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Original Article

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Renal Manifestation of COVID-19 and its Association with Severity of Disease in a Tertiary Care Hospital of South India

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ABSTRACT

Objective: Kidney manifestation of coronavirus disease-2019 ranges from proteinuria and hematuria to acute kidney injury. The occurrence of acute kidney injury ranges from 0.5% to 80% across various studies. This study was conducted to know the kidney manifestation of coronavirus disease-2019 in the south Indian population and its association with severity of disease.

Methods: This is a retrospective cohort study that assessed coronavirus disease-2019-positive patients admitted from September 1, 2020, to October 31, 2020. Data were collected by accessing electronic medical records. Proteinuria and hematuria were assessed by dipstick. Lab data including serum creatinine were noted. Creatinine on 7 ± 2, 14 ± 4, and 45 ± 15 (after discharge) days was captured. Descriptive analysis was done in frequency and proportions for categorical variables and mean and standard deviation for continuous variables. Chi-square test was used to compare kidney manifestations based on the severity of coronavirus disease-2019. Kruskal–Wallis and Mann–Whitney tests were used to compare mean values of different inflammatory markers and severity of coronavirus disease-2019, acute kidney injury, proteinuria, and hematuria.

Results: A total of 1561 patients admitted during the study period were screened. After exclusion criteria, 426 patients were enrolled. The occurrence of acute kidney injury was 14.8%. Proteinuria was seen in 75 patients (17.6%) and hematuria in 39 patients (9.15 %); 47.5% of patients with acute kidney injury, 45.9 % with proteinuria, and 34.4 % with hematuria had severe coronavirus disease-2019 illness. The recovery of acute kidney injury at a mean duration of 45 ± 15 days post-discharge was 83.63 %.

Conclusion: Kidney involvement is not uncommon in patients with coronavirus disease-2019. The presence of acute kidney injury, proteinuria, and/or hematuria is associated with increased mortality among patients hospitalized with coronavirus disease-2019.

Keywords: AKI, COVID-19, hematuria, proteinuria

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INTRODUCTION

Coronaviruses belong to a group of viruses affecting animals and humans. Toward the end of 2019, a novel coronavirus was recognized to be the cause of a cluster of pneumonia cases in the city of Wuhan, China. This virus then rapidly spread to neighboring cities ensuing in an epidemic in China, followed later to other countries across the globe. It was in February 2020 that the World Health Organization named this disease as coronavirus disease 2019 (COVID-19) and declared the outbreak a global pandemic in March 2020.[1] The virus causing COVID-19 was designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The spectrum of COVID-19 infection ranges from asymptomatic infection to those developing severe and critical illness. Most of the patients who are symptomatic develop mild flu-like illness. Severe disease (like

pneumonia and hypoxia) occurs in around 15%-20% of symptomatic patients. Though healthy people of any age can be affected, individuals with advanced age and/or with underlying comorbid conditions are predominantly affected and are more susceptible to develop severe illness.[2,3]

Acute respiratory distress syndrome (ARDS) is one of the most important complications of severe illness. Apart from the tropism of SARS- CoV-2 to the respiratory epithelium, it can also cause multi-organ dysfunction involving the liver, kidneys, heart, and the digestive tract.[2,3]

Kidney involvement in COVID-19 can range from proteinuria and hematuria to acute kidney injury (AKI). Acute kidney injury occurs commonly and is an important and serious extra-pulmonary complication. The occurrence of AKI ranges from 0.5 % to 80% across various studies.[4-6] The reported incidence of AKI was low in the initial literature, but according to a recent meta-analysis, AKI was found in about 28% of hospitalized patients. Our study was conducted to find the occurrence of kidney manifestation of COVID-19 in the south Indian population and its association with the severity of illness.

METHODS

This study is a retrospective cohort study, conducted at a tertiary care teaching hospital and a designated COVID-19 center in south India. After prior approval from the Ethic Committe of M.S. Ramaiah Medical College (Date: May 31, 2021, Decision no: MSRMC /EC/S P-05/ 05-20 21), we retrospectively assessed COVID-19-positive patients of age more than 15 years of either gender who were admitted to this hospital from September 1, 2020 to October 31, 2020. Pregnant women and patients with inadequate lab data were excluded from the study. Patients with preexisting kidney disease and kidney transplant recipients were also not included in the study.

All the patients included in the study were diagnosed to have COVID-19 in accordance with the guidelines published by the Ministry of Health and Family Welfare, government of India, and were positive for SARS-COV-2 RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) by nasopharyngeal and/or throat swabs.

Retrospective data were collected by accessing the electronic medical records of the patients. Demographic data, clinical characteristics, comorbid conditions, and laboratory data were collected. Lab data included complete blood count, kidney function test, liver function test, HbA1C, D-dimer, Lactate dehydrogenase (LDH), serum Ferritin, and C-reactive protein (CRP). The presence of hematuria and/or proteinuria was assessed by urine dipstick test. Repeat serum creatinine values at a mean duration of 7 ± 2 and 14 ± 4 days during hospitalization were also captured. None of the patients with proteinuria, hematuria, or kidney dysfunction had undergone kidney biopsy. Serum creatinine values on follow-up at a mean duration of 45 days after discharge, of patients with persistently elevated serum creatinine at the time of discharge, were accessed using medical records of the patients.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences software for Windows version 22.0 (IBM Corp., Armonk, NY, USA) and *P*-value <.05 was considered statistically significant.

Descriptive analysis of all the explanatory and outcome parameters was done in frequency and proportions for categorical variables, whereas in mean and standard deviation for continuous variables. Chi-square test was used to compare the various stages of AKI, proteinuria, presence of hematuria, and hyperkalemia based on the severity of COVID-19 and other categorical variables as appropriate. Kruskal–Wallis and Mann–Whitney tests were used to compare the mean values of different inflammatory markers based on clinical severity of COVID-19, AKI, proteinuria, and hematuria. Mann–Whitney test was used to compare mean values of different laboratory parameters between patients with and without AKI.

Definitions

Patients with COVID-19 were classified clinically into mild, moderate, and severe categories according to guidelines published by the Ministry of Health and Family Welfare, government of India.

A mild case was defined as a patient with an uncomplicated upper respiratory tract infection without evidence of dyspnea or hypoxia (normal saturation).

A moderate case was defined as a patient with the presence of clinical features of dyspnea and/or hypoxia, including oxygen saturation (SpO_2) < 94% on room air and respiratory rate ≥ 24 per minute.

A severe case was defined as a patient with clinical signs of pneumonia plus one of the following: respiratory rate >30 per

MAIN POINTS

- Coronavirus disease-2019 (COVID-19) can have multi-organ dysfunction involving the kidney, liver, heart and gastrointestinal system apart from primarily affecting the lungs.
- Renal involvement in COVID-19 may present as proteinuria, hematuria and/or Acute kidney injury (AKI). We noted the occurrence of proteinuria in 17.6 %, hematuria in 9.15 % and AKI in 14.8% of patients admitted with COVID-19.
- The presence of AKI, proteinuria, and/or hematuria was associated with increased mortality among patients hospitalized with COVID-19.
- The renal recovery rate was high (83.63%) among survivors of COVID-19 with AKI.

minute, severe respiratory distress, and SpO2 < 90% on room air. Patients with ARDS, sepsis, or septic shock were also included in this category.

Acute kidney injury was defined by the Kidney Disease Improving Global Outcomes (KDIGO) AKI criteria which define AKI as any of the following:

- increase in serum creatinine by ≥0.3 mg/dL within 48 hours; or
- increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days.

The KDIGO criteria for AKI were applied using only serum creatinine values, as urine output data were not available.

RESULTS

Baseline Data and Demographic Characteristics

Overall, 1561 patients admitted with COVID-19 during the study period were screened; 144 patients had preexisting kidney disease, out of which 68 patients were CKD stage 5 on maintenance hemodialysis and 76 patients were CKD on conservative management. After considering the inclusion and exclusion criteria, 426 patients were enrolled in the study. The mean age of the patients was 53.02 ± 16.17 years and a majority of them were in the age group of 41-70 years, comprising 63.3% of total cases; 65% of the affected patients were males.

Fever was present in 34.5% of patients, while cough was noted in 28.2% of patients. Most of the patients (85.6%) had mild (44.1%) or moderate (41.5%) disease, while severe disease was seen in 14.3% of patients. The following comorbidities were seen in the study population: diabetes mellitus (DM) - 36.4%, hypertension (HTN) - 27.7%, ischemic heart disease (IHD) - 3.3%, chronic obstructive pulmonary disease/asthma - 7.3%.

Baseline demographic data comparing patients with kidney manifestation and patients without kidney manifestation showed that the mean age was higher (62.5 ± 13.6 years) in patients with kidney manifestation when compared to 51.4 ± 16 years in patients without kidney manifestation. Comorbid conditions including DM, HTN, and IHD were more commonly associated with patients with kidney manifestation (Table 1).

Table 1. Comparison of Demographic and Comorbid Conditions in COVID-19 Patients With and Without Renal Manifestation (AKI)

Variable	Category	With Renal Manifestation (AKI)		Without Renal Manifestation (AKI)		*P*
		Mean	SD	Mean	SD	
Age	Mean and SD	62.5	13.6	51.4	16.0	<.001*,a
		n	%	n	%	
Gender	Males	43	68.3%	234	64.5%	.56[b]
	Females	20	31.7%	129	35.5%	
DM	Absent	32	50.8%	239	65.8%	.02*,b
	Present	31	49.2%	124	34.2%	
HTN	Absent	35	55.6%	273	75.2%	.001*,b
	Present	28	44.4%	90	24.8%	
IHD	Absent	57	90.5%	355	97.8%	.003*,b
	Present	6	9.5%	8	2.2%	
COPD/ Asthma	Absent	54	85.7%	341	93.9%	.02*,b
	Present	9	14.3%	22	6.1%	

AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; SD, standard deviation.
*Statistically significant; [a]Mann–Whitney Test; [b]Chi-square test.

Lab Data

The occurrence of AKI in the study population was 14.8%; 59 patients (13.85%) had AKI at admission, 4 patients developed AKI during the course of hospitalization, 51 (86.4%) patients had stage 1 AKI at admission, and stage 2 and stage 3 AKI was seen in 8.5% and 5.1% of patients at admission, respectively (Table 2). Out of the 4 patients who had AKI during the hospital stay, 2 each had stage 1 and stage 2 AKI. Three patients needed kidney replacement therapy in the form of sustained

Table 2. Distribution of AKI During Admission and Hospitalization Period Among Study Patients

Variable	Category	Total		Admission		T1		T2	
		n	%	n	%	n	%	n	%
AKI	Absent	0	0.0	0	0.0	7	11.1	24	38.2
	Stage 1	53	84.1	51	86.4	45	71.4	28	44.4
	Stage 2	7	11.1	5	8.5	9	14.3	5	7.9
	Stage 3	3	4.8	3	5.1	2	3.2	6	9.5

T1, 7 ± 2 days of hospitalization; T2, 14 ± 4 days of hospitalization.
AKI, acute kidney injury.

Table 3. Distribution of Patients with Varying Grades of Proteinuria

Variable	Category	n	%
Proteinuria	1+ Proteinuria	52	69.3
	2+ Proteinuria	14	18.7
	3+ Proteinuria	7	9.3
	4+ Proteinuria	2	2.7
	Total	75	100.0

low-efficiency dialysis (SLED), out of which 2 patients underwent 4 sessions of SLED and 1 patient underwent 2 sessions of SLED, all eventually succumbing to the illness.

Dipstick proteinuria was positive in 75 patients (17.6%), while dipstick hematuria was positive in 39 patients (9.15 %). Most patients had 1+ proteinuria (52 patients: 69.3%) and 2 patients (2.7%) had nephrotic range (4+) proteinuria on dipstick test (Table 3). Hyperkalemia was the most common electrolyte abnormality seen in the study population, being present in 40 patients (9.3%).

Patients with AKI, proteinuria, and/or hematuria were more likely to have severe COVID-19 illness. Twenty-nine (47.5%) out of 63 patients with AKI had severe disease, while 45.9% of patients with proteinuria and 34.4% of patients with hematuria had severe COVID-19 illness and these findings were statistically significant (Table 4).

Patients having comorbid conditions like DM, HTN, and IHD were more prone to develop severe COVID-19 illness and more likely to have AKI. Proteinuria was seen more commonly in patients with DM, HNT, and IHD in comparison to those without these comorbidities. Hypertensive patients were more likely to

Table 4. Comparison of Various Stages of AKI, Proteinuria, Presence of Hematuria, and Hyperkalemia with Severity of COVID-19 Using Chi-Square Test

		Mild		Moderate		Severe			
Variable	Category	n	%	n	%	n	%	χ^2	*P*
AKI	Absent	177	94.1	154	87.0	32	52.5	64.295	<.001*
	Present	11	5.9	23	13.0	29	47.5		
Proteinuria	Absent	172	91.5	146	82.5	33	54.1	44.391	<.001*
	Present	16	8.5	31	17.5	28	45.9		
Hematuria	Absent	177	94.1	170	96.0	40	65.6	55.064	<.001*
	Present	11	5.9	7	4.0	21	34.4		
Hyperkalemia	Absent	175	93.6	161	91.0	48	80.0	9.864	.007*
	Present	12	6.4	16	9.0	12	20.0		

*Statistically significant.
AKI, acute kidney injury; COVID-19, coronavirus disease-2019.

Table 5. Comparison of Clinical Severity of COVID-19 with Comorbid Conditions of Patients Using Chi-Square Test

		Mild		Moderate		Severe		
Comorbidity	Category	n	%	n	%	n	%	*P*
DM	Absent	147	78.2	96	54.2	28	45.9	<.001*
	Present	41	21.8	81	45.8	33	54.1	
HTN	Absent	158	84.0	114	64.4	36	59.0	<.001*
	Present	30	16.0	63	35.6	25	41.0	
IHD	Absent	186	98.9	171	96.6	55	90.2	.004*
	Present	2	1.1	6	3.4	6	9.8	
COPD/Asthma	Absent	176	93.6	165	93.2	54	88.5	.39
	Present	12	6.4	12	6.8	7	11.5	

COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease-2019; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease.
*Statistically significant.

Table 6. Comparison of Presence of AKI with Comorbid Conditions of Patients Using Chi-Square Test

Comorbidity	Category	AKI Present		AKI Absent		*P*
		n	%	n	%	
DM	Absent	32	50.8	239	65.8	0.02*
	Present	31	49.2	124	34.2	
HTN	Absent	35	55.6	273	75.2	0.01*
	Present	28	44.4	90	24.8	
IHD	Absent	57	90.5	355	97.8	0.003*
	Present	6	9.5	8	2.2	
COPD/ASTHMA	Absent	54	85.7	341	93.9	0.02*

AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease.
*Statistically significant.

Table 7. Comparison of Presence of Proteinuria with Comorbid Conditions of Patients Using Chi-Square Test

Comorbidity	Category	Proteinuria Present		Proteinuria Absent		*P*
		n	%	n	%	
DM	Absent	37	49.3	234	66.7	.005*
	Present	38	50.7	117	33.3	
HTN	Absent	44	58.7	264	75.2	.004*
	Present	31	41.3	87	24.8	
IHD	Absent	70	93.3	342	97.4	.07
	Present	5	6.7	9	2.6	
COPD/ Asthma	Absent	65	86.7	330	94.0	.03*
	Present	10	13.3	21	6.0	

COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease.
*Statistically significant.

develop hematuria. All these findings were statistically significant (Table 5, 6, 7).

Lymphopenia was seen both in patients with or without kidney manifestation but more commonly in patients with kidney manifestation. The mean values of LDH, D-dimer, and inflammatory markers (CRP, serum ferritin) were higher in the study population but much higher in patients with kidney manifestation and also in patients with severe disease (Table 8).

A total of 15 patients out of 61 severe cases had multi-organ dysfunction and required inotrope support and 11 patients required invasive ventilation. A total of 11 deaths (2.58%) were observed in the study population, out of which 8 patients (72.5%) had AKI, 7 patients (63.6%) had proteinuria, and 5 patients (45.5%) had hematuria which was statistically significant (Table 9).

Comparison of Baseline and Repeat Serum Creatinine Values

Among survivors of COVID-19 patients with AKI (55 patients out of 63 patients), 24 patients (43.63%) recovered from AKI at a mean time interval of 14 ± 4 days during hospitalization

Table 8. Comparison of Mean Values of Inflammatory Markers (CRP, Ferritin), LDH, D-Dimer with Clinical Severity of COVID- 19, AKI, Proteinuria, and Hematuria

Variables	Category	CRP		Ferritin		LDH		D-Dimer	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
COVID 19 Severity	Mild	2.16	3.95	165.46	192.97	261.19	169.64	0.86	1.00
	Moderate	6.34	7.66	297.94	268.46	320.54	142.25	1.27	1.34
	Severe	10.83	9.40	351.52	280.94	426.25	232.10	2.42	2.30
	P	<.001*,a		<.001*,a		<.001*,a		<.001*,a	
AKI	Absent	4.48	6.74	223.58	238.15	294.74	169.00	1.15	1.36
	Present	8.92	8.94	378.87	280.22	392.35	203.93	1.86	1.93
	P	<.001*,b		<.001*,b		<.001*,b		<.001*,b	
Proteinuria	Absent	4.29	6.70	240.30	248.42	290.03	144.81	1.16	1.41
	Present	9.10	8.47	276.70	260.66	398.72	268.92	1.68	1.73
	P	<.001*,b		.26b		<.001*,b		.006*,b	
Hematuria	Absent	4.88	7.16	238.36	242.27	296.99	153.00	1.19	1.41
	Present	7.73	7.90	330.91	315.57	430.15	314.52	1.92	1.95
	P	.02*,b		.03*,b		<.001*,b		.003*	

*Statistically significant; aKruskal–Wallis test; bMann–Whitney test.
AKI, acute kidney injury; COVID-19, coronavirus disease-2019; CRP, C-reactive protein; SD, standard deviation.

Table 9. Comparison of Mortality Rate with Presence of AKI, Proteinuria, Hematuria and Comorbidities Among Patients Using Chi-Square Test

Variables	Category	Alive		Dead		*P*
		n	%	n	%	
AKI	Absent	360	86.7	3	27.3	<.001*
	Present	55	13.3	8	72.7	
Proteinuria	Absent	347	83.6	4	36.4	<.001*
	Present	68	16.4	7	63.6	
Hematuria	Absent	381	91.8	6	54.5	<.001*
	Present	34	8.2	5	45.5	
DM	Absent	266	64.1	5	45.5	.21
	Present	149	35.9	6	54.5	
HTN	Absent	301	72.5	7	63.6	.52
	Present	114	27.5	4	36.4	
IHD	Absent	402	96.9	10	90.9	.27
	Present	13	3.1	1	9.1	
COPD/Asthma	Absent	388	93.5	7	63.6	<.001*
	Present	27	6.5	4	36.4	

AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease.
*Statistically significant.

and 31 patients (56.36%) had persistently elevated serum creatinine at discharge. The follow-up serum creatinine values of these patients after discharge, at a mean duration of 45 ± 15 days, revealed that 22 patients had complete recovery from AKI (83.63% kidney recovery rate among survivors), 5 patients had partial recovery or persistently elevated serum creatinine levels, and 4 patients were lost to follow-up.

DISCUSSION

Acute kidney injury is an important and serious extra-pulmonary complication of COVID-19. The exact mechanism of AKI development in patients with COVID-19 remains obscure. The mechanisms which have been hypothesized include cytokine storm syndrome due to sepsis, direct virus-induced kidney cellular injury, hypercoagulability with microangiopathy, rhabdomyolysis, and drug-induced AKI. Clinical studies and autopsy results have demonstrated that SARS-CoV-2 can directly infect the kidney. Viral replication in the podocytes and tubules may induce AKI in COVID-19 as per published literature.[7] Electron microscopic examination of kidney biopsy from COVID-19 patients has shown virus-like particles in the tubular epithelium indicating tubular cell invasion by SARS-CoV-2, and viral RNA has also been demonstrated in kidney tissue from patients with COVID-19. It has been shown that there is an expression of surface angiotensin-converting enzyme 2 on the proximal tubular cells of the nephrons, which is key for the coronavirus to bind and gain entry into the target cells.[8,9]

Our study retrospectively assessed patients admitted with COVID-19 illness. Proteinuria was the commonest kidney manifestation of COVID-19 in our study, occurring in 17.6% of patients followed by AKI (14.8%), hyperkalemia (9.3%), and hematuria occurring in 9.15% of patients.

There are important aspects that need to be looked into when the assessment of proteinuria is being done. It is worthwhile to know if prior documentation of proteinuria was done in patients having proteinuria during COVID-19 illness. Knowledge of the baseline level of proteinuria is also crucial in the assessment of AKI. But, most often, prior medical records are not available to validate if the detection of proteinuria is a new occurrence or a preexisting finding. Therefore, after detection of proteinuria in a COVID-19 patient, one needs to be cautious before assuming that the proteinuria is associated with the acute illness itself.

The occurrence of AKI in our study population was 14.8% and hyperkalemia was observed in 9.3% of patients. According to a systematic review and meta-analysis of kidney manifestation in COVID-19, the incidence of AKI was 11% and hyperkalemia was seen in 12.5% of patients.[10] Another recent meta-analysis by Silver et al[11] based on 53 studies comprising 30 639 COVID-19 cases, established the prevalence of AKI to be 28%. As per the available literature, the rate of AKI varies considerably among patients with COVID-19, ranging from 0.5% to 80% across various studies.[4-6] The variability in the AKI rates could be attributed to differences in patient characteristics, differences in geographic locations, race/ethnicity, and disease severity. Published studies from Europe and the United States found AKI prevalence of 20%-40% in COVID-19 patients,[5,12,13] whereas initial studies from China reported lesser percentages of patients with AKI.[14-21] Advanced age, presence of DM, and severe COVID-19 illness are independent risk factors for the development of AKI.

Our study also revealed that COVID-19 patients with AKI, proteinuria, or dipstick hematuria were likely to have severe disease and were associated with excess mortality. The presence of AKI was associated with increased odds of death among COVID-19 patients (odds ratio: 17.45). Our findings were consistent with a meta-analysis by Robbins-Juarez et al,[4] which showed that the pooled odds ratio was 15.27 among COVID-19 patients with AKI.

According to our study, the kidney recovery rate was high (83.63%) among survivors of COVID-19 with AKI who did not require kidney replacement therapy, though all the 3 patients with COVID-19 illness who needed kidney replacement therapy eventually succumbed to the disease.

Our study had some limitations. First of all, pre-admission urine analysis reports of the study population were not available and hence it was difficult to ascertain the presence or absence of proteinuria and hematuria before admission. Secondly, proteinuria and hematuria were assessed using a urine dipstick test. Urine for dipstick protein test provides only a semi-quantitative estimation and hence urine quantification of protein excretion is better reflected by 24-hour urinary protein or spot urine protein : creatinine ratio. Thirdly, the mean duration of follow-up of patients after discharge was relatively shorter (45 ± 15 days) to assess the long-term outcome of AKI in these patients.

CONCLUSION

Kidney involvement is not uncommon in patients with COVID-19, particularly in patients with severe illness. The presence of AKI, hematuria, and/or proteinuria is associated with excess mortality among patients hospitalized with COVID-19. Long-term follow-up studies of COVID-19 patients are required to investigate the effect on kidney outcome.

Ethics Committee Approval: Ethical committee approval was received from the Ethic Committe of M.S. Ramaiah Medical College (Date: May 31, 2021, Decision no: MSRMC /EC/S P-05/ 05-20 21).

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