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Letter to the Editor

NOTA: Nuestra publicación se inicia en la página marcada con el número 94; mostrada en la siguiente página.
Titulada: "Association of the Delta SARS-CoV-2 variant with 28-day hospital mortality between December 2020 and September 2021".

Dynamic changes of serum SARS-CoV-2 antibody levels in COVID-19 patients

Dear Editor,

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in December 2019 and spread rapidly and globally, leading to a worldwide pandemic currently. As of April 4, 2022, more than 489 million confirmed COVID-19 cases and 6 million deaths were reported to WHO around the world.[1] Evaluating the durability of the humoral immune response to SARS-CoV-2 is essential to understand the susceptibility of COVID-19 patients to the same virus after recovered from the infection. Recently, it has been reported in neutralization assays using SARS-CoV-2 virus that neutralization antibodies titer is correlated with protection against reinfection.[2] Serum immunoglobulin M (IgM) and immunoglobulin G (IgG) against SARS-CoV-2 were detectable within the first several weeks after symptom onset.[3] To date, there are few data on long-term of antibodies response to SARS-CoV-2 after initial infection. Here, the aim of this study is to investigate the duration or stability of viral-specific humoral responses in COVID-19 recovered patients.

This was a retrospective study involving 61 hospitalized patients with laboratory-confirmed COVID-19 in the Renmin Hospital of Wuhan University, Wuhan, China from January 17, 2020 to March 7, 2020. Patients received follow-up visits form February 25, 2020 to January 29, 2021. Each patient had at least two antibody tests, with a total of 173 serum samples collected. The time points were defined as the days after symptom onset in which samples were collected. From the first to fourth time point, it was days 1–30, 31–60, 61–120, and 296–368, respectively. The serum antibodies against SARS-CoV-2 (IgM, IgG and neutralization antibodies) were detected by a chemiluminescent immunoassay (YHLO Biotech, Shenzhen, China). The samples were processed and analyzed according to the manufacturer's instructions. Values $\geq$ 10 AU/mL are considered positive. This study was approved by the Ethics Committee of Renmin Hospital of Wuhan University (Approve No. WDRY2020-K073). Continuous variables were present as median and interquartile range (IQR) and the Kruskall-Wallis test was applied. A p-value less than 0.05 was statistically significant. All statistical analyses and scientific graphics were made by using SPSS 20.0.

From 17 January 2020 to 7 March 2020, a total of 61 COVID-19 patients were recruited in our study. The median age was 34 years (IQR, 30–47). 72.13% (44/61) were women and 27.87% (17/61) men. 29, 53, 30 and 61 specimens were collected 1–30 days, 31–60 days, 61–120 days, and 296–368 days after the onset of symptoms, respectively. We illustrate the overall profile of serum IgM, IgG, and neutralization antibodies against SARS-CoV-2 from day 1 to 368 after illness onset in Table 1 and Fig 1.

The median serum IgM level was 22.79 (IQR, 6.45, 150.97) AU/mL in 1–31 days, reduced to 17.61 (IQR, 3.65, 57.05) AU/mL in 31–60 days, increased to 31.58 (IQR, 11.38,125.22) AU/mL in 61–120 days, but the difference was not statistically significant. The IgM level in days 296 to 368 reduced to 2.66 (IQR, 1.16, 8.22) AU/mL, which decreased significantly compared with other time periods (Fig. 1). The positive rates of IgM were 65.52%, 58.49%, 80.00% and 22.95%, respectively (Fig. 2).

The median serum IgG level was 86.67 (IQR, 46.88, 208.04) AU/mL in 1–31 days, increased to 123.67 (IQR, 56.22, 191.01) AU/mL in 31–60 days and 158.94 (IQR, 115.69, 232.16) AU/mL in 61–120 days, but the difference was not statistically significant. The IgG level in days 296 to 368 reduced to 36.32 (IQR, 14.68,78.68) AU/mL, which decreased significantly compared with other time periods (Fig. 1). The positive rates of IgG were 96.55%, 100.00%, 100.00% and 81.97%, respectively (Fig 2).

The median serum neutralization antibodies level was 35.32 (IQR, 12.16, 160.60) AU/mL in 1–31 days, increased to 54.43 (IQR, 23.98, 145.74) AU/mL in 31–60 days and 80.13 (IQR, 56.98, 202.36) AU/mL in 61–120 days, but the difference was not statistically significant. The neutralization antibodies level in days 296 to 368 markedly reduced to 14.30 (IQR, 7.77, 27.9) AU/mL, which decreased significantly compared with other time periods (Fig. 1). The positive rates of neutralization antibodies were 79.31%, 92.45%, 100.00% and 67.21%, respectively (Fig. 2).

Some studies performed at the beginning of the COVID-19 pandemic showed that the amount of anti-SARS-COV-2 IgM/IgG antibodies decreased in several months post onset of symptoms.[4,5] However, Gong X et al. found that anti-SARS-CoV-2 IgG can last for at least 9 months in patients with a history of natural infection.[6] Kaygusuz S et al. also showed that both IgG and neutralization antibodies levels continued unabated after 9 months of follow-up.[7] Yousefi Z et al. found that the level of anti-SARS-CoV-2 IgG antibody was detectable at their highest level for 3 months, and a certain amount of anti-SARS-COV-2 IgG antibody could be detected in the serum of recovered patients up to 15 months.[8] The humoral immunity persisted for up to 18 months in patients with mild COVID-19.[9] The maximum duration of neutralizing antibodies and IgG antibodies could be long-lasting based on Linear Mixed Models, especially IgG.[10]

Our study has several limitations such as small sample size, retrospective study, and different sample collection time. The relationship between clinical features and antibody dynamics, such as disease severity, was not discussed.

According to the present study's results, despite the decrease in the amount of IgG and neutralization antibodies in 297–368 days,

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Association of the Delta SARS-CoV-2 variant with 28-day hospital mortality between December 2020 and September 2021

Dear Editor,

The spreading of SARS-CoV-2 variants of concern (VOCs) have been associated with a surge of COVID-19 cases and the burden of the healthcare systems worldwide (https://www.who.int/en/activities/tracking-SARS-CoV-2-variants). In response, the Reference center for the Network of COVID-19 Genomic Surveillance in the Canary Islands (Spain) was established in our laboratories by the regional public health system. We tracked the early emergence of the Alpha variant [1] and described the introduction and dynamics of four VOCs in the region from December 2020 to September 2021 [3]. There are major concerns that some VOCs may cause increased disease severity. In this journal, Strålin and colleagues have reported higher rates of hospitalization, severe illness and death among those infected with the Alpha variant (B.1.1.7) compared to non-VOC lineages [5]. Since the Delta (B.1.617.2) variant has been associated with even higher disease severity compared with Alpha (B.1.1.7) [6], here we aimed to retrospectively assess the association between infection by the two major VOCs circulating in the Canary Islands (Spain) archipelago during the period and 28-day mortality among a cohort of hospitalized patients.

The study was conducted at the University Hospital Nuestra Señora de Candelaria (HUNSC) (Santa Cruz de Tenerife, Spain). The institutional review board approved the study (approval CHUNSC_2020_24). As previously described [3], nasopharyngeal swab samples were collected in the Canary Islands archipelago from December 2020 to September 2021. Of the 8224 samples analysed throughout the study period, clinical and patient data were available for only a subset of 5544 samples, out of which 532 samples were collected from hospitalized patients in our center. To exclude samples from patients who attended the hospital for causes unrelated to COVID-19 or who could have had a nosocomial SARS-CoV-2 infection, we included in the analysis only those patients who were hospitalized between one and 21 days from symptoms onset. Sample collection, genome sequencing and lineage assignment are briefly described in the supplementary material and further detailed elsewhere [3]. Logistic and Cox proportional hazard regression models adjusting for patient age, sex, days of hospital stay, and personal history of comorbidities were used to assess whether infection by VOCs in hospitalized patients was associated with 28-day hospital mortality.

Clinical and demographic information of the study population is included in **Table S1**. A total of 423 genome sequences were identified as Alpha (B.1.1.7) or Delta (B.1.617.2 and sublineages). Delta was found in a slightly lower proportion of elderly (>50 years) patients (59.2%) compared with Alpha (65.9%), probably reflecting a larger proportion of vaccinated individuals in that age range when Delta was circulating (May to September 2021) [3]. Despite this, and the higher proportion of vaccination when Delta circulated (50–75% of the population with ≥1 dose between July and September 2021) than when Alpha cir-

Table 1
Association results of SARS-CoV-2 VOCs infections with 28-day mortality among hospitalized patients.

	Logistic regression Odds Ratio (95% CI)	*p*-value	Cox regression Hazard Ratio (95% CI)	*p*-value
Lineage (Delta (B.1.617.2 and sublineages) *vs.* Alpha (B.1.1.7))	2.24 (1.11–4.78)	0.029	2.28 (1.18–4.39)	0.014
Age (years old)	1.06 (1.03–1.09)	4.68×10^{-6}	1.05 (1.03–1.07)	1.20×10^{-6}
Sex (male)	2.45 (1.17–5.40)	0.020	2.03 (1.06–3.88)	0.031
Length of hospital stay (days)	0.98 (0.95–1.01)	0.415	0.93 (0.89–0.97)	2.64×10^{-4}
Comorbidities*	1.65 (0.69–4.21)	0.271	1.55 (0.66–3.60)	0.309

CI, confidence interval.
*Detailed in Table S1.

culated (1–35% of the population with ≥1 dose between January and June 2021) (https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/pbiVacunacion.htm), infection by Delta lineages was associated with higher 28-day hospital mortality compared to that of Alpha irrespective of the model (Table 1). Age and male sex were also consistent predictors of higher 28-day hospital mortality.

As a limitation, we did not have access to the vaccination status of the patients. This is mainly due to the lack of a centralized system in Spain where patient vaccination status is stored and to the large proportion of the floating or non-resident population in the islands, such as holidaymakers, nomadic workers, or migrants, who lack health status information in the local databases. We aimed to mitigate the bias caused by this by focusing on hospitalized patients, under the idea that their vaccination level was less relevant for disease severity once the patient was hospitalized. Taken together, hospitalized cases with Delta or any of its sub-lineages were associated with higher mortality compared to those with Alpha, adding to the evidence supporting that Delta was more severe than pre-existent SARS-CoV-2 variants [2,4,6].

Author contributions

CF conceived the idea, the experimental design and supervised the project. LC, JAF, JMLS, HRP, HGC, AIC, RGM, and DGMA conducted the sequencing experiments. JAF, HGC, ODG, and DGMA collected patient data. LC, JMLS, AVF, and CF performed the analysis and interpreted the results. CF obtained the funding. CF and LC drafted the first version of the manuscript and prepared the tables. All authors contributed to manuscript revision and read and approved the submitted version.

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Declaration of Competing Interest

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

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.04.030.

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Very low rates of severe COVID-19 in children hospitalised with confirmed SARS-CoV-2 infection in London, England"

We read with interest the publication by Chappell et al. reporting a very low risk of severe COVID in immunosuppressed children in England.[1]

Compared to adults, children and young people (CYP) are more likely to remain asymptomatic or develop mild symptoms when exposed to SARS-CoV-2, and less likely to develop severe disease, be hospitalised, or die of COVID-19.[2] In adults, hospitalisation and case fatality rates due to COVID-19 are regularly used to measure disease severity with new variants and following vaccination.[3] The disconnect between infection and severe disease after successful COVID-19 immunisation programmes, for example, has been a primary driver for many countries to remove mitigations even with the emergence of more transmissible variants.

In CYP, COVID-19 fatalities are rare and the use of COVID-19 hospitalisations as a proxy for disease severity,[4] is questionable because of the high rates of incidental (asymptomatic or mild) infections identified during routine SARS-CoV-2 screening of all CYP presenting to hospital. Two years into the pandemic, there are still limited data on the risk of hospitalisation for severe COVID-19 in CYP. We, therefore, undertook a retrospective case-note review of CYP admitted to a large paediatric hospital in London with PCR-confirmed SARS-CoV-2 infection over 14-month period covering the alpha, delta and omicron variant waves (Fig. 1a and b).

St. George's Hospital is a large teaching hospital providing acute paediatric A&E, general and specialist paediatric, oncological, surgical and neurosurgical, orthopaedic and trauma, NICU and PICU care for children in South London. CYP aged 0–18 years with a SARS-CoV-2 PCR-positive result between 01 December 2020 and 31 January 2022 were identified through the hospital microbiology laboratory database and their electronic medical records reviewed by two independent paediatricians. Case rates for 0–18-year-olds in London were obtained from national community testing data.[5] We excluded children with PIMS-TS, which typically occurs 2–6 weeks after SARS-CoV-2 infection by which time SARS-CoV-2 PCR-tests are usually negative. Confirmed cases were categorised into:

(i) Incidental: admitted for an unrelated illness, but SARS-CoV-2 PCR-positive on routine screening
(ii) Contributory: SARS-CoV-2 potentially contributed to hospitalisation
(iii) Severe COVID-19: SARS-CoV-2 was the primary reason for hospitalisation

During the 14-month period, there were 33,775 CYP A&E attendances and 3593 hospitalisations at St. George's Hospital. Of these, 147 were hospitalised with a positive SARS-CoV-2 PCR-test. The distribution of incidental and contributory cases closely followed community infection rates in London, but hospitalisations for severe COVID-19 occurred mainly during the alpha wave, with very few cases during the delta or omicron waves despite large numbers of community infections in the same age-group.

Incidental infections accounted for 83 (57%) cases and included CYP admitted for surgical (24/83, 29%), neurological (12/83, 14%), trauma (10/83, 12%) and other illnesses (e.g. eating disorders, neonatal jaundice; 37/83,45%). Cases where SARS-CoV-2 likely contributed to hospitalisation (49/147, 33%) had clinical presentations that were typical of other childhood viral illnesses. Most CYP (32/49, 65%) presented with fever and respiratory symptoms, or fever with inadequate oral intake, which warranted admission for observation and/or sepsis screen with antibiotic cover until bacterial cultures returned negative after 48 h; 26% (13/49) in this category were aged <3 months. Other presentations included acute exacerbation of asthma (7/49, 14%), febrile convulsions (4/49, 8%) and other presentations (e.g. diarrhoea and vomiting, feeding difficulties, lethargy; 6/49, 12%). Symptoms were generally mild and only five required supplemental oxygen during their short hospital stay.

Thus, only 15 children (10%) were hospitalised with severe COVID-19 presenting as pneumonitis, mainly during the alpha variant wave (10/15, 67%), and in older CYP (9/15 [60%] were aged 12–18 years) with comorbidities (11/15, including 8 with immunosuppression) (Table 1). Thirteen CYP required supplemental oxygen, seven required intensive care and all recovered.

In our hospital, more than half the CYP hospitalised with a positive SARS-CoV-2 PCR-test had incidental infection. In a further third, SARS-CoV-2 likely contributed to hospitalisation with clinical presentations that were typical of other respiratory viruses that are currently not circulating in England because of the physical distancing measures imposed during various lockdowns.[6] This group included mainly high-risk CYP (young infants, immunocompromised) who typically presented with fever and mild respiratory symptoms but were hospitalised to rule serious underlying infection. Of the few CYP hospitalised with COVID-19 pneumonitis, most were adolescents and nearly all had underlying conditions, especially immunosuppression. They all recovered, consistent with current literature reporting favourable outcomes, including for CYP with comorbidities and immunosuppression.[1,7] Vaccinating children against COVID-19 will further reduce the small risk of severe disease,[8-10] but, since current vaccines provide only limited short-term protection against infection or mild disease,[8,9] the virus will likely continue to contribute indirect hospitalisations, just like other respiratory viruses. In conclusion, unlike adults, hospitalisation with a positive SARS-CoV-2 PCR-test is not a useful marker of severe COVID-19 in children. Our findings demonstrate that, not only do CYP have a very low risk of hospitalisation with SARS-CoV-2 infection, but the vast majority of hospitalised CYP (especially healthy CYP) with confirmed SARS-CoV-2 infection do not have severe COVID-19, irrespective of SARS-CoV-2 variant, while the minority with severe COVID-19 recovered without complications. The very low rate of severe COVID-19 during the omicron variant wave is also reassuring.