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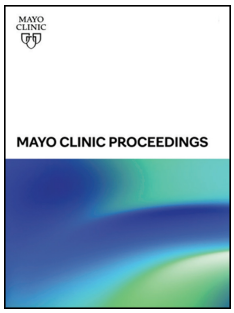

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Impact of COVID-19 vaccination on post-COVID syndrome across clinical definitions and phenotypes: a prospective multicenter cohort study

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Abstract

Objectives: To assess the impact of COVID-19 vaccination on distinct clinical definitions and phenotypes of post-COVID syndrome (PCS) and identify risk factors for PCS despite vaccination.

Methods: Data were drawn from the German National Pandemic Cohort Network (NAPKON), including adult COVID-19 patients with known vaccination status recruited between December 2, 2020, and February 13, 2023. PCS prevalence was assessed using 3 clinical definitions: the broad WHO definition (any sequelae at 3 months), symptom clusters (Fatigue, Respiratory, Cognitive), and a symptom-based PCS score reflecting clinical severity. Multivariable logistic regression was employed to estimate the protective effect of vaccination.

Results: Among 756 patients, 26% were fully vaccinated (≥2 doses) before infection. Vaccination was associated with a significantly reduced risk of PCS according to the WHO definition (OR 0.555, 95% CI 0.339–0.906), the PCS score (OR 0.536, 95% CI 0.335–0.856), the Respiratory Cluster (OR 0.508, 95% CI 0.295–0.875), and the Cognitive Cluster (OR 0.443, 95% CI 0.213–0.923). In contrast, no protective association was observed for the Fatigue Cluster (OR 0.917, 95% CI 0.554–1.519). The favorable association with vaccination was particularly observed in patients with mild acute symptoms, regardless of hospitalization. The protective effect of vaccination persisted at 12-month follow-up, although fatigue remained unaffected.

Conclusion:-Findings indicate that broader PCS definitions may mask clinically relevant heterogeneity and support the need for differentiated, phenotype-oriented definitions that reflect clinical presentations of PCS, including differential responses to vaccination. Such refined clinical definitions may facilitate exploration of whether these phenotypes reflect distinct underlying pathophysiological mechanisms.

Clinical Trials registration

NAPKON is registered on ClinicalTrials.gov (identifier: NCT04768998).

Key words

Post-COVID syndrome, long COVID, PASC, vaccines, SARS-CoV-2, fatigue

Abbreviations

PCS	Post-COVID syndrome
WHO	World Health Organization

OR	Odds Ratio
CI	Confidence Interval
NAPKON	German National Pandemic Cohort Network
SUEP	Cross-sectoral Platform in NAPKON
COVID	Coronavirus disease
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
CCI	Charlson Comorbidity Index
3MFU	3-month follow-up
12MFU	12-month follow-up

Introduction

Following an infection with SARS-CoV-2, a substantial proportion of patients experience post-acute sequelae, commonly referred to as post-COVID syndrome (PCS), post-COVID condition, or long COVID.[1, 2] PCS is characterized by a wide range of symptoms, with fatigue, respiratory, and cognitive impairments being the most common. Some individuals are severely affected, to the point where they are unable to work or even leave their homes.[3]

According to the consensus definition of the World Health Organization (WHO), symptoms must be present for at least 2 months and persist beyond 3 months after an infection with SARS-CoV-2.[4] However, this definition has been criticized for its lack of specificity.[5] Therefore, clinically oriented scores, such as the PCS score, have been developed to classify severity grades.[6] Similarly, PCS subtypes based on symptom phenotypes aim to provide a more nuanced understanding of the condition, facilitating tailored clinical management.[7]

The advent of highly effective vaccines against SARS-CoV-2 has raised new questions about their potential impact on the incidence of PCS. A recent review reported that vaccination prior to infection was associated with a reduced risk of developing long-term sequelae in 10 out of 12 studies.[8] However, the review highlighted the heterogeneity of PCS definitions, follow-up periods, or study populations, which complicated the interpretation and comparability. Previous studies provided only limited insight into how vaccination affects clinical severity or specific PCS symptoms, leaving gaps in understanding how vaccination affects the broader spectrum of PCS. Moreover, little is known to which extent vaccination influences various risk factors associated with PCS.

The present study aims to address these gaps by examining the impact of preventive vaccination prior to infection on the prevalence and clinical expression across different definitions of PCS utilizing data from a prospective, multi-center cohort in Germany with a 12-month follow-up. Additionally, it seeks to identify significant risk factors for the development of PCS despite vaccination.

Methods

Study population

This study analyzed data from the Cross-Sectoral Platform (SUEP) of the German National Pandemic Cohort Network (NAPKON). The SUEP includes SARS-CoV-2 positive patients from all sectors of the German healthcare system, including university hospitals, non-university hospitals, and the outpatient sector. Patients completed detailed questionnaires at baseline (maximum 96h after SARS-CoV-2 detection), 3 months (3MFU), and 12 months (12MFU) after enrollment, either face-to-face or via telephone. Depending on the health care sector of recruitment, additional interim surveys were

conducted. The questionnaires included comprehensive clinical information on the short- and long-term course of COVID-19, including patient-reported outcome measures (PROMs), imaging data, and biosamples, along with a detailed medical history and socio-demographic information. The NAPKON study design has been previously described.[9]

NAPKON was initiated in July 2020, and patients for the present study were included from December 2, 2020, to February 13, 2023. By May 13, 2023, the latest study update, a total of 2,680 patients had been enrolled in the SUEP cohort. For this analysis, we included all adult patients (age ≥ 18 years) with follow-up information available for at least 3 months and known COVID-19 vaccination status prior to infection. The case numbers differ across the PCS definitions due to varying rates of missing data for the symptoms required by each definition (see results). As 12-month data were not available for all patients, we focused our analyses on the 3-month time point and report 12-months analyses in the appendix.

In the SUEP, each patient was asked whether they had received one or more doses of a SARS-CoV-2 vaccine, with vaccination dates recorded where applicable. To ensure an accurate assessment of vaccination status, only vaccinations at least 6 weeks before baseline were considered to allow sufficient time for an immunological response prior to infection, and 31 patients with invalid vaccination dates (e.g., identical dates for the first and second dose) were excluded.

Sequencing data for SARS-CoV-2 variants were available for only 276 patients. Analyses restricted to sequenced cases would have disproportionately reflected Alpha infections, likely due to more frequent sequencing during the early pandemic phase. As a result, virus variants could not be included as covariates in the main regression model. To obtain a more representative distribution of virus variants within the cohort, we therefore imputed variants based on the predominant circulating variant in Germany at the time of infection, as reported in the weekly surveillance reports of Germany's public health institute (https://public.data.rki.de/t/public/views/IGS_Dashboard/DashboardVOC?%3Aembed=y&%3AisGuestRedirectFromVizportal=y).

Symptoms and PCS definitions

According to the diagnostic criteria for PCS, symptoms must persist for at least 3 months following the onset of COVID-19. To ensure that symptoms were attributable to COVID-19, we included only those that began no earlier than 28 days before and no later than 12 weeks after baseline, recognizing that the infection date and baseline date may not align in the dataset. Additionally, PCS symptoms must have persisted for at least 2 months. Symptom duration was recorded using predefined categorical time intervals in the dataset (e.g., "1 day", …, "8-14 days",…, „61-120 days", „121-180 days", "181-365 days", "ongoing"). To allow a consistent comparison across the 3 PCS definitions, we standardized the

symptom assessment time frame. Thus, aligned with the categorical data limits, we considered only symptoms with a duration of at least 61–120 days and used the maximum symptom duration. For symptoms reported as *ongoing*, the date of the most recent interview was used to approximate symptom duration or cessation. Using this approach, we evaluated the prevalence of PCS for 3 clinical definitions, which primarily differ in the symptoms they include:

1. WHO definition of PCS

The WHO defines PCS as any sequela persisting 3 months after the onset of COVID-19 and lasting for at least 2 months.[4] Due to the broad and non-specific nature of this definition, we included all 31 symptoms recorded in the NAPKON-SUEP database as potential PCS symptoms: fever, loss of appetite, lymph node swelling, dizziness, headache, ear pain, chest pain, myalgia, arthralgia, skin or mucosal changes, sore throat, rhinorrhea, nasal congestion, sneezing, coughing, dyspnea, wheezing, abdominal pain, nausea, vomiting, diarrhea, taste disorders, smell disorders, visual impairment, oculomotor disorders, aphasia, neuralgia, ataxia, orientation disorder or confusion, cognitive impairments, and other symptoms (including fatigue). Patients with missing data for any symptom were excluded from the analysis for the WHO definition.

2. Symptom clusters

The symptom clusters were defined by adapting the framework by the Global Burden of Disease Long COVID Collaborators to our dataset [7]: The Fatigue Cluster includes symptoms such as fatigue, dizziness, headache, myalgia, or arthralgia. The Respiratory Cluster includes coughing, dyspnea, wheezing, or other respiratory-related symptoms. The Cognitive Cluster includes orientation disorder, confusion, cognitive impairments, or other symptoms of impaired cognitive function. Patients were assigned to a given cluster if they exhibited at least 1 of the corresponding symptoms. To ensure accuracy and consistency, 2 authors independently coded and validated the assignment of symptoms. Patients could be assigned to multiple clusters if their symptoms overlapped. Missing data for symptoms defining the clusters led to variations in case counts across clusters.

3. Post-COVID syndrome score

The PCS score was originally developed in the Population-Based Platform (POP) cohort of NAPKON and later adapted for the SUEP cohort.[6, 10] This study uses the version without PROMs. The score evaluates 12 symptom complexes: chemosensory deficits, fatigue, exercise intolerance, joint or muscle pain, ear-nose-throat ailments, coughing/wheezing, chest pain, gastrointestinal ailments, neurological ailments, dermatological ailments, signs of infection, and sleep disturbances. Each symptom complex is assigned a weighted value ranging from 2 to 7, reflecting the clinical severity of these symptoms. The final score

encompasses 4 categories: no PCS (0 points), mild PCS (>0 to ≤10.75), moderate PCS (>10.75 to ≤26.25), and severe PCS (>26.25).

Data analysis

For the descriptive analysis, we calculated the mean (M) and standard deviation (SD) for metric variables, and the absolute and relative frequencies for categorical or dichotomous variables. Group differences in categorical variables were tested for statistical significance using the chi-squared test, while differences in means were analyzed using analysis of variance (ANOVA). Statistical significance was defined as P values below .05.

In the multivariable analysis, we used logistic regression models for each PCS definition to estimate the odds ratios (OR) of potential risk factors for PCS. For this purpose, the ordinal PCS score was dichotomized into a binary variable (no PCS vs. PCS of any severity). A log-ordinal regression model was performed as a sensitivity analysis for the PCS score. Covariates included in the multivariable models were selected using stepwise regression from the descriptive variables listed in Table 1, or based on their relevance as established in previous studies.[11] Stepwise selection was performed using conventional thresholds, with variables entering the model at $p<.15$ and being removed at $p>.20$. Model fit was assessed using Pseudo-R^2. Due to limited data on SARS-CoV-2 sequencing in 276 patients, the virus variants were not included in the model. To ensure model stability given limited subgroup sample sizes, fully vaccinated (≥2 doses) and boosted individuals (≥3 doses) were combined in this model.

All statistical analyses were performed using STATA version 18.0 and R 4.4.2.

Ethics statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. For the NAPKON-SUEP cohort, primary ethical approval was obtained from the Ethics Committee of the Department of Medicine at Goethe University Frankfurt (approval ID: 20-924). All additional study sites received approval from their respective local ethics committees. NAPKON is registered on ClinicalTrials.gov (identifier: NCT04768998). Ethical approval for the present study was granted by the Ethics Committee of the University Hospital and Faculty of Medicine of the Eberhard Karls University Tübingen (approval ID: 421/2022BO2).

Results

Study population

The cohort comprised 787 adults with COVID-19, of whom 756 had valid information on vaccination status prior to infection and were included in the analysis. The number of patients assessed differed

depending on the PCS definition applied: 579 patients for the WHO definition, 627 for the Fatigue Cluster, 589 for the Respiratory Cluster, 717 for the Cognitive Cluster, and 606 for the PCS score (Figure 1).

Mean age was 53.9 years, with a majority being male (n=439, 58.1%) and hospitalized during the acute phase of COVID-19 (n=632, 83.7%). According to the WHO Clinical Progression Scale adapted to the NAPKON dataset, most patients had moderate acute COVID (n=474, 66.6%). Based on imputed data, the predominant SARS-CoV-2 variants were Alpha (n=298, 39.4%), Delta (n=213, 28.2%), and Omicron (n=141, 18.6%). Regarding vaccination, 43 (5.7%) patients had received a single dose, while 196 (25.9%) had received ≥2 prior to infection. A detailed characterization of the study population is provided in Table 1.

Among vaccinated individuals, 189 (83.6%) received mRNA vaccines, 13 (5.8%) vector-based vaccines, and 24 (10.6%) a combination of both. Patients who received ≥2 doses were less likely to be hospitalized and experienced less severe courses of acute COVID-19 compared to unvaccinated individuals. Based on imputed data, Omicron was the most prevalent variant among vaccinated individuals, whereas Alpha dominated among the unvaccinated, reflecting the vaccine availability and prioritization policy after the Alpha wave. A more detailed comparison of vaccinated and unvaccinated patients is shown in Supplemental Table 1.

Assessment of PCS at 3 months

In the total sample, the most commonly reported PCS-related symptoms at 3 months were respiratory problems (n=190, 32.2%), fatigue (n=95, 13.3%), and cognitive impairment (n=86, 12.0%) (Figure 2). Based on the WHO definition, 367 patients (63.4%) experienced at least 1 sequela 3 months after infection (Table 1). Regarding specific symptom clusters, 44.3% of patients (n=233) exhibited symptoms from at least 1 cluster; of these, 174 patients (27.8%) reported symptoms from the Fatigue Cluster, 190 (32.3%) from the Respiratory Cluster, and 86 (12%) from the Cognitive Cluster. Using the PCS score, which emphasizes certain clinical conditions, a total of 285 patients (47.0%) had PCS. Of these patients, 27.0% had mild PCS, 16.7% moderate PCS, and 3.3% severe PCS.

Effect of vaccination on PCS risk

Vaccination prior to infection was inversely associated with PCS across all definitions except for the Fatigue Cluster. Among vaccinated (≥1 doses) and unvaccinated patients, 104 (52.3%) and 263 (69.2%) met the WHO definition of PCS, 55 (25.6%) and 119 (28.9%) were in the Fatigue Cluster, 38 (18.8%) and 152 (39.3%) in the Respiratory Cluster, 17 (7.6%) and 69 (14.0%) in the Cognitive Cluster, and 77 (37.0%) and 208 (52.3%) met the PCS criteria according to the PCS score, respectively (Table 1).

We used a multivariable logistic regression model developed through stepwise regression to estimate the influence of vaccination on PCS while controlling for age, sex, BMI, hospitalization status, and comorbidities (Table 2). Vaccination with ≥2 doses significantly reduced the likelihood of PCS according to the WHO definition (OR 0.555, 95% CI 0.339–0.906), the PCS score (OR 0.536, 95% CI 0.335–0.856), the Respiratory Cluster (OR 0.508, 95% CI 0.295–0.875), and the Cognitive Cluster (OR 0.443, 95% CI 0.213–0.923). Thus, the model confirmed the protective effect of vaccination in all PCS definitions except for the Fatigue Cluster (OR 0.917, 95% CI 0.554–1.519).

Sensitivity analyses using an alternative model, a log-ordinal model for the PCS score, and a balanced cohort-design (only patients with completed 12-MFU) yielded results consistent with the primary analyses (Supplemental Tables 2, 3, and 4). In another sensitivity analysis using vaccination categories of 0–1–2–3+ doses, the overall protective effect of vaccination persisted, although effect sizes and statistical significance varied by PCS definition (Supplemental Table 5). Sensitivity analyses including the imputed (Supplemental Table 6) and non-imputed virus variants (Supplemental Table 7) indicated a statistically non-significant trend toward a protective effect of vaccination. However, these results should be interpreted with caution due to potential misclassification in the imputed analyses and the substantially reduced sample size in the non-imputed analyses.

Depending on the model, n=75 to n=109 patients (13–18%) were excluded because of missing covariates, most frequently due to missing BMI values. Supplemental Table 8 provides a descriptive comparison between included and excluded patients, showing only small differences between groups.

We also analyzed the effect of vaccination on the 5 most prevalent symptoms with sufficient case counts (Supplemental Table 9). Vaccination with ≥2 doses was associated with a reduction of all 5 symptoms except fatigue.

Other predictive factors for PCS

In the descriptive analysis (Table 1), patients with PCS according to the WHO, the Respiratory Cluster, and the PCS score were more frequently hospitalized during acute COVID-19 and experienced more severe acute disease. Additionally, these patients were more likely to have at least 1 comorbidity. However, in the Fatigue and Cognitive Clusters, these observations were not statistically significant, except for clinical severity in the Cognitive Cluster.

The multivariable logistic regression model identified predictive factors for PCS across all 3 PCS definitions (Table 2). An inverted U-shaped association with age was observed in all definitions, with a decreasing probability of PCS in younger and older individuals. A significant risk elevation for PCS in women was observed only in the WHO definition (OR 1.547, 95% CI 1.020–2.344), although a similar trend was noted in all definitions except for the Respiratory Cluster. Hospitalization increased the risk

of PCS according to the WHO definition, the PCS score, and in the Respiratory Cluster, with the strongest association observed in patients treated on ICU, who had a markedly higher likelihood of symptoms in the Respiratory Cluster (OR 5.435, 95% CI 2.141–13.799). In contrast, hospitalization was associated with a reduced risk of symptoms in the Fatigue and Cognitive Cluster. The predictive effect of comorbidities varied across PCS definitions. In particular, neuropsychiatric comorbidities significantly increased the risk of PCS in the WHO definition (OR 2.052, 95% CI 1.076–3.915) and in the Fatigue Cluster (OR 1.924, 95% CI 1.114–3.322). Conversely, immunodeficiency reduced the risk of PCS across all definitions.

The inclusion of specific comorbidities increases the number of variables included in the main model and could lead to unstable results. Therefore, we applied an alternative model substituting clinical severity during acute COVID-19 for hospitalization and using the Charlson Comorbidity Index (CCI)[12] instead of specific comorbidities (Supplemental Table 2). This sensitivity analysis yielded robust results with respect to the vaccination effect, supporting the validity of the main model. A severe acute course of COVID-19 significantly increased the risk of PCS in the Respiratory and Cognitive Clusters. Additionally, a higher CCI was associated with an increased risk of PCS across all definitions.

Assessment at 12 months

Valid data at 12 months after baseline were available for 562 patients, of whom 127 (22.6%) had received ≥2 vaccine doses prior to infection. Across all definitions, the proportion of patients with PCS declined only slightly compared with the three-month assessment (Supplemental Table 10).

Notably, the proportion of unvaccinated patients with PCS increased further. Specifically, 77.9% of patients with PCS according to the WHO definition, 73.7% in the Fatigue Cluster, 84.5% in the Respiratory Cluster, 89.7% in the Cognitive Cluster, and 78.5% with PCS according to the PCS score were unvaccinated. There were significantly more unvaccinated individuals among patients with PCS than among those without PCS, except in the Fatigue Cluster. In the 12-month regression models, receiving ≥2 vaccine doses remained a negative predictor of PCS across all definitions, although the effect was not statistically significant in the Fatigue Cluster (OR 0.971, 95% CI 0.512–1.843). The predictive effects of most other covariates remained consistent to three months (Supplemental Tables 11, 12).

Vaccinated individuals at risk for PCS

We compared PCS rates between unvaccinated patients and those fully vaccinated (≥2 vaccine doses) (Figure 3 and Supplemental Tables 13–17). Patients with only 1 vaccination were excluded in the following due to the empirical results described above and the unclear clinical classification. Given the limited number of vaccinated individuals with symptoms in the Cognitive Cluster (n=14), this PCS

definition was not included in the forest plot in Figure 3, and the odds ratios in Supplemental Table 16 should be interpreted with caution. Similarly, small sample sizes prevented reliable conclusions regarding the effectiveness of specific vaccine types or their interaction with SARS-CoV-2 variants, which is why these variables were also not included in the forest plots.

Across all PCS definitions, vaccinated individuals with the lowest PCS rates were those aged 35–49 years, with no comorbidities, no polypharmacy, or a history of never smoking. There was no difference between sexes. Regarding disease severity during the acute phase of COVID-19, vaccination was particularly beneficial for those who experienced mild acute symptoms, regardless of hospitalization status. However, in the Respiratory Cluster, this association did not reach statistical significance. A beneficial association with vaccination was observed in patients both with and without pre-existing conditions, with a modestly greater effect among those without comorbidities. Interpretation of the effects of specific pre-existing conditions was limited by small sample sizes. Notably, within the Fatigue Cluster, vaccinated individuals with neuropsychiatric comorbidities exhibited an increased risk of developing PCS.

In addition to the main regression model in Table 2, we calculated a regression model using the same variables as in the main model, but exclusively for individuals with ≥2 vaccine doses (Supplemental Table 18). Again, due to the limited number of vaccinated patients with cognitive symptoms, we did not calculate this regression for the Cognitive Cluster. Although the model did not reach statistical significance, some variables displayed trends consistent with the main model. Across all definitions, women remained at risk for PCS, and the U-shaped association of PCS with age was preserved. Hospitalization status remained a statistically non-significant risk factor for vaccinated patients in most definitions but not in the Fatigue Cluster. Regarding comorbidities, neuropsychiatric conditions were a strong predictor of PCS across all definitions and had an even stronger influence than in the main model. The trend for a protective effect of immunodeficiency persisted across all definitions. Building on the regression model restricted to individuals with ≥2 vaccine doses, we conducted an additional analysis including vaccine type (Supplemental Table 19). The results were consistent with those of the main model. Given the very limited sample sizes in this analysis, findings should be interpreted with particular caution and considered exploratory. As a further sensitivity analysis, we calculated a regression model analogous to the main model, including vaccinated and unvaccinated patients but excluding the variable for vaccination status, and observed consistent results (Supplemental Table 20).

Discussion

By analyzing a multi-center prospective cohort in Germany, we observed that individuals who received ≥2 vaccine doses prior to infection with SARS-CoV-2 had a significantly lower risk of developing PCS

across various clinical definitions, with the exception of the Fatigue Cluster. This study aligns with previous research supporting the protective effect of SARS-CoV-2 vaccination in mitigating long-term sequelae of COVID-19.[8, 13, 14] However, our study goes beyond prior investigations by incorporating clinical definitions of PCS such as symptom clusters and a clinical PCS score, thus providing a more nuanced assessment of PCS phenotypes and severity.

Impact of COVID-19 vaccination prior to infection

A recent meta-analysis reported a reduction in PCS risk among fully vaccinated individuals, with an OR of 0.76 (95% CI 0.65–0.89).[14] In our cohort, we observed an even stronger protective effect, with an OR of 0.555 (95% CI 0.339–0.906) for the WHO definition of PCS, OR 0.536 (95% CI 0.335–0.856) for the PCS score, OR 0.508 (95% CI 0.295–0.875) for the Respiratory Cluster, and OR 0.443 (95% CI 0.213–0.923) for the Cognitive Cluster. This pronounced effect may be attributed to the high proportion of patients hospitalized for acute COVID-19 in our sample. Notably, the protective effect of vaccination remained stable or even slightly increased at the 12-month assessment, aligning with recent evidence suggesting a durable protective effect against PCS.[15] With respect to single-dose vaccination, our data indicated a non-significant protective trend. The lack of statistical significance is likely due to the limited sample size of single-dose recipients (n=43). A meta-analysis of 10 studies found no significant protective effect following a single vaccine dose,[14] whereas a large Swedish cohort study reported a modest but significant reduction in PCS risk.[16] Evaluation of waning immunity after vaccination is complex and depends on factors such as virus variants, booster vaccinations, and re-infections.[17] Therefore, and given the limited number of patients with sufficient time between vaccination and infection, we did not perform additional analyses on waning immunity. However, we acknowledge that this remains an important question for future research.

An intriguing finding was that neither the symptom fatigue nor the Fatigue Cluster showed a significant association with vaccination. Our results are consistent with previous studies reporting limited effectiveness of COVID-19 vaccination in preventing fatigue. For example, a prospective survey conducted during the omicron wave in the US found no difference in the prevalence of fatigue between fully vaccinated and unvaccinated individuals at both 3 and 6 months after infection.[18] Similarly, a study conducted before the emergence of the omicron variant found no significant difference in fatigue between fully vaccinated and unvaccinated individuals, despite a protective effect of vaccination on several other PCS symptoms.[19] An analysis of the STOP-COVID registry at 12 months also found no reduction in the likelihood of fatigue among fully vaccinated individuals.[20] However, other studies have reported a protective effect of vaccination against fatigue. A retrospective study from the US found a lower likelihood of developing fatigue in vaccinated individuals,[21] and a study from Israel reported that receiving 2 vaccine doses was associated with a 64% reduction in the risk of experiencing fatigue

following COVID-19.[22] Likewise, a US study analyzing the impact of a bivalent vaccine observed a risk reduction for fatigue after vaccination.[23] These conflicting findings underscore the need for further research on the relationship between vaccination and fatigue.

A potential explanation for our findings is that fatigue, as captured by the symptom cluster, may have a distinct underlying pathogenesis. COVID-19 vaccines have been demonstrated to reduce the risk of hospitalization during acute COVID-19,[24] which may represent one mechanism through which they confer protection against PCS. A previous study employing a mathematical model of the immune response to COVID-19 vaccination suggested that vaccination reduces viral load in the acute phase, thereby limiting tissue damage and severe acute COVID-19. However, it does not prevent viral persistence.[25] This observation may help explain our results, as the severity of acute COVID-19 and hospitalization were not identified as risk factors for the Fatigue Cluster, in contrast to other PCS definitions (Tables 1 and 2). Consistent with our findings, a retrospective analysis conducted in the UK similarly reported no association between fatigue and the severity of acute COVID-19.[26] Furthermore, in our study, vaccination demonstrated a significantly stronger protective effect against fatigue in individuals who were not hospitalized or who experienced mild acute COVID-19 (Figure 3). This suggests that while vaccination may reduce the severity of acute infection, thereby lowering the risk of most post-acute sequelae, it may have a limited effect on the central mechanisms underlying fatigue. Currently, mechanisms like neuroinflammation, dysfunction of the blood-brain barrier, or viral persistence and reactivation are discussed for neurologic sequelae of COVID-19.[27] Our findings suggest that post-viral fatigue may partly evade mechanisms currently discussed for vaccine-induced immunity like attenuation of the severity of acute COVID-19 or viral clearance.[28]

Notably, neuropsychiatric comorbidities emerged as a significant risk factor for PCS in the Fatigue Cluster, even among vaccinated individuals. However, we did not distinguish between neurological (e.g., stroke, Parkinson's disease) and psychiatric comorbidities, and sample sizes within comorbidity subgroups were partly small. Despite this limitation, our results are consistent with previous studies suggesting that pre-existing mental health conditions may increase susceptibility to fatigue and other PCS symptoms [29]. However, the association between preexisting mental health disorders and fatigue has also been observed in non-COVID-19 control groups.[30]

A strength of our study is the stratified analysis of COVID-19 vaccine effectiveness based on distinct patient characteristics. There is limited evidence on how vaccine effectiveness varies across factors such as sex, age, and pre-existing conditions. An early study using the COVID Symptom Study app reported greater effectiveness of 2 vaccine doses in preventing symptoms lasting 28 days or more among younger adults (18–59 years).[31] Despite the differences in methodology, these findings align with our results. The Swedish cohort study reported higher vaccine effectiveness in men compared to

women and in patients with diabetes compared to those with other comorbidities.[16] In our analysis, both sexes benefited equally, especially patients without comorbidities.

Another intriguing finding was that immunodeficiency appeared to confer a protective effect against PCS. This supports the hypothesis that immune dysregulation and hyperactivation are key etiological factors in the development of PCS,[32, 33] a concept also explored in therapeutic studies.[34] However, while clinical studies on this topic remain limited, there is no clear evidence that immunodeficiency provides a protective effect. In fact, studies have even reported an increased risk of PCS among patients with primary immunodeficiency,[35, 36] contradicting our findings, which were limited to individuals with acquired immunodeficiency. This discrepancy should be addressed in future studies.

Prevalence and PCS phenotypes across distinct definitions

In our cohort, 63.4% of patients reported persistent symptoms at 3 months after infection when applying the WHO definition, a rate comparable to prior studies using broad PCS criteria.[37] While the WHO definition of PCS encompasses a large number of individuals, it lacks specificity and does not differentiate between clinical phenotypes or disease severity.

In contrast, when applying specific symptom clusters, PCS prevalence ranged from 12.0% in the Cognitive Cluster to 32.3% in the Respiratory Cluster. Using the PCS score, which integrates symptom severity, 47.1% of patients were categorized as having PCS, including 3.3% with severe PCS. This is in line with a previous study in the NAPKON-SUEP cohort, which reported a PCS prevalence of 42% based on the PCS score [10]. Furthermore, PCS symptoms showed only a modest decline between the 3-month and 12-month assessments across all definitions, which is consistent with previous longitudinal studies indicating that PCS symptoms can persist for over a year, particularly among unvaccinated individuals.[38]

Our findings are limited by small sample sizes in several subgroup analyses, resulting in reduced statistical power. Accordingly, the findings should be interpreted as exploratory and considered hypothesis-generating, requiring replication in larger and more diverse cohorts (e.g., with a higher proportion of outpatients). Nevertheless, these clinical-epidemiological observations, interpreted in the context of current literature, underscore the complexity of PCS and emphasize the need for refined classification criteria that reflect clinical presentations of PCS, including differential responses to vaccination. Also, risk factors commonly reported in the literature, such as female sex and hospitalization during acute COVID-19,[39, 40] were not consistently associated with PCS when specific symptom clusters, such as the Fatigue and Cognitive Cluster, were considered. Additionally, the predictive value of comorbidities varied depending on the PCS definition applied, emphasizing the role of different pre-existing conditions in specific PCS manifestations. This suggests that distinct

pathophysiological mechanisms may underlie different manifestations of PCS, based on pre-existing comorbidities.[41]

To better understand the pathological basis of the diverse manifestations of PCS, numerous studies have focused on identifying distinct clinical phenotypes or clusters that may be driven by unique underlying pathophysiological mechanisms.[42] However, the influence of vaccination on these emerging phenotypes remains less well studied.[43] Our findings indicate that prior vaccination does not affect all PCS phenotypes equally.

Thus, our study underscores the advantages of clinical PCS definitions over the broad WHO definition, which may encompass a heterogeneous patient population. In contrast, clinical PCS definitions that account for specific symptom clusters may be better suited for identifying relevant subgroups with common pathophysiological pathways. Distinguishing between different symptom constellations and severity levels within the broad PCS spectrum is crucial for improving diagnostic accuracy and optimizing patient care. Future research should focus on developing standardized criteria that allow for a more granular differentiation of PCS subtypes, while integrating biological data wherever possible, thereby facilitating both clinical decision-making and research efforts. This will also be essential for other post-acute infection syndromes, especially as routine clinical testing for SARS-CoV-2 becomes less frequent.

Strengths and Limitations

This study uses data from a large national multicenter cohort and is the first to analyze the impact of vaccination on distinct PCS phenotypes. However, it has several limitations. First, our study was observational, which limits causal inference. Second, all symptoms were self-reported and may therefore be subjected to recall bias or reduced objectivity. Third, this study did not include a SARS-CoV-2 negative control group. Fourth, our cohort exhibited an above-average disease burden with a correspondingly high prevalence of comorbidities. In particular, 84% of the patients required hospitalization during the acute phase of COVID-19. This may bias the results toward more severe acute courses and limits the generalizability of our findings to patients with mild infections. Fifth, findings may not apply to non-European cohorts. Sixth, only patients with confirmed SARS-CoV-2 infection were included, which probably underestimates the effectiveness of vaccines to prevent PCS, given that the vaccination prevents symptomatic infection.[44] Seventh, a subgroup analysis by vaccine type could not be conducted. Previous research has demonstrated that BNT162b2 is not only more effective than ChAdOx1 in preventing acute infection, but also in reducing the risk of long-term sequelae.[45]

Finally, due to incomplete sequencing of SARS-CoV-2 variants, we did not include the virus variant as a covariate in the main regression model. While most unvaccinated individuals in our cohort were

infected with the Alpha variant, the majority of vaccinated individuals contracted the Omicron variant. Consequently, we cannot rule out that the observed association between vaccination and PCS risk reduction may be partially confounded by variant-specific effects rather than being solely attributable to vaccination itself. Previous studies have shown that the PCS prevalence varies across virus variants, with higher rates observed in individuals infected with the Delta and pre-Delta variants compared to those infected with Omicron.[46, 47] However, after adjusting for vaccination status, this difference was no longer significant.[48] Similarly, a study involving 441,583 patients found that approximately one-third of the variation in PCS prevalence was attributable to era- and variant-related factors, whereas two-thirds was attributable to the effects of vaccination.[49] In our study, the sensitivity analysis incorporating imputed virus variants indicated a trend toward a protective effect of vaccination, although this did not reach statistical significance. While residual confounding cannot be entirely excluded, our findings suggest that the observed protective association is unlikely to be solely attributable to differences in variant distribution. Future studies with comprehensive viral sequencing data are warranted to disentangle these effects and yield more precise estimates of vaccine effectiveness against PCS.

Conclusion

This study provides evidence that SARS-CoV-2 vaccination is associated with a significantly reduced risk of PCS across multiple definitions, with the exception of fatigue-related symptoms. Our findings support the need for differentiated PCS classifications, which capture distinct clinical presentations, including differential responses to vaccination. In particular, symptom-based definitions and weighted symptom scores may be better suited than broader definitions to identify clinically meaningful subtypes of PCS and to capture disease severity in routine care and research settings. Clinically oriented PCS definitions will be crucial to inform targeted interventions and to improve comparability of future studies.

Given the exploratory nature of our analyses, refinement of PCS definitions will require validation across larger and more diverse cohorts, as well as integration of biological markers to elucidate the mechanisms underlying PCS in vaccinated individuals, particularly those experiencing persistent fatigue. Moreover, studies evaluating the impact of waning immunity and booster vaccination on PCS are needed.

Figure Legends

Figure 1. Flowchart study population.

Abbreviations: NAPKON-SUEP = Cross-Sectoral Platform of the National Pandemic Cohort Network; 3MFU = 3-month follow-up.

Figure 2. Most frequent post-COVID symptoms at 3 months.

*fever, rhinorrhea, nasal congestion, earache, sneezing, sore throat, lymph node swelling
**dyspnoa, coughing, wheezing
***incl. hair loss

Figure 3. Forest plots depicting risk factors for post-COVID syndrome in vaccinated compared to unvaccinated individuals.

[a] Binary logistic regressions with PCS risk as outcome, adjusting for vaccination status (reference = unvaccinated; number of vaccinations against SARS-CoV-2 given at least 6 weeks before baseline).
[b] All characteristics are measured at baseline.
[c] Body Mass Index: kg/m^2; normal weight (<24.9), overweight (25-29.9), adiposity (>30).
[d] During the acute phase of COVID-19.
[e] According to the WHO criteria adapted for NAPKON-SUEP, mild: no hospitalization and no oxygen, moderate: hospitalized and no oxygen or oxygen by mask or nasal prongs (<15 l/min), severe: hospitalized and oxygen by NIV or high flow (>15 l/min).
[f] Comorbidities diagnosed at least 28 days before baseline. Multiple counts of the same disease and acute illnesses are excluded.
[g] Comorbidities were recorded in main diagnostic groups, validated by 2 authors independently using ICD-11 codes and plain text information. Reference is none of the respective comorbidities.
[h] Medication ≤5; medication administered at least 28 days before baseline and taken continuously for at least 12 weeks.

Declarations

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Authors contributions

TK performed the statistical analysis and interpreted the data; CF wrote the manuscript and interpreted the data; HN and AS contributed to drafting the manuscript; SJ was involved in the conception of the study; all authors critically reviewed and approved the final version of the manuscript.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being

reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethics Statement

Ethical approval for the present study was granted by the Ethics Committee of the University Hospital and Faculty of Medicine of the Eberhard Karls University Tübingen (approval ID: 421/2022BO2).

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Table 1: Patient characteristics across post-COVID definitions at 3 months[a] (continued below)

			WHO Definition					Symptom Cluster[k]						
	total		No post-COVID		post-COVID		P value[l]	Fatigue		P value[l]	Respiratory		P value[l]	Cognitive		P value[l]
Total, *n (%)*	756		212	(36.6)	367	(63.4)		174	(27.8)		190	(32.3)		86	(12.0)	
Age[b], *mean (SD)*	53.9	(16.1)	53.1	(17.3)	55.2	(15.0)	.129	54.9	(14.6)	.452	56.5	(13.4)	**.010**	54.2	(12.7)	.708
Sex, *n (%)*																
- men	439	(58.1)	133	(62.7)	205	(55.9)	.106	97	(55.8)	.328	114	(60.0)	.935	43	(50.0)	.128
- women	317	(41.9)	79	(37.3)	162	(44.1)		77	(44.2)		76	(40.0)		43	(50.0)	
BMI[c], *mean (SD)*	28.0	(5.9)	26.9	(5.6)	28.5	(6.1)	**.003**	28.9	(6.1)	**.015**	29.5	(6.1)	**.000**	29.8	(5.5)	**.005**
Vaccination[c], *n (%)*																
- no vaccination	517	(68.4)	117	(55.2)	263	(71.7)	**.000**	119	(68.4)	.705	152	(80.0)	**.000**	69	(80.2)	.084
- 1 dose	43	(5.7)	14	(6.6)	20	(5.4)		9	(5.2)		6	(3.2)		3	(3.5)	
- 2 doses	91	(12.0)	43	(20.3)	36	(9.8)		20	(11.5)		9	(4.7)		5	(5.8)	
- ≥3 doses	105	(13.9)	38	(17.9)	48	(13.1)		26	(14.9)		23	(12.1)		9	(10.5)	
Virus variant[e], *n (%)*																
- alpha	298	(39.4)	63	(29.7)	153	(41.7)	**.008**	66	(37.9)	.662	96	(50.5)	**.000**	46	(53.5)	.051
- delta	213	(28.2)	71	(33.5)	105	(28.6)		54	(31.0)		47	(24.8)		17	(19.8)	
- omicron	141	(18.6)	54	(25.5)	61	(16.6)		29	(16.7)		24	(12.6)		13	(15.1)	
- other	104	(13.8)	24	(11.3)	48	(13.1)		25	(14.4)		23	(12.1)		10	(11.6)	
Hospitalized[f], *n (%)*																
- no	123	(16.3)	57	(26.9)	48	(13.1)	**.000**	25	(14.4)	.240	11	(5.8)	**.000**	16	(18.6)	.625
- yes	632	(83.7)	155	(73.1)	318	(86.9)		149	(85.6)		179	(94.2)		70	(81.4)	
ICU	*131*	*(20.7)*	*23*	*(14.8)*	*77*	*(24.2)*	***.019***	34	*(22.8)*	*.108*	*44*	*(24.6)*	***.007***	19	*(27.1)*	*.077*
other	*501*	*(79.3)*	*132*	*(85.2)*	*241*	*(75.8)*		115	*(77.2)*		*135*	*(75.4)*		51	*(72.9)*	
Clinical severity[g], *n (%)*																
- mild	121	(17.0)	55	(27.8)	48	(13.6)	**.000**	25	(15.0)	.167	11	(5.9)	**.000**	16	(19.3)	**.012**
- moderate	474	(66.6)	124	(62.6)	231	(65.4)		111	(66.5)		127	(68.7)		46	(55.4)	
- severe	117	(16.4)	19	(9.6)	74	(21.0)		31	(18.5)		47	(25.4)		21	(25.3)	
Charlson Comorbidity Index[h], *mean (SD)*	1.09	(1.6)	1.04	(1.7)	1.20	(1.7)	.258	1.34	(1.8)	**.039**	1.20	(1.6)	.459	0.94	(1.5)	.494
No. of comorbidities[i], *n (%)*																
- none	199	(26.3)	65	(30.7)	79	(21.5)	**.014**	37	(21.3)	.130	37	(19.5)	**.015**	18	(20.9)	.173
- ≥1	557	(73.7)	147	(69.3)	288	(78.5)		137	(78.7)		153	(80.5)		68	(79.1)	
Comorbidities[i,j], *n (%)*																
- cardiovascular	187	(24.8)	51	(24.1)	100	(27.3)	.389	50	(28.7)	.284	56	(29.6)	**.033**	15	(17.4)	.130
- hypertension	295	(39.2)	85	(40.1)	152	(41.5)	.735	73	(42.0)	.312	89	(47.1)	**.038**	39	(45.4)	.180
- pulmonary	138	(18.3)	30	(14.1)	84	(23.0)	**.010**	36	(20.7)	.638	45	(23.8)	.062	17	(19.8)	.812
- kidney	89	(11.8)	24	(11.3)	44	(12.0)	.801	25	(14.4)	.221	21	(11.1)	.622	12	(14.0)	.281

- liver	57	(7.6)	16	(7.5)	31	(8.5)	.696	20	(11.5)	**.045**	18	(9.5)	.196	7	(8.1)	.778
- rheumat.-immun.	37	(4.9)	7	(3.3)	22	(6.0)	.150	12	(6.9)	.316	10	(5.3)	.782	6	(7.0)	.299
- diabetes	110	(14.6)	32	(15.1)	53	(14.5)	.841	24	(13.8)	.850	33	(17.5)	.279	11	(12.8)	.713
- neoplasia	120	(15.9)	34	(16.4)	60	(16.4)	.911	32	(18.4)	.417	29	(15.3)	.770	9	(10.5)	.181
- neuropsychiatric	109	(14.5)	21	(9.9)	64	(17.5)	**.014**	37	(21.3)	**.005**	28	(14.8)	.988	13	(15.1)	.747
- thyroid	80	(10.6)	18	(8.5)	47	(12.8)	.115	23	(13.2)	.210	26	(13.8)	.066	10	(11.6)	.571
- gastrointestinal	82	(10.9)	18	(8.5)	49	(13.4)	.076	26	(14.9)	.113	26	(13.8)	.215	10	(11.6)	.847
- immunodeficiency	50	(6.6)	22	(10.4)	16	(4.4)	**.005**	9	(5.2)	.343	6	(3.2)	**.012**	3	(3.5)	.238
- other diseases	300	(39.8)	68	(32.2)	171	(46.7)	**.001**	91	(52.3)	**.001**	86	(45.5)	**.047**	44	(51.2)	**.010**
Smoker, *n (%)*																
- never	381	(56.1)	114	(57.0)	192	(56.5)	.726	88	(54.7)	.927	103	(59.6)	.418	40	(50.6)	.434
- no, but former	237	(34.9)	66	(33.0)	120	(35.3)		56	(34.8)		53	(30.6)		32	(40.5)	
- yes	61	(9.0)	20	(10.0)	28	(8.2)		17	(10.5)		17	(9.8)		7	(8.9)	

	PCS Score								
	No		**mild**		**moderate**		**severe**		**P value**[l]
Total, *n (%)*	321	(53.0)	164	(27.0)	101	(16.7)	20	(3.3)	
Age[b], *mean (SD)*	52.3	(17.2)	56.0	(15.7)	55.7	(14.6)	54.6	(9.3)	.064
Sex, *n (%)*									
- men	194	(60.4)	102	(62.2)	52	(51.5)	9	(45.0)	.176
- women	127	(39.6)	62	(37.8)	49	(48.5)	11	(55.0)	
BMI[c], *mean (SD)*	27.3	(5.8)	28.1	(5.9)	28.8	(6.4)	29.9	(6.1)	.060
Vaccination[c], *n (%)*									
- no vaccination	190	(59.2)	120	(73.2)	71	(70.3)	17	(85.0)	**.008**
- 1 dose	20	(6.2)	9	(5.5)	3	(3.0)	2	(10.0)	
- 2 doses	57	(17.8)	18	(11.0)	8	(7.9)	0	-	
- ≥3 doses	54	(16.8)	17	(10.3)	19	(18.8)	1	(5.0)	
Virus variant[e], *n (%)*									
- alpha	111	(34.6)	72	(43.9)	39	(38.6)	13	(65.0)	.073
- delta	90	(28.0)	45	(27.4)	28	(27.7)	6	(30.0)	
- omicron	79	(24.6)	29	(17.7)	18	(17.8)	1	(5.0)	
- other	41	(12.8)	18	(11.0)	16	(15.9)	-	-	
Hospitalized[f], *n (%)*									
- no	70	(21.8)	23	(14.0)	9	(8.9)	2	(10.0)	**.009**
- yes	251	(78.2)	141	(86.0)	92	(91.1)	18	(90.0)	
ICU	*40*	*(15.9)*	*35*	*(24.8)*	*17*	*(18.5)*	*2*	*(11.1)*	.144
other	*211*	*(84.1)*	*106*	*(75.2)*	*75*	*(81.5)*	*16*	*(88.9)*	
Clinical severity[g], *n (%)*									
- mild	68	(22.4)	23	(14.3)	9	(9.0)	2	(11.8)	**.001**
- moderate	205	(67.7)	103	(64.0)	75	(75.0)	13	(76.4)	

- severe	30	(9.9)	35	(21.7)	16	(16.0)	2	(11.8)	
Charlson Comorbidity Index[h], *mean (SD)*	0.95	(1.6)	1.28	(1.8)	1.39	(1.7)	1.00	(1.3)	.058
No. of comorbidities[i], *n (%)*									
- none	96	(39.9)	39	(23.8)	17	(16.8)	8	(40.0)	**.026**
- ≥1	225	(70.1)	125	(76.2)	84	(83.2)	12	(60.0)	
Comorbidities[i,j], *n (%)*									
- cardiovascular	71	(22.1)	52	(31.7)	28	(28.0)	4	(20.0)	.117
- hypertension	125	(39.1)	65	(49.6)	46	(46.0)	7	(35.0)	.611
- pulmonary	47	(14.6)	39	(23.8)	28	(28.0)	4	(20.0)	**.010**
- kidney	35	(10.9)	21	(12.8)	14	(14.0)	3	(15.0)	.799
- liver	20	(6.2)	10	(6.1)	12	(12.0)	3	(15.0)	.122
- rheumat.-immun.	10	(3.1)	13	(7.9)	7	(7.0)	-	-	.063
- diabetes	45	(14.0)	27	(16.5)	16	(16.0)	2	(10.0)	.804
- neoplasia	51	(15.9)	28	(17.1)	18	(18.0)	4	(20.0)	.930
- neuropsychiatric	40	(12.5)	26	(15.9)	20	(20.0)	3	(15.0)	.303
- thyroid	23	(7.2)	26	(15.9)	11	(11.0)	2	(10.0)	**.030**
- gastrointestinal	33	(10.3)	17	(10.4)	18	(18.0)	3	(15.0)	.176
- immunodeficiency	28	(8.7)	8	(4.9)	5	(5.0)	-	-	.183
- other diseases	114	(35.6)	69	(42.1)	47	(47.0)	8	(40.0)	.185
Smoker, *n (%)*									
- never	162	(54.7)	87	(56.9)	58	(63.7)	11	(57.9)	.669
- no, but former	104	(35.2)	54	(35.3)	25	(27.5)	5	(26.3)	
- yes	30	(10.1)	12	(7.8)	8	(8.8)	3	(15.8)	

[a] All characteristics are measured at baseline. Discrepancies between absolute numbers and the total row are due to missing values for the respective characteristic. For metric variables the number of missing values was: age=0; BMI=106; Charlson Comorbidity Index=2.
[b] In years.
[c] Body Mass Index: kg/m².
[d] Vaccination against SARS-CoV-2 given at least 6 weeks before baseline.
[e] Missing values were imputed with the dominant variant in Germany at the time of infection according to the RKI weekly reports (https://public.data.rki.de/t/public/views/IGS_Dashboard/DashboardVOC?%3Aembed=y&%3AisGuestRedirectFromVizportal=y).
[f] During the acute phase of COVID-19.
[g] According to the WHO criteria adapted for NAPKON-SUEP, mild: no hospitalization and no oxygen, moderate: hospitalized and no oxygen or oxygen by mask or nasal prongs (<15 l/min), severe: hospitalized and oxygen by NIV or high flow (>15 l/min).
[h] According to Charlson et al.[12]
[i] Comorbidities diagnosed at least 28 days before baseline. Multiple counts of the same disease and acute illnesses are excluded.
[j] Comorbidities were recorded in main diagnostic groups, validated by 2 authors independently using ICD-11 codes and plain text information; %=proportion of patients with the comorbidity to all patients with valid information on the respective comorbidity.
[k] According to Global Burden of Disease Long COVID Collaborators.[7] Case numbers and proportions reported only for patients to whom the respective cluster applies. The clusters may overlap.
[l] Group differences assessed by chi-squared test or t-test. Bold font denotes statistical significance (P value≤.05).

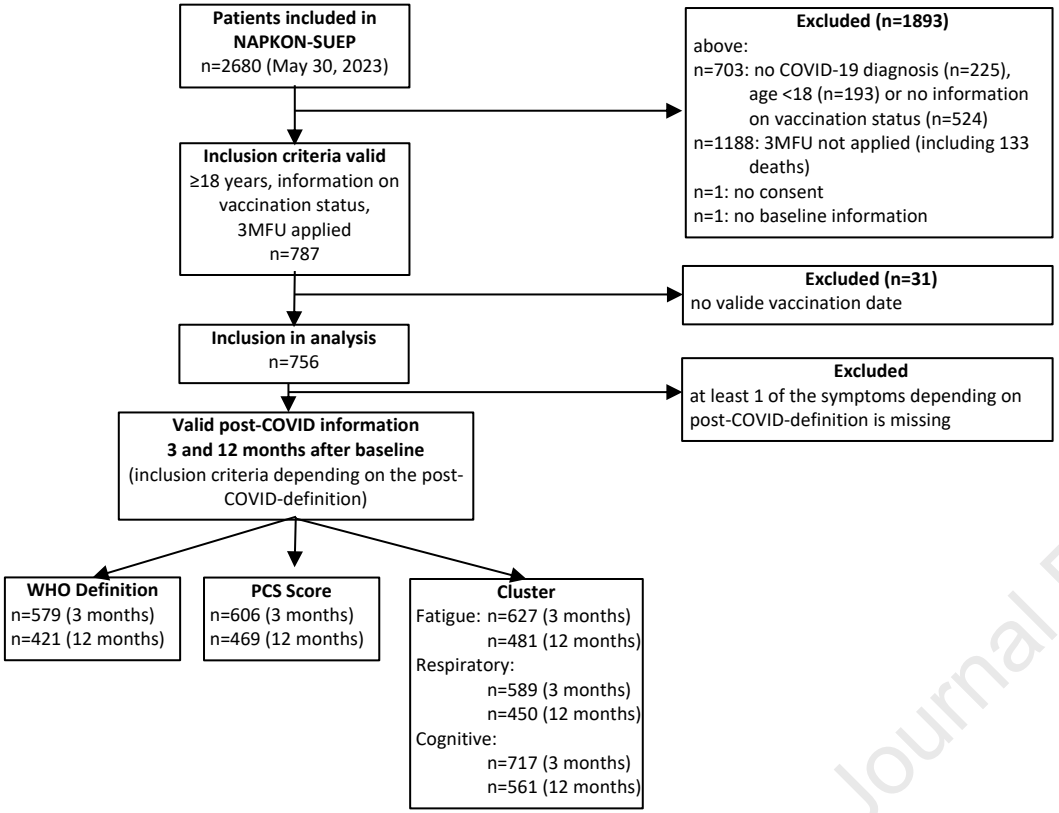
Table 2: Multivariable logistic regression models for post-COVID at 3 months[a]

	WHO Definition		Fatigue Cluster		Respiratory Cluster		Cognitive Cluster		PCS Score[g]	
	OR	**(95%-CI)**	**OR**	**(95%-CI)**	**OR**	**(95%-CI)**	**OR**	**(95%-CI)**	**OR**	**(95%-CI)**
Age[b]	**1.082**	**(1.003;1.167)**	**1.120**	**(1.032;1.217)**	**1.146**	**(1.048;1.253)**	**1.205**	**(1.062;1.367)**	**1.108**	**(1.031;1.190)**
Age squared	**0.999**	**(0.999;1.000)**	**0.999**	**(0.998;1.000)**	**0.999**	**(0.998;1.000)**	**0.998**	**(0.997;1.000)**	**0.999**	**(0.999;1.000)**
Sex										
- men (ref.)										
- women	**1.547**	**(1.020;2.344)**	1.218	(0.807;1.839)	0.973	(0.640;1.480)	1.350	(0.809;2.252)	1.147	(0.784;1.679)
BMI[c]	1.017	(0.976;1.059)	1.031	(0.993;1.071)	1.023	(0.985;1.061)	1.030	(0.983;1.079)	1.011	(0.976;1.048)
Vaccination[d]										
- no vaccination (ref.)										
- 1 dose	0.591	(0.241;1.446)	0.910	(0.351;2.357)	0.555	(0.197;1.562)	0.403	(0.088;1.847)	0.555	(0.234;1.316)
- ≥2 doses	**0.555**	**(0.339;0.906)**	0.917	(0.554;1.519)	**0.508**	**(0.295;0.875)**	**0.443**	**(0.213;0.923)**	**0.536**	**(0.335;0.856)**
Hospitalized[e]										
- no (ref.)										
- ICU	**2.375**	**(1.102;5.119)**	0.888	(0.406;1.945)	**5.435**	**(2.141;13.799)**	0.577	(0.231;1.441)	1.332	(0.644;2.753)
- other ward form	1.405	(0.758;2.604)	0.682	(0.355;1.312)	**3.556**	**(1.543;8.194)**	**0.324**	**(0.142;0.738)**	1.053	(0.573;1.937)
Comorbidities[f]										
- cardiovascular	1.097	(0.636;1.893)	1.473	(0.853;2.541)	1.663	(0.964;2.868)	0.604	(0.288;1.269)	1.355	(0.816;2.249)
- hypertension	0.688	(0.419;1.131)	0.934	(0.571;1.528)	0.834	(0.509;1.365)	1.343	(0.723;2.495)	**0.623**	**(0.392;0.988)**
- pulmonary	1.330	(0.780;2.270)	0.743	(0.436;1.266)	1.122	(0.671;1.876)	0.869	(0.440;1.715)	1.528	(0.940;2.483)
- kidney	1.833	(0.809;4.156)	1.879	(0.915;3.859)	1.235	(0.588;2.593)	**2.736**	**(1.073;6.973)**	1.822	(0.895;3.709)
- liver	0.903	(0.396;2.062)	1.772	(0.836;3.754)	1.202	(0.552;2.615)	1.045	(0.396;2.755)	1.324	(0.617;2.844)
- rheumat.-immun.	1.272	(0.471;3.432)	1.187	(0.510;2.765)	0.763	(0.296;1.964)	1.711	(0.572;5.126)	1.711	(0.717;4.081)
- diabetes	0.773	(0.418;1.432)	0.669	(0.351;1.274)	0.954	(0.524;1.737)	0.674	(0.295;1.540)	0.943	(0.533;1.667)
- neoplasia	0.938	(0.533;1.653)	1.019	(0.577;1.801)	0.973	(0.486;1.569)	0.671	(0.294;1.530)	0.974	(0.579;1.639)
- neuropsychiatric	**2.052**	**(1.076;3.915)**	**1.924**	**(1.114;3.322)**	0.857	(0.477;1.538)	0.981	(0.474;2.029)	1.547	(0.892;2.684)
- thyroid	1.124	(0.577;2.189)	1.231	(0.650;2.332)	1.734	(0.911;3.301)	1.140	(0.491;2.645)	1.763	(0.938;3.314)
- gastrointestinal	1.581	(0.779;3.206)	1.264	(0.657;2.430)	1.754	(0.912;3.375)	1.370	(0.582;3.213)	1.221	(0.655;2.274)
- immunodeficiency	**0.230**	**(0.082;0.640)**	**0.268**	**(0.094;0.767)**	**0.226**	**(0.072;0.712)**	0.265	(0.058;1.200)	**0.289**	**(0.109;0.763)**
- other diseases	1.410	(0.898;2.214)	1.521	(0.974;2.373)	1.002	(0.643;1.561)	**1.861**	**(1.073;3.226)**	0.977	(0.642;1.488)
N	502		533		514		608		520	
Pseudo R^2	.092		.066		.121		.101		.075	

[a] All characteristics are measured at baseline. Bold font denotes statistical significance (P value≤.05).
[b] In years.
[c] Body Mass Index: kg/m^2.
[d] Vaccination against SARS-CoV-2 given at least 6 weeks before baseline.
[e] During the acute phase of COVID-19.

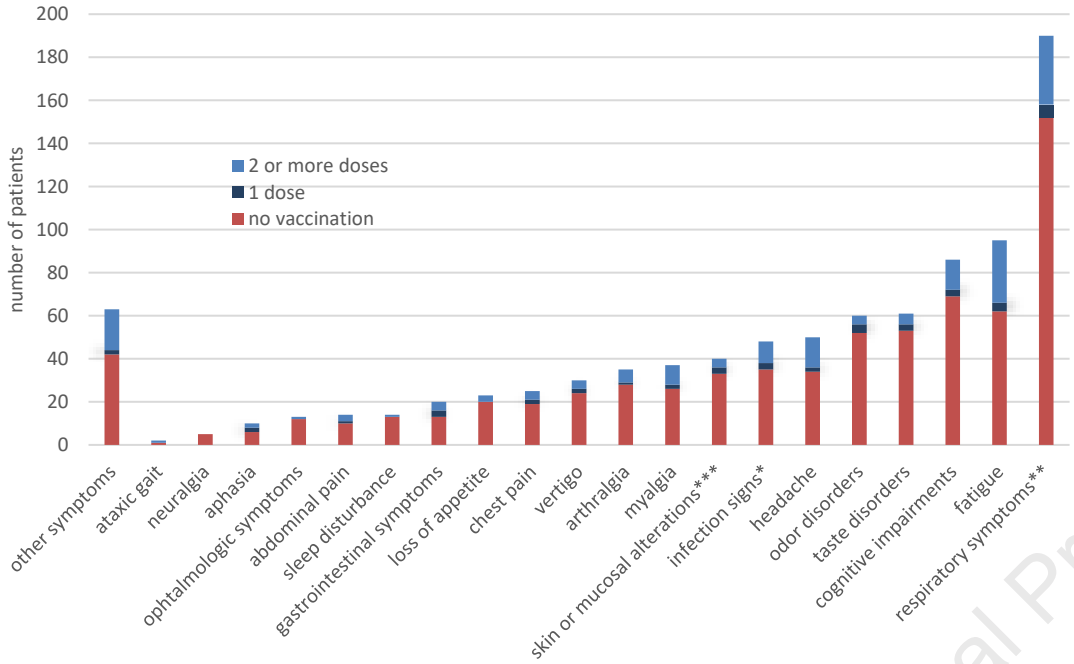
[f] Comorbidities diagnosed at least 28 days before baseline. Multiple counts of the same disease and acute illnesses are excluded. Comorbidities recorded in main diagnostic groups, validated by 2 authors independently using ICD-11 codes and plain text information. Reference is none of the respective comorbidities.
[g] The original categories were dichotomized into no vs. at least mild post-COVID syndrome.

Figure 1: Flowchart study population



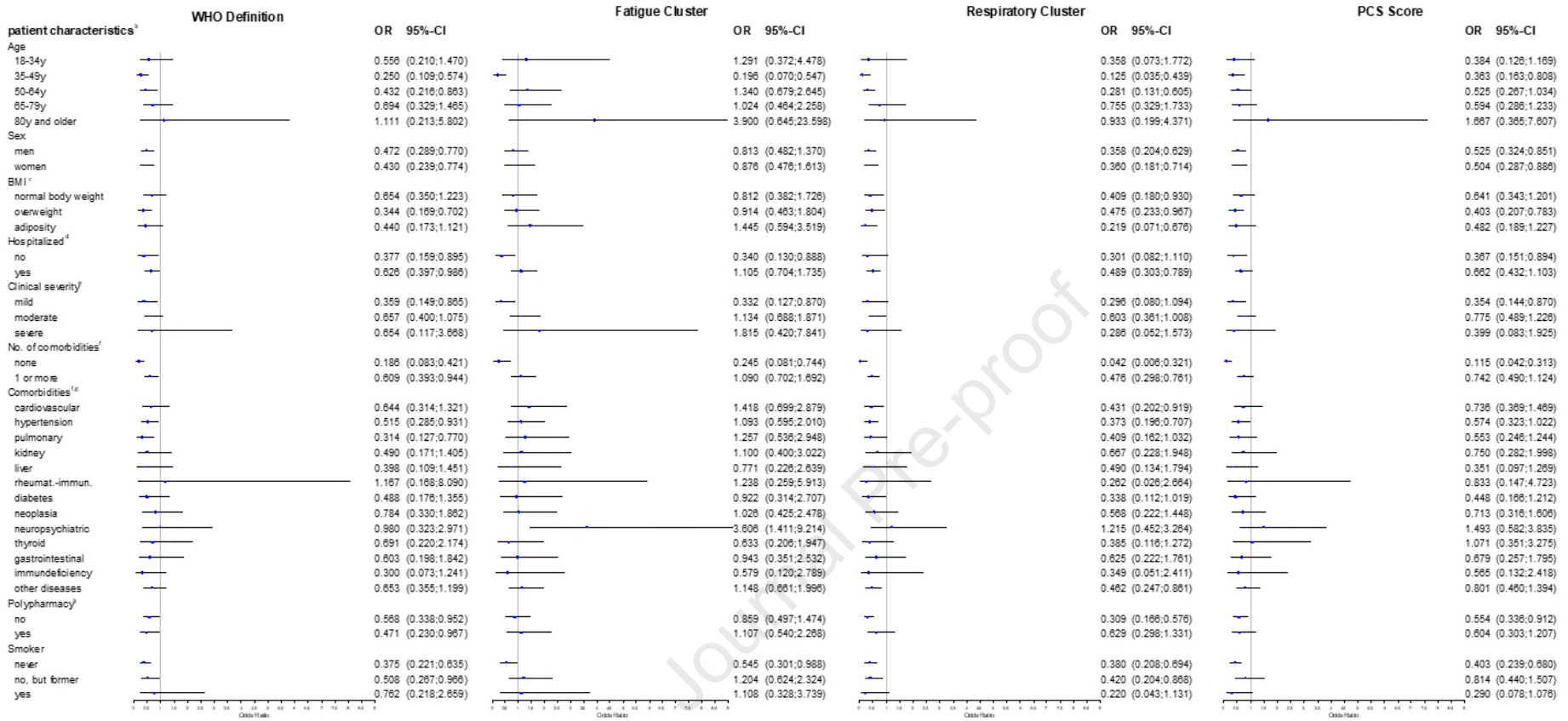
Abbreviations: NAPKON-SUEP = Cross-Sectoral Platform of the National Pandemic Cohort Network; 3MFU = 3-month follow-up.

Figure 2: Most frequent post-COVID symptoms at 3 months



*fever, rhinorrhea, nasal congestion, earache, sneezing, sore throat, lymph node swelling
**dyspnoa, coughing, wheezing
***incl. hair loss

Figure 3: Forest plots depicting risk factors for post-COVID syndrome in vaccinated compared to unvaccinated individuals



[a] Binary logistic regressions with PCS risk as outcome, adjusting for vaccination status (reference = unvaccinated; number of vaccinations against SARS-CoV-2 given at least 6 weeks before baseline).
[b] All characteristics are measured at baseline.
[c] Body Mass Index: kg/m²; normal weight (<24.9), overweight (25-29.9), adiposity (>30).
[d] During the acute phase of COVID-19.
[e] According to the WHO criteria adapted for NAPKON-SUEP, mild: no hospitalization and no oxygen, moderate: hospitalized and no oxygen or oxygen by mask or nasal prongs (<15 l/min), severe: hospitalized and oxygen by NIV or high flow (>15 l/min).
[f] Comorbidities diagnosed at least 28 days before baseline. Multiple counts of the same disease and acute illnesses are excluded.
[g] Comorbidities were recorded in main diagnostic groups, validated by 2 authors independently using ICD-11 codes and plain text information. Reference is non of the respective comorbidities.
[h] Medication ≥5; medication administered at least 28 days before baseline and taken continuously for at least 12 weeks.

CRediT author statement

Tanja Kraus: Methodology, Formal analysis, Writing - original draft; **Christian Förster:** Conceptualization, Writing - original draft, Supervision; **Hendrik Napierala**: Methodology; **Anne Schimpf:** Writing - original draft; **Stefanie Joos:** Resources; **all authors:** Writing - review editing.