Gross Hematuria after the COVID-19 mRNA Vaccination: Nationwide Multicenter Prospective Cohort Study in Japan

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Key Points

- Little is known about the clinicopathological characteristics and renal outcomes in the patients with gross hematuria (GH) after the vaccination.
- To fill a clinicopathological knowledge gap regarding vaccination and GH, we conducted a nationwide multicenter prospective cohort study.
- GH is more likely to occur in patients with IgA nephropathy, with a female bias, but without progressive exacerbation of renal function.

Abstract

Background In the past 3 years, cases of gross hematuria (GH) after the vaccination for coronavirus disease 2019 in patients with IgA nephropathy (IgAN) have been frequently reported worldwide. However, the postevent renal prognosis of these patients, their clinical backgrounds, and underlying mechanisms remain unknown. Therefore, we conducted a nationwide multicenter prospective cohort study in Japan.

Methods We analyzed laboratory findings at the time of the first presentation to the hospital and 3 and 6 months after in patients with GH after the vaccination and histopathological findings in their kidney biopsy specimens. Moreover, changes in pathological biomarkers of IgAN such as galactose-deficient IgA1 (Gd-IgA1) and its immune complexes were also evaluated.

Results During the study period, 127 newly presenting patients with GH after the vaccination were enrolled, with a clear female bias (73.2%). GH was observed after the second or subsequent vaccinations in most patients (92.9%). Of the 37 patients undergoing kidney biopsy before the vaccination, 36 patients had been diagnosed with IgAN/IgA vasculitis (IgAV). In the remaining 90 patients, 69 of the 70 who newly underwent kidney biopsy were diagnosed with IgAN (n=67)/IgAV (n=2). Their histopathology did not show a high incidence of acute lesions such as endocapillary hypercellularity and crescentic lesions. Most cases showed a temporary increase in proteinuria, but no sustained worsening in renal function. Among the biomarkers measured, serum Gd-IgA1 and immune complexes were comparable throughout the observation period; however, only urinary Gd-IgA1 was increased at the time of GH.

Conclusions We found that GH after the vaccination is more likely to occur in patients with IgAN/IgAV, with a female bias, but without progressive exacerbation of renal function. Although further investigation is needed regarding causal relationship between vaccination and GH, this study provides many insights into the molecular mechanisms of GH.

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Introduction

Vaccines against coronavirus disease 2019 (COVID-19), mainly mRNA-based vaccines, either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna), have been administered worldwide and have provided effective protection against severe COVID-19 infection.[1] Although these vaccines

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have a favorable safety profile,[2–5] recent studies have discussed their clinical associations with relapse of preexisted GN or the *de novo* onset, including IgA nephropathy (IgAN), IgA vasculitis (IgAV), minimal change disease, membranous nephropathy, and antineutrophil cytoplasmic antibody-related vasculitis.[6,7] Although there are many reported cases suspected to be associated with COVID-19 vaccination, the clinical characteristics and outcomes of these patients have not been sufficiently examined.

IgAN is the most common type of GN, clinically characterized by the presence of gross hematuria (GH) after upper respiratory traffic infection.[7] Negrea *et al.* have first reported the case of two patients with IgAN showing GH after the COVID-19 vaccination in June 2021.[8] Several reports have addressed the cases of postvaccine GH in patients with IgAN.[6,7] Immediately after the vaccine was initiated by health care provider in Japan, we conducted a web-based short-term survey to investigate the association between GH and COVID-19 vaccination and found 27 patients with GH after receiving the COVID-19 vaccination.[9] Among these patients, 19 (70.4%) were already diagnosed with IgAN at the onset of GH, and none of the patients progressed to severe renal dysfunction. A kidney biopsy was performed after the vaccination in four patients, all of whom were diagnosed with IgAN. Thus, we hypothesize that patients with GH after the COVID-19 vaccination are likely to have IgAN and that their renal outcome is not poor. However, as this web-based questionnaire was a once-off survey and the number of patients was limited, we could not determine the detailed clinical or pathological characteristics and long-term renal prognosis of the patients. To fill this knowledge gap, we conducted nationwide multicenter prospective cohort study to analyze the renal prognosis and clinical characteristic of a large number of patients with GH. In addition, changes in pathological biomarkers were also evaluated for the association of underling mechanism. The aims of this study were to present the clinical and epidemiologic characteristics and follow-up findings of cases of GH that were diagnosed in temporal proximity to vaccination.

Methods

Study Design and patients

Patients aged ≥18 years who presented to the hospital with GH after the COVID-19 vaccination were recruited. All patients visited any of the 22 Japanese hospitals that participated in the prospective observational study by Joint Research Team from the Progressive Renal Diseases Research, Research on intractable disease from the Ministry of Health, Labor and Welfare in Japan between May 11, 2021, and October 31, 2022. Patients were followed-up for 6 months after presenting with GH. This study was approved by the Ethics Review Board of Juntendo University Facility of Medicine (M19-0223 and E21-0117) and the Ethics Committee of the Japanese Society of Nephrology (JSN) (2021_93) and followed the tenets of the Declaration of Helsinki. As this was a prospective, observational cohort study, information about the study plan was disseminated, patients were provided the opportunity to refuse participation in this study, and informed consent was obtained from individuals willing to participate in this study.

Clinical Measurements

For each patient, the following data were extracted from their records: demographic characteristics, medical history, medications, treatment during the observation period, and detailed information about GH. The laboratory data were also recorded. We indicated the date at the time of the first presentation to the hospital with GH after the COVID-19 vaccination as GH 0 and the date 3 and 6 months after GH 0 as GH 3 and GH 6, respectively. Serum and urine samples at GH 0, GH 3, and GH 6 were collected and stored at −80°C. The eGFR was using the following formula: eGFR (ml/min per 1.73 m^2)=194×creatine$^{-1.094}$×age$^{-0.287}$ (×0.739 for women).[10] Microhematuria was defined as ≥5 red blood cells/high power field in the urinary sediment. Urinary protein excretion was evaluated using the urinary protein/creatinine ratio (UPCR). Body mass index was calculated as body wt(kg) divided by height in meters squared (m^2). The mean arterial pressure (mm Hg) was calculated as the diastolic BP plus the pulse pressure divided by three. The type of vaccine used, GH details, and medical history were self-reported by each patient. A standardized set of criteria for defining IgAN remission was used and was stated as follows[11]: (*1*) three consecutive negative results over 6 months in urinary occult blood tests, (*2*) urinary sediment red blood cell count of <5/high-power field, and (*3*) UPCR <0.3 g/gcreatinine (g/gCr) (proteinuria remission).

ELISA

Serum and urinary galactose-deficient IgA1 (Gd-IgA1) levels were measured *via* ELISA using a specific mAb (KM55 mAb), according to the manufacturer's instructions (Immuno-Biological Laboratories, Fujioka, Japan).[12,13] Serum IgA/IgG-immune complexes (ICs) were measured using a cross-capture ELISA, as previously described.[14] These biomarkers were only measured in patients for whom serum and urine samples were available.

Histopathological Analysis

All kidney biopsy slides were reviewed by nephropathologists and scored according to the revised Oxford classification criteria: mesangial hypercellularity (M0, <50%; M1, ≥50% of the glomeruli), endocapillary hypercellularity (E0, absent; E1, present), segmental glomerulosclerosis (S0, absent; S1, present), tubular atrophy and interstitial fibrosis (T0, 0%–24%; T1, 25%–49%; and T2, ≥50% of the cortical area), and cellular or fibrocellular crescents (C0, absent; C1, 1%–24%; and C2, ≥25% of the glomeruli).[15–17] To investigate the clinical and pathological characteristics of patients who developed GH after vaccination, we selected 78 patients who were diagnosed with IgAN at Juntendo University Hospital between May 11, 2018, and October 31, 2019, as the nonvaccinated group.

Statistical Analyses

Continuous variables are presented as medians and interquartile ranges or means and SD, as appropriate. Nonparametric continuous variables were compared using the Mann–Whitney *U* and Kruskal–Wallis tests. Categorical variables are presented as percentages and compared using Pearson chi-squared and Fisher exact test. All statistical analyses were performed using Stata/MP version 17.0

(StataCorp, College Station, TX). Statistical significance was set at $P < 0.05$.

Results

Characteristics of Patients with Postvaccine GH

During the study period, 127 patients with GH after the COVID-19 vaccination were enrolled. The median age of the patients was 39.9 (range, 18–81) years, and 93 (73.2%) patients were female (Table 1). Except for the 10- to 19-year-old group, female patients presented with GH more frequently than did male patients in all age groups. All patients in the known received an mRNA COVID-19 vaccination, all of which were first-generation vaccines. Most patients experienced GH within 3 days after the second or third dose (Table 1), and GH resolved within a week, except in one patient. Most patients had mild adverse events, such as fever, fatigue, or myalgia, associated with the COVID-19 mRNA vaccination. The most frequent adverse reaction was fever (90.6%). None of the patients developed COVID-19 during the observational period. Ten and two patients were treated for hypertension and diabetes, respectively, before vaccination. The detailed clinical characteristics of the patients with GH are summarized in Table 1. The detailed laboratory findings of these patients at the onset of GH are summarized in Table 2.

Renal Outcomes in the Patients with GH

We followed up the patients enrolled in this study for 6 months and evaluated the final diagnosis and renal outcomes after GH (Figure 1). Although the levels of UPCR peaked at GH 0 and decreased at GH 6 (Figure 2A), the serum creatinine levels (Figure 2B) and eGFR (Figure 2C) were comparable between GH 0 and GH 6. Although four patients had mild deterioration of renal outcomes, none of the patients in our cohort developed a 1.5-fold increase in serum creatinine from baseline. We also analyzed proteinuria before the appearance of GH in 59 cases for whom data were available, confirming that the proteinuria temporarily increased after the vaccination (data not shown).

Medical History of the Patients Presenting with GH

In our cohort, 37 of the 127 (29.1%) patients had already been diagnosed with IgAN (n=35)/IgAV (n=1) or proliferative glomerulonephritis with monoclonal IgG deposits before the onset of GH (Figure 1). Regarding the treatment of these prediagnosed 36 patients, 12 had undergone tonsillectomy, 14 had a history of corticosteroid administration, and one continued prednisolone at the onset of GH. Seventeen patients were prescribed renin-angiotensin-aldosterone system inhibitors (Table 1). Nine patients did not achieve clinical remission for IgAN[11] at the GH event (Figure 1). Of the 90 undiagnosed patients with GH, 64 had a medical history of hematuria and/or proteinuria before the vaccination (Figure 1). Twenty-eight patients had only hematuria, two had only proteinuria, and 18 showed both hematuria and proteinuria, as revealed by urine dipstick tests at annual health checkups prior to GH. The remaining 16 patients had abnormal urine findings with unknown details. Nine patients of the 90 undiagnosed patients experienced vaccine-unrelated GH before the vaccination. No differences were observed in gender ratio or age between diagnosed and undiagnosed patients before GH (Table 2).

Diagnosis of Patients with GH after the COVID-19 Vaccination

Kidney biopsies were performed in 70 of the 90 undiagnosed patients (Figure 1). Immunofluorescence staining revealed glomerular IgA and C3 deposition (Figure 3A) and electron microscopy revealed electron-dense deposits in the glomerular mesangial region of 69 patients. Thus, most of the patients, except three, were diagnosed with IgAN (n=67). Two patients were diagnosed as IgAV because they developed skin purpura after the COVID-19 vaccination. We stained 30 of 70 kidney biopsy specimens with KM55, a mAb specific for Gd-IgA1,[18–20] and found that all patients were positive for KM55 (Figure 3B and Supplemental Figure 1), further confirming the diagnosis of primary IgAN in these patients.

Pathological Findings in Patients with GH after the COVID-19 Vaccination

Next, we investigated the pathological characteristics of 69 patients diagnosed with IgAN or IgAV, whom we classified here as the postvaccine GH group. The median duration from the onset of GH to kidney biopsy was 78 (interquartile range, 37–119) days. According to the Oxford pathological classification of 62 cases with available results were analyzed,[15–17] mesangial hypercellularity (M1) was observed in eight (12.9%) patients, endocapillary cellularity (E1) in 18 (29.0%) patients, segmental glomerulosclerosis/adhesion lesions (S1) in 32 (51.6%) patients, tubular atrophy/interstitial fibrosis (T1) in four (6.5%) patients, and cellular/fibrocellular crescents (C1) in 29 (46.8%) patients (Table 3). Expansion of the mesangial matrix was observed in all patients.

To investigate whether certain pathological characteristics were specifically observed in patients with IgAN and with GH after the COVID-19 vaccination or not, we compared the pathological findings of the patients in the postvaccine GH group with those of 78 vaccine-unrelated patients with IgAN (the nonvaccinated group), who were diagnosed at Juntendo University Hospital between May 11, 2018, and October 31, 2019, before COVID-19 pandemic. No differences were observed in clinical characteristics and serological findings between the vaccine and the nonvaccinated group, except for differences in gender ratio (Table 3). Statistically significant differences in C lesion were not observed in both groups, but patients in the postvaccine GH group showed lower E1 and T1+2 scores than did those in the nonvaccinated group (Table 3).

Changes in the Levels of Several Biomarkers of the Patients Who Newly Underwent Kidney Biopsy during the Cohort Study

We next evaluated the temporal trends of the pathological biomarkers of IgAN, including serum IgA, IgA/C3 ratio,[21] serum and urinary Gd-IgA1,[22,23] and IgA/IgG-ICs.[14] In 44 patients, 26 patients who were treated during the observation period or whose serum and urine samples were not available or who were diagnosed other than IgAN/IgAV were excluded(Figure 1). The detailed laboratory findings of these patients are summarized in Table 4. Serum

Table 1. Clinical characteristics of all the patients

Variables	All Participants (N=127)
Age, yr (range), % (No.)	39.6 (18–81)
10–19	4.7 (6)
20–29	25.2 (32)
30–39	22.8 (29)
40–49	20.5 (26)
50–59	17.3 (22)
≥60	9.4 (12)
Female sex, % (n)	73.2 (93)
Type of COVID-19 vaccine, % (No.)	
Pfizer BNT162b2	51.2 (65)
Moderna mRNA-1273	40.2 (51)
Unknown	8.6 (11)
Vaccine dose, % (No.)	
First dose only	4.7 (6)
Second dose only	60.6 (77)
Third dose only	27.6 (35)
Forth dose only	1.6 (2)
Both first and second doses	0.8 (1)
Both second and third doses	3.1 (4)
All first, second, and third doses	1.6 (2)
Time from vaccination to GH, d, % (No.)	
1	18.1 (23)
2–3	74.0 (94)
4–7	4.7 (6)
≥8	3.1 (4)
Duration of GH after the vaccination, d, % (No.)	
1	15.0 (19)
2–3	57.5 (73)
4–7	16.5 (21)
≥8	0.8 (1)
Unknown	10.2 (13)
Adverse reactions at GH (multiple answers allowed), % (No.)	
Fever (≥37.0°C)	90.6 (115)
Fatigue	17.3 (22)
Headache	5.5 (7)
Muscle pain	11.8 (15)
Pain at the application site	9.5 (12)
Back pain	3.9 (5)
None	3.9 (5)
Unknown	4.7 (6)
Treatment history before the vaccination (multiple answers allowed), % (No.)	
Tonsillectomy	9.4 (12)
Steroid pulse therapy	9.4 (12)
Oral corticosteroid	1.6 (2)
RAS-I	13.4 (17)
None	80.0 (99)
Medication at GH, % (No.)	
Oral corticosteroid use	1.2 (1)
RAS-I use	13.4 (17)
None	85.8 (109)
Treatments received after GH, % (No.)	
TSP	4.7 (6)
Tonsillectomy	5.5 (7)
Steroid pulse therapy	7.9 (10)
RAS-I	1.6 (2)
None	80.3 (102)
History, % (No.)	
Hypertension	7.9 (10)
Diabetes	1.6 (2)

Clinical characteristics of all 127 patients who presented with gross hematuria after the coronavirus disease 2019 vaccination. Values for categorical variables are presented as numbers (percentages). COVID-19, coronavirus disease 2019; GH, gross hematuria; RAS-I, renin–angiotensin–aldosterone system inhibitors; TSP, tonsillectomy with steroid pulse therapy.

Table 2. Laboratory findings at gross hematuria presentation

Variable	All Participants (N=127)	Undiagnosed Patients (n=90)	Diagnosed Patients (n=37)
Age, yr (range)	39.9 (18–81)	39.9 (18–81)	39.8 (18–69)
Female sex, % (*No.*)	73.2 (93)	75.6 (68)	67.6 (25)
Time from GH to recruitment, d	28 (10–72)	34 (14–82)	18 (5–61)
BMI, kg/m^2	22.4 (19.9–24.1)	22.8 (20.2–24.4)	21.9 (19.2–23.8)
MAP, mm Hg	89.1 (83.1–94.3)	89.3 (83.3–94.8)	88.9 (82.9–94.1)
s-Cr, mg/dl	0.71 (0.61–0.89)	0.68 (0.58–0.83)	0.81 (0.66–0.99)
eGFR, ml/min per 1.73 m^2	77.0 (61.0–89.2)	82.2 (68.6–94.1)	68.2 (48.2–85.5)
UPCR, g/gCr	0.38 (0.15–1.04)	0.36 (0.15–0.96)	0.42 (0.19–1.47)
IgA, mg/dl	308.5±111.6	306.3±109.8	309.9±126.1

Laboratory findings of all 127 patients who presented with gross hematuria after the coronavirus disease 2019 vaccination. Values for categorical variables are presented as numbers (percentages); values for continuous variables are presented as medians (interquartile ranges) or means±SDs. BMI, body mass index; GH, gross hematuria; MAP, mean atrial pressure; s-Cr, serum creatinine; UPCR, urinary protein/creatinine ratio.

IgA levels, IgA/C3 ratio, and Gd-IgA1 levels were comparable between GH 0 and GH 6 (Figure 4, A–C). The serum IgA/IgG ICs levels were also unchanged at GH 0 and GH 6, whereas a slight increase was observed at GH3 (Figure 4D). Although serum Gd-IgA1 were comparable throughout the observation period, urinary Gd-IgA1 was increased at the time of GH and declined in parallel with the change in proteinuria (Figure 4E).

Discussion

In past 3 years, several cases of patients with IgAN presenting with GH after the COVID-19 mRNA vaccination have been reported.[7] However, their detailed characteristics and long-term renal outcomes have not been evaluated. To address these questions, we conducted a 6-month prospective nationwide multicenter cohort study in 127 patients presenting with GH after the COVID-19 vaccination in Japan. With respect to clinical characteristics in these patients, we found that GH was more frequently observed in female patients (73.2%) than in male patients and after the second and subsequent vaccinations (92.9%). Although several patients had increased proteinuria at the onset of GH, the exacerbation of renal function after the COVID-19 vaccination was largely transient. The medical history of our patients and the pathological findings of those who newly underwent biopsy demonstrated that the onset of GH after the COVID-19 mRNA vaccination strongly indicates the presence of IgAN. Finally, we found that the levels of biomarkers involved in the pathogenesis of IgAN did not clearly increase at the onset of GH, except for urinary Gd-IgA1. This is the first study to evaluate clinicopathological characteristics of patients with GH after the COVID-19 vaccination. In addition, our long-term prospective nationwide multicenter cohort study also revealed the renal prognosis with changes of pathological biomarkers on a large scale in a 6 months.

This study demonstrated that GH after the COVID-19 vaccination had two unique clinical characteristics. First, patients with GH were skewed toward females, comprising 73.2% of the cases; this result was consistent with our previous survey (female, 81.4%).[9] In vaccine-unrelated IgAN, the male-to-female ratios are 2:1 in North America and 1:1 in Japan and Asian countries.[24–26] Before the COVID-19 pandemic in our hospital, the male-to-female ratio was 1:1, as shown in Table 3. Given that postvaccine GH is more commonly observed in female patients than in male patients, it is plausible to hypothesize that gender bias may affect GH after the COVID-19 vaccination. In this regard, we recently reported that toll-like receptor (TLR) 7, which is located on the X chromosome,[27,28] is involved in the pathogenesis of IgAN.[29,30] TLR7 is also a key pathogenic factor in SLE, an autoimmune disease with female bias.[31] TLRs are a family of innate immune receptors whose activation is critical for triggering innate and adaptive immune responses, among which TLR7 recognizes endogenous or exogenous single-stranded RNAs.[32] TLR7 is also known to be involved in the pathogenesis of SLE.[33] Although there are several reports investigating the association of COVID-19 vaccine and SLE,[34,35] a direct causal relationship remains unclear. Albeit controversial, it was reported that mRNA vaccines might activate TLR7[28,36]; thus, it is possible that TLR7 may be involved in the mechanism of GH after the COVID-19 vaccination, leading to female bias. Second, GH appeared mostly after the second and third doses (92.9%), whereas nephrotic syndrome in patients with minimal change disease is often observed more than 1 week after the first dose.[7] Given this observation, the adaptive immune system may be involved in appearance of GH after the COVID-19 vaccination in IgAN. Previously, it has been considered that IgAN is exacerbated *via* mucosal infection; however, this study showing that GH can be observed in IgAN even after a systemically delivered vaccine that bypass the mucosal immune system suggest the possibility that trigger at mucosal surface is not always indispensable for the appearance of GH. Further investigation is needed to determine whether mucosal or systemic immune dysregulation, or both, is involved in the pathogenesis of IgAN.

To the best of our knowledge, this is the first study that investigated the change of biomarkers associated with the development of IgAN in patients with GH after the COVID-19 vaccination. We measured several serum and urine biomarkers, such as serum IgA, IgA/C3 ratio, Gd-IgA1 into IgG-ICs, and urinary Gd-IgA1. As the levels of these serum biomarkers increase at diagnosis in patients

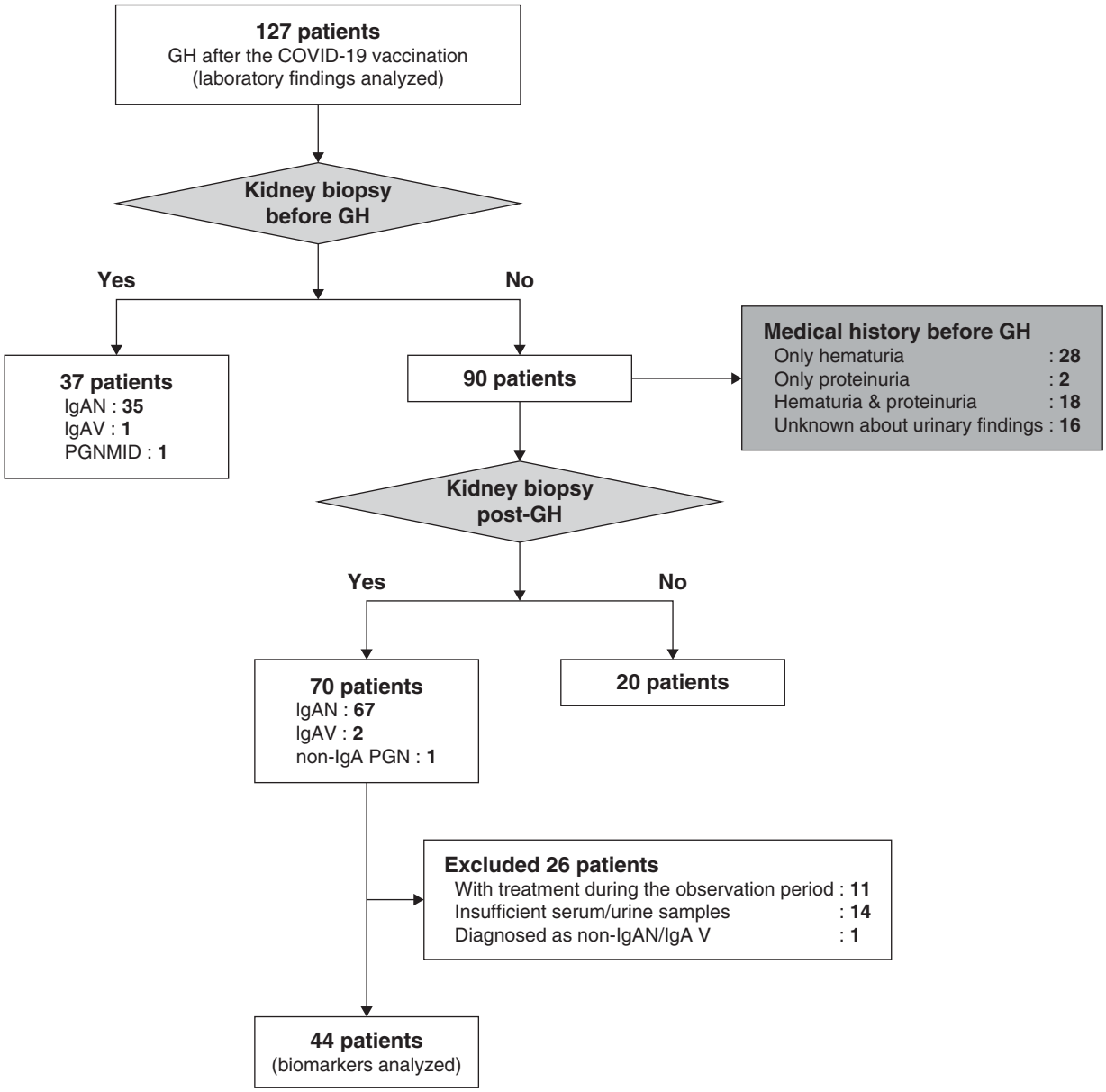

Figure 1. Diagnostic flow of patients. We followed up the patients who enrolled in this study for 6 months and investigated the renal outcomes in patients with GH. Thirty-seven patients were diagnosed with IgAN, IgAV, or PGNMID before GH. Kidney biopsies were performed in 70 of the 90 undiagnosed patients, IgAN was diagnosed in 67 patients, IgAV was diagnosed in two patients, and non-IgA PGN was diagnosed in one patient. We measured the levels of biomarkers involved in the development of IgAN and examined 44 patients who newly underwent kidney biopsy, excluding 26 patients who were treated during the observation period, whose serum and urine samples were not available and diagnosed non-IgAN/IgAV. COVID-19, coronavirus disease 2019; GH, gross hematuria; IgAN, IgA nephropathy; IgAV, IgA vasculitis; non-IgA PGN, proliferative GN with no IgA deposition; PGN, proliferative glomerulonephritis; PGNMID, proliferative GN with monoclonal IgG deposits.

with IgAN,[14,21,22] we initially hypothesized that their serum levels would be elevated at GH 0. However, contrary to our hypothesis, there were no differences in serum levels of these biomarkers at GH 0 and 6. By contrast, urinary Gd-IgA1 level increased at GH onset (Figure 4E). One possible explanation for this is that only a small fraction of specific Gd-IgA1 has strong affinity for glomeruli involved in GH induction after the COVID-19 vaccination. Moreover, the serum IgA-IgG ICs levels were slight increased at GH 3 although serum Gd-IgA1 was not, suggesting the hypothesis that specific fraction of Gd-IgA1, not all of the Gd-IgA1, was increased by vaccination (Figure 4, C and D). In this regard, we have recently revealed that the IgA type autoantibodies against mesangial surface protein, β2-spectrin, are present in serum from patients with IgAN, and these autoantibodies can selectively bind to mesangial region.[37] As IgA deposited in the kidney in IgAN is known to be Gd-IgA1,[19,20] it has been hypothesized that anti β2-spectrin IgA possesses the properties of Gd-IgA. Thus, it is possible that the levels of these types of specific

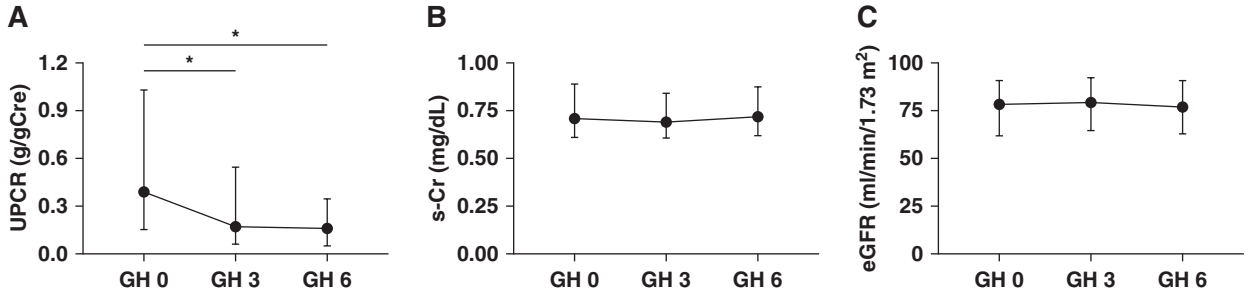

Figure 2. Changes in renal function of registered patients. Changes in renal function of 127 patients with GH after the COVID-19 vaccination (A–C). UPCR (A), s-Cr (B), and eGFR (C) at GH 0, GH 3, and GH 6, respectively. *$P < 0.05$. GH 0, the time of the first presentation to the hospital with GH; GH 3, 3 months after GH 0; GH 6, 6 months after GH 6; s-Cr, serum creatinine; UPCR, urinary protein/creatinine ratio.

Gd-IgA1 are increased by COVID-19 vaccination. However, this hypothesis requires further investigation.

We evaluated the pathological findings of GH patients who had recently been diagnosed with IgAN. In the post-vaccinated GH group, the number of patients with glomerular sclerosis was lower. Given that S lesions in IgAN are formed as a result of persistent glomerular inflammation and podocyte damage, it is possible that patients with GH in our cohort may have a relatively short history of disease onset. This hypothesis is supported by the fact that tubular atrophy/interstitial fibrosis (T lesion), a chronic region, was less frequently observed in the postvaccine GH group. By contrast, acute lesions (E and C lesions) were observed in both groups, with almost equal frequency. Therefore, it was

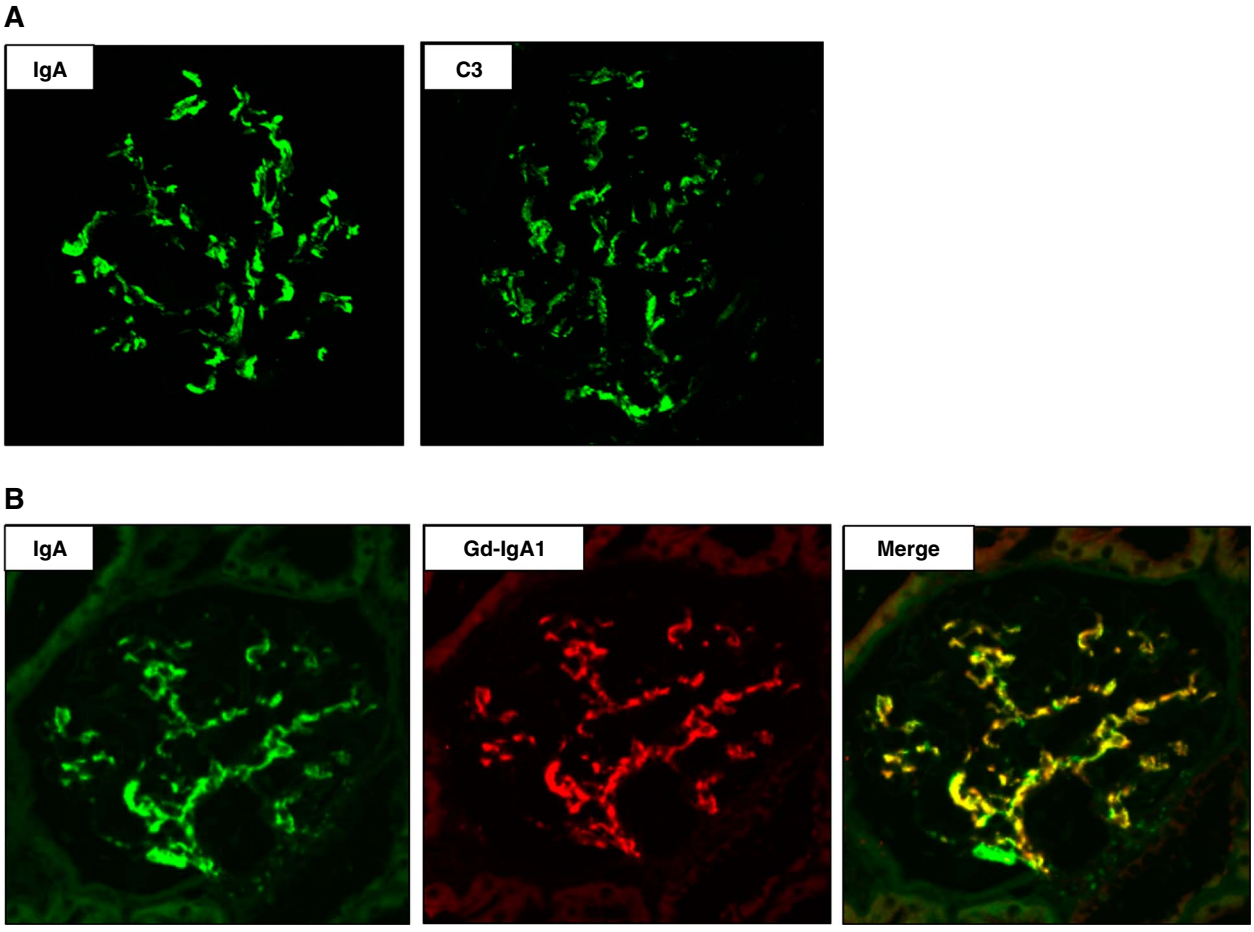

Figure 3. Glomerular IgA/Gd-IgA1 staining of undiagnosed patients with GH. Representative immunofluorescence staining of kidney biopsy samples from undiagnosed patients. Kidney sections were stained with anti-IgA (left) and C3 (right) antibodies (A) and anti-IgA (green) and anti-Gd-IgA1 mAb (KM55) (red) (B) (×400 original magnification). Gd-IgA1, galactose-deficient IgA1.

Table 3. Comparison of clinical characteristics and pathological findings (Oxford MEST-C classification) between the postvaccine gross hematuria group and nonvaccinated group

Variables	Postvaccine GH Group (n=69)	Nonvaccinated Group (n=78)	P Value
Age, yr (range)	37.9 (18–81)	38.8 (15–70)	0.554
Female sex, % (*No.*)	71.0 (49)	47.4 (37)	0.001[a]
s-Cr, mg/dl	0.68 (0.60–0.84)	0.81 (0.67–0.94)	0.109
eGFR, ml/min per 1.73 m^2	82.2 (69.5–93.7)	81.5 (64.2–96.5)	0.828
UPCR, g/gCr	0.40 (0.20–1.03)	0.69 (0.46–1.37)	0.085
IgA, mg/dl	317.1±112.2	308.0±88.9	0.587
C3, mg/dl	105.3±14.8	100.2±20.2	0.096
IgA/C3 ratio	3.07±1.10	3.16±1.01	0.363
Oxford MEST-C classification, % (No.)	(n=62)	(n=78)	
M1	12.9 (8)	24.4 (19)	0.130
E1	29.0 (18)	59.0 (46)	<0.001[a]
S1	51.6 (32)	59.0 (46)	0.384
T1+2	6.5 (4)	33.3 (26)	<0.001[a]
C1+2	46.8 (29)	32.1 (25)	0.075

Comparison of clinical characteristics, laboratory findings, and Oxford MEST-C classification between the postvaccine gross hematuria group and nonvaccinated group. The postvaccine gross hematuria groups comprised 69 patients diagnosed with IgA nephropathy/IgA vasculitis and with gross hematuria after the coronavirus disease 2019 vaccination, and the nonvaccinated group comprised 78 patients diagnosed with IgA nephropathy without gross hematuria after the coronavirus disease 2019 vaccination, at Juntendo University Hospital between May 11, 2018, and October 31, 2019. For the Oxford MEST-C classification in the postvaccine gross hematuria group, 62 patients with available results were analyzed. Categorical variables are presented as numbers (percentages); values for continuous variables are presented as medians (interquartile ranges) or means±SDs. GH, gross hematuria; s-Cr, serum creatinine; UPCR, urinary protein/creatinine ratio.
[a]P<0.05.

Table 4. Clinical characteristics at presentation of patients who newly underwent kidney biopsy without treatment

Variables	All Participants (n=44)
Age, yr (range)	39.0 (19–61)
Female sex, % (*No.*)	75.0 (33)
Type of COVID-19 vaccine, % (No.)	
Pfizer BNT162b2	61.4 (27)
Moderna mRNA-1273	38.6 (17)
Time from GH to recruitment, d, % (No.)	28 (14–72)
BMI, kg/m^2	22.3 (18.1–33.8)
MAP, mm Hg	90.3 (69.0–110.9)
s-Cr, mg/dl	0.67 (0.62–0.80)
eGFR, ml/min per 1.73 m^2	82.0 (71.9–88.7)
BUN, mg/dl	13.1±4.6
UPCR, g/gCr	0.37 (0.18–0.82)
U-RBC, /HPF, % (No.)	
<4	4.5 (2)
5–9	4.5 (2)
10–19	13.6 (6)
30–49	20.5 (9)
>50	56.8 (25)
IgA, mg/dl	325.5±97.8
C3, mg/dl	104.4±15.8
IgA/C3 ratio	3.14±0.94

Laboratory findings of the patients who newly underwent kidney biopsy for 6 months and examined 44 patients, excluding 26 cases who were treated during the observation period, whose serum and urine samples were not available and diagnosed non-IgA nephropathy/IgA vasculitis. Values for categorical variables are presented as numbers (percentages); values for continuous variables are presented as medians (interquartile ranges) or means±SDs. BMI, body mass index; COVID-19, coronavirus disease 2019; GH, gross hematuria; HPF, high-power field; MAP, mean atrial pressure; s-Cr, serum creatinine; UPCR, urinary protein/creatinine ratio; U-RBC, urinary red blood cells.

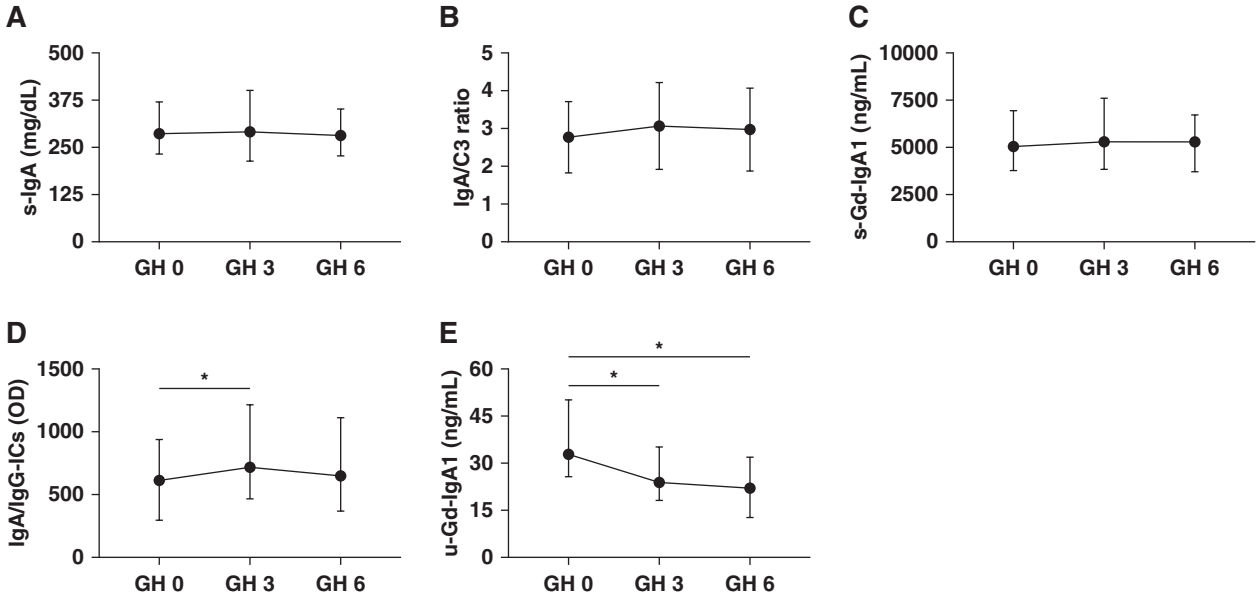

Figure 4. Changes in biomarkers in patients with newly diagnosed IgAN. Changes in the serum and urinary biomarker levels of 44 patients who newly underwent kidney biopsy and were not treated during the study or whose were serum and urine samples were available, at GH 0, GH 3, and GH 6 are shown. (A) IgA levels. (B) Serum Gd-IgA1 levels. (C) Serum IgA/C3 ratio. (D) Serum IgA/IgG-IC levels. (E) Urinary Gd-IgA1 levels. IgA/IgG-IC, s-Gd-IgA1, and u-Gd-IgA1 levels were measured in 44 stored samples. *$P<0.05$. ICs, immune complexes; s-Gd-IgA1, serum galactose-deficient IgA1; u-Gd-IgA1, urinary galactose-deficient IgA1.

thought that the pathogenesis of GH was not closely associated with E or C lesions. The Kidney Disease Improving Global Outcomes guidelines have suggested that patients with IgAN with frequent acute lesions should be typically treated with immunosuppressive therapy.[38,39] However, most of the patients with GH after the COVID-19 vaccination in our cohort, with or without acute lesions, showed clinical improvement without such immunosuppressive treatment. These data suggest that the presentation of GH after the COVID-19 vaccination does not mean that immunosuppressive therapy is urgently needed. Therefore, the treatment should be determined according to the clinical course other than GH.

Another point of interest is that chronic glomerular inflammation, such as expansion of mesangial matrix and glomerular sclerosis, was observed in the patients with newly diagnosed IgAN in the present cohort, suggesting that nephritis may have existed before appearance of GH after the vaccination. Furthermore, 71.1% of our undiagnosed patients had a history of abnormal urinary findings before the vaccination (Figure 1). Therefore, present findings suggested that COVID-19 mRNA vaccination may be mainly involved in the transient exacerbation of the symptoms of preexisting or subclinical, but not lead to the development of *de novo* IgAN. Furthermore, the acute manifestation of postvaccine GH may have highlighted the high prevalence of undiagnosed or preclinical IgAN at least in Japan.

Our study has some limitations. First, all patients included in this study were Japanese. Thus, generalization of our results to patients from other racial backgrounds and/or countries is difficult. Previously, the IgAN working group of the Research Group on Advanced Renal Disease, Ministry of Health, Labor and Welfare, and the JSN jointly reported the study, which was analyzed based on a questionnaire survey conducted on all JSN council members.[9] This study is a prospective study conducted by the same members following the previous study. Therefore, our study was widely known to JSN members, and furthermore, hospitals that are the core of IgAN treatment throughout Japan served as contact points and participated in the study, thus reflecting well the situation in Japan regarding the postvaccine GH. However, we believe that further validation is needed in the future. Second, most COVID-19 vaccines administered in Japan are mRNA vaccines during this observation, and other types of vaccines are less commonly administered. Therefore, it is possible that the GH cases in our cohort were biased toward mRNA only, and further verification is required to determine whether GH also occurs with other types of vaccines or only with mRNA-based vaccines. Third, most cases in this study showed no sustained worsening in renal function. However, we should carefully consider the fact that the postvaccine GH patients studied in this study did not include cases of severe disease or renal failure. We believe that further analysis is needed in this regard. Finally, because this prospective cohort study is a case series without a control group, the causal relationship between vaccination and GH is unclear. Moreover, we cannot prove with certainty that the vaccine resulted in development of *de novo* onset or relapse of the IgAN.

In conclusion, our prospective, multicenter observational cohort study reveals that GH after the vaccination is more likely to occur in patients with IgAN/IgAV and with a female bias. Moreover, among the biomarkers measured, only urinary Gd-IgA1 level significantly increased at the time of GH, suggesting that specific Gd-IgA1, not all, are

carried to the glomerulus and thus may be involved in GH appearance. However, further studies are required on causal relationship between vaccination and GH, the molecular mechanisms of disease, and gender bias.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/KN9/A559.

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Data Sharing Statement

All data are included in the manuscript and/or supporting information.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/A558.

Supplemental Figure 1. Glomerular deposition of galactose-deficient IgA1 (KM55) and IgA in the study.

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