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NEPHROLOGY - ORIGINAL PAPER

Impact of COVID 19 pandemic on patients requiring renal biopsy

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Abstract

Introduction The disruption of healthcare services in coronavirus disease (COVID)19 pandemic was widespread particularly due to lockdown curbs. This study was undertaken to see the effect of this pandemic on subjects requiring renal biopsy.

Materials and method Renal biopsies performed during the COVID 19 pandemic between April 2020 and December 2020 (Group 1) were compared with those in pre-COVID period between June 2019 and February 2020 (Group 2). Indication of biopsies, syndromic diagnosis and all baseline laboratory characteristics were retrieved from the hospital records.

Results 130 and 191 patients were biopsied in groups 1 and 2, respectively. Patients in group 1 were younger compared with group 2 (32.55 ± 15.60 and 36.37 ± 16.96 years, respectively, p value 0.038). The mean serum creatinine value in group 1 was significantly higher than in group 2 (3.21 ± 2.08 and 2.68 ± 2.02 mg/dl respectively, p value: 0.023). Group 1 comprises a significantly higher percentage of rapidly progressive renal failure patients (RPRF) (39.3 vs 28, p value 0.046). A higher percentage of nephrotics was biopsied in group 2 vs group 1 (46.9 vs 30.4 respectively, p value 0.008). The treatment protocol remained similar in both the groups. Evaluation of the transplant biopsies revealed a nonsignificant higher number of rejections in group 1 (11 out of 18) as compared to group 2 (5 out of 16), p value 0.100. Combined rejection saw a lesser use of rATG in group 1.

Conclusion COVID pandemic induced restrictive measures could have led to selective high risk patients with RPRF as presumptive diagnosis and higher creatinine values getting biopsied. Higher rejections were noticed in transplant recipients pointing towards the need of establishing a more efficient support system for managing such patients.

Keywords COVID · Biopsy · Renal

Introduction

Negative impact of coronavirus disease (COVID) 19 on renal care services in India has been highlighted by Prasad et al. and Chandra et al. [1, 2]. The disruptions were multifaceted. Conversion of a section of the hospital to a COVID centre, diversion of the staff to COVID dedicated hospitals, rigorous lockdown measures, financial constraints owing to loss of jobs, poor transport facilities, fear of COVID in patients, all led to a fall in patient footfall in the hospitals. As per the hospital's protocol all patients requiring hospitalization for any reason were required to get a COVID 19 report (RT-PCR).

Considering the hardships faced by the patients, there was a likelihood that the visit to a nephrologist could have been deferred, particularly if the symptoms were not of serious nature and manageable by a local general physician. This could have led to a preventable worsening of renal functions and in certain cases induced irreversibility to the basic pathology. This calls for elaborate research to study the impact of COVID 19 on renal diseases requiring a renal biopsy to guide future management as there is a scarcity of information regarding how COVID pandemic affected such patients. The results from this study can help in formulating strategies to provide timely support to such patients.

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Material and methods

We retrospectively analyzed the renal biopsies done at this tertiary care centre between April 2020 and December 2020 (Group 1) during the onset of COVID -19 pandemic and enforcement of a lockdown followed by a gradual unlocking. These were compared with those done in the pre-COVID period between June 2019 and February 2020 (Group 2). All the renal biopsies were performed by either of the two nephrologists working in the department of Nephrology. The biopsy specimens were analyzed by a single pathologist with her team of residents and technicians. Two biopsy cores were taken, one each for light microscopy (LM) and immunofluorescence (IF). All the biopsies were performed under real time ultrasound guidance (Sono Site M-TURBO® [Fujifilm Sonosite, Bothell, WA, USA], using the curvilinear probe of 3.5 MHz). 16-gauge automated biopsy gun was used in adults. 18-gauge gun was used for children less than 8 years of age. Post biopsy, a provisional report was usually available within 48 h. After initiation of the optimal treatment plan, patients were discharged and were called after 7 days with a formal report. Time taken by the patients for their first follow-up and adherence to the scheduled appointment since their day of biopsy along with the baseline laboratory characteristics were retrieved from the hospital records.

Indications for renal biopsy were categorized into different syndromes namely nephrotic syndrome, nephritic syndrome, rapidly progressive renal failure (RPRF), chronic kidney disease (CKD), acute kidney injury and asymptomatic urinary abnormality. Nephrotic syndrome was defined as proteinuria > 3.5 g/24 h/1.73 m^2 along with hypoalbuminemia, edema and hyperlipidemia. Nephritic syndrome was diagnosed on the basis of hypertension, oliguria, hematuria and edema. Rapidly progressive renal failure was defined as a rapid decline in glomerular filtration rate (GFR) over a period of more than a week to less than three months. CKD was defined as GFR of < 60 ml/min/1.73m^2 with proteinuria lasting greater than 3 months. CKD patients underwent renal biopsy only when the kidney sizes were within normal limits. Acute kidney injury was defined as sudden fall in GFR over hours to a week. A combination of the features of nephrotic and nephritic syndrome was defined as nephrotic–nephritic syndrome. Asymptomatic urinary abnormality was defined as microscopic hematuria and/or sub-nephrotic proteinuria with absence of clinical symptoms or signs. A histologic pattern of diffuse global glomerulosclerosis (DGGS) was assigned to biopsies with a minimum of eight glomeruli, of which more than 50% showed sclerosis; affecting at least half of the capillary tuft.

All methods followed in this study were carried out in accordance with the provisions of the Declaration of Helsinki. Informed consent was obtained from all subjects.

Statistical analyses were performed using the SPSS version 20.0 (SPSS, Chicago, IL, USA). Descriptive statistics (mean ± standard deviation [SD]) was used for continuous variables. Independent *t* test was used to compare continuous variables. Chi-square or Fisher's Exact test was used to compare categorical variables between the two groups. A 2-sided $p < 0.05$ was considered statistically significant.

Results

A total of 130 and 191 patients were biopsied in Group 1 and group 2 respectively. Of these 2 in the group 1 and 5 in the group 2 did not come for a follow-up. 5 patients contacted COVID from Group 1 including 2 renal transplant recipients. One non transplant patient died of COVID whereas both the transplant recipients survived with no impact on their renal function tests. Mean time taken by the patients for their first follow-up in OPD was 8.51 ± 1.3 days in the group 1 compared to 8.6 ± 1.17 days in the group 2. 30 (26.7%) patients (nontransplant) in group 1 reported facing problems in procuring medicine. Only 2 transplant recipients conveyed problems in getting medications. 36 (32.14%) patients (nontransplant) in group 1 missed their scheduled appointments as compared to 18 (10.28%) patients in group 2 (*p* value: < 0.001).

Overall, the patients were of a younger age group (Table 1). The mean age of the patients in the group 1 was significantly lower than those in the group 2 (32.55 ± 15.60 and 36.37 ± 16.96 years respectively, *p* value 0.038). Both the groups were similar in sex distribution. The mean serum creatinine value in group 1 was significantly higher than in group 2 (3.21 ± 2.08 and 2.68 ± 2.02 mg/dl respectively, *p* value: 0.023).

The syndrome wise distribution of cases in Table 2 shows a significantly higher percentage of nephrotic patients in group 2 (46.9) compared to group 1 (30.4) with a *p* value of 0.008. A statistically significant higher percentage of rapidly progressive renal failure patients were seen in group 1 (39.3) in comparison to group 2 (28) with a *p* value of 0.046. Rest of the syndromes were comparable in both the groups.

Histological diagnosis of nontransplant biopsies (Table 3) revealed a significantly higher number of membranous glomerulopathy cases in group 2 vs group 1 (19 vs 4, *p* value 0.043). The rest of histological findings was similar in both the groups. IgA nephropathy was the most common glomerulonephritis reported in both the groups. Analysis of the rapidly progressive renal failure cases showed a higher value of s. creatinine value of 4.62 ± 1.85 mg/dl in group 1 compared to 4.09 ± 1.88 mg/dl in group 2 which was statistically significant (*p* value: 0.013, not shown in table). Histological analysis of RPRF cases (Table 4) revealed a significantly higher

Table 1 Clinical and laboratory characteristics

	Group 1, *n*-130	Group 2, *n*-191	*p* value
Age (years)	32.55 ± 15.60	36.37 ± 16.96	0.038
Sex	M-98 (76%), F-31 (24%)	M-138 (72%), F-54 (28%)	0.484
First follow-up (days)	8.51 ± 1.3	8.6 ± 1.17	0.526
Hb (g/dl)	10.42 ± 1.77	10.7 ± 2.21	0.228
Platelet	208 ± 73.05	195 ± 54.92	0.069
Urea (mg/dl)	72.29 ± 35.74	57.45 ± 28.12	0.001
S. Creatinine (mg/dl)	3.21 ± 2.08	2.68 ± 2.02	0.023
S. Sodium (mEq/l)	134.51 ± 12.69	136.21 ± 13.15	0.249
S. Potassium (mEq/l)	4.32 ± 0.68	3.78 ± 0.87	0.781
S_albumin (g/dl)	2.85 ± 0.94	2.42 ± 0.86	< 0.001
Urine albumin (mg/dl)	163.37 ± 107.06	149.78 ± 95.41	0.233
Urine WBC (cells/HPF)	5 (2–10)	7 (2–15)	0.421
Urine RBC (cells/HPF)	11 (1–30)	14 (3–30)	0.143

n number of subjects, *Hb* hemoglobin, *HPF* high power field, *RBC* red blood cells, *WBC* white blood cells

Table 2 Syndromic diagnosis

Syndrome	Group 1, non allograft, *n*-112	Group 2, non allograft, *n*-175	*p* value
Nephrotic	34 (30.4)	82 (46.9)	0.008
RPRF	44 (39.3)	49 (28)	0.046
CKD	11 (9.8)	17 (9.71)	0.976
AKI	13 (11.6)	20 (11.4)	0.963
Nephritic	5 (4.5)	2 (1.1)	0.201
Nephrotic–nephritic	5 (4.5)	3 (1.7)	0.430
AUA	0	2 (1.1)	

n number of subjects, *AUA* asymptomatic urinary abnormality, *RPRF* RAPIDLY progressive renal failure, *AKI* ACUTE kidney injury, () percentage

percentage of diffuse global glomerulosclerosis cases in group 1 (16) as compared to group 2 (8) with a *p* value of 0.027.

Among all biopsies, a higher percentage of renal allograft biopsies were recorded in group 1 (13.8%) compared to group 2 (9.1%). Out of a total of 105 transplant recipients in follow-up at this centre, allograft biopsy was performed in 16 during the COVID pandemic period (group 1). 2 patients had to undergo 2 biopsies each during the said time. In the pre-COVID period (group 2), out of a total of 90 patients 15 patients underwent allograft biopsy with one recipient requiring 2 biopsies. Transplant biopsies (Table 5) showed a nonsignificant higher number of rejections in group 1 (11) compared to group 2 (5). Transplant recipients in group 1 had a higher mean s. creatinine than in group 2 (2.37 ± 0.64 vs 2.05 ± 1.02 mg/dl) though not statistically significant.

Discussion

In our study, only a small number of patients contacted COVID 19. The low incidence of COVID in our cases could stem from the fact that all the patients were individually counselled regarding minimization of travel, social distancing and use of masks. Also, the first wave of COVID 19 in India was much weaker than the second wave noticed in the months of April and May of the year 2021. COVID infections could have been much higher in the second wave. Problems faced by the patients in getting the prescribed medicine was likely due to limited availability of these in the remote areas along with transportation and financial issues. For transplant patients an effort was made by the transplant coordinator to check for the compliance and availability of medications during pandemic period through virtual medium. Missing of scheduled appointments was significantly higher in group 1 at 32.14% compared to group 2 (10.28%). Rathi M et al. have reported an even higher percentage of 54% incidence of missed regular appointments [3].

Mean age of the patients in group 1 was lower than group 2. This could stem from the fact that younger subjects in the age group of 30–40 years are usually the earning members of the family and are more likely to seek hospitalization for their ailments. The reported mean age is in line with other studies from India [4, 5]. Our study has shown a much higher percentage of RPRF cases in both the groups (39.3% in group 1 and 28% in group 2 respectively) as compared to that reported from other centres ranging from 10 to 20% [6, 7]. The present study showed a higher s. creatinine value in patients with syndromic diagnosis of RPRF in group1 compared to group 2. DGGS was histologically seen in 36.36% of RPRF cases in group 1 in comparison to 16.32% in group 2. All these findings point towards the fact that RPRF cases with high s. creatinine cases were the more symptomatic

Table 3 Histological diagnosis (excluding renal allograft biopsies)

	Group 1, Non allograft, *n*-112		Group 2, Non allograft, *n*-175		*p* value
	Number (percentage)	Treatment	Number(percentage)	Treatment	
MCD	17 (15.2)	Prednisolone	23 (13.1)	Prednisolone	0.481
FSGS	12 (10.7)	Prednisolone	21 (12)	Prednisolone	0.885
IgA	21 (18.7)	18-prednisolone 3-no immunosuppression	24 (13.7)	18-prednisolone 6-no immunosuppression	0.324
MPGN	4 (3.6)	Prednisolone	4 (2.3)	Prednisolone	1.0
MGN	4 (3.6)	3-modified ponticelli 1-no immunosuppression	19 (10.8)	12-modified ponticelli 4-no immunosuppression 3-Rituximab	0.043
DGGS	21 (18.7)	No immunosuppression	18 (10.3)	No immunosuppression	0.023
C3GN	9 (8)	Prednisolone	14 (8)	Prednisolone	0.681
AIN	6 (5.4)	2-prednisolone 4-no immunosuppression	4 (2.3)	2-prednisolone 2-no immunosuppression	1.0
ATIN	5 (4.5)	2-prednisolone 3-no immunosuppression	6 (3.4)	2-prednisolone 4-no immunosuppression	0.752
Amyloidosis	3 (2.7); 2 primary, 1 secondary		8 (4.6); 5 primary, 3 secondary		0.544
HN	3 (2.7)	No immunosuppression	3 (1.7)	No immunosuppression	1.0
PIGN	2 (1.8)		4 (2.3)		1.0
DN	4 (3.6)	No immunosuppression	8 (4.6)	No immunosuppression	1.0
Crescentic GN	1 (0.9); immune complex	Prednisolone + oral cyclophosphamide	9 (5.1); 6 Pauciimmune, 3 immune complex	Paucimmune-EUVAS protocol Immune complex—prednisolone + oral cyclophosphamide	0.160
c1q	0		1 (0.6)		
Lupus nephritis	0		6 (3.4)	3-ClassIII—Eurolupus 2-Class IV—NIH 1-Class V—prednisolone + cyclophosphamide	
TMA	0		3 (1.7)	PLEX + prednisolone	

n number of subjects, *GN* glomerulonephritis, *FSGS* focal segmental glomerulosclerosis, *MCD* minimal change disease, *MN* membranous nephropathy, *MPGN* membranoproliferative *GN*, *IgAN* IgA nephropathy, *LN* lupus nephritis, *DN* diabetic nephropathy, *ATIN* acute tubulointerstitial nephritis, *AIN* acute interstitial nephritis, *ATN* acute tubular necrosis, *PIGN* post infectious GN, *TMA* thrombotic microangiopathy, *EUVAS* European Vasculitis Study, *PLEX* plasma exchange, *NIH* National Institute of Health. () percentage

ones with rapid worsening of symptoms who required an expert care, not possible in remote areas prompting them to make an in-person visit to this tertiary care hospital. A high percentage of histological DGGS cases points towards the possibility of their late referral or delay in seeking a medical opinion leading to irreversible pathological damage. Hakroush et al. have reported a fall in number of renal biopsies performed in COVID period followed by a late surge in post COVID phase citing lockdown situation and downplay of constitutional symptoms by the patients [8, 9]. Although, they did not find any difference in the histological diagnosis between the two periods [8].

Cases of nephrotic syndrome can be managed in the peripheral centres by the use of diuretics and other supportive therapies if not severe or associated with complications. Such patients probably did not venture to the tertiary care centre during lockdown due to the pandemic. This explains the reason behind the higher number of nephrotic patients biopsied in group 2. IgA nephropathy was identified as the most common form of primary glomerulonephritis which is different from what has been reported by Bhalla et al. and Muthu et al. who reported minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) respectively as the most common primary glomerulonephritis in their studies [5, 7]. The treatment offered to the nontransplant patients in both the groups included use of prednisolone, mycophenolate mofetil and cyclophosphamide with no significant difference between the groups. Rituximab was used only in group 2, in membranous nephropathy patients. Delaying the nonurgent biopsies of nephrotics and prioritizing patients at high risk of developing end stage renal disease has been suggested by Bomback et al. [10]. Also

Table 4 Histological diagnosis of rapidly progressive renal failure (RPRF)

RPRF	Group 1, Non allograft; *n*-44		Group 2, Non allograft; *n*-49		*p* value
	Numbers	Treatment	Numbers	Treatment	
FSGS	3	Prednisolone	6	Prednisolone	0.494
IgA	11	Prednisolone	12	Prednisolone	0.889
MPGN	1	Prednisolone	1	Prednisolone	1.0
DGGS	16	No immunosuppression used	8	No immunosuppression used	0.027
C3GN	5	2-prednisolone + cyclophosphamide 3-prednisolone + MMF	6	4-prednisolone + cyclophosphamide 2-prednisolone + MMF	0.927
AIN	2	Prednisolone	0		0.215
ATIN	1	No immunosuppression	2	1-prednisolone	1.0
HN	1	No immunosuppression	3	No immunosuppression	0.619
PIGN	1	Prednisolone	0		0.467
DN	1	No immunosuppression	3	No immunosuppression	0.619
Crescentic GN	2	Prednisolone + inj. cyclophosphamide every 15 days × 6 doses	6	4-prednisolone + oral cyclophosphamide 2-prednisolone + inj. cyclophosphamide every 15 days × 6 doses	0.275
Lupus nephritis	0		2	Class IV—NIH protocol	0.496

n number of subjects, *GN* glomerulonephritis, *FSGS* FOCAL segmental glomerulosclerosis, *MCD* minimal change disease, *MN* membranous nephropathy, *MPGN* membranoproliferative GN, *IgAN* IgA nephropathy, *LN* lupus nephritis, *DN* diabetic nephropathy, *ATIN* acute tubulointerstitial nephritis, *AIN* acute interstitial nephritis, *ATN* acute tubular necrosis, *PIGN* post infectious GN, *TMA* thrombotic microangiopathy, *MMF* mycophenolate mofetil, *NIH* National Institute of Health

Table 5 Histological diagnosis in renal allograft biopsies

Transplant biopsies	Group 1, Allograft *n*-18,		Group 2, Allograft *n*-16		*p* value
Diagnosis	Numbers	Treatment	Diagnosis	Treatment	
ABMR	5	6 sessions of plasmapheresis, IVIG 30 g and single dose of 375 mg/m^2 rituximab	0		0.046
BCR	2	Pulse methylprednisolone	1	Pulse methylprednisolone	1.00
TCMR	3	2-acute TCMR IA/IB—pulse methylprednisolone 1-Acute TCMR IIa—rATG	1	Acute TCMR IA—pulse methylprednisolone	0.604
Combined	1	Active ABMR + acute TCMR IA—plasmapheresis, IVIG 30 g, single dose of 375 mg/m^2 rituximab and pulse methylprednisolone	3	2-(active ABMR + acute TCMR IA)—plasmapheresis, IVIG 30 g, single dose of 375 mg/m^2 rituximab and rATG 1-(active ABMR + acute TCMR IIB)—plasmapheresis, IVIG 30 g, single dose of 375 mg/m^2 rituximab and pulse methylprednisolone	0.322
No evidence of rejection, s/o ATN	2		6		0.110
CNI toxicity	3	CNI dose reduced	4	3-CNI dose reduced; 1-CNI changed to sirolimus	0.681
TG	1		0		
Recurrence of basic disease	1 (IgA nephropathy)		0		
Viral cytopathy (BKV)	0		1	MMF dose reduced	

n number of subjects, *ABMR* antibody mediated rejection, *BCR* borderline cellular rejection, *TCMR* T cell mediated rejection, *CNI* calcineurin inhibitor, *BKV* BK virus, *ATN* acute tubular necrosis, *rATG* rabbit anti-thymocyte globulin, IVIG intravenous IG. Allograft biopsies-based Banff Classification of Renal Allograft Pathology 2017

lowering the immmunosupressive burden in such patients along with use of alternative antiproteinuric strategies has been advocated [10]. We at our centre followed the same protocol in deciding for biopsy and necessary treatment in the pandemic phase as that in the pre pandemic period.

As far as renal transplant recipients were concerned, they were often in touch with the kidney transplant unit through telephonic conversations and the precautions advised to them were of a similar nature as those advised during the COVID period. Despite that, an alarming higher rate of rejections with greater s. creatinine values were seen during the COVID period (group 1) which on thorough assessment points to several possible causes. The follow-up during COVID was primarily through hospital telemedicine services [11] or other virtual platforms and the frequency of laboratory testing had to be decreased because of the existent constraints that may have let to suboptimal monitoring and late detection of graft dysfunction. In addition, the urgency of performing biopsy had to be balanced with COVID testing and other financial and transport issues. There could have been a shortage of immunosuppressants due to financial reasons or nonavailability in local areas. Psychological stress due to ongoing COVID 19 pandemic in transplant recipients might have been high which could have gone undetected or untreated. This could well have led to drug default leading to higher number of rejections. Antibody mediated rejections were only seen in group 1 and were managed with immunoglobulin (IVIG), plasmapheresis and rituximab which was in line with the usual protocol followed at this centre. T cell mediated rejections of category IA and IB were treated with methylprednisolone in both the groups. Rabbit antithymocyte globulin (rATG) was used to treat T cell mediated rejection II reported only in group 1. Combined rejections saw use of IVIG, methylprednisolone, plasmapheresis, rituximab and rATG in group 2 compared to group 1 in which IVIG, methylprednisolone, plasmapheresis and rituximab were used. Higher immunosuppression requirement for battling combined rejections could have discouraged the use of rATG in group 1 during COVID 19 period. A trend of decreased use of lymphphocyte depleting agents as induction agents in transplants was seen in the pandemic period citing lower targeted immunosuppression [12], but recommendations for managing rejections are far from clear.

Conclusion

COVID-19 pandemic impaired the smooth functioning of the existing health infrastructure making it difficult for the non-COVID patients to timely access the healthcare. Efforts are needed to reinforce the faith and confidence of the non-COVID population with renal ailments in the hospital services and enable a timely intervention and follow-up thereby preventing a rapid loss of renal functions in the vulnerable set of patients. Answering the unmet needs of the renal transplant recipients like social, mental and financial support is equally important to ensure proper compliance. Framework for a timely laboratory study and enabling in-person visit for an indicated biopsy is required. More information is needed with respect to the use of particular immunosuppressants in various types of glomerulonephritis and rejections.

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Availability of data and materials The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have declared that no conflict of interest exists.

Ethics approval and consent to participate Written consent was taken from all the eligible participants. Since it was a retrospective analysis of anonymous data, ethical committee's approval was not sought.

Informed consent Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Experimental protocols The protocol for the research project within which the work was undertaken conforms to the provisions of the Declaration of Helsinki.

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