

## Determine Consequences of Delay in Referring to Hospital in Patients with COVID-19 in Shahid Mostafa Khomeini Hospital of Ilam Province

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### Abstract

**Background:** COVID-19 is a systemic infection with a significant impact on the hematopoietic system and hemostasis. Infected subjects are at high risk for coagulation diseases such as venous thromboembolism.

**Objectives:** The aim of the present study was to investigate the consequences of delayed referral of patients with COVID-19 in Ilam.

**Methods:** In this investigation, a present prospective study was performed in 2020 on the registry data of patients with COVID-19 disease in the infectious ward of Shahid Mostafa Khomeini Hospital in Ilam. In this study, the effect of delay in hospitalization from the onset of the first symptom of the disease on death and intubation of patients in special and general wards in 2350 patients with COVID-19 was investigated. The statistical software of SPSS 16 was used for analyzing data.

**Results:** The results of univariate logistic regression analysis for the main causes of death due to COVID-19 disease according to hospitalization in ICU and general ward showed that the variables of age, sex, marital status, heart disease, blood pressure, diabetes, chronic lung disease, chronic disease Kidney, neurological disease, cancer, and delayed referral were statistically significant which were associated with death at the 5% error level. The chance of death for delayed referral in ICU patients is equal (OR ICU ADMISSION = 1.06; 95% CI, 1.01-1.12; P value=0.01) and in normal ward patients (OR =0.88; 95% CI, 0.79-0.97), the P-value=0.01 was obtained.

**Conclusions:** The final regression model which was adjusted to the other variables, in hospitalized patients, each day of delay in hospitalization meant a 0.08% increase in the odds of mortality rate and a 0.05% increase in the odds of intubation.

**Keywords:** Referral delay, complications, COVID-19.

## 1. Introduction

Coronavirus is an important pathogen that primarily targets the human respiratory system. The previous epidemics of coronaviruses included Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), which were identified as factors that pose a major threat to public health [1]. From the mid-September 2019, a number of patients were hospitalized with an initial diagnosis of pneumonia of unknown origin. These individuals were epidemiologically linked to a Chinese Wuhan seafood market. Sequencing of lower respiratory tract samples revealed a new coronavirus which was entitled coronavirus [2].

Within eight weeks, the virus spread around the world to the point where the World Health Organization (WHO) declared it a global epidemic on March 11. By March 14, in addition to China, the pandemic has affected more than 150 countries [3]. In Iran, the first official news of the death of a patient with COVID-19 was announced on February 19. As of March 16, 14991 subjects had been infected with COVID-19, 853 had died of the disease, and 4996 had recovered [4].

The clinical symptoms of patients with COVID-19 are rapidly transforming. Symptoms reported in the previous studies were mainly related to the respiratory system such as fever, dry cough, fatigue, and myalgia. Non-respiratory symptoms included nausea, vomiting, and diarrhea. Unfortunately, there is no pathognomonic clinical feature that can reliably distinguish COVID-19 from other routine viral infections [5-8]. There is currently no specific vaccine or antiviral drug for the treatment of critically ill patients. Management of the illness focuses primarily on providing supportive care,

such as oxygenation, ventilation, and control of fluids. Hybrid therapy with low-dose, antiviral systemic corticosteroids, and interferon inhalation is part of the management process of COVID-19 [9].

Since COVID-19 has no approved treatment, it is important to prevent its spread in the community. The main points in preventing the spread of the virus are observing hand hygiene, social distancing, and quarantine. Expansion of facilities for testing and diagnosis along with strict quarantine rules in the community will also reduce secondary cases [10].

COVID-19 is a systemic infection with a significant impact on the hematopoietic system and hemostasis. Infected subjects are at high risk for coagulation diseases such as venous thromboembolism. If central arteries are not managed professionally, COVID-19 patients with ARDS may eventually develop multiple organ failures, even if they have no other underlying disease or are not at an advanced age [11, 12].

In Rong *et al.*, the effect of delayed diagnosis on disease transmission was investigated with a newly formulated dynamic model. Sensitivity analysis and numerical simulation show that early diagnosis and shortening the waiting time for diagnosis cannot eradicate COVID-19, but can effectively reduce virus replication, significantly reduce transmission, and effectively prevent COVID disease investigate the effect of delay in diagnosis on the disease transmission with a new formulated dynamic model. Sensitivity analyses and numerical simulations reveal that improving the proportion of timely diagnosis and shortening its given waiting time cannot eliminate COVID-19, but can effectively decrease the basic reproduction number, significantly reduce the transmission risk, and

effectively prevent the endemic of COVID-19. [13].

In the study of Melashu Balew Shiferaw *et al.*, out of 170 included tuberculosis patients, 162 patients were studied with a response rate of 95.3%. The proportion of tuberculosis patients who had delayed diagnosis was 59.9%. The mean time of health-seeking after developing the symptom of tuberculosis was 7.6 weeks. Tuberculosis patients with extra pulmonary site involvements were about four times more likely to be delayed in seeking health services (OR: 4.00, 95% CI: 1.77–9.03) as compared with patients who were exposed to the pulmonary TB. New patients were about three times more likely to come lately for TB diagnosis (OR: 2.94, 95% CI: 1.26–6.84) as compared with patients who had the previous history of treatment. Patients who had no information about TB before they started TB treatment were further around three times to be delayed (OR: 3.37, 95% CI: 1.43–8.00) as compared with those who had the information. More than 50% of TB patients reported in health-seeking relatively a longer time. Strengthening the health education activities for the community about tuberculosis and capacity building of the health care provider to increase suspicion of identifying tuberculosis and the early diagnosis is crucial [14].

In this study, we are going to assess the hypothesis whether there is a direct relationship between a delay in hospitalization and patient mortality, length of hospital stay, need for intensive care, and exacerbation of pulmonary complications. We are to provide the results of the study to health policymakers to help them reduce treatment costs, the length of hospital stay, as well as the mortality rate of patients with COVID-19.

## 2. Objectives

Considering the prevalence of COVID-19 disease in the world and its impact on human health, the consequences of delayed referral of COVID-19 patients to health centers in terms of length of hospital stay, ICU admission, intubation rate, and mortality is one of the objectives of this research.

## 3. Methods

The present study is a retrospective cohort in 2020 on the registry data of patients with COVID-19 in the infectious diseases wards of Shahid Mostafa Khomeini Hospital in Ilam province as a specialized referral center for patients with COVID-19.

For data collection, the demographic profile form (including questions about age, gender, and marital status) as well as questions about the history of CVD disease, hypertension, COPD, Diabetes, Kidney disease, Neurologic Disease, Cancer, pneumonia, and intubation status Death, and Delay in referral (days) were used. Delay in referrals were recorded by “days” and based on the history of the patient.

In this study, the effect of delay in hospitalization from the onset of the first symptom of the disease, on patient mortality and intubation in the ICU and general wards were evaluated in 2350 patients with COVID-19. In this registry, 96% of patients reported a delay of 1 to 60 days. After collecting and entering the data into Stata 12, the effect of the delay on mortality as well as the intubation rate were analyzed using logistic regression models in Stata Software 12.

## 4. Results

The average number of days of referral delay is listed in Table 1 according to the different variables for deceased patients requiring intubation and hospitalization in the ICU. For instance, the average delay in referral

was 5.64 days in patients with viral pneumonia and those who died and 5.56 days in those who were survived (Table 1).

**Table 1.** Frequency of average days of delay in hospitalization according to different variables

Variable	ICU admission		Intubation		Death		
	yes	no	yes	no	yes	no	
Number of days delay in hospitalization (mean ± SD)	Male	5.51(0.2)	5.54(0.2)	5.53(0.3)	5.53(0.1)	5.54(0.3)	5.53(0.1)
	Female	5.10(0.2)	5.52(0.2)	5.61(0.3)	5.40(0.1)	5.47(0.3)	5.42(0.2)
	Married	5.31(0.2)	5.55(0.1)	5.52(0.2)	5.48(0.1)	5.48(0.2)	5.49(0.1)
	Single	5.47(0.9)	5.29(0.4)	5.84(1.2)	5.24(0.4)	5.75(1.3)	5.26(0.4)
	Heart Disease	5(0.3)	5.12(0.3)	4.98(0.4)	5.07(0.3)	5.01(0.3)	5.07(0.3)
	HTN	5.33(0.3)	5.50(0.3)	5.48(0.3)	5.43(0.2)	5.48(0.3)	5.44(0.2)
	COPD	4.64(0.5)	5.52(0.4)	4.79(0.6)	5.36(0.4)	4.97(0.5)	5.28(0.4)
	Diabetes	5.35(0.3)	5.46(0.3)	5.35(0.4)	5.44(0.2)	5.43(0.4)	5.43(0.2)
	Kidney disease	4.88(0.5)	4.69(0.6)	4.76(0.7)	4.76(0.5)	4.81(0.6)	4.74(0.5)
	Neurologic Disease	4.62(0.6)	4.59(0.5)	4.44(0.6)	4.68(0.5)	4.58(0.5)	4.62(0.5)
	Cancer	4.55(0.6)	7.81(2.1)	5.45(0.6)	6.56(1.7)	4.79(0.5)	7.46(2.1)
	Pneumonia	5.41(0.2)	5.64(0.1)	5.70(0.2)	5.56(0.1)	5.69(0.2)	5.56(0.1)

The results in Tables 2 and 3 showed that due to the fact that the clinical situation of patients requiring hospitalization is different in ICU and general wards, they have certain different patient histories. In this study, we analyzed the effect of referral delay and other variables on mortality as well as their intubation rate in two groups of ICU and non-ICU patients (Tables 2 and 3).

As can be seen in Table 3, the univariate logistic regression analysis was performed on the main causes of death due to COVID-19 based on ICU and general ward hospitalization which showed that the variables of age, sex, marital status, heart disease, blood pressure, diabetes, chronic lung disease, chronic renal disease, neurological diseases, cancer, and delay in referral had a statistically significant relationship with death at the error rate of 5%. The odds ratio of mortality for delay in referral was equal in ICU and non-ICU patients (Table 2). Meanwhile, this value

was less than one in patients hospitalized in general wards.

The results of univariate logistic regression analysis for factors affecting intubation for COVID-19 indicated that the variables of age, marital status, heart disease, diabetes, neurological disease, pneumonia, cancer, and delay in referral had a statistically significant relationship with mortality at the error rate of 5% and the odds ratio of intubation for delay in referral was obtained (Table 3).

In order to determine the general effect of delay in referral on mortality and intubation rates, all significant variables with a value of  $\leq 0.2$  were entered the adjusted and final model. In the multivariate model, the adjustment was performed for significant variables in univariate analysis to determine the effect of delay in referral on mortality and intubation rates. Odds ratio for the effect of delay in referral on mortality in ICU and general ward (non-ICU) patients was 1.08 and 0.98, respectively, and the odds ratio for the effect of delay in

referral on intubation was 1.05 (Tables 4).

**Table 2.** Univariate logistic regression models of factors for mortality in COVID-19 disease for hospitalized patients

Variable Risk Factors	ICU hospitalized= yes		ICU hospitalized= no	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Age	1.02 (1.01-1.03)	<0.001*	1.07 (1.05–1.09)	<0.001*
Sex				
Female	1**	-	1	-
Male	1.46 (1.04–2.04)	0.03*	1.08 (0.59–1.96)	0.79
Marital Status				
Married	1	-	-	-
Single	1.83 (0.71–4.72)	0.20*	-	-
CVD disease				
No	1	-	1	-
Yes	0.87 (0.61–1.23)	0.42	3.81 (2.09–6.95)	<0.001*
Hypertension				
No	1	-	-	-
Yes	1.25 (0.89–1.74)	0.19*	1.98 (1.08–3.68)	0.03*
COPD				
No	1	-	1	-
Yes	1.53 (0.83–2.83)	0.17*	5.08 (2.28–11.31)	<0.001*
Diabetes				
No	1	-	1	-
Yes	1.27 (0.89–1.81)	0.18*	0.91 (0.41–1.96)	0.79
Kidney disease				
No	1	-	1	-
Yes	2.29 (1.13-4.65)	0.02*	1.22 (0.29–5.14)	0.79
Neurologic Disease				
No	1	-	1	-
Yes	1.49 (0.79–2.80)	0.21	5.34 (2.37–12.94)	<0.001*
Cancer				
No	1	-	1	-
Yes	3.82 (1.62–9.02)	0.002*	6.43 (2.15–19.26)	0.001*
pneumonia				
No	1	-	1	-
Yes	1.12 (0.71–1.76)	0.63	0.86 (0.42–1.76)	0.68
Delay in referral (day)	1.06 (1.01–1.12)	0.01*	0.88 (0.79–0.97)	0.01*

**Table 3.** Univariate logistic regression models of factors for intubation in COVID-19 disease for hospitalized patients

<b>Variable Risk Factors</b>	<b>Intubation Odds Ratio (95% CI)</b>	<b>P-value</b>
<b>Age</b>	1.01 (1.00 -1.02)	0.02*
<b>Sex</b>		
Female	1**	-
Male	1.19 (0.86 – 1.67)	0.29
<b>Marital Status</b>		
Married	1	-
Single	2.17 (0.81 – 5.78)	0.12*
<b>CVD disease</b>		
No	1	-
Yes	0.69 (0.49 – 0.98)	0.04*
<b>Hypertension</b>		
No	1	-
Yes	1.17 (0.83 – 1.63)	0.37
<b>COPD</b>		
No	1	-
Yes	1.92 (1.02 – 3.61)	0.04*
<b>Diabetes</b>		
No	1	-
Yes	1.22 (0.86 – 1.74)	0.26
<b>Kidney disease</b>		
No	1	-
Yes	1.15 (0.59 – 2.25)	0.67
<b>Neurologic Disease</b>		
No	1	-
Yes	1.55 (0.81 – 2.89)	0.19*
<b>Cancer</b>		
No	1	-
Yes	2.49 (1.13 – 5.51)	0.02*
<b>pneumonia</b>		
No	1	-
Yes	1.60 (1.01 – 2.53)	0.05*
<b>Delay in referral(day)</b>	1.05 (1.00 – 1.10)	0.04*

In other words, the odds of death in COVID-19 patients who had delay in referrals was 1.08 times higher than in patients who survived in the ICU. In fact, delay in referral is a risk factor for death in COVID-19 patients admitted to the ICU (Table 4). In addition, the odds of intubation in patients with delay in referral were 1.05, which showed that delay in referral is a risk factor for the

rate of intubation in COVID-19 patients admitted to the ICU. Based on the results of the final regression model which were adjusted to other variables, each day of delay in hospitalization for patients with COVID-19 admitted to the ICU, meant an increase of 0.08% in the odds of mortality and an increase of 0.05 in the odds of intubation.

**Table 4.** Adjusted models with multi-variable logistic regression for effect of delay in referral to hospital on COVID-19 disease mortality

Variable Risk Factors	ICU hospitalized= yes		ICU hospitalized= no	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
<b>Age</b>	1.02 (1.01-1.04)	0.001*	1.06 (1.03-1.08)	<0.001*
<b>CVD disease</b>				
No	1	-	1	-
Yes	0.73 (0.47-1.11)	0.14	2.27 (1.13-4.53)	0.02*
<b>Hypertension</b>				
No	1	-		-
Yes	1.11 (0.73-1.68)	0.64	0.83 (0.42-1.64)	0.59
<b>COPD</b>				
No	1	-	1	-
Yes	1.47 (0.74 -2.92)	0.27*	3.55 (1.45-8.71)	0.006*
<b>Diabetes</b>				
No	1	-	1	-
Yes	1.22 (0.82-1.82)	0.18*	0.82 (0.36-1.86)	0.64
<b>Kidney disease</b>				
No	1	-	1	-
Yes	2.52 (1.12-5.68)	0.03*	0.97 (0.21-4.51)	0.97
<b>Neurologic Disease</b>				
No	1	-	1	-
Yes	1.78 (0.85-3.70)	0.12	3.91 (1.41-10.81)	0.009*
<b>Cancer</b>				
No	1	-	1	-
Yes	4.59 (1.69-12.52)	0.003*	5.98 (1.71-20.86)	0.005*
<b>Delay in referral (day)</b>	1.08 (1.02-1.13)	0.003*	0.93 (0.84-0.1.03)	0.17

## 5. Discussion

The findings of this study showed that with increasing age, the mortality rate of patients admitted to ICU and general wards increased, which is in line with the results of the study of CICERI *et al.*, (15). In the study of LI *et al.*, it was shown that old age acts as an effective factor in hospitalization of patients, which is consistent with the results of this study.

According to the findings, there was no difference between the risk of mortality in men and women. In the systematic review and meta-analysis of ZHANG *et al.*, in the group of patients with COVID-19 and cancer, in which 15

articles were included with a sample size of 3019, it was indicated that only the age of over 65 and male gender could be factors effective in mortality of patients with COVID-19 (16). Furthermore, in the study of PECKHAM *et al.*, which included 3,111,714 patients with COVID-19, the findings revealed that the mortality rate was higher in men than women (17), which is not consistent with the results of this study. The reasons for the lack of this similarity seem to be related to the sample size. This has been a cohort study, while the mentioned studies have been meta-analyses and had a large sample size.

According to the findings of this study, it was shown that hypertension has acted as a risk factor to increase patient mortality, while there was no relationship between diabetes and patient mortality. In the systematic review and meta-analysis of Tian et al., using a group of 14 original articles with a sample size of 4659, it was revealed that blood pressure and diabetes act as one of the influential factors in the mortality of patients with COVID-19. Moreover, laboratory findings related to the increase of heart diseases such as ALT, AST, D Dimer, and Troponin-I showed a significant increase (18), which is in line with the results of this study.

According to the findings of this study, cancer was one of the factors affecting intubation and mortality of patients with COVID-19, which is consistent with the results of CICERI *et al.*, who reported higher mortality rates in cancer patients (16). Also in the study of SOROURI et al., which included patients with and without cancer who were infected with COVID-19, it was illustrated that in these patients, the mortality and intubation rates were 50.9 and 50.9%, respectively, while in other patients, this rate was 16% and 23.6% (19), which is consistent with the results of this study in terms of increased mortality in patients with underlying cancer.

## 5. Conclusion

The findings of the present study showed that a statistically significant relationship was observed between the delay in referral and mortality of patients with COVID-19. As the delay in referral increased, the mortality rate of patients increased.

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Ilam University of Medical Sciences, Ilam, Iran.

## Footnotes

### Authors' Contribution

YJ, AM, AG, IA contributed to all stages of the study, including conceptualization, data collection, data analysis, and manuscript writing.

### Conflict of Interest

The authors declare no conflict of interest.

### Ethical Considerations

All participants signed informed consent. The Ethics Committee of Ilam University of Medical Sciences approved the current research (IR.MEDILAM.REC.1399.261).

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