ORIGINAL ARTICLE

Association of systemic complications with mortality in coronavirus disease of 2019: A cohort study on intensive care unit patients

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Background: Since the beginning of the coronavirus disease of 2019 (COVID-19) pandemic, concerns raised by the growing number of deaths worldwide. Acute respiratory distress syndrome (ARDS) and extrapulmonary complications can correlate with prognosis in COVID-19 patients. This study evaluated the association of systemic complications with mortality in severely affected COVID-19 patients. **Materials and Methods:** This retrospective study was done on 51 intensive care unit (ICU)-admitted COVID-19 adult patients who were admitted to the ICU ward of Khorshid hospital, affiliated with Isfahan University of Medical Sciences. Only the patients who had a definite hospitalization outcome (dead vs. survivors) were included in the study. Daily clinical and paraclinical records were used to diagnose in-hospital complications in these patients. **Results:** The sample was comprised of 37 males (72.5%) and 14 females (27.4%). The median age of patients was 63 years (Min: 20, Max: 84), with the mortality rate of 47.1%. In total, 70.6% of patients had at least one coexisting disorder. Chronic kidney disease was associated with the worse outcome (29.16% of dead patients against 3.70 of survived ones). Mechanical ventilation was used in 58.8% of patients. Patients who had received invasive ventilation were more likely to die (87.50% of dead patients against 7.40 of survivors), Complications including sepsis and secondary infections (odds ratio: 8.05, confidence interval: 2.11–30.63) was the strongest predictors of mortality. **Conclusion:** Complications including sepsis and secondary infections can increase the risk of death in ICU-admitted COVID-19 patients. Therefore, it is substantial that the physicians consider preventing or controlling these complications.

Key words: Coronavirus disease 2019, extrapulmonary manifestations, Iran, systemic complications

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INTRODUCTION

The influx of patients with coronavirus disease of 2019 (COVID-19) to hospitals has decreased hospital resources since December 2019.[1,2] Intensive care unit (ICU) admissions depend on the health-care system's ICU capacity and disease severity.[3]

The disease has become unpredictable due to the diversity of the symptoms and severity in different individuals.[4] Multi-organ involvement nature of COVID-19 has mostly influenced its prognosis.[5] The vast majority of critically ill patients present with systemic complications besides extreme respiratory insufficiency.[6,7] Acute respiratory distress syndrome (ARDS) and cardiovascular complications are

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counted as the leading causes of mortality.[8-10] Furthermore, acute kidney injury (AKI) was seen in COVID-19 patients, which was associated with a poor prognosis.[11] However, other complications can intensify the disease course, such as liver complications, disseminated intravascular coagulation (DIC), and brain complications.[12-15] Therefore, identifying these factors can help us to reduce in-hospital complications and thus mortality. The novelty of this study relies on daily-based evaluation of the disease course (with a specific focus on complications) in survived vs. deceased patients. Furthermore, the variation in laboratory findings was compared in the two mentioned groups. The evaluation of the daily course of the disease can provide us valuable information about the possible lethal systemic complications during the admission course, which has been rarely done before.

This retrospective study investigated the association of systemic complications with mortality in patients with COVID-19, hospitalized in ICU.

METHODS

Study design and participants

This retrospective study was performed from February 27, 2020, to April 13, 2020, on 51 COVID-19 pneumonia patients who were admitted to the ICU of Khorshid hospital, affiliated with Isfahan University of Medical Sciences. Patients were selected through convenience sampling method. The daily medical records of patients who were admitted to the ICU were collected, and those who had a definite hospitalization outcome (dead vs. survivors) were included. Clinical diagnosis of COVID-19 was confirmed using the result of reverse-transcriptase-polymerase-chain-reaction (RT-PCR). The confirmation of COVID-19 was done using the nasopharynx and oropharynx swab specimens according to the World Health Organization (WHO) RT-PCR protocol.[16] The minimum sample size recommended by PASS software was 51 patients (Alpha = 0.05, Power = 0.80, and Odd Ratio 4.91 based on previous research[17]). The data of patients for whom the result of RT-PCR were not available and those who were not admitted to the ICU were excluded. This study was approved by the Isfahan University of Medical Sciences ethics committee (IR. MUI. MED. REC.1398.737). Informed consent was obtained from patients or their first-degree families.

Data collection

A data gathering form was designed to include demographics, initial symptoms, co-existing disorders, and past medical histories. Patients who had resistant hypoxemia decreased level of consciousness, hemodynamic instability, hypercapnia/respiratory exhaustion, or those who developed complications were transferred to the ICU ward. Daily ICU records, including daily vital signs, imaging findings (computerized tomography [CT] scan/chest X-ray), daily laboratory results, medication dose and frequency, daily progress, ventilation data, electrocardiogram (ECG), and echocardiography were collected from patients' ICU records.

Chest CT scan and chest X-ray were reported by two experienced radiologists (S. H. A. and A. S.). In addition, ECG and echocardiography were reported by an experienced cardiologist (I. Z.). All complications were diagnosed and managed by a multidisciplinary team. Diagnosed complications were then charted in the daily ICU records. The cut-off date for data collection was April 13, 2020.

Outcomes

Demographic information, including age, gender, and patients' underlying disease, was reported in two groups of patients according to their outcomes (death vs. survivors). Furthermore, laboratory results variations were compared in the two groups. Daily complications were shown for all patients as day-by-day in figures.

Definitions

All complications, including ARDS, sepsis, secondary infection, cardiac ischemic event, cardiac arrhythmias, renal complications, pulmonary thromboembolism (PTE), pneumothorax, electrolyte imbalance, DIC, Bronchiolitis obliterans organizing pneumonia, brain complications, and liver complications, were defined and diagnosed based on the International Classification of Diseases (ICD-10).

Statistical analysis

Descriptive and inferential statistics available in SPSS 24 (IBM Corp. Armonk, NY, USA) were used to analyze collected data. Frequency and percentage were used to describe discreet variables, though the median and interquartile range were presented for continuous variables. A line graph was used to show the difference in laboratory changes over the admission course in the two groups of deceased and discharged. The correlation between discontinuous variables and treatment outcomes (death vs. survivor) was investigated using the Chi-square test, the level of significance and the odds ratio, and the upper and lower bounds of 95% confidence interval (CI) were reported. The point-biserial correlation was done to investigate the correlation between the continuous variables and treatment outcomes. In addition, binary logistic regression analysis was done to predict the effect of symptoms, therapeutic medications, and systemic complications on treatment outcomes. The inter method was applied to data, and besides the overall fitness of model, odds ratio with CI and *P* values, along with sensitivity and specificity of the model, were calculated and reported. Before performing each statistical

analysis, its basic assumptions were examined (expected frequency for Chi-square, absence of multicollinearity among the independent variables, and linearity to the logit for logistic regression, equality of variance, and normality of variances for point-biserial correlation). No evidence indicating the violation of these assumptions was observed. Because the dependent variable was dichotomous, and the purpose of the study was to examine the relationship and predict based on a series of continuous (interval and ordinal) and categorical independent variables, data were handled using methods suitable for predicting dichotomous dependent variables. In order to control the variations in patients' caring and treatment methods (as confounding variables), data were gathered from only one medical center. Other probable confounding factors such as demographic variables and past medical history were considered and analyzed. Because individuals included in the study have all the needed information, there were no missing data to handle.

RESULTS

Descriptive data

In this study, 51 ICU patients were included, of whom 27 patients (52.9%, confidence interval [CI]: 0.39–0.67) discharged with good condition, and 24 (47.1%, CI: 0.33–0.66) patients died the following admission. The median age of all patients was 63 years (Min: 20, Max: 84. The sample was comprised of 37 males (72.5%, CI: 0.60–0.85) and 14 females (27.4%, CI: 0.15–0.40). The median ICU duration of patients was 11 days (Min: 1, Max: 45). Mild-to-severe fever (temperature above 37.8°C) was reported in 28 patients (62.2%, CI: 0.49–0.76). Basic observations of patients' presenting symptoms on admission indicated the following as the most common symptoms: fever (62.7%, CI: 0.49–0.76), cough (66.7%, CI: 0.54–0.80), and 70.6% (CI: 0.58–0.83) of all patients had at least one coexisting disorder. Hypertension (37.3%, CI: 0.23–0.51) and coronary heart disease (37.3%, CI: 0.23–0.51) were the most common coexisting disorders amongst those admitted, followed by diabetes (29.4%, CI: 0.17–0.42).

Mechanical ventilation was used in 58.8% (CI: 0.45–0.72) of patients, and the median duration of both invasive and noninvasive ventilation was measured to be 1.06 and 4.51 days, respectively. In overall, 62.7% (CI: 0.49–0.76) of patients received oseltamivir, 72.5% (CI: 0.60–0.85) received hydroxychloroquine, 60.8% (CI: 0.47–0.74) received Lopinavir/Ritonavir, 7.8% (CI: 0.01–0.15) received ribavirin, 70.6% (CI: 0.58–0.83) received systemic glucocorticoids. Demographic characteristics, paraclinical findings, and clinical information are summarized in Table 1. Laboratory investigations on the 1st day of hospital admission showed that 7.7% (CI: 0.01–0.15) of patients had white blood cell (WBC) count of lower than 4000 per μL of blood, and 12.8% (CI: 0.04–0.23) of patients' had WBC count >10,000 per microliter of blood. The differential lymphocyte count was over 1500 in 7.9% (CI: 0.01–0.15) of patients. C-reactive Protein (CRP) was raised in 85.3% (CI: 0.76–0.96) of patients [Table 2].

Outcome associations

Older patients were more likely to die (Odds ratio 1.09, 95% CI 1.03–1.55, $P = 0.003$). Myalgia was the only presenting symptom showing a positive association with the outcome of treatment, and those presenting with myalgia were more likely to be discharged (odds ratio 0.16, 95% CI 0.05–0.57, $P = 0{\cdot}003$). The analysis of patients' past medical records showed those with Chronic Kidney Disease (CKD) had worse outcomes and were more likely to die (odds ratio 10.71, 95% CI 1.21–94.96, $P = 0{\cdot}01$). Those patients who received invasive ventilation were more likely to die (odds ratio 87.5, 95% CI 13.34–573.95, $P = 0{\cdot}0001$).

Figure 1 illustrates the daily variations in laboratory findings, including prothrombin time (PT), lymphocyte count, Creatinine (Cr), platelet (Plt) count, International Normalized Ratio (INR) level, and WBC count.

Other analyses

Cr level measurements were also not significantly different between the deceased and survivor groups on the majority of days. Only on the 11th and 12th day of admission, a significant difference was noted, and Cr measurements were higher among those recovered. PLT count graph reveals fluctuations within the scores of two groups, while there was only a significant difference observed on days 4 and 6. The mean score was higher amongst the recovered patients. The WBC graph also indicates consistent changes between the two groups, and the statistical analysis revealed the absence of any significant differences between the two groups during the study. Figures 2 and 3 show the patients' initial symptoms, medications, complications, and progress daily.

Among all patients recruited, sepsis, secondary bacterial infection, and arrhythmia event was more observed. Thirteen patients (25.5%, CI: 0.14–0.37) did not develop any complications [Table 3]. As shown in Table 4, the logistic regression analysis showed that complications including sepsis and secondary infection could significantly cause a difference between the survived and deceased patients. The presence of these complications is associated with a higher possibility of death. Because of a wide range of complications and low sample size each complication has a wide CI, so more studies with larger sample size are needed.

With regards to deceased patients, the accuracy of the statistical model to predict the outcome was

Table 1: Characteristics of deceased and surviving patients with COVID-19 infection in in ICU

Variable	All patients (*n*=51)	Death (*n*=24)	Survivors (*n*=27)	*P*
Demographics				
Age median (IQR) – years	63 (19)	71 (13.25)	56 (15)	0.001
Male sex – no./51 (%)	37/51 (72.54)	17/24 (70.83)	20/27 (74.07)	0.796
Co-existing disorders (past medical history):				
Any – no./51 (%)	36/51 (70.58)	20/24 (83.33)	16/27 (59.25)	0.051
Diabetes – no./51 (%)	15/51 (29.41)	10/24 (41.66)	5/27 (18.51)	0.066
Hypertension – no./51 (%)	19/51 (37.25)	11/24 (45.83)	8/27 (29.62)	0.234
Cardiovascular disease – no./51 (%)	19/51 (37.25)	9/24 (37.50)	10/27 (37.03)	0.989
Cerebrovascular disease – no./51 (%)	3/51 (5.88)	3/24 (12.50)	0/27 (0)	0.061
COPD – no./51 (%)	2/51 (3.92)	1/24 (4.16)	1/27 (3.70)	0.930
Asthma – no./51 (%)	2/51 (3.92)	1/24 (4.16)	1/27 (3.70)	0.929
Malignancy (any type) – no./51. (%)	3/51 (5.88)	3/24 (12.50)	0/27 (0)	0.062
Chronic kidney dx – no./51 (%)	8/51 (15.68)	7/24 (29.16)	1/27 (3.70)	0.001
Chronic liver disease – no./51 (%)	1/51 (1.96)	1/24 (4.16)	0/27 (0)	0.279
HIV – no./51 (%)	0/51 (0)	0/24 (0)	0/27 (0)	-
Others – no./51 (%)	15/51 (29.41)	5/24 (20.83)	10/27 (37.03)	0.210
Past drug history				
ARBs – no./51 (%)	10/51 (19.60)	4/24 (16.66)	6/27 (22.22)	0.623
ACE inhibitors – no./51 (%)	4/51 (7.84)	2/24 (8.33)	2/27 (7.40)	0.904
Others – no./51 (%)	29/51 (56.86)	14/24 (58.33)	15/27 (55.55)	0.843
Serum minerals				
Median potassium (K) (IQR) – mmol/l	3.7 (0.5)	3.7 (0.5)	3.6 (0.58)	0.652
Median sodium (Na) (IQR) – mmol/l	133 (5)	133 (3)	134 (4.75)	0.687
Median calcium (Ca) (IQR) – mg/dL	8.2 (1.25)	8.09 (1.56)	8.35 (1.15)	0.144
Median Mg (IQR)	2 (0.4)	1.95 (0.28)	2.05 (0.38)	0.270
Median *P* (IQR)	2.92 (1)	2.9 (2.15)	2.96 (0.90)	0.132
Blood gas				
Metabolic acidosis– no./total no. (%)	3/15 (20)	3/9 (33.33)	0/6 (0)	0.109
Respiratory acidosis– no./total no. (%)	6/15 (40)	1/9 (11.11)	5/6 (83.33)	0.009
Metabolic alkalosis– no./total no. (%)	0/15 (0)	0/9 (0)	0/6 (0)	-
Respiratory alkalosis– no./total no. (%)	1/15 (6.66)	0/9 (0)	1/6 (16.66)	0.207
Metabolic acidosis and respiratory acidosis– no./total no. (%)	2/15 (13.33)	2/9 (22.22)	0/6 (0)	0.224
Metabolic acidosis and respiratory alkalosis– no./total no. (%)	3/15 (20)	3/9 (33.33)	0/6 (0)	0.110
Metabolic alkalosis and respiratory acidosis– no./total no. (%)	0/15 (0)	0/9 (0)	0/6 (0)	-
Metabolic alkalosis and respiratory alkalosis– no./total no. (%)	0/15 (0)	0/9 (0)	0/6 (0)	-
The need for ventilator				
Mechanical ventilation (noninvasive+invasive) – no./51 (%)	30/51 (58.82)	22/24 (91.66)	8/27 (29.62)	0.001
Noninvasive – no./total no. (%)	12/51 (23.52)	5/24 (20.83)	7/27 (25.92)	0.673
Invasive – no./total no. (%)	23/51 (45.09)	21/24 (87.50)	2/27 (7.40)	0.007
Mean duration of non-invasive	1.06 (2.34)	0.79 (1.86)	1.30 (2.71)	0.453
Mean duration of invasive	4.51 (7.72)	7.95 (8.62)	1.44 (5.29)	0.009
Supplementary O_2				
Any type (canula + mask) – no./51 (%)	44/51 (86.27)	18/24 (75)	26/27 (96.29)	0.028
Canula – no./total no. (%)	21/51 (41.17)	4/24 (16.66)	17/27 (62.96)	0.007
Mask – no./total no. (%)	32/51 (62.74)	16/24 (66.66)	16/27 (59.25)	0.587
O_2 liter median (IQR)	6.1 (8)	7.5 (8.32)	4.3 (3.6)	0.743
Medications				
Oseltamivir – no./51 (%)	32/51 (62.74)	16/24 (66.66)	16/27 (59.25)	0.589
Hydroxychloroquine – no./51 (%)	37/51 (72.54)	16/24 (66.66)	21/27 (77.77)	0.381
Lopinavir/Ritonavir – no./51 (%)	31/51 (60.78)	13/24 (54.16)	18/27 (66.66)	0.358
Ribavirin – no./51 (%)	4/51 (7.84)	1/24 (4.16)	3/27 (11.11)	0.350
Systemic glucocorticoids – no./51 (%)	36/51 (70.58)	18/24 (75)	18/27 (66.66)	0.514
Outcomes				
Discharged from ICU – no./51 (%)	27/51 (52.94)			

IQR=Interquartile range; ICU=Intensive care units; COPD=Chronic obstructive pulmonary disease; HIV=Human immunodeficiency virus; ARBs=Angiotensin II receptor blockers; ACE=Angiotensin-converting enzyme; K=Potassium; Na=Sodium; Ca=Calcium; Mg=Magnesium; *P*=Phosphorus; O2=Oxygen

Table 2: First day of hospital symptoms, vital signs, in deceased and surviving patients with COVID-19 infection

Variable	All patients (*n*=51), *n* (%)	Death (*n*=24), *n* (%)	Survivors (*n*=27), *n* (%)	*P*
First day of hospital symptoms				
Fever – no./51 (%)	32/51 (62.74)	13/24 (54.16)	19/27 (70.37)	0.233
Chills – no./51 (%)	25/51 (49.01)	12/24 (50)	13/27 (48.14)	0.896
Dyspnea – no./51 (%)	30/51 (58.82)	14/24 (58.33)	16/27 (59.25)	0.947
Cough – no./51 (%)	34/51 (66.66)	13/24 (54.16)	21/27 (77.77)	0.069
Sore throat – no./51 (%)	5/51 (9.80)	1/24 (4.16)	4/27 (14.81)	0.196
Anorexia – no./51 (%)	9/51 (17.64)	3/24 (12.50)	6/27 (22.22)	0.358
Fatigue – no./51 (%)	16/51 (31.37)	9/24 (37.50)	7/27 (25.92)	0.373
Nausea – no./51 (%)	11/51 (21.56)	3/24 (12.50)	8/27 (29.62)	0.142
Vomiting – no./51 (%)	10/51 (19.60)	3/24 (12.50)	7/27 (25.92)	0.231
Body ache/myalgia – no./51 (%)	24/51 (47.05)	6/24 (25)	18/27 (66.66)	0.001
Abdominal pain – no./51 (%)	3/51 (5.88)	0/24 (0)	3/27 (11.11)	0.087
Diarrhea – no./51 (%)	8/51 (15.68)	2/24 (8.33)	6/27 (22.22)	0.169
Headache – no./51 (%)	8/51 (15.68)	0/24 (0)	8/27 (29.62)	0.005
Dizziness – no./51 (%)	1/51 (1.96)	0/24 (0)	1/27 (3.70)	0.340
Expectoration – no./51 (%)	17/51 (33.33)	5/24 (20.83)	12/27 (44.44)	0.069
Chest pain – no./51 (%)	0/51 (0)	0/24 (0)	0/27 (0)	-
Decrease level of consciousness (LOC) – no./51 (%)	4/51 (7.84)	2/24 (8.33)	2/27 (7.40)	0.90
First day of hospital admission vital signs				
Median temperature (IQR) – °C	38 (1.2)	37.9 (1.2)	38 (1.3)	0.263
Distribution of temperature≥37.8°C – no./total no. (%)	28/45 (62.22)	12/20 (60)	16/25 (64)	0.232
Peripheral capillary oxygen saturation (SpO2) %	85 (10)	85 (12.75)	87 (12)	0.671
SpO2<93% – no./total no. (%)	43/51 (84.31)	21/24 (87.50)	22/27 (81.48)	0.559
Median respiratory rate (IQR) –/minutes	25 (10)	25 (10)	26 (12)	0.353
Median heart rate (IQR) –/minutes	99 (27)	97 (29.25)	100 (28)	0.921
Median systolic blood pressure (IQR) – mm Hg	133 (25)	139 (29.75)	126 (29)	0.144
Median diastolic blood pressure (IQR) – mm Hg	79.5 (12.75)	75.5 (19.5)	81 (10)	0.182
Median GCS score	15 (0)	15 (0)	15 (0)	0.380
First day of hospital admission laboratory findings				
White-cell count				
Median (IQR) – per mm3	6500 (3500)	6700 (3750)	6500 (3500)	0.261
Distribution				
<4000 per mm^3 – no./total no. (%)	3/39 (7.69)	1/18 (5.55)	2/21 (9.52)	
4000–10,000 per mm^3 – no./total no. (%)	31/39 (79.48)	13/18 (72.22)	18/21 (85.71)	
>10,000 per mm^3 – no./total no. (%)	5/39 (12.82)	4/18 (22.22)	1/21 (4.76)	
Lymphocyte count				
Median (IQR) – per mm3	830.20 (398.08)	838.65 (494.22)	814.55 (350.85)	
Distribution				
<1500 per mm^3 – no./total no. (%)	3/38 (7.89)	2/18 (11.11)	1/20 (5)	0.487
Neutrophil count				
Median (IQR) – per mm^3	5103.6 (3598.55)	5402.55 (4620.30)	5103.6 (3450.02)	
Distribution				
<1800 per mm^3 – no./total no. (%)	3/38 (7.89)	2/18 (11.11)	1/20 (5)	0.198
1800–7800 per mm^3 – no./total no. (%)	30/38 (78.94)	12/18 (66.66)	18/20 (90)	
>7800 per mm^3 – no./total no. (%)	5/38 (13.15)	4/18 (22.22)	1/20 (5)	
Platelet count				
Median (IQR) – per mm^3	171,000 (66,000)	174,500 (80,250)	166,000 (52,500)	0.749
Distribution				
<150,000 per mm^3 – no./total no. (%)	14/39 (35.89)	8/18 (44.44)	6/21 (28.57)	-
Hb				
Median (IQR) – g/dL	13.6 (2.9)	13.2 (3.65)	13.7 (2.6)	0.679
Hct				
Median (IQR)	44.1 (9.33)	43.1 (11.70)	44.9 (8.6)	0.414

Contd...

Table 2: Contd...

Variable	All patients (*n*=51), *n* (%)	Death (*n*=24), *n* (%)	Survivors (*n*=27), *n* (%)	*P*
CRP				
Positive – no./total no. (%)	29/34 (85.29)	12/16 (75)	17/18 (94.44)	0.137
ESR				
Median (IQR) – mm/h	47 (44)	66.5 (62.25)	44 (25)	
>22 mm/h – no./total no. (%)	30/35 (85.71)	13/16 (81.25)	17/19 (89.47)	0.486
PTT				
Median (IQR) – s	33 (8.5)	33 (8)	33 (11)	
>39 s – no./total no. (%)	6/34 (17.64)	3/17 (17.64)	3/17 (17.64)	1.023
PT				
Median (IQR) – s	13 (0)	13 (0.4)	13 (0)	
>13 s – no./total no. (%)	7/34 (20.58)	4/17 (23.52)	3/17 (17.64)	0.669
INR				
>1.2 – no./total no. (%)	3/33 (9.09)	2/16 (12.50)	1/17 (5.88)	0.513
LDH				
Median (IQR) – U/l	871 (544)	936 (544)	871 (167)	
>530 U/l – no./total no. (%)	4/5 (80)	1/2 (50)	3/3 (100)	0.174
CPK				
>195 U/l – no./total no. (%)	2/4 (50)	1/2 (50)	1/2 (50)	0.997
Trop positive – no./total no. (%)	9/39 (23.07)	6/18 (33.33)	3/21 (14.28)	0.417
Cr				
Median (IQR) – μmol/l	99.008 (48.62)	96.356 (157.57)	99.008 (30.498)	
≥133 μmol/l – no./total no. (%) d4	9/39 (23.07)	6/18 (33.33)	3/21 (14.28)	0.156
AST				
Median (IQR) – U/l	51 (40.75)	46.5 (34.50)	63 (61.5)	
>40 U/l – no./total no. (%)	28/34 (82.35)	13/16 (81.25)	15/18 (83.33)	0.869
ALT				
Median (IQR) – U/l	33.50 (36.25)	22 (20.50)	54 (36)	
>40 U/l – no./total no. (%)	15/36 (41.66)	4/17 (23.52)	11/19 (57.89)	0.037
ALP				
Median (IQR) – U/l	162 (67)	155 (109.75)	165 (66)	
>300 U/liter – no./total no. (%)	4/35 (11.42)	2/16 (12.50)	2/19 (10.52)	0.860
Alb:				
Median (IQR)	4 (1.06)	3.985 (1.22)	4.07 (0.70)	0.451
<5.2 – no./total no. (%)	36/36 (100)	16/16 (100)	20/20 (100)	
T.Billi:				
Median (IQR)	0.86 (0.55)	0.87 (0.48)	0.85 (0.65)	
>1.2– no./total no. (%)	6/26 (23.07)	3/14 (21.42)	3/12 (25)	0.884
D.Billi:				
Median (IQR)	0.25 (0.27)	0.255 (0.32)	0.24 (0.29)	
>0.3 – no./total no. (%)	9/27 (33.33)	4/14 (28.57)	5/13 (38.46)	0.583

IQR=Interquartile range; GCS=Glasgow Coma Scale; Hb=Hemoglobin; Hct: Hematocrit; CRP=C-reactive protein; ESR=Erythrocyte sedimentation rate; PTT=Partial thromboplastin time; PT=Prothrombin time; INR=International normalized ratio; LDH=Lactate dehydrogenase; CPK=Creatinine kinase; Cr=Creatinine; AST=Aminotransferase; ALT=Alanine aminotransferase; ALP=Alkaline phosphatase; Alb=Albumin; T.Billi=Total bilirubin; D.Billi=Direct bilirubin

87.5% (sensitivity), and in patients who survived, the accuracy was 74.1% (specificity). Nagelkerke R^2 of the model was 0.62, which means adding predictors to the baseline model, improving model fit compared to null model.

The role of the lack of complications in predicting the treatment outcome (death or recovery) was analyzed separately, and the results showed that lack of complications between deceased and recovered patients is associated with the chance of recovery. Nagelkerke R^2 of model was 0.29, which means adding the lack of complications to the baseline model, improving in model fit compared to the null model.

Besides, the lack of complications in 68.6% of patients accurately predicted the outcome of treatment (i.e., death or recovery).

DISCUSSION

A minority of patients with COVID-19 would require transfer to ICU to receive specialist care.[18,19] However, this

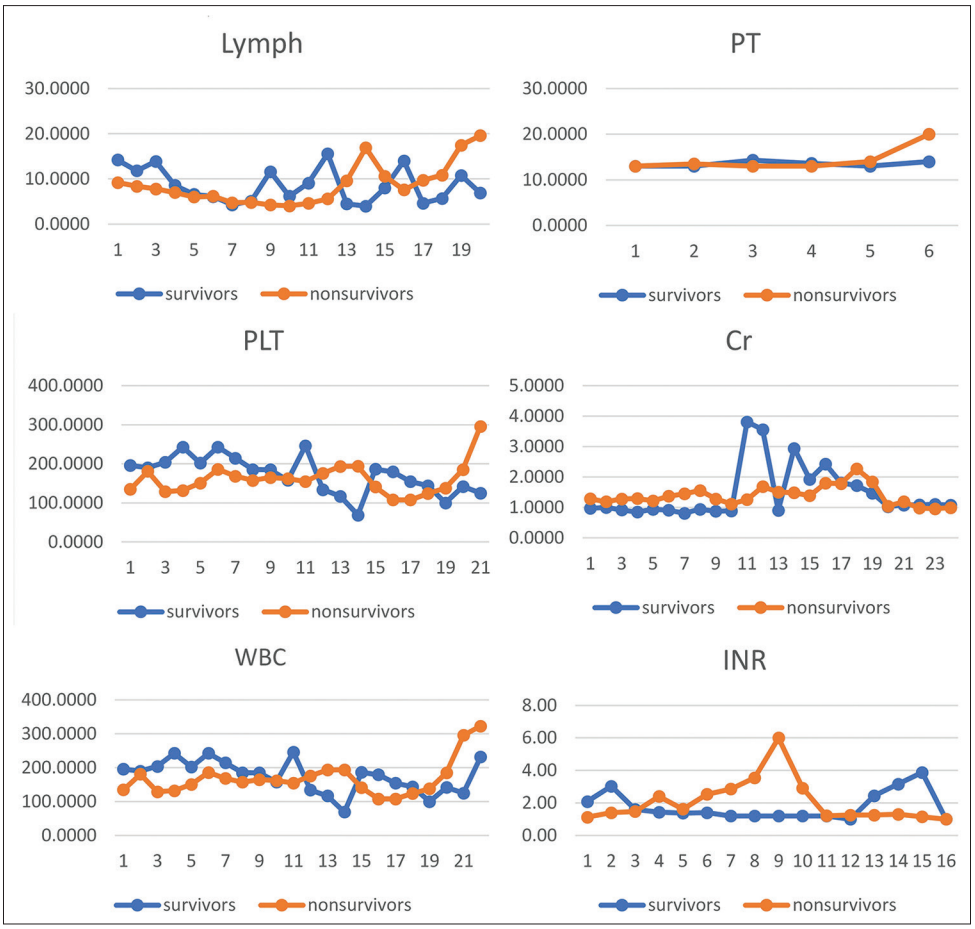

Figure 1: Daily variations in laboratory findings, compared in deceased and surviving patients

Table 3: In-hospital complications of intensive care unit-admitted patients

Variable	All patients (*n*=51; 100)	Death (*n*=24; 47.05)	Survivors (*n*=27; 52.94)	*P*
Sepsis-yes./51 (%)	12 (23.52)	10 (41.66)	2 (7.40)	0.005
ARDS-yes./51 (%)	4 (7.84)	3 (12.50)	1 (3.70)	0.031
Secondary infection-yes./51 (%)	12 (23.52)	10 (41.66)	2 (7.40)	0.037
Ischemic event-yes./51 (%)	7 (13.72)	5 (20.83)	2 (7.40)	0.042
Arrhythmia event-yes./51 (%)	23 (45.09)	14 (58.33)	9 (33.33)	0.954
Renal complication-yes./51 (%)	6 (11.76)	5 (20.83)	1 (3.70)	0.328
PTE-yes./51 (%)	2 (3.92)	1 (4.16)	1 (3.70)	0.896
Pneumothorax-yes./51 (%)	3 (5.88)	3 (12.50)	0	0.991
Electrolyte imbalance-yes./51 (%)	4 (7.84)	3 (12.50)	1 (3.70)	0.079
DIC-yes./51 (%)	4 (7.84)	3 (12.50)	1 (3.70)	0.131
BOOP-yes./51 (%)	0	0	0	0.958
Brain complication-yes./51 (%)	2 (3.92)	1 (4.16)	1 (3.70)	1.00
Liver complication-yes./51 (%)	1 (1.96)	0	1 (3.70)	0.004
No complication	13 (25.49)	1 (4.16)	12 (44.44)	0.001

ARDS=Acute respiratory distress syndrome; PTE=Pulmonary thromboembolism; DIC=Disseminated intravascular coagulation; BOOP=Bronchiolitis obliterans organizing pneumonia

fraction of the patients presents with different complications caused by COVID-19. Here, we investigated in-hospital complications that may affect COVID-19 patients' outcomes.

The most important complications among all patients in the course of admission were arrhythmia event, sepsis, secondary infection, ischemic event, renal complications, and ARDS, but other complications were observed as well. Our analysis showed that complications including sepsis and secondary infection had affected mortality the most.

Sepsis and secondary infection were the most expected complications in our study, correlating with the high rate of mortality, which is consistent with the findings

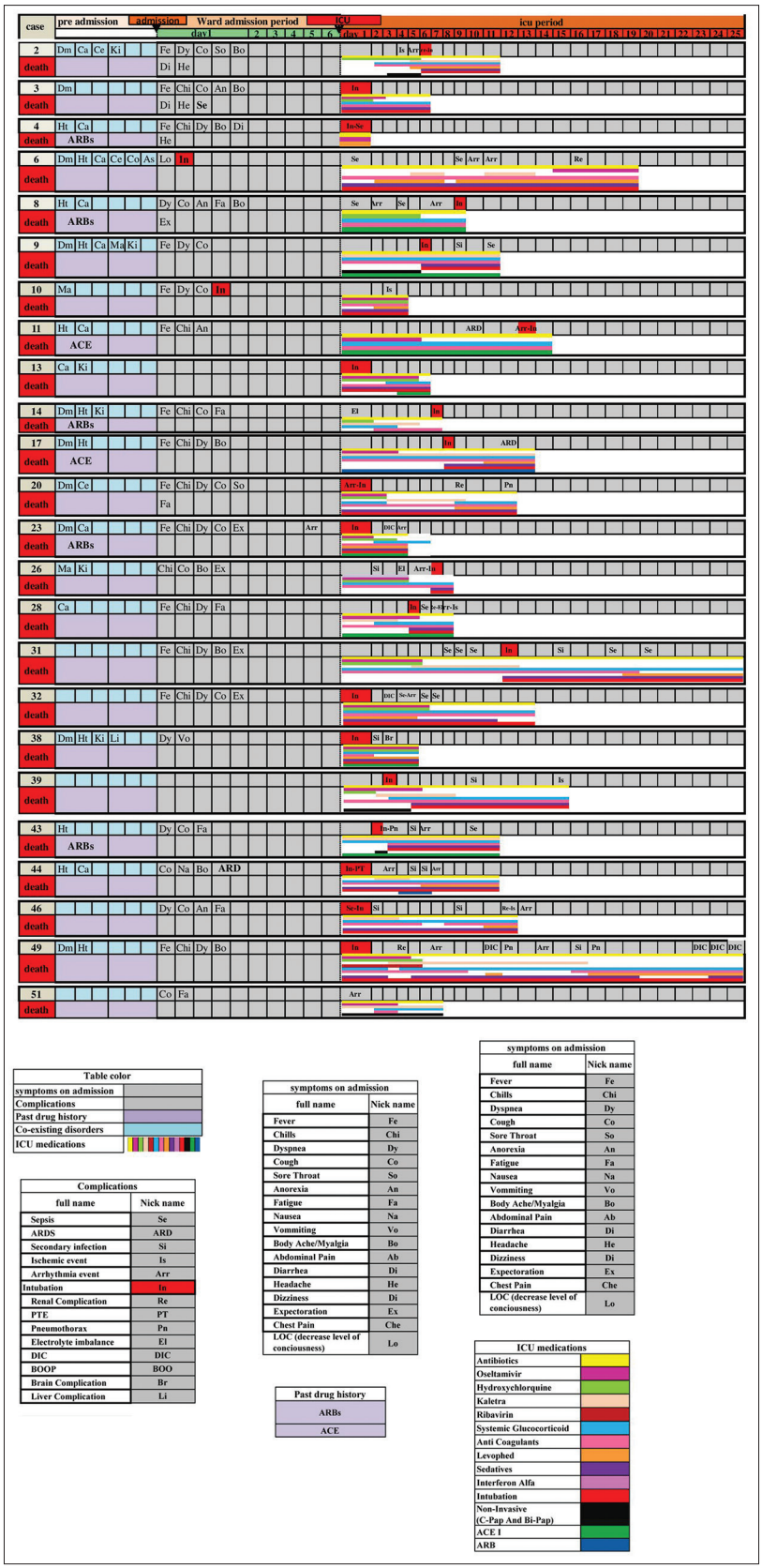

Figure 2: Deceased patients' daily progress

by Kumar *et al*.[20] COVID-19 is also associated with other complications. Neurological complications of COVID-19 can be divided into those affecting the central nervous system and peripheral nervous system.[21] We noted the

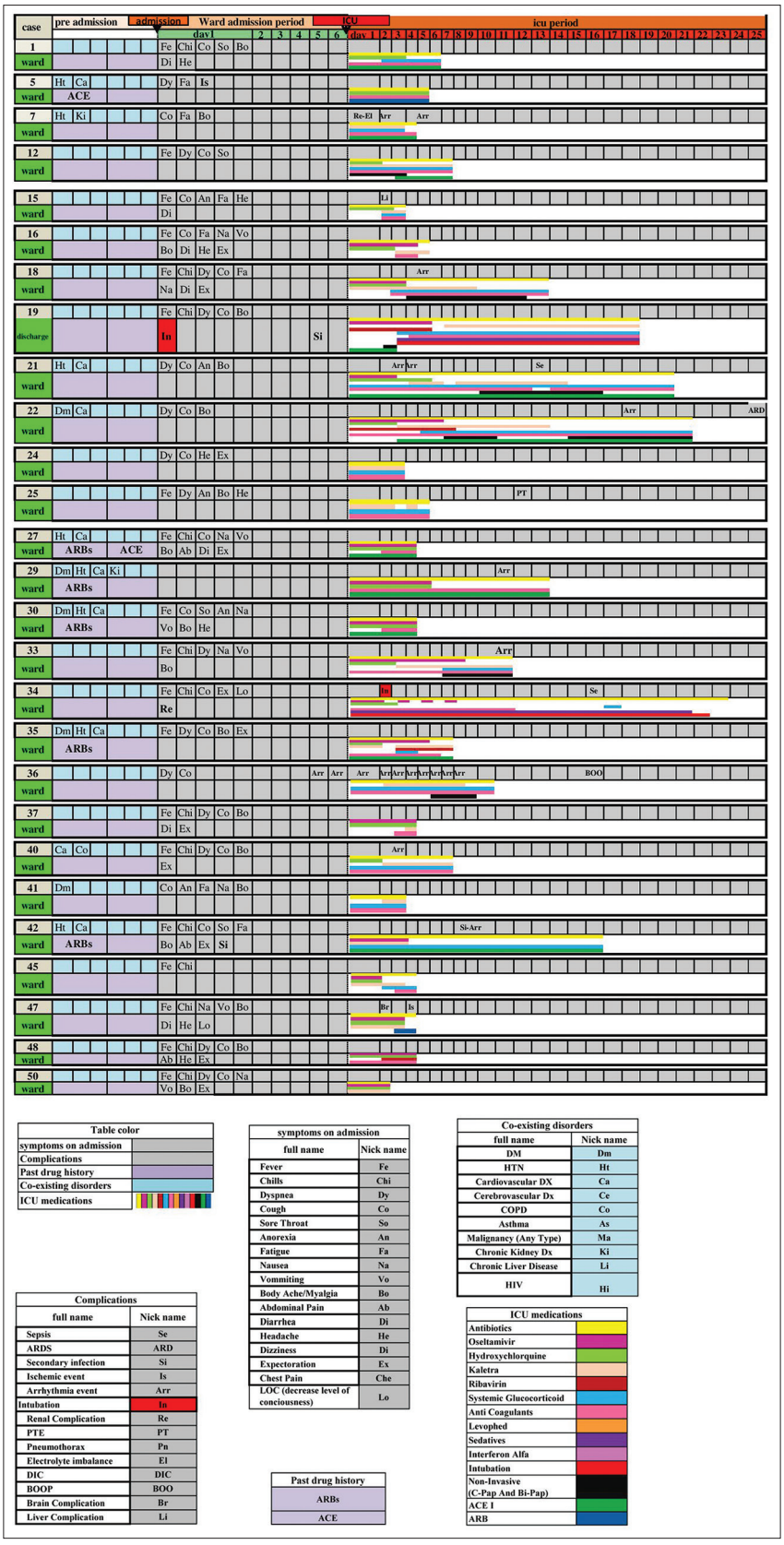

Figure 3: Discharged patients' daily progress

incidence of neurological impairments among the patients admitted to be 3.9%. This figure was 4.2% in deceased patients and 3.7% in discharged patients. In comparison, neurological findings including motor and memory

Table 4: The result of logistic regression for predicting definite outcome based on patients' complications

Predictor	OR	95% CI	*P*
Complication	18.40	2.16–156.57	0.008
Sepsis and secondary infection	8.05	2.11–30.63	0.002
No complication	0.05	0.006–0.462	0.008

OR=Odds ratio; CI=Confidence interval

impairment were noted in 14% of patients admitted to ICU, as shown by an observational study conducted in France.[22]

The arrhythmogenic effect of COVID-19 is not confirmed yet.[10] The arrhythmia observed in COVID-19 patients may be attributable to the use of hydroxychloroquine, azithromycin, and Kaletra. The majority of clinical trials worldwide included hydroxychloroquine to treat severe cases of COVID-19.[23,24] The present study was not an exception; hence, it would be difficult to attribute the incidence of arrhythmia (45.1%) to COVID-19 alone.

SARS-CoV-2 mainly targets ACE-2 receptors on cell membranes, which are abundant in blood vessels. In a similar mechanism to MERS-CoV, patients may suffer from thrombotic microangiopathies such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome.[25] The incidence of thrombotic events in the present study was 3.9% among all patients (4.2% in deceased vs. 3.7% among discharged). In contrast, this figure was noted to be 31% in a larger cohort of ICU patients in the Netherlands.[26] Therefore, prophylactic antithrombotic treatment should be part of the clinical trials in patients admitted to ICU.[27] We noted the incidence of PTE to be 3.9% based on CT pulmonary angiogram findings, complicating the clinical state of COVID-19 patients. Patients with COVID-19 often experience coagulation impairments necessitating the administration of prophylactic heparin.[28] It is alarming that PTE may still occur despite adequate treatment with low molecular weight heparin.[29]

The incidence of secondary infection was noted to be 14.5% among those discharged alive and 19.5% among those who died in a cohort study by Amit *et al*. We noted these figures to be 41.7% and 7.4% among deceased and survived patients in our study, respectively. Furthermore, the incidence of sepsis was noted to be 23.5% in general, 41.7% in deceased patients, and 7.4% among discharged patients in our study in comparison with the results of the cohort study by Amit *et al*., which reported the following figures: 13.5% among all patients, 4.3% among discharge patients, and 21% in patients who died.[30]

AKI is strongly associated with the clinical course and outcome in patients admitted to the hospital with COVID-19. Yang *et al*. showed that serum Cr elevation was 9.6%, and the elevation of BUN was 13.7%.[31] In our study, renal complications and electrolyte imbalance were observed in 20.8% and 12.5% of the deceased patients and 3.7% of the discharged patients, respectively. AKI incidence in all patients with COVID-19 is estimated to be 3%–15%, while this proportion increases significantly to 15%–50% in patients admitted to ICU.[32] The mortality rate is reported to be higher among patients with renal complications.[33] The result of our study showed that patients with CKD had a poorer outcome and were more likely to die, similar to results by Adapa *et al*.'s study.[34]

A previous cohort study by Zhou *et al*. indicated fever, cough, sputum production, and fatigue as the most common presenting symptoms, while an epidemiological study showed that 20% of patients could be asymptomatic.[35] Rodriguez-Morales *et al*. reported fever, cough, and dyspnea as the most common initial presentations, respectively.[36] Similarly, the following prevalence of symptoms was noted in the present study: cough (66.7%), fever (62.7%), and dyspnea (58.8%). In our study, myalgia and headache were the only presenting symptoms associated with a positive outcome (discharge). However, a meta-analysis by He *et al*. concluded that headache and myalgia are general characteristics of the disease and are not more prevalent in mild or severe patients.[37] Therefore, more investigation is needed to confirm this finding due to the limited number of patients in our study.

In a large-scale study on patients with COVID-19 admitted to ICU in Italy, 68% of patients were suffering from at least one underlying disorder, and hypertension was the most common condition. The most prevalent chronic disease affecting those who died in ICU was also noted to be hypertension.[38] Besides, Rodriguez-Morales *et al*. showed that ICU admission was needed by 20.3% of patients admitted to the hospital, 32.8% of patients were diagnosed with ARDS, and 6.2% presented with shock. The mortality rate was noted to be 13.9% among hospitalized patients. These results are consistent with our findings, which showed that hypertension and chronic heart disease were the most common coexisting disorders in admitted patients. ARDS can directly correlate with patients' mortality; hence, it can be used as a predictive factor of mortality.[39]

Grasselli *et al*. showed that most patients admitted to ICU (99%) required invasive or noninvasive respiratory support. This proportion was noted to be 58.8% in our study. Moreover, up to 88% of patients admitted to ICU may require endotracheal intubation, and 11% may only require noninvasive ventilation. These proportions were 45.1% and 23.5% in our study, respectively. We noted that 87.5% of patients who died required invasive ventilation, as

consistent with our findings, patients who were intubated had a higher death likelihood.[38]

The most common causes of ICU admission amongst patients were noted to be a respiratory failure and subsequent hypoxemia.[40] Our study did not note a correlation between the need for noninvasive ventilation and outcome, whereas patients who required invasive ventilation were more likely to die.

We did not observe a significant difference between laboratory findings among deceased and survived patients; However, ALT over 40/L was associated with a higher chance of discharge. In contrast, Elevated WBC, high ALT and AST, raised LDH, increased procalcitonin can predict the risk of ICU admission, ARDS, and Mortality.[41] This study identified more significant complications, which can help clinicians to recognize lethal complications and reduce mortality. Furthermore, these findings can help policymakers allocate ICU beds to a more critical patient group.

There were certain limitations in this study. We recorded a large volume of clinical and paraclinical information daily. Despite providing valuable information, the heterogeneous nature of data led to a multiplicity of analyses. On the other hand, the categorical nature of most variables made it impossible to use methods with higher statistical power, which may have led to false-positive findings. Although all medical centers in Iran follow the same treatment protocols, each hospital, depending on the facilities and specialized staff, may have some differences in patients' management. Therefore, generalization of the findings of this study to other centers' patients, especially in small cities and low-income provinces, needs to be done with caution.

CONCLUSION

Patients with systemic complications including sepsis and secondary bacterial infection had more adverse outcomes with significantly associated with mortality. In addition, intubated patients had a worse prognosis compared to those who required noninvasive ventilation. Therefore, it is necessary to recognize lethal complications early and prevent the patients' clinical course's worsening. Future studies are needed to evaluate the incidence of COVID-19 complications daily in a multicenter cohort of patients.

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Conflicts of interest

There are no conflicts of interest.

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