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# Insights into new-onset autoimmune diseases after COVID-19 vaccination

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## Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in more than 670 million infections and almost 7 million deaths globally. The emergence of numerous SARS-CoV-2 has heightened public concern regarding the future course of the epidemic. Currently, the SARS-CoV-2 Omicron variant has rapidly become globally dominant in the COVID-19 pandemic due to its high infectivity and immune evasion. Consequently, vaccination implementation is critically significant. However, growing evidence suggests that COVID-19 vaccination may cause new-onset autoimmune diseases, including autoimmune glomerulonephritis, autoimmune rheumatic diseases, and autoimmune hepatitis. Nevertheless, the causal relationship between COVID-19 vaccines and these autoimmune diseases remains to be demonstrated. In this review, we provide evidence that vaccination induces autoimmunity and summarize possible mechanisms of action, such as molecular mimicry, activation by bystanders, and adjuvants. Our objective is not to refute the importance of vaccines, but to raise awareness about the potential risks of COVID-19 vaccination. In fact, we believe that the benefits of vaccination far outweigh the possible risks and encourage people to get vaccinated.

**Keywords:** autoimmune disease ; COVID-19; SARS-CoV-2; vaccines; vaccination

## 1 Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In March 2020, the World Health Organization declared COVID-19 a global pandemic[1]. As of 31 January 2023, the Johns Hopkins University Center for Systems Science and Engineering reported that the worldwide number of confirmed infections has exceeded 670 million worldwide, resulting in nearly 7 million deaths [2]. Since the outbreak began, national governments have adopted various strategies to manage the pandemic, including strict quarantine, complete lockdowns, and mask-wearing, which have effectively reduced the spread of SARS-CoV-2. However, given the trade-off between infection control measures and socioeconomic development, the development and production of vaccines will now take precedence over other actions[3].

Vaccines are indispensable in preventing and controlling over 20 life-threatening diseases, such as diphtheria, tetanus, pertussis, influenza, and measles[4]. Moreover, vaccines are critical tools in the fight against the COVID-19 pandemic. The World Health Organization reports that there are currently 176 vaccine candidates in clinical development, including Protein subunit (PS), Viral Vector (non-replicating) (VV<sub>nr</sub>), DNA, Inactivated Virus (IV), RNA, Viral Vector (replicating) (VV<sub>r</sub>), Virus Like Particle (VLP), VV<sub>r</sub> + Antigen Presenting Cell (VV<sub>r</sub> + APC), Live Attenuated Virus (LAV), VV<sub>nr</sub> + Antigen Presenting Cell (VV<sub>nr</sub> + APC), and Bacterial antigen-spore expression vector (BacAg-SpV)[5]. Most vaccines developed by researchers worldwide are currently administered by intramuscular (IM) injection. However, COVID-19 intranasal (IN) vaccines are being developed to provide protective mucosal immunity in addition to eliciting antibody-mediated and cell-mediated immunity [6]. Unfortunately, several SARS-CoV-2 variants have emerged globally, including Alpha (B.1.1.7)[7], Beta (B.1.351)[8], Gamma (P.1)[9], Delta(B.1.617.2)[10]and Omicron (B.1.1.529) [11], and others. Undoubtedly, the emergence of variants poses a huge challenge to vaccine development.

Although vaccination against COVID-19 has proven to be effective in reducing disease severity and mortality, some people are hesitant to get vaccinated due to concerns about side effects[12]. Recently, reports have emerged suggesting that COVID-19 vaccines may cause rare autoimmune diseases, including autoimmune glomerulonephritis[13], autoimmune rheumatic

diseases[14], and autoimmune hepatitis[15]. These adverse events have increased public skepticism about vaccination. However, the causal relationship between COVID-19 vaccination and these autoimmune phenomena needs further investigation. Previous studies have suggested that vaccines can trigger autoimmunity through mechanisms such as molecular mimicry, bystander activation, anti-idiotypic network, and epitope spreading[16]. Based on current evidence, we provide a summary of the rare autoimmune diseases that may be induced by COVID-19 vaccines and discuss possible underlying mechanisms.

## 2. Methods

This review aims to provide a comprehensive analysis of the emergence of rare autoimmune diseases following COVID-19 vaccination. A systematic PubMed search was conducted to identify relevant literature on COVID-19 vaccination and new-onset autoimmune phenomena published up to 1st February 2023. Inclusion criteria encompassed case reports, case series, original articles, letters to the editor, and reviews. Additionally, the references and related citations for the resulting articles were examined for potential inclusion. Search terms utilized included: “COVID-19 Vaccine”, “SARS-CoV-2 vaccine”, “autoimmune diseases”, “IgA glomerulonephritis”, “membranous nephropathy”, “membranous nephropathy”, “lupus nephritis”, “systemic lupus erythematosus”, “focal segmental glomerulosclerosis”, “ANCA-associated nephritis”, “thrombotic microangiopathy”, “autoimmune rheumatic diseases”, “Rheumatoid arthritis”, “antiphospholipid syndrome”, “adult-onset Still’s disease”, “ANCA associated vasculitis”, “giant cell arteritis”, “Sjogren’s syndrome”, “Behcet disease”, “autoimmune hepatitis”, “type 1 diabetes mellitus”, “autoimmune hemolytic anemia”, “vaccine-induced immune thrombocytopenia and thrombosis”, “myocarditis”, “alopecia areata”, “autoimmune thyroid diseases”, “Guillain-barre syndrome”, “molecular mimicry”, “adjuvants”, “Bystander Activation”, “epitope diffusion”, and “polyclonal activation”.

## 3. Results

To facilitate comprehension, we organized our findings into distinct categories. Specifically, these categories comprise Immune-mediated nephropathy, autoimmune rheumatic diseases,

autoimmune hepatitis, type 1 diabetes mellitus, autoimmune hemolytic anemia, as well as additional autoimmune conditions.

### **3.1 Immune-mediated nephropathy**

#### **3.1.1 IgA nephropathy( IgAN)**

IgA nephropathy (IgAN) is the most prevalent primary form of glomerulonephritis worldwide, and its clinical presentation ranges from asymptomatic microscopic hematuria to rapidly progressive glomerulonephritis[17]. Reports have emerged on the potential of COVID-19 vaccination to induce IgAN, as well as relapse of previously treated cases. Among the published cases, 39 individuals experienced new-onset IgAN following vaccination, with a male predominance of 61.5% (24/39)[18–41].(Table 1). The vast majority of these cases (approximately 90%) involved mRNA vaccines, while only three were associated with Viral vector vaccines, and one with an inactivated vaccine. The mRNA vaccine's lipid nanoparticle formulation may activate CD4<sup>+</sup> and CD8 T<sup>+</sup> cells at a higher rate. In most instances (14/39), patients reported experiencing symptoms within 1 to 2 days after receiving the second dose, with gross hematuria being the most common initial symptom following vaccination (excluding cases with missing data), followed by albuminuria. Notably, the majority of these individuals had a history of microscopic hematuria or occult blood before vaccination and developed macroscopic hematuria shortly after receiving the vaccine. This suggests that these individuals may have had a pre-existing, undiagnosed IgAN and that the vaccine may have hastened disease progression as a predisposing factor.

Among this group of patients, we also observed several noteworthy phenomena. For instance, Mokos et al. reported the first instance of IgAN in a renal transplant recipient following the administration of the adenovirus vector SARS-CoV-2 vaccine, which suggests a heightened possibility of adverse reactions in immunocompromised solid organ recipients[37]. Additionally, Nakatani et al. reported the first case of new-onset IgA vasculitis with IgAN soon after receiving the mRNA vaccine, which highlights the need for careful follow-up to prevent new glomerulonephritis in the presence of significant purpura following vaccination[41].

The majority of the reported cases recover spontaneously within a short period of time with conservative treatment, although some cases may necessitate steroids, immunosuppressants, and dialysis to achieve remission. Fortunately, patients who did not exhibit obvious symptoms before

vaccination or only had asymptomatic microscopic hematuria may be less likely to require additional treatment. Therefore, individuals in this group need not worry excessively about receiving the COVID-19 vaccine.

**Table 1. Reported cases of de novo IgAN following COVID-19 vaccination**

Authors	Age	sex	PMH	Timeline of symptom onset	Type of Vaccine	Begin of symptoms	Laboratory features	treatment	outcome
Abdel-Qader et al.	12	M	N	<1 day after 1st dose	mRNA	GH;AKI; proteinuria	Scr:1.77mg/dl; proteinuria :1.7 g/l; RBC: 1920/ul; Renal biopsy: IgAN	steroid	R
Mohamed et al.	50	M	seasonal allergy	2 wk after 1st dose	mRNA	skin rash; proteinuria	UPCR:1.1 g/day; Renal biopsy: IgAN Skin biopsy:IgA vasculitis;	steroid	R
Niel et al.	13	F	N	<1 day after 1st dose	mRNA	MH;asthenia; Muscle pain; fever	SCR: 3.57 mg/dl; proteinuria:3.9 g/d; Renal biopsy: IgAN	steroid; HD	R
Okada et al.	17	F	AH	4 days after 1st dose	mRNA	GH; proteinuria	SCR: 0.58 mg/dl; Renal biopsy: IgAN	Conservative	CR
Fujita et al.	40	F	Occult blood	9 days after 1st dose	mRNA	GH:Fever; Chills; shivering; back pain; general malaise;	SCR: 0.53 mg/dl; RBC: 100/HPF; ALB: 3 g/dl; Renal biopsy: IgAN	TPE	CR
Yokote et al.	36	F	MH;RA Proteinuria;	11 days after 1st dose	mRNA	GH	SCR: 0.9 mg/dl; UPCR: 15.6 g/g; RBC:>100/HPF; Renal biopsy: IgAN	Steroid; immunosuppressive	R
	19	M	MH	18 h after 2nd dose	mRNA	GH	SCR: 0.97 mg/dl; RBC: 50-99/HPF; UPCR: 1.5 g/g; Renal biopsy: IgAN	RASi	R
Anderegg et al.	39	M	HTN	Immediate after 2nd dose	mRNA	Fever;GH flu-like symptoms	AKI;Renal biopsy: IgAN	Steroid ; immunosuppressive	R
	81	M	N	after 2nd dose	mRNA	flu-like symptoms	Renal biopsy: IgAN	Steroid ; immunosuppressive	R
Klomjit et al.	38	M	NA	2 wk after 2nd dose	mRNA	UK	Scr:1.6mg/dL; protein:0.32g/d; RBC:51-100/HPF; Renal biopsy: IgAN	plasmapheresis Conservative	NA
	44	F	NA	2 wk after 1st dose	mRNA	UK	Scr:2.5mg/dL; protein:14 g/d; RBC:21-30 /HPF; ALB:3.7g/dl; Renal biopsy: IgAN	steroid	NR
	66	F	NA	2 wk after 1st dose	mRNA	UK	Scr:1.5mg/dL; protein:1.2 g/d; RBC:51 - 100 /HPF; ALB:4.1g/dl; Renal biopsy: IgAN	steroid	R
	62	M	NA	6 wk after 1st dose	mRNA	UK	Scr:2.2mg/dL protein:0.9 g/d RBC:31 - 40 /HPF ALB:4.2g/dl Renal biopsy: IgAN	Conservative	R
Lo et al.	28	F	MH	3 h after 2nd dose	mRNA	GH	SCR: 72 μmol/L; UPCR: 320mg/mmol Renal biopsy: IgAN	Conservative	CR

Hanna et al.	17	M	N	<1 day after 2nd dose	mRNA	GH;AKI Proteinuria;	SCR: 1.78 mg/dl; ALB: 3.8 g/dl; Renal biopsy: IgAN	steroid	R
Nihei et al.	28	F	GH; proteinuria	7 days after 2nd dose	mRNA	GH; fever	RBC: >100/HPF; UPCR: 0.13 g/g; Renal biopsy: IgAN	Conservative	R
Abramson et al.	30	M	N	1day after 2nd dose	mRNA	GH;proteinuria	SCR: 1.02 mg/dl; UPCR: 0.8 g/g; RBC: >30/HPF; Renal biopsy: IgAN	RASi	PR
Tan et al.	41	F	GDM	1day after 2nd dose	mRNA	Headache; GH generalized myalgia	RBC: >200 ; UPCR: 7.58g/g; SCr:541mmol/L; Renal biopsy: IgAN	steroid; immunosuppressive	NA
	60	F	N	1day after 2nd dose	mRNA	GH	RBC: >200 ll; UPCR: 2.03 g/g; SCr:153mmol/L; Renal biopsy: IgAN	steroid;TPE Immunosuppressive	NA
Park et al.	50	M	HTN	1day after 2nd dose	mRNA	NA	SCR: 1.54 mg/dl; Renal biopsy: IgAN	RASi	PR
	22	F	N	2day after 2nd dose	mRNA	NA	SCR: 0.8mg/dl; Renal biopsy: IgAN	Conservative	R
	39	F	N	2day after 2nd dose	mRNA	NA	SCR: 0.8 mg/dl; Renal biopsy: IgAN	Conservative	R
	67	M	HTN	1mo after 2nd dose	mRNA	NA	SCR: 2.90 mg/dl; Renal biopsy: IgAN	steroid;	PR
Lim et al.	42	F	N	1day after 2nd dose	mRNA	GH ; proteinuria	SCR: 0.4 mg/dl; UTP: 7 g/d; Renal biopsy: IgAN	RASi	PR
Uchiyama et al.	15	M	MH	1day after 2nd dose	mRNA	GH:Fever; myalgia	SCR: 0.97 mg/dl; numerous RBC; Renal biopsy: IgAN	Conservative	R
	18	M	MH	2 day after 2nd dose	mRNA	GH	SCR: 0.82 mg/dl; numerous RBC; Renal biopsy: IgAN	Conservative	R
Kudose et al.	50	F	HTN; Obesity; APS	2 day after 2nd dose	mRNA	GH; fever; generalized body aches	SCR: 1.7 mg/dl; UPCR: 2 g/g; RBC: >50/HPF; Renal biopsy: IgAN	Conservative	R
	19	M	MH	2 day after 2nd dose	mRNA	GH	SCR: 1.2 mg/dl; numerous RBC; Renal biopsy: IgAN	Conservative	R
Horino et al.	17	M	MH	2 day after 2nd dose	mRNA	fever;GH headache	SCR: 0.70 mg/dl; RBC: >100/HPF; Renal biopsy: IgAN	Tonsillectomy ; steroid	PR
Srinivasan et al.	35	M	Nephrolithiasis UC	2 day after 2nd dose	mRNA	GH;foamy urine	SCR: 1.3 mg/dl; UPCR: 0.656 g/g; Renal biopsy: IgAN	immunosuppressive	PR
Morisawa et al.	16	M	AH	2 day after 2nd dose	mRNA	Fever ; GH	SCR: 1.1 mg/dl; UPCR:0.28 g/g; Renal biopsy: IgAN	Steroid ; immunosuppressive	R
	13	F	AH	2 day after 2nd dose	mRNA	Fever ; GH	SCR: 0.54 mg/dl; UPCR: 1.99 g/g; Renal biopsy: IgAN	Conservation	R
Alonso et al.	30	M	MPGN type 1; CKD;KT	34 day after 2nd dose	mRNA	NA	SCR: 1.65 mg/dl; hematuria: 150/ml; Renal biopsy: IgAN	Steroid	NR
Mokos et al.	73	M	HTN; KT ;AAN	5 wk after 2nd dose	Viral vector	lower leg edema	SCR: 1.67 mg/dl ;UTP: 1.4 g/d, RBC: 3-5/HPF; Renal biopsy: IgAN	RASi	NR
Fenoglio et al.	74	M	UK	6 wk after 1st dose	Viral vector	RF;NS	Renal biopsy: IgAN	Steroid ; hemodialysis	NA



	79	M	UK	61 days after 1st dose	Viral vector	RF;NS	Renal IgAN	biopsy:	Steroid; immunosuppressive Conservation	NA	F, female;
Chen et al.	55	M	N	<1day after 1st dose	mRNA	AKI;general malaise abnormal liver function; nausea;vomiting	Scr: 1.94 mg/dl; UTP:11.57 g; Renal biopsy: IgAN			NR	M, male; IgAN, IgA nephropat
Ran et al.	58	M	N	2 days after 1st dose	inactivated	GH;dizziness; generalized body aches; lower limb edema	Scr: 7.45 mg/dL; RBC:>100/HPF; UTP:3.79g; Renal biopsy: IgAN		Steroid;dialysis	NA	hy; F, female; M, male;
Nakatani et al.	47	M	HTN	19 days after 1st dose	mRNA	purpuric eruption	Proteinuria:3 + ; occult blood :3 + Skin biopsy:IgA vasculitis Renal biopsy: IgAN		Steroid	PR	HTP, hypertension; MH, microscop

pic hematuria ; AH, asymptomatic hematuria; GH, gross hematuria; AKI, acute kidney injury; CKD, Chronic Kidney Disease; NS, nephrotic syndrome;RF, renal failure; KT, kidney transplantation; AAN, aristolochic acid nephropathy; APS,antiphospholipid syndrome; UC, ulcerative colitis; MPGN type 1;membranous proliferative glomerulonephritis type 1 ;RF, rheumatoid arthritis; GDM, gestational diabetes mellitus; Scr, Serum creatinine; ALB, serum albumin; RBC, red blood cell; UTP,24-hurine protein;UPCR, urine protein-to-creatinine ratio; HD, hemodialysis; RASi,renin-angiotensin-aldosterone system inhibition;TPE, Therapeutic plasma exchange;N,none; CR, complete remission; PR, partial remission; NA, non-applicable; NR, no response;R, response.

### 3.1.2 membranous nephropathy(MN)

Membranous nephropathy (MN) is a glomerular disease characterized by the thickening of the glomerular capillary walls and accounts for approximately 30% of cases of nephrotic syndrome in adults[42]. This review identified 18 cases of de novo MN after COVID-19 vaccination [13,25,43–53](Table 2), with a male-to-female ratio of 17:5. The first reported case of new-onset MN following COVID-19 vaccination was by Gueguen et al[46]. Of these 18 cases, 14 cases (9 after the second dose) occurred following mRNA vaccines, 3 cases after viral vector vaccines, and 1 case after the first dose of the inactivated vaccine. Interestingly, mRNA vaccines appear to induce new-onset MN more frequently than viral vector vaccines and inactivated vaccines, which may be attributed to the higher immunogenicity of mRNA[54]. Most patients did not have a history of autoimmune or other glomerulonephritis and only developed nephrotic syndrome after vaccination. Immunotherapy was administered to all cases (except for those without a stated treatment regimen or effect), leading to clinical remission. M-type phospholipase A2 receptor (PLA2R) is a major target antigen involved in idiopathic membranous nephropathy in adults[55]. Of the patients in this group, three were PLA2R antibody-positive, suggesting a possible loss of tolerance to PLAR2 antigen following COVID-19 vaccination[47,48,50].

However, further studies are needed to elucidate the underlying mechanisms of COVID-19 vaccination and new-onset MN.

**Table 2. Reported cases of de novo MN after COVID-19 vaccination**

Authors	Age	sex	PMH	Timeline of symptom onset	Type of Vaccine	Begin of symptoms	Laboratory features	treatment	outcome
Fenoglio et al.	82	M	N	after 2nd dose	mRNA	NS	Renal biopsy: MN	rituximab	NA
	67	F	N	after 2nd dose	mRNA	NS	Renal biopsy: MN	rituximab	NA
	82	F	N	after 2nd dose	mRNA	NS	Renal biopsy: MN	Steroid	NA
Caza et al.	54	M	NA	1 days after 2nd dose	mRNA	NS	Scr:1.3; Proteinuria:2+; ALB:3.4; Hematuria:positive	Steroid; Rituximab	NR
	68	M	NA	4 wk after 1st dose	Viral vector	NS;AKI; CKD	Renal biopsy: MN; Scr:3.3; Proteinuria:0.6; ALB:3.4; Renal biopsy: MN	diuretic	NR
	47	M	NA	6 days after 2nd dose	mRNA	NS	Scr:0.7; Proteinuria:2.7; ALB:2.3; Hematuria:positive; Renal biopsy: MN	N	PR
Thammathawat et al.	53	M	N	1 wk after 1st dose	inactivated	intermittent lower extremity edema, daily urinary proteinuria	Scr:1.5 mg/dL; Proteinuria:3+; RBC:2+; ALB:2.3 g/dL; UPCR:13.4 g/g; Renal biopsy: MN	Steroid; immunosuppressive	CR
Da et al.	70	M	N	1 wk after 1st dose	mRNA	generalized edema	ALB:1.7g/L; Scr:1.29mg/dL; cholesterol:9.24mmol/L; Renal biopsy: MN	Irbesartan; diuretic; warfarin	NR
Klomjit et al.	50	F	NA	4 wk after 2nd dose	mRNA	Joint pain proteinuria	Scr:0.7mg/dL; protein:6.5 g/d; RBC:3-10 /HPF; ALB:3.5g/dl	Conservative	R
Gueguen et al.	76	M	HTP; UV-treated cutaneous mycosis fungoid	4days after 1st dose	mRNA	edema	ALB:1.6g/L; Scr:0.86mg/dL	rituximab	PR
Rashid et al.	56	M	HTP	1 month after 1st dose	mRNA	Fatigue; exertional dyspnea; lower urinary tract symptoms	Scr:13.96mg/dL; ALB:2.2g/L; Hematuria:2+; Renal biopsy: MN with positive PLA2R	Rituximab; HD	R
Psyllaki et al.	68	M	N	1 wk after 1st dose	mRNA	lower extremities edema	ALB:2.9g/L; eGFR:70 mL/min/1.73 m <sup>2</sup> ; Renal biopsy: MN with positive PLA2R	Rituximab	PR
Chavarot et al.	66	M	HTP; Left nephrectomy;	8 wk after 2nd dose	mRNA	NA	Scr:1.36mg/dL; immunohistochemistry: MN	Conservative	NA
Paxton et al.	22	M	eczema epilepsy	1 month after 2nd dose	mRNA	lower limb edema lethargy	Scr:0.72mg/dL; ALB:8g/L; Proteinuria:7 g/d; UPCR:700.4 mg/mmol; Renal biopsy: MN with positive PLA2R	Rituximab	PR
Saigal et al.	32	M	NA	2 wk after dose	Viral vector	NS	NA	Steroid; cyclophosphamide	PR
	47	M	NA	11 days after dose	Viral vector	Isolated proteinuria	NA	RASi	CR
Fornara et al.	52	F	NA	49 days after	mRNA	NA	Scr:0.6mg/dL	RASi	stable

GARG et al.	50	F	N	dose 5 wk after 2nd dose	mRNA	edema ; proteinuria	Proteinuria:8,720 mg/g; Rena biopsy:MN (NELL-1 positive)	conservative	R	F, female; M, male;mem branous
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nephropathy, MN; HTP, hypertension; AKI, acute kidney injury; CKD, Chronic Kidney Disease; NS, nephrotic syndrome; Scr, Serum creatinine; ALB, serum albumin; RBC, red blood cell; UTP, 24-hour urine protein; UPCR, urine protein-to-creatinine ratio; HD, hemodialysis; RASi, renin-angiotensin-aldosterone system inhibition; N, none; CR, complete remission; PR, partial remission; NA, non-applicable; NR, no response; R, response.

### 3.1.3 Lupus nephritis (LN)

Systemic lupus erythematosus (SLE) is an autoimmune disease with a range of variable features, yet its pathogenesis and precise mechanism remain unclear. Lupus nephritis (LN), one of the most severe organ complications of SLE, is a form of glomerulonephritis that is histologically classified into six distinct classes [56]. To date, at least 12 cases of new-onset SLE induced by COVID-19 vaccination have been reported in the literature, of which two were male and the rest were female [57–68] (Table 3). Most cases developed two to three weeks after vaccination (Table 3). Although the exact evidence to elucidate the relationship between SLE and COVID-19 vaccine is not available, there are some potential mechanisms between COVID-19 vaccination and SLE, including molecular mimicry [69], type I interferons and inflammatory mediators production via stimulation of toll-like receptors (TLR) [70] and vaccine adjuvants triggering autoimmune events [71], among others. Previous studies have reported flares of SLE triggered by other vaccines such as hepatitis-B, and H1N1 [72, 73]. Therefore, the possibility of a similar effect cannot be denied.

To date, only three cases of new-onset LN following COVID-19 vaccination have been reported [74–76] (Table 4), with two cases following viral vector vaccination and one case following mRNA vaccination. The age range of the cases varied widely (14 to 60 years), and initial symptoms were diverse. Nevertheless, the serological profiles were generally similar, showing elevated ANA titers, positive anti-dsDNA antibody, and low complement levels. All three patients received immunosuppressive therapy, resulting in varying degrees of remission.

While these findings suggest that the COVID-19 vaccine may trigger the onset of LN in susceptible populations, a definitive cause-effect relationship between COVID-19 vaccination and LN has not yet been established.

Author	Age	Gender	PMH	Timeline of symptom onset	Type of Vaccine	Scoring of SLE	Serology profile	Diagnose
Patil	22	F	infective jaundice (non-B)	2 wk after 1st dose	Viral vector	22	ANA,anti-dsDNA	SLE with anemia of chronic diseases
Nune	24	M	N	2 wk after 2nd dose	mRNA	21	ANA,anti-dsDNA ,low C3 and C4	SLE with ecrotizing lymphadenitis
Hidaka	53	F	Bronchial asthma, Vogt–Koyanagi–Harada	few days after 1st and 2nd dose	mRNA	20	ANA ,low C3 and C4	SLE with Evans syndrome

**Table3. Reported cases of SLE after COVID-19 vaccination**

F, female; M, male; ANA, anti-nuclear antibody; anti-dsDNA, antibody recognizing double-stranded DNA; anti-SSA, anti-Sjögren syndrome A antibody; anti-SSB, anti-Sjögren syndrome B antibody; anti-RNP, anti-ribonuclear protein antibody; anti-Sm, anti-Smith antibody; anti-Rib-P, anti-ribosomal P protein antibody; C3, complement 3; C4, complement 4; SLE, systemic lupus Erythematosus; AA, alopecia areata; APS, antiphospholipid syndrome; PMH, past medical history. Scoring of SLE is based on the 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria.

Author	Age	Sex	PMF	Pre-existing disease, Hashimoto disease	Time of symptom onset	Type of Vaccine	Begin of symptoms	Serology profile	treatment	outcome
Gamonal	27	F	N		3 wk after 2nd dose	Viral vector		ANA,anti-dsDNA, anti-Sm,anti-SSA, low C3 and C4		SLE with AA
Rios	42	F	three pregnancies with two spontaneous abortions		2 wk after 1st dose	mRNA		ANA,anti-dsDNA, low C4		SLE with secondary APS
Wang	37	F	N		2 wk after 1st dose	Viral vector		ANA, anti-dsDNA, low C3		SLE with acrocyanosis
Mousa	22	F	N		1 wk after 1st dose	mRNA		ANA, anti-dsDNA, low C3 and C4		SLE with acute pancreatitis vasculitic rash
Raviv	24	M	N		2 days after 1st dose	mRNA		ANA,anti-Rib-P, anti-chromatin (nucleosomal), low C3		SLE
Báez	27	F	type 1 diabetes mellitus		2 wk after 2nd dose	mRNA		ANA,anti-SSA,anti-SSB, anti-dsDNA,low C4		SLE
Lemoine	68	M	N		2 days after 1st dose	mRNA		ANA,anti-dsDNA, p-ANCA with anti-MPO specificity		SLE
Khanna	18	F	autism		1 wk after 1st dose	mRNA		ANA,anti-RNP, anti-Sm, low C3 and C4		SLE
Ghang	20	F	N		10 days after 1st dose	mRNA		ANA,anti-SSA, anti-SSB		SLE

**Table4. Reported cases of LN after COVID-19 vaccination**

F, female; M, male; ANA,anti-nuclear antibody; anti-dsDNA,antibody recognizing double-stranded DNA; anti-RNP,anti-ribonuclear protein antibody;anti -Sm. anti-Smith antibody; N,none;NA, non-applicable; R, response.

### 3.1.4 Focal segmental glomerulosclerosis (FSGS)

Focal segmental glomerulosclerosis (FSGS) is a heterogenous syndrome that arises from podocyte injury caused by various factors, and it represents a major cause of kidney disease worldwide[77]. Recently, five cases of de novo FSGS after COVID-19 vaccination have been reported[13,78–81](table5), with four of the cases following mRNA vaccine and one following the

Authors	Age	Sex	PMF	Pre-existing disease	Time of symptom onset	Type of Vaccine	Begin of symptoms	Serology profile	treatment	outcome
Zavala-Miranda et al.	23	F	N		1 wk after 1st dose	Viral vector	eyelid edema foamy urine hair loss	ANA;anti-dsDNA; low C3 and C4	mycophenolate mofetil; glucocorticoids; hydroxychloroquine; diuretics	R
Kim et al.	60	F	N		after 2nd dose	Viral vector	asthenic;did not eat well	ANA; anti-dsDNA; anti-Sm;low C3 and C4	methylprednisolone; cyclophosphamide; Prednisolone; hydroxychloroquine	R
Nelson et al.	14	M	N		2 days after 3rd dose	mRNA	non-photosensitive facial rash	ANA;anti-dsDNA; anti-Sm;anti-RNP low C3 and C4	Prednisone; mycophenolate mofetil; Losartan; hydroxychloroquine	R

viral vector vaccine. The majority of patients were women (3/5, 60%) and below 30 years of age (4/5,80%). Nephrotic syndromes characterized by edema and proteinuria developed in almost all

patients after vaccination, and renal biopsy confirmed FSGS. In addition to conservative treatment, all five patients received steroid therapy, and three also received immunosuppressive therapy. Most cases responded well to regular immunosuppression. However, Jha et al. reported a case of a 21-year-old male patient who developed de novo FSGS after ChAdOx1 nCoV-19 vaccination and did not respond to steroid + tacrolimus + rituximab therapy, unlike the other four patients [78]. It is difficult to establish a definite causal relationship between COVID-19 vaccination and FSGS, due to the small number of reported cases. Nevertheless, previous studies have suggested that mRNA vaccines may elicit T cell responses, and T-cell-mediated immune response could potentially trigger podocyte damage [82].

Overall, these findings suggest that COVID-19 vaccination may induce FSGS in some susceptible individuals. Further studies are needed to determine the underlying mechanisms and to identify risk factors associated with FSGS after COVID-19 vaccination.

#### Table 5. Reported cases of FSGS after COVID-19 vaccination

F, female; M, male; focal segmental glomerulosclerosis; FSGS; IHD, ischemic heart disease; TTP, thrombotic thrombocytopenic purpura; HT, hypothyroidism; HTP, hypertension; MH, Microscopic hematuria; NS, nephrotic syndrome; PLA2R, phospholipase A2 receptor; Scr, Serum creatinine; ALB, serum albumin; UPCr, urine protein-to-creatinine ratio; C3, complement C3; C4, complement C4; N, none; R, remission; PR, partial remission; NA, non-applicable; NR, no response.

#### 3.1.5 Others

In addition to the aforementioned adverse events induced by COVID-19 vaccination, other

Authors	Age	sex	PMH	Timeline of symptoms onset	Type of vaccine	Begin of symptoms	Laboratory features	treatment	outcome
Jha et al.	21	M	N	12 days after 1st dose	Viral vector	facial puffiness; lower limb swelling	Scr: 1.06 mg/dl; protein: 4+; ALB: 0.9 g/dl; Renal biopsy: FSGS	steroid; tacrolimus; rituximab	NR
Dorman et al.	20	F	Vegan diet	5 days after 1st dose	mRNA	generalized edema	Scr: 0.47 mg/dl; proteinuria; UPCr: 10.3 g/g; ALB: 120 mg/dl; Renal biopsy: FSGS	prednisolone; diuretic; lipid-lowering; vitamin substitution	PR
Fenoglio et al.	24	F	N	after 2nd dose	mRNA	NS	Renal biopsy: FSGS	Glucocorticoids	NA
Lim et al.	29	M	N	7 days after 1st dose	mRNA	edema; decreased urine output	Scr: 1.24 mg/dL; protein: 4+; ALB: 2.5 g/dL; UPCr: 6.12 g/g; C3: 144 mg/dL; C4: 65 mg/dL; Renal biopsy: FSGS	prednisolone; diuretics; angiotensin receptor blocker; statin	R
Marega et al.	80	F	TTP; HT; HTP; IHD	2 wk after 2nd dose	mRNA	weight increased; generalized edema	Scr: 2 mg/dL; ALB: 2 g/dL; proteinuria: 300 mg/dL; MH; PLA2R Ab: Positive; kidney biopsy: FSGS superimposed on MN	Steroids; cyclophosphamide	R

autoimmune manifestations have also been reported in some cases, including ANCA-associated

nephritis, thrombotic microangiopathy (TMA), and others.

Kim et al. reported a case of a 72-year-old woman who presented with anorexia, abdominal pain, and fever after receiving the mRNA vaccine. Laboratory tests showed occult blood (2+), proteinuria (2+), microscopic hematuria, and elevated serum creatinine levels (1.25 mg/dL). Serological tests revealed positive ANCA titers and antibodies against MPO. Based on renal biopsy results, ANCA-associated pauci-immune crescentic glomerulonephritis was diagnosed. After high-dose steroid treatment and plasmapheresis, the patient's symptoms and renal function improved[83].

Fabritiis et al. reported a case of a 35-year-old previously healthy man who developed moderate fatigue one day after receiving the first dose of mRNA vaccine, coupled with dysgeusia, myalgia, pharyngodynia, and foamy urine. Laboratory tests showed nephrotic proteinuria, microhematuria. Kidney biopsy showed some ultrastructural alterations suggestive of an initial phase of renal TMA and complete remission of proteinuria and microhematuria was achieved in four weeks after high-dose steroid treatment[84]. However, Bitzan et al. reported five cases of TMA after influenza vaccination before[85]. To date, there are few reports of thrombotic microangiopathy following COVID-19 vaccination, suggesting that the underlying pathogenic relationship remains to be explored.

## **3.2 Autoimmune rheumatic diseases (ARDs)**

### **3.2.1 Rheumatoid arthritis (RA)**

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease characterized by the presence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) that cause inflammation[86]. Seven cases of de novo RA following COVID-19 vaccination have been reported, with a higher incidence in women (4/7, 57%)[14,87–91]. Four of these were reported after the mRNA vaccine and one after the Viral vector vaccine. Yonezawa et al. reported the first case of de novo seropositive RA after COVID-19 mRNA vaccination[87]. In most cases, patients presented with early symptoms of arthritis, such as morning stiffness, swelling, and pain. Serological tests showed positive RF and ACPA. Treatment included steroids, with four cases treated with methotrexate, two with hydroxychloroquine, and one with tocilizumab. Most patients responded well to the treatment and achieved varying degrees of clinical remission.

However, Nahra et al. reported that symptoms recurred in patients after the prednisone dosage was reduced to less than 10mg per day[88].

### **3.2.2 Antiphospholipid syndrome (APS)**

Antiphospholipid syndrome (APS) is a unique form of autoantibody-induced thrombophilia characterized by recurrent thrombosis and pregnancy complications. Lupus anticoagulant is the most significant predictor of APS-related features[92]. Moreno-Torres et al. recently reported a case of APS following an mRNA COVID-19 vaccine. The patient, a 27-year-old woman with a previous history of selective immunoglobulin A deficiency and paucisymptomatic COVID-19, presented with fever, digital ischemia, and abdominal pain 36 hours after receiving the first dose of BNT162b2 mRNA vaccine. Laboratory tests showed the presence of lupus anticoagulant. The patient was treated with low-dose prednisone, hydroxychloroquine, adjusted low-molecular-weight-heparin (LMWH) and thrice-weekly hemodialysis [93].

In another case, Molina-Rios et al. reported a 42-year-old woman with a history of three pregnancies, two of which resulted in spontaneous abortions. She presented with inflammatory polyarthralgia, bilateral synovitis, and bilateral Achilles tendon enthesopathy two weeks after receiving the first dose of the mRNA vaccine. Combined with laboratory data and imaging findings, SLE and secondary APS were considered[94].

### **3.2.3 Adult-onset Still's disease (AOSD)**

Adult-onset Still's disease (AOSD) is a rare auto-inflammatory disorder of unknown etiology characterized by a high spiking fever, arthralgia, evanescent rash, and striking leucocytosis with neutrophilia[95]. A total of twenty-two cases of new-onset AOSD were reported in patients presenting with macroscopic hematuria following COVID-19 vaccination, with a male-to-female ratio of 4:7[96–110]. Ten cases were reported following the mRNA vaccine, with five after the second dose, and the remainder following the viral vector vaccination, with one case reported after the second dose. Fever was the first symptom in all patients after vaccination, which was sometimes accompanied by other symptoms, such as sore throat, arthritis, headache, and others. As the disease progressed, most patients developed skin rashes. Laboratory tests showed elevated leukocytosis and CRP in most patients, while some patients showed an increase in liver enzymes. The vast majority of patients respond to steroid therapy, with a few requiring tocilizumab therapy.



However, Gasparotto et al. reported a case of a 50-year-old female who did not go into remission after steroid and anti-IL1 treatment[101].

The exact pathogenesis of AOSD is not fully understood, but previous studies have shown that innate immune system activation is involved, with Toll-like receptors (TLRs) possibly activating the innate immune system with subsequent cytokine overproduction, especially ongoing aberrant IL-1, IL-18, IL-6, and TNF- $\alpha$ [95].

### **3.2.4 ANCA-associated vasculitis (AAV) and Giant cell arteritis(GCA)**

Antineutrophil cytoplasmic autoantibodies (ANCA) associated vasculitis (AAV) is a rare autoimmune disorder that involves severe small-vessel vasculitis and is characterized by a loss of tolerance to neutrophil primary granule proteins such as leukocyte proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA). AAV is classified into three types based on clinical features, namely granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA)[111]. A total of 17 new-onset AAV cases have been reported, including 5 cases of PR3-ANCA vasculitis, 9 cases of MPO-ANCA vasculitis, and 3 cases of dual-positive MPO- and PR3-ANCA vasculitis[112–120]. The majority of cases were women (11/17, 64.7%). Of these 17 cases, 13 cases were reported following the mRNA vaccines, 3 were reported following viral vector vaccines, and 1 was reported following inactivated vaccines. All patients received steroid therapy, while some also received hemodialysis (2/17,11.8%), plasmapheresis (7/17,41.2%), cyclophosphamide (11/17,64.7%), and rituximab(6/17,35.3%). Christodoulou et al. reported the first case of a healthy patient who developed de novo MPO-ANCA vasculitis shortly after COVID-19 vaccination and responded to steroids and cyclophosphamide but relapsed immediately after COVID-19 infection[121]. This finding suggests that both SARS-CoV-2 infection and vaccination may induce vasculitis and involve similar immune mechanisms.

Furthermore, So et al. have reported a new case of new-onset MPA following COVID-19 vaccination. A 42-year-old healthy male presented with general weakness, shortness of breath, edema, gross hematuria, and significant weight loss after receiving a second dose of mRNA vaccine. Elevated MPO antibodies and histological findings lead to the diagnosis of MPA. After receiving glucocorticoid therapy, rituximab, and plasma exchange, the patient's symptoms

improved[129]. However, the exact mechanism by which COVID-19 vaccines induce AAV is not yet well understood.

Giant cell arteritis (GCA) is a rare inflammatory disease affecting medium and large blood vessels, with clinical manifestations including headache, scalp tenderness, jaw and tongue pain, and visual disturbances[130]. There were five new-onset cases of GCA reported, with three patients developing symptoms after the mRNA vaccine and one patient after the first dose of the viral vector vaccine[131–135]. Four (80%) patients presented with headaches, while two (40%) patients presented with jaw claudication. Scalp tenderness was observed in two (40%) cases. Most patients responded to steroid therapy. Mungmungpantipantip et al. suggest that COVID-19 vaccination may increase blood viscosity, which may lead to inflammation resulting in arteritis[136]. However, the underlying pathogenesis of GCA remains unclear and may be associated with COVID-19 vaccines.

### **3.2.5 Sjogren's syndrome (SS) and Behçet's disease (BD)**

Ramos-Casals et al. documented the first case of subclinical Sjogren's syndrome (SS) occurring 10 days after the first dose of the ChAdOx1 nCoV-19 vaccine (Oxford/AstraZeneca). A 55-year-old male with a history of colon carcinoma presented with widespread petechiae, bleeding gums, and hematuria following vaccination. Laboratory tests revealed a platelet count of  $3 \times 10^9/L$ , positive IgG antibodies, ANA, and anti-Ro52 antibodies[137].

Tagini et al. described the first case of a new-onset Behçet's disease (BD) developing 15 days after the second dose of the SARS-CoV-2 mRNA-1273 vaccine. A woman in her late 20s with a medical history of polycystic ovary syndrome presented with a 1-week history of general malaise and her first episode of painful oral and genital ulcers after vaccination. BD was suspected based on clinical presentation, and the patient rapidly recovered after receiving prednisone 1 mg/kg/day[138].

### **3.3 Autoimmune hepatitis (AIH)**

Autoimmune hepatitis (AIH) is a chronic liver disease characterized by elevated serum transaminase levels, elevated immunoglobulin G levels, the presence of autoantibodies, and interface hepatitis on liver histology[139]. The first case of AIH following COVID-19 vaccination was reported by Brill et al. in a 35-year-old female who developed AIH one week after receiving

the first dose of COVID-19 vaccine (Pfizer-BioNTech) in her third month postpartum[140]. Although immunoglobulin G levels were not elevated as typically seen in AIH, histology showed the presence of eosinophils, which are also observed in liver damage caused by drugs or toxins. However, both conditions have also been reported in AIH[141,142]. To date, COVID-19 vaccines that induce AIH include mRNA vaccines, viral vector vaccines, and inactivated vaccines, with mRNA vaccines accounting for the majority and inactivated vaccines accounting for the least[15,140,143–168]. Clayton-Chubb et al. reported for the first time a case of adenovirus-based vaccine eliciting AIH. A 36-year-old male physician with a history of hypertension but no history of liver disease developed AIH following the first dose of the ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca)[152]. Mekritthikrai et al. reported the first case of AIH flare-up after receiving an inactivated COVID-19 vaccine. A 52-year-old woman without previous liver disease was diagnosed with AIH after receiving 2 doses of inactivated COVID-19 vaccine (CoronaVac)[157].

Although an increasing number of reports have linked COVID-19 vaccination to the development of AIH, the mechanisms remain unclear. Vojdani et al. found that antibodies to the SARS-CoV-2 spike protein cross-reacted with transglutaminase 3 (TTG3), transglutaminase 2 (TTG2), and other proteins, suggesting that SARS-CoV-2 may trigger autoimmunity[169]. Furthermore, previous reports described a relationship between vaccination and the development of AIH, including influenza vaccines[170], which suggest that COVID-19 vaccines may also induce AIH. The cases presented above indicate that different types of vaccines have different potentials for inducing autoimmunity, and the mechanisms by which they promote autoimmunity may also differ slightly. For mRNA vaccines, adjuvant activity and binding to pattern recognition receptors (PRRs), such as Toll-like receptors, may trigger T and B cell immune responses[171,172]. For viral vector vaccines, adjuvants or binding to model receptors, particularly TLR9, may be involved[173]. Inactivated vaccines may exert immune effects through adjuvants and molecular mimicry[157].

### **3.4 Type 1 diabetes mellitus (T1DM)**

Type 1 diabetes mellitus (T1DM) is an autoimmune endocrine disorder characterized by symptoms such as polyuria, nocturia, enuresis, lethargy, polydipsia, weight loss, and abdominal

pain[174]. Out of the 13 cases analyzed (6 men and 7 women), approximately 54% did not have any medical history of autoimmune diseases, while 15% of patients had a history of vitiligo, type 2 diabetes mellitus, and Hashimoto's thyroiditis[175–183]. While 10 patients received the mRNA vaccine, 2 received the inactivated vaccine. Almost all of the patients exhibited classic symptoms of diabetes, such as thirst, polyuria, polydipsia, and fatigue, and showed remission after insulin treatment, with one patient getting worse after medical nutrition therapy.

Tang et al. reported the first case of a 50-year-old healthy male who developed fulminant type 1 diabetes mellitus (FT1DM) after receiving an inactivated COVID-19 vaccine. The patient experienced fever and an abrupt onset of polydipsia and polyuria 5 days after vaccination. Laboratory tests at presentation revealed hyperglycemia, ketosis, metabolic acidosis, and a positive result for susceptibility human leukocyte antigen (HLA) alleles for FT1DM (DQB1\*02:03/03:03 and DRB1\*09:01/09:01). However, the patient's islet function was almost completely lost 4 weeks after initial presentation. Tang et al. suggested that genetic susceptibility and autoimmunity might be involved in the pathogenesis of FT1DM, indicating that vaccination might trigger autoimmunity in individuals with susceptible genetic backgrounds and cause FT1DM[176]. Additionally, Sasaki et al. proposed that there might not be a single mechanism responsible for the loss of islet function and the development of hyperglycemia associated with Covid-19 vaccination, as new-onset T1DM patients with positive autoantibodies developed symptoms 4-7 weeks after vaccination, while patients with negative autoantibodies showed symptoms within a week after vaccination. The type of vaccine may also be a contributing factor to the difference in onset times[181].

MDA5 is a crucial innate pathogen recognition protein that has been shown to play a role in the immune response to COVID-19 mRNA vaccines. According to Sakurai et al., MDA5 recognizes RNA from these vaccines and triggers the synthesis of type I interferons. This immune response may interfere with insulin production, proinsulin conversion, and mitochondrial function in pancreatic  $\beta$ -cells, leading to the development of diabetes[180].

### **3.5 Autoimmune hemolytic anemia(AIHA)**

To date, studies on vaccine-induced autoimmune hematologic disorders have been focused on cases of vaccine-associated thrombosis with thrombocytopenia (VITT), while reports of other vaccine-related hematologic diseases are uncommon. Autoimmune hemolytic anemia (AIHA) is one such rare disorder characterized by the accelerated destruction of autologous red blood cells (RBCs) due to autoantibodies[184].

Of the 9 new-onset cases of AIHA reported, of which 6 patients developed symptoms following the mRNA vaccine, and 3 patients developed symptoms after the viral vector vaccine[185–190]. In laboratory tests, all the patients showed decreased levels of Hb and haptoglobin, increased levels of LDH and bilirubin, and a positive direct antiglobulin test (DAT). Treatment involved steroid therapy for all patients, while 4 (44%) patients were treated with rituximab or immune globulin, and 2 (22%) patients received supportive RBC transfusions. One patient received plasmapheresis or mycophenolate mofetil.

The mechanism by which COVID-19 vaccines induce AIHA remains unclear. Angileri et al. proposed that molecular mimicry may be involved. Ankyrin-1 (ANK-1) is an erythrocyte membrane protein that is essential for erythrocyte differentiation and function. They found that ANK-1 shares a putative immunogenic antigenic epitope (amino acids LLLQY) with 100% identity with Spike's predicted immunogenic epitope 750-SNLLLQYGSFCTQL-763 for B cells. Thus, the viral spike glycoprotein encoded by mRNA vaccines could induce the production of antibodies against spike protein, which may cross-react with ANK-1 RBC protein through molecular mimicry, leading to AIHA[191].

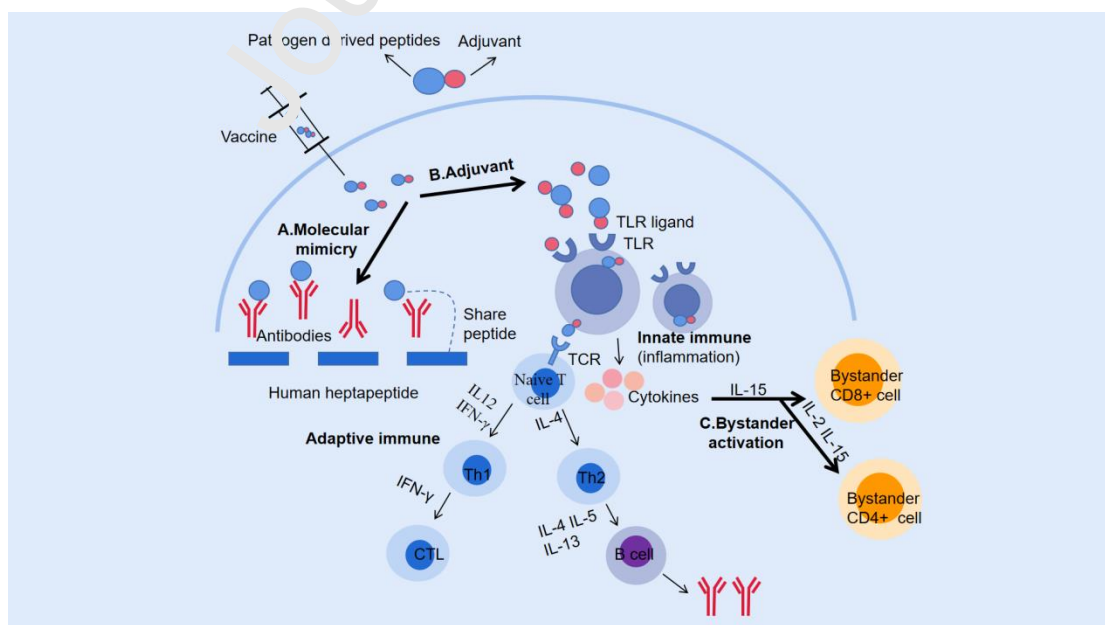
### 3.6 Others

In addition to the adverse events previously described, COVID-19 vaccination has also been associated with various autoimmune manifestations. These include vaccine-induced immune thrombocytopenia and thrombosis (VITT), myocarditis, alopecia areata(AA), autoimmune thyroid diseases, and Guillain-barre syndrome (GBS). Pavord et al. conducted a prospective cohort study involving 294 patients with suspected VITT. The syndrome is characterized by thrombosis, thrombocytopenia, elevated D-dimer, and positive platelet factor 4 (PF4) antibodies, which were observed 5 to 30 days after SARS-CoV-2 vaccination [192]. Myocarditis is another rare

complication reported after COVID-19 vaccination. Fichadiya et al. reported a case of a 60-year-old healthy male with no past medical history who developed heart failure (NHYA class 4) symptoms and suspected myocarditis four weeks after receiving the first dose of COVID-19 vaccine (mRNA1273, Moderna)[193]. Alopecia Areata(AA), classified as an autoimmune disease with an unknown cause, has also been linked to COVID-19 vaccination. Lee et al. reported a case of an 80-year-old man who developed AA after the first dose of the COVID-19 vaccine(BNT162b2)[194]. Additionally, several thyroid disorders such as Graves' disease, subacute thyroiditis, and others, have been reported following COVID-19 vaccination[195]. Guillain-Barré syndrome (GBS) is an acute disorder of the nervous system and is one of the autoimmune neurological diseases. McKean and Chircop reported a case of a 48-year-old man with dyslipidemia who developed GBS following the first dose of the COVID-19 vaccine (Vaxzevria)[196].

Recent findings suggest that the incidence of autoimmune diseases triggered by COVID-19 vaccines is on the rise, highlighting the pressing need to identify high-risk and vulnerable populations. Furthermore, it is essential to gather more evidence to confirm the link between COVID-19 vaccines and autoimmunity. To this end, several mechanisms have been proposed to elucidate the causal relationship, which will be detailed in the subsequent section.

#### 4 Mechanisms of COVID-19 Vaccine-induced Autoimmune Diseases



**Fig.1. Schematic illustration of mechanisms inducing autoimmune diseases following COVID-19 vaccination.**

A. Following vaccination, vaccine antigens can trigger an immune response in the body. However, due to the presence of a heptapeptide that is shared between the SARS-CoV-2 spike glycoprotein and human proteins, vaccine antigens may also attack human proteins with similar structures via the molecular mimicry pathway. B. Adjuvants in vaccines can act as ligands for pattern recognition receptors (PRRs), such as toll-like receptors (TLR), bind to them to mobilize innate immune cells and secrete massive cytokines, and induce an innate immune response. Additionally, adjuvants also enhance the induction of adaptive immune responses to vaccine antigens. Upon binding to T-cell receptors (TCRs), antigens activate naive T-cells, which differentiate into Th1 or Th2 cells under the influence of different cytokines. Th1 cells primarily stimulate cellular responses, including the production of cytotoxic T lymphocytes (CTLs) that can eliminate infected cells, while Th2 cells promote humoral responses, such as B-cell proliferation, differentiation, and secretion of neutralizing antibodies. C. During the innate immune response following vaccination, the immune system produces a large number of cytokines, which may induce autoimmunity through the bystander activation pathway. This includes the activation of bystander CD8<sup>+</sup> T cells primarily under the action of IL-15 and the activation of CD4<sup>+</sup> T cells primarily under the influence of IL-2. PRRs, pattern recognition receptors; TLR, Toll-like receptor; TCR, T cell receptor; CTL, Cytotoxic T lymphocyte.

**4.1 Molecular Mimicry and Immune Cross-reaction**

The term molecular mimicry refers to the structural similarity between specific human proteins and certain disease-causing elements contained in vaccines. This similarity may result in immune cross-reaction, where the immune system mistakes human proteins for pathogens and attacks them, leading to autoimmune diseases [69]. Segal et al. have suggested several examples of vaccine-induced autoimmune diseases associated with molecular mimicry and immunological cross-reaction. These include influenza (H1N1) vaccines and Guillain-Barre syndrome (GBS), hepatitis B virus vaccines and multiple sclerosis (MS), and human papillomaviruses (HPV) and systemic lupus erythematosus (SLE) [69]. The mechanisms of molecular mimicry and immune cross-reaction may also play an important role in inducing autoimmune diseases following post-SARS-CoV-2 vaccination. Kanduc et al. have analyzed abundant heptapeptide sharing between SARS-CoV-2 spike glycoprotein and human proteins [197]. Therefore, antibodies produced by the body against the SARS-CoV-2 spike protein after vaccination may cross-react with the host and cause autoimmune diseases.

**4.2 Adjuvants**

Adjuvants are substances that accelerate, prolong, or enhance antigen-specific immune responses without having any specific antigenicity. They stimulate the immune system and

increase the response to vaccines [198]. Toll-like receptors (TLRs) are a group of PRRs present on the innate immune system cells that recognize pathogens and initiate a response to infection. Adjuvants act as TLR ligands, binding to TLRs and leading to the initiation of innate immune responses, followed by adaptive immune responses [199]. However, adaptive antibody responses can also occur even in the absence of TLR ligands, as noted by Gavin et al.[200]. The concept of "ASIA-Autoimmune/inflammatory Syndrome Induced by Adjuvants" has been proposed by Shoenfeld and Agmon-Levin, suggesting that adjuvants can trigger immune-mediated diseases [201]. Nevertheless, more studies are needed to confirm the role of adjuvants in the development of COVID-19 vaccine-mediated autoimmune diseases.

### 4.3 Bystander Activation

Bystander activation refers to the cytokine-dependent, T and B cell receptor-independent activation of T and B cells [202,203]. In viral infections, Tough et al. reported for the first time that T-cell proliferation is driven by cytokines instead of TCRs and that memory cells may require minimal TCR ligation or be completely independent of TCRs. They require only intermittent exposure to IFN I released during viral infection to promote the long-term memory carried by CD8+ cells [204]. Additionally, Boynar suggested that bystander activation of CD4+ T cells may involve IL-2 and other cytokines [205]. In adjuvant-containing vaccines or adjuvants alone, T cells can be activated via bystander pathways; however, the migration of these activated auto-reactive cells to the site of inflammation and the mass secretion of cytokines may be sufficient to induce autoimmune pathologies, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and type 1 diabetes [202]. Therefore, it is highly probable that bystander activation is involved in the autoimmunity phenomena that occur following COVID-19 vaccination.

### 4.4 Others

In addition to the mechanisms discussed above, two other mechanisms involved in the development of vaccine-induced autoimmune diseases are epitope diffusion and polyclonal activation of B cells. Epitope spreading(ES) refers to an immune response to an epitope that is different from the dominant epitope and has no cross-reaction. This immune response can spread to different epitopes on the same protein (intramolecular ES) or to epitopes on other proteins



(intermolecular ES) [206]. Studies by Cornaby et al. have shown that intermolecular and intramolecular B cell ES contribute to the development of numerous autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, Graves' disease, and Multiple sclerosis [207].

Polyclonal activation and proliferation of B cells are induced by long-lasting or constant immune system activation[208]. In some cases, this activation leads to the formation of circulating immune complexes, which can eventually cause damage to self-tissues.

## 5 conclusion

Since the outbreak of COVID-19, its impact on the global economy, politics, and other aspects has been significant. In December 2021, the SARS-CoV-2 Omicron variant quickly became the dominant strain in the COVID-19 pandemic. Notably, Omicron contains numerous mutations in the spike protein that confer high immune evasion, and Shen's research suggests that a booster dose of the COVID-19 vaccine is critical for generating neutralizing antibody responses against Omicron [209]. Given Omicron's high infectivity, although it is less pathogenic than previous strains, a large number of cases would still overwhelm healthcare systems[210]. In this case, further optimization of the COVID-19 vaccine, such as changing the route of administration or adjusting vaccination strategies (e.g., adopting sequential immunization), is of great significance for controlling infections and alleviating public health pressure[211]. However, it is important not to ignore the potential side effects of vaccination.

In this comprehensive review, we have discussed rare autoimmune diseases that may potentially arise following COVID-19 vaccination, such as autoimmune glomerulonephritis, autoimmune rheumatic diseases, and autoimmune hepatitis, among others. However, the true incidence of these diseases after vaccination remains difficult to determine, as not all cases are or will be reported. Further exploration is necessary to establish a causal relationship between COVID-19 vaccines and the aforementioned autoimmune diseases.

It is important to emphasize that vaccines are generally safe and necessary for disease prevention. The benefits of COVID-19 vaccination significantly outweigh the theoretical risks, and we strongly encourage worldwide vaccination to build immune protection in the population.

Nevertheless, it is our responsibility to remain vigilant and actively understand the serious adverse events associated with COVID-19 vaccines, critically evaluate vaccine safety, and increase public and healthcare worker awareness regarding vaccination. This will enable prompt identification, diagnosis, and treatment of these autoimmune diseases following vaccination through the recognition of their clinical and laboratory features.

## **Declarations**

### **Competing interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### **Authors' contributions**

Study concept and design: Q.G.L. and X.X.L. Literature search and data collection: M.G..Drafting of the manuscript: M.G., X.X.L. and Q.G.L.. X.M.C. and Q.G.L. made critical revisions of the review. All authors read and approved the final manuscript. Q.G.L. takes responsibility for the integrity of the content and the accuracy of analysis.

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### **Availability of data and materials**

Data will be made available on request.

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## Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Highlights

1. Despite vaccination against COVID-19 is effective in reducing disease severity and mortality, COVID-19 Vaccines may cause rare autoimmune diseases.
2. Whether there is a causal relationship between COVID-19 vaccination and these autoimmune phenomena needs to be further explored.
3. These autoimmune phenomena may be induced by vaccines through some mechanisms, such as molecular mimicry, bystander activation, adjuvants.
4. We believe that the benefits of COVID-19 vaccination far outweigh the potential risks and encourage global vaccination for COVID-19.