Risk factors of death in mechanically ventilated COVID-19 patients: a retrospective multi- center study

Mohammadreza Salehi
Department of Infectious Disease, Imam Khomeini Hospital complex, Tehran University of Medical Sciences

Mohammad-Taghi Beig Mohammadi
Department of Anesthesiology & critical care, Imam Khomeini Hospital complex, Tehran University of Medical Sciences

Seyed Hamidreza Abtahi
Department of pulmonary and critical care medicine, Thoracic Research Center, Imam Khomeini Hospital complex, Tehran University of Medical Sciences, Tehran. Iran

Samrand-Fattah Ghazi
Department of Anesthesiology & critical care, Imam Khomeini Hospital complex, Tehran University of Medical Sciences

Abolfazl Sobati
Department of nursing and midwifery, Tehran University of Medical Sciences. Clinical Nurse, Imam Khomeini Hospital Complex, Tehran, Iran

Rama Bozorgmehr
Shohada-e Tajrish Hospital, Shahid Beheshti University of Medical Sciences

Seyed Ali Dehghan Manshadi
Department of Infectious Disease, Imam Khomeini Hospital complex, Tehran University of Medical Sciences

Saeed Reza Jamali Siahkali
Department of Infectious Disease, Ziaeian Hospital, Tehran University of Medical Sciences

Mostafa Mohammadi
Department of Anesthesiology & critical care, Imam Khomeini Hospital complex, Tehran University of Medical Sciences

Banafsheh Moradmand Badie
Australasian Bone Marrow Transplant Recipient Registry (ABMTRR), Sydney, Australia

Ensiyeh Rahimi (ensiyehrahimi@gmail.com)
Department of Infectious Disease, Imam Khomeini Hospital complex, Tehran University of Medical Sciences

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Abstract

Introduction: Despite the improvement in COVID-19 therapeutic management the mortality of mechanically ventilated COVID-19 patients remains high. In this study, we determined risk factors of mortality in these cases.

Methods: This retrospective study examined clinical and paraclinical data of COVID-19 patients mechanically ventilated at the time of hospitalization to ICU admission until death or discharge from hospital between April and September in 2021 in three COVID-19 referral hospitals.

Results: One hundred twenty-five patients (60% male, mean age 62 ± 15.18, range 17 to 97 years old) were recruited to this 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 groups, also diarrhea was not reported in non-survivors, but reported in 9.5% of survivors (P = 0.02). The mean age of 74 non-survivors was higher than 51 survivors (65.1 ± 14.17 vs 56.9 ± 15.41, P = 0.003). The intubation time since the patients were admitted to hospitals was not significantly different between the two groups (3.38 ± 2.88 days vs 4.16 ± 3.42 days, P = 0.34). The mean LDH and D-dimer at the time of ICU admission were significantly higher in the non-survivors group (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, interfrone beta-1a, and low dose corticosteroids were significantly higher in the survivors group (P = 0.009, P = 0.001, P = 0.000).

Conclusion: Success of weaning and hospital discharge among mechanically ventilated COVID-19 patients are probably higher in younger patients with lower D-dimmer and LDH levels that received low dose corticosteroids during treatment.

Introduction

The coronavirus disease 2019 (COVID-19) worldwide pandemic outbreak has been identified since December 2019. [1]. It can 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 will required admission to the intensive care units (ICUs) due to acute hypoxemic respiratory failure[3]. The mortality rate in critically ill COVID-19 patients were diverse. [4] Mortality rate in patients requiring intubation and mechanical ventilation (MV) was 25 to 57%[5,6]. While, the mortality rate in patients admitted in the ICUs was 50 to 65%[7,8,9].

Factors such as age, diabetes, hypertension, coronary heart disease and increased d-dimer are characterized with poor prognosis [10]. Including early factors associated with worse outcomes and a

higher risk of intubation in COVID-19 patients are age [11], male gender [12,13,14,15] and elevated LDH values [16,17].

Acute respiratory distress syndrome (ARDS) is one of the manifestations of COVID-19 and may require intubation and MV[18]. Early reports suggested that patients may benefit from early intubation during a period of severe hypoxia [19]. Since the early phase of the COVID-19 pandemic, the guidelines in China [20], United Kingdom [21], United States of America [22] and Australia [23] 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 [24,25,26]. 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 [27].

The approaches to treatment of COVID-19 continue to advance. Later management shifted towards delaying intubation as much as possible using non-invasive ventilation[28]. According some studies timing of intubation may have no effect on mortality and morbidity in patients with COVID-19[29].

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 the management of the patients.

Methods

Study population and data collection

This was a retrospective, 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 1th April and 1th September 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, laboratory features were extracted and recorded in the data sheet. The hospitalized management data were collected 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.

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-values less than 0.05 were considered statistically significant.

Results

After evaluated 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 versus the survivors (P=0.003). Table-1

About 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 intubation duration was 4.16 days in the non survivors group and was 3.38 days in the survivors, and there was not significant difference between the two groups in intubation durations (P=0.34).

Most of the critically ill patients, 100 (81.3%) were admitted to the emergency resuscitation room and then they were transferred to ICU, and about 23 (18.7%) of critically ill patients were transferred from other wards.

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 two survivors and non-survivors groups (P>0.05). Table-1

Table-1. Baseline demographic and clinical characteristic of the patients admitted to ICU with COVID-19.

	All Patients (n=125)	Survivors (n=51)	Non-Survivors (n=74)	P-value
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
Respiratory Support				
• Nasal Cannula	6 (5%)	6%	4.3%	
• O2 Mask	32 (26.9%)	32%	23.2%	
• Bag Reserve Mask	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 Extention on the first chest CT Scan				0.42
• Mild	8 (10%)	14%	5.4%	
• 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)	0.34
• 1 th day	33 (26.6%)	12 (23.5%)	21 (28.4%)	
• 2 th day	23 (18.5)	13 (25.5%)	10 (13.5%)	

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%) of patients had diarrhea. Diarrhea was significantly detected higher in the survivor group than the non-survivors group (P=0.02). Table-2

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

In the laboratory markers, the mean LDH level was 747 (3-1924) ±414 U/L on the first day of ICU admission. The mean LDH level in 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 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 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%) of patients developed nosocomial infections. 14 (18.9%) were in the non-survivors group and 9 (17.6%) in the survivor group.

Post COVID-19 nosocomial infection was not significantly difference between the two groups (p=0.85).

According to the first lung CT scan, most patients 73 (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

Table 3. Underlying Diseases and Drug History				
	All Patients	Survivors	Non-Survivors	P-value
Underlying Diseases				
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
Drug History				
Losartan	29 (23.2%)	28%	20%	
Atorvastatin	29 (23.2%)	15%	29%	
Aspirin	21 (16.8%)	5.9%	24.3%	0.007
Metformin	12 (9.6%)	16%	5%	0.055
Insulin	9 (7.2%)	7%	8%	

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% in 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

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 difference 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 difference between the two groups (P=0.15). There were not significant different in prescribing vitamin C, naproxen, and diuretics between the two groups (P>0.05).

Last but not least, 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 difference between the two groups (P=0.1).

Table 4. Treatment

	All Patients	Survivors	Non Survivors	P-value
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

Discussion

This retrospective study compared two groups of COVID-19 patients in survivors and non-survivors groups in terms of the characteristics (clinical and para-clinical) and hospitalized management these patients were critically ill and they were admitted as well as intubated and in the ICU.

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 [30]. Additionally the multivariate logistic analysis in similar study indicated that higher age was a risk factor for disease progression[31]. Elderly individuals are physically frail and are likely to have several comorbidities, which not only increases the risk of pneumonia [32] but also affects their prognosis [33].

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 [34,35]. In present study hypertension and diabetes mellitus were the most prevalent comorbidities.

hypertension was identified as the most common comorbidity in the present study population [36,37]. Overrepresentation of hypertension among patients with COVID-19 was discussed by several investigators, as reviewed by Sardu et al [38]. In Guan's study, hypertension was reported as an independent risk factor for severe COVID-19 [39], 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 [40,41,42].

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[43]. Furthermore, about 6% of the patients had gastrointestinal symptoms, and this was less than 15% in previous studies [44,45,46]. On the contrary to the similar studies, diarrhea was more frequent in the survivors than non-survivors [47].

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 [48]. In mechanically ventilated patients, mortality rate was between 50% to 97%[49,50].

Almost half of the patients 56 (45%) were intubated during the first two days of hospitalization. Although, similar to Paputsi's study [51] 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 [52,53,54].

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[55,56]. However, Lui's study suggested that the extent and characteristics of the lesion had no statistical significance on disease outcomes [57].

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. Sharifpour's study showed that median CRP correlates with severity of COVID-19 and it was an independent predictor of mortality [58]. 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 [59]. Moreover CRP was associated with a higher risk of intubation in similar studies [60,61].

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 [62,63].

Additionally, the higher d-dimer level was associated with the poor outcome and in Bhargava's study, high d-dimer level was associated with a intubation risk [64].

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 [65]. 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 [66]. In Zuo's study showed that APACHE II score greater than or equal to 17 serves as an early warning indicator of death [67].

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 critical ill patients [68].

The Remdesivir prescription was an effective treatment for saving COVID-19 patients and also it could short the time of recovery in adults who were hospitalized with Covid-19 [69]. In addition, the remdesivir reported in the “Solidarity” international clinical trial conducted by the World Health Organization (WHO), as an little effective or non-effective medication on hospitalized COVID-19 cases [70]. 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 taken to achieve clinical improvement and could not be beneficial[71,72], 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 [73]. Other studies suggested that the appropriate dose of glucocorticoids at early stages could inhibit the elevated of inflammatory cytokines, thereby preventing continued exacerbation of lung injury[74].

Edalatifard's study suggested that methylprednisolone pulse could be an efficient therapeutic agent for hospitalized severe COVID-19 patients at the pulmonary phase [75].

Betaferon was identified as an effective therapy for COVID-19 patients, which was reported by Bosi et al as well effective [76]. Rahmani's study showed that IFN β-1b may decrease risk of ICU admission and mechanical ventilation [77].

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[78]. Karoly's study said that hydroxychloroquine and lopinavir/ritonavir have no significant effects on the patients outcome[79]. 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[80].

In summary, this multi-center retrospective study revealed that there were many risk factors for predicting mortality in COVID-19 patients, but based on 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 D-dimmer and LDH that received Remdesivir or betaferon and corticosteroids during hospitalization.

Declarations

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Ethical approval and Consent to participate: The protocol of the study was approved by the Ethics Committee of Tehran University of Medical Sciences. This project was approved by the Institutional Review Board of Tehran University of Medical Sciences [IR.TUMS.VCR.REC.1399.175].

The study is retrospective. It was not possible to use written consent. According to the Medical Ethics Committee, patients' information remains confidential. Patients agreed to receive routine treatment upon arrival at the hospital. Then they received the treatment they needed. Finally, they were analyzed based on the treatment received in different groups.

Consent for publication:

We the authors give our consent for the publication of identifiable details within the text to be published in the Journal of Critical Care.

Data Availability Statement:

All data generated or analysed during this study are included in this published article.

Author contribution :

Mohammadreza Salehi Conceptualization, Funding acquisition, Project administration, Supervision, Writing – editing & reviewed the manuscript Mohammad Taghi Beigmohammadi Investigation, Resources & reviewed the manuscript hamidreza abtahi Visualization & reviewed the manuscript samrand fattah ghazi Visualization & reviewed the manuscript abolfazl sobati Formal analysis & reviewed the manuscript rama bozorgmehr Data curation & reviewed the manuscript seyed ali dehghan manshadi Funding acquisition, Methodology & reviewed the manuscript saeed reza jamali siahkali Visualization & reviewed the manuscript mostafa mohammady Methodology & reviewed the manuscript banafsheh moradmand badie Data curation & reviewed the manuscript ensiyeh rahimi Writing & reviewed the manuscript

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