Asian Journal of Research in Infectious Diseases

9(1): 43-52, 2022; Article no.AJRID.81451
ISSN: 2582-3221

Pattern and Outcome of COVID -19 in Kidney Transplant Recipients Admitted in a Tertiary Care Centre during the Second Wave of the Pandemic in India: A Retrospective Study

Deepak Kumar Panigrahi [a*], Sahil Bagai [a], Kunal Raj Gandhi [a], Pallavi Prasad [a], Sunil Kumar [a], Kamakshi Singh [a], Tauseef Ahamad [a], Harleen Singh [a], Vandana Prasad [a], Shivanand Shrishail Nuchi [a], Gagan Deep Chhabra [a], Rahul Grover [a] and Dinesh Khullar [a]

[a] Department of Nephrology, Max Super Speciality Hospital, Saket, New Delhi, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJRID/2022/v9i130261

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/81451

Short Research Article

Received 15 December 2021
Accepted 19 January 2022
Published 25 January 2022

ABSTRACT

Background and Aim: Coronavirus disease 2019 (COVID-19) in kidney transplant recipients (KTR) is associated with an increased risk of complications than in the general population. The double mutant variant of the coronavirus was responsible for the deadly second wave of the pandemic in India. So, we conducted this retrospective case study to look for the pattern and outcome of the hospitalized KTR affected with COVID-19 in our tertiary care center during the second wave.
Study Design: This was single centre retrospective study.
Place and Duration of Study: COVID-19 affected KTR admitted to Max Super Speciality Hospital, Saket, New Delhi during the second wave of the pandemic in the months of April and May 2021 were included in the study.
Materials and Methods: All the necessary data were taken from the computerised records. Clinical and biochemical characteristics of the survivors and non-survivors were studied. The factors associated mortality were analysed.

**Corresponding author: E-mail: drdeepaklhmc@gmail.com;*

Results: Out of the 16 participants, all were males. The mean age of the population was 52.50±14.39 years. Overall mortality was 31.3% (Five out of 16). The oxygen saturation at presentation, computed tomography severity scores (CTSS) and the level of inflammatory markers were significantly different between the groups (P<0.05). The ratio of absolute neutrophil count to absolute lymphocyte count (ANC/ALC) was significantly higher in the non-survivors. No difference was noted as far as vaccination status was concerned.
Conclusions: Covid-19 during the second wave was more infectious and virulent than during the first wave. Higher CT severity score on presentation, raised inflammatory markers and a higher neutrophil to lymphocyte ratio should alert the clinician about the probable adverse outcome. Further large-scale multicentre studies are needed to accurately characterise the role of vaccines in the KTR population.

Keywords: COVID-19; kidney transplant recipients; CT severity score.

1. INTRODUCTION

The new coronavirus disease 2019 (COVID-19) infection, which emerged in the Wuhan city, China, in December 2019, is one of the worst pandemics that are known to mankind. By July 21, 2021, infections related to COVID-19 caused 4101414 reported deaths worldwide [1]. In India the count was 419014 (1.34%) [2]. Recently, India experienced the worst ever pandemic that has affected the country almost after 100 years. There was a sharp surge in the daily positivity rate, increasing from 1.62% on 1st March 2021 to around 20% on 13th May 2021 [3]. The SARS-CoV-2 double mutant strain B.1.617, possessing the key structural mutations Glu484Gln and Leu452Arg in the spike protein, is highly infectious and is regarded as the central cause of the COVID-19 surge in India [4,5]. It affected largely the younger nonvaccinated population leading on to high morbidity and mortality. Patients with kidney transplants seem to be at particularly high risk for severe COVID-19 disease. And there was a higher mortality in these kidney transplant recipients (KTR) during the second wave as compared to the first wave in India. However, data on this population during the second wave is lacking. So, we conducted this retrospective study to see the pattern and outcome of COVID-19 in KTRs during the second wave of the pandemic in a tertiary care centre in North India.

2. MATERIALS AND METHODS

This was single centre retrospective cohort study. This was approved by the institute ethics committee and consent was waived off as this was a retrospective study from the hospital records only. The primary objective was to study the clinical profile and outcome of COVID-19 affected KTR admitted to the hospital during the second wave of the pandemic from 1st April to 31st May 2021. Secondary objective was to assess the factors associated with mortality in this population. The primary outcome was mortality among the participants. The study population comprised of KTRs aged 18 years and above irrespective of the duration of transplant who were being admitted in our hospital in the months of April and May 2021. Key exclusion criteria was baseline eGFR < 30 ml/min/1.73 m2. The diagnosis of COVID-19 was confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) or Cartridge Based Nucleic Acid Amplification Test (CBNAAT) or Rapid Antigen Test (RAT) from nasopharyngeal (nasal) and oropharyngeal (throat) swab. Data of all the participants were taken from the case files. The population was divided into three groups according to the following criteria [6].

a. Mild: KTRs presented with mild symptoms including fever, cough, without shortness of breath or hypoxia, and uncomplicated upper respiratory tract infections.

b. Moderate: Patients demonstrated clinical features of pneumonia including fever, cough, dyspnoea, hypoxia with oxygen saturation (SpO2) <94% (range 90%–94%) on room air, and respiratory rates of 24–30/min.

c. Severe: Patients had advanced signs of clinical pneumonia plus 1 of the following clinical criteria: respiratory rate >30/min, severe respiratory distress, and SpO2 <90% on room air.

All the blood investigations including the values of inflammatory markers (interleukin -6, c-

reactive protein, ferritin, D-dimer) were noted. The CT severity scores were also noted.

Among the treatment protocol, supplemental oxygen was given in moderate and severe illness. Patients were shifted to intensive care units (ICU) if respiratory failure set in. All of our admitted patients were on triple drug immunosuppression with tacrolimus, antiproliferative (mycophenolate mofetil or azathioprine) and steroids. In all cases antiproliferative agent was stopped. Tacrolimus was continued (except in cases of very severe infection) with a target trough level of 5-7 ng/dl. In all cases, prednisolone was replaced with intravenous methyl-prednisolone or dexamethasone. Prophylactic anticoagulation with unfractionated or low molecular weight heparin was done in moderate and severe disease and those with high D-dimer levels or with other risk factors for deep vein thrombosis (DVT). Remdesivir was given in moderate and severe cases if felt needful by the treating doctor. Convalescent plasma was considered in patients with severe disease in cases of clinical nonresponse in the initial stage of this pandemic. However, this practice was stopped after it was discontinued from the practice guideline advisory by Government of India. The interleukin-6 (IL-6) receptor antibody tocilizumab was used in very selected cases with severe disease with highly raised IL-6 values. Other supportive treatments were prescribed as per the treating clinician's discretion.

Data were analysed by SPSS version 25 and presented as mean (SD), median (IQR) and frequency (percentage). Categorical variables were compared in two groups by using Chi-square/Fisher exact test as applicable. Continuous variables were compared by independent t test (following normal distribution) or Wilcoxon rank sum test (for skewed data) as applicable. A P value of < 0.05 was considered as statistically significant.

3. RESULTS

A total of 16 KTR affected with COVID-19 were included in this retrospective study. All the participants were male (100%). The other baseline demographic parameters of the whole cohort are shown in Table 1.

Out of 16, five (31.25%) did not survive. The comparison of various important parameters between the nonsurvivors and survivors is shown in the following table. There was no significant difference between the groups as far as age, BMI, blood group types, induction agent types or associated co-morbidities are concerned. The oxygen saturation at presentation, CT severity scores, level of inflammatory markers were significantly different between the groups ($P<0.005$). ANC/ALC ratio was significantly higher in the nonsurvivors (Table 2).

4. DISCUSSION

The second wave that hit the Indian subcontinent was one of the worst disasters in the history of the country. The presentation was more severe as compared to the first wave. The morbidity and mortality were also higher [4,7]. The major hit of the second wave in India occurred in the months of April and May 2021. So, we studied the outcome of COVID-19 in KTR admitted in our institute during these two months period only [8]. All the admitted KTR were males. So, we could not assess the impact of gender on the mortality. The mortality rate reported in solid organ transplant recipients varies from 5-28% [9-13]. In a yet unpublished study from our institute the mortality rate recorded in this cohort during the first wave was 17.1%. Similarly, in an Indian multicentre study during the first wave mortality rate among KTR was 11.8% [14]. In the current study the mortality rate was found to be higher i.e 31.3%. The proportion of KTR with severe disease was more (56.3% vs14%) as compared to the above Indian study conducted during the first wave of the pandemic [14]. It might be due to the more virulence nature of the mutant strain. Especially, the double mutated variant B.1.617 was highly infectious and contributed to the exponential rise in cases [3,4]. It has got two important mutations, the E484Q and L452R in the receptor-binding domain (RBD) of the spike protein, which increases its angiotensin converting enzyme-2 (ACE2) receptor binding activity. This enhances the transmission capability of this variant leading to a greater spread and severity of the disease [5,15]. Because of these specific mutations in the spike proteins, the antibody binding capability is reduced. This additionally facilitates immune escape and confers increased virulence of the mutants [15].

Table 1. Baseline parameters of the population

Parameters	Frequency (N=16)
Age in years (Mean±SD)	52.50±14.39
Males (N, %)	16, 100%
Weight in Kgs (Mean±SD)	66.78±9.32
Height in cms (Mean±SD)	163.63±7.96
BMI in kg/m^2 (Mean±SD)	24.97±3.27
Blood Group (N, %)	
A	1 (6.3%)
B	8 (50%)
AB	1 (6.3%)
O	6 (37.5%)
Native Disease (N, %)	
Diabetic Nephropathy	5 (31.3%)
CGN	3 (18.7%)
PKD	0
Unclassified	8 (50.0%)
Comorbidities (N, %)	
DM	5 (31.3%)
Hypertension	14 (87.50%)
Hypothyroid	01 (6.3%)
CAD	02 (12.5%)
Induction Agent (N, %)	
rATG	12 (75.00%)
Basiliximab	04 (25.00%)
ABO incompatibility (N, %)	03(18.8%)
History of prior Rejection (N, %)	02 (12.5%)
PTDM (N, %)	05 (31.3%)
Baseline creatinine in mg/dl (median, IQR)	1.25(1.10-1.90)
Presentation creatinine in mg/dl (median, IQR)	1.80(1.15-3.17)
Symptoms at presentation (N, %)	
Fever	14 (87.5%)
Cough	08 (50.0%)
Shortness of breath	12 (75%)

Parameters	Frequency (N=16)
Loose stool	2 (12.5%)
Oxygen saturation at presentation (Mean ± SD)	91.00±4.13
Clinical Severity (N, %)	
Mild	03 (18.7%)
Moderate	04 (25.0%)
Severe	09 (56.3%)
Haemoglobin in g/dl (Mean±SD)	11.60±2.28
Total Leukocyte Count (median, IQR)	8000(7575-9650)
ALC (median, IQR)	300(125-765)
Platelet Count (median, IQR)	1.70(1.50-2.60)
ANC/ALC	32.94(7.14-61.21)
Serum Albumin in g/dl (Mean±SD)	2.95±0.74
SGOT (median, IQR)	36.00(28.50-122.25)
SGPT (median, IQR)	40.50(20.75-85.00)
Tacrolimus level	6.15(5.20-7.27)
CT Severity score out of 25 (median, IQR)	14.50 (9.25-17.50)
IL-6 level (median, IQR)	22.02(7.84-107.27)
D-dimer (median, IQR)	1110.50(428.85-1676.00)
Procalcitonin (median, IQR)	1.02(0.40-2.62)
Ferritin (median, IQR)	689.50(291.50-1647.50)
CRP (median, IQR)	81.82(21.06-170.11)
Treatment Received (N, %)	
Doxycycline	14 (87.50%)
Remdesivir	13 (81.25%)
Plasma infusion	06 (37.5%)
Mortality (N, %)	05(31.3%)

BMI- Body Mass Index, CGN- Chronic Glomerulonephritis, PKD- Polycystic Kidney Disease, DM- Diabetes Mellitus, CAD- Coronary Artery Disease, rATG- rabbit Anti Thymocyte globulin, PTDM- Post Transplant Diabetes Mellitus, IQR- Interquartile range, ANC- Absolute Neutrophil Count, ALC- absolute Lymphocyte Count, SGOT- Serum Glutamic Oxaloacetic transaminase, SGPT- Serum Glutamic Pyruvic Transaminases, CT- Computed Tomography, IL-6- Interleukin-6, CRP- C reactive protein

Table 2. Comparison of parameters between nonsurvivors and survivors

Parameters	Nonsurvivors (N=5)	Survivors (N=11)	P value
Age in years (Mean±SD)	56.20±8.52	50.82±16.49	0.50
Males (N, %)	05 (100%)	11 (100%)	-
Weight in Kgs (Mean±SD)	68.40±4.82	66.05±10.91	0.65
Height in cms (Mean±SD)	159.00±5.78	165.73±8.13	0.12
BMI in kg/m^2 (Mean±SD)	27.12±2.47	24.00±3.20	0.07
Blood Gp (N, %)			
A	1 (20%)	0 (0%)	
B	3 (60%)	5 (45.5%)	0.33
AB	0 (0%)	1 (9.1%)	
O	1 (20%)	5 (45.5%)	
Native Disease (N, %)			
Diabetic Nephropathy	04(66.7%)	10 (34.5%)	0.19
Comorbidities (N, %)			
DM	02(40.0%)	03 (27.3%)	0.61
Hypertension	04 (80%)	10 (90.9%)	0.54
Hypothyroid	01 (20%)	0 (0%)	0.12
CAD	0 (0%)	02 (18.2%)	0.30
ABO incompatibility (N, %)	0 (0%)	03 (27.3%)	0.19
Induction Agent (N, %)			
ATG	04 (80%)	08(72.7%)	1.00
Basiliximab	01 (20%)	03 (27.3%)	
History of prior Rejection (N, %)	0 (0%)	02 (18.2%)	0.57
PTDM (N, %)	02 (40%)	03 (27.3%)	0.61
Baseline creatinine in mg/dl (median, IQR)	1.3(1.15-1.70)	1.2 (1.1-2.2)	0.73
Presentation creatinine in mg/dl (median, IQR)	1.90 (1.65-2.35)	1.60 (1.10-4.60)	0.56
Symptoms at presentation (N, %)			
Fever			
Cough	05 (100%)	09 (81.8%)	0.30
Shortness of breath	01 (20%)	07(63.6%)	0.10
Loose stool	05(100%)	07 (63.6)	0.11
	0 (0%)	02(18.2%)	0.30
Oxygen saturation at presentation (Mean ±	87.20±1.30	92.73±3.79	0.008

Parameters	Nonsurvivors (N=5)	Survivors (N=11)	P value
SD)			
Severity (N, %)			
Mild	0 (0%)	03 (27.3%)	
Moderate	0(0%)	04 (36.4%)	0.05
Severe	05 (100%)	04 (36.4%)	
Haemoglobin in g/dl (Mean±SD)	11.60±1.57	11.60±2.61	1.00
Total Leukocyte Count (median, IQR)	8200 (5550-14750)	8000(7800-9200)	0.95
Absolute Lymphocyte Count (median, IQR)	100.00 (50.00-240.00)	450.00(240.00-980.00)	0.011
Platelet Count (median, IQR)	1.65 (1.25-2.38)	2.4(1.5-2.7)	0.64
ANC/ALC	91.20(54.81-104.50)	8.61(6.45-34.94)	0.003
Serum Albumin in g/dl (Mean±SD)	2.22±0.58	3.28±0.55	0.004
SGOT (median, IQR)	165.00 (38.00-700.00)	30.00(18.00-50.00)	0.02
SGPT (median, IQR)	86.00 (50.00-534.50)	34.00(18.00-48.00)	0.04
Tacrolimus level	7.19(4.90-9.02)	6.10(5.20-6.50)	0.57
CT Severity score out of 25	18.00 (15.50-21.00)	10.00(9.00-15.00)	0.01
IL-6 level (median, IQR)	120.40 (99.94-433.55)	18.53(3.85-23.90)	0.002
D-dimer (median, IQR)	2399.00(1587.00-7207.00)	716.00(258.00-1253.00)	0.004
Procalcitonin (median, IQR)	4.21(1.80-21.40)	0.512(0.25-1.22)	0.008
Ferritin (median, IQR)	1938 (929.00-3616.50)	562.00(250.00-1163.00)	0.02
CRP (median, IQR)	184.80(161.72-251.60)	27.32(18.82-100)	0.002
Vaccinated with at least 1 dose (N, %)	01 (20%)	06(54.5%)	0.19
Treatment Given (N, %)			
Remdesivir	05 (100%)	09 (81.8%)	0.30
Plasma infusion	05 (100%)	01 (9.1%)	0.005

BMI- Body Mass Index, CGN- Chronic Glomerulonephritis, PKD- Polycystic Kidney Disease, DM- Diabetes Mellitus, CAD- Coronary Artery Disease, rATG- rabbit Anti Thymocyte globulin, PTDM- Post Transplant Diabetes Mellitus, IQR- Interquartile range, ANC- Absolute Neutrophil Count, ALC- absolute Lymphocyte Count, SGOT- Serum Glutamic Oxaloacetic transaminase, SGPT- Serum Glutamic Pyruvic Transaminases, CT- Computed Tomography, IL-6- Interleukin-6, CRP- C reactive protein

A number of factors including advanced age, associated co-morbidities, induction therapy, history of rejections, higher level of inflammatory markers, are thought to be contributing to increased mortality in KTR with COVID-19. However, in our study we did not find any of the above factors to be significantly different between the nonsurvivors and survivors. Although the mean age of the nonsurvivors is higher than that of the survivors, no statistically significant difference was seen. Similarly, there was no statistically significant difference between the groups as far as the choice of induction agent or history of prior rejection is concerned. This could be due to the fact that the mean duration of acquiring COVID-19 post-transplant in our cohort was little longer i.e 7.28±4.70 years. The oxygen saturation at presentation were significantly low in the nonsurvivors correlating with the severity of disease. CT severity scores were higher in the nonsurvivors too. Chest CT imaging plays an important role in the diagnosis evaluation and prognostication of COVID-19. Imaging features like multiple ground-glass opacities (GGO) and/or consolidations are described in patients with COVID-19 pneumonia in various literature [16-18]. The 25 point CT severity scores correlated well with the increasing requirement of supplemental oxygen and increasing duration of hospitalisation in a retrospective study [19].

The levels of inflammatory markers like IL6, D-dimer, CRP and ferritin were significantly higher in the nonsurvivors. After the viraemic phase, the inflammatory responses play a critical role in the progression of COVID-19 [20,21]. Rapid viral replication triggers immune responses which leads onto recruitment of macrophages and monocytes and induce the release of cytokines and chemokines. The resultant cytokine storm leads onto more inflammatory destruction [22-24]. However, on regression analysis, we did not find any causal association of these parameters with mortality. It might be due to fact that these parameters are highly interrelated with each other. Similar was the finding in the previous multicentric study conducted in India [14]. Another parameter that is the neutrophil to lymphocyte ratio is thought to predicting mortality in some previous studies [25,26]. In our study we could see that the neutrophil to lymphocyte ratio was higher in the nonsurvivors. We could also find the absolute lymphocyte count was significantly low in them. There might have been some cytopathic effect of the virus on T lymphocytes, and T lymphocyte damage might be an important factor that determines the severity of the illness [27-29].

So, this is one of the early studies of the COVID-19 affected KTR during the second wave in India. It gives us a better insight into the pattern and outcome of coronavirus disease in these vulnerable population. Our study has got some limitations. The first and the foremost is that the sample size was too small. So, we could not conclusively define the causal association of various parameters with mortality. Secondly, the treatment protocol for the disease has been constantly evoluting. So, the treatment received by the participants was not uniform. Third, the effect of vaccination could not be studied well as most of the vaccinees had received only one dose of the vaccine. Again, at the timeframe at which the study was conducted, only those KTR who were of 45 years or older were eligible for vaccines as per the national guideline.

5. CONCLUSIONS

The coronavirus disease during the second wave was more infectious and virulent than during the first wave. Higher CT severity score on presentation, raised inflammatory markers and a higher neutrophil to lymphocyte ratio should alert the clinician about the probable adverse outcome. Further large scale multicentric studies are needed to accurately characterise the role of vaccines in the KTR population.

CONSENT AND ETHICAL APPROVAL

This was approved by the institute ethics committee and consent was waived off as this was a retrospective study from the hospital records only.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Coronavirus disease (COVID-19) – World Health Organization [Internet]. Who.int; 2021.
[cited 21 July 2021].
Assessed 21 July 2021.
Available:https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=CjwKCAjwi9-

HBhACEiwAPzUhHPIB2e79M9pxmlGw1r5rG-vrKj6sqCfHgFjCUrPyTSzR-8tV6RrzahoCxAMQAvD_BwE.
2. India Fights Corona COVID-19 [Internet]. MyGov.in; 2021 [cited 21 July 2021]. Assessed 21 July 2021. Available: https://www.mygov.in/covid-19.
3. Kumar S. Second wave of COVID-19: emergency situation in India. J Travel Med. 2021;28(7): taab082.
4. Asrani P, Eapen MS, Hassan MI, Sohal SS. Implications of the second wave of COVID-19 in India. Lancet Respir Med. 2021;9(9): e93-e94.
5. Cherian S, Potdar V, Jadhav S, et al. SARS-CoV-2 Spike Mutations, L452R, T478K, E484Q and P681R, in the Second Wave of COVID-19 in Maharashtra, India. Microorganisms. 2021; 9(7):1542.
6. Clinical Management Protocol: COVID-19. Assessed 21 July 2021. Available: https://www.mohfw.gov.in/pdf/ Clinical Management Protocol for COVID19.pdf.
7. Jain VK, Iyengar KP, Vaishya R. Differences between First wave and Second wave of COVID-19 in India. Diabetes Metab Syndr. 2021;15(3):1047-1048.
8. Kar SK, Ransing R, Arafat SMY, Menon V. Second wave of COVID-19 pandemic in India: Barriers to effective governmental response. EClinical Medicine. 2021;36:100915.
9. Yi Stephanie G, Rogers A W, Saharia A, Aoun M, Faour, R, Abdelrahim M, Knight R, et.al. Early Experience With COVID-19 and Solid Organ Transplantation at a US High-volume Transplant Center, Transplantation. 2020 ;104 (11):2208-2214.
10. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med. 2020;382(24):2372–2374.
11. Columbia University Kidney Transplant Program. Early Description of Coronavirus 2019 Disease in Kidney Transplant Recipients in New York. J Am Soc Nephrol. 2020;31(6):1150-1156.
12. Pereira MR, Mohan S, Cohen DJ, Husain SA, Dube GK, Ratner LE, Arcasoy S, Aversa MM, Benvenuto LJ, Dadhania DM, Kapur S, Dove LM, Brown RS Jr, Rosenblatt RE, Samstein B, Uriel N, Farr MA, Satlin M, Small CB, Walsh TJ, Kodiyanplakkal RP, Miko BA, Aaron JG, Tsapepas DS, Emond JC, Verna EC. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. Am J Transplant. 2020;20(7):1800-1808.
13. Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V et.al. Covid-19 and Kidney Transplantation. N Engl J Med. 2020;382(25):2475-2477.
14. Kute VB, Bhalla AK, Guleria S, Ray DS, Bahadur MM, Shingare A, Hegde U et al. Clinical Profile and Outcome of COVID-19 in 250 Kidney Transplant Recipients: A Multicenter Cohort Study from India. Transplantation. 2021;105(4):851-860.
15. Kunal S, Aditi, Gupta K, Ish P. COVID-19 variants in India: Potential role in second wave and impact on vaccination. Heart Lung. 2021;50(6):784-787.
16. Hu Y, Zhan C, Chen C, Ai T, Xia L. Chest CT findings related to mortality of patients with COVID-19: A retrospective case-series study. PLoS One. 2020;15(8): e0237302.
17. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatr Pulmonol. 2020;55(5):1169-1174.
18. Li Y, Xia L. Coronavirus Disease 2019 (COVID-19): Role of Chest CT in Diagnosis and Management. AJR Am J Roentgenol. 2020;214(6):1280-1286.
19. Saeed GA, Gaba W, Shah A, et al. Correlation between Chest CT Severity Scores and the Clinical Parameters of Adult Patients with COVID-19 Pneumonia. Radiol Res Pract. 2021; 2021:6697677.
20. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4.
21. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020;20(4):400–2.
22. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020;20(6):363-374.
23. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of

COVID19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420–2.

24. Zeng F, Huang Y, Guo Y, et al. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. Int J Infect Dis. 2020;96:467-474.
25. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX, Luo M, Chen L, Zhao Y. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020;81(1): e6-e12.
26. Liu Y, Du X, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020;81(1):e6-e12.
27. Liu WJ, Zhao M, Liu K, Xu K, Wong G, Tan W, et al. T-cell immunity of SARS-CoV: implications for vaccine development against MERS-CoV. Antivir Res. 2017;137:82–92.
28. Shi Y, Wang Y, Shao CA-O, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives on immune responses. Cell Death Differ. 2020;27(5):1451–4.
29. Liu J, Liu Y, Xiang P, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med. 2020;18: 206.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/81451