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SHORT COMMUNICATION

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Antibody responses to common viruses according to COVID-19 severity and postacute sequelae of COVID-19

Marianna Karachaliou[1] | Otavio Ranzani[1] | Ana Espinosa[1,2,3,4] | Susana Iraola-Guzmán[5] | Gemma Castaño-Vinyals[1,2,3,4] | Marta Vidal[1] | Alfons Jiménez[1] | Marc Bañuls[1] | Eva Alonso Nogués[6] | Ruth Aguilar[1] | Judith Garcia-Aymerich[1,2,3] | Rafael de Cid[5] | Carlota Dobaño[1,7] | Gemma Moncunill[1,7] | Manolis Kogevinas[1,2,3,4]

[1]ISGlobal, Barcelona, Spain

[2]CIBER Epidemiologia y Salud Pública (CIBERESP), Madrid, Spain

[3]Department of Experimental and Health Sciences, Universitat Pompeu Fabra (UPF), Barcelona, Spain

[4]IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain

[5]Genomes for Life-GCAT Lab, Germans Trias i Pujol Research Institute (IGTP), Badalona, Spain

[6]Banc de Sang i Teixits (BST), Barcelona, Spain

[7]CIBER Enfermedades Infecciosas (CIBERINFEC), Barcelona, Spain

Correspondence

Marianna Karachaliou, Environment and Health over the Lifecourse Program, Barcelona Institute for Global Health (ISGlobal), 88 Doctor Aiguader Rd., 08003 Barcelona, Spain.
Email: marianna.karachaliou@isglobal.org

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Abstract

Limited research suggests that certain viruses reactivate in severe-acute-respiratory-syndrome-coronavirus 2 infection, contributing to the development of postacute sequelae of COVID-19 (PASC). We examined 1083 infected individuals from a population-based cohort, and assessed differences in plasma immunoglobulin (Ig)G and immunoglobulin A levels against Epstein-Barr virus (EBV), cytomegalovirus, varicella zoster virus (VZV), BK polyomavirus, KI polyomavirus, WU polyomavirus (WUPyV), respiratory syncytial virus, and Adv-36 according to the severity of previous COVID-19 and PASC history. Individuals who had experienced severe COVID-19 had higher antibody responses to latent viruses. Ever PASC, active persistent PASC, and PASC with neuropsychiatric symptoms were associated with higher immnoglobulin G to EBV early antigen-diffuse, VZV, and WUPyV even among individuals without previous severe COVID-19.

KEYWORDS

COVID-19, herpesviruses, long COVID, postacute sequelae of COVID-19, polyomaviruses

1 | BACKGROUND

Long COVID or postacute sequelae of COVID-19 (PASC) is a chronic disease state that follows acute infection with severe-acute-respiratory-syndrome-coronavirus 2 (SARS-CoV-2).[1] Symptoms manifest across a wide spectrum of severity, duration, and recurrence pattern, affecting multiple organ systems. Not all SARS-CoV-2-infected individuals develop PASC, and the incidence is reported to be at least 10%.[2]

Understanding the factors that make certain individuals more vulnerable to PASC is crucial for identifying those at risk and developing targeted interventions to prevent and manage PASC symptoms. Our research, along with others, has shown that several factors such as female sex, age, smoking, obesity, comorbidities, and the severity of previous SARS-CoV-2 infection are associated with a higher risk of PASC. Conversely, vaccination appears to have a protective effect against the development of PASC.[3] Although the exact mechanisms underlying these associations are not well understood, an immunological component is highly suspected,[4,5] with specific immune response patterns evident both during the acute phase of the infection and beyond.[6] In support of this, emerging research shows reactivation of latent viruses during acute COVID-19[2] and in individuals experiencing PASC symptoms.[4]

We sought to describe whether COVID-19 severity and PASC are associated with differential antibody responses to common viruses in a population-based study of middle-aged adults in Catalonia, Spain. We applied multiplex serology to assess the antibody responses against a panel of viruses that usually remain at a latent state in our body, including three herpesviruses (Epstein-Barr virus [EBV], cytomegalovirus [CMV], varicella zoster virus [VZV]) and three polyomaviruses (BK polyomavirus [BKPyV], KI polyomavirus [KIPyV], WU polyomavirus [WUPyV]), and the common respiratory viruses respiratory syncytial virus (RSV) and Adv-36, to which we are continuously exposed.

2 | METHODS

2.1 | Study design and population

Within GCAT (www.gcatbiobank.org), a population-based cohort, we examined 1083 individuals who (i) had provided blood samples in 2023 to measure antibody responses against common viruses and (ii) were identified as SAS-CoV-2 infected (see below for details). These individuals were followed-up at multiple time points (2020, 2021, 2023) as part of the COVID-19 population-based cohort network in Catalonia (COVICAT/CONTENT) (www.isglobal.org/en/-/content). At the different follow-up assessments, all eligible participants were invited to complete an online questionnaire, and a subset was invited to provide a blood sample. In 2023, participation rate in blood sample donation was similar between people with and without PASC. Ethical approval was obtained by the ethics committees at the Hospital Universitari Germans Trias i Pujol (CEI no PI-13-020 GCAT) (CEI no. PI-20-182 COVICAT) and the Parc de Salut Mar (CEIM-PS MAR, no. 2020/9307/I). All participants provided informed consent.

2.2 | COVID-19 infection and severity

We identified SARS-CoV-2 infected participants from different sources (self-reported diagnosis/positive testing in questionnaires, SARS-CoV-2 serology indicative of a SARS-CoV-2 infection and electronic health records of the Epidemiological Surveillance Emergency Service of Catalonia of the Department of Health) across follow-ups (2020, 2021, and 2023).[7,8] Further, we defined infected participants as having experienced a severe acute COVID-19 if they required hospitalization or admission to the intensive care unit (ICU), or a non-severe COVID-19 (all other infected participants including asymptomatic).

2.3 | Postacute sequelae COVID-19

PASC (ever, never) was defined following a modified WHO definition, as one or more persisting COVID-19 related symptoms for a duration of at least 3 months, which could not be explained by an alternative diagnosis based on responses in 2021 and 2023 surveys.[9] This definition aligns with the recent definition proposed by NASEM.[1] We screened for the following symptoms/signs: fever or low-grade fever, loss of appetite, dry cough, dyspnea/shortness of breath, persistent chest pain/tightness, throat pain, other respiratory problems, tiredness/unusual fatigue, confusion/loss of speech/loss of movement, chills/vertigo/dizziness, loss of taste or smell, headache, other cognitive or neurological problems, conjunctivitis, other problems with dry eyes/mouth, diarrhea, nausea/vomiting, skin rashes, other dermatological problems, muscle/joint pain, other muscular problems, hematological, endocrine, psychological or psychiatric, cardiovascular, menstrual problems and renal problems. Participants identified in electronic health records with COVID-19 sequelae (ICD-10 B94.8) or PASC (U09.9) during the study period were also considered PASC cases.

Active PASC cases in 2023 were participants with ongoing long-term symptoms (presence of symptoms the last week before completing the 2023 questionnaire). These cases were further classified as (i) active persistent or (ii) active recent, taking into account whether PASC was onset in 2021 (yes, no, respectively). PASC phenotypes were defined a priori based on the presence of symptoms/signs from a specific system as follows: (i) neuropsychiatric (headache, tiredness/unusual fatigue, chills, vertigo, dizziness, tingling sensation, loss of taste or smell, cognitive and neurological problems, psychological and psychiatric problems), (ii) muscular problems, (iii) respiratory, (iv) skin/mucous (skin problems, dry eyes and/or mouth), (v) cardiovascular, (vi) gastrointestinal (abdominal pain, digestive problems), (vii) endocrine (endocrine and menstrual disturbances), (viii) renal and (ix) hematological.

2.4 | Serological analysis of common viruses

In 2023 follow-up, blood samples were collected at the Blood and Tissue Bank and sent refrigerated to GCAT laboratory to be processed within 24 h. Plasma was aliquoted and sent frozen to ISGlobal laboratory for serological analysis using quantitative suspension array technology with 384 well plates and FlexMap-3D analyzer. immnoglobulin G (IgG) and immunoglobulin A (IgA) levels (median fluorescence intensity) were measured against a panel of 12 antigens from eight viruses: three viral capsid proteins 1 from three polyomaviruses (BKPyV, KIPyV, WUPyV), four Epstein-Barr virus (EBV) antigens (ZEBRA, EBNA-1, early antigen-diffuse [EA-D], VCA p18), two CMV antigens (pp65, pp150), one Varicella-zoster virus envelope glycoprotein (VZV gE), one Adenovirus 36 antigen (Adv36 fiber protein) and one RSV antigen (G glycoprotein) (Supporting Information S1: Table S1). Correlation matrix of antibody responses to different antigens is presented in Supporting Information S1: Figure S1. We focused on these viruses given their pathogenic characteristics and the IS-Global laboratory's experience and capability in performing multiplex assay for them.

2.5 | Statistical analysis

We applied linear regression models to assess the association between COVID-19 severity (severe vs. nonsevere) and PASC (ever; active persistent in 2023, active recent in 2023; PASC phenotypes vs. never PASC) with the $\log_{10}$-transformed antibody levels against common viruses measured in 2023 follow-up. Results were expressed as percentage change in the geometric mean and 95% confidence intervals (CIs). We considered the following variables as potential confounders: age (continuous), sex (male, female), highest attained educational level (primary or less, secondary, university), number of COVID-19 vaccine doses up to the time of serology (0–4), current smoking (yes, no) and chronic diseases.[7] When anti-VZV responses were examined as outcome, we excluded participants vaccinated against herpes zoster the previous year ($n = 8$). We performed all aforementioned statistical analyses using Stata/SE (version 14; StataCorp LLC.).

3 | RESULTS

Among the participants who provided a blood sample in 2023 follow-up ($n = 1{,}395$), we identified 1,083 SARS-CoV-2 infected people since 2020 of which 32 (2.9%) had ever experienced severe COVID-19 (requiring admission to the hospital or ICU) and 273 (25.2%) were defined as ever PASC. Characteristics of the 1083 SARS-CoV-2 infected individuals overall and by PASC are presented in Supporting Information S1: Table S2.

3.1 | COVID-19 severity and antibody responses to common viruses

SARS-CoV-2 infected participants who had experienced severe infection had higher IgG levels against all the latent viruses screened (EBV EA-D, CMV pp65, VZV, BKPyV, KIPyV, and WUPyV) compared to those infected without previous severe infection (Table 1). No associations were revealed with IgA-specific responses (Supporting Information S1: Table 3).

3.2 | PASC and antibody responses to common viruses

Infected participants with ever PASC presented higher IgG levels against EBV EA-D, VZV, BKPyV, and WUPyV versus those who never developed PASC (Table 2). In active persistent cases of PASC these responses were of greater magnitude while lower IgG and IgA responses against EBV Zebra and lower IgG against RSV were also detected (Table 2, Supporting Information S1: Table S4).

PASC cases with neuropsychiatric symptoms presented higher IgG levels against EBV EA-D, VZV, KIPyV, and WUPyV *vs.* those who never developed PASC (Table 2). Among PASC cases with

TABLE 1 Association (% change [95% CI]) of COVID-19 severity with IgG responses against common pathogens.

	Severe COVID-19 (admitted to hospital/ICU) ($n = 32$)	
	% Change (95% CI)	p-Value
EBV		
EA-D	41.5 (10.9, 80.6)	0.005
EBNA-1	−2.6 (−31.6, 38.7)	0.882
VCA p18	11.7 (−16.8, 50.2)	0.459
Zebra	−13.9 (−37.2, 17.9)	0.350
CMV		
CMV-pp150	55.4 (−0.6, 143.1)	0.053
CMV-pp65	39.9 (9.8, 78.4)	0.007
VZV	56.5 (21.4, 101.8)	0.001
BKPyV	46.1 (7.4, 98.8)	0.016
KIPyV	72.8 (34.1, 122.9)	<0.001
WUPyV	78.4 (42.2, 123.9)	<0.001
RSV	−2.7 (−17.4, 14.4)	0.735
Adv-36	4.3 (−13.4, 25.7)	0.653

Note: Estimates from linear regression models adjusted for age, sex, education, vaccine doses, smoking and chronic illness. Reference group is SARS-CoV-2 infected people who did not required admission to hospital or intensive care unit (ICU).

TABLE 2 Association [% change (95% CI)] of PASC with IgG responses against common pathogens.

	Ever (*n* = 272)		Active persistent (*n* = 63)		With neuropsychiatric symptoms/signs (*n* = 192)	
	% change (95% CI)	*p*-Value	% change (95% CI)	*p*-Value	% change (95% CI)	*p*-Value
EBV						
EA-D	12.2 (1.9, 23.7)	0.019	24.3 (3.9, 48.7)	0.017	18.4 (5.9, 32.4)	0.003
EBNA-1	−1.1 (−14.1, 13.8)	0.878	−14.4 (−34.1, 10.9)	0.239	3.2 (−12.2, 21.4)	0.702
VCA p18	11.3 (−1.1, 25.1)	0.074	7.2 (−10.8, 28.8)	0.460	13.3 (−6.3, 36.9)	0.197
Zebra	−6.4 (−17.4, 6.1)	0.301	−27.2 (−42.2, −8.0)	0.008	−9.2 (−21.4, 4.9)	0.191
CMV						
CMV-pp150	10.1 (−7.7, 31.5)	0.286	34.1 (−3.9, 87.3)	0.085	13.3 (−7.7, 39.2)	0.231
CMV-pp65	4.5 (−5.1, 15.1)	0.363	12.1 (−6.4, 34.2)	0.215	6.7 (−4.7, 19.2)	0.259
VZV	13.8 (3.1, 25.7)	0.011	24.5 (3.5, 49.8)	0.020	17.7 (5.0, 32.1)	0.005
BKPyV	13.1 (0.06, 27.8)	0.049	8.4 (−10.5, 31.2)	0.407	15.2 (−5.4, 40.5)	0.160
KIPyV	10.7 (−0.01, 22.5)	0.050	10.9 (−7.9, 33.5)	0.276	12.5 (0.04, 26.5)	0.049
WUPyV	13.1 (3.3, 23.9)	0.008	21.7 (2.6, 44.5)	0.024	16.8 (5.2, 29.7)	0.004
RSV	1.9 (−4.4, 8.7)	0.558	−11.7 (−21.7, −0.5)	0.042	0.6 (−6.5, 8.4)	0.862
Adv-36	0.7 (−6.4, 8.4)	0.842	−1.4 (−14.1, 13.3)	0.840	3.6 (−4.8, 12.8)	0.409

Note: Estimates from linear regression models adjusted for age, sex, education, vaccine doses, smoking and chronic illness. Reference group is SARS-CoV-2 infected people who never developed PASC.

Abbreviation: PASC, postacute sequelae of COVID-19.

symptomatology from other systems, the respiratory phenotype was associated with higher IgA levels against BKPyV and KIPyV, and the skin phenotype with higher IgA against BKPyV (Supporting Information S1: Table S5).

We repeated the aforementioned analyses after excluding participants with severe COVID-19. Associations remained between active persistent PASC with IgG to EBV EA-D (positive), IgG and IgA to EBV Zebra (negative), and PASC cases with neuropsychiatric symptoms with IgG to EBV EA-D, VZV, and WUPyV (all positive) (Supporting Information S1: Table S6).

4 | DISCUSSION

We identified links of COVID-19 severity and PASC with antibody responses to common viruses in one of the largest studies in the field that is population-based and incorporates prospectively collected data at critical time points during the pandemic (2020, 2021, and 2023). Severe COVID-19 cases presented elevated antibody responses to latent viruses assessed long time after the acute infection [median (IQR): 31 months (25–37)]. Responses against EBV, VZV, and a respiratory polyomavirus, WUPyV, were higher in people with PASC and particularly among active persistent cases and PASC with neuropsychiatric symptoms, even among those with nonsevere previous acute COVID-19 infection.

Antibody responses against EBV have been previously examined in people with COVID-19 and PASC, but the results have been mixed and inconclusive due to methodological shortcomings mainly related to study design,[10] serological assays[11] and lack of data on the severity of acute infection and confounding factors.[12,13] We utilized a population-based sample of infected people and measured antibody responses against multiple EBV antigens, including those indicative of virus reactivation (EA-D).[14] We observed high antibody reactivity against the EBV EA-D antigen among individuals with previous severe COVID-19 and PASC. Active persistent PASC cases exhibited high reactivity against EBV EA-D but low reactivity against Zebra, a transcription factor involved in initiating the switch from latent to lytic replication of the virus. This atypical antibody profile may reflect a specific immunological signature for persistent PASC cases and warrants confirmation in other samples as it holds potential prognostic value. Additionally, individuals with immune system dysfunction are expected to present atypical profiles in EBV serology.[14] The blunted RSV antibody responses observed in active persistent PASC may also indicate immunologic suppression in these individuals.

In line with EBV reactivation, were results of elevated antibody levels against VZV and WUPyV in people with severe COVID-19 and PASC. Chen et al. showed higher risk of herpes zoster in COVID-19 patients, which is the manifestation of VZV reactivation in the dorsal root ganglion.[15] One study has previously investigated VZV responses in people with PASC and found a positive association.[16]

Beyond herpesviruses, little is known on the association of PASC with the immune responses to other viruses. Only one study potentially examined association with polyomaviruses (VirScan) and PASC but did not identify an association.[17] We are the first to report an association between COVID-19 severity and PASC with antibody responses to WUPyV. WUPyV is found in respiratory samples in the general population and in people with respiratory infection including with SARS-CoV-2[18] but still its association with disease remains speculative.

Virus reactivation can cause damage through multiple mechanisms, including ones mediated by the immune system.[17] We hypothesized that the reactivated pathogens will be linked with specific long-term symptoms according to their site of latency in the body. PASC cases presenting with neuropsychiatric symptoms had elevated IgG against EBV, VZV, KIPyV, and WUPyV. Both EBV and VZV are neurotropic viruses. On the other hand, KIPyV and WUPyV reside primarily in the respiratory tract and it is unlikely to have neuropersistent potential. Nonetheless, the brain is also sensitive to stimulus from peripheral infections.[19] IgA responses to polyomaviruses in PASC cases with respiratory and skin involvement also indicate virus reactivation.[20]

Strengths of the study include a population-based sample and a strategy to identify SARS-CoV-2 infected participants combining self-reported information along with diagnoses at the health care system and serology, overcoming several methodological pitfalls. Also, we evaluated IgG and IgA responses against a spectrum of viruses and antigens. However, our study is limited due to the lack of serial blood samples that would allow the analysis of antibody kinetics.

In summary, we observed elevated antibody responses against latent viruses in people with severe COVID-19. PASC was associated with elevated responses against EBV, VZV, and WUPyV even among patients without previous severe COVID-19. Whether latent pathogens reactivation have a pathogenic role in PASC needs to be ascertained.

AUTHOR CONTRIBUTIONS

All authors satisfy the criteria for authorship. Marianna Karachaliou, Manolis Kogevinas, Gemma Moncunill, Carlota Dobaño, and Rafael de Cid designed the study; Marianna Karachaliou, Ana Espinosa, Otavio Ranzani, Susana Iraola-Guzmán, and Gemma Castaño-Vinyals did the data editing and statistical analysis; Susana Iraola-Guzmán, Gemma Castaño-Vinyals, Eva Alonso Nogués, Ruth Aguilar, Carlota Dobaño, Gemma Moncunill, Marc Bañuls, and Rafael de Cid contributed in data acquisition; Marianna Karachaliou, Manolis Kogevinas, Ana Espinosa, Otavio Ranzani, Gemma Moncunill, Carlota Dobaño, Rafael de Cid, and Judith Garcia-Aymerich drafted the manuscript and all authors contributed to interpretation of the work. All authors reviewed the manuscript critically for important intellectual content, gave final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Ethical approval was obtained by the ethics committees at the Hospital Universitari Germans Trias i Pujol (CEI no PI-13-020 GCAT) (CEI no. PI-20-182 COVICAT) and the Parc de Salut Mar (CEIM-PS MAR, no. 2020/9307/I). All participants provided informed consent.

ORCID

Marianna Karachaliou http://orcid.org/0000-0002-3014-0747
Carlota Dobaño http://orcid.org/0000-0002-6751-4060

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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