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SYSTEMATIC REVIEWS

Nephrotic syndrome following COVID-19 vaccination: a systematic review

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Abstract

Background Severe acute respiratory syndrome coronavirus 2 infection has caused significant morbidity and mortality. Vaccines produced against this virus have proven highly effective. However, adverse events following vaccination have also been reported. One of them is nephrotic syndrome, that can be associated with different pathologic pictures. This review aims to provide a wider understanding of incidence, etiopathogenesis, and management of nephrotic syndrome following vaccination against SARS-CoV-2.

Methods and results A literature search was undertaken using appropriate keywords in various databases like PubMed, Google Scholar, Europe PMC, and Science Direct. Twenty-one articles were included following qualitative assessment. Data of 74 patients from these articles were included.

Discussion The pathogenesis of nephrotic syndrome following COVID vaccination has been widely attributed to the activation of angiotensin-converting enzyme-2 receptors, leading to podocyte effacement. Relapses have also been reported in patients with prior history of nephrotic syndrome following COVID-19 vaccination. A renal biopsy is necessary to identify

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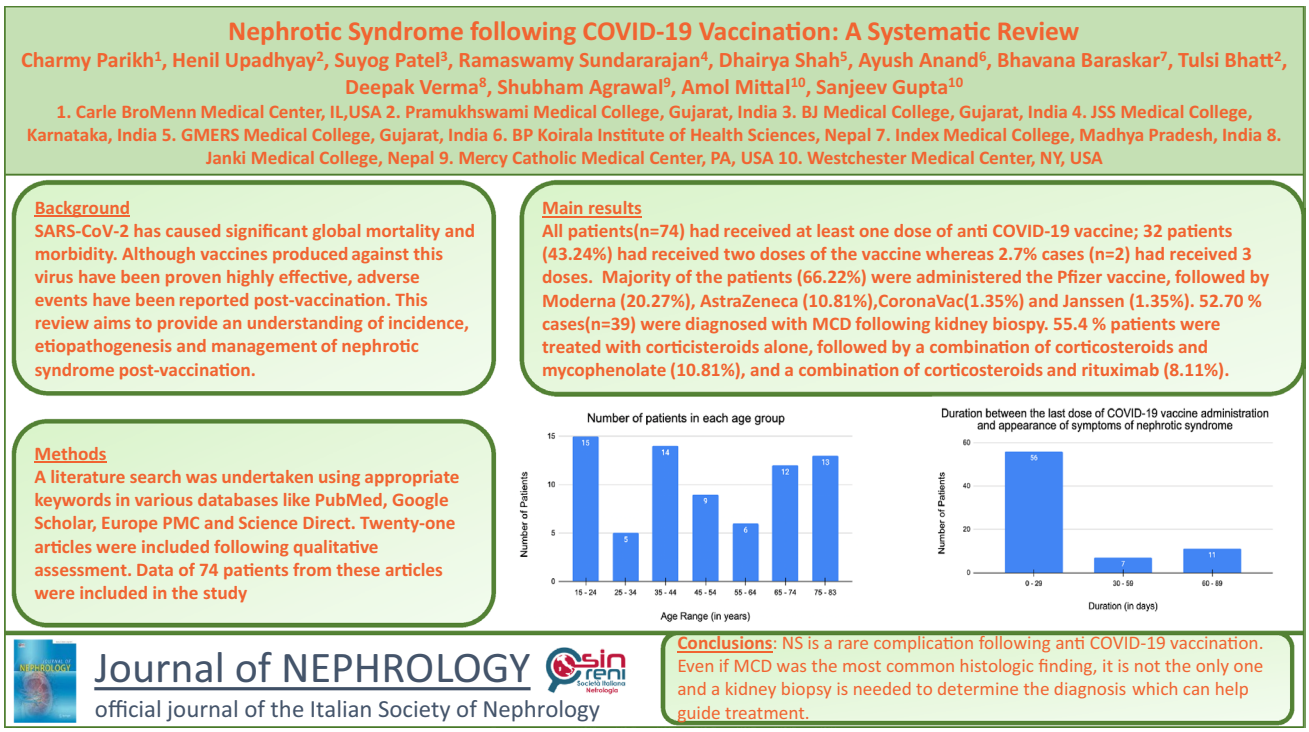
the histopathological picture. Management of COVID-19 vaccine-induced nephrotic syndrome was mainly reported as successfully attainable with corticosteroids and supportive management.

Conclusion Further investigations will help in establishing an early diagnosis and salvaging kidney function.

Graphical abstract



Keywords Nephrotic syndrome · COVID-19 · Vaccination · Systematic review

Introduction

In 2019, COVID-19 emerged as a major global health issue causing morbidity and mortality. Initially assumed to be a respiratory illness, the disease is now acknowledged as having multisystem involvement, and a post-COVID syndrome has also been identified [1, 2]. Due to the lack of treatments, a global immunization effort has emerged. Along with social distancing, vaccination has proven to be an effective prevention strategy to contrast the pandemic. Nearly 60% of the world's population has now been vaccinated against the SARS-CoV-2 virus [3].

BNT162b2 (Pfizer), ChAdOx1 nCoV-19 (AstraZeneca), mRNA-1273 (Moderna) and PiCoVacc (CoronaVac) are some of the vaccines that were produced by pharmaceutical corporations within a short period [4–6]. The efficacy of COVID-19 immunization programs has been extensively described in the literature, but several local and systemic adverse responses have also been reported, including discomfort at the injection site, exhaustion, fever, headache, myalgia, anaphylaxis, myocarditis, and thrombocytopenia [7].

Though uncommon, cases of nephrotic syndrome following COVID-19 immunization have been reported in people of all ages and gender. Kidney biopsy was performed in numerous patients, and pathological findings consistent with minimal change disease (MCD), membranous nephropathy (MN), anti-neutrophil cytoplasmic antibody (ANCA) vasculitis, immunoglobulin A (IgA) nephropathy, and anti-glomerular basement membrane nephropathy were detected [8]. Furthermore, some individuals have experienced a recurrence of nephrotic syndrome after receiving the COVID-19 vaccine [8].

The mechanism of nephrotic syndrome post-COVID-19 vaccination is still unclear. Each vaccine may have a different interaction with the recipient leading to the development of nephrotic syndrome, with one theory being an immune response by the T-cells [8]. Diagnosis relies on the usual clinical and laboratory findings, while a kidney biopsy was needed for the identification of the specific kidney disease [9].

Pooling the data from published cases and series may help defining the pathophysiology and the management options for nephrotic syndrome in such patients and lead to the identification of high-risk groups. With these aims in mind, we have reviewed the available literature to determine the possible etiological factors, the available management modalities, and the prognosis.

Materials and methods

Search strategy

For the literature search, we went through papers published in PubMed, Europe PMC, Google Scholar, and Science Direct on nephrotic syndrome post-COVID-19 vaccination from January 2020 to June 2022. The keywords (including all commonly used abbreviations of these terms) used in the search strategy were as follows: "SARS-CoV-2" OR "CoV2" OR "COVID-19" AND "Vaccine" AND "Nephrotic Syndrome". The strategy was developed under the supervision of SG and AM.

Criteria for study inclusion and exclusion

Inclusion Criteria: Patients who received at least one dose of COVID-19 vaccine with a diagnosis of nephrotic syndrome following COVID-19 vaccination. Original studies, review articles, case reports in English were included.

Exclusion Criteria: (1) Animal studies and in-vitro studies (2) Articles with no abstract (3) Letters to the editor and commentaries.

Data extraction (selecting and coding)

After the initial literature search, the authors removed duplicate articles and included all eligible studies. Primary screening was done by reading the abstract, and if any queries were raised, the authors went through the whole article. After a preliminary review, the authors went through the full-text article for the final inclusion of the study in the systematic review. References of all the included articles were screened. At all steps, conflicts were resolved by the senior authors (SG and AM). The data included in the study were study design, methods, patient demographic details, the country where the study was done, the clinical features, laboratory, and imaging reports, the kidney biopsy, if available, treatment and the patient's outcome. After the data were extracted, they were cross-checked for quality assessment. The studies for which complete data was unavailable were excluded. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were applied (Fig. 1) [10]. The authors were not able to register their review because PROSPERO was experiencing delays in processing registrations.

Risk of bias (quality) assessment

Studies were ranked as good, fair and poor quality. The quality assessment tools used were: (1) Joanna Briggs Institute Checklist for Case Reports/Case Series (2) Newcastle Ottawa Scale for Observational Studies (3) AMSTAR Checklist for Systematic Review/Meta-Analysis.

Strategy for data synthesis

For statistical analysis, we used Microsoft Excel 2013 Data Analysis Toolpack. Continuous data were expressed as mean ± standard deviation based on the distribution of values. The findings of the study were summarized in tables and figures.

Results

Search results and study characteristics

Twenty-one peer-reviewed articles (18 case reports and 3 case series) were retrieved. A total of 74 patients were included. The patients were divided into two groups: new cases of nephrotic syndrome ($n = 40$, 54.05%) and relapse of nephrotic syndrome post-COVID-19 vaccination ($n = 34$, 45.95%). All cases ($n = 74$) had biochemical and all but 6 had histological confirmation of nephrotic syndrome.

The key findings of all the articles are summarized in Tables 1 and 2.

Demographic characteristics

The mean age of the patients was 49.21 ± 22.13 years (Mean ± SD) (Fig. 2); 30 patients were females (40.54%), and 44 were males (59.46%).

COVID-19 vaccination status

All patients ($n = 74$) had received at least one dose of the anti COVID-19 vaccine. Thirty-two patients (43.24%) had received two doses of anti COVID-19 vaccine, whereas 2 patients (2.70%) had received three doses. The remaining 40 patients (54.05%) had received only one dose of anti COVID-19 vaccine. Regarding the type of vaccine administered, 49 had received the BNT162b2 (Pfizer) vaccine (66.22%), 15 the mRNA-1273 (Moderna) vaccine (20.27%), and 8 patients the ChAdOx1 nCoV-19 (AstraZeneca) vaccine (10.81%). One patient received the PiCoVacc (CoronaVac) and one patient the Ad26.

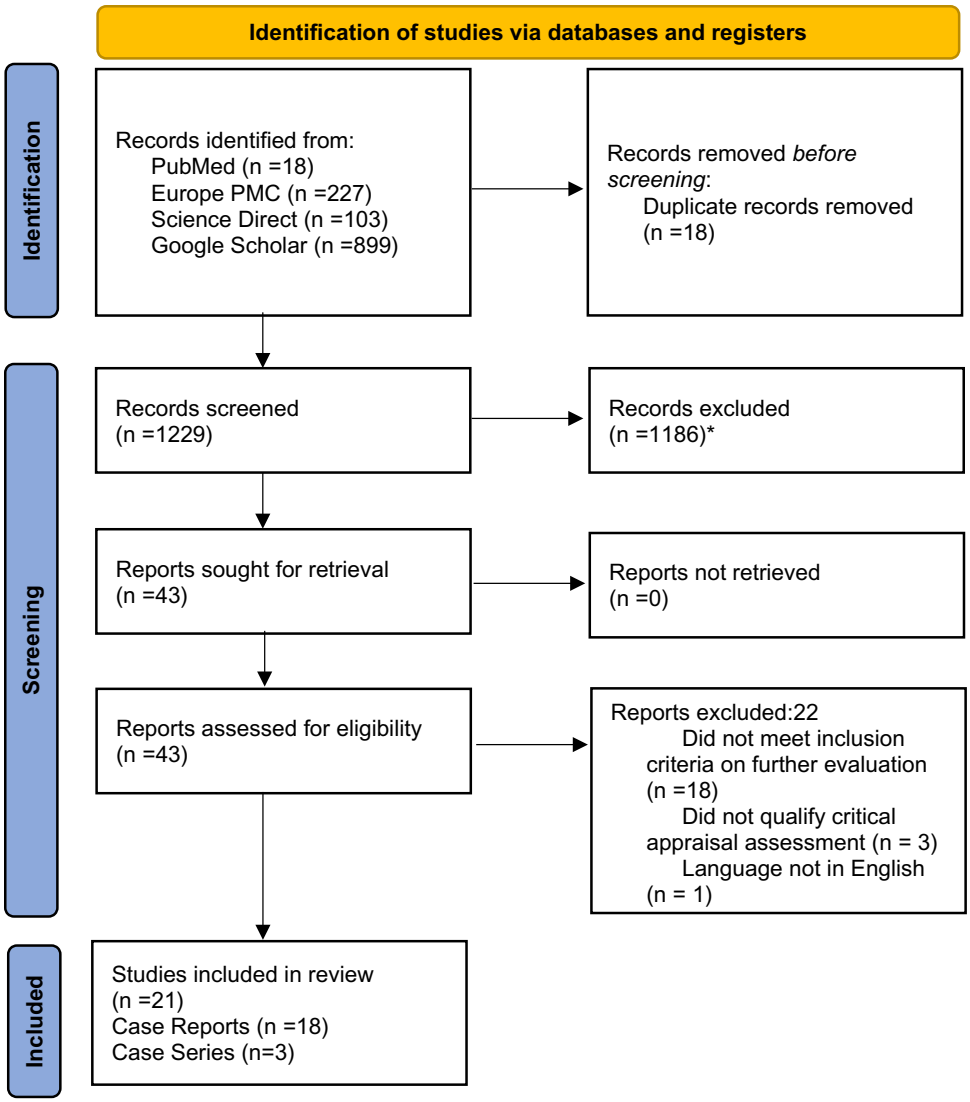


Fig. 1 PRISMA 2020 flow diagram

COV.2 (Janssen) vaccine (1.35% each). The median interval of time between the last dose of anti COVID-19 vaccine and the appearance of clinical symptoms leading to the diagnosis of nephrotic syndrome was 20 days (Fig. 3).

Kidney biopsy findings

Out of the reported cases, 39 patients were diagnosed with minimal change disease (MCD), accounting for 52.70% of cases, 1 patient was diagnosed with MCD plus acute interstitial nephritis (AIN), and 1 patient was diagnosed with MCD plus acute tubular necrosis (ATN). Electron microscopy results were reported in 10 patients and revealed diffuse effacement of foot processes (Table 3). Autoimmune tests were reported in 21 cases and were positive in 5 cases. Acute tubular injury was reported in 6 cases (8.11%).

Drugs used in treatment and the outcome

In our review, we observed that the majority (47.3%) of patients were treated with corticosteroids alone. About 10.81% were treated with corticosteroids and mycophenolate, and 8.11% were treated with corticosteroids and rituximab. Rituximab alone was given to 5.41% of patients. Around 53.84% of MCD patients received only corticosteroids as treatment, 33.33% of MCD patients received medications like calcineurin inhibitors, cyclosporine, rituximab, mycophenolate, or rituximab in addition to corticosteroids. However, only 12.82% received treatment other than corticosteroids, which included treatment with rituximab or mycophenolate (Table 4). In our review, 43 patients showed complete remission (58.11%), 3 showed partial remission (4.05%), and 4 patients showed no remission (5.41%). Around 68.29% of MCD cases completely resolved after treatment, while

Table 1 Cases of new-onset nephrotic syndrome post-COVID-19 vaccination

Patient No	Age	Gender	Name of vaccine	Biopsy findings	Treatment	Outcome
1 [11]	50	M	BNT162b2	MCD	CS	CR
2 [9]	71	M	ChAdOx1 nCoV-19	MCD	CS	CR
3 [12]	45	F	BNT162b2	MCD	CS	CR
4 [13]	43	M	mRNA-1273	MCD	CS	CR
5 [14]	60	M	BNT162b2	MCD, AKI	CS	CR
6 [15]	50	M	Ad26.COV.2	MCD	MP	CR
7 [16]	75	M	BNT162b2	MCD	MP	CR
8 [17]	67	F	PiCoVacc	MCD	CS	NA
9 [18]	22	M	ChAdOx1 nCoV-19	MCD	CS	CR
10 [19]	15	M	BNT162b2	N/A	CS	CR
11 [20]	80	F	BNT162b2	MCD, AIN	CS	CR
12 [21]	55	F	BNT162b2	MCD	CS	CR
13 [22]	38	M	BNT162b2	IgAN	Conservative	NA
14 [22]	44	M	mRNA-1273	IgAN, AIN	CS	NR
15 [22]	66	M	mRNA-1273	IgAN	CS	R
16 [22]	62	M	BNT162b2	IgAN	Conservative	NR
17 [22]	77	M	BNT162b2	Atypical anti-GBM nephritis	CS, Mycophenolate	NR
18 [22]	83	M	mRNA-1273	MCD, ATN	CS	R
19 [22]	50	F	BNT162b2	NELL-1 MN	Conservative	R
20 [22]	82	F	mRNA-1273	MPO-ANCA	CS, Rituximab	R
21 [23]	18	M	BNT162b2	N/A	CS	CR
22 [24]	80	F	BNT162b2	FSGS	CS, Cyclophosphamide	CR
23 [25]	56	M	mRNA-1273	MN	CS, Rituximab	CR
24 [26]	74	M	ChAdOx1 nCoV-19	IgAN	CS	NA
25 [26]	82	F	BNT162b2	MN	CS	NA
26 [26]	79	M	ChAdOx1 nCoV-19	IgAN	CS, Rituximab	NA
27 [26]	78	F	BNT162b2	TIN	CS	NA
28 [26]	36	M	BNT162b2	MCD	Rituximab	NA
29 [26]	67	F	BNT162b2	MN	Rituximab	NA
30 [26]	82	M	mRNA-1273	MCD	CS	NA
31 [26]	54	F	mRNA-1273	MCD	CS	NA
32 [26]	60	F	mRNA-1273	MPGN	CS	NA
33 [26]	39	F	BNT162b2	SLE	CS, Mycophenolate	NA
34 [26]	57	F	BNT162b2	TIN	CS	NA
35 [26]	42	F	BNT162b2	MCD	MC	NA
36 [26]	79	F	ChAdOx1 nCoV-19	Vasculitis	CS, Cyclophosphamide	NA
37 [26]	24	F	BNT162b2	FSGS	CS	NA
38 [26]	65	F	ChAdOx1 nCoV-19	TIN	CS	NA
39 [26]	20	M	BNT162b2	MCD	Rituximab	NA
40 [26]	82	M	BNT162b2	MN	Rituximab	NA

MCD minimal change disease, *AKI* acute kidney injury, *AIN* acute interstitial nephritis, *IgAN* IgA nephropathy, *ATN* acute tubular necrosis, *FSGS* focal segmental glomerulosclerosis, *MN* membranous nephropathy, *TIN* tubulointerstitial nephritis, *MPGN* membranoproliferative glomerulonephritis, *SLE* systemic lupus erythematosus, *CS* corticosteroids, *MP* methylprednisolone, *CR* complete remission, *R* response, *NR* no response, *PR* partial remission, *NA* not available, *M* male, *F* female

2 cases partially resolved. None of the studies reported any complications of immunosuppressive therapy. Data was not available for 24 patients (32.43%).

Discussion

Adverse events (both local and systemic) following anti COVID-19 vaccination are well documented in

Table 2 Cases of relapse of nephrotic syndrome post-COVID-19 vaccination

Patient No	Age	Gender	Name of vaccine	Biopsy findings	Treatment	Outcome
1 [27]	39	M	BNT162b2	N/A	CS	CR
2 [20]	40	M	BNT162b2	MCD	CS, Cyclosporine	CR
3 [22]	67	F	mRNA-1273	MCD	CS, Rituximab	R
4 [22]	29	F	BNT162b2	FSGS	CS, Tacrolimus	R
5 [22]	39	M	BNT162b2	MN	Tacrolimus	R
6 [22]	70	M	mRNA-1273	MN	Obinutuzumab	N/A
7 [22]	19	M	mRNA-1273	IgAN	Conservative	N/A
8 [28]	25	F	mRNA-1273	MCD	CS	CR
9 [29]	16	M	BNT162b2	MCD	CS	CR
10 [30]	38	M	BNT162b2	MCD	CS, Mycophenolate	CR
11 [30]	67	F	BNT162b2	FSGS	CS, Mycophenolate	PR
12 [30]	74	M	BNT162b2	MCD	CS, Calcineurin Inhibitor	PR
13 [30]	46	F	BNT162b2	MCD	CS, Calcineurin Inhibitor	CR
14 [30]	23	M	BNT162b2	MCD	CS, Obinutuzumab	CR
15 [30]	30	F	BNT162b2	MCD	CS, Rituximab	CR
16 [30]	36	F	BNT162b2	MCD	CS, Rituximab	CR
17 [30]	41	F	BNT162b2	MCD	CS, Calcineurin Inhibitor	CR
18 [30]	16	M	BNT162b2	N/A	CS	CR
19 [30]	19	M	BNT162b2	MCD	CS	CR
20 [30]	48	M	mRNA-1273	MCD	CS, Mycophenolate	CR
21 [30]	40	M	BNT162b2	MCD	CS	CR
22 [30]	46	F	BNT162b2	FSGS	Cyclophosphamide	NR
23 [30]	83	M	ChAdOx1 nCoV-19	MCD	CS	N/A
24 [30]	53	F	BNT162b2	MCD	CS	CR
25 [30]	25	M	BNT162b2	MCD	CS, Mycophenolate	CR
26 [30]	19	M	BNT162b2	MCD	CS	CR
27 [30]	15	M	BNT162b2	N/A	CS	CR
28 [30]	31	M	BNT162b2	MCD	CS	CR
29 [30]	21	M	BNT162b2	N/A	CS	NR
30 [30]	42	M	ChAdOx1 nCoV-19	MCD	CS	PR
31 [30]	72	M	BNT162b2	MCD	CS, Mycophenolate	N/A
32 [30]	18	F	BNT162b2	MCD	CS, Mycophenolate	CR
33 [30]	16	F	mRNA-1273	MCD	CS	CR
34 [30]	72	M	BNT162b2	MCD	CS	N/A

MCD minimal change disease, *AKI* acute kidney injury, *AIN* acute interstitial nephritis, *IgAN* IgA nephropathy, *ATN* acute tubular necrosis, *FSGS* focal segmental glomerulosclerosis, *MN* membranous nephropathy, *TIN* tubulointerstitial nephritis, *MPGN* membranoproliferative glomerulonephritis, *SLE* systemic lupus erythematosus, *CS* corticosteroids, *MP* methylprednisolone, *CR* complete remission, *R* response, *NR* no response, *PR* partial remission, *NA* not available, *M* male, *F* female

literature [4]. Nephrotic syndrome has been reported as a relatively common side effect of anti COVID-19 vaccines; the most commonly reported cause of nephrotic syndrome has been minimal change disease [11, 15, 32]. Cases of acute kidney injury [17, 32], IgA nephropathy [33–35], ANCA glomerulonephritis [36] and membranous nephropathy [37] have also been reported. While most cases of nephrotic syndrome were reported after the administration of the Pfizer vaccine, some cases following the use of the AstraZeneca and the Moderna vaccines have also been reported [9, 13, 38]. Cases of nephrotic syndrome presented either as a new-onset disease or a relapse secondary to vaccine administration [19].

The most common biopsy changes noted in our review were minimal change disease (52.7%) and membranous nephropathy (8.11%). The exact pathogenesis is unknown; however, a widely acknowledged hypothesis is that T-cells release a circulating factor that causes damage to podocytes [39, 40]. Another possible mechanism of podocyte foot process effacement could be the enhanced stimulation of antigen-presenting and B cells [41]. Minimal change disease has been reported following the administration of several

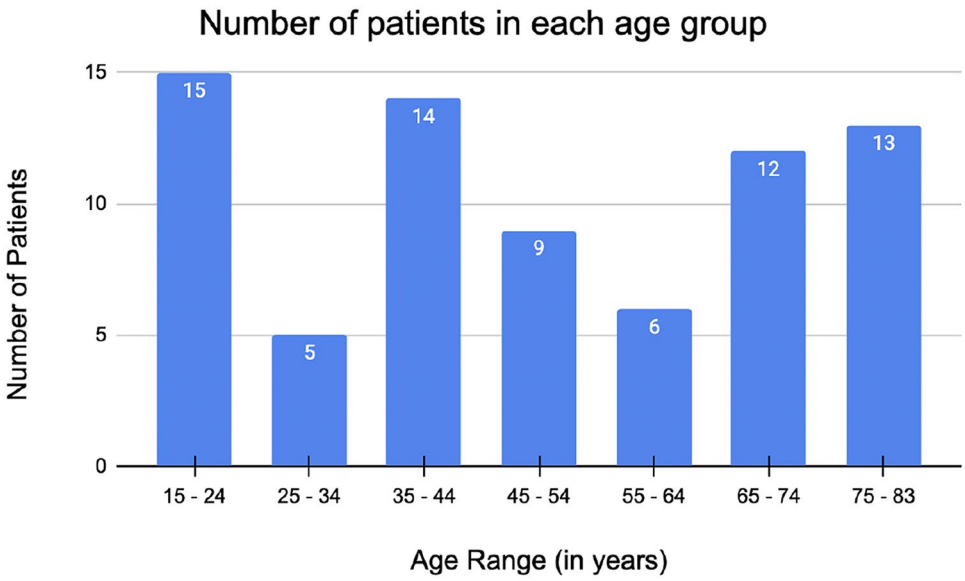


Fig. 2 Total number of patients ($n=74$) in each age group (in years)

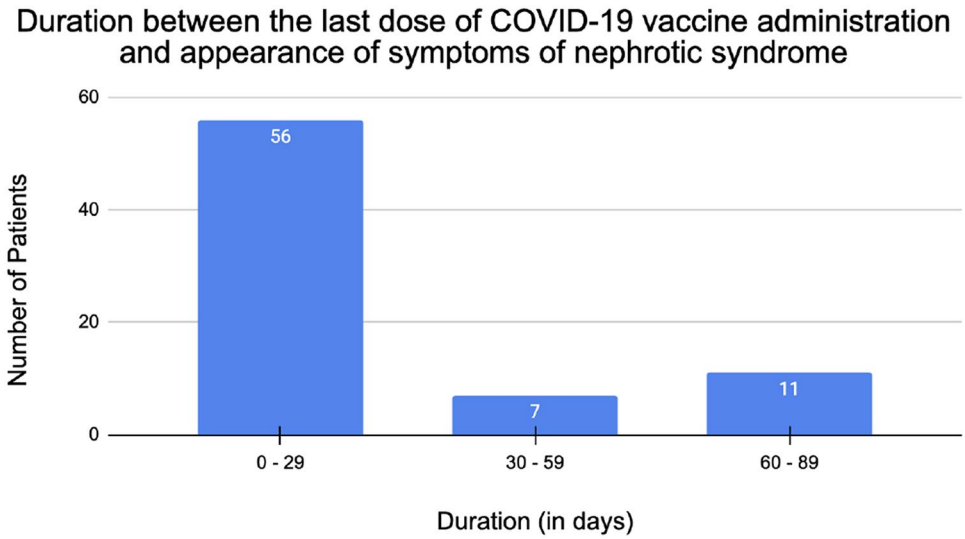


Fig. 3 Shows the length of time between the last dose of COVID-19 vaccine and the appearance of symptoms of nephrotic syndrome

other vaccines such as influenza [42], measles [43], hepatitis B [44], and anti pneumococcal [45] vaccine. The results of the COVID-19 vaccine trials show that humoral and T-cell responses are induced, simulating acute infection [46]. It has also been reported that BNT162b2 vaccine induces the production of cytokines like IFN-γ and IL-2 along with SARS-CoV-2 S-specific neutralizing antibodies [47]. While the causal relationships have not been established, T cell response to the COVID-19 vaccine could be involved in the pathogenesis of the nephrotic syndrome.

Another aspect to consider is the involvement of the angiotensin converting enzyme (ACE)2 receptor, which plays a role in the pathogenesis of COVID-19 [48]. While the mechanism is unclear, ACE2 causes SARS-COV-2 infection of the podocyte and podocyte effacement [49]. Fig. 4 summarizes the two hypotheses of the pathogenesis of minimal change disease/nephrotic syndrome post-COVID vaccination.

The clinical presentation of the nephrotic syndrome can vary from asymptomatic to severe illness. All 74 patients described in this review presented with typical clinical symptoms.

In our series, the diagnostic approach to nephrotic syndrome after COVID-19 vaccination was similar to that for nephrotic syndrome outside of the vaccine context; kidney biopsy was perfomed in the vast majority of the cases.

The cases of nephrotic syndrome gathered in this review occurred after different anti COVID-19 vaccines (mainly Pfizer-BioNTech, Moderna, Oxford-AstraZeneca, Janssen, and CoronaVac). In all cases, the presenting symptoms were lower limb and periorbital edema. Pleural effusion was noted in a few cases only. Laboratory studies showed proteinuria,

Table 3 Kidney biopsy findings in the patients

Kidney biopsy findings	Number of patients	Percentage (%)
MCD	39	52.7
MN	6	8.11
Not Available	6	8.11
IgAN	6	8.11
FSGS	5	6.76
TIN	3	4.05
SLE	1	1.35
MCD, AIN	1	1.35
MPO-ANCA	1	1.35
Vasculitis	1	1.35
NELL-1 MN	1	1.35
IgAN,AIN	1	1.35
MPGN	1	1.35
MCD, ATN	1	1.35
Atypical anti-GBM nephritis	1	1.35
MCD, AKI	1	1.35
All cases	74	100.00

MCD minimal change disease, *MN* membranous nephropathy, *IgAN* IgA nephropathy, *FSGS* focal segmental glomerulosclerosis, *TIN* tubulointerstitial nephritis, *SLE* systemic lupus erythematosus, *AIN* acute interstitial nephritis, *MPO-ANCA* myeloperoxidase anti-neutrophil cytoplasmic antibodies, *NELL-1 MN* nerve epidermal growth factor-like 1 membranous nephropathy, *MPGN* membranoproliferative glomerulonephritis, *ATN* acute tubular necrosis, *AKI* acute kidney injury

Table 4 Frequency of various drugs used to treat patients with nephrotic syndrome post-COVID-19 vaccination

Drugs used	Frequency of patients	Percentage (%)
Corticosteroids	41	55.4
Corticosteroids, Mycophenolate	8	10.81
Corticosteroids, Rituximab	6	8.11
Conservative	4	5.41
Rituximab	4	5.41
Corticosteroids, Calcineurin Inhibitor	5	6.75
Corticosteroids, Cyclophosphamide	2	2.70
Tacrolimus	1	1.35
Cyclophosphamide	1	1.35
Corticosteroids, Obinutuzumab	1	1.35
Obinutuzumab	1	1.35
All cases	74	100.00

hypoalbuminemia, and hyperlipidemia, similar to what was observed in nephrotic syndrome caused by triggers [9, 11, 13, 15, 54].

More than half (54.05%) of the patients in our review had received only one dose of the COVID-19 vaccine when

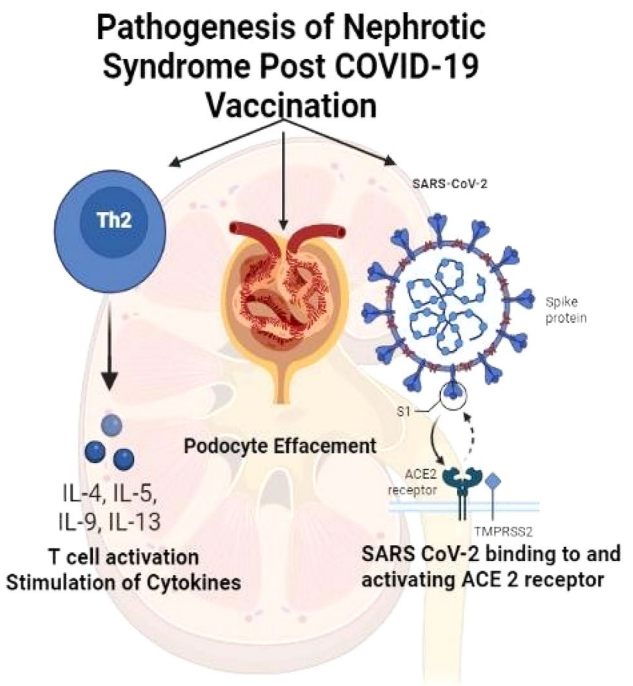


Fig. 4 Pathogenesis of minimal change disease/nephrotic syndrome post-COVID vaccination

they developed the nephrotic syndrome, and only 43.24% patients had received two doses of COVID-19 vaccine. The majority of patients (75.6%) reported in this review presented symptoms within one month of COVID-19 vaccine administration, while no patient presented symptoms 3 months after vaccination. This finding is consistent with the fact that antibody levels had significantly decreased four months after vaccination, as reported in the study by Bansal et al, who described that exosomes carrying the SARS-CoV-2 spike proteins were detectable in blood on day 14 post vaccination when the antibodies against the spike proteins were still not detectable in the sera [56].

Since inappropriate production of mRNA in a tissue can result in local tissue damage and subsequent myocarditis, neuropathies or vasculopathies, the same pathogenesis could result in podocyte damage in the nephrons and subsequent development of nephrotic syndrome [58]. There are certain limitations to our review. Most of the studies that we included in our review were case reports. Due to a very short follow-up time, late complications could not be identified. We were not able to include data regarding all the vaccines approved for use by the World Health Organization to date. We have included a diverse patient population, but due to the paucity of reported data, its association with ethnicity or a particular population group could not be established.

Conclusions

Nephrotic syndrome is a rare complication following anti COVID-19 vaccination. Even if minimal change disease was the most common histologic finding, it is not the only one and a kidney biopsy is needed to determine the diagnosis, which can help guide treatment. Steroids alone or in various combinations were used for management.

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Data availability Not applicable.

Declarations

Conflict of interests The authors declare that they have no conflict of interest.

Ethical approval Approval from the institutional review board was not required for this study.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this retrospective review, formal consent is not required.

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