14(1.15,8.53)	0.025
COPD (yes)	5.84(1.51,22.60)	0.011
CVA (yes)	3.68(1.47,9.21)	0.005
Cancer (yes)	2.69(1.07,6.73)	0.035
Number of underlying diseases (≥1)	2.53(1.45,4.39)	0.001
GC (yes)	6.19(3.29,11.67)	<0.001
Kaletra (yes)	0.51(0.31,0.83)	0.007
HCQ (yes)	0.12(0.06,0.22)	<0.001
Sofosbuvir (yes)	0.22(0.11,0.43)	<0.001

Table 3. Multivariate logistic regression results for readmission of COVID-19 patients

Characteristics	Adjusted OR (95%CI)	p-value
Ever smokers (yes)	2.94(0.79,10.93)	0.107
Opium use (yes)	2.05(0.47,8.92)	0.340
Number of underlying diseases (≥1)	2.86(1.34,6.07)	0.006
ICU admission (yes)	1.08(0.49,2.40)	0.845
Chest CT infiltration (yes)	0.59(0.22,1.56)	1.56
GC (yes)	8.31(3.68,18.79)	<0.001

and various underlying diseases has been previously reported in different studies. HTN, COPD, and pulmonary fibrosis have been frequently associated with a higher risk of readmission (7,13). A Spanish study showed that immunocompromised patients were also more likely to be readmitted (12). Moreover, some studies, including ours, demonstrated that the higher number of comorbidities is associated with a higher rate of readmission (3,9). In line with our results, a large Korean study represented higher risk of readmission in patients with some underlying diseases like DM, HTN, dementia and those who had at least one underlying disease (3).

The reason why GC therapy increases the readmission rate, is probably due to the fact that patients who received GC, had more severe pulmonary involvement and less oxygen saturation than patients treated with oral antiviral therapy (according to Iranian national protocol for the treatment of COVID19 (11). As it is recommended in many international guidelines, we do not start treatment with GC until oxygen saturation is decreased. As a result, patients who are candidates for treating with corticosteroids have more pulmonary involvement. Perhaps, the greater risk of readmission in patients treated with GC is related to more pulmonary involvement.

In contrast to our results, prescribing GC did not increase the rate of readmission in the Spanish study; this difference may be related to the time of prescription; we considered prescription of GC

during the hospitalization while they included only the patients discharged with GC (12).

The univariate analysis showed that smoking or opium use were risk factors for hospital readmission. This effect might be mediated by various factors such as socioeconomic condition, employment, education, social support, and social determinants of health (14). As shown in previous studies, pneumonia and respiratory distress were the most common causes of readmission (9). Hospital readmitted patients with COVID-19 has not yet been widely evaluated, however, assessing the causes of readmission is necessary to identify preventable causes (9).

According to this study, patients with a medical condition have higher risk of readmission than patients with no underlying disease and this is justifying some therapeutic guidelines (like Iranian national protocol) of COVID-19 that recommends patients with at least one underlying disease were considered as the priority for hospitalization. Therefore, it seems that in the emergency department, patients with underlying diseases should be given priority to diagnostic and therapeutic procedures and also in allocation of the facilities. Also, regarding the use of medical treatment, patients who received GC had a higher rate of readmission versus the patients received Kaletra, HCQ, and Sofosbuvir. Similar to our study, the Korean one showed lower rate of readmission in patients treated with HCQ and Kaletra and it may be due to milder type of the disease in patients treated with oral agents (3). Similar to ours, an American study demonstrated that the type of ventilation and intubation rate had no difference between readmitted and non-readmitted patients (9).

We showed no difference in sex, age and the duration of the admission in two groups; but a Korean study showed a higher rate of readmission in male and older patients and also in those with shorter length of staying at the first admission in readmitted group; these differences may be related to the larger number of study population in the Korean one (7590 patients) compared with ours (1357 patients) (3).

Patients received glucocorticoids obviously presented the more severe form of disease. It is associated with the effect of glucocorticoid on immune system; using glucocorticoid leads to immunodeficiency that supports the previous studies which shows that host immune system plays an important role for reactivation of the SARS-COV-2 virus (10). Before the multivariate adjustment, smoking, opium use, ICU admission and chest CT infiltration had significant relationships with increasing the risk of readmission in univariate analysis; but these significant relationships disappeared after multivariate logistic regression and this shows the fact of micro vision and accuracy of the analysis.

Limitations and strengths

Obtaining and gathering information from several tertiary centers and including a relatively large number of patients were the strengths of our study. However, there are some limitations. First of all, we could not provide more detailed information such as clinical characteristics of the patients. A lot of missing data were detected in records. Moreover, this study was conducted at the middle of the pandemic and the characteristics might be differing during the pandemic.

Conclusion

This study showed that 7.29% of COVID-19 patients were readmitted; therefore, it is very important to recognize the risk of readmission at first visit and plan a better therapeutic program and intensive care for high-risk patients. It seems that in the emergency department, patients with more than one underlying disease should be given the priority to diagnostic and therapeutic procedures and also in allocation of the facilities. Moreover, those who received glucocorticoids during hospitalization should be closely followed in the early days after discharge. Further studies are required to evaluate the risk factors of readmission and solutions to reduce the rates of patient return to the hospital.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with appropriate guidelines and reviewed and approved by the Local Ethics Committee of Iran University of Medical Sciences (Approval No: IR.IUMS.REC.1399.053). Written informed consent was obtained from the patients to participate.

Consent for publication

Written informed consent was obtained from the patients to publish their documents.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Acknowledgement

We would like to express our appreciation to chair of Endocrinology and Metabolism Research Institute of Iran.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this study.

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