Patient-reported experiences of persistent post-Covid-19 conditions after hospital discharge during the pandemic's second and third waves in Switzerland: a post-hospitalization survey

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Abstract

Background: Hospitalized SARS-CoV-2-infected patients should recover within a few weeks. However, even those with mild versions can have signs and symptoms lasting four weeks or longer. These post-COVID conditions (PCC) comprise various new, returning, or ongoing conditions and symptoms that can last months, years, or cause disability. There have been no studies of PCC using self-reporting by discharged SARS-CoV-2-infected patients to complement clinical and biomarker studies.

Objective: Investigate self-reported, persistent PCC among SARS-CoV-2-infected patients discharged during the pandemic's second and third waves.

Methods: Following a literature review, an ad hoc paper questionnaire on PCC was designed, pretested, and posted to all eligible inpatients discharged between October 2020 and April 2021. At four months after discharge, we collected data on PCC and scores for the Multidimensional Fatigue Inventory (MFI), the Patient Health Questionnaire-4 (PHQ-4), a Brief Memory Screening Scale (Q3PC), and a post-traumatic stress disorder scale (PCL-5). Descriptive, inferential, and multivariate linear regression statistics were computed to assess PCC symptomatology, associations, and differences regarding sociodemographic characteristics and hospital length of stay (LOS). We computed whether our variables of interest could significantly predict patients' MFI scores.

Results: Of the 1993 valid questionnaires returned, 245 were from discharged SARS-CoV-2-infected patients. That sub-sample's median age was 71. Only 28.2% of SARS-CoV-2 infected respondents were symptom-free after four months. Significant differences were found between men's and women's numbers of PCC symptoms (P = .003) and LOS (P > .001): men had more symptoms and longer LOS. No significant differences were found between age groups (P = .500) and hospitalization units (P = .092). Significant differences were found between self-reported PHQ-4 scores during hospitalization and four months after (P < .001), with higher scores among hospitalized patients. Three-quarters (76.4%) of the respondents affected by COVID-19 reported memory loss and concentration disorders (Q3PC). No significant differences regarding the median MFI score of 56 were found in the sociodemographic variables. Significant differences were found between the median PCL-5 score and LOS, with higher scores among respondents with longer stays (P = .009). Multivariate linear regression allowed us to calculate that the combination of PHQ-4, Q3PC, and PCL-5 scores, adjusted for age, sex, and LOS, did not significantly predict MFI scores (R2 = 0.093 (F (3/197) = 1.500; P = .216 adjusted R2 = 0.061.).

Conclusions: The majority of SARS-CoV-2-infected inpatients presented with PCCs at four months after discharge, with

complex clinical pictures. Only one-third of them were symptom-free during that time. MFI scores were not directly related to self-reported depression, anxiety, or post-traumatic scores adjusted for age, sex, or LOS. More research is needed to explore PCC and fatigue based on the self-reported health experiences of discharged SARS-CoV-2-infected inpatients.

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Abstract

Background:
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those with mild versions can have signs and symptoms lasting four weeks or longer. These post-COVID conditions (PCC) comprise various new, returning, or ongoing conditions and symptoms that can last months, years, or cause disability. There have been no studies of PCC using self-reporting by discharged SARS-CoV-2-infected patients to complement clinical and biomarker studies.

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Investigate self-reported, persistent PCC among SARS-CoV-2-infected patients discharged during the pandemic's second and third waves.

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Results:

Of the 1993 valid questionnaires returned, 245 were from discharged SARS-CoV-2-infected patients. That sub-sample's median age was 71. Only 28.2% of SARS-CoV-2 infected respondents were symptom-free after four months. Women had significantly more persistent PCC symptoms than men (P = .003). Patients with a hospital LOS ≥ 11 days had significantly more PCC symptoms too (P < .001)": women had more symptoms and longer LOS. No significant differences were found between the age groups of 18–64, 65–74, and ≥ 75 years old (P = .500), or between ICUs and other hospitalization units (P = .092). Significantly higher PHQ-4 scores were self-reported by patients during their hospitalization than four months after (P < .001). Three-quarters (76.4%) of the respondents affected by COVID-19 reported memory loss and concentration disorders (Q3PC). No significant differences in the median MFI score of 56 were associated with sociodemographic variables. Patients with a hospital LOS of ≥ 11 days had a significantly higher median PCL-5 score (P = .009). Multivariate linear regression allowed us to calculate that the combination of PHQ-4, Q3PC, and PCL-5 scores, adjusted for age, sex, and LOS (of either ≥ 11 days (median 2 symptoms; IQR 1–5) or < 11 days), did not significantly predict MFI scores (R^2 = 0.093 (F (3/197) = 1.500; P = .216 adjusted R^2 = 0.061.).

Conclusion:

The majority of SARS-CoV-2-infected inpatients presented with PCCs at four months after discharge, with complex clinical pictures. Only one-third of them were symptom-free during that time. Based on our findings, MFI scores were not directly related to self-reported depression, anxiety, or post-traumatic scores adjusted for age, sex, or LOS. More research is needed to explore PCC and fatigue based on the self-reported health experiences of discharged SARS-CoV-2-infected inpatients.

Keywords:

PREMs; long COVID; fatigue; post-traumatic stress disorder; depression; anxiety; SARS-CoV-2 infection.

Introduction

During the COVID-19 pandemic's second and third waves, health-care systems focused on dispensing the best available care and preventing the over-saturation of health-care services [1-3]. Most marshalled their resources to manage successive waves of hospital admissions and intensive care cases, prioritizing vaccination efforts to protect as many people as possible from severe cases of COVID-19 [4]. Given the widespread and multifarious nature of the post-COVID-19 conditions

(PCC) experienced by populations infected by SARS-CoV-2, coupled with shortcomings in understanding viral-onset illnesses, it is unsurprising that there have been few standardized follow-up assessments of patients' functioning, disability, and health [5-7]. Patients were sometimes discharged without plans for rehabilitation or any recording of their chronic post-COVID symptoms [3]. Meanwhile, SARS-Cov-2's infected a significant proportion (> 10%) of Switzerland's population, dramatically increasing the number of pneumonia and multi-organ and its associated risk factors for severe disease and death; less is known about the potential long-term complications of infection [8]. The World Health Organization (WHO) defined three criteria for the diagnosis of a PCC: i) a positive antigenic or serological test for the SARS-CoV-2 virus or, despite a negative test during an acute phase of illness, either a chest CT scan indicative of acute SARS-CoV-2 infection, or a typical presentation of that ii) the presence of symptoms beyond two months after the onset of symptoms or the acute phase of the disease; and iii) the absence of other reasons or diagnoses that may explain these symptoms [9].

A recent study found that seven months after COVID-19 onset, 45% of patients had not returned to their previous level of work participation and continued to have a significant symptom burden [10]. Alkodaymi et al.'s systematic review examining the enduring signs and symptoms of COVID-19 reported pulmonary sequelae, neurological disorders, impaired concentration, generalized anxiety disorder, impairments to functional mobility, fatigue, muscle weakness, and constitutional symptoms: half the patients included had a PCC lasting for more than six months [11]. O'Mahoney et al. systematic review and meta-analysis of COVID-19's long-term effects reported that at least 45% of COVID-19 survivors were experiencing at least one unresolved symptom after four months [12]. Fatigue was the most persistent symptom, with a prevalence among hospitalized, non-hospitalized, and mixed-patient cohorts of 28.4%, 34.8%, and 25.2%, respectively [12]. Fatigue could be due to the excessive respiratory efforts related to the respiratory complications of a SARS-CoV-2 infection [13]. However, the lack of a gold standard for assessing fatigue, as well as this symptom's subjective nature, makes it a poorly evaluated condition. Fatigue is observed in many medical conditions, including cancer, neurodegenerative disorders, rheumatological diseases, and heart failure, but it can also be an isolated symptom with unknown underlying causes, as in the case of chronic fatigue syndrome [14]. Other studies have reported pulmonary abnormalities as persistent PCC months after hospital discharge, with radiological abnormalities and impaired pulmonary function [3, 8, 15]. Xu et al. reported stroke, encephalitis, seizures, and conditions including major mood swings and brain fog months after the initial onset of a SARS-CoV-2 infection [16, 17]. Additionally, COVID-19 has been associated with extending the emotional and behavioral issues surrounding post-traumatic stress disorder (PTSD) [10]. Individuals recovering from COVID-19 may be at a greater risk of depression, anxiety, PTSD, and substance use disorder [18-20]. Considering the total number of COVID-19 cases worldwide, the disease's combined effects have the potential to result in many different PCC [21]. The exact number of people 10%−20% of the individuals who contracted COVID-19 experienced persistent symptoms for weeks, months, and even up to two years following their infection [12].

This paper highlights how PCC should not be limited to biological health markers but should include self-reported everyday functioning after an infection, and experiences of any signs or symptoms should also be given attention.

Our guiding research questions were: What are the persistent symptoms of PCC among SARS-CoV-2-infected inpatients/respondents four months after discharge? How do these patients describe the severity of fatigue, depression, anxiety, memory loss, and PTSD? The present study explored the following neutral hypotheses:

1. There is no significant difference between men and women, age groups, hospitalization wards, and lengths of stay in self-reported scores for fatigue, depression, anxiety, memory loss, and PTSD at four months.
2. Self-reported fatigue scores cannot be significantly explained by the combination of self-

reported persistent PCC symptoms, depression, anxiety, memory loss, or PTSD scores.

Methods

Design, Research Population, Setting and Recruitment.

A PREMs survey was conducted among all the inpatients discharged from the Valais Hospitals between October 14, 2020, and April 22, 2021, to collect data about their hospital experiences and particularly any residual symptoms, at four months post-discharge, among the SARS-CoV-2-infected patients during the pandemic's second and third waves. The Valais Hospitals are a multisite public hospital that recorded more than 40,000 hospitalizations and more than 650,000 ambulatory visits in 2022-[22].

Study Framework

Based on the principles of patient and public involvement, patient-reported experience measures (PREMs) of health-care delivery have recently become an essential component for recording overall health-care system performance [22, 23]. PREMs are directly related to the Institute of Healthcare Improvement's Quintuple Aim concept [24], whose key transformative health-care objectives are improving patients' experiences, attaining better health outcomes, boosting clinician well-being, lowering costs, and ensuring health equity. The present paper reports on the health symptoms experienced by SARS-CoV-2-infected inpatients four months after their discharge during the COVID-19 pandemic's second and third waves [25].

The Data Collection Instrument.

In the absence of a standardized, validated tool for collecting data on PCC, the research team designed a self-reporting questionnaire based on a literature review of PREMs concepts and the epidemiology and consequences of PCC and then pretested it with four patients (Suppl. File 1) [26, 27]. The paper questionnaire was posted to all eligible patients at four months post-discharge and included a prepaid envelope for its return. Besides concepts involving PCC, the questionnaire investigated discharged patients' health, fatigue, post-traumatic stress, cognitive impairments and other remaining symptoms reported by the participants.

Post-COVID-19 Conditions

Health symptoms after a SARS-CoV-2 infection

The study investigated the self-reported physical and mental health symptoms of SARS-CoV-2-infected inpatients discharged home. Respondents were presented a list of health conditions whose presence or absence they reported [28-31]. These included: persistent weight loss, loss of sense of smell, loss of sense of taste, fever, cold, sore throat, sensations of burning or electricity in upper and lower limbs, persistent paresthesia in the hands or feet, a mobility disorder in one of the limbs, shortness of breath at rest and during daily activities, daily coughing, pain or discomfort in the chest area, hair loss, headaches, muscle aches, the need for home-care since leaving hospital, fatigue and other health conditions reported by the responder.

Multidimensional Fatigue Inventory - MFI

The MFI is a self-administered questionnaire assessing different aspects of fatigue: general fatigue, mental fatigue, decreased activity, and motivation [32]. The explored items of the MFI scale are reported in Suppl. file 2. Validated mainly for situations involving cancer, in French and German, and with a Cronbach's alpha for reliability of r = 0.84, this Likert-like scale has possible responses ranging from 1 "Completely disagree" to 5 "Completely agree". The higher the total score—ranging from 20 to 100—the greater the fatigue. No cutoff points or classifications have been documented

using the original scale. Fatigue is a particularly interesting health condition because it is the most prevalent symptom in clinical studies involving PCC and has been explored as a dependent variable in multivariate linear regression analysis [12, 18].

Brief Memory Scale - Q3PC

The Q3PC self-reporting memory scale was used to explore memory loss and attention difficulties among SARS-CoV-2-infected respondents. They were asked: (i) Do you experience frequent memory loss? (ii) Do you feel that you are slower when reasoning, planning activities, or solving problems? and (iii) Do you have difficulties paying attention? For each question, the response options were 0 “Never”, 1 “Rarely”, 2 “Sometimes”, 3 “Often” and 4 “Very often” [33]. The higher the score, the worse the participants experienced memory and attention difficulties. The Q3PC’s psychometric properties showed a good Cronbach’s alpha coefficient of .72 [34].

Patient Health Questionnaire-4 - PHQ-4

The four-item, composite, self-reported PHQ-4 was used to assess anxiety. It was built from the Generalized Anxiety Disorder Scale (GAD-2) and two questions identifying a depressive state from the PHQ-2 scale. The two items exploring depression are validated based on the DSM-IV diagnostic criteria for depression, including depressed mood and lack of interest [35]. The two GAD-2 questions investigate feelings of nervousness and anxiety and the ability to control one’s worries. The PHQ-4 and GAD-2 are scored 0 “Never”, 1 “Some days”, 2 “> 50% of days, and 3 “Almost every day”, with total possible scores of 0–12 for the PHQ-4 and 0–6 for the GAD-2 scale. The PHQ-4 was assessed at baseline during hospitalization and four months after discharge. The questionnaire has good psychometric properties, with a Cronbach’s alpha of .78.

Post-Traumatic Stress Disorder Checklist-5 - PCL-5

The PTSD Checklist (PCL-5) was developed to identify individuals with and without post-traumatic stress disorder (PTSD) and is based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DMS-5). The checklist includes 20 self-administered items answered using a symptom severity rating ranging from 0 “Not at all” to 4 “Extremely”. Total PCL-5 scores range from 0 (indicating no symptoms) to 80 (indicating very severe symptoms). The cutoff score between “no pathological PTSD symptoms” and “pathological PTSD symptoms” has been estimated at around 30 to 33: the recommended threshold for a diagnosis of PTSD is 33 points, and a score > 30 requires additional investigations [36]. The scale has been translated, culturally adapted, and validated in French, showing excellent internal consistency (Cronbach’s alpha .94) and a test–retest reliability of r = 0.89 [37]. Forte et al. validated the Italian version of PCL-5 during the COVID-19 pandemic, demonstrating its items’ excellent internal consistency .94 [38].

Respondents’ sociodemographic and hospital trajectory data

Seven closed questions were used to ask participants about their sociodemographic data (e.g. sex, age, marital status, educational level) and hospital trajectory as a patient.

Data collection procedure

Following ethics approval by the Human Research Ethics Committee of the Canton of Vaud (2021-01263), the Valais Hospital’s data science warehouse provided the contact details of all the adult inpatients (18 years and older) discharged alive to their home or a nursing home between June 21 and November 13, 2021. Eligible patients received a letter by post, including the PREMs questionnaire and an invitation to participate in the survey by completing the attached paper questionnaire. An information sheet explained the background to the study, the data sought, and our participant data protection strategy (Suppl 1). Anonymously completing the paper questionnaire and returning it in

the prepaid envelope provided was considered a proxy for participants' informed consent. A reminder was sent out four weeks later (Figure 1).

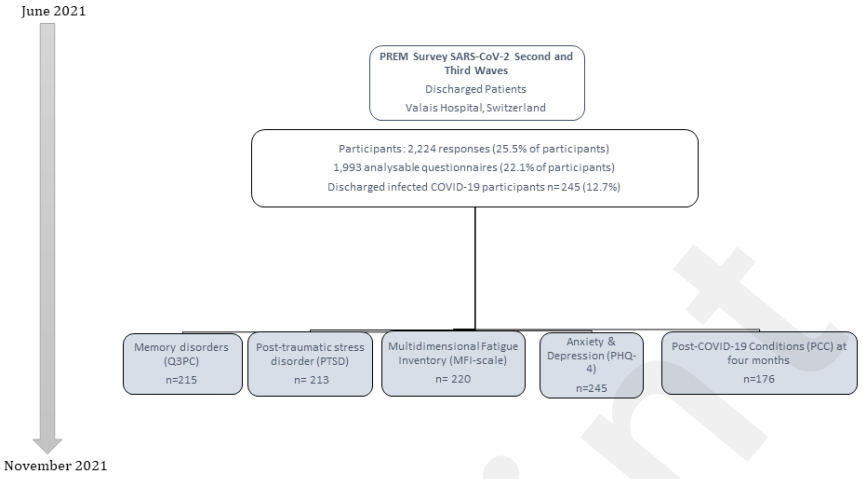

Figure 1. Data collection strategy for post-COVID conditions during Switzerland's second and third waves of COVID-19 in 2020–2021.

Statistical Analysis

Participants' data were anonymized and good research practices for this type of study were respected, as per the Declaration of Helsinki [39]. Data from the self-reported questionnaires were extracted into an Excel© spreadsheet (Microsoft, Redmond, Washington, USA), cleaned, and imported into IBM SPSS® software, version 28 (IBM Corp, Armonk, New York, USA), for analyses.

Power

With a margin of alpha error (.05), a Power of 1-B err prob .80 and an effect size of .5, the total sample size was estimated at 242 participants. However, a statistically significant sample size might not have to be as big in our PREMs survey because it examines patient experiences of their regular care. Our survey extracted valuable information from respondents about their hospitalization experiences and persistent PCC [40].

Data exclusion

We analyzed the number of responses and missing values for each variable and reported them in our tables (n = answers) [41].

Statistics

Descriptive statistics for the population included frequencies, distributions, and leading trends. Parametric properties were analyzed for the normality of their distributions and the equality of their variances. Nonparametric tests were performed for variables with non-normal distributions describing SARS-COV-2-infected respondents' scores and health conditions. To test our hypotheses, we computed chi-square statistics for the categorical variables in the contingency tables. Data collected using Likert scales were analyzed using descriptive and inferential statistics and applied the Mann–Whitney and Kruskal–Wallis tests. Because of some extreme outliers, hospital length of stay (LOS) was recoded as a dichotomous variable of 1–11 days or > 11 days, based on the median

patient LOS of 11 days [42-44]. Associations were calculated using Spearman's correlation between MFI scores and the number of self-reported PCC and sociodemographic characteristics. We computed a linear multivariate regression model to explore the relationships between MFI scores and the independent variables of patients' PHQ-4, Q3PC, and PCL-5 scores. The model estimated each predictor's net impact, other things being equal, giving predictions for the entire sample, not just specific individuals. We computed the internal consistencies of the PHQ-4, Q3PC, and PCL-5 scales using Cronbach's alpha coefficients. Values are ≤ 1, with values ≥ 0.7 being generally considered "acceptable" [45]. The results were considered statistically significant when $P < .05$. All *P-values* were based on two-tailed tests, and a biostatistician supervised and reviewed all the analyses.

Ethical considerations

The Valais Hospitals, the University of Applied Sciences and Arts Western Switzerland's Institute of Health, Valais/Wallis, and the Human Research Ethics Committee of the Canton of Vaud all approved the present study's research protocol. The Human Research Ethics Committee of the Canton of Vaud (2021-01263) authorized the survey and the extraction of the population-based cohort's data from administrative patient records in the hospital's patient register.

Results

Of 8693 eligible respondents hospitalized during the COVID-19 pandemic's second and third waves, between October 2020 and April 2021, 1993 returned valid questionnaires (with > 50% of questions completed), representing 89.6% of the questionnaires returned (n = 2224; Figure 1). A total of 245 (11%) of those respondents had a confirmed COVID-19 infection—a positive test for SARS-CoV-2—and had been hospitalized for acute COVID-19 symptoms.

Sociodemographic Characteristics of the Sample

The infected sample's median age was 71, with more men participating than women. Most of the respondents were married and educated to the vocational diploma level. The median hospital LOS was 11 days. Table 1 shows respondents' sociodemographic data.

Table 1. Distribution of COVID-19-infected discharged inpatients' sociodemographic data in Valais Hospitals during the second and third waves in 2020 and 2021.

Variables	SARS-CoV-2-infected respondents	*P*
Sex (n = 245)		< .001[1]
Man (n, %)	145 (59.0)	
Woman (n, %)	100 (41.0)	
Age (years) (n = 245)		< .001[1]
Median (IQR 1–3)[2]	71 (62.7–77)	
Min–Max	31–96	
Marital status (n = 236)		< .001[1]
Single (n, %)	20 (8.5)	
Married (n, %)	148 (62.7)	
Divorced/separated (n, %)	23 (9.7)	
Widowed (n, %)	45 (19.1)	
Education, (n = 231)		< .001[1]
Primary school (n, %)	77 (33.3)	
Vocational diploma (n, %)	103 (44.6)	
Higher education/university (n, %)	51 (22.1)	

Note: [1]= Chi-squared exact test; [2] IQR 1–3 = Interquartile 25%–75%

Persistent symptoms four months after COVID-19 infection

Sixty-nine COVID-19 infected respondents reported being symptom-free at four months. The remaining 176 reported a total of 643 persistent PCC symptoms, with a median of 3 symptoms related to PCCs, with a maximum of 15. Nineteen respondents reported clinical pictures involving multiple clustered comorbidities or symptoms such as problems breathing, concentrating, hearing, and sleeping, kidney failure, lack of strength, hallucinations, gastric problems, anxiety, memory and balance problems, and joint pains. The top three persistent symptoms were breathing difficulties during physical effort, muscle pain, and shortness of breath at rest (Table 2). Women had significantly more persistent PCCs (3 symptoms) than men (2 symptoms). Patients with hospital LOS ≥ 11 days (2 symptoms) had more persistent PCCs too (versus < 11 days LOS with 1 symptom). No significant differences were found between age groups or between ICUs and other hospitalization units. Significant differences in persistent PCCs were found between women (3 symptoms) and men (2 symptoms; $P = .003$) and depending on hospital LOS of either ≥ 11 days (2 symptoms) or < 11 days (1 symptom; $P < .001$). No significant differences were found between age groups or hospitalization units. The second section of Table 2 presents the distribution of persistent PCCs at four months, as reported by the respondents.

Table 2. Persistent symptoms four months after SARS-CoV-2 infection in the Valais Hospitals during the second and third waves in 2020 and 2021.

Variables	Median (IQR 1–3)[1]	*P*
Sex (n = 245)		
Men (n = 145)	2 (0–2)	
Women (n = 100)	3 (1–5)	.003[1]
Age category (n = 242)		
18–64 years (n = 71)	2 (1–4)	
65–74 years (n = 84)	2 (1–4)	
75 years and older (n = 87)	2 (1–5)	.500[1]
Hospitalization unit (n = 245)		
ICU (n = 41)	2 (1–5)	
Other units (n= 204)	2 (1–4)	.092[1]
Length of stay (n = 210)		
< 11 days (n = 154)	1 (0–4)	
≥ 11 days (n = 56)	2 (1–5)	<. 001[1]
Persisting PCC symptoms after 4 months	**n (%)**	
Breathing difficulties when active	104 (16.2)	
Muscle pain	77 (12.0)	
Breathing difficulties at rest	56 (8.7)	
Daily coughing	45 (7.0)	
Sensory disorder in hands or feet	40 (6.2)	
Hair loss	35 (5.4)	
Headaches	34 (5.3)	
Neuropathic pain in limbs	30 (4.7)	
Need for home-care since hospital discharge	29 (4.5)	
Pain or discomfort in the chest area	28 (4.4)	
Cold	26 (4.0)	
Mobility disorder in a limb	25 (3.9)	
Loss of sense of smell	24 (3.7)	

Loss of sense of taste	23 (3.6)
Sore throat	18 (2.8)
Fever	16 (2.5)
Continuing weight loss	13 (2.0)
Other symptoms	20 (3.1)

Note.
[1]= Chi-Square test; Other self-reported symptoms: Joint pain (n = 3; 1.2%), balance disorder (n = 2; 0.8%), sleep disorder (n = 2; 0.8%), memory impairment (n = 2; 0.8%), renal decompensation (n = 2; 0.8%), hearing loss (n = 1; 0.4%), anxiety (n = 1; 0.4%), gastric problems (n = 1; 0.4%), hallucination (n = 1; 0.4%), lack of strength (n = 1; 0.4%), concentration disorder (n = 1; 0.4%), and pneumonia (n = 1; 0.4%); [1] IQR 1–3 = Interquartile 25%–75%

The Multidimensional Fatigue Inventory: MFI

The overall median MFI score among all respondents was 56, showing that most respondents reported moderate to high MFI scores. No significant differences were found between MFI scores and patients' sociodemographic, hospitalization unit, and LOS variables (Table 3). Our sample's MFI scale scores had an internal consistency coefficient Cronbach alpha of .451, considered a low level [46]. Suppl. File 2 presents the detailed results.

Table 3. Distribution of respondents' Multidimensional Fatigue Inventory scores based on age, sex, hospitalization unit, and LOS in the Valais Hospitals during the second and third waves in 2020 and 2021.

Variables	Median (IQR 1–3)[1]	*P*
Sex (n = 216)		.363[1]
Woman (n = 91)	55 (48–60)	
Man (n = 125)	56 (51–59)	
Age category (n = 220)		.122[2]
18–64 years (n = 64)	56.5 (50.2–63)	
65–74 years (n = 79)	56 (52–59)	
75 years and older (n = 77)	54 (48.5–59)	
Hospitalization unit (n = 220)		.201[1]
ICU (n = 36)	54 (49.2–57)	
Other units (n = 184)	56 (50.2–60)	
Length of stay (n = 219)		.706[1]
< 11 days (n = 104)	56 (50–59)	
≥ 11 days (n = 115)	55 (50–60)	

Note. [1] = U Mann–Whitney test; [2] = Kruskal–Wallis test; [1] IQR 1–3 = Interquartile 25%–75%

Memory, concentration, and attention disorders: Brief Memory Screening Scale Q3PC

Forty COVID-19 respondents reported suffering from memory loss often to very often, with 109 and 62 declaring mild and no memory loss, respectively. Thirty-four respondents reported feeling slowness when reasoning daily problems, 102 declared rarely or sometimes feeling slowness, and 75 reported never feeling slowness in daily reasoning. Thirty-three respondents reported often or very often having difficulty concentrating, 82 rarely or sometimes felt concentration problems, and 100 reported no concentration problems. The majority of COVID-19 respondents (n=166) reported one or more disorders on the Q3PC scale, with an overall median of 3 positive responses across the whole group of 245 subjects. Considering the cutoff point of ≥ 1 positive question, 166 respondents present memory loss disorders with a median score of 3. No significant differences were found related to sex, age, or hospital trajectory. Contrarily, a significant difference was found regarding hospital LOS, with patients hospitalized for ≥ 11 days having higher Q3PC scale scores (Table 4). The Q3PC scale's internal consistency demonstrated an excellent Cronbach's alpha coefficient of .892 [46]. Suppl. File 2 presents the detailed results.

Table 4. Distribution of concentration, attention, and memory disorder scores on the Q3PC scale in the Valais Hospitals during the second and third waves in 2020 and 2021.

Variables	Median (IQR 1–3)[3]	*P*
Sex (n = 213)		.966[1]
Women (n = 90)	3.9 (1–6)	
Men (n = 123)	3.8 (1–6)	
Age category (n = 217)		.075[2]
18–64 years (n = 64)	4.5 (1.2–7)	
65–74 years (n = 78)	3 (0–6)	
75 years and older (n = 75)	3 (1–6)	
Hospitalization unit (n = 217)		.201[1]
ICU (n = 36)	3 (3–6)	
Other units (n = 181)	4 (1–6)	
Length of stay (n = 216)		.032[1]
< 11 days (n = 103)	3 (1–5)	
≥ 11 days (n = 113)	4 (1–6)	

Note. [1] = U Mann–Whitney test; [2] = Kruskal–Wallis test; ICU = intensive care unit: [3] IQR 1–3 = Interquartile 25%–75%

Depression and anxiety disorders: PHQ-4

After four months, 14 respondents still had an elevated score for symptomatic health issues and 16 presented a moderate score for symptomatic mental health impairment. Significant differences between men (median = 0) and women (median = 1; *P* = .034), between ICU patients (median = 1) and patients in other hospital unit (median = 1; *P* = .041), and between hospital LOS ≥ 11 days (median = 1) and < 11 days (median = 1; *P* = .032), were found four months after a SARS-CoV-2 infection. No significant differences were found between the age groups (*P*= .820) (Table 5). The PHQ-4 scale's internal consistency showed an excellent Cronbach's alpha of .881 [46]. Suppl. File 2 presents the detailed results.

Table 5. Distribution of the PHQ-4 scores among respondents at four months post-SARS-CoV-2 infection in the Valais Hospitals during the second and third waves in 2020 and 2021.

Variables	Median (IQR 1–3)[3]	*P*
Sex (n = 241)		*.034*[1]
Women (n = 100)	1 (0–4)	
Men (n = 141)	0 (0–3)	
Age category (n = 238)		*.820*[2]
18–64 years (n = 64)	1 (0–3)	
65–74 years (n = 87)	0 (0–2)	
75 years and older (n = 87)	1 (0–3)	
Hospitalization unit (n = 245)		*.041*[1]
ICU (n = 41)	2 (0–4)	
Other units (n = 204)	0 (0–3)	
Length of stay (n = 244)		*.028*[1]
< 11 days (n = 120)	1 (0–2)	
≥ 11 days (n = 124)	1 (0–4)	

Note. [1] = U Mann–Whitney test; *[2]= Kruskal–Wallis test; ICU = intensive care unit; [3] IQR 1–3 = Interquartile 25%–75%

Post-Traumatic Stress Disorder Assessment: PCL-5

The overall median PCL-5 score among the SARS-CoV-2-infected respondents was 12. Significant differences were found between the respondents' hospital LOS of either ≥ 11 days or < 11 days, with higher PCL-5 scores among respondents with longer LOS (*P* = .009). No differences were found regarding sex, between ICU patients and other hospitalization unit patents, or between the age groups (Table 6). The PCL-5 scale's internal consistency showed an excellent Cronbach's alpha coefficient

of .949 [46]. Supplementary File 2 presents the detailed results.

Table 6. Distribution of PCL-5 scores according to sex, age category, hospitalization unit, and LOS in the Valais Hospitals during the second and third waves in 2020 and 2021.

Variables	Median (IQR 1–3)[3]	*P*
Sex (n = 211)		.347[1]
Women (n = 87)	17.5 (4–26)	
Men (n = 124)	14.7 (4–21.7)	
Age category (n = 215)		.061[2]
18–64 years (n = 64)	13.5 (6–31.7)	
65–74 years (n = 78)	13.2 (3–17.2)	
75 years and older (n = 73)	16.2 (3.5–25.5)	
Hospitalization unit (n = 215)		.1841
ICU (n = 36)	20.5 (5–31.5)	
Other units (n = 179)	14.7 (4–21)	
Length of stay (n = 214)		.009[1]
< 11 days (n = 105)	12.7 (4–19.5)	
≥ 11 days (n = 109)	18.7 (4–30)	

Note. [1] = Mann–Whitney test; [2] = Kruskal–Wallis test; [3] IQR 1–3 = Interquartile 25%–75%

Associations between MFI scores and numbers of post-COVID-19 symptoms

We computed a Spearman association between MFI scores and patients' numbers of persistent PCC COVID-19 symptoms, but no associations were found (r_s = 0.063; *P* = .356).

Fatigue score predictivity of persistent PCC symptoms and health questionnaire, memory disorder, and post-traumatic stress disorder scores

A multivariate linear regression was computed to investigate how well the combination of numbers of persistent PCC symptoms and the PHQ-4, Q3PC, and PCL-5 scores predicted MFI scores. When adjusted for sex, age, and hospital LOS, they did not significantly predict FMI scores, with an R^2 = .093 (*P* = .216) and an adjusted R^2 = .061. According to Cohen, this was a low effect [47]. The beta weights and determining values, presented in Table 7, indicate that the Q3PC and PCL-5 scores contributed the most to predicting the MFI scores.

Table 7. Multivariate linear regression analysis of the number of persistent PCC symptoms and PHQ-4, Q3PC, and PCL-5 scores, adjusted for age, sex, and LOS, predicted MFI scores in the Valais Hospitals during the second and third waves in 2020 and 2021 (n = 245).

Variables	B	Std. Error	Exp (B)	t	Sig.	95% confidence interval	
						LB	UB
Intercept	52.536	1.236		42.519	< .001	50.100	54.972
PCC symptoms	-.314	.293	-.084	-1.073	.284	-.892	.263
PHQ4	-.633	.293	-.180	-2.162	.032	-1.211	-.056
Q3PC	.642	.274	.202	2.344	.020	.102	1.181
PCL-5	.108	.072	.152	1.502	.135	-.034	.249
ADJUSTMENT							
Intercept	57.091	5.384		10.605	< .001	46.474	67.708
PCC symptoms	-.259	.298	-.069	-.871	.385	-.847	.328
PHQ4	-.545	.295	-.160	-1.847	.066	-1.127	.037

Q3PC	.646	.273	.203*	2.362	.019	.107	1.185
PCL-5	.108	.072	.153*	1.497	.136	-.034	.250
Sex	1.562	1.517	.072	1.030	.304	-1.430	4.555
Age	-.071	.066	-.078	-1.074	.284	-.201	.059
LOS	-1.669	1.556	-.079	-1.072	.285	-4.738	1.401

Note. * = Contributing to predicting MFI scores; PHQ4 = health questionnaire; Q3PC = memory, concentration, and attention disorders scale; PCL-5 = post-traumatic stress disorders scale; LOS = length of stay.

Discussion

Principal Results

The majority of patients infected with and hospitalized for SARS-CoV-2 presented with persistent PCC, often with complex clinical pictures; a wide range of symptoms were described. Less than a third of discharged infected patients were symptom-free after four months.

The PREMs concept has been recognized as a valuable means of collecting patients' self-reported data, helping to assess health-care system performance using relevant concepts and mostly self-reporting tools [23]. By giving a voice to health-care end-users, we consider our self-reported empirical data collection to be a relevant scientific approach, coherent with those developed by the Institute for Healthcare Improvement [48, 49]. PREMs are now unquestionably recognized as a sensitive method of reporting on accessibility, communication, continuity, and health-care system confidence [50].

Our sample of patients with persistent PCC comprised more men than women, but our results showed that women reported significantly higher numbers of PCC symptoms than men. Indeed, sex differences in outcomes were reported during earlier coronavirus outbreaks, so the differences in the current study are unsurprising. Currently, the sex-related long-term consequences of PCC remain poorly studied [51]. However, the studies by Tran et al. (85% women) [52] and Bai et al. [53] were consistent with our results, showing that women had significantly higher numbers of PCC symptoms than men.

Our findings suggested that self-reported depression, anxiety, PTSD, and health impairments did not significantly predict the MFI scores reported by our respondents. We postulated numerous ideas about our results. Firstly, the use of self-reporting questionnaires played a central role in the assessment of signs and symptoms. However, self-reported questionnaires can be a barrier to producing reliable answers from participants with the same clinical presentation [54]. Consequently, one disadvantage of our self-reporting questionnaire could be invalid answers. Respondents may not answer truthfully about such sensitive issues as depression or anxiety because of a social desirability bias. Another issue could be a response bias, which is an individual's tendency to respond in a certain way regardless of the question, known as either acquiescent response bias (ticking YES responses) or non-acquiescent response bias (ticking NO responses). Respondents with elevated levels of depression, anxiety, or PTSD may have under-reported certain categories of symptoms compatible with COVID-19. This could have important effects on how well certain variables are able to predict MFI scores for persistent PCC among SARS-CoV-2-infected respondents. Another potential problem might be how clear or understandable items were for discharged older adult patients, raising the risk of questions being interpreted differently. Moreover, highly structured questionnaires may induce participants to answer in ways that do not match their true views [55]. Another explanation could be that the presence of cognitive impairment, depressive disorders, or fatigue influence patients' answers. A growing number of investigations concerning PCC have used self-reporting questionnaires that were not specifically developed for PCC but rather for respiratory conditions (Medical Research Council Dyspnea Scale), anxiety disorders (Generalized Anxiety Disorder Assessment), and depression (Patient Health Questionnaire) [56]. The development of validated tools specifically to assess PCC would increase comparability and epidemiological robustness, as recommended by Bull et al. and Beattie et al. [22, 57], but this is still ongoing.

Finally, we hypothesize the presence of floor or ceiling effects in the ad hoc questionnaire [58, 59].

Comparison with Prior Work

Collecting data on PCC at four months was in line with existing studies exploring persistent PCC. The systematic review conducted by O'Mahoney et al. included 194 studies of PCC among hospitalized and non-hospitalized patients that reported assessments from 28 to 387 days after COVID-19 infection, with an average follow-up of 124 days [12].

Our findings about persistent PCC symptoms were consistent with existing literature on fatigue, pain, memory impairments, breathlessness, and psychological and distress disorders. O'Mahoney et al. mentioned that the most important prevalent PCC symptoms were fatigue (28.4%), pain/discomfort (27.9%), impaired sleep (23.5%), breathlessness (22.6%), and impaired memory (22.3%), corroborating the systematic review by Salari et al., who also mentioned the appearance of a fatigue syndrome four weeks after the onset of COVID-19 symptoms [60]. Moreover, numerous studies have reported persistent fatigue to be a major PCC symptom: despite patients receiving medical and health-care, their severe fatigue showed little or no improvement three to six months after treatment, and worse, PCC fatigue may persist for more than six months [12, 60, 61].

Multiple authors have reported that long COVID can present a similar clinical picture to chronic fatigue syndrome or other persisting illnesses [62-64]. Our multivariate linear regressions tested whether MFI scores could be significantly predicted by other symptoms experienced by patients and related to fatigue, such as depression, anxiety, somatic health, or post-traumatic disorders. Recent research has reported a relationship between long COVID fatigue, chronic fatigue syndrome, physical deconditioning, and mental and somatic disorders [63-65].

Neurological symptoms reported by our respondents—in the form of cognitive and attention impairments—corroborated with Guo et al., who reported that SARS-CoV-2 infection affected multiple patients with neurological symptoms and neural damage, affecting between 10% and 25% of SARS-CoV-2-infected patients with cognitive and attention impairments [66]. Furthermore, Price reported symptoms of cognitive impairment in about 62% of adults with PCC symptoms, compared with 30% among those who had never had post-COVID-19 symptoms [67].

Multiple studies have reported specific aspects of the hospitalization experience to be associated with psychological difficulties and stress among patients severely affected by COVID-19, and those effects were long-term [68, 69]. However, the physical, psychological, and functional problems of patients with PCC recovering at home must be considered together [70, 71]. Research on PTSD and SARS-CoV-2 infections indicated that psychological distress was more severe among groups that had contracted the infection than among other severely ill patients hospitalized at the same time [20, 69]. These studies documented the post-hospitalization psychological difficulties that manifested themselves in stress, fear, depression, persistent acute confusion, and disorders based on continuous stressors such as sleep and memory disorders and attention difficulties [68, 72].

Our results revealed the physical and emotional consequences of living with PCC, including stress and mood disorders. The scientific community needs to better understand these health issues, and they need to be more clearly explained to health policy decision-makers. People suffering from PCC symptoms deserve close symptom and biological monitoring using new or existing health-care services resources [31, 73, 74]. What causes PCC symptoms, including chronic fatigue, and why only certain people experience them, still requires further exploration, as recent systematic reviews have noted [51, 75]. Recent studies have made it apparent that many COVID-19 patients suffer persistent PCC symptoms, even after the acute infection has been treated. These symptoms may be specific to COVID-19 or secondary symptoms related to hospitalization, including hospitalization in intensive care units [2, 3, 73]. Self-reported PHQ-4 scores were in line with the online Swiss Corona Immunitas study describing self-reported PHQ-4 scores in the more acute phases of COVID-19 infection, among hospitalized and non-hospitalized participants. Indeed, lingering systematic somatic symptoms were associated with higher PHQ-4 scores [76].

Overall, our results indicated that only one-third of our SARS-CoV-2-infected respondents reported being free of PCC symptoms after four months. This was substantially higher than the 10% to 20% proportions of PCC sequelae at four months mentioned in the reports of the UK's National Institute of Health and Care Excellence, its Royal College of General Practitioners and Healthcare Improvement Scotland, and the WHO [73, 77, 78]. We hypothesize that this difference was due to the severity of the SARS-CoV-2 infections among our hospitalized respondents. However, this was not entirely supported by our data and needs more detailed research data. Health-care systems worldwide will face significant pressure on their services providing care for patients with PCC, including their morbidity and the health-care costs of optimally managing those individuals [79, 80].

Limitations

This study had some limitations, nevertheless. The PREMs approach shows the limits of using self-reported questionnaires when they become cognitively burdensome to PCC patients and fail to comprehensively capture the spectrum of symptoms. Consequently, we cannot directly engage with the underlying biological mechanisms. Furthermore, our study design failed to give any precise estimates of symptom persistence, and it relied on respondent recall four months after the initial illness. Furthermore, among those respondents infected by SARS-CoV-2, we had no way of estimating the extent to which apparent PCCs might have been the consequences of other illnesses. Finally, we relied on the self-reporting of symptoms rather than objective physiological or cognitive measures. As such, our results should be seen as complementary to, rather than a replacement for, analyses using patients' electronic health records and other prospective cohort studies.

Nonetheless, our PREMs survey may lack rigor and the accuracy of the information provided cannot be verified. In addition, the results should be interpreted with caution and not be considered as generalizable in other regions for PCC infected patients discharged home.

Conclusions

The present study highlighted that PCC long after a SARS-CoV-2 infection, with certain patients suffering persistent clusters of related health issues. Fatigue, cognitive impairments, and breathlessness were the most prevalent symptoms reported, found throughout patients' PCC trajectories and commonly cited as PCC in numerous other studies [12]. The fatigue they felt could not be properly explained by other potential mental and physical health issues or etiologies in our sample.

Persistent PCC will surely have long-term implications for individuals and society. Given the challenges and negative effects that individuals with PCC must face, more studies conducted using patient-reported experience measures to investigate PCCs will bring further insights. One fundamental question requiring further investigation is how the differences in the prevalence of PCCs vary according to a range of sociodemographic correlates. The need for a broader understanding of and more information about PCC could be filled by investigating the lived experiences of patients, as they are ideally placed to contribute their expert opinions. Our results are relevant to patients, clinicians, and policymakers regarding the long-term outcomes of COVID-19, the need to support appropriate PCC treatment pathways, and the need for future studies aligned with PCC.

Consent to publication

Not applicable

Statement of ethical approval and acceptance of the research guidelines

The present study's research protocol was approved by the Valais Hospitals, the HES-SO Valais/Wallis, Sion, Valais, and the Human Research Ethics Committee of the Canton of Vaud. All

our research was carried out in accordance with relevant methodological guidelines and regulations. The Human Research Ethics Committee of the Canton of Vaud (2021-01263) authorized the survey and the extraction of the population-based cohort's data from administrative, electronic patient records in the hospital's patient register. Informed consent was obtained from all the subjects and/or their legal representative(s). Furthermore, patients and relatives who completed the paper questionnaire and returned it in the prepaid envelope provided were considered to have given their consent to participate in the study.

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ChatCBT statement

We hereby declare that no generative AI resource has been used in any proportion of the manuscript.

Competing interests statement

None declared.

Conflict of interest

None declared.

Data availability statement

The results described within our paper have been aggregated and reported so as to ensure the privacy of personal health information, as required by Swiss cantonal and federal law. Valais Hospitals' COVID-19 PREMs data are archived in its medical data warehouse center, which is a secure, audited computer environment. Requests to access these datasets should be sent to nadine.tacchini-jacquier@hopitalvs.ch.

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Authors' contributions

NTJ, SM, and HV had the original idea and provided the conceptual and methodological expertise to design the study. EB, NTJ, SM, NC and HV were significant contributors to the writing of the manuscript. All the authors read, edited, and approved the final manuscript and consented to its publication.

Abbreviations

DMS-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
GAD: Generalized Anxiety Disorder Scale
IQR: inter-quartile range
LOS: length of stay
MFI: Multidimensional Fatigue Inventory
PCC: post-COVID-19 conditions
PCL-5: post-traumatic stress disorder scale
PHQ-4: Patient Health Questionnaire-4

PREMs: Patient-reported experience measures
PTSD: post-traumatic stress disorder
Q3PC: Brief Memory Screening Scale
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
WHO: World Health Organization

Multimedia Appendixes:

- Figure 1. Data collection strategy

Supplementary files

- Supplementary file 1
- Supplementary file 2

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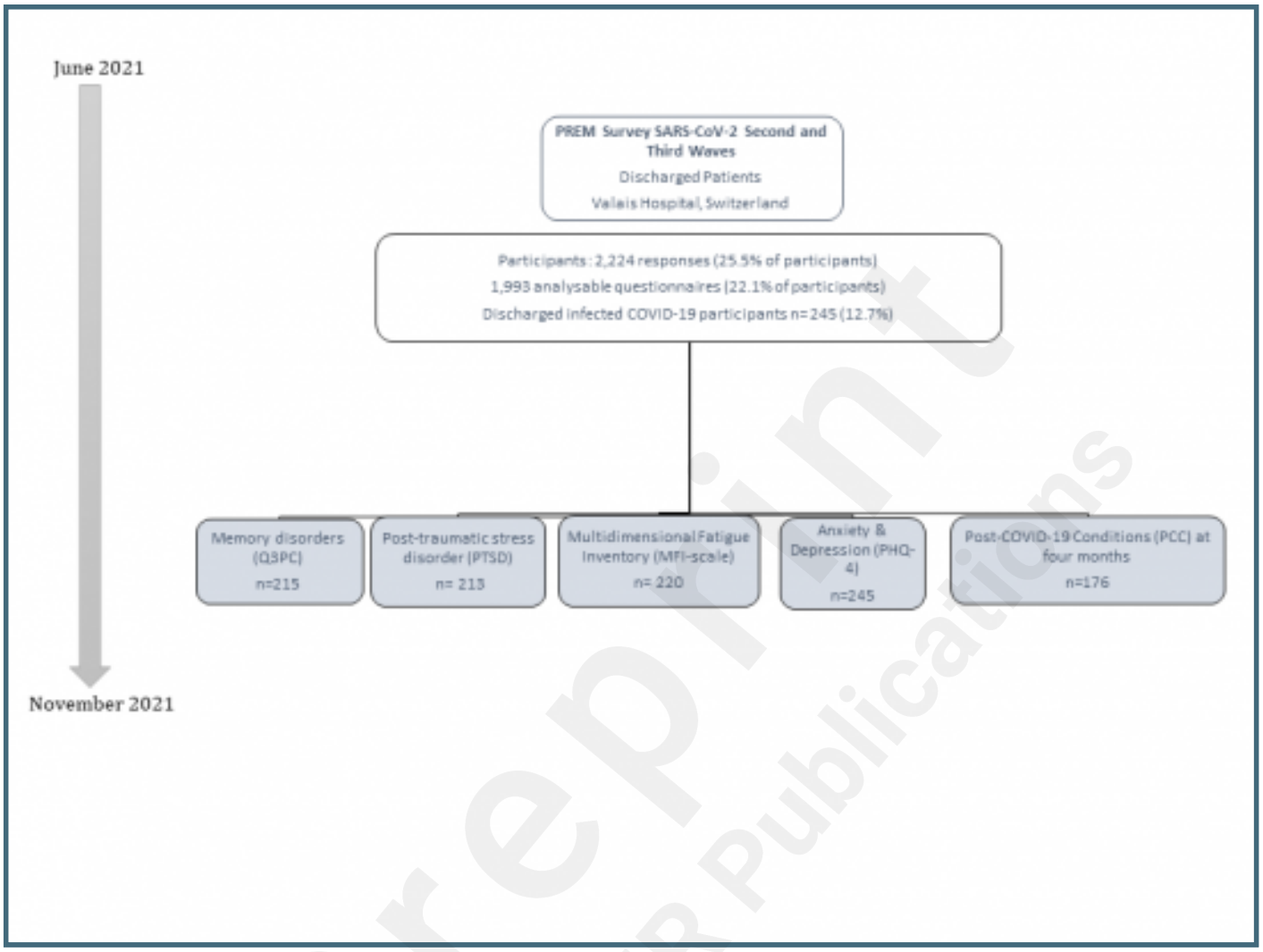
Supplementary Files

Figures

Data collection strategy.



Multimedia Appendixes

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Self-reporting questionnaire.
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Related publication(s) - for reviewers eyes onlies

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