Risk Factors of Death in Mechanically Ventilated COVID-19 Patients: A Multi-Center Study From Iran

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Abstract- Despite the improvement in COVID-19 therapeutic management the mortality of mechanically ventilated COVID-19 patients remains high. In this study, we determined the risk factors of death in these cases. This cross-sectional study evaluated clinical and paraclinical features of mechanically ventilated COVID-19 patients at the time of hospital admission until death or discharge from hospital between April and September in 2021 in three COVID-19 referral hospitals. The patients were divided into survivors and non-survivors and then the characteristics were compared. One hundred twenty-five patients (60% male, mean age 62±15.18, range 17 to 97 years old) were recruited to the study. 51(40%) survived and 74 (60%) didn't survive. At the time of hospital admission, the vital signs were not significantly different between the survivors and non-survivors, although diarrhea was not reported in non-survivors, but reported in 9.5% of survivors (*P*=0.02). The mean age of non-survivors was higher (65.1±14.17 vs 56.9±15.41, *P*=0.003). The intubation time since the patients were admitted was not significantly different between the two groups (3.38±2.88 days vs 4.16±3.42 days, *P*=0.34). The mean of serum LDH and D-dimer at the time of ICU admission were significantly higher in the non-survivors (863±449 vs 613±326, *P*=0.01; 4081±3342 vs 542±634, *P*=0.009; respectively). However, the mean CRP was not significantly different between the two groups (76±66.4, 54±84.3; *P*=0.1). Mean APACHE-II score was higher in the non-survivors than the survivors (15 vs 13; *P*=0.01). Use of remdesivir, interferon beta-1a, and low dose corticosteroids were significantly higher in the survivors group (*P*=0.009, *P*=0.001, *P*=0.000). Success of weaning and ICU discharge among mechanically ventilated COVID-19 patients are probably higher in younger patients with lower D-dimmer and LDH that received remdesivir, interferon beta-1a and low dose corticosteroids, while the intubation time did not seem to play a role on patients' outcome.

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Keywords: COVID-19; Mechanical ventilation; Extubation; Mortality risk factors

Introduction

The coronavirus disease 2019 (COVID-19) worldwide pandemic outbreak has been identified since

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December 2019 (1). It could lead to severe illness that requires critical care in about 5% of confirmed infection (2). The studies have shown that 6 to 10 % of patients required admission to the intensive care units (ICUs) due to acute hypoxemic respiratory failure (2). The mortality rate in critically ill COVID-19 patients was diverse (3). Mortality rate in patients requiring intubation and mechanical ventilation (MV) was 25 to 57% (4,5). While the mortality rate in non-intubated patients admitted in the ICUs was 50 to 65% (6-8).

Factors such as age, diabetes, hypertension, coronary heart disease and increased d-dimer were associated with poor prognosis (4). Including early factors associated with worse outcomes and a higher risk of intubation in COVID-19 patients were old age (9), male gender (10-13) and elevated LDH values (14,15).

Acute respiratory distress syndrome (ARDS) is one of the manifestations of COVID-19 and may require intubation and MV (16). Early reports suggested that patients may benefit from early intubation during a period of severe hypoxia (17). Since the early phase of the COVID-19 pandemic, the guidelines in China (18), United Kingdom (19), United States of America (20) and Australia (21) recommended early intubation of hypoxemic patients with COVID-19 to avoid complications. The latter studies reported that delaying intubation of ARDS patients may be associated with adverse outcomes (22-26). Another study found late intubation was associated with longer ICU length of stay and longer duration of MV. They found that expired patients had a longer time to intubation than recovered patients (25).

The approaches to treatment of COVID-19 continue to advance. Later management shifted towards delaying intubation as much as possible using non-invasive ventilation (17,26).

The effect of many factors in the outcome of the COVID-19 patients under mechanical ventilation are still unknown. Determining the factors that predict outcomes in intubated patients with COVID-19 can help make changes that will eventually improve the patients management.

Materials and Methods

Study population and data collection

This was a cross-sectional, multicenter study on critically ill COVID-19 patients who were received O2 under mechanical ventilation in ICUs, in three COVID-19 centers (Imam Khomeini Hospital complex, Ziaeian Hospital, and Shohadaye Tajrish Hospital), Tehran, Iran between April 1st and September 1st 2021.

A diagnosis of COVID-19 was confirmed for all cases by polymerase chain reaction (PCR) of SARS-CoV-2 RNA from nasopharyngeal swab or other respiratory samples. Initially, according to the inclusion and exclusion criteria, the patients registered in the hospital's electronic system and admitted to the ICUs were recruited, then patients' demographic, clinical and laboratory features were extracted and recorded in the data sheet. The hospitalized management data were also recorded and analyzed.

Inclusion and exclusion criteria

The inclusion criteria consist of age more than16 years, the cause of intubation is respiratory failure due to COVID-19, mechanical ventilation period more than 48 hours.

The exclusion criteria were intubation and mechanical ventilation for other reasons (heart failure, pulmonary thromboembolism, pneumothorax and loss of consciousness), the cases were extubated from the recruitment process and then again were intubated, patients who have not been discharged from ICU or not expired at the end of the study, ICU admission less than 48 hours and pregnant women.

Eventually, the patients were divided into survivor (Patients who had successful weaning and ICU discharge) and non-survivor (who died in the ICU under mechanical ventilation) groups and then the characteristics were compared between two groups.

Statistical analysis

The comparative analysis in the distribution of patient characteristics between the survivors and non-survivors groups are presented with 95% confidence intervals. Continuous variables were analyzed with the Mann-Whitney U test. Bivariate analysis was performed by using chi-square tests. *P* less than 0.05 were considered statistically significant.

Results

After evaluating 312 critically ill COVID-19 cases, 125 MV patients were recruited. The mean age was 62 years (range 17 to 97). Of those, 75 patients (60%) were male. Overall, 74 (59%) patients died (non survivors group), and 51(41%) patients (survivors group) were successfully weaned, extubated and discharged. The mean age was significantly higher between the non-survivors (65.1±14.17) versus the survivors (56.9±15.41) (*P*=0.003) (Table 1).

Table 1. Clinical characteristic of the mechanically ventilated patients with COVID-19 and comparison survivors with non-survivors

Characteristics		All Patients (n=125)	Survivors (n=51)	Non-Survivors (n=74)	*P*
Age (years)		61.7±15.18 (17-97)	56.9±15.41 (24-95)	65.1±14.17 (17-97)	0.003
Sex	**Male**	75 (60%)	32 (62.7%)	43 (58.1%)	0.6
	Female	50 (40%)	19 (37.3%)	31 (41.9%)	
Initial Vital Sign	**Temperature**	37.3°C±0.7 (36-40)	37.2°C±0.6 (36-39)	37.3°C±0.8 (36-40)	0.27
	Oxygen Saturation	81.7%±14.9 (40-99)	80.5%±13.5 (40-97)	76.5%±16.3 (40-99)	0.91
	Systolic Blood Pressure (mmHg)	123.5±28 (110.6-210)	126.4±28.8 (50.3-210.9)	118.7±30.9 (110.6-210.11)	0.19
	Respiratory Rate (breath/min)	24 ±10 (12-82)	24.4 ±13.4 (12-82)	23.9 ±7.3 (12-40)	0.3
	Pulse Rate (beat/min)	94 ±14 (60-126)	95.2 ±13.9 (60-120)	93.8 ±14.5 (65-120)	0.23
Blood Biochemistry on Admission	**White Blood Cell Count (*10^9 /L)**	11.3±16.8 (0.2-18.2)	10.2±4.7 (3-25)	12.1±21.5 (0.2-18.2)	0.54
	Lymphocyte count (*10^9 /L)	153±124 (37-675)	146±137 (38-675)	125±99 (37-510)	0.61
	Hemoglobin (g/dl)	12.2±2.9 (1-19)	12.1±2.8 (3-18)	12.2 ±3 (1-19)	0.84
	Platelet count(*10^9/L)	192.8±97.5 (13-451)	208±95 (52-451)	182.2±98 (13-425)	0.14
	C-reactive protein(mg/L)	68±74.3 (4-456)	54±84.3 (4-456)	76±66.4 (5-283)	0.16
	ESR	42.7±35.5 (1-140)	39.3±32.4 (3-118)	45.2±37.9 (1-140)	0.46
	Lactate Dehydrogenase (U/L)	747±414 (3-1924)	613±326 (3-1541)	863±449 (5-1924)	0.01
	Creatinine (mg/dl)	1.6±1.4 (0.2-10.7)	1.5±1.04 (0.6-6.7)	1.6±1.6 (0.2-10.7)	0.55
	AST (U/L)	49.7±39.5 (4-269)	47±47.5 (6-269)	51.4±33 (4-185)	0.65
	ALT (U/L)	37.1±26.7 (7-151)	38±31.7 (10-151)	36.3±22.9 (7-126)	0.72
	Bilirubin T	0.8 ±0.6 (0.3-4)	0.8±0.4 (0.3-1.8)	0.8±0.75 (0.3-4)	0.83
	Bilirubin D	0.4±0.2 (0.1-1.3)	0.4±0.2 (0.2-0.8)	0.4±0.28 (0.1-1.3)	0.95
	D-Dimer (µg/dl)	2508±3058 (3-10000)	542±634 (3-2000)	4081±3342 (136-10000)	0.009
	Procalcitonin (ng/mL)	13.1±26.1 (0-76)	17.5±24.7 (0-35)	11.8±28 (0-76)	0.8
	Troponin 1 (ng/mL)	31±120 (0-360)	1.3±3.1 (0-12)	56.1±160 (0-630)	0.11
	Pro BNP*	10168±13723 (31-35000)	1910±2189 (362-3458)	11544±14410 (31-35000)	0.37
VBG	**PH**	8 (7-10)	9 (7-10)	7.16 (7-8)	0.14
	P O2 (mmHg)	53.6(10-379)	62.5 (10-379)	46.7 (18-114)	0.21
	P CO2 (mmHg)	45.2 (7-83)	47.6 (7-83)	43 (15-78)	0.16
	FiO2	97 (90-100)	93.7 (90-95)	99 (92-100)	0.03
Severity Score	**APACHE score I**	14.1±3.7(2-22)	13	15	0.01
	APACHE score II	20.5±7.3(4-40)	19	22	0.02
Nosocomial infections		23 (18.4%)	18.9%	17.6%	0.85

Cont. table 1.

Respiratory Support	**Nasal Cannula**	6 (5%)	6%	4.3%	0.32
	Mask	32 (26.9%)	32%	23.2%	
	Mask Reservoir Bag	76 (63.9%)	62%	65.2%	
	CPAP**	2 (1.7%)	0%	2.9%	
	Without Respiratory Support	3 (2.5%)	0%	4.3%	
Lung CT Scan					
Both Lung Involvement		73 (92%)	90.5%	94.6%	0.49
Pulmonary Extension on the first chest CT scan	**Mild**	8 (10%)	14%	5.4%	0.42
	Moderate	46 (57.5%)	53.5%	62.2%	
	Severe	26 (32.5%)	32.6%	32.4%	
Tracheostomy		10 (8%)	6 (11.8%)	4 (5.4%)	0.19
Arrhythmia		5 (4%)	1 (2%)	4 (5.4%)	0.33
Organ Failure	**Respiratory Failure**	65 (52%)	5 (9.8%)	60 (81.1%)	0.000
	Heart Failure	56 (44.8%)	8 (15.7%)	48 (64.9%)	0.000
	Kidney Failure	11 (8.8%)	1 (2%)	10 (13.5%)	0.025
Intubation Day		4.4 (1-14)	3.38 (1-14)	4.16 (1-14)	
1st day		33 (26.6%)	12 (23.5%)	21 (28.4%)	0.34
2nd day		23 (18.5)	13 (25.5%)	10 (13.5%)	

* B-type natriuretic peptide **Continuous positive airway pressure

33 (26.6%) patients were immediately intubated on the first day of admission, 23 (18.5%) patients were intubated on the second day, and only 7 (5.6%) patients were intubated after 14 days of hospitalization.

The average time of intubation and placing the patient under mechanical ventilation since the patient hospitalization was 4.16 days in the non survivors group and 3.38 days in the survivors, and there was not significant difference between the two groups (*P*=0.34).

Most of the critically ill patients, 100 (81.3%) were admitted to the emergency room and then they were transferred to ICUs, and about 23 (18.7%) of patients were primary admitted at the wards from clinic and then transferred to ICUs.

About 54 (74%) of the non-survivors group and 46 (92%) of the survivors group were admitted from the emergency resuscitation room. Hospitalization from emergency room was significantly associated with successfully weaning, extubation and discharged (*P*=0.01).

The vital signs at admission day included mean body temperature 37.3° C (36-40), mean room air SpO2 81.7% (40-99), mean systolic blood pressure 123.5 mmHg (110.6-210), mean respiratory rate 24 breath/min (12-82) and mean pulse rate 94 beats/min (60-126). The vital signs at admission day were not significantly different between the survivors and non-survivors (*P*>0.05) (Table 1).

In the first visit, among the common symptoms diarrhea was not reported in any of the non-survivors group, while in the survivors group 7 (9.5%) patients had diarrhea. Diarrhea was significantly detected higher in the survivor group than the non-survivors group (*P*=0.02) (Table 2).

In the laboratory markers, the mean serum LDH level was 747 (3-1924)±414 U/L on the first day of ICU admission. The mean LDH level in the non survivors group was 863 (5-1924)±449 U/L and in the survivors group was 613 (3-1541)±326 U/L. The mean LDH level was significantly elevated in the non survivors (*P*=0.01). The mean serum d-dimer was 2508 (3-10000)±3058 ng/ml on the first day of ICU admission. The mean d-dimer in the non survivors group was 4081 (136-10000) ±3342 ng/ml and in the survivors group was 542 (3-2000)±634 ng/ml. D-dimer was significantly higher in the dead patients (*P*=0.009). The mean serum C-reactive protein (CRP) was 68 (4-456)±74.3 mg/L. The mean CRP in the non-survivors group was 76 (5-283)±66.4 mg/L and in the survivors group was 54 (4-456)±84.3 mg/L. Although the average of CRP in the dead patients was clearly higher, this inflammatory marker was not significantly different between the two groups (*P*=0.1). There was not significantly different in the mean of white blood cell count (WBC), lymphocyte percentage, lymphocyte count, platelet, hemoglobin, ESR, creatinine, liver function enzymes, procalcitonin, PO2, PCO2, PH, Pro BNP and troponin-1 between non survivors and survivors groups (*P*>0.05) (Table 1).

Among intubated patients, 23 (18.4%) patients developed nosocomial infections. 14 (18.9%) were in

the non-survivors group and 9 (17.6%) in the survivor group.

Rate of post COVID-19 nosocomial infections was not significantly difference between the two groups (*P*=0.85).

According to the first lung CT scan, 73 patients (92%) had involvement in both lungs. The percentage of both lungs involvement in CT Scans (94.6% versus 90.5%) was not significantly different between the two groups (*P*=0.49). In terms of the pulmonary extension in the first CT scan, 10% (5.4% versus 14%) patients had mild involvement, 57.5 % (62.2% versus 53.5%) patients had moderate involvement and 32.5% (32.4% versus 32.5%) patients had severe involvement. The imaging pulmonary involvement was not significantly different between the two groups (*P*=0.42).

Overall, 10 (8%) of patients underwent tracheostomy during MV. About 5.4% of the non-survivors and 11.8% of the survivors group underwent tracheostomy. Although the percentage of tracheostomy in the dead patients was low, but there was not significantly difference between the two groups (*P*=0.19).

The cause of death in all patients was respiratory, heart, or renal failure. About half of the cause of death in both groups (52%) was respiratory failure, (81.1% of the non-survivors group and 9.8% of the survivors group). About 44.8% had died with heart failure (64.9% of the non survivors group and 15.7% of the survivors group) and also, 8.8% cause of death was renal failure (13.5% of the non survivors group and 2% of the survived group) (overall).

End organ damage was significantly higher in the non survivors group compared to the survivors group (*P*<0.05).

Mean APACHE -II score was 15 (22% prediction mortality rate) in the non survivors group and 13 (19% prediction mortality rate) in the survivors group. APACHE scoring was significantly higher in the dead patients compared to alive patients (*P*=0.016).

Underlying diseases are common in all patients. Common comorbidities in the patients included hypertension (34.4%), diabetes mellitus (24.8%), and ischemic heart disease (20%). The underlying diseases were not significantly different between the two groups. (Table 3).

The most common past medications used by patients included losartan (23.2%), atorvastatin (23.2%), aspirin (21%), metformin (12%) and insulin (9%). Although metformin use was higher in the non survivors group than the survivors group, however there was close to being statistically significant in metformin use between the two groups (*P*=0.055). About 24.3% of the dead patients and 5.9% in the alive cases were using Aspirin. Aspirin receiving in past history was significantly higher in the non survivors group (*P*=0.007) (Table 3).

The antiviral regimens were compared between the two groups, and the remdesivir, and interferon beta-1a (betaferon) were significantly higher prescribed in the survivors group than non-survivors group. (*P*<0.05). (Table 4).

Table 2. First visit symptoms of the mechanically ventilated patients with COVID-19 and comparison survivors with non-survivors

	All Patients	Survivors	Non-Survivors	*P*
Dyspnea	96 (76.8%)	42 (82.4%)	54 (73%)	0.08
Cough	77 (61.6%)	31 (60.8%)	46 (62.2%)	0.06
Myalgia	34 (27.2%)	14 (27.5%)	20 (27%)	0.12
Fatigue	34 (27.2%)	15 (29.4%)	19 (25.7%)	0.24
Weakness	33 (26.4%)	19 (37.3%)	14 (18.9%)	**0.022**
Chills	29 (23.2%)	12 (23.5%)	17 (23%)	0.08
Fever	27 (21.6%)	9 (17.6%)	18 (24.3%)	0.07
Anorexia	24 (19.2%)	7 (13.7%)	17 (23%)	0.09
Loss of Consciousness	23 (18.4%)	10 (19.6%)	13 (17.6%)	0.5
Nausea	19 (15.2%)	10 (19.6%)	9 (12.2%)	0.06
Vomiting	18 (14.4%)	7 (13.7%)	11 (14.9%)	0.08
Headache	10 (8%)	4 (7.8%)	6 (8.1%)	0.1
Shortness of Breath	7 (5.6%)	4 (7.8%)	3 (4.1%)	0.4
Diarrhea	7 (5.6%)	7 (9.5%)	0 (0%)	**0.02**
Abdominal Pain	6 (4.8%)	3 (5.9%)	3 (4.1%)	0.6
Chest Pain	6 (4.8%)	6 (11.8%)	0 (0%)	**0.002**
Runny Nose	6 (4.8%)	4 (7.8%)	2 (2.7%)	0.09
Sore Throat	2 (1.6%)	2 (3.9%)	0 (0%)	0.1
Decreased Sense of Smell and Taste	2 (1.6%)	2 (3.9%)	0 (0%)	0.4
Hemoptysis	2 (1.6%)	1 (2%)	1 (1.4%)	0.8
Cyanosis	1 (0.8%)	1 (2%)	0 (0%)	0.6
Sneezing	0 (0%)	0 (0%)	0 (0%)	0.4

Table 3. Underlying diseases and drug history

Underlying Diseases		All Patients	Survivors	Non-Survivors	*P*
Hypertension		43 (34.4%)	18 (35%)	25 (33%)	0.86
Diabetes Mellitus		31 (24.8%)	13 (25%)	18 (24%)	0.88
Ischemic Heart Diseases		26 (20%)	9 (17%)	17 (23%)	0.47
Kidney Dysfunction		11 (9%)	4 (8%)	7 (9%)	0.75
Malignancy		8 (6%)	2 (4%)	6 (8%)	0.34
Asthma		7 (5.6%)	5 (9.8%)	2 (2.7%)	0.09
Chemotherapy		5 (4%)	2 (4%)	3 (4%)	0.97
Hemodialysis		3 (2.4%)	0 (0%)	3 (4%)	0.14
Pulmonary thromboembolism		2 (1.6%)	0 (0%)	2 (3%)	0.23
Obesity		1 (0.8%)	1 (2%)	0 (0%)	0.22
Transplantation		1 (0.8%)	0 (0%)	1 (1.3%)	0.4
Liver Dysfunction		1 (0.8%)	1 (1.9%)	0 (0%)	0.22
	Losartan	29 (23.2%)	28%	20%	0.10
	Atorvastatin	29 (23.2%)	15%	29%	0.095
Drug History	**Aspirin**	21 (16.8%)	5.9%	24.3%	0.007
	Metformin	12 (9.6%)	16%	5%	0.055
	Insulin	9 (7.2%)	7%	8%	0.065

Table 4. COVID-19 treatment agents

	All Patients	Survivors	Non-Survivors	*P*
Remdesivir	40 (32%)	23 (45%)	17 (22%)	0.009
Betaferon	45 (36%)	27 (52%)	18 (24%)	0.001
Hydroxychloroquine	86 (68.5%)	33 (64%)	53 (71%)	0.41
Kaletra (Lopinavir/ritonavir)	40 (32%)	19 (37%)	21 (28%)	0.29
Atazanavir/ritonavir	53 (42.4%)	24 (47%)	29 (39%)	0.38
Oseltamivir	31 (24.8%)	11 (21%)	20 (27%)	0.48
Low Dose Corticosteroids	71 (56.8%)	39 (76%)	32 (43%)	0.000
Pulse corticosteroid therapy	46 (36.8%)	23 (45%)	23 (31%)	0.11
IVIG	28 (22.4%)	17 (33%)	11 (14%)	0.15
Antibiotic	110 (88%)	42 (82%)	68 (91%)	0.10
Vitamin C	40 (32%)	18 (35%)	22 (29%)	0.51
Vasopressor	24 (19.2%)	7 (13.7%)	17 (33%)	0.001
Benzodiazepine	24 (19.2%)	5 (9.8%)	19 (37%)	0.000
Diuretic	62 (49.6%)	27 (52%)	35 (47%)	0.53
Naproxen	34 (27.2%)	10 (19%)	24 (32%)	0.11
Acetaminophen	48 (38.4%)	26 (50%)	22 (29%)	0.016

Corticosteroids were prescribed 76% in the survivors group and 43% in the non survivors group, and it was significantly higher in the alive patients (P=0.000). Corticosteroids therapy decreased mortality significantly.

Pulse corticosteroid therapy was prescribed 45% in the survivors and 31% in the non survivors group. Pulse corticosteroid therapy was not significantly different between the two groups (P=0.11). Intravenous Immune Globulin (IVIG) was prescribed 33% in the survivors and 14% in non survivors group. IVIG prescription was not significantly different between the two groups (P=0.15). There were not significant difference in prescribing vitamin C, naproxen, and diuretics between the two groups (P>0.05).

Nevertheless, antibiotics were prescribed in 88% of patients. They were prescribed for 82% in the survivors and 91% in the dead cases. Antibiotic therapy was not significantly different between the two groups (P=0.1).

Discussion

This study compared two groups of critically ill COVID-19 patients under mechanically ventilation as survivors and non-survivors in terms of the characteristics (clinical and para-clinical) and hospitalized management.

In this study, the mean age of the non-survivors was significantly higher than the survivors. About 90% of fatal cases occurred among patients aged 65 years or older (26,27). Additionally the multivariate logistic analysis in similar study indicated that age was a risk factor for disease progression (28). Older individuals are physically frail and are likely to have several comorbidities, which not only increases the risk of pneumonia (29) but also affects their prognosis (30).

Underlying diseases was common in all admitted patients. The assessment of comorbidities is an essential component in determining the prognosis of several diseases, especially pneumonia (31,27). In the present study hypertension and diabetes mellitus were the most prevalent comorbidities.

Hypertension was identified as the most common comorbidity in the present study population (32,33). Overrepresentation of hypertension among patients with COVID-19 was discussed by several investigators, as reviewed by Sardu *et al*., (34). In Guan's study, hypertension was reported as an independent risk factor for severe COVID-19 (35), however, in this study, hypertension was not a risk factor for mortality.

There were identified other comorbidities such as ischemic heart diseases and kidney dysfunction in preset study, which also detected in other studies. The association between renal failure and a mortality outcome for patients with COVID-19, has also been reported by other authors (35-37).

Dyspnea and cough were the most prevalent symptoms on admission among critically ill patients with COVID-19 in our study. This is similar to what was reported by Rahmanzadeh *et al*., (38). Furthermore, about 6% of the patients had gastrointestinal symptoms, and this was less than 15% in previous studies (32,39). On the contrary to similar studies, diarrhea was more frequent in the survivors than non-survivors (40).

The mortality rate among the critically ill patients admitted to ICU and those requiring mechanical ventilation was 59%. Previous studies reported a wide range of mortality rates (20-62%) among critically ill patients with COVID-19 admitted to ICU (41). In mechanically ventilated patients, mortality rate was 50% to 97% (7,42).

Almost half of the patients 56 (45%) were intubated during the first two days of hospitalization. Although, similar to Paputsi's study (43) there was no significant difference observed for the day of intubation between the two groups. While the latter studies reported that delaying intubation of critically ill patients with ARDS may be associated with adverse outcomes (26,22,23).

In agreement with the previous reports, the results confirmed that all patients had abnormal findings in chest CT scans, and bilateral multiple lobular involvements were the most frequent chest CT findings among ICU patients (24,32). However, Luis' study suggested that the extent and characteristics of the lesion had no statistical significant difference on disease outcomes (43).

Elevated CRP is an important inflammatory marker. Although the average of CRP was high in both groups, it was higher in the non-survivors than survivors, and the difference between the two groups was not significant. Therefore, CRP levels could not be selected as a prognostic factor (28). Sharifpour's study showed that median CRP correlates with severity of COVID-19, and it was an independent predictor of mortality (16). Also, in Wang's study, in the early stage of COVID-19, CRP levels were positively correlated with lung lesions and could reflect disease severity (44). Moreover, CRP was associated with a higher risk of intubation in similar studies (15,44).

The present study suggested that the elevated LDH was a factor associated with the poor prognosis of COVID-19 infection. However, the elevated LDH values have been recently shown to be associated with increased risk of severe COVID-19 pneumonia and mortality (45,46).

Additionally, increased d-dimer level was associated with the poor outcome and in Bhargava's study, high d-dimer level was associated with an intubation risk (46).

The APACHE score was a prognostic factor, and it was associated with mortality in MV patients with COVID-19. The APACHE score has been widely used to predict the outcome of critically ill patients (41). In addition, the mean APACHE II score of the survivors and non-survivors were 13 and 15, respectively. A recent study showed the median APACHE II score of survivors and deaths in critically ill patients with COVID-19 were 14 and 18 (47). Zuo's study showed that APACHE II score greater than or equal to 17 serves as an early warning indicator of death (48).

In this study, like the Kato's study, the most patients undergoing anti-viral treatment were also proactively undergoing anti-bacterial treatment (88%). Although antibiotics do not have a therapeutic role in COVID-19 infections, appropriate antibiotic regimen can be administered to treat secondary infections in critically ill patients (49).

The Remdesivir prescription was an effective treatment for saving COVID-19 patients and also it could shorten the time of recovery in adults who were hospitalized with Covid-19 (50). In addition, the remdesivir reported in the "Solidarity" international clinical trial conducted by the World Health Organization (WHO), as a little effective or non-effective medication on hospitalized COVID-19 cases (51). On the contrary, some studies in line with the Solidarity study revealed that treatment with remdesivir did not lead to a significant reduction in the time to achieve clinical improvement and could not be

beneficial (52,53), however considering the extent of the Solidarity study: "it has been difficult to eliminate the confounding factors".

Our results showed that corticosteroids decreased mortality rate significantly and it was an effective treatment for the COVID-19 patients.

Recent studies advised that using glucocorticoids in viral pneumonia can easily aggravate the disease and increase the risk of secondary infections, leading to an increase in mortality rate, thus advocating against the use of glucocorticoids (54). Other studies suggested that the appropriate dose of glucocorticoids at early stage could inhibit the elevated of inflammatory cytokines, thereby preventing continued exacerbation of lung injury (55).

Edalatifard's study suggested that methylprednisolone pulse therapy could be an efficient therapeutic agent for hospitalized severe COVID-19 patients at the pulmonary phase (56).

Betaferon was identified as an effective therapy for COVID-19 patients, which was reported by Bosi et al as well effective (57). Rahmani's study showed that IFN β-1b may decrease risk of ICU admission and mechanical ventilation (58).

Our findings revealed that prescribing antiviral agents included hydroxychloroquine, lopinavir/ritonavir, atazanavir/ritonavir, and oseltamivir did not lead to a significant clinical improvement. Also, IDSA guideline did not recommended the use of hydroxychloroquine and lopinavir/ritonavir (59). Karoly's study said that hydroxychloroquine and lopinavir/ritonavir have no significant effects on the patients' outcome (60). In Horby's study patients hospitalized with Covid-19, those who received hydroxychloroquine did not have a lower incidence of death at 28 days than those who received usual care (61).

In summary, there were many risk factors for predicting mortality in COVID-19 patients, but based on the findings of this study, we can probably say that among critically ill COVID-19 patients under MV, the chance of survival was higher in younger patients with lower serum d-dimmer and LDH that received Remdesivir, betaferon and corticosteroids during hospitalization. Although, tracheostomy was non-significantly seen more in survivors, but the intubation time did not seem to play a role on patients' outcome.

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