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ORIGINAL ARTICLE

Relapse rate in children with nephrotic syndrome during the SARS-CoV-2 pandemic

Benedetta Chiodini[1] · Anita Sofia Bellotti[2] · William Morello[2] · Chiara Bulgaro[2] · Ilaria Farella[3] · Mario Giordano[3] · Giovanni Montini[2] · Khalid Ismaili[1] · Karl Martin Wissing[4]

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Abstract

Background Viral upper respiratory tract infections trigger nephrotic syndrome relapses. Few data exist on the impact of the SARS-CoV-2 pandemic on the risk of relapse in children with idiopathic nephrotic syndrome (INS).

Methods In a Belgian and Italian cohort of children with INS, we performed a retrospective analysis on the number and duration of relapses observed in 3 different periods in 2020: first COVID period, February 15–May 31; second COVID period, June 1–September 14; third COVID period, September 15–December 31. Relapse rates were compared to those of the previous 5 years (PRECOVID period). For the years 2019 and 2020, all causes and INS relapse-related hospitalizations were recorded. Hospitalizations and deaths due to SARS-CoV-2 infection were also recorded. In the Belgian cohort, SARS-CoV-2 serologies were performed.

Results A total of 218 patients were enrolled, and 29 (13.3%) were diagnosed with new-onset INS during the COVID period. Relapse rates per 1000 person-days were as follows: 3.2 in the PRECOVID period, 2.7 in the first COVID period, 3.3 in the second COVID period, and 3.0 in the third COVID period. The incidence rate ratio for the total COVID period was 0.9 (95%CI 0.76 to 1.06; $P=0.21$) as compared to the PRECOVID period. During 2020, both the proportion of patients hospitalized for recurrence (14.2% vs. 7.6% in 2019; $P=0.03$) and the rate of hospitalization for recurrence (IRR 1.97 (95%CI 1.35 to 2.88); $P=0.013$) were higher compared to 2019. In December 2020, anti-SARS-CoV-2 antibodies were detected in 31% of the Belgian cohort. Patients with positive and negative SARS-CoV-2 serology did not differ significantly in relapse rate (2.4 versus 4.2 per 1000 person-days). The number of new INS cases remained similar between 2020, 2019, and 2018.

Conclusion The first year of the SARS-CoV-2 pandemic did not significantly affect the relapse rate in children with INS. No serious infections were reported in this population of immunosuppressed patients.

Keywords Idiopathic nephrotic syndrome · Children · SARS-CoV-2 infection · COVID-19 · Relapse

Introduction

Idiopathic nephrotic syndrome (INS) is the most common glomerular disease in childhood [1]. Its pathogenesis remains unclear despite strong evidence suggesting a role for immune dysregulation [2]. Although most children respond to steroids, relapses occur in 60–90% of patients [2, 3]. Viral upper respiratory tract infections are the most frequent trigger [4, 5]; however, not all relapses can be correlated to an infection. Other associated risk factors are seasonal changes with a spring peak [6] and mental stress [4, 6].

The SARS-CoV-2 pandemic started at the end of 2019 in China and reached Europe in February 2020 [7]. In the following months, infection rates varied with seasonal changes and in response to local restrictive measures [7].

Benedetta Chiodini, and Anita Sofia Bellotti contributed equally to this work, as well as Khalid Ismaili and Karl Martin Wissing.

✉ Benedetta Chiodini
benedetta.chiodini@huderf.be

[1] Department of Pediatric Nephrology, Hôpital Universitaire Des Enfants Reine Fabiola, Université Libre de Bruxelles, Brussels, Belgium

[2] Pediatric Nephrology, Dialysis and Transplant Unit, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico Di Milano, via Commenda 9, 20122 Milan, Italy

[3] Pediatric Nephrology and Dialysis Unit, Pediatric Hospital "Giovanni XXIII", 70123 Bari, Italy

[4] Department of Nephrology, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel, Brussels, Belgium

In 2020, children and adolescents accounted for only 2–8% of the total confirmed cases [8, 9]. The course of COVID-19 in children is usually milder as compared to adults [8, 10, 11]. Nevertheless, serious complications, such as COVID-19-associated multisystem inflammatory condition (MIS-C), have been documented in a minority of cases [9].

While it would be reasonable to presume that children and adolescents with INS should be at higher risk of SARS-CoV-2 infection due to their immunocompromised status, current data suggest that the incidence in immunosuppressed children is similar to that of the general pediatric population and the prognosis is usually favorable [12–, 13–17]. Relapses have been documented in children with INS during SARS-CoV-2 infection [18, 19]. However, the only available study reported no increase in relapse rates during the first months of the pandemic [20].

In the present study, we aimed to investigate the incidence of relapses in a European cohort of children with INS during the first year of the SARS-CoV-2 pandemic.

Methods

We performed a retrospective analysis of relapse rates in children with INS during the COVID-19 pandemic as compared to the previous 5 years. We reviewed all available digital and nondigital records and collected data from all children aged up to 18 years with a diagnosis of INS followed at Hôpital Universitaire des Enfants Reine Fabiola (HUDERF) in Brussels, Belgium; at Cà Granda, Ospedale Maggiore Policlinico in Milan, Italy; and at Pediatric Hospital Giovanni XXIII in Bari, Italy. INS was defined as a nephrotic range proteinuria that has a urinary protein:creatinine ratio (uPr/uCr) > 2 g/g associated with hypoalbuminemia (serum albumin < 25 g/l) and edema [21, 22]. All patients were treated according to the most recent international guidelines [22, 23]. Biopsies were not routinely performed in steroid-sensitive patients [23]. Genetic and steroid-resistant forms of NS were not included. Steroid resistance was defined as a lack of response to 6 weeks of oral steroid treatment followed by 3 high-dose boluses of intravenous steroid and by another 2 weeks of oral steroid [21, 23]. The study flow diagram is represented in Fig. 1.

We compared the number and duration of relapses observed in 3 different time intervals during the pandemic with the previous 5 years (the PRECOVID period). The 3 different COVID periods were defined as follows: the first COVID period from February 15 to May 31, 2020, the second COVID period from June 1 to September 14, 2020, and the third COVID period from September 15 to December 31, 2020 (Fig. 2). The first and especially the third COVID periods correspond to times of greater diffusion of the infection in Europe, while the second COVID period had a much lower infection rate [7] (Fig. 3). For patients diagnosed with INS before January 1, 2015, the PRECOVID period was considered as the period from January 1, 2015, to February 14, 2020. For those diagnosed afterwards, the PRECOVID period was considered as the period from the day of first remission to February 14, 2020.

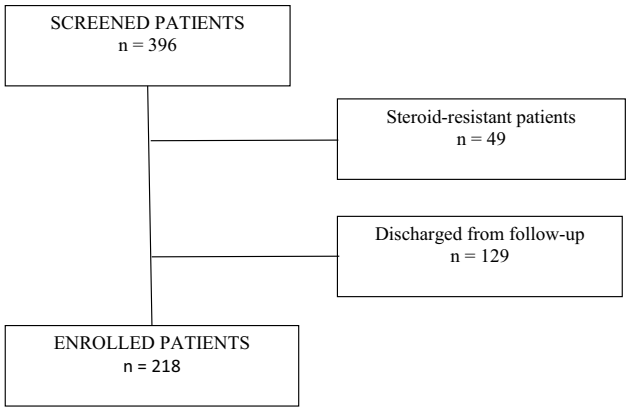

Fig. 1 Study flow diagram

A total of 30 children were diagnosed with new-onset INS in the three participating centers during the year 2020. Twenty-nine of them had their first remission after the start of the first COVID period (Fig. 2). These children were considered at risk of relapse from the date of remission of the initial episode of nephrotic syndrome.

The following data were collected: gender, date of birth, date of diagnosis, date of first remission, start date, and end date of each relapse from January 1, 2015, until December 31, 2020.

Relapse was defined as 3 + proteinuria on urinary dipstick for 3 consecutive days or uPr/uCr > 2 g/g. Remission was defined as uPr/uCr < 0.2 g/g or negative urinary dipstick; if the exact date of remission was not recorded, a standard 7-day duration was attributed to the relapse.

Treatment regimens were recorded for each patient during each of the COVID periods and classified as "no treatment," "oral treatment," "anti-CD20 treatment," or "oral + anti-CD20 treatment." Patients receiving only oral steroids for less than 50% of each time interval were classified as "no treatment."

For the years 2019 and 2020, hospitalizations for all causes and INS relapse-related hospitalizations were recorded.

Hospitalizations and deaths due to SARS-CoV-2 infection were also recorded. In the Belgian cohort, a SARS-CoV-2 serology test was performed using the ELISA SARS-COV-2 Euroimmun IgG kit in all patients during or at the end of the third COVID period.

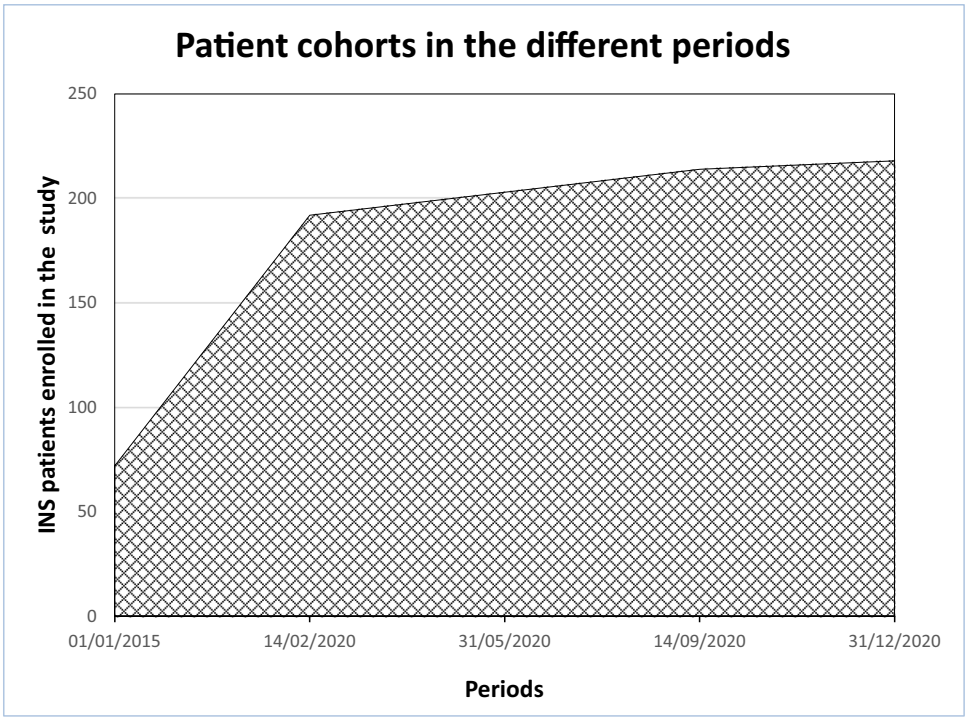

Fig. 2 For patients diagnosed with INS before January 1, 2015, the PRECOVID period was considered as the entire period from January 1, 2015, to December 14, 2020. For patients diagnosed with INS after January 1, 2015, the PRE-COVID period was considered as the period from the first day of their first remission to December 14, 2020

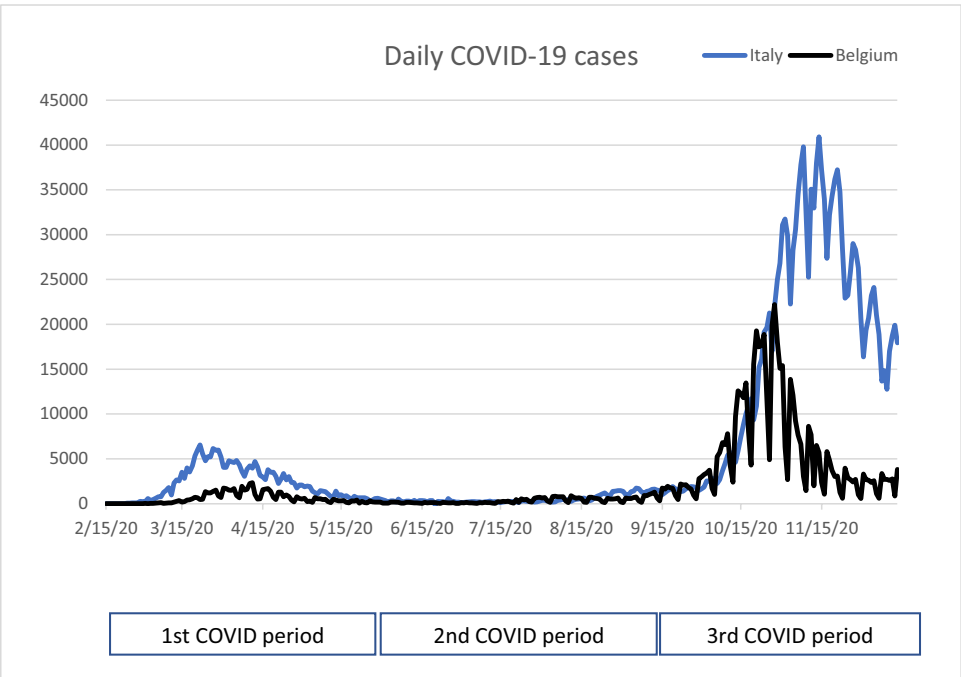

Fig. 3 Daily COVID-19 cases in Italy and Belgium during the first COVID period (from February 15 to May 31, 2020), the second COVID period (from June 1 to September 14, 2020), and third COVID period (from September 15 to December 31, 2020)

The study was approved by the local ethics committee (protocol reference number: P2020/360/B4062020000103), and informed consent was obtained from parents or legal guardians.

Data collection was limited to essential information needed to perform the analysis. The data file of the combined cohort used for analysis was kept on password-protected computers.

Statistical analysis

The primary endpoint was the incidence rate of proteinuria relapse per 1000 days at risk. For each patient, the total number of relapses during the 4 periods was calculated, as well as the duration of each episode. Time at risk was considered as the total time in which the patient did not have proteinuria during each period.

Table 1 Characteristics of the patients included and their treatment in the three COVID periods

	All patients	Group BXL	Group MI	Group BA	P^1
Patients (*N*, %)	218 (100%)	43 (19.7%)	140 (64.2%)	35 (16.1%)	
Age at diagnosis in years, median (IQ)	3.36 (2.4–5.4)	2.9 (2.3–4.1)	3.37 (2.3–5.5)	4.4 (2.7–6.5)	0.1[2]
Gender					0.58
Males (*N*, %)	140 (64.2%)	26 (60.5%)	89 (63.6%)	25 (71.4%)	
Females (*N*, %)	78 (35.8%)	17 (39.5%)	51 (36.4%)	10 (28.6%)	
Treatment during COVID period 1 (*N*, %)					< 0.001
NO	53 (24.3%)	3 (7%)	48 (34.2%)	2 (5.7%)	
Oral	132 (60.5%)	36 (83.7%)	82 (58.6%)	14 (40%)	
Anti-CD 20 (rituximab)	15 (6.9%)	1 (2.3%)	1 (0.7%)	13 (37.4%)	
Oral and anti-CD 20	2 (0.9%)	2 (4.7%)	0 (0%)	0 (0%)	
NA	16 (7.3%)	1 (2.3%)	9 (6.4%)	6 (17.14%)	
Treatment during COVID period 2 (*N*, %)					< 0.001
NO	55 (25.2%)	5 (11.6%)	47 (33.6%)	3 (8.6%)	
Oral	139 (63.8%)	35 (81.4%)	86 (61.4%)	18 (51.4%)	
Anti-CD 20 (rituximab)	16 (7.3%)	0 (0%)	2 (1.4%)	14 (40%)	
Oral and anti-CD 20	2 (0.9%)	2 (4.7%)	0 (0%)	0 (0%)	
NA	6 (2.8%)	1 (2.3%)	5 (3.6%)	0 (0%)	
Treatment during COVID period 3 (N, %)					< 0.001
NO	60 (27.5%)	5 (11.6%)	50 (35.7%)	5 (14.3%)	
Oral	139 (63.8%)	33 (76.7%)	89 (63.6%)	17 (48.6%)	
Anti-CD 20 (rituximab)	13 (6.0%)	0 (0%)	0 (0%)	13 (37.1%)	
Oral and anti-CD 20	5 (2.3%)	5 (11.6%)	0 (0%)	0 (0%)	
NA	1 (0.5%)	0 (0%)	1 (0.7%)	0 (0%)	

Oral, steroids, and/or calcineurin inhibitors and/or mycophenolic acid; anti CD-20, humanized monoclonal antibody against CD-20 (rituximab); NA, information not available

[1] *P* value for null hypothesis of no difference between the three centers

[2] Tested by one-way ANOVA for age at diagnosis. All other hypothesis tests done with Fisher's exact test

Incidence rates of relapse during the different periods were calculated by dividing the number of events by time at risk and by using Poisson regression. Incidence rates of relapse during the different periods were compared using random intercept Poisson regression modelling with patient ID as cluster variable. Incidence rate ratios with the PRECOVID periods as reference were calculated using the STATA mepoisson command. *P* values < 0.05 were considered statistically significant.

The effect of covariates on the risk of proteinuria relapses during the total COVID period was investigated by adding the following variables to a standard Poisson regression model: center, age at diagnosis, gender, symptoms compatible with SARS-CoV-2 infection (during the three COVID periods), and positive SARS-CoV-2 serology (limited to the Belgian cohort).

The impact of the COVID epidemic on total hospitalizations and hospitalizations for proteinuria relapse was investigated for the years 2019 (PRECOVID) and 2020 (COVID). The number of patients with at least one hospitalization was compared for these 2 years by standard McNemar's hypothesis testing using the STATA mcc command. Difference in incidence rates was compared by random intercept Poisson regression modelling with patient id as cluster variable using the STATA mepoisson command. All statistical analysis was conducted using STATA 15.0 (College Station, TX, 77,845, USA, www.stata.com).

Results

Cohort

Two hundred eighteen patients were enrolled in the study: 43 (19.7%) from Brussels, 140 (64.2%) from Milan, and 35 (16.1%) from Bari.

The entire cohort was composed of 78 (35.8%) girls and 140 (64.2%) boys, and the sex ratio girls:boys was consistent across the three centers (Table 1). Twenty-nine patients (13.3%) had their first remission and became at risk of recurrence during the COVID periods, between February 15 and December 31, 2020.

Table 2 Incidence rate of proteinuria relapse per 1000 days at risk during the PRECOVID period and in the three COVID periods

Period	Number of patients	Period at risk for proteinuria; (median IQR)	Total days at risk	Number of relapses	Duration of relapse in days; (median IQR)	Incidence rate of relapses (/1000 pd (95% CI))	IRR (95% CI)[1]	*P*
PRECOVID period	189	1318 (549–1777)	216,069	695	11.3 (7.3–16)	3.2 (3 to 3.5)	Ref	
1st COVID period	203	106 (102–106)	19,995	53	9.5 (6–15)	2.7 (2 to 3.5)	0.79 (0.60 to 1.05)	0.11
2nd COVID period	212	105 (98.5–105)	21,198	70	8 (6.5–12)	3.3 (2.6 to 4.1)	0.98 (0.76 to 1.26)	0.88
3rd COVID period	218	107 (101–107)	22,330	68	8.8 (6.5–12)	3.0 (2.4 to 3.9)	0.90 (0.70 to 1.16)	0.42
COVID period (total)	218	312.5 (298–318)	63,037	191	9 (7–14)	3.0 (2.6 to 3.5)	0.90 (0.76 to 1.06)	0.21

Incidence rate ratio calculated with random-intercept Poisson regression with patient id as cluster variable with the corresponding *P* value for the null hypothesis of no difference in incidence rates between the PRECOVID period (reference), the three COVID periods, and the total COVID period

The median age at INS diagnosis was 3.36 years (IQR 2.4–5.4) (Table 1). Although some differences exist in terms of immunosuppressive treatment between the 3 centers, this remained consistent in the 3 COVID periods (Table 1).

Relapses

The number of relapses and the corresponding incidence rates that occurred during each period are summarized in Table 2.

In the PRECOVID period, during the 216,069 days at risk for the 189 INS patients, 695 episodes of proteinuria relapse were recorded with an incidence rate of relapse of 3.2 per 1000 person-days. A median of 3 relapses (IQR 1–6) was observed (minimum 0–maximum 16 relapses), with a median duration of each proteinuria episode 11.3 days.

During the first COVID period (from February 15 to May 31, 2020), 53 episodes of proteinuria relapse were recorded in 203 INS patients with an incidence rate of 2.7 per 1000 person-days. The median duration of each proteinuria episode was 9.5 days (IQR 6–15).

During the second COVID period (from June 1 to September 14, 2020), 70 episodes of proteinuria relapse were recorded in 212 INS patients with an incidence rate of 3.3 per 1000 person-days. The median duration of each proteinuria episode was 8 days (IQR 6.5–12).

In the third COVID period (from September 15 to December 31, 2020), 68 episodes of proteinuria relapse were observed in 218 INS patients with an incidence rate of 3.0 per 1000 person-days. The median duration of each proteinuria episode was 8.8 days (IQR 6.5–12).

In the entire COVID period (from February 15 to December 31, 2020), 191 episodes of proteinuria relapse were observed in 218 patients with an incidence rate of 3.0 per 1000 person-days, with a median duration of each relapse 9 days (IQR 7–14).

The incidence rates of proteinuria relapse tended on average to be lower by approximately 10% during the three COVID periods. This did not attain statistical significance as compared to the PRECOVID periods, neither for the individual COVID periods nor for the total COVID period (IRR 0.90 (95% CI 0.76 to 1.06); $P=0.21$) (Table 2).

Of the 43 children in the Belgian cohort, 42 (98%) were tested for anti-SARS-CoV-2 antibodies during or at the end of the third wave, and 13 (31%) presented a positive result. Children who presented a positive SARS-CoV-2 serology had a relapse rate of 2.4 (95% CI 1.3 to 4.6) per 1000 person-days, whereas children with a negative SARS-CoV-2 serology had a relapse rate of 4.2 (95% CI 3.1 to 5.8) per 1000 person-days. The risk ratio associated with a positive serology was 0.57 (95%CI 0.27 to 1.18; $P=0.13$).

Overall hospitalizations, SARS-CoV-2-related hospitalizations, and deaths

In order to investigate the impact of the COVID pandemic on hospitalizations, data on the overall numbers of hospitalizations and hospitalizations for recurrence of proteinuria relapse were collected for the years 2019 and 2020 (Table 3). Although the number of patients hospitalized did not differ significantly between 2019 (19.1%) and 2020 (24.1%), the rate of hospitalization for all causes tended to be higher in 2020 (0.33/py vs. 0.22/py; IRR 1.44 (95%CI 0.99 to 2.08); $P=0.054$). The number of patients hospitalized for recurrence was significantly higher in 2020 (14.2% vs. 7.6% in 2019; $P=0.03$) with also a marked increase in the incidence rate of hospitalization (IRR 1.97 (95%CI 1.35 to 2.88); $P=0.013$) (Table 3). None of the hospitalizations in 2020 were attributed to SARS-CoV2 infection and none of

Table 3 Number of patients with hospitalization and number of hospitalization episodes during 2019 and 2020

	Year	*N* patients (%)[1]	*P*[2]	*N* hospital (IR/py)[3]	IRR (95%CI)[4]	*P*[4]
Total hospitalizations	2019	40/210 (19.1%)		47/210 0.22 (0.17 to 0.30)	Ref	
	2020	53/218 (24.1%)	0.45	71/218 0.33 (0.26 to 0.41)	1.44 (0.99 to 2.08)	0.054
Hospitalizations for recurrence	2019	16/210 (7.6%)		20/210 0.10 (0.06 to 0.14)	Ref	
	2020	31/218 (14.2%)	0.03	41/218 0.18 (0.14 to 0.26)	1.97 (1.35 to 2.88)	0.013

[1]Number of patients with at least one hospitalization during the year

[2]*P* value of McNemar's test for paired categorical data

[3]Number of hospitalization episodes during the year of follow-up. The incidence rate (IR) is expressed per year follow-up

[4]Incidence rate ratio calculated with random-coefficient Poisson regression with patient id as cluster variable with the corresponding *P* value for the null hypothesis of no difference in incidence rates between the year 2019 and 2020

the patients followed in the cohort died during the COVID period.

Incidence of new INS cases

We investigated the effect of the COVID-19 pandemic on the occurrence of new cases. The number of patients newly diagnosed with INS in the three participating centers remained stable over time and was 30 in 2020, 28 in 2019, and 29 in 2018.

Discussion

Although growing evidence shows that children, even if immunosuppressed [12, 15] are at lower risk of severe COVID-19 infection compared to the adult population [8], data on the impact of the pandemic on the relapse rate in children affected with INS remain scarce.

Our multicentric retrospective study shows that, during the first year of the SARS-COV-2 pandemic, the incidence of relapses was not statistically different when compared to the previous 5 years. These results are in line with the data presented by Harambat et al. [20], who did not find any increase in the relapse rate during the first COVID-19 wave in a cohort of 111 INS children, when compared to the same period of the previous year [20]. Furthermore, Crane et al. reported a statistically significant lower relapse rate during the pandemic as compared to the previous 5 years, speculating that this difference could be related to the decreased rates of viral infections [24].

Our findings corroborate the fact that, although SARS-CoV-2 is a potential trigger for relapses [4, 5, 20], restrictive measures and the consequent decline of upper viral respiratory infections may have counterbalanced the effect of the pandemic on the risk of relapse [25]. Indeed, in Italy and Belgium a nationwide lockdown was imposed between March and May 2020 and severe restrictions such as curfew and the closure of public services like malls and parks were restored in November. All schools remained closed until September 2020 and in December 2020 high schools either closed again or started a rotation system of in situ/distance learning. Mental stress related to prolonged isolation does not appear to have caused an increase in relapse rates.

Moreover, in our cohort, the risk of relapse did not increase even in children with a previous documented SARS-CoV-2 infection, as shown in a small subset of patients who tested positive for SARS-CoV-2 antibodies. To the best of our knowledge, no other studies have investigated the risk of relapse in SARS-CoV-2-infected INS patients. However, the limited number of subjects included in this sub-analysis is not sufficient to draw any firm conclusions. A larger study would be required to assess whether SARS-CoV-2 infection is associated with a higher relapse rate in INS patients.

In addition, we were able to show that the incidence of new INS cases remained stable over a 3-year period (from 2018 to 2020), with no modifications during the pandemic. No other groups have up to now addressed this issue.

In our cohort, the number of patients hospitalized for INS recurrence was significantly higher in 2020 compared to the previous year. This is most likely the consequence of the restrictive measures applied by the Belgian and Italian governments at the height of the pandemic. These restrictions made it very difficult for patients to visit outpatient clinics. Consequently, clinicians probably had a greater tendency to admit relapsing patients.

No deaths and/or COVID-related hospitalizations have been reported in our entire cohort, and none of the 13 patients with a previous SARS-CoV-2 infection documented by serology experienced serious symptoms or complications. This is in line with the conclusions of a nationwide study performed by the Italian Society of Paediatric Nephrology during the first wave. Among 1572 children with immunosuppression or chronic kidney disease (CKD), of which 41% were affected by INS, none experienced severe COVID-19 [15]. Moreover, this is in accordance with the results of a recent systematic review of the literature, which highlighted a benign course in all published cases of SARS-COV-2

infections in children with INS from Western countries and a good response to steroids in cases of relapse [26]. Conversely, relapse was identified as a predictor of worse outcomes in a study performed in 4 pediatric nephrology centers in New Delhi [27].

Our study has several limitations. We were unable to test patients for SARS-CoV-2 infection at each relapse due to the scarcity of diagnostic tests during the first months of the pandemic; therefore, we could not precisely quantify the number of covid-related relapses. Moreover, data collection ended on December 31, 2020, and did not include the following waves of the pandemic, in which the pediatric population was more extensively involved.

Strengths of the present study are a thorough review of relapse rates recording the duration of each period of relapse in a large cohort of children. This allowed us to generate reliable data on time at risk for relapse, relapse rates, and the median duration of proteinuria relapses.

In conclusion, our data are globally encouraging: the first year of the SARS-CoV-2 pandemic did not significantly affect the relapse rate in children with INS and no serious infections were reported in this particularly fragile population of immunosuppressed patients. Moreover, the stability of the relapse rate throughout the first year of the pandemic should encourage doctors and families to avoid unnecessary restrictions for affected children and to allow their return to a normal social life.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00467-022-05702-2.

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