15-MONTH ATTRIBUTES OF POST-COVID SYNDROME IN THERAPEUTICALLY VACCINATED OUTPATIENTS

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Background

In the fourth year of the coronavirus disease 2019 (COVID-19) pandemic, long-term post-COVID syndrome (PCS) following *severe acute respiratory syndrome coronavirus type 2* (SARS-CoV-2) infections poses a significant challenge for patients and health systems globally. Whilst COVID-19 vaccinations prior to *SARS-CoV-2* infection reduce the risk of PCS, the role of therapeutic vaccination in PCS recovery remains controversial. We present a 15 months longitudinal, prospective and observational cohort study to examine long-term clinical courses, PCS recovery with and without vaccination as well as humoral immune responses in initially unvaccinated PCS patients.

15-months post-infection, **Post-COVID syndrome (PCS)** occurred in 30% of outpatients. Recovery of PCS was observed similarly in both therapeutically vaccinated and unvaccinated patients.

Methods

A total of 227 COVID-19 convalescents of our initial mild COVID-19 outpatient cohort (N=958) from which longitudinal data was available were included in this study (Fig.1A). PCS was defined according to the WHO definition. 76.7% (174/227) of individuals received at least one vaccination between 10 and 15 months after first SARS-CoV-2 infection (Fig.1B). Receptor binding domain (RBD)-specific SARS-CoV-2 immunoglobulin G (IgG) and distinct symptom phenotypes (P) were longitudinally assessed for 15 months. Using binomial regression models, odds ratios (OR) with 95% confidence interval (95%CI) of descriptive, longitudinal variables associated with long-term PCS were calculated.

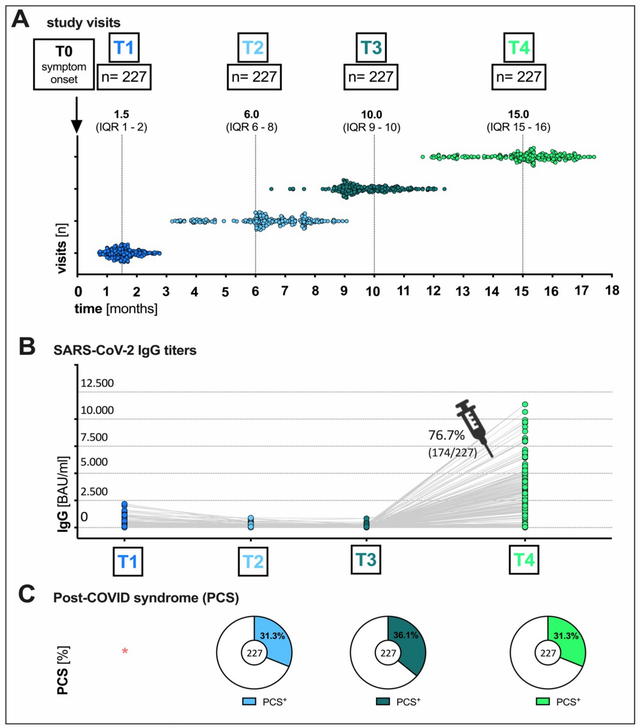

Figure 1
Total visits and humoral immune response of patients at the post-COVID outpatient clinic of the UHC April 6th till August 16th 2022. **A** Median time (months) of the respective visit (T1, T2, T3 and T4) after the onset of symptoms (T0): T1 1.5 (IQR 1–2), T2 6.0 (IQR 6–8), T3 10.0 (IQR 9–10) and T4 15.0 (IQR 15-16). **B** SARS-CoV-2 immunoglobulin G (IgG) titers over time, pre and post vaccination. **C** Distribution of PCS at each visit.

UHC, University Hospital Cologne; IQR, interquartile range; T0, symptom onset; T1, first study visit; T2, second study visit; T3, third study visit; T4 fourth study visit; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; BAU, binding antibody protein; ml, milliliter.

* According to the PCS definition by WHO, PCS not existent earlier than 3 months after symptom onset.

Results

36.1% (82/227) and 31.3% (71/227) of patients had PCS at months 10 and 15 (Fig.1C and Fig.4A). SARS-CoV-2 IgG titers were equally distributed over time among age groups, sex, and PCS (Fig.3). PCS occurred in 30.5% (53/174) of vaccinated and 34.0% (18/53) of unvaccinated patients (Fig.4A). Between 6 and 10 months (ΔT2/T3: not yet vaccinated) and 10 and 15 months (ΔT3/T4: vaccinated) after symptom onset (Fig.4B), a comparable fraction of PCS patients recovered (ΔT2/T3: 22.5% and ΔT3/T4: 20.0%). Fatigue/dyspnea (P2) and not anosmia/ageusia (P1) constituted PCS at month 15 (P2 23.9% versus P1 1.4%). Headache (P4) and diarrhea (P5) at baseline remained risk factors for PCS at months 15, respectively (P4: OR 2.01 (95%CI 1.11-3.52), p= .018; P5: OR 3.01(95%CI 1.44-5.94), p= .002).

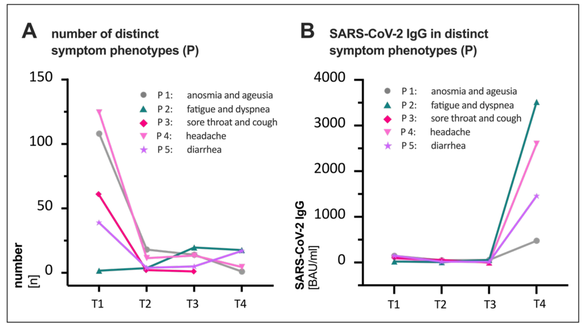

Figure 2 **A** Distribution of distinct symptom phenotypes (P) at the respective visit (T1, T2, T3 and T4) **B** SARS-CoV-2 immunoglobulin G (IgG) titers (BAU/ml) in distinct phenotypes over time. SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; BAU, binding antibody protein; ml, milliliter.

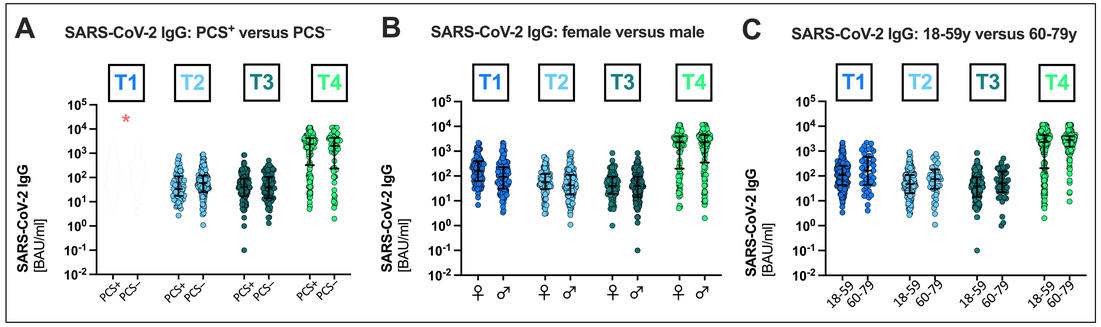

Figure 3 Stratified SARS-CoV-2 immunoglobulin G (IgG) titers (BAU/ml) based on **A** presence/absence of post-COVID syndrome (PCS), **B** sex and **C** age. PCS+, patients with PCS; PCS−, patients without PCS; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; BAU, binding antibody protein; ml, milliliter; y, years.
* According to the PCS definition by WHO, PCS not existent earlier than 3 months after symptom onset.

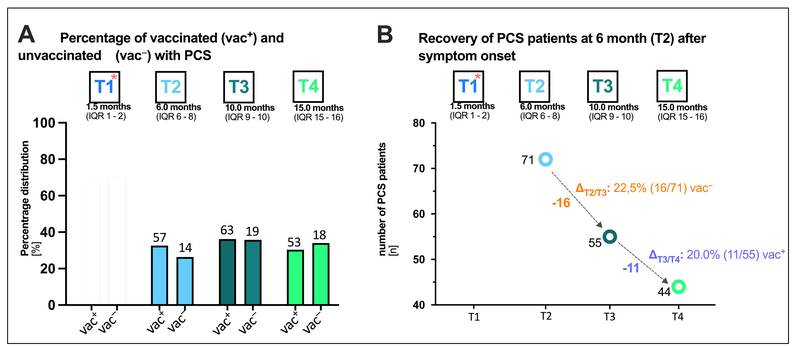

Figure 4 PCS in vaccinated and unvaccinated SARS-CoV-2 convalescents **A** Absolute (n) and percentage (%) distribution of patients with post-COVID syndrome (PCS) at the respective visit (T1, T2, T3, T4). **B** Recovery of PCS patients between T2 and T3 (ΔT2/T3) without vaccination and between T3 and T4 (ΔT2/T3) following vaccination, respectively. WHO, world health organisation.
* According to the PCS definition by WHO, PCS not existent earlier than 3 months after symptom onset.

Conclusions

Our results indicate, that distinct symptom phenotypes change longitudinally: Baseline symptoms were not dominant in long-term PCS 15 months after mild COVID-19. Recovery of PCS was observed similarly in both therapeutically vaccinated and unvaccinated patients. Thus, development of targeted PCS therapeutics is needed to improve patient care and future epidemiological investigations.

References

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