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Original Article

Survival Analysis of Delta versus Omicron Variants in COVID-19 Intensive Care Unit (ICU)

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ABSTRACT

Objective: COVID-19 has presented numerous epidemiological and clinical pictures from its beginning and much effort has been paid to detect the behavior of disease and its new types. Therefore, in this study, we aimed to compare the in-hospital survival time of Delta and Omicron variant patients admitted to the intensive care unit.
Methods: This was a secondary data analysis of the QCOVICU data registry of 200 COVID-19 patients admitted to the ICU of Shahid Beheshti-Amir Al-Momenin Hospital of Qom City, in 2021. Likewise, time to event data, demographics, and baseline laboratory data was collected. Time of transfer to ICU, survivals, and possible predictors of hazards of death was compared within the variants of Omicron and delta.
Results: Two hundred patients (62.98±19.94 years old, 94 females/106 males; 100 Delta and 100 Omicron variant) participated in this study. Fifty percent of the population had died. Cross-tabulation showed comparable death rates among variants of delta and omicron (50.5% vs. 51%; p=0.999). There was a statistically significant higher time to ICU admission in Delta variant victims than in Omicron variant victims. The mean survival time of delta variant patients was 21.52 days (95% CI: 17.96 – 25.09) which was statistically higher than the mean survival of omicron patients (17.15 days, 95% CI: 13.65-20.64, p=0.018). The mean survival time of delta variant patients was statistically higher than omicron patients (21.52 vs. 17.15 days, p=0.018). Gender, age (years), and lymphocyte count were significant predictors of mortality based on the Cox regression analysis (P>0.05). There was a 5.9 times higher risk of mortality in females compared with males' gender after adjusting for other variables and a 5.6% increase in death risk with a 1-year increase in age, and a 31.8% decrease in death risk with a 1% lymphocyte percentage increase.
Conclusion: Critically patients with Delta variant are getting ICU admitted later and withstand more days at ICU than Omicron patients. It seems that Omicron variant causes sudden deterioration of the patient's condition.

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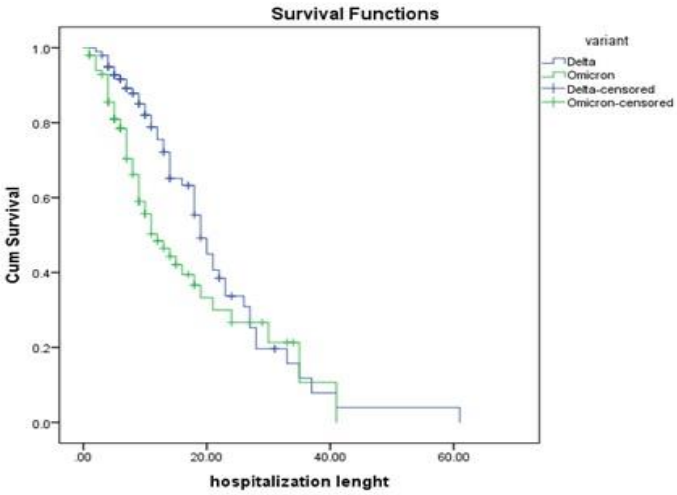
GRAPHICAL ABSTRACT



Introduction

According to the International Committee on Classification of viruses, the Sars-COV-2 virus, in the family of coronaviruses, have had caused widespread epidemics with a wide range of clinical entities in several countries since late 2019 [1-7]. Researchers are still investigating the possibility of animal intermediaries in the COVID-19 transmission to humans [8]. Initial reports indicate that patients with COVID-19 were related to store-related activities [9]. After the widespread pandemic, every year new variant of COVID-19 started to emerge. COVID-19's latest strain, Omicron, was spinning in different countries and the number of new viruses went on the rise [10]. Omicron virus is a new strain and mutated type of coronavirus or SARS-CoV-2, which was identified for the first time in South Africa in November 2021 [11, 12]. According to research, more than 50 mutations have occurred in this type of coronavirus [13]. This new strain of coronavirus is known to emerge as part of the natural process of viruses, that viruses evolve and castrate until they have the possibility of infecting people, multiplying, and is transmitted from person to person, according to the declaration of World Health Organization (WHO) [10]. All strains and variants of viruses are not dangerous and only those that can infect and transmit people are dangerous and we should be concerned about them [10]. Compared with previous variants like Delta, Omicron's severity of the disease is not well studied, especially in Iran. Given that the rapid genetic and evolutionary diversity in the emergence of the new COVID-19 variant, it is necessary to have estimates of their pathogenicity in comparison to each other.

Materials and Methods

This was a secondary data analysis study. The protocol of this study was registered at Qom University of Medical Sciences with Ethical Code of "IR.MUQ.REC.1401.095" and confirmed with all QCOVICU data registry stakeholders. All ethical consideration for the protection of the privacy of patient data was taken into account.

Data source

QCOVICU data registry was used for this study [11]. This registry includes a dataset of 200 COVID-19 patients admitted to the ICU of Shahid Beheshti-Amir Al-Momenin Hospital of Qom City, in 2021. The data is collected, retrospectively, by a chart review method, using a standard checklist and trained abstractors.

Study population

The whole QCOVICU study population was used in this investigation with no age refinements.

Variables

Demographic variables of age and sex were used. There were no pre-existing disease data in the registry. Age was used as a continuous variable. Laboratory data serial measurements were not retrieved from the QCOVICU dataset, while the admission time laboratory data was collected. The length of hospital stay was considered as the time variable. The length of ICU stay was also collected. The hospital stay with the subtraction of ICU stay was considered as the time of ICU admission which was considered as a variable to address how fast people's medical situation get deteriorated and an ICU hospitalization gets a necessity. Death was the final outcome. Discharge was a censored event.

Data preparation

All the data was stratified based on the status of the COVID-19 variant. The categories of death and COVID-19 variant were mixed to make a new variable named "status", which had 4 categories of Delta variant survivor, Delta variant victim, Omicron variant survivor, and Omicron variant victim.

Statistical analysis

The description of data was performed by numbers and percentages for categorical data as well as by the mean and standard deviation for the continuous data. All analyses were performed on SPSS version 24. One-way ANOVA was utilized to compare the time of transfer to ICU between groups and the post hoc Tukey test for further comparison. Kaplan–Meier test was used to calculate the survival time that we stratified based on the variant of the virus using the log-rank test. All other variables were entered into a Cox regression for the assessment of death hazard ratios. Chi-square was used for cross-tabulation.

Results and Discussion

QCOVICU data registry is described elsewhere [14]. However, there were 200 patients with a mean age of 62.98±19.94 years old, ranging from 2 to 98 years old of which 94 are female. There are 100 Delta and 100 Omicron variant patients. Fifty percent of the population had been died. The mean hospitalization length was 11.93±9.23 days. ICU length of stay was 4.72±6.47 days. The mean LDH was 699.06 U/L; theCRP average within the dataset was 66.63 mg/L; the mean CPK was 425.97 mcg/L; the mean creatine was 1.38 mg/dL; the mean platelet was 200.55 count per microliter, the mean ESR was 42.65 mm/hr, the mean WBC was 9009 count per microliter; the mean neutrophil, and lymphocyte percentage were 82.29 and 12.97 counts per microlite, respectively. Cross-tabulation showed comparable death rates among variants of delta and omicron (50.5% vs. 51%; p=0.999).

As shown in Figure 1, the mean survival time of Delta variant patients was 21.52 days (95% CI: 17.96 – 25.09) which was statistically higher than the mean survival of omicron patients (17.15 days, 95% CI: 13.65-20.64, p=0.018).

Gender, age (years), and lymphocyte count were significant predictors of mortality based on the Cox regression analysis ($p < 0.05$). The hazard ratio for the female gender was 5.97 (95% CI 1.58-22.46, $p = 0.008$) times more than male subjects, indicating a higher risk of mortality for females compared with the male gender after adjusting for other variables. The hazard ratio for age was 1.056 (95% CI 1.018-1.097, p =0.004), showing a 5.6% increase in death risk with a 1-year increase in age. The hazard ratio for lymphocyte count was 0.682 (95% CI 0.473-0.985, p =0.041), showing a 31.8% decrease in death risk with a 1% lymphocyte percentage increase, as presented in Table 1.

Figure 2 displays the time of transfer to the ICU in COVID-19 patients. Patients who survived the Delta variant had a shorter time of transfer to the ICU (7.24±3.99 days) compared with victims (9.28±10.59 days). Patients who survived the Delta variant had a shorter time of transfer to the ICU (7.97±5.97 days) compared with victims (4.41±5.88 days). There was a statistically significant higher time to the ICU admission in Delta variant victims than in Omicron variant victims (p=0.001). Our study's results showed the possibility of gradual clinical status deterioration in Delta variant patients compared with the Omicron variant.

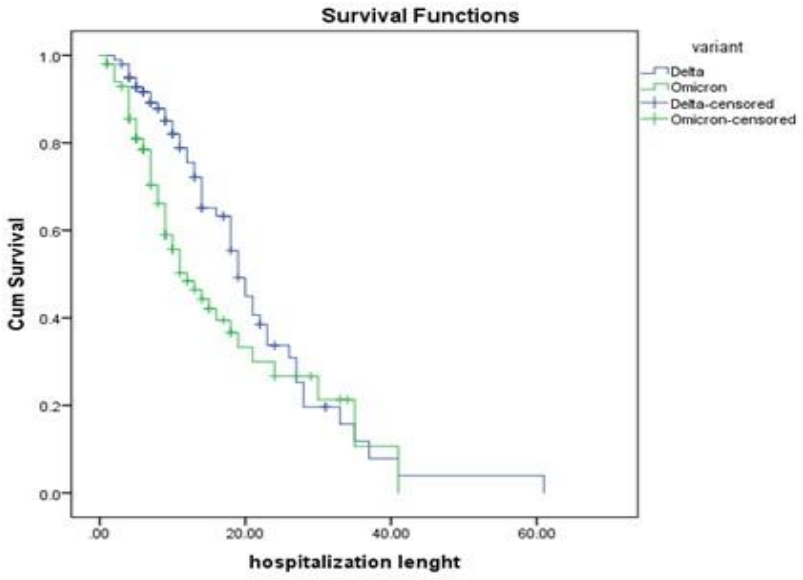


Figure 1: Kaplan–Meier curve of the variant of COVID-19 for survival time

Table 1: Cox regression analysis of hazard ratios for study variables

	B	HR	95.0% CI for HR		P
			Lower	Upper	
Variant (Delta vs. Omicron)	-0.424	0.654	0.230	1.863	0.427
Gender (female vs. male)	1.787	5.973	1.588	22.463	0.008
Age	0.055	1.056	1.018	1.097	0.004
LDH	0.000	1.000	0.998	1.002	0.752
CRP	0.003	1.003	0.989	1.017	0.653
CPK	0.001	1.001	1.000	1.001	0.081
Creatinine	-0.581	0.559	0.202	1.546	0.263
Platelet	-0.003	0.997	0.990	1.004	0.425
ESR	0.015	1.015	0.994	1.037	0.156
WBC	0.000	1.000	1.000	1.000	0.524
Neutrophil percentage	-0.150	0.860	0.636	1.164	0.329
Lymphocyte percentage	-0.382	0.682	0.473	0.985	0.041

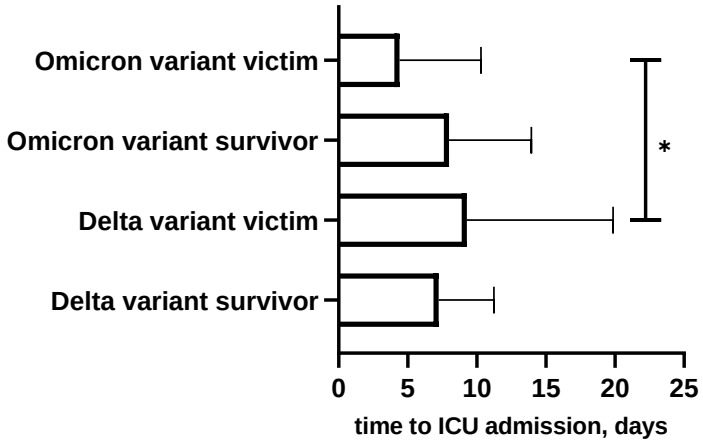


Figure 2: Time of transfer to the ICU in COVID-19 patients

However, it cannot be conclusive as the results of our time-to-event analysis indicate that Omicron survival in ICU is less than delta. This might show that in case of getting critically ill, Omicron manifests much more severely, whilst our study has some other limitations that we cannot generalize our findings. We did not study vaccination status, treatments provided for patients, and preexisting diseases. It seems that the Omicron variant causes sudden deterioration of the patient's condition. However, outcome measures like using mechanical ventilation would better fit this study question.

In a study by Murillo-Zamora *et al.*, hospital stay length was 9.7 ± 7.9 and 7.1 ± 5.8 for Delta and Omicron with significant differences, respectively [15]. In our study, it was 13.94±9.91 and 9.95±8.08 for Delta and Omicron which matches Murillo-Zamora *et al.* study, while our participants were ICU admitted and might have had longer hospitalization due to this fact. In another study, the same pattern of lengthier hospitalization of delta ones than omicron was observed in inpatient mild and moderate cases of COVID-19. Death rates were also comparable between delta and omicron patients [16]; as well as our study.

However, there were statistically significantly fewer hazards of death in Omicron than Delta in the study of Nyberg *et al.* [14]. While we found faster ward-to-ICU transfer in omicron than delta, we did not evaluate the effects of other variables on this, but Tobin *et al.* [18] showed that age was significantly affecting the time of ward-to-ICU transfer. Yet, we found that the hazard ratio for the age was 1.056 (95% CI 1.018-1.097, p =0.004), showing a 5.6% increase in death risk with a 1-year increase in age. Most other studies have evaluated the effect of the variants of SARS-COV2 on the hazards of the admission to hospital [19]. In the NHS datasets of the UK, fewer hazards of mortality were observed for omicron than Delta [20]. This is in contrast with our findings, but the main population of the study was not ICU-admitted. Sampling would be important in the determination of rates of mortality. Yadav *et al.* chose a random sample of hospitalized patients and found similar rates of mortality among Delta and Omicron variants as well as our study. However, the hospitalization length was longer in the Omicron group [21].

The results of the study suggested that patients with the Delta variant who did not survive had a long time to transfer to the ICU than those who survived. This is somewhat different from other studies like the Dahn *et al.* study, where the mortality rates were higher during the surge period for both COVID-19 positive and negative patients who required unexpected ICU transfer within 24 hours of admission to a non-ICU level of care. However, it should be noted that Dahn *et al.* did not specifically differentiate between different variants of COVID-19 [22]. In Hashmi *et al.*'s study, the median time to transfer to the ICU was 2.5 days. This is shorter than the time of transfer to ICU reported in our study for both victims and survivors of Delta variant. However, Hashmi *et al.*'s study did not differentiate between different variants of COVID-19, and the study sample and design were different from our study [23]. Chen *et al.*'s study evaluated the transfer outcomes of critically ill COVID-19 patients who required mechanical ventilation. our study also assessed the time of transfer to the ICU, but focused on the Delta and Omicron variants. The mortality rates reported in Chen *et al.*'s [24] study were similar between the transferred patients and emergency department admits, which is different from our study where Delta variant victims had a statistically significant higher time to the ICU admission than Omicron variant victims.

Limitations

Potential unknown and known factors might affect the study findings as well as the vaccination status, treatments provided for patients, and preexisting diseases of patients.

Strengths and weaknesses

The strengths of this study were the comparison of the outcome of Delta and Omicron variants of COVID-19 based on the adjusted laboratory data, assessed with standard kits, and performed in a single center with the same laboratory machine and teams, while its generalizability got affected due to being the single center and these findings

should be interpreted with cautions for providing health policies of other clinical centers.

Conclusion

In the present study, the expression of serotonin and ghrelin was not changed by elemental iron, *Curcuma xanthorrhiza* Roxb., or the combination treatment. Our study is the first to identify a correlation between the induction of restricted feed and expression of serotonin and ghrelin. However, malnutrition was successfully induced in rats. However, no significant differences were observed between the treated groups. Further research is required to determine the effects of iron and *Curcuma xanthorrhixa* Roxb. supplementation in the presence of food restrictions. Additional analyses using enhanced macronutrient diets and supplementation following the malnutrition induction period should be performed. The present study suggests the scope for future research with a more detailed examination of the containment of active compounds in *Curcuma xanthorrhixa* Roxb., usage of different doses, and a more extended period of observation.

Acknowledgments

Despite the limitations of the study, we highlighted the importance of monitoring new COVID-19 variants on patients' outcomes. Healthcare providers need to consider the potential clinical differences among COVID-19 variants when providing care and making treatment decisions.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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