Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Risk for uveitis relapse after COVID-19 vaccination

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ABSTRACT

Objectives: Several studies suggested that coronavirus disease 2019 (COVID-19) vaccination may lead to uveitis, a vision-threatening condition often associated with a variety of autoimmune or autoinflammatory diseases. This study aims to explore factors that influence the risk of uveitis relapse after COVID-19 vaccination to guide the prevention of disease.

Methods: Uveitis relapse was evidenced by worsening activity of intraocular inflammation (e.g. anterior chamber cells, vitreous haze) as defined by the Standardization of Uveitis Nomenclature Working Group. Time to uveitis relapse since the administration of each dose of COVID-19 vaccine was compared across participants with modifiable variables.

Results: The primary analysis included 438 non-COVID-19 participants with 857 doses of COVID-19 vaccine administered in total. The median age was 41 years (interquartile range, 30 to 51), and 57.3% were female. A total of 39 episodes of uveitis relapse events occurred in 34 patients after the receipt of a dose of COVID-19 vaccine within 30 days. The median time to relapse after vaccination was 5 days (interquartile range, 1 to 14). Concomitant use of systemic glucocorticoids at the time of vaccination was independently associated with a decrease in risk of relapse after vaccination (HR, 0.23 [95% CI, 0.07–0.74]; P value = 0.014). There was a trend in attenuating the risk of relapse with increasing prednisone dose from none to less than 20 mg per day and then to 20 mg per day or greater (P value for trend = 0.029).

Conclusions: Concomitant treatment with systemic glucocorticoids for uveitis at the time of COVID-19 vaccination was associated with a dose-dependent lower risk of uveitis relapse after vaccination.

1. Introduction

Vaccines and boosters remain the best way to protect against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as well as its variants, the virus that causes coronavirus disease 2019 (COVID-19). While no major safety warnings were reported in initial clinical trials [1–4], the safety profile of COVID-19 vaccines was not fully defined because only healthy or medically stable adults were involved in earlier trials and the follow-up was limited. Emerging safety signals are increasingly being noted as additional people are vaccinated, especially in certain clinically vulnerable populations.

Results of several case reports, case series or cohorts described the newly active or worsening uveitis after inoculation with various COVID-19 vaccines worldwide [5–11]. Uveitis is a vision-threatening inflammatory condition, often associated with a variety of autoimmune or autoinflammatory diseases, such as ankylosing spondylitis, juvenile idiopathic arthritis, Behçet's disease, inflammatory bowel disease, psoriasis, systemic lupus erythematosus and sarcoidosis [12]. Although the causal link has not yet been confirmed, certain findings were consistent across these reports suggesting the close temporal association between COVID-19 vaccination and uveitis flares [8–10,13]. Nevertheless, uveitis flares following COVID-19 vaccination appear to be an unusual event, which was estimated to occur merely in 0.9 cases per million doses or less varied by vaccine types [13]. The recurrence of uveitis is therefore likely to depend on multiple factors but not solely on vaccination itself. Whether certain populations can be identified as the most at-risk persons to guide the prevention of uveitis flares remains an urgent question. Here, we report this observational study to characterize the risk factors of uveitis relapse after COVID-19 vaccination among patients with a history of uveitis.

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2. Methods

2.1. Study design and population

We conducted surveillance for uveitis flares occurring after COVID-19 vaccination at the First Affiliated Hospital of Chongqing Medical University, Chongqing, China between June 2021 and April 2022. This academic, university-affiliated hospital has established a specialized uveitis care center that managed 15,373 uveitis patient encounters as of 2018 and could be qualified to carry out the sentinel surveillance [14]. We performed a retrospective analysis of historical clinical factors of patients to identify if some exposures were associated with the risk of uveitis flares after COVID-19 vaccination. Ethical approval for the study was obtained and written informed consent was waived by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. The rationale was that the study did not impact routine clinical care and that the study and data analysis were retrospective in nature with all protected health information de-identified. Thus, this study involved no more than minimal risk and the waiver would not adversely affect the rights or welfare of the participants. The study procedures were complied with the provisions of the Declaration of Helsinki. The funding agency had no role in study design, data collection, data analysis, data interpretation or writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

All patients who had a history of any forms of uveitis according to international criteria [15,16] and received at least one dose of COVID-19 vaccine were eligible to be enrolled as study participants. To preclude the effect of SARS-CoV-2 infection on uveitis, confirmed COVID-19 cases by the real-time reverse transcription polymerase chain reaction tests on nasopharyngeal and nasal swabs were not included in the study. During the study period, two inactivated SARS-CoV-2 vaccines, CoronaVac (Sinovac) and BBIBP-CorV (Sinopharm), an adenovirus vectored vaccine, Ad5-nCoV (CanSino), and a protein subunit vaccine, ZF2001 (Zhifei), were available for adults and children (aged 3 years or older) under emergency use authorization in China [1–4]. Both CoronaVac (Sinovac) and BBIBP-CorV (Sinopharm) are the inactivated whole-virion vaccine prepared with SARS-CoV-2 strains inoculated in African green monkey kidney cells (Vero cells) [1,2]. ZF2001 (Zhifei) is a protein subunit vaccine with the tandem-repeat dimeric receptor-binding domain of the SARS-CoV-2 spike protein as the antigen [3]. Ad5-nCoV (CanSino) is an adenovirus vectored vaccine prepared with the replication-defective, human adenovirus type 5 as a vector expressing the S protein of SARS-CoV-2 [4].

In this study, the event of interest was uveitis relapse occurring after the administration of any dose of COVID-19 vaccine within 30 days. The 30-day observation window was chosen based on published studies [8–10], beyond which the relapse was considered unlikely to be related to COVID-19 vaccination. We determined each participant's status of having or not having uveitis relapse at enrollment and collected their vaccination history as well as other demographic and historical clinical factors. To examine the potential risk factors associated with uveitis relapse, we analyzed if some exposures, such as patient demographics and historical clinical factors, were associated with the time to uveitis relapse since the administration of each dose of COVID-19 vaccine. There were no missing data with regard to the relapse status of study participants. We defined that the event outcome did not occur if no relapse after vaccination was observed before day 30, or the administration of the next dose, or the study visit (whichever occurred earlier), and therefore, participants had their time-to-event data censored on that time point. The exposures of interest in this study included age, sex, duration of uveitis, uveitis anatomical classification, uveitis etiological classification (infectious or non-infectious), uveitis associated systemic diseases (e.g. Vogt-Koyanagi-Harada disease, Behçet disease, ankylosing spondylitis), number of relapses in the last year, time since the last relapse, medical history and comorbidities (hypertension, diabetes, obesity, malignancies, history of tuberculosis and antibiotic allergy), concomitant medication at the time of vaccination (systemic corticosteroid or noncorticosteroid immunomodulatory therapies), and vaccine dose and type. All these variables were available among study participants and were collected from predetermined standardized medical records.

2.2. Study procedures and assessments

Each participant was assessed for uveitis status through symptom tracking, history taking, and ophthalmic examination. Routine examinations included slit-lamp biomicroscopy, ophthalmoscopy, tonometry and measurements of visual acuity and refraction. Examinations of fundus photography, optical coherence tomography and fundus fluorescein angiography were carried out according to clinical needs. We retrieved historical medical records of each patient kept at the study site and performed a chart review. A uveitis relapse was evidenced by any worsening activity of intraocular inflammation (e.g. anterior chamber cells, vitreous haze) as defined by the Standardization of Uveitis Nomenclature (SUN) Working Group relative to the last visit condition [17]. COVID-19 vaccination status and history of patients were verified via access to the Health Code System in which per-dose vaccination information, including dates, sites and vaccine types, were documented as part of continuing public health surveillance of COVID-19 by the local health administrative sectors. Data on demographic characteristics, medical history, clinical management and treatments were collected by means of query of medical records at the study site.

2.3. Statistical analysis

Categorical data were expressed as numbers and percentages of the total group of participants. Continuous data were presented as medians and interquartile ranges (IQRs). The unit of primary analysis was by vaccine dose. We constructed a mixed-effects Cox regression model to analyze the time-to-event data per dose with accounting for the correlation of repeated measures on an individual [18]. Cox proportional hazards assumptions were not violated. In a multivariable model, hazard ratios (HRs) with 95% confidence intervals (CIs) for uveitis relapse were estimated by further adjusting for the variables of interest, including age, sex, dose and type of vaccines, and other variables with P value less than 0.2 in unadjusted analysis. We examined the linear trend by re-modeling factors as continuous variables. All statistical tests used were two-sided. No missing data were imputed, as the analysis included each person for whom the variables of interest were available. Statistical analysis was performed with R version 3.5.0 (R Foundation for Statistical Computing).

3. Results

3.1. Characteristics of study participants

During the study period, a total of 506 consecutive uveitis patients who had received at least one dose of COVID-19 vaccine were identified. Of these, 68 patients were excluded from the analysis because they had unreliable or missing vaccination records that could not be verified through the Health Code System or because they had missing information on variables of interest. Thus, the primary analysis included 438 participants with 857 doses of COVID-19 vaccine administered in total (Fig. 1). Among these participants, 78 (17.8%) had received one dose of vaccine, 301 (68.7%) had received two doses, and 59 (13.5%) had received three doses. Of 857 doses of vaccine administered, 436 (50.9%) were CoronaVac (Sinovac), 270 (31.5%) were BBIBP-CorV (Sinopharm), 146 (17.0%) were ZF2001 (Zhifei), and 5 (0.6%) were Ad5-nCoV (CanSino). Inactivated SARS-CoV-2 vaccines accounted for the majority (82.4%) of the total doses. Of 857 doses of COVID-19 vaccine, 277 were administered in patients who were concomitantly treated with

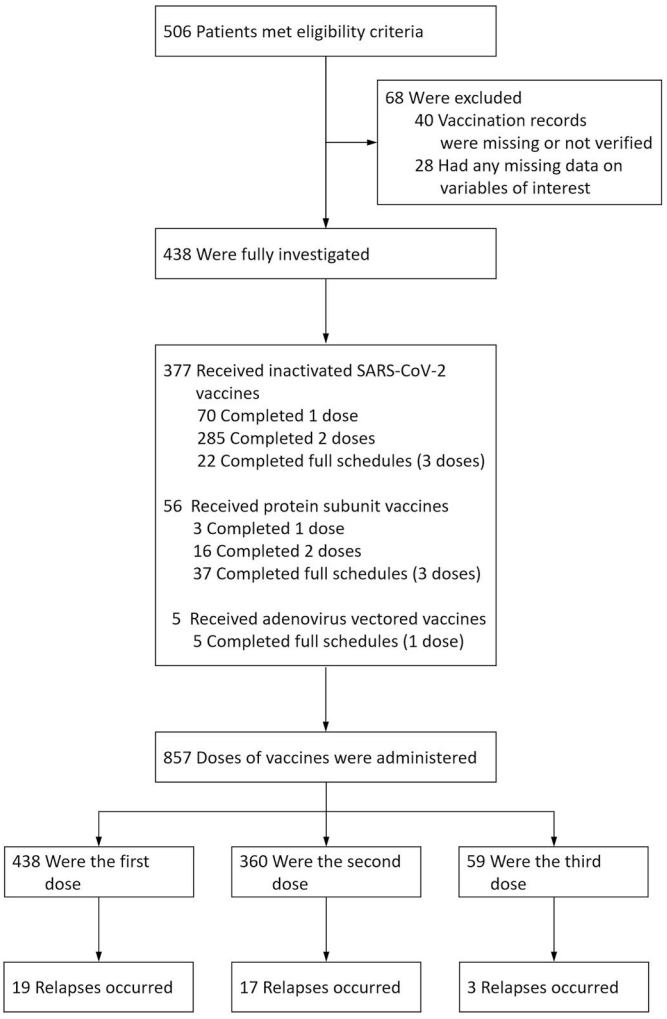

Fig. 1. Investigation of Uveitis Relapse in Patients Who Had Received COVID-19 Vaccines. The complete inactivated SARS-CoV-2 vaccine schedules included three doses of CoronaVac (Sinovac) or three doses of BBIBP-CorV (Sinopharm). The complete protein subunit vaccine schedules included three doses of ZF2001 (Zhifei). The complete adenovirus vectored vaccine schedule included one dose of Ad5-nCoV (CanSino).

systemic glucocorticoids for uveitis at the time of vaccination, 252 were administered in those concomitantly treated with cyclosporine, 76 were administered in those concomitantly treated with chlorambucil, and 17 were administered in those concomitantly treated with adalimumab. Demographic characteristics and vaccination status of the study population are summarized in Table 1. All participants were Chinese. The median age at the administration of the first dose of vaccine was 41 years (interquartile range, 30 to 51). This vaccinated cohort included 13 (3%) children or adolescents aged 16 years or younger and 29 (6.6%) adults aged 60 years or old. Female patients represented 57.3% of the cohort.

3.2. Uveitis relapse after COVID-19 vaccination

A total of 39 episodes of uveitis relapse events occurred in 34 patients after the receipt of a dose of COVID-19 vaccine within 30 days, among which 5 patients had a repeated event following each separate dose. There were 19 episodes of relapse after the first dose of vaccine, 17 episodes after the second one, and 3 episodes after the third one (Fig. 1). The median time to uveitis relapse after vaccination was 5 days (interquartile range, 1 to 14). There seemed to be three peak periods for uveitis relapse: 1-to-3 days post vaccination, 7-to-9 days (about 1 week) post vaccination, and 13-to-15 days (about 2 weeks) post vaccination (Fig. 2). No events of relapse occurred anymore from day 16 to day 30 since the administration of a dose of vaccine in the cohort. Of these 34 patients with relapse, 15 (44.1%) had anterior uveitis, 8 (23.5%) had posterior uveitis, and 11 (32.4%) had panuveitis. We did not observe any evidence that the new event of uveitis was different from the previous specific cause or diagnosis of uveitis entities for each patient. Classification of uveitis entities of these 34 cases according to the SUN Working Group criteria are provided in Supplementary Table S1. Idiopathic or undifferentiated uveitis was the most common category (55.9%), followed by late-stage Vogt-Koyanagi-Harada disease (11.8%), spondyloarthritis/HLA-B27-associated anterior uveitis (8.8%), and Behçet disease uveitis (8.8%). Clinical manifestations of uveitis relapse disclosed by ophthalmic examinations are summarized in Supplementary Table S2. Systemic glucocorticoids were primarily used for the treatment of uveitis flares after vaccination in 29 patients (85.3%), and dexamethasone intravitreal implant was initiated in one case (2.9%). Combined noncorticosteroid systemic immunomodulatory therapies included cyclosporine (61.8%), chlorambucil (11.8%) and adalimumab (11.8%) (Supplementary Table S3).

Table 1
Demographic characteristics of individuals who had received COVID-19 vaccines.

Characteristics	Overall	One Dose	Two Doses	Three Doses
No. of individuals	438	78	301	59
Age, median (IQR), year	41 (30–51)	33 (24–49)	42 (31–51)	45 (30–52)
Age group, year, no. (%)				
0–16	13 (3.0)	7 (9.0)	6 (2.0)	0 (0.0)
17–44	238 (54.3)	48 (61.5)	161 (53.5)	29 (49.2)
45–59	158 (36.1)	18 (23.1)	114 (37.9)	26 (44.1)
≥60	29 (6.6)	5 (6.4)	20 (6.6)	4 (6.8)
Sex, no. (%)				
Female	251 (57.3)	42 (53.8)	178 (59.1)	31 (52.5)
Male	187 (42.7)	36 (46.2)	123 (40.9)	28 (47.5)
Specific vaccine, no./total doses (%)[a]				
CoronaVac (Sinovac)	436/857 (50.9)	40/78 (51.3)	372/602 (61.8)	24/177 (13.6)
BBIBP-CorV (Sinopharm)	270/857 (31.5)	30/78 (38.5)	198/602 (32.9)	42/177 (23.7)
ZF2001 (Zhifei)	146/857 (17.0)	3/78 (3.8)	32/602 (5.3)	111/177 (62.7)
Ad5-nCoV (CanSino)	5/857 (0.6)	5/78 (6.4)	0/602 (0.0)	0/177 (0.0)

Abbreviation: IQR, interquartile range.
[a] CoronaVac (Sinovac) and BBIBP-CorV (Sinopharm) were inactivated SARS-CoV-2 vaccines. Ad5-nCoV (CanSino) was the adenovirus vectored vaccine. ZF2001 (Zhifei) was the protein subunit vaccine.

3.3. Risk factors for uveitis relapse

In a crude analysis, treatment with either systemic glucocorticoids (HR, 0.24 [95% CI, 0.09–0.69]; P = 0.008) or cyclosporine (HR, 0.36 [95% CI, 0.14–0.93]; P = 0.034) at the time of COVID-19 vaccination was associated with a reduced risk of uveitis relapse after vaccination (Table 2). In addition, patients with a 3- to 5-year history of uveitis had a lower risk of uveitis relapse after COVID-19 vaccination as compared with those with a 2-year history or less (HR, 0.33 [95% CI, 0.12–0.90]; P = 0.031) (Table 2). Nevertheless, the relapse risk was not lower in those with a history of uveitis of 6 years or longer than that in those with a 2-year history or less (HR, 0.68 [95% CI, 0.31–1.46]; P = 0.320), which suggested that the duration of uveitis had no dose-response effect on the risk of relapse. No excess risk was detected for certain COVID-19 vaccine type or dose. P value less than 0.2 was yielded in unadjusted analysis for history of uveitis, time since the last relapse, use of systemic glucocorticoids and use of cyclosporine, all of which were entered into the multivariable model along with other variables of interest including age,

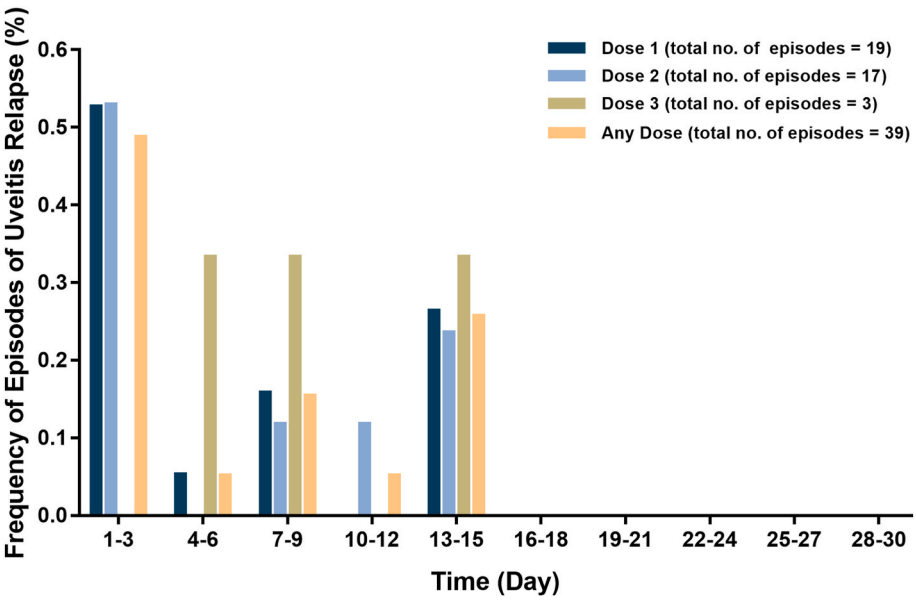

Fig. 2. Time to onset of uveitis relapse after COVID-19 vaccination. Histograms indicate the frequency of episodes of uveitis relapse after the administration of any dose of COVID-19 vaccine or after the administration of certain dose of COVID-19 vaccine, as indicated.

sex, dose and type of vaccines. In the multivariable-adjusted analysis, only concomitant use of systemic glucocorticoids at the time of vaccination was independently associated with a decrease in risk of relapse after vaccination (adjusted HR, 0.23 [95% CI, 0.07–0.74]; P = 0.014) (Table 2). After multivariable adjustment, the hazard ratios for relapse did not differ evidently between cyclosporine users and nonusers (Table 2). Among 857 doses of observations in this cohort, combination treatment with cyclosporine and systemic glucocorticoids at the time of vaccination had accounted for 89.7% of that with cyclosporine. An unadjusted subgroup analysis limited to glucocorticoid nonusers did not show that cyclosporine monotherapy was associated with the risk of uveitis relapse (HR, 0.62 [95% CI, 0.08–4.65]; P = 0.642). Therefore, the observed relationship between cyclosporine use and relapse risk in the prior crude analysis was biased towards the confounding effect of the use of systemic glucocorticoids. No other variables of interest were shown to be associated with the risk of uveitis relapse after COVID-19 vaccination.

3.4. *Effect of glucocorticoid dose*

The inverse relationship between the use of systemic glucocorticoids at the time of vaccination and the risk of uveitis relapse after vaccination appeared to be dose-dependent (Fig. 3). Each observation was categorized as no glucocorticoid use, use of less than 20 mg per day, or use of 20 mg per day or greater, according to the dose of systemic glucocorticoids (the equivalent dose of prednisone) that had been stable for at least one week prior to each COVID-19 vaccine. After adjusting for age, sex, dose of vaccines, vaccine type, history of uveitis, time since the last relapse, and use of cyclosporine, the relapse risk was lower with prednisone use of less than 20 mg per day than with no use of glucocorticoids (adjusted HR, 0.29 [95% CI, 0.09–0.98]; P = 0.047). A much lower risk was observed for use of 20 mg per day or greater, although with a wider confidence interval (adjusted HR, 0.13 [95% CI, 0.01–1.18]; P = 0.070). There was a trend in attenuating the risk of relapse with prednisone use from none to less than 20 mg per day and then to 20 mg per day or greater (adjusted common HR per level increase, 0.34 [95% CI, 0.13–0.89]; P value for trend = 0.029) (Fig. 3A). When the analysis was restricted to the observation on events after the first exposure to vaccine, a consistent trend for a shift in the direction of lower relapse risk was observed with increasing dose of prednisone use, although the analysis based on a subset of observations was not powered for estimates with narrow confidence intervals (Fig. 3B).

4. Discussion

In this surveillance study involving uveitis patients without prior SARS-CoV-2 infection, a decreased risk of uveitis relapse after COVID-19 vaccination was detected with concomitant use of systemic glucocorticoids at the time of vaccine administration. The protective effect of systemic glucocorticoids appeared to be dose-dependent, with greater extent of glucocorticoid use being associated with lower incidence of uveitis relapse. Our study showed some extent of the benefits of systemic glucocorticoid retention in patients with uveitis at the time of COVID-19 vaccination.

Findings of this study extend our understanding of the possible association between COVID-19 vaccination and onset of uveitis flares [8–11], particularly with regard to potential host factors that could modify the relationship. The precise mechanism of vaccine-associated uveitis remains unclear in most patients but is recognized to be closely linked to overactive host immune responses or inflammatory processes that may similarly occur in the development of autoimmune or autoinflammatory conditions [19,20]. Our study provides some evidence showing that therapeutic corticosteroid immunosuppression may moderate the hyperreactivity to COVID-19 vaccines. This notion was in line with the finding of a latest systematic review that showed a diminished immunogenicity and reactogenicity of COVID-19 vaccines in immunocompromised populations, especially with the use of corticosteroids [21]. In addition, several reports indicated that uveitis post COVID-19 vaccination was adequately controlled and responded quickly to the corticosteroid therapy [8,22–24], suggesting that the underlying mechanistic link to the development of uveitis flares would be blocked and corrected in part by glucocorticoids. The inverse association between glucocorticoid use at the time of vaccination and risk of uveitis relapse after vaccination was further supported by the dose-response relationship we observed in this study.

Our study provides evidence supporting the benefits of systemic glucocorticoid retention in patients with uveitis at the time of COVID-19 vaccination. Some studies raised concerns about the glucocorticoid use during the COVID-19 pandemic: glucocorticoid treatment for non-infectious uveitis imposed an increased risk of COVID-19 infection,

Table 2
Hazard ratios for uveitis relapse after COVID-19 vaccination.

Variable	No. of Events	Total Dose[a]	Unadjusted Analyses		Multivariable-Adjusted Analyses[b]	
			Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Entire cohort	39	857	–	–	–	–
Age, year						
0–16	1	19	1.03 (0.16–6.80)	0.978	1.56 (0.26–9.51)	0.631
17–44	24	457	1 [Reference]	–	1 [Reference]	–
45–59	13	324	0.76 (0.36–1.59)	0.458	0.80 (0.38–1.69)	0.552
≥60	1	57	0.32 (0.04–2.39)	0.269	0.43 (0.06–3.05)	0.396
Male Sex	15	366	0.83 (0.41–1.68)[c]	0.607	0.84 (0.40–1.78)[c]	0.654
Dose of vaccines						
First	19	438	1 [Reference]	–	1 [Reference]	–
Second	17	360	1.10 (0.62–1.97)	0.741	1.01 (0.56–1.84)	0.971
Third	3	59	1.19 (0.35–4.01)	0.780	0.94 (0.27–3.24)	0.919
Vaccine type[d]						
Inactivated SARS-CoV-2 vaccine	29	706	1 [Reference]	–	1 [Reference]	–
Protein subunit vaccine	10	146	1.64 (0.75–3.57)	0.215	1.57 (0.68–3.61)	0.287
Adenovirus vectored vaccine	0	5	Not estimated[e]	–	Not estimated[e]	–
History of uveitis, year						
0–2	20	310	1 [Reference]	–	1 [Reference]	–
3–5	5	231	0.33 (0.12–0.90)	0.031	0.37 (0.13–1.08)	0.068
≥6	14	316	0.68 (0.31–1.46)	0.320	0.66 (0.28–1.55)	0.338
No. of relapses in the last year						
0	14	359	1 [Reference]	–	–	–
1	13	298	1.13 (0.55–2.33)	0.746	–	–
≥2	12	200	1.58 (0.64–3.87)	0.321	–	–
Time since the last relapse, month						
0–2	16	249	1 [Reference]	–	1 [Reference]	–
3–6	5	144	0.54 (0.20–1.45)	0.224	0.62 (0.21–1.84)	0.389
7–12	4	105	0.58 (0.20–1.68)	0.314	0.80 (0.26–2.41)	0.689
>12	14	359	0.60 (0.28–1.25)	0.172	0.50 (0.23–1.11)	0.089
Anatomical classification						
Intermediate, posterior or panuveitis	23	499	1 [Reference]	–	–	–
Anterior uveitis	16	358	0.96 (0.48–1.94)	0.912	–	–
Infectious uveitis	4	63	1.46 (0.42–5.07)[c]	0.556	–	–
Uveitis associated systemic diseases						
Vogt-Koyanagi-Harada disease	4	83	1.06 (0.37–3.03)[c]	0.909	–	–
Behçet disease	2	49	0.93 (0.21–4.02)[c]	0.920	–	–
Ankylosing spondylitis	0	21	Not estimated[e]	–	–	–
Self-reported history and comorbidities						
Hypertension	4	88	1.04 (0.30–3.64)[c]	0.954	–	–
Diabetes	1	34	0.61 (0.08–4.47)[c]	0.623	–	–
Obesity	2	25	1.81 (0.47–6.97)[c]	0.390	–	–
Malignancies	1	10	2.54 (0.29–22.03)[c]	0.396	–	–
History of tuberculosis	1	30	0.70 (0.09–5.32)[c]	0.730	–	–
History of antibiotic allergy[f]	3	57	1.21 (0.27–5.48)[c]	0.808	–	–
Concomitant medication at the time of vaccination						
Systemic glucocorticoids	4	277	0.24 (0.09–0.69)[c]	0.008	0.23 (0.07–0.74)	0.014
Cyclosporine	5	252	0.36 (0.14–0.93)[c]	0.034	1.34 (0.42–4.30)	0.625
Chlorambucil	0	76	Not estimated[e]	–	–	–
Adalimumab	0	17	Not estimated[e]	–	–	–

[a] The unit of analysis was by vaccine dose. A mixed-effects Cox regression model was used to account for the correlation of repeated measures on an individual.
[b] Variables included in the multivariable-adjusted analyses were age, sex, dose of vaccines, vaccine type, history of uveitis, time since the last relapse, use of systemic glucocorticoids, and use of cyclosporine.
[c] The reference for the hazard ratio is the absence of the corresponding risk factor.
[d] The inactivated SARS-CoV-2 vaccines included CoronaVac (Sinovac) and BBIBP-CorV (Sinopharm). The adenovirus vectored vaccine was Ad5-nCoV (CanSino). The protein subunit vaccine was ZF2001 (Zhifei).
[e] Data were not estimated because the precise estimates could not be obtained when no events occurred in the group.
[f] Allergy to antibiotics included penicillin reported from 17 patients, sulfamycin from 7 patients, cephalosporin from 6 patients, levofloxacin from 1 patient, and terramycin from 1 patient in this study.

hospitalization and in-hospital death [25,26]. Nevertheless, these studies were limited to an observation period in 2020, during which the study population was not widely vaccinated [25,26]. Current circumstance and clinical practice have varied due to differences in pathogenicity, transmission capacity and immune-escape potency of the prevalent SARS-CoV-2 variants, such as omicron BA.1/1.1 variant [27]. Despite a lower vaccine-induced immunogenicity under immunosuppression [28,29], real-world, population-based data provided reassuring results that vaccines remained effective in the prevention of COVID-19 in immunocompromised individuals who were taking glucocorticoids and disease-modifying antirheumatic drugs [30]. In addition, a recent observation suggested that short-term treatment with low-dose corticosteroids in the peri-vaccination period decreased the side effects of an adenovirus-vectored vaccine (ChAdOx1 nCoV-19), which was not accompanied by discernible abrogation of vaccine-elicited serologic antibody response [31]. This finding is noteworthy because it represents the possibility of balancing efficacy and safety of COVID-19 vaccines in certain clinically vulnerable populations by properly incorporating glucocorticoid therapy. Further research is warranted to broadly evaluate the benefits versus risks of glucocorticoid use for patients with uveitis at the time of vaccination, especially in the current era of widespread COVID-19 vaccination and booster shots.

One of main strengths of our study is the chosen of study population in China who had never been exposed to SARS-CoV-2 infection. Several

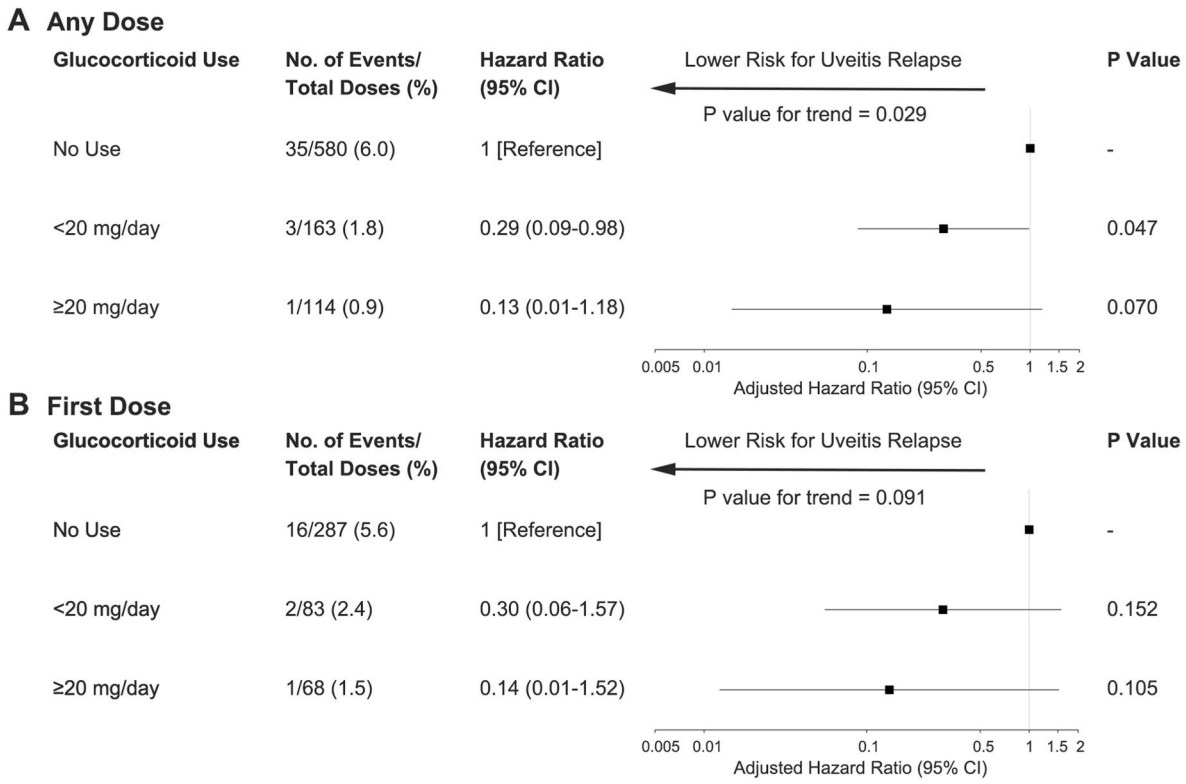

Fig. 3. Glucocorticoid Dose and Risk of Uveitis Relapse after COVID-19 Vaccination. Glucocorticoid use was defined as concomitant systemic treatment at the time of administration of each COVID-19 vaccine on a dose that had been stable for at least a week. Data are expressed as the equivalent doses of prednisone. Hazard ratios for uveitis relapse after any dose (A) or the first dose (B) were adjusted for age, sex, dose of vaccines, vaccine type, history of uveitis, time since the last relapse, and use of cyclosporine. The mixed-effects Cox regression model was used to account for the correlation of repeated measures on an individual, if necessary.

studies reported the onset of intraocular inflammation temporally associated with SARS-CoV-2 infection in adults and children [32–34]. Complete exclusion of study participants from natural exposure to SARS-CoV-2 infection eliminates such potential confounding in the analysis. In addition, uveitis relapse cases and relapse-free controls were consecutively enrolled in parallel during a contemporaneous study period, ensuring that they were comparable in backgrounds especially with respect to the way their COVID-19 vaccines were supplied and administered. Furthermore, information on each dose of COVID-19 vaccine has been verified in line with electronic vaccination administrative system, which prevents misclassification in determining vaccine exposure. To minimize the potential for confounding bias, we included a variety of covariables for adjustment in the multivariable analysis, particularly accounting for the primary noncorticosteroid immunomodulatory agent that was concomitantly used.

There are several limitations to our study. First, we notice that inactivated SARS-CoV-2 vaccines made up 82.4% of those administered. The vaccine availability and vaccination strategies in China may differ from those in other parts of the world. Whether our results are generalizable to a broader population, especially mRNA COVID-19 vaccine recipients, requires further validation. Second, similar to other studies of observational nature [9,11], we did not provide definitive proof for the cause-and-effect relationship between COVID-19 vaccination and uveitis flares. Our study only focused on observing one specific event (uveitis relapse) that occurred temporally later than exposure to COVID-19 vaccines. To consolidate such a link, we limited our observation within the 30-day window after COVID-19 vaccination, which would possibly avoid the misdetection of relapse events caused by other potential factors unrelated to vaccination. Third, due to a rare incidence of relapse episodes, this hypothesis-generating study may not be statistically powered to examine a number of risk factors, especially those with a smaller effect size in association. The susceptibility factor identified so far could only account for a limited proportion of variance in the relapse risk. Our data underscore the need to consider a larger targeted number of expected events in the design of future studies. Fourth, to accrue more events of interest, the sentinel surveillance was conducted in a specialized uveitis care center and was not a population-based study. Therefore, the overall rate of uveitis relapse in this study seems higher than what has been previously reported [13]. We recognize that interpretation of our study may be limited by potential selection bias and that further validation in population-based cohorts is needed. Fifth, data were not available concerning the prognosis of patients after the treatment of uveitis relapse. Further studies on the prognosis are warranted to estimate the burden of uveitis relapse after COVID-19 vaccination.

In conclusion, this observational study suggested that concomitant treatment with systemic glucocorticoids for uveitis at the time of COVID-19 vaccination was associated with a dose-dependent lower risk of uveitis relapse after vaccination.

Ethics approval

Ethical approval for the study was obtained and written informed consent was waived by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. The study procedures were complied with the provisions of the Declaration of Helsinki.

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Author statement

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Declaration of competing interest

The authors declare that they have no competing interests.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2022.102925.

References

[1] M.D. Tanriover, H.L. Doğanay, M. Akova, H.R. Güner, A. Azap, S. Akhan, Ş. Köse, F. Erdinç, E.H. Akalın, F. Tabak Ö, H. Pullukçu, Ö. Batum, S. Şimşek Yavuz, Ö. Turhan, M.T. Yıldırmak, İ. Köksal, Y. Taşova, V. Korten, G. Yılmaz, M.K. Çelen, S. Altın, İ. Çelik, Y. Bayındır, İ. Karaoğlan, A. Yılmaz, A. Özkul, H. Gür, S. Unal, Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey, Lancet 398 (2021) 213–222.

[2] N. Al Kaabi, Y. Zhang, S. Xia, Y. Yang, M.M. Al Qahtani, N. Abdulrazzaq, M. Al Nusair, M. Hassany, J.S. Jawad, J. Abdalla, S.E. Hussein, S.K. Al Mazrouei, M. Al Karam, X. Li, X. Yang, W. Wang, B. Lai, W. Chen, S. Huang, Q. Wang, T. Yang, Y. Liu, R. Ma, Z.M. Hussain, T. Khan, M. Saifuddin Fasihuddin, W. You, Z. Xie, Y. Zhao, Z. Jiang, G. Zhao, S. Mahmoud, I. ElTantawy, P. Xiao, A. Koshy, W. A. Zaher, H. Wang, K. Duan, A. Pan, Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial, JAMA 326 (2021) 35–45.

[3] L. Dai, L. Gao, L. Tao, S.R. Hadinegoro, M. Erkin, Z. Ying, P. He, R.T. Girsang, H. Vergara, J. Akram, H.I. Satari, T. Khaliq, U. Sughra, A.P. Celi, F. Li, Y. Li, Z. Jiang, D. Dalimova, J. Tuychiev, S. Turdikulova, A. Ikram, N. Flores Lastra, F. Ding, M. Suhardono, E. Fadlyana, J. Yan, Z. Hu, C. Li, I.Y. Abdurakhmonov, G. F. Gao, Efficacy and safety of the RBD-dimer-based covid-19 vaccine ZF2001 in adults, N. Engl. J. Med. 386 (2022) 2097–2111.

[4] S.A. Halperin, L. Ye, D. MacKinnon-Cameron, B. Smith, P.E. Cahn, G.M. Ruiz-Palacios, A. Ikram, F. Lanas, M. Lourdes Guerrero, S.R. Muñoz Navarro, O. Sued, D. A. Lioznov, V. Dzutseva, G. Parveen, F. Zhu, L. Leppan, J.M. Langley, L. Barreto, J. Gou, T. Zhu, Final efficacy analysis, interim safety analysis, and immunogenicity of a single dose of recombinant novel coronavirus vaccine (adenovirus type 5 vector) in adults 18 years and older: an international, multicentre, randomised, double-blinded, placebo-controlled phase 3 trial, Lancet 399 (2022) 237–248.

[5] R.H. ElSheikh, A. Haseeb, T.K. Eleiwa, A.M. Elhusseiny, Acute uveitis following COVID-19 vaccination, Ocul. Immunol. Inflamm. 29 (2021) 1207–1209.

[6] E. Yasuda, W. Matsumiya, Y. Maeda, S. Kusuhara, Q.D. Nguyen, M. Nakamura, R. Hara, Multiple evanescent white dot syndrome following BNT162b2 mRNA COVID-19 vaccination, Am. J. Ophthalmol. Case Rep. 26 (2022), 101532.

[7] P. Mahendradas, S.B. Mishra, R. Mangla, S. Sanjay, A. Kawali, R. Shetty, B. Dharmanand, Reactivation of juvenile idiopathic arthritis associated uveitis with posterior segment manifestations following anti-SARS-CoV-2 vaccination, J. Ophthalmic. Inflamm. Infect. 12 (2022), 022-00294.

[8] N. Ferrand, M. Accorinti, M. Agarwal, C. Spartalis, P. Manni, N. Stuebiger, M. Zierhut, COVID-19 vaccination and uveitis: epidemiology, clinical features and visual prognosis, Ocul. Immunol. Inflamm. 11 (2022) 1–9.

[9] T. Rabinovitch, Y. Ben-Arie-Weintrob, T. Hareuveni-Blum, B. Shaer, V. Vishnevskia-Dai, S. Shulman, H. Newman, M. Biadsy, D. Masarwa, N. Fischer, O. Yovel, S. Goldfeather-Ben Zaken, Z. Habot-Wilner, UVEITIS after the BNT162b2 mRNA vaccination against SARS-CoV-2 infection: a possible association, Retina 41 (2021) 2462–2471.

[10] E. Bolletta, D. Iannetta, V. Mastrofilippo, L. De Simone, F. Gozzi, S. Croci, M. Bonacini, L. Belloni, A. Zerbini, C. Adani, L. Fontana, C. Salvarani, L. Cimino, Uveitis and other ocular complications following COVID-19 vaccination, J. Clin. Med. 10 (2021) 5960.

[11] O. Tomkins-Netzer, S. Sar, O. Barnett-Griness, B. Friedman, H. Shyriaieva, W. Saliba, Association between Vaccination with the BNT162b2 mRNA COVID-19 Vaccine and Non-infectious Uveitis: a Population-Based Study, Ophthalmology, 2022.

[12] Z. Zhong, G. Su, A. Kijlstra, P. Yang, Activation of the interleukin-23/interleukin-17 signalling pathway in autoinflammatory and autoimmune uveitis, Prog. Retin. Eye Res. 16 (2020), 100866.

[13] M.T.M. Wang, R.L. Niederer, C.N.J. McGhee, H.V. Danesh-Meyer, COVID-19 vaccination and the eye, Am. J. Ophthalmol. 240 (2022) 79–98.

[14] P. Yang, Z. Zhong, L. Du, F. Li, Z. Chen, Y. Zhu, W. Zhang, F. Huang, X. Ye, G. Su, A. Kijlstra, Prevalence and clinical features of systemic diseases in Chinese patients with uveitis, Br. J. Ophthalmol. 18 (2020) 2020–315960.

[15] Standardization of Uveitis Nomenclature (SUN) Working Group, Development of classification criteria for the uveitides, Am. J. Ophthalmol. 228 (2021) 96–105.

[16] J. Deschenes, P.I. Murray, N.A. Rao, R.B. Nussenblatt, International uveitis study group (IUSG): clinical classification of uveitis, Ocul. Immunol. Inflamm. 16 (2008) 1–2.

[17] D. Jabs, R. Nussenblatt, J. Rosenbaum, Standardization of Uveitis Nomenclature (SUN) Working Group, Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop, Am. J. Ophthalmol. 140 (2005) 509–516.

[18] P.C. Austin, A tutorial on multilevel survival analysis: methods, models and applications, Int. Stat. Rev. 85 (2017) 185–203.

[19] E.T. Cunningham Jr., R.S. Moorthy, F.W. Fraunfelder, M. Zierhut, Vaccine-associated uveitis, Ocul. Immunol. Inflamm. 27 (2019) 517–520.

[20] J.A. Leibowitz, A.T. Woods, M.M. Kesselman, B.S. Mayi, Uveitis as a predictor of predisposition to autoimmunity, Cureus 12 (2020), e7451.

[21] S. Galmiche, L.B. Luong Nguyen, E. Tartour, X. de Lamballerie, L. Wittkop, P. Loubet, O. Launay, Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review, Clin. Microbiol. Infect. 28 (2022) 163–177.

[22] L.I. Mudie, J.D. Zick, M.S. Dacey, A.G. Palestine, Panuveitis following vaccination for COVID-19, Ocul. Immunol. Inflamm. 29 (2021) 741–742.

[23] A.W. Al-Allaf, A. Razok, Y. Al-Allaf, L. Aker, Post-COVID-19 vaccine medium-vessel vasculitis and acute anterior uveitis, causation vs temporal relation; case report and literature review, Ann. Med. Surg. (Lond) 75 (2022), 103407.

[24] J.H. Hwang, Uveitis after COVID-19 vaccination, Case Rep. Ophthalmol. 13 (2022) 124–127.

[25] Y. Sun, D.C. Miller, I. Akpandak, E.M. Chen, B.F. Arnold, N.R. Acharya, Association between immunosuppressive drugs and COVID-19 outcomes in patients with non-infectious uveitis in a large US claims database, Ophthalmology 16 (2022), 00362-00361.

[26] D.C. Miller, Y. Sun, E.M. Chen, B.F. Arnold, N.R. Acharya, The association between noninfectious uveitis and coronavirus disease 2019 outcomes: an analysis of United States claims-based data, Ophthalmology 129 (2022) 334–343.

[27] P.E. Brown, S.H. Fu, A. Bansal, L. Newcombe, K. Colwill, G. Mailhot, M. Delgado-Brand, A.C. Gingras, A.S. Slutsky, M. Pasic, J. Companion, Bogoch II, E. Morawski, T. Lam, A. Reid, P. Jha, B.A. Omicron, 1/1.1 SARS-CoV-2 infection among vaccinated Canadian adults, N. Engl. J. Med. 386 (2022) 2337–2339.

[28] U.M. Geisen, D.K. Berner, F. Tran, M. Sümbül, L. Vullriede, M. Ciripoi, H.M. Reid, A. Schaffarzyk, A.C. Longardt, J. Franzenburg, P. Hoff, J.H. Schirmer, R. Zeuner, A. Friedrichs, A. Steinbach, C. Knies, R.D. Markewitz, P.J. Morrison, S. Gerdes, S. Schreiber, B.F. Hoyer, Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort, Ann. Rheum. Dis. 80 (2021) 1306–1311.

[29] V. Furer, T. Eviatar, D. Zisman, H. Peleg, D. Paran, D. Levartovsky, M. Zisapel, O. Elalouf, I. Kaufman, R. Meidan, A. Broyde, A. Polachek, J. Wollman, I. Litinsky, K. Meridor, H. Nochomovitz, A. Silberman, D. Rosenberg, J. Feld, A. Haddad, T. Gazzit, M. Elias, N. Higazi, F. Kharouf, G. Shefer, O. Sharon, S. Pel, S. Nevo, O. Elkayam, Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study, Ann. Rheum. Dis. 80 (2021) 1330–1338.

[30] C. Shen, M. Risk, E. Schiopu, S.S. Hayek, T. Xie, L. Holevinski, C. Akin, G. Freed, L. Zhao, Efficacy of COVID-19 vaccines in patients taking immunosuppressants, Ann. Rheum. Dis. 81 (2022) 875–880.

[31] J. Yang, J.H. Ko, J.Y. Baek, J. Hong, S. Ha, B. Lee, K. Huh, S.Y. Cho, C.I. Kang, D. R. Chung, Y.J. Kim, E.S. Kang, K.R. Peck, Effects of short-term corticosteroid use on reactogenicity and immunogenicity of the first dose of ChAdOx1 nCoV-19 vaccine, Front. Immunol. 12 (2021), 744206.

[32] A. Santamaria, J. Chang, C. Savarain, SARS-CoV-2 among the potential viral triggers for vogt-konayagi-harada disease: first case report and literature review, Ocul. Immunol. Inflamm. 26 (2021) 1–7.

[33] C. Mazzotta, E. Giancipoli, Anterior acute uveitis report in a SARS-CoV-2 patient managed with adjunctive topical antiseptic prophylaxis preventing 2019-nCoV spread through the ocular surface route, Int. Med. Case Rep. J. 13 (2020) 513–520.

[34] J. Wong Chung, Ö. Engin, T.F.W. Wolfs, T.J.C. Renson, J.H. de Boer, Anterior uveitis in paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2, Lancet 397 (2021), 00579-00571.