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COVID-19 in kidney transplant recipients; an Indian experience

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ABSTRACT

Introduction: Kidney transplant recipients appear to be at high risk for severe COVID-19 illness due to chronic immunosuppression and coexisting conditions.

Objectives: We aimed to study the clinical characteristics, laboratory and radiological results, treatment aspects and clinical outcomes of kidney transplant patients with COVID-19.

Patient and Methods: Twenty consecutive kidney transplant patients with COVID-19 pneumonia from two tertiary care centers from India were retrospectively studied from July 1 to Oct 31, 2020.

Results: Of 20 patients, 18 required admission; mean age was 42.8±9.39 years and 18 out of 20 (90%) were male. Symptom onset to testing time was a mean of 3.05±1.47 days. All patients were on triple immunosuppression. The median time since transplantation to COVID-19 was 3.75 years (IQR 2.37-5.41). Fever, cough and breathlessness were the most common presenting symptoms. Nine out of twenty (45%) had severe COVID-19 while six out of 20 (30%) required intensive care. Twelve (60%) patients had lymphopenia. Additionally mycophenolate was withheld in seventeen out of twenty (85 %) and enoxaparin and intravenous methylprednisolone were administered in all hospitalized patients while remdesivir was prescribed in 16 out of 20 (80%). Moreover, acute kidney injury (AKI) was seen in five out of 20 (25%) since one of died (5%). After a median hospital stay of 8.5 days (IQR 6.75-15.5), seventeen patients were discharged from the hospital.

Conclusion: COVID-19 infection in kidney transplant recipients is usually a moderate-severe form. COVID-19 should be a differential diagnosis for fever in this high-risk population however lymphopenia may not be seen in all. Antimetabolite withdrawal, intravenous steroid, anticoagulation and early remdesivir were all found to be safe and effective strategies for improving outcomes. Early diagnosis and timely treatment may decrease mortality in this high-risk population.

Implication for health policy/practice/research/medical education:
This study highlights the fact that strategies such as withdrawal of antimetabolite, intravenous steroid, thromboprophylaxis and early remdesivir administration were all found to be safe and effective in kidney transplant recipients and have an impact in bringing down mortality. Our study provides clinical and prognostic information that may be useful in the management of transplant patients infected with COVID-19.

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Original Article

Introduction

When SARS-CoV-2 was detected in December 2019, it has rapidly evolved into an infection which is challenging to health care providers and policymakers. On 27th January 2020, India reported its first case of COVID-19 (1). World Health Organization (WHO) declared it a pandemic on 11th March 2020. India announced a national emergency and lockdown of various phases from 24th March 2020 (2). The general consensus on viral susceptibility in transplant recipients is that immunosuppression exposes them to a higher risk of a severe infection, particularly in the presence of comorbidities (3). First report on COVID-19

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infected transplant patients belongs to Zhang et al (4), while few case reports highlighted these patients' clinical profiles (5-7). However, there is significant heterogeneity in the population, clinical profile, treatment strategies and high mortality in the reported data (5-7). There is no conclusive opinion on the optimal management of immunosuppression, interpretation of inflammatory parameters, risk of cytokine storm and the safety and efficacy of remdesivir in renal transplant recipients (6, 7). Even after a year of its onset, the pandemic continues to spread unabated. Apart from two case reports, more extensive case studies are lacking from the Indian population (2,8).

Objectives

This study aimed to evaluate the clinical characteristics, laboratory and radiological results, treatment aspects and clinical outcomes of kidney transplant patients with COVID-19 and to know the outcome of these patients and to identify poor prognostic markers.

Patients and Methods

Study design

We conducted a retrospective study of consecutive patients seen between July 1, 2020 and October 30, 2020 at two transplant centers in Karnataka, India; namely, Kasturba Medical College, Manipal, Manipal Academy of higher education, Manipal and SDM college of medical sciences and hospital, Dharwad.

All adult (>18 years of age) kidney transplant recipients diagnosed with COVID-19 infection by real-time polymerase chain reaction assay (RT-PCR) at our hospitals were included. Demographic, clinical, biochemical, treatment, outcome and follow-up data were collected. They were categorized into mild, moderate, severe and critical COVID-19 infection, as per the National Institute of Health (NIH) severity scoring (9). Patients with mild infection were observed in home isolation and others admitted to the hospital. Treatment decision on reducing immunosuppression, use of antiviral remdesivir, steroids and antibiotic prescription was based on physician/ nephrologists' discretion. During the pandemic, both centers had dedicated telephone access for transplant recipients and they were called for examination, testing, admission, treatment and follow up whenever necessary by the transplant team.

Outcomes

The outcomes studied were severity of the disease, presence of acute kidney injury (AKI) based on Kidney Disease Initiative Global Outcome (KDIGO) creatinine criteria, intensive care unit (ICU) requirement and complete recovery and also mortality.

Statistical analysis

All statistical analyses were made applying Statistical Package for the Social Sciences (SPSS) software version 20.0. Continuous variables were expressed as mean and standard deviations if normally distributed and median with an interquartile range for non-normally distributed. Categorical variables were expressed as frequencies and percentages.

Results

Baseline features

Of 20 patients, 18 (90%) were male with the mean age of 42.8±9.39 years. The baseline characteristics and clinical features are presented in Table 1. Median time since the transplant was 3.75 years (IQR 2.37-5.41). All were on a triple immunosuppression regimen with steroids, mycophenolate, and tacrolimus. Seventeen out of twenty (85%) were live related renal allograft recipients. Fever was the most common presenting symptom, followed by cough and breathlessness. The mean duration from symptom onset to COVID-19 testing was 3.05±1.47 days. Five of them reported having a COVID-19 infected family member and the remaining 15 were presumed to be community-acquired.

Inflammatory parameters

Lymphopenia was seen in 12 (60%) patients, 10 (50%) had ferritin levels higher than 300 ng/mL. Serum C-reactive protein levels were higher than 10 mg/L in 14 (70%), while six had high D-dimer level (>0.5 µg/mL) and three of cases had thrombocytopenia (Table 2).

Management of COVID-19

Two patients, who had mild scores, were managed on outpatient basis with teleconsultation. Remaining eighteen patients who were admitted, nine (45%) had severe COVID-19. Six out of twenty (33%) required intensive care (30%) and four (20%) required mechanical ventilation. AKI was noticed in five cases (25%) among which, one patient required renal replacement therapy. Sixteen patients received remdesivir, while no adverse events in the form of elevation of liver enzymes or worsening of graft function was noted. Remdesivir was administered at 200 mg on day 1 and 100 mg/d for 4 days. Only one patient were treated with hydroxychloroquine at 100 mg twice a day for 5 days. All admitted patients received intravenous methylprednisolone (40 mg every 12 hours till discharge) and the remaining two patients on home isolation received 20 mg/d of oral prednisolone. The hospitalized patients were discharged on 20 mg/d of prednisolone.

Empirical antibiotics (ceftriaxone or piperacillin-tazobactam or imipenem) were administered in 16

Table 1. Baseline characteristics of patients

Variables	Values
Age (y)	42.8±9.39
Gender: male	18 (90)
Donor	
Living related	17 (85)
Deceased	3 (15)
Co-morbidities	
Diabetes mellitus	8 (40)
Hypertension	18 (90)
Ischemic heart disease	3 (15)
Obesity	4 (20)
Hepatitis B virus infection	2 (10)
Baseline creatinine (mg/dL)	1.28 (1.1-1.60)
Baseline eGFR (mL/min/1.73 m^2)	64.02±22.14
Ongoing ACE/ARB therapy	3 (15)
Time since transplant (years)	3.75 y (2.37-5.41)
Induction	
Basiliximab	11 (55)
Antithymocyte globulin	5 (25)
None	4 (20)
Baseline immunosuppression	
Steroid dose, mg/dL	7.37 ± 2.36
Mycophenolate dose, mg/dL	1131.5 ± 280.97
Tacrolimus dose, mg/dL	2.5±1.10
Presenting symptom	
Fever	20/20 (100)
Cough	11/20 (55)
Breathlessness	9/20 (45)
Diarrhea	5/20 (25)
Days from symptom onset to RT-PCR testing	3.05±1.47
Hospitalization	18/20 (90)
COVID Ward	12/18 (66)
COVID ICU	06/18 (33)
Hypoxia (<94% oxygen saturation)	09/20 (45)
Non invasive Ventilation	02/20(10)
Invasive Ventilation	02/20(10)
Chest radiographic findings consistent with viral pneumonia	18/20 (90)

Note: All data reported as n/N (%), n (%), mean, median (IQR).
Abbreviations: eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ICU, intensive care unit.

admitted patients. Prophylactic dose enoxaparin was used in all inpatients. Patients who were on angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (15%) were allowed to continue them.

Management of immunosuppression

Immunosuppressive management included the antimetabolites' withdrawal in 17 of 20 patients (86%) (Table 3). Antimetabolites were reduced by half in patients who were isolated at home. Tacrolimus was stopped in one patient with critical COVID-19 infection and shock.

Table 2. Baseline laboratory parameters

Variables	Values
White-cell count, (10^3/uL)	6.4 (2.1–16.4)
Lymphocyte count (10^3/uL)	0.920 (0.369–2.580)
Lymphopenia (<1.0 ×10^3/uL)	12/20 (60)
Severe lymphopenia (<0.700 ×10^3/uL)	06/20 (30)
Platelet count, 10^9/L	194(65-350)
Thrombocytopenia (<150 per 10^9/L)	3/20 (15)
Serum Creatinine, mg/dL	1.735 (1.35-2.03)
Aspartate transaminase, U/L	28(20-41.75)
Alanine transaminase, U/L	32((21.75-41)
Ferritin, ng/mL	355 (85–2000)
Level >300 ng/mL	10/20(50)
Level >900 ng/mL	6/20 (30)
D-dimer, µg/mL	0.9 (0.2–3.9)
Level >0.5, µg/mL	6/20 (30)
Level >3, µg/mL	2/20 (10)
C-reactive protein, mg/dL	17.46 (1–346.7)
Level >5 mg/dL	18/20 (90)
Level >10 mg/dL	14/20(70)
Procalcitonin, ng/mL	0.18 (0.05– 7)
Level >0.2, ng/mL	3/20 (15)
Lactate dehydrogenase, IU/L	278 (170–838)
Level >400 IU/L	06/20(30)

Note: All data reported as median (IQR), n/N (%)

Course and outcome

After a median hospital stay of 8.5 days (6.75-15.5 days), 17 patients were discharged from the hospital, with a mortality of 5% (1/20). At a median follow-up of 21 days (range; 11 to 28 days), AKI was recovered in three patients. One patient who had chronic graft dysfunction with a nadir creatinine of 4.8 mg/dL in the last follow up had dialysis-dependent renal failure and did not recover. This patient is continued to be on hemodialysis. The patient who died had a critical COVID-19 infection and was requiring invasive ventilation. Although this case had AKI, he died due to ventricular tachycardia after six days of hospitalization before requiring any renal replacement therapy. Two patients on non-invasive ventilation and one on invasive ventilation recovered completely. Two patients, who were under home isolation, did not have any worsening of clinical status. Among the twenty patients, one patient had Klebsiella pneumoniae in sputum culture and another had methicillin-resistant Staphylococcus aureus. In the rest of the patients, including the patient who died, the blood and urine cultures were sterile. After complete recovery, the baseline dose of antimetabolites was restarted and steroids were tapered over 2-3 weeks to the previous dose.

Table 3. Comparison of features of our patients with other reported studies

Features	Studies						
	Pereira et al (5)	**Bossini et al (10)**	**Cravedi et al (6)**	**Lubetzky et al (7)**	**Kates et al (11)**	**Benotmane et al (12)**	**Our study**
Setting	Two center, USA	Multicenter, Italy	Multicenter: USA, Italy, Spain	Two center, USA	Multicenter: USA, Spain	Single center France	Two center, India
Study time in 2020	March-April	March-April	March-May	March-April	March-April	March-April	July-October
Online publication	24 April	6 July	10 July	17 July	7August	10 August	-
Number	90	53	144	54	318	40	20
Age	57 (46-68)	60 (50-67)	62 (52-69)	57 (29-83)	56 (4-66)	64 (55-68)	42.8±9.39
Asian race	5 (6)	NA	NA	6 (11)	18 (6)	NA	20 (100)
Deceased donor	NA	45 (53)	112 (77.8)	17 (31)	NA	NA	03 (15)
Comorbidities							
DM	41 (46)	11 (21)	75 (52)	16 (30)	170 (54)	19 (48)	08 (40)
HTN	58 (46)	42 (79)	137 (95)	50 (93)	299 (76.3)	32 (80)	18 (90)
ATG[a]	NA	17 (44)	85 (62.5)	39 (72)	NA	18/40	05 (25)
Onset to testing time, days	4 (2-7)	7 (4-10)	6.0 (3.0-8.0)	8.2±6.0	NA	4.0 (3.0-7.0)	3.05±1.47
Presented with							
Fever	63 (70)	51 (96)	96 (67)	40 (74)	186 (59)	38 (95)	20 (100)
Dyspnea	39 (43)	15 (28)	97 (67.8)	28 (52)	187 (59)	28 (78)	9 (45)
Time from transplant to COVID, years	6.64 (2.98-10.61)	9.2 (4-16)	5.0 (2.0-9.25)	4.7 (0.3-35)	5.0 (2.0-1.0)	6.6 (2.8-14.6)	3.75 (2.37-5.41)
Lab parameters							
Creatinine, mg/dL	1.89 (1.15-3.85)	2.4 (1.7-4.0)	1.5 (1.1-1.9)	2.6±2.3	NA	NA	1.73 (1.35-2.03)
Lymphocytes	0.7 (0.34-1.09)	0.59 (0.43-1.09)	0.94 (0.5-3.08)	0.6 (0.3-1.0)	0.7 (0.4-1.0)	NA	0.92 (0.36-2.58)
LDH	NA	263 (213-323)	317 (261-408.25)	NA	NA	NA	278 (170-838)
CRP	68.5 (15.4-126)	39 (16-103)	41 (11.5-125.35)	11.4 (5.3-30.2)	NA	NA	17.46 (1.0-346)
Ferritin	801.5 (270-1514)	433 (284-872)	1260 (525.5-2620)	1498 (383-2626)	NA	NA	355 (85-2000)
D-dimer	1.35 (0.69-3.08)	0.41 (0.10-0.67)	1.12 (0.62-2.06)	0.39 (0.27-0.589)	NA	NA	0.9 (0.2-3.9)

Table 3. Continued

Features	Studies						
	Pereira et al (5)	Bossini et al (10)	Cravedi et al (6)	Lubetzky et al (7)	Kates et al (11)	Benotmane et al (12)	Our study
ISP							
AM Withdrawn	42/48 (88)	51/53 (96.3)	91/144 (67.9)	24/54 (44)	270/482 (56)	34/34 (100)	17/20 (86)
AM Halved	-	-	-	15/54 (28)	48/482 (10)		2/20 (10)
Tacrolimus							
Withdrawn	10/56 (18)	42/53	32/131 (25)	17/54 (32)	NA	15/35 (43)	1/20 (5)
Halved dose	-	9/53	-	-	NA	-	-
Antibiotics usage	45 (66)	53 (100)	106 (74.1)	21 (39)	110 (35)	40 (100)	16/18 (80)
COVID-19 therapy							
HCQS	62 (91)	39 (74)	101 (70.6)	32 (62)	197 (62)	15 (38)	1 (5)
Tocilizumab	14 (21)	8 (15)	19 (13)	2 (4)	39 (11)	4 (10)	0 (0)
Remdesivir	2 (3)	NA	9 (6.3)	2 (4)	9 (3)	NA	16 (80)
Heparin/anticoagulation	NA	23 (43.3)	NA	NA	NA	NA	18 (90)
I.V steroids	16 (24)	18 (33)	NA	5 (9.2)	35 (11)	14 (35)	18 (90)
Mechanical ventilation	24 (35)	9 (20)	42 (29)	11 (28)	87 (34)	NA	04 (20)
ICU need	23 (34)	10 (25)	43 (30)	NA	107 (42)	NA	06 (33)
AKI	NA	15 (33)	74 (25)	21 (39)	130 (40)	NA	05 (25)
Hospital stay duration, days	NA[b]	11 (7-16)	15 (8-22)	NA	NA	NA	8.5 (6.75-15.5)
Death	16 (24)	15 (33)	46 (32)	7 (18)	57 (18)	9 (23)	1 (5)

Abbreviations: NA, not available; DM, diabetes mellitus; HTN, hypertension; ATG, anti thymocyte globulin; LDH-Lactate dehydrogenase; CRP, C-reactive protein; ISP, immunosuppression; AM, antimetabolite; COVID-19, coronavirus disease 2019; HCQS, Hydroxychloroquine; IV, intravenous; ICU, intensive care unit; AKI, acute kidney injury.
All data are in median (IQR), mean ±S D, n(%), n/N(%)
[a] ATG used for induction at the time of transplantation; [b] 15 patients were still hospitalised at the time of reporting; Lymphocytes in $10^3/\mu L$.

Discussion

Our study reports the clinical features and outcomes of twenty COVID-19 infected renal transplant recipients. Regardless of two case reports, there are no large case series from India.

Compared to previous reports (Table 3), our patients were younger and predominantly comprised of live related transplants. The mean time from onset of symptoms and COVID-19 diagnosis was 3.05±1.47 days, which is earlier than other studies (Table 3). We presume, our patients reported early, as there was an increased awareness among the public on COVID-19 testing and severity of the disease.

Patients in our study had multiple co-morbidities, which are known to predict poor prognosis in COVID-19 infection (3). Most of our patients had moderate to severe COVID-19 infection. Nearly 50% of our patients had dyspnea, tachypnea and hypoxia at presentation. These three features significantly predicted poor prognosis in a study by Pereira et al (5). Twelve patients (44%) had severe-critical COVID-19 infection in their study. They speculated that treatment before the onset of hypoxia might help uncover the efficacy of the administered drugs (5). Likewise, in a study by Lubetzky et al, 15 patients (27%) had a mild infection, 26(48%) had moderate, while 24% had severe-critical COVID-19 disease (7).

In the general population, lymphopenia (<1.0 × 10^3/µL), elevated CRP (>100 mg/L), LDH (>400 IU/L), serum ferritin (>300 ng/mL), procalcitonin (>0.5 ng/mL), and D-dimer (>0.5 µg/mL) are bad prognostic markers for COVID-19 (13,14). However, there are conflicting reports on the significance of these parameters in transplant patients. In the study by Pereira et al, none of the above inflammatory markers were predictive of a severe disease except for procalcitonin (5).

In another study, median values of 16.5, 0.6, 0.5and 1152 for CRP, procalcitonin, D-dimer, and serum ferritin, predicted risk of death respectively (7). Severe lymphopenia (<0.700 ×10^3/µL) and an elevated LDH (>400 IU/L) heralded a poor prognosis in another series (6, 7). These variations in the significance of inflammatory markers could be due to a smaller sample size or the effects of immunosuppressive medications. Our study population had several patients with poor prognostic markers, as depicted in Tables 2 and 3.

AKI (AKI) is common in COVID-19 infected renal transplant recipients (Table 3). AKI in this setting is proposed to be due to decreased renal blood flow, sepsis and cytokine storm (7). Acute tubular injury, collapsing glomerulopathy, myoglobin cast nephropathy were noted in non-transplant COVID-19 infection patients who had undergone renal biopsy (15), however there are sparse data on renal allograft biopsy. Active antibody-mediated rejection, chronic active antibody-mediated rejection, IgA nephropathy, thrombotic microangiopathy and acute tubular injury were the findings seen in a case series with three renal transplant biopsies (16). Hence, the possibility of rejection in the background of modified immunosuppression cannot be ruled out without a biopsy. Five of our patients had AKI and three recovered. One patient with AKI died and another had chronic graft dysfunction before COVID-19 disease. Hence, none of them were considered for allograft biopsy. Allograft biopsy should be considered in transplant patients with non-recovering AKI or proteinuria.

Being a novel disease, strategies for modification of immunosuppression are not tested. On one hand, the immunosuppression may itself delay the viral clearance, and on the other hand, withdrawal is feared to cause an immune reconstitution/cytokine storm and may even predispose to rejection (5,7). In viral infections like cytomegalovirus and BK virus, it is general practice to decrease or stop antimetabolites. In addition, a low-lymphocyte count portends a poor prognosis. We stopped antimetabolites in our hospitalized patients from the day of diagnosis and halved it in home isolated patients until complete recovery, however there were no rejection episodes seen. Therefore, the withdrawal of mycophenolate may be indeed beneficial (3). Several studies reported decreasing or withholding tacrolimus (Table 3). We did not change the tacrolimus dose, except in one patient with a critical COVID-19 infection.

Most of the published studies were from patients during March-April 2020 timeframe (Table 3). The recovery trial results on the mortality benefit of steroids were reported in June 2020. A meta-analysis of seven trials concluded that systemic corticosteroids' administration compared with usual care or placebo was associated with a lower 28- day all-cause mortality (17). Studies report using systemic corticosteroids in 9-35% of the patients (Table 3). Intravenous (IV) steroid was used in all admitted patients in our study.

Remdesivir is a nucleotide analog, which is one of the many drugs repurposed for COVID-19. Multicentric studies and registries reported so far in renal transplant patients neither had a significant number of patients on remdesivir nor reported its outcome, probably because there was not much evidence for its use in the early pandemic (Table 3). Remdesivir trials have excluded this high-risk population (18, 19). In our patients, we have used remdesivir early and all tolerated it well. We found that none of our patients developed clinically significant transaminitis or worsening of graft function. There is no available data on the interaction of tacrolimus with remdesivir (20). Therapeutic drug monitoring was not conducted in our study, as it was not available in-house

and lockdown due to COVID-19. However, there was no worsening of serum creatinine during the treatment period or follow up. Hence, we presume there could be no clinically significant drug interaction. Nevertheless, therapeutic drug monitoring should be conducted where available.

COVID-19 associated inflammation is known to cause coagulopathy. Autopsy studies have shown that patients had a frequent thromboembolic disease and pulmonary microthrombi. Anticoagulant administration was reported to decrease mortality risk and the need for mechanical ventilation (21). In our study, all admitted patients were treated with a prophylactic dose of enoxaparin until discharge (Table 3).

Mortality in our study was 5% at twenty-one days. Although nearly half of our patients were having severe COVID-19. Our study had lower mortality when compared to the mortality of 18-32 % reported in various studies (Table 3). The good outcome noted in our study is presumably due to following reasons. Since the pandemic appeared in India later than in other countries, there was time to assimilate information from the rapidly evolving literature and establish COVID-19 RT-PCR diagnostic facilities. Younger age, earlier diagnosis, predominantly live related transplanted patients with lesser transplant vintage, earlier withdrawal of anti-metabolite and timely initiation of treatment with intravenous steroid, enoxaparin and also early remdesivir therapy, all could have had a substantial contribution for better results. Our study's outcome may not be unique to India per se and maybe more related to the factors mentioned above. Data from more extensive studies during the 'later era' of COVID-19 therapeutics would better recognize the importance of therapeutics in the outcomes (3).

Our study gives an important message that kidney transplant recipients' outcomes could be favorable if diagnosed and treated early. More extensive studies, trials, systematic reviews and meta-analysis may shed more light on the importance of early diagnosis and management. Even though the mass administration of COVID-19 vaccines has begun in few countries, vaccine safety or efficacy in immunosuppressed patients can only be known in due course (22). COVID-19 safety practices should be strictly enforced until the pandemic is declared to have subsided.

Conclusion

Kidney-transplant recipients infected with COVID-19 usually have moderate to severe disease with mortality of 5%. Lymphopenia may not be seen in all participants. Strategies such as withdrawal of antimetabolite, intravenous steroid, thromboprophylaxis and early remdesivir prescription all were found to be safe and effective. COVID-19 should be a differential diagnosis for either fever, cough or dyspnea in kidney transplant recipients while early diagnosis and timely treatment may improve outcomes in this high-risk population.

Limitations of the study

Our study's primary limitation is that this is a retrospective study with a small sample size from only two centers from India, hence our findings cannot be generalized.

Authors' contribution

BG, SPN and RM contributed to study design, preparation of the manuscript and final revision. NND and MB participated in retrieval of data, and wrote parts of paper. IRR contributed to data analysis and interpretation of the data. RPA and VS participated in critical review of manuscript for important intellectual content. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients. The study protocol was approved by the institutional ethics committee of Kasturba Medical College and Kasturba Hospital, Manipal (IEC 797-2020) And SDM College of Medical Sciences and Hospital (IEC 2021/02). Additionally, ethical issues (including plagiarism, data fabrication and double publication) were completely observed by the authors.

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