Comparison of the prognosis and mortality of Sars-Cov-2 variants in critically ill patients

ABSTRACT

Backround

Since the beginning of the pandemic,the globally circulation of SARS-CoV-2 has caused the virus to constantly mutate,resulting in the emergence of new variants.Some of these variants have been designated as variants of concern(VOC),defined by the WHO as variants associated with increased infectivity,increased disease severity,or change in clinical disease presentation.

Aim and objective

We aimed to evaluate and compare the prognosis and mortality of the critically ill patients infected with SARS-CoV-2 and SARS-CoV-2 variants.

Materials and methods

A total of 335 critically ill patient who were positive for SARS-CoV-2 by polymerase chain reaction enrolled in the study.

Results

Hypertension was significantly higher in the patients in delta group(p=0,02).The presence of comorbidity was statistically significantly associated with mortality in all groups(p <0,05). Unvaccinated patients were significantly higher in all groups and being unvaccinated was associated with mortality in all groups(p <0,05).Mortality was statistically significantly associated with all groups(p=0,01).The delta variant poses a higher risk of mortality compared to other variants(p=0,0001).

Conclusion

The study indicates that severe disease requiring intensive care admission were common in the elderly.Hypertension was higher in the patients in delta group and the presence of comorbidity was associated with mortality in all variant types of COVID-19.Severe disease requiring intensive care admission was more common in the unvaccinated population, regardless of variant type, and being

unvaccinated was associated with mortality.All variant types were associated with mortality, but the mortality risk was higher in patients infected with delta variant compared to other variants.

Key words: COVID-19,variants of concern,mortality,prognosis,unvaccinated

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first detected in Wuhan, China, in December 2019 and rapidly spread all over the world. The World Health Organization (WHO) declared Coronavirus disease of 2019 (COVID19) a global pandemic in March 2020.[1]

All viruses, including SARS-CoV-2 that cause COVID-19, evolve continuously as changes in the genetic code (genetic mutations) occur during the replication of the genome. Most genetic variations occur as a result of drift and have little or no effect on the traits of the virus. Since the beginning of the pandemic, the globally circulation of SARS-CoV-2 has caused the virus to constantly mutate, resulting in the emergence of new variants. Some of these variants have been designated as variants of concern (VOC), defined by the WHO as variants associated with increased infectivity, increased disease severity, or change in clinical disease presentation.[2]

The first identified SARS-CoV-2 VOC was the Alpha variant (B.1.1.7), that was first documented in the United Kingdom in September 2020[3] and had increased transmissibility compared with the previous wildtype lineage.[4] The other VOCs were the Beta variant (B.1.351) which was first documented in South Africa in October 2020 and the Gamma variant (P.1), that was first documented in Brazil in November 2020.[5] The delta variant (B.1.617.2) was first documented in India in December 2020 and was designated as a VOC on May 6, 2021.[6] The viral load of the delta variant was higher than the other VOCs[7] and the delta variant has been associated with a higher risk of hospitalization, more severe outcomes, admission of ICU, and mortality than other variants.[8-10]

Various studies have been conducted examining the high contagiousness, the need for hospitalization, disease severity and mortality rates of these variants.[8-11]

We aimed to evaluate and compare the prognosis and mortality of the critically ill patients infected with SARS-CoV-2 and SARS-CoV-2 variants in our study.

MATERIALS AND METHODS

Study Design

This retrospective single center observational study was performed between May 1st,2021 and September 30th,2021 in Ersin Arslan Training and Research Hospital Mücahitler Covid Intensive Care

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Patients

All patients who were admitted to Ersin Arslan Training and Research Hospital Mücahitler Covid Intensive Care Units due to COVID-19 infection from May 1st,2021 and September 30th,2021 were included (n=375). The exclusion criteria was negative PCR(polymerase chain reaction) (n=40). At last, 335 patients were enrolled the study.

Clinical data collection

Data was collected a five month period (May 2021 –September 2021) using the intensive care units(ICUs) database; all patients who tested positively for COVID-19 were evaluated. Data collection included demographic data, comorbidities, vaccination status, PCR test results, severity of disease. Prognosis was evaluated in terms of mortality, need of renal replacement therapy, need of mechanical ventilation and the length of ICU stay. According to the PCR test results, the patients were grouped as follows; SARS-CoV-2 (Orf1ab+N), delta (B.1.617.2), alpha (B.1.1.7), other mutant (beta, gamma, eta, zeta, theta, lota; one of the variants containing E484K mutation) .

Statistical analysis

The sample size was determined 95% confidence interval and 90% power of test in this study. Chi-Square Test was used for statistical analyzed.

RESULTS

Characteristics of Patients With COVID-19

A total of 335 critically ill patients with positive PCR test enrolled our study. Of these patients 154 (45,97%) were in SARS-CoV-2 group, 121 (36,11%) were in delta group, 51 (15,22%) were in the other mutant group and 9 (2,68%) were in the alpha group. The patients of SARS-CoV-2 group involved 89 male, 65 female, delta group 68 male,53 female, other mutant group 30 male, 21 female and alpha group 6 male,3 female . Although male gender was more common in all groups, there was no statistically significant relationship.

The mean age of patients with SARS-CoV-2 group was 64,48±2,18, delta group was 64,74±2,81, the other mutant group was 64,8±4,3 and the alpha group was 66,9±7,28. Compared to the other groups,the proportion of the patients aged between 41-60 was significantly higher in SARS-CoV-2 group(p=0,05). In SARS-CoV-2 group 57 (30,64%), in delta group 85 (45,69%), in other mutant group 37 (19,89%) and in alpha group 7 (3,76%) patients had comorbidty. Hypertension was significantly higher in the patients in delta group(p=0,02). The presence of comorbidity was statistically significantly associated with mortality in all groups(p <0,05).

44 (48,8%) patients in SARS-CoV-2 group, 29 (32,2%) patients in delta group, 13 (14,4%) patients in other mutant group, 4 (4,4%) patients in alpha group were fully vaccinated. Unvaccinated patients were significantly higher in all groups and being unvaccinated was associated with mortality in all groups (p<0,05) .(Table 1,Table 2)

Outcomes

The patients who needed tracheal intubation were significantly higher in SARS-CoV-2 group (p=0,04). There was no significantly difference for needing renal replacement theraphy among the groups. The length of icu stay were in SARS-CoV-2 group; 10,31±1,37 days, in delta group 9,73±1,2 days, in other mutant group 9,76±1,52days and in the alpha group 7,9±4,7 days respectively. Mortality rate was from high to low as SARS-CoV-2, delta, other mutant and alpha groups, and mortality was statistically significantly associated with all groups (p=0,01). The delta variant poses a higher risk of mortality compared to other variants(p=0,0001). (Table 1,Table 2)

Table 1.Characteristics and outcomes of patients with Covid19

Parameters	**n**	**Mean**	**SD**	**95% CI**
Ages	335	64.6 (20-95)	14.98	± 1.52
20-40	17	5.1%	0.23	± 0.02
41-60	106	31.7%	0.46	± 0.04
>60	212	63.2%	0.48	± 0.04
Gender				
Male	193	57.6%	0.49	± 0.05
Female	142	42.4%		
Comorbidity				
Yes	186	55.5%	0.48	± 0.05
No	149	44.5%		
Hospital Stay (days)	335	9.95 (1-45)	Tem.47	± 0.79

	Sars-CoV-2	**Delta**	**Other Mutant**	**Alpha**
	n(%)	n(%)	n(%)	n(%)
Gender	154 (45,97%)	121 (36,11%)	51 (15,22%)	9 (2,68%)

Male	89 (46.1%)	68 (35,2%)	30 (15,5%)	6 (3,1%)
Female	65 (45,7%)	53 (37,3%)	21 (14,7%)	3 (2,1%)
Ages	64,48±2,18	64,74±2,81	64,8±4,3	66,9±7,28
20-40	5(29,4%)	9(52,9%)	3(17,6%)	0
41-60	57(53,7%)	31(29,2%)	16(15%)	2(1,8%)
>60	92(43,4%)	81(38,2%)	32(15%)	7(3,3%)
Comorbidity				
	57(30,64%)	85(45,69%)	37(19,89%)	7(3,76%)
Diabetes mellitus	47(40,8%)	40(34,7%)	23(20%)	5(4,3%)
Hypertension	58(49,5%)	33(28,2%)	21(17,6%)	5(4,2%)
Cardiovascular disease	42(47,7%)	29(32,9%)	14(15,9%)	3(3,4%)
Chronic kidney failure	11(40,7%)	11(40,7%)	4(14,8%)	1(3,7%)
Other comorbid disease	50(45,8%)	41(37,6%)	11(10,0%)	7(6,4%)
No comorbidity	97(65,1%)	36(24,1%)	14(9,4%)	2(1,3%)
Vaccination				
Completed	44(48,8%)	29(32,2%)	13(14,4%)	4(4,4%)
Uncompleted	16(43,2%)	14(37,8%)	6(16,2%)	1(2,7%)
Unvaccinated	93(44,9%)	78(37,6%)	32(15,4%)	4(1,9%)
Intubation	106(50,2%)	72(34,1%)	28(13,2%)	5(2,3%)
Dialysis	21(44,6%)	15(31,9%)	8(17,0%)	3(6,3%)
Length of icu stay	10,31±1,37	9,73±1,2	9,76±1,52	7,9±4,7
Mortality	88(47,0%)	68(36,3%)	26(13,9%)	5(2,6%)

Table 2. Statistical analysis data of the study according to the variables

	SARS-CoV-2 p< / ODDS	**Delta p< / ODDS**	**Other Mutant p< / ODDS**	**Alpha p< / ODDS**	**Intubation p< / ODDS**	**Mortality p< / ODDS**
Ages						
20-40	0.1	0.1	0.7	0.4	**0.003 / 0.227**	**0.0002 / 0.096**
41-60	**0.05 / 1.583**	0.07 / 0.638	0.9	0.5	**0.05 / 0.636**	**0.01 / 0.567**
>60	0.2	0.2	0.9	0.3	**0.001 / 2.085**	**0.0001 / 2.526**
Gender						
Male	0.9	0.6	0.8	0.5	0.3	0.2
Female	0.9	0.5	0.9	0.8	0.3	0.2
Comorbidity						
Hypertension	0.3	**0.02 / 0.580**	0.3	0.1	0.7	**0.0001 / 1.037**
Diabetes mellitus	0.1	0.7	0.07 / 1.714	0.1	0.8	**0.0001 / 0.843**
Coronary artery disease	0.7	0.4	0.8	0.6	0.8	**0.0001 / 1.198**
Chronic renal failure	0.5	0.6	0.9	0.7	0.9	**0.0001 / 0.988**
No comorbidity	**0.0001 / 4.222**	**0.0001 / 0.379**	0.07	0.1	0.9	0.1
Dialysis	0.8	0.5	0.7	0.09 / 3.205	**0.0001 / 7.679**	**0.0001 / 6.646**
Intübation times (days)						

1-4						**0.0001 / 14.186**
5-8	0.2	0.2	0.7	0.6		**0.0001 / 10.438**
>8	0.4	0.8	0.2	0.7		**0.0001 / 5.806**
Hospital Stay (days)						
1-5	**0.0001 / 1.302**	0.7	**0.0001 / 0.632**	**0.0001 / 2.825**	**0.0001 / 0.212**	**0.0001 / 0.347**
6-10	**0.0001 / 0.714**	0.1	**0.0001 / 1.589**	**0.0001 / 0.278**	**0.0001 / 0.874**	**0.0001 / 1.014**
11-15	**0.0001 / 0.968**	**0.0001 / 0.910**	0.1	**0.0001 / 1.217**	**0.0001 / 3.052**	**0.0001 / 2.152**
>15	**0.0001 / 1.130**	**0.0001 / 1.076**	0.1	**0.0001 / 0.512**	**0.0001 / 6.186**	**0.0001 / 2.156**
Intübation	**0.04 / 1.598**	0.3	0.1	0.6		**0.0001 / 91.142**
Mortality	**0.01 / 1.004**	**0.0001 / 1.024**	**0.0001 / 0.795**	**0.0001 / 0.989**		
Vaccine						
Completed	0.5	0.3	0.8	0.2	0.2	0.1
Uncompleted	**0.0001 / 0.883**	**0.0001 / 1.087**	0.1	**0.0001 / 1.007**	**0.0001 / 0.746**	**0.0001 / 0.817**
Unvaccinated	**0.0001 / 0.896**	**0.0001 / 1.195**	**0.0001 / 1.049**	**0.0001 / 1.485**	0.1	**0.05 / 1.464**

DISCUSSION

The severe SARS-CoV-2 virus has evolved continuously since the onset of the COVID-19 pandemic in December 2019, with many variants emerging around the world. To date, many studies have been conducted comparing the genomic, clinical and laboratory features of these variants.[12-14] In this study, we grouped patients hospitalized in ICU with the diagnosis of COVID-19 according to variant types and analyzed their demographic characteristics and clinics.

Peckham et al. reported that males and females are at equal risk of infection from a large-scale meta-analysis of 3,111,714 global cases of COVID-19. These large-scale data show that although there is no gender difference in the proportion of people infected with SARS-CoV-2, males are at a significantly higher risk of serious illness and death than females.[15] In our study, which supports the literature, there was no significant difference in terms of gender between the groups and in the whole population, although male gender was more common in all groups.

Venkatraja et al. found in their study that the age of the deceased was high in all variants, indicating that elderly individuals infected with any variant of COVID-19 are at high risk of death. However, the median age of recovery was lowest for delta (40 years) for recovered patients infected with different VOCs, and it was alarming that the delta variant lowered the mean age of recovery.[16] In our study, our population was severe covid 19 patients hospitalized in the intensive care unit. Similar to previous studies, the mean age in all groups was >60 years. In addition, the number of patients aged 40-60 years was higher in the SARS-CoV-2 group.

Osibagun et al., in their study in which they examined 2184 COVID-19 patients with comorbidities, they discovered that the most common comorbidities were hypertension and diabetes, and that patients

with 2 or more comorbidities were more likely to die from COVID-19.They also found that the comorbidities predicting death were hypertension, diabetes, kidney disease, cancer, and HIV.[17] Wern hang et al., in a meta-analysis, defined that hypertension as a comorbidity has the highest prevalence in COVID-19 patients. While patients with chronic kidney disease are at higher risk of death, hypertension, diabetes and cancer have been found to significantly exacerbate the severity of COVID-19 in patients resulting in mortality.[18] Gunadi et al., in their study examining the association of SARS-CoV-2 delta variant with the outcomes of COVID-19 patients, determined that; comorbidities,including obesity, diabetes, and hypertension, were independent prognostic factors for the mortality of patients with COVID-19.[19] In our study we found that hypertension was higher in the patients in delta group and the presence of comorbidity was associated with mortality in all variant types of COVID-19.

As a result of extensive research, the effectiveness of the vaccine against B.1.1.7, B.1.351 and B.1.617.2 has been demonstrated. A study of B.1.617.2 showed a reduction in clinical severity with a faster reduction in viral loads in vaccinated individuals.[20-23] Bayrakçı et al. found in their study that unvaccinated patients required more lung involvement, hospital stay, higher CT scores, and more intensive care needs.[24] We determined that unvaccinated patients were higher in all groups and according to our study being unvaccinated was associated with mortality.

Endotracheal intubation rates vary between 3.2% and 88% in recent studies. This rate difference may be due to variability in study populations, study environments, or intubation criteria.[25-27] Endotracheal intubation rate was 62,98% in our study and was higher in SARS-CoV-2 group.

Gupta et al., in their multicenter cohort study, found that 20.6% of the patients admitted to the intensive care unit developed acute kidney injury requiring renal replacement therapy after admission to the intensive care unit, and 54.9% of these patients died within 28 days of admission.[28] According to our study there was no difference among the groups for needing renal replacement theraphy but needing renal replacement theraphy was associated with mortality.

Venkatraja et al also found that patients infected with the Delta variant and/or its descendants were associated with a significant increased probability of death from COVID-19 compared to other variants.[16]

Patone et al. determined that patients with lineage B.1.1.7 were at increased risk of 28-day mortality compared with patients with non-B.1.1.7 SARS-CoV-2.[29]

In their study, Challen et al. found that the risk of death due to infection with alpha is likely to be increased and if this finding can be generalized to other populations, infection with alpha has the potential to cause significantly additional deaths compared to previously circulating variants.[30]

In our study, we found that all variant types were associated with mortality, but the mortality risk was higher in patients infected with delta variant compared to other variants.

CONCLUSION

This study analyzed the characteristics, prognosis and mortality of the critically ill patients infected with SARS-CoV-2 and SARS-CoV-2 variants. We showed that severe disease requiring intensive care admission were common in the elderly. And also we showed that hypertension was higher in the patients in delta group and the presence of comorbidity was associated with mortality in all variant types of COVID-19. Severe disease requiring intensive care admission was more common in the unvaccinated population, regardless of variant type, and being unvaccinated was associated with mortality. All variant types were associated with mortality, but the mortality risk was higher in patients infected with delta variant compared to other variants.

Consent

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

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No financial support has been received

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Conflict of Interest

All authors declare no conficts of interest

Ethical approval

Gaziantep University Medical Ethics Committee 2021/322 numbered approval have been received

This article has not been presented at any congresses or scientific meetings.

It has not been sent to any scientific journal other than this journal.

REFERENCES

1. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed. 2020 Mar 19;91(1):157-160. doi: 10.23750/abm.v91i1.9397. PMID: 32191675; PMCID: PMC7569573.
2. WHO. Tracking SARS-CoV-2 variants. May 31, 2021. https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/ (accessed June 6, 2021)
3. Wise J. Covid-19: New coronavirus variant is identified in UK. BMJ. 2020 Dec 16;371:m4857. doi: 10.1136/bmj.m4857. PMID: 33328153.
4. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD,et al.; CMMID COVID-19 Working Group; COVID-19 Genomics UK (COG-UK) Consortium, Diaz-Ordaz K, Keogh R, Eggo RM, Funk S, Jit M, Atkins KE, Edmunds WJ. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021 Apr 9;372(6538):eabg3055. doi: 10.1126/science.abg3055. Epub 2021 Mar 3. PMID: 33658326; PMCID: PMC8128288.
5. World Health Organization (WHO). Tracking SARS-CoV-2 Variants. Available online: https://www.who.int/en/activities/ tracking-SARS-CoV-2-variants/ (accessed on 26 October 2021).
6. European Centre for Disease Prevention and Control. Threat Assessment Brief: Emergence of SARS-CoV-2 B.1.617 Variants in India and Situation in the EU/EEA. Available online: https://www.ecdc.europa.eu/en/publications-data/threatE-assessmentemergence-sars-cov-2-b1617-variants (accessed on 26 October 2021)
7. Luo CH, Morris CP, Sachithanandham J, Amadi A, Gaston DC, Li M,et al. Infection with the SARS-CoV-2 Delta Variant is Associated with Higher Recovery of Infectious Virus Compared to the Alpha Variant in both Unvaccinated and Vaccinated Individuals. Clin Infect Dis. 2021 Dec 18:ciab986. doi: 10.1093/cid/ciab986. Epub ahead of print. PMID: 34922338.
8. Sheikh A, McMenamin J, Taylor B, Robertson C; Public Health Scotland and the EAVE II Collaborators. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet. 2021 Jun 26;397(10293):2461-2462. doi: 10.1016/S0140-6736(21)01358-1. Epub 2021 Jun 14. PMID: 34139198; PMCID: PMC8201647.
9. Fisman DN, Tuite AR. Progressive increase in virulence of novel SARS-CoV-2 variants in Ontario, Canada. medRxiv [Preprint]. (2021). doi: 10.1101/2021.07.05.21260050 .
10. Ong SW, Chiew CJ, Ang LW, Mak TM, Cui L, Toh MP, et al. . Clinical and virological features of SARS-CoV-2 variants of concern: a retrospective cohort study comparing B.1.1.7

(Alpha), B.1.315 (Beta), and B.1.617.2 (Delta). *SSRN J.* (2021). 10.2139/ssrn.3861566. [Epub ahead of print].

11. Fisman DN, Tuite AR. Evaluation of the relative virulence of novel SARS-CoV-2 variants: a retrospective cohort study in Ontario, Canada. CMAJ. 2021 Oct 25;193(42):E1619-E1625. doi: 10.1503/cmaj.211248. Epub 2021 Oct 4. PMID: 34610919; PMCID: PMC8562985.
12. Challen R, Brooks-Pollock E, Read JM, Dyson L, Tsaneva-Atanasova K, Danon L. Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study. BMJ. 2021 Mar 9;372:n579. doi: 10.1136/bmj.n579. PMID: 33687922; PMCID: PMC7941603.
13. Paredes MI, Lunn SM, Famulare M, Frisbie LA, Painter I, Burstein R,et al. Associations between SARS-CoV-2 variants and risk of COVID-19 hospitalization among confirmed cases in Washington State: a retrospective cohort study. medRxiv [Preprint]. 2021 Oct 27:2021.09.29.21264272. doi: 10.1101/2021.09.29.21264272. PMID: 34729567; PMCID: PMC8562551.
14. Ryu BH, Hong SI, Lim SJ, Cho Y, Hwang C, Kang H,et al. Clinical Features of Adult COVID-19 Patients without Risk Factors before and after the Nationwide SARS-CoV-2 B.1.617.2 (Delta)-variant Outbreak in Korea: Experience from Gyeongsangnam-do. J Korean Med Sci. 2021 Dec 20;36(49):e341. doi: 10.3346/jkms.2021.36.e341. PMID: 34931500; PMCID: PMC8688347.
15. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR,et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun. 2020 Dec 9;11(1):6317. doi: 10.1038/s41467-020-19741-6. PMID: 33298944; PMCID: PMC7726563.
16. Venkatraja B, Srilakshminarayana G, Krishna Kumar B. The Dominance of Severe Acute Respiratory Syndrome Coronavirus 2 B.1.617 and Its Sublineages and Associations with Mortality during the COVID-19 Pandemic in India between 2020 and 2021. Am J Trop Med Hyg. 2021 Nov 17;106(1):142-149. doi: 10.4269/ajtmh.21-0812. PMID: 34788739; PMCID: PMC8733510.
17. Osibogun A, Balogun M, Abayomi A, Idris J, Kuyinu Y, Odukoya O,et al. Outcomes of COVID-19 patients with comorbidities in southwest Nigeria. PLoS One. 2021 Mar 15;16(3):e0248281. doi: 10.1371/journal.pone.0248281. PMID: 33720975; PMCID: PMC7959379.
18. Ng WH, Tipih T, Makoah NA, Vermeulen JG, Goedhals D, Sempa JB, et al.Comorbidities in SARS-CoV-2 Patients: a Systematic Review and Meta-Analysis. mBio. 2021 Feb 9;12(1):e03647-20. doi: 10.1128/mBio.03647-20. PMID: 33563817; PMCID: PMC7885108.

19. Gunadi, Hakim MS, Wibawa H, Marcellus, Setiawaty V, Slamet,et al. Is the Infection of the SARS-CoV-2 Delta Variant Associated With the Outcomes of COVID-19 Patients? Front Med (Lausanne). 2021 Dec 9;8:780611. doi: 10.3389/fmed.2021.780611. PMID: 34957154; PMCID: PMC8695874.
20. Abu-Raddad LJ, Chemaitelly H, Butt AA; National Study Group for COVID-19 Vaccination. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med. 2021 Jul 8;385(2):187-189. doi: 10.1056/NEJMc2104974. Epub 2021 May 5. PMID: 33951357; PMCID: PMC8117967.
21. Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L,et al.; 2019nCoV-501 Study Group. Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021 May 20;384(20):1899-1909. doi: 10.1056/NEJMoa2103055. Epub 2021 May 5. PMID: 33951374; PMCID: PMC8091623.
22. Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E,et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ. 2021 May 13;373:n1088. doi: 10.1136/bmj.n1088. PMID: 33985964; PMCID: PMC8116636.
23. Chia PY, Ong SWX, Chiew CJ, Ang LW, Chavatte JM, Mak TM,et al. Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine breakthrough infections: a multicentre cohort study. Clin Microbiol Infect. 2021 Nov 23:S1198-743X(21)00638-8. doi: 10.1016/j.cmi.2021.11.010. Epub ahead of print. PMID: 34826623; PMCID: PMC8608661.
24. Bayrakci Onur, Onay Mehmet, Altay Çetin Murat, Bayrakci Sinem, Binboğa Ali Burak. CT Score and Prognosis of Vaccinated and Unvaccinated Patients in COVID 19 Pneumonia .AJMAH 2021;19(12):124-130.
25. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H,et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May;8(5):475-481. doi: 10.1016/S2213-2600(20)30079-5. Epub 2020 Feb 24. Erratum in: Lancet Respir Med. 2020 Apr;8(4):e26. PMID: 32105632; PMCID: PMC7102538.
26. Marini JJ, Gattinoni L. Management of COVID-19 Respiratory Distress. JAMA. 2020 Jun 9;323(22):2329-2330. doi: 10.1001/jama.2020.6825. PMID: 32329799.
27. Arnal JM, Chatburn R. Paying attention to patient self-inflicted lung injury. Minerva Anestesiol. 2019 Sep;85(9):940-942. doi: 10.23736/S0375-9393.19.13778-9. Epub 2019 May 3. PMID: 31064175.
28. Gupta S, Coca SG, Chan L, Melamed ML, Brenner SK, Hayek SS,et al.; STOP-COVID Investigators. AKI Treated with Renal Replacement Therapy in Critically Ill Patients with

COVID-19. J Am Soc Nephrol. 2021 Jan;32(1):161-176. doi: 10.1681/ASN.2020060897. Epub 2020 Oct 16. PMID: 33067383; PMCID: PMC7894677.

29. Patone M, Thomas K, Hatch R, Tan PS, Coupland C, Liao W,et al. Mortality and critical care unit admission associated with the SARS-CoV-2 lineage B.1.1.7 in England: an observational cohort study. Lancet Infect Dis. 2021 Nov;21(11):1518-1528. doi: 10.1016/S1473-3099(21)00318-2. Epub 2021 Jun 23. PMID: 34171232; PMCID: PMC8219489.
30. Challen R, Brooks-Pollock E, Read JM, Dyson L, Tsaneva-Atanasova K, Danon L. Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study. BMJ. 2021 Mar 9;372:n579. doi: 10.1136/bmj.n579. PMID: 33687922; PMCID: PMC7941603.