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ABSTRACT

Objectives We evaluated the effectiveness of COVID-19 vaccines and monoclonal antibodies (mAbs) against postacute sequelae of SARS-CoV-2 infection (PASC).

Design and setting A retrospective cohort study using a COVID-19 specific, electronic medical record-based surveillance and outcomes registry from an eight-hospital tertiary hospital system in the Houston metropolitan area. Analyses were replicated across a global research network database.

Participants We identified adult (>18) patients with PASC. PASC was defined as experiencing constitutional (palpitations, malaise/fatigue, headache) or systemic (sleep disorder, shortness of breath, mood/anxiety disorders, cough and cognitive impairment) symptoms beyond the 28-day postinfection period.

Statistical analysis We fit multivariable logistic regression models and report estimated likelihood of PASC associated with vaccination or mAb treatment as adjusted ORs with 95% CIs.

Results Primary analyses included 53,239 subjects (54.9% female), of whom 5929, 11.1% (95% CI 10.9% to 11.4%), experienced PASC. Both vaccinated breakthrough cases (vs unvaccinated) and mAb-treated patients (vs untreated) had lower likelihoods for developing PASC, aOR (95% CI): 0.58 (0.52–0.66), and 0.77 (0.69–0.86), respectively. Vaccination was associated with decreased odds of developing all constitutional and systemic symptoms except for taste and smell changes. For all symptoms, vaccination was associated with lower likelihood of experiencing PASC compared with mAb treatment. Replication analysis found identical frequency of PASC (11.2%, 95% CI 11.1 to 11.3) and similar protective effects against PASC for the COVID-19 vaccine: 0.25 (0.21–0.30) and mAb treatment: 0.62 (0.59–0.66).

Conclusion Although both COVID-19 vaccines and mAbs decreased the likelihood of PASC, vaccination remains the most effective tool for the prevention of long-term consequences of COVID-19.

INTRODUCTION

Over the course of last 3 years, the COVID-19 caused by SARS-CoV-2 has resulted in over 600 million cases and over 6 million deaths globally.1 Involvement of organ systems beyond the upper and lower respiratory tract has been well established among patients with SARS-CoV-2 infection.2 Over the course of the pandemic, several treatment modalities have been developed for reducing acute illness duration and mortality associated with SARS-CoV-2.3 However, it is established that SARS-CoV-2 infection will continue to have longer term sequelae among infected populations. The epidemiological and clinical burden of such chronic consequences of SARS-CoV-2 infection remain unquantified.

More specifically, persistence or re-emergence of a constellation of symptoms and conditions weeks or months after contracting has been referred to as postacute sequelae of SARS-CoV-2 infection (PASC).4 The epidemiology and biology of PASC is yet to be established, and there are no specific therapeutic...
options to ameliorate or prevent PASC. Though there is limited, and emerging evidence of COVID-19 vaccine induced protection against PASC,\(^5\) the real-world effectiveness (RWE) of either COVID-19 vaccination or use of anti-SARS-CoV-2 monoclonal antibodies (mAbs) has not been systematically demonstrated, particularly in the USA. We evaluated RWE of COVID-19 vaccines and anti-SARS-CoV-2 mAbs against PASC in a diverse US metropolitan population and further replicated our findings using a global research network database.

**METHODS**

Our primary analyses entailed a retrospective cohort study design using the Houston Methodist COVID-19 Surveillance and Outcomes Registry (CURATOR). Houston Methodist is an eight-hospital tertiary healthcare system with an extensive primary and emergency care network across the greater Houston Texas region, serving one of the most diverse US populations of around 7 million. Detailed design and rationale of CURATOR have been previously reported.\(^6\) Briefly, CURATOR is an institutional review board (IRB) approved COVID-19 specific bioinformatics pipeline that captures sociodemographic, comorbidity, disease severity, hospitalisation, treatment, including mAbs, and outcomes data on all COVID-19 phenotypes (tested positive/negative, hospitalised/non-hospitalised and/or vaccinated). CURATOR is a longitudinal data repository with >90% of patients having data on retrospective pre-COVID-19 (since March 2016) encounters, and all patients having prospective post-COVID-19 healthcare utilisation encounters across the Houston Methodist system. Houston Methodist was one of the first state-designated vaccination centres for the greater Houston metropolitan area and initiated its vaccination campaign as per a risk-based tiered approach on 15 December 2020. Anti-SARS-CoV-2 mAbs were administered as per consistently defined clinical criteria following emergency use authorisation of mAb treatment for COVID-19 by the US Food and Drug Administration.\(^7\)

Using CURATOR, we identified adult patients (≥18 years) with a positive PCR test result for COVID-19 and flagged those who survived beyond 28 days of their initial diagnosis. Using International Classification of Diseases Version 10 (ICD-10) codes, we defined PASC as the reported new onset of at least one PASC-associated constitutional (palpitations, malaise/fatigue and headache) or systemic (sleep disorders, shortness of breath, mood/anxiety disorders, cough and cognitive impairment) symptoms/conditions identified by the Centers for Disease Control and Prevention (CDC).\(^8\) A PASC-related symptom cannot be documented pre-COVID-19 diagnosis and either begins or persists 28 days after diagnosis. Additionally, if a symptom/condition appeared in a patient’s medical record within 28 days of COVID-19 diagnosis but was not documented after the 28-day mark, the symptom/condition was considered ‘resolved’ and was not PASC related. Vaccine efficacy against PASC was evaluated among breakthrough cases only, which were defined as cases with positive PCR tests after achieving complete immunisation (>14 days after two doses of mRNA vaccines or a single dose of the Ad26.COV2.S vaccine).

We fit multivariable logistic regression models and report adjusted ORs and 95% CIs as likelihood estimates of PASC associated with COVID-19 vaccination status and mAb treatment. Models were adjusted for age (18–39, 40–64, 65+ years), sex, race, ethnicity, Charlson Comorbidity Index (CCI; 0–1, 2–4, 5+),\(^9\) and COVID-19 illness severity categorised as mild/ambulatory disease (no hospitalisation), hospitalised with moderate disease (with/without oxygen) and hospitalised with severe disease (intubation, ventilation or extracorporeal membrane oxygenation).\(^10\) Models were also adjusted for state (Texas) area deprivation index (ADI; 0–3, 4–6, 7+), a composite measure of socioeconomic disadvantage,\(^11\)\(^12\) using the University of Wisconsin’s Neighbourhood Atlas.\(^13\) The Neighbourhood Atlas uses Census and American Community Survey data to capture information on 17 education, employment, housing quality and poverty metrics.

We externally validated our findings by using the TriNetX Analytics Network,\(^14\) a deidentified global research network that comprises electronic medical record (EMR) data across 57 healthcare organisations from six different countries. Case definitions, PASC criteria, vaccination and mAb use were similarly characterised. All analyses were replicated and adjusted for age, sex, CCI and severe COVID-19. Other variables included in the primary analyses were missing for a significant proportion of the TriNetX sample. All analyses were conducted with the statistical software ‘R’ V.4.1.0.

**Patient and public involvement**

There was no direct patient or public involvement in the design and conduct of this study.

**RESULTS**

In our primary analyses (3 March 2020–20 November 2021), we identified 55 192 adult PCR positive patients, of whom 1953 (3.5%) were excluded due to missing or unverifiable data. Our final cohort of 53 295 subjects (females: 54.9%, mean (sd) age: 51.6 (17.8) years, median (IQR) CCI: 1 (0–2)) included 3781 (7.1%) breakthrough COVID-19 cases and 4635 (8.7%) mAb-treated patients. Furthermore, 70.6% of our sample had mild ambulatory disease, 23.0% were hospitalised with moderate disease and 6.4% were hospitalised with severe disease. Overall, 5929, 11.1% (95% CI 10.9 to 11.4), met the PASC criteria. The comparative demographic and clinical characteristics of individuals with and without PASC are presented in table 1.

In the fully adjusted models, both vaccinated (breakthrough) COVID-19 cases (vs unvaccinated) and anti-SARS-CoV-2 mAb-treated patients (vs untreated) had a lower likelihood for developing PASC, aOR (95% CI):
Additionally, females (vs males) were more likely to experience PASC (aOR (95% CI): 1.52 (1.44 to 1.61]), as were middle-aged (40–65 years) COVID-19 survivors compared with older individuals (≥65 years) (aOR (95% CI): 1.25 (1.17 to 1.34)). Compared with COVID-19 patients with low CCI scores (0–1), patients with CCI of 2–4 and those with CCI of 5+ had the higher likelihood of experiencing PASC, aORs (95% CI): 2.21 (2.06 to 2.38) and 3.30 (2.54 to 4.02), respectively. Individuals with higher ADI scores (vs ADI 0–3) demonstrated lower odds of experiencing PASC, ADI 4 to 6: aOR (CI) 0.87 (0.81 to 0.92), 7+: 0.81 (0.74 to 0.88) and patients hospitalised with moderate disease also were less likely to have experience PASC compared with mild ambulatory cases, aOR (95% CI) 0.81 (0.76 to 0.87). Figure 1A provides a schematic representation of factors associated with PASC including protective effect sizes for vaccination and mAbs for individual PASC symptoms/conditions.

The frequencies of constitutional and systemic PASC symptoms among the overall, the vaccinated and the mAb treated individuals are presented in table 2. Shortness of breath was the most common symptom, observed among 2578 (43.5%) PASC patients. This was followed by mood/anxiety disorders, 1001 (16.9%), and sleep disorders, 957 (16.1%). COVID-19 vaccination was associated with decreased odds of developing all constitutional and systemic symptoms except for changes in taste and smell, whereas mAb was associated with decreased likelihood of persistent shortness of breath and the new onset of mood/anxiety disorders. Across all PASC symptoms, vaccines conferred a relatively lower likelihood (greater protection) of experiencing PASC as compared with mAb treatment (table 2).

The replication dataset included 631683 patients (females: 55.4%, mean (SD) 48.7 (18.1) years. Among
Figure 1  Factors associated with PASC and individual PASC symptom/conditions for breakthrough and mAb-treated COVID-19 survivors. (A) Likelihood of developing PASC following vaccination or mAb administration, demonstrated as aORs (95% CI) adjusted for all other reported covariates. ¹Compared with age 65+ years; ²compared with males; ³compared with non-Hispanic white/Caucasian; ⁴compared with ADI 0–3; ⁵compared with CCI 0–1; ⁶compared with ambulatory; mild COVID-19 disease. (B) aORs (95% CI) of developing individual PASC symptoms for vaccines (red) and mAb (blue). Estimates adjusted for all covariates reported in figure 1A. ADI, area deprivation index; aOR, adjusted OR; CCI, Charlson comorbidity index; mAbs, monoclonal antibodies; PASC, postacute sequelae of SARS-CoV-2 infection.

Table 2  Frequencies of individual constitutional and systemic symptoms in the overall PASC group and among the vaccinated and mAb-treated individuals

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Total PASC (n=5929)</th>
<th>Vaccinated PASC (n=332)</th>
<th>mAb treated PASC (n=444)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Constitutional symptoms:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitation</td>
<td>591 (10.0)</td>
<td>25 (7.5)</td>
<td>50 (11.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>832 (14.0)</td>
<td>30 (9.0)</td>
<td>52 (11.7)</td>
</tr>
<tr>
<td>Malaise and/or fatigue</td>
<td>882 (14.9)</td>
<td>42 (12.7)</td>
<td>76 (17.1)</td>
</tr>
<tr>
<td><strong>Systemic symptoms:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>474 (8.0)</td>
<td>21 (6.3)</td>
<td>41 (9.2)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>2578 (43.5)</td>
<td>160 (50.9)</td>
<td>185 (41.7)</td>
</tr>
<tr>
<td>Taste and/or smell changes</td>
<td>74 (1.2)</td>
<td>3 (0.9)</td>
<td>9 (2.0)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>957 (16.1)</td>
<td>50 (15.1)</td>
<td>71 (16.0)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>248 (4.2)</td>
<td>17 (5.1)</td>
<td>32 (7.2)</td>
</tr>
<tr>
<td>Mood/anxiety disorders</td>
<td>1001 (16.9)</td>
<td>31 (9.3)</td>
<td>59 (13.3)</td>
</tr>
</tbody>
</table>

* n (%).
PASC, postacute sequelae of SARS-CoV-2 infection.
whom, 70 648, 11.2% (95% CI 11.1 to 11.3) were identified as experiencing PASC. Similar protective effects against PASC were observed for COVID-19 vaccine: aOR (95% CI) 0.25 (0.21 to 0.30) and mAb treatment: 0.62 (0.59 to 0.66). Whereas female sex: aOR (95% CI) 1.48 (1.46 to 1.51) and higher CCI (2– to 4 vs 0–1): aOR (95% CI) 2.13 (2.09 to 2.18) and (5+ vs 0–1): 2.84 (2.77, 2.91) was associated with higher likelihood of PASC. Mood/ anxiety disorders were the most frequently reported PASC symptom (24.4%), followed by shortness of breath (22.0%) and malaise/fatigue (21.0%). Both vaccines and mAb decreased likelihood of developing all PASC symptoms/conditions. As with our primary analysis, the likelihood of PASC reduction was consistently greater among vaccinated breakthrough COVID-19 cases as compared with those who were treated by anti-SARS-CoV-2 mAbs. Results of the replication analysis are reported in online supplemental tables 1-2 and online supplemental figure 1.

**DISCUSSION**

PASC has the potential to become a formidable public health challenge; and despite unresolved case definitions and unexplained underlying pathophysiology, the phenomenon is well documented. Beyond conservative management, there are no specific treatment options.

Based on our case definitions, in our primary analyses, 11.1% of COVID-19 survivors experienced PASC beyond the conventionally defined 4-week duration, which were highly corroborated (11.2%) by our replication analyses of over half a million COVID-19 patients. Prior estimates of PASC or ‘long-COVID’, using direct surveys among smaller numbers of patients, primarily from European countries, vary drastically between 10% and 80%. Our literature review informs that this wide range reflects differences across studies in conditions/symptoms included in PASC criteria, the time lag between PASC assessment and acute COVID-19 illness, and perhaps most importantly the survey methodology applied. Most studies reporting higher PASC/long COVID estimates implemented open ended questions potentially without excluding COVID-19 survivors with prior histories of similar conditions/symptoms. In fact, a prior study of 4182 participants that prospectively assessed SARS-CoV-2 PCR positive patients for prespecified conditions using a ≥28 day post-COVID-19 timepoint, while excluding patients with prior history of such conditions, reported PASC estimates very similar to our analyses (13.3%, CI 12.3 to 14.4).

Given that we used clinical encounters for identifying PASC, it is possible that our estimates represent a more severe or clinically significant PASC experience for which medical care was sought by COVID-19 survivors. Regardless, even with potential underestimation, our data suggests approximately 5 million individuals across the USA may be experiencing PASC, which translates into major direct and indirect healthcare and socioeconomic consequences.

Our analyses uniquely demonstrate RWE of both COVID-19 vaccine and use of anti-SARS-CoV-2 mAbs against PASC. Prior reports from the UK and France have demonstrated that individuals with either completed or partial COVID-19 vaccination series are less likely to have long-term COVID-19 symptoms. However, to our knowledge, no direct comparisons across US populations exist. It is likely that PASC has a multifactorial aetiology involving a combination of a heightened and prolonged immune response, an autoantibody driven immunomodulatory process and even an active or persistent SARS-CoV-2 infection. Therefore, it is plausible that a boosted immunity either through vaccination or mAbs may confer protection against PASC. We found vaccination to be potentially more effective at preventing PASC than mAbs. This may be explained by vaccines providing longer term protective immunomodulation, as well as higher levels of cellular immunity and viral neutralisation. Furthermore, though not causal in nature, our data seem to suggest that PASC are increasingly experienced by individuals across their prime economically productive life years. These findings corroborate with a prior report demonstrating poor post-COVID-19 recovery among those aged 40–59 years (compared with younger or older individuals). All together, these findings have important public health implications particularly with regards to widespread misinformation and persistent vaccine hesitancy.

Our findings also confirm the previously reported higher likelihood of PASC among females. Differential regulation of immune response between females and males is well documented, and although there is ongoing research to understand precise mechanism of PASC, the differences in underlying immune response are postulated to drive sex differences in the development of PASC. We report a relative lack of association between experiencing PASC and severity of acute COVID-19 illness. Though a prior study demonstrated lower likelihood of full post-COVID-19 recovery among patients who received mechanical ventilation, it was not ascertainable if PASC was clearly distinguishable from a broader post-ICU syndrome in these patients. Furthermore, the authors reported that several ongoing mental and physical aspects among COVID-19 survivors were unrelated to acute severity. It is therefore likely that the full gamut of factors that encompass PASC have different biological and psychosocial mechanisms that need to be fully explored in future work.

Though our findings were replicated with data from a global research network, the limitations of our primary analyses include the use of EMR from a single healthcare system, hence limiting broader generalisability. EMR-driven case definitions may underestimate the burden of PASC and may be influenced by drivers of healthcare utilisation. However, our estimates were adjusted for important demographic characteristics including measures of social deprivation. As over 90% of vaccinated patients in our sample received the Pfizer-BioNTech vaccine, we are limited in providing valid comparative estimates between different vaccines for PASC prevention. Additionally, given the observational design and retrospective nature of our analyses, cautious interpretations of causality are warranted. Finally, replication of our findings particularly on data derived from prospective systematic
evaluation for PASC across larger and more demographically and clinically heterogeneous cohorts remains necessary.

Nevertheless, our results underscore the burgeoning population health implications of PASC and highlight the critical role of vaccinations as a pivotal public health tool in potentially mitigating risk and ameliorating long-term effects of COVID-19.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants but Houston Methodist Institutional Review Board (IRB) ID: PRO00025445 exempted this study. This work was carried out under an approved protocol for the Houston Methodist COVID-19 Surveillance and Outcomes Registry (HM CURATOR) by the Houston Methodist Research Institute Institutional Review Board (HMIRB). HM CURATOR has been approved by the HM IRB as an observational quality of care registry for all suspected and confirmed patients with COVID-19. HM IRB granted CURATOR a waiver of informed consent and Health Insurance Portability and Accountability Act authorisation in accordance with current federal regulations.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data are available on reasonable request. All requests for deidentified data should be made to the corresponding author. All reasonable requests will be evaluated by the CURATOR Data Governance and Sharing Committee in the light of institutional policies and guidelines.

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