Exploring the temporal relationship between stigma, disease manifestations, and health outcomes in post COVID-19 condition: a longitudinal descriptive study

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Summary

Background Stigma is defined as a deeply discrediting attribute. Post COVID-19 Condition (PCC) is now recognized to be a source of health-related stigma and discrimination capable of negatively impacting the well-being of those affected. Our purpose was to explore the relationship between PCC-related stigma, disease manifestations, and health outcomes over time.

Methods Using previously validated instruments to measure PCC-related stigma, symptoms, depression, quality of life, function, and occupational status, we conducted a longitudinal descriptive study in a cohort of individuals with confirmed PCC between May 12 and August 13, 2023 in the Canadian city of Edmonton.

Findings Ninety-nine consenting participants completed study questionnaires 3–24 months following an initial diagnosis of PCC (enrollment) and again a mean (SD) of 1.6 (0.26) years later (follow-up). Individuals experienced marked variability in study scores over time. Measures of central tendency proved inadequate to detect changes within the cohort. There was minimal attenuation of stigma scores between enrollment and follow-up despite a "return to normal" from earlier pandemic responses: the change in mean stigma score from enrollment to follow-up was −0.2 ($p = 0.97$). Significant correlations were found between enrollment stigma and symptoms, depression, function, and quality of life measured at follow-up ($r = 0.45$–0.55). Similar correlations were noted between enrollment stigma and follow-up composite disease manifestation, health outcome, and global well-being scores ($r = 0.39$–0.54). Multivariate multiple regression demonstrated statistically significant associations between the change in stigma from enrollment to follow-up and symptoms, depression, functional status, and quality of life ($B = -0.45$ to -0.11). When participants were categorized as "improved stigma at enrollment" vs. "unchanged or worse stigma at enrollment", changes in stigma over time appeared to be predictive of disease manifestations and health outcomes at follow-up (Cohen's $d = 0.43$–0.77).

Interpretation This study provides insights into the temporal relationship between PCC-related stigma, disease manifestations, and health outcomes and could establish a foundation for screening, prognostication, treatment, and other efforts to mitigate the impact of stigma.

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Keywords: Disease manifestations; Post COVID-19 condition; Health outcomes; Health-related stigma; Stigma; SARS-CoV-2

Introduction

Stigma, as defined by Erving Goffman in 1963, is a deeply discrediting attribute or characteristic.[1] Stigmatization refers to social processes that enable the devaluation of others through labelling and stereotypes.[2] Discrimination, in turn, can be thought of as behaviours that endorse stereotypes and disadvantage those so labelled.[3]

A wide range of health conditions, infectious and non-infectious, acute and chronic, concealable and

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Research in context

Evidence before this study

Stigma from any number of traits and characteristics is now recognized to be a social determinant of health that can undermine the well-being of both individuals and populations. Post COVID-19 Condition (PCC or long COVID) is the latest in a long lineage of stigmatizing health disorders. The COVID-19 pandemic has created circumstances favorable to the study of the temporal evolution of PCC-related stigma.

Added value of this study

This longitudinal descriptive study involved the use of a validated psychometric instrument, the Post COVID-19 Condition Stigma Questionnaire (PCCSQ), to estimate PCC-related stigma at two points in time an average of 1.6 years apart (early pandemic, late pandemic) in a cohort with well-documented SARS-CoV-2 infections complicated by PCC. Changes in stigma were compared to other aspects of lived experience including symptoms, depression, functional status, quality of life, and work status.

Implications of all the available evidence

The balance of evidence currently available further reinforces PCC as a complex polyphenotypic illness with substantial potential to negatively impact multiple aspects of health and well-being. Importantly, this study suggests that persistent PCC-related stigma is a likely contributor to increased disease burden and poor health outcomes over time.

unconcealable, have the potential to stigmatize.[4,5] Over six decades of research has linked health-related stigma to multiple important consequences, including: psychological stress and distress; restricted participation in social activities; loss of life chances relating to education, social benefits, employment, and financial security; ongoing risk of transmission of infectious diseases; reluctance to seek or disclose a diagnosis; reduced willingness to comply with treatment recommendations; more rapid advancement of the underlying condition; increased disability, morbidity, and mortality; and, undermining of preventative public health efforts.[2,3] In short, stigma is now considered a social determinant of health that can negatively influence the health outcomes of those affected.[6]

Post COVID-19 Condition (PCC), defined by the World Health Organization (WHO) as the continuation or development of new symptoms 3 months after an initial acute SARS-CoV-2 infection, with symptoms lasting for at least 2 months, and with no other explanation, appears poised to join the long list of stigmatizing health conditions.[7,8] Investigators have developed methods to measure PCC-related stigma.[9,10] Long COVID stigma has been linked to anxiety, depression, and reduced mental health-related quality of life.[11] Stigma has been shown to be a barrier limiting access to healthcare for those with long COVID. In other words, PCC-related stigma is now recognized to be a global phenomenon, often compounded by race, occupation, socioeconomics, religion, and vaccination status, with the potential to negatively impact individual patients, their friends and family, and entire communities.[12]

Our group recently described the development of a novel instrument, the Post COVID-19 Stigma Questionnaire (PCCSQ), designed to estimate the stigma experienced by individuals suffering from PCC.[9] This preliminary study involved quantification of disease manifestations and stigma at a single point in time in a cohort of individuals meeting diagnostic criteria for PCC following a PCR-confirmed SARS-CoV-2 infection.

With a growing recognition that PCC is an important complication of COVID-19, affecting up to 15% of people after an acute infection, that PCC is known to undermine the long-term health outcomes of those affected, and that there is a need to better understand how stigma evolves over time, we conducted a longitudinal descriptive study with the following objectives: to measure PCC-related stigma in our original PCCSQ study cohort at a second point in time; to explore the relationship between PCC-related stigma, disease manifestations, and health outcomes as the condition progresses over time; and to determine if stigma measured early in the course of PCC could be predictive of disease manifestations and health outcomes at a later point in time.[13–15]

Methods

Ethics

This study was approved by the University of Alberta Research Ethics Board (Pro 00107350) in early 2023. All study participants received verbal and written descriptions of the study details, were given an opportunity to have questions answered, provide informed consent, and were notified that consent could be withdrawn at any time.

Inclusion/exclusion criteria and consent

Participants included in this study were required to meet the following criteria: a member of the original PCCSQ evaluation cohort (English speaking; age ≥18-years; a positive Polymerase Chain Reaction (PCR) test for SARS-CoV-2; at least 12 weeks since the onset of acute infection); internet access.[11]

Research question

How does the stigma associated with long COVID impact the disease manifestations, health outcomes,

and overall well-being of those affected as the condition evolves over time?

Hypotheses

We formulated the following hypotheses with which to operationalize our research question: a decrease in PCC-related stigma over time will be associated with a lower symptom burden, lower levels of depression, improvements in functional status, improvements in quality of life, and a change in occupational status from not working to working; PCC-related stigma measured early in the course of long COVID is predictive of future estimates of disease burden, health outcomes, and overall well-being at later points in time.

Power calculation

A power calculation was performed to estimate the number of participants required for this study. The effect size for the correlation between PCC-related stigma and the variables of our study (symptoms, depression, functional status, quality of life, and occupational status) is thought be moderate (r = 0.38–0.64). We used the mean of these values as an expected effect size, set the alpha at 0.05, and our desired power to 0.80. This yielded a minimum required sample size estimate of n = 33. In anticipation of participant dropout during the prolonged interval between the two data collection events as well as possible response incompleteness associated with the use of lengthy data collection instruments, we continued to recruit until we had reached 99 of the 145 participants of the original PCCSQ validation cohort.

Protocol

We attempted to contact all 145 members of our original PCCSQ evaluation cohort by telephone.[11] Those who responded were provided detailed information describing the follow-up study. Informed consent was tracked electronically. Consenting participants received an email link to a battery of online follow-up survey instruments.

Existing response data collected during the original PCCSQ evaluation study (early PCC, enrollment phase) was matched to the more recent responses from consenting participants who completed the entire battery of surveys as outlined above (later PCC, follow-up phase). Anonymized identifiers and a secure follow-up study database were employed to ensure participant confidentiality.

Study instruments

To measure stigma and the hypothesized correlates, we selected six instruments: the PCCSQ,[9] a modified version of the Edmonton Symptom Assessment System Revised (ESAS-r),[16] the Patient Health Questionnaire-9 (PHQ-9),[17] the Post-COVID Functional Scale (PCFS),[18] and the European Quality of Life—5 Dimensions—5 Levels (EQ5D5L index).[19] A standardized questionnaire was used to document occupational status. Approval was obtained for use of all study instruments when required.

Study variables

The PCCSQ consists of 40 items sampling across multiple aspects of perceived stigma. A five-point Likert scale was utilized to record subject responses to each item: strongly disagree (1), disagree (2), neutral (3), agree (4), strongly agree (5).

Total Stigma Score (TSS) was defined as the sum of all responses on the instrument. The minimum possible score (1 × 40 items = 40) indicates low perceived stigma. The maximum possible score (5 × 40 = 200) indicates high levels of stigma.

For each participant, TSS-1 was defined as the sum of responses on the PCCSQ administered during the PCCSQ enrollment phase. TSS-2 was defined as the sum of responses on the PCCSQ during the follow-up phase. Delta TSS (stigma trajectory) was calculated by determining the mathematical difference between TSS-1 and TSS-2. Although minimal clinically important differences are not known, positive and negative delta TSS values were interpreted as relative increases or decreases in perceived stigma, respectively.

Instruments validated to quantify PCC symptomatology were not available at the time of the original PCCSQ evaluation study (enrollment). As a result, a modified version of the ESAS-r was utilized to capture symptom score and intensity. For purposes of comparability, this instrument was used in the follow-up study as well. Participants rated each symptom on a scale from 0/10 (none) to 10/10 (maximum). The total symptom score was defined as the sum of symptom ratings.

Total scores on the PHQ-9, PCFS, and EQ5D5L index were used to estimate depression, functional status, and quality of life respectively.

PCC-related *disease manifestations* were estimated by the sum of standardized ESAS-r and PHQ-9 scores (Disease Manifestations Composite Score, DMCS). Similarly, PCC-related *health outcomes* were operationalized using the sum of standardized PCFS, EQ5D5L total, and work status scores (Health Outcome Composite Score, HOCS). The sum of DMCS and HOCS was used as a surrogate for *overall well-being* (Global Well-Being Composite Score, GWBCS).[20]

Statistics

Study data were collected and managed using REDCap electronic data capture tools hosted by the Women & Children's Health Research Institute at the University of Alberta.[21] Microsoft Excel was used to conduct all statistical analyses.[22] Frequency distributions for each variable were prepared and inspected to ensure that the data met the assumptions for our analysis procedures.

	PCCSQ evaluation cohort	PCC-related stigma follow-up cohort	
	Enrollment survey data	Enrollment survey data	Follow-up survey data
Participants (n)	145	99	99
SARS-CoV-2 PCR Positivity to survey completion (days)	322 (96–671)	331 (96–675)	926 (594–1215)
World Health Organization declaration of pandemic to survey completion (days)	605 (457–797)	593 (457–778)	1188 (1157–1250)
Age (years)	48.2 (21.8–79.7)	48.9 (21.8–79.7)	50.6 (23.4–81.3)
Women	96 (66.2%)	75 (75.8%)	
Man	47 (32.4%)	24 (24.2%)	
Gender not disclosed	2 (1.4%)	0 (0.0%)	
White	108 (74.5%)	80 (81.0%)	
Visible Minority	18 (19.3%)	11 (11.1%)	
Indigenous	8 (5.5%)	6 (6.1%)	
Ethnicity not disclosed	1 (0.7%)	1 (1.0%)	
Home during acute COVID	78 (53.7%)	54 (54.5%)	
Emergency Room during acute COVID	24 (16.5%)	17 (17.2%)	
Hospital admission during acute COVID	24 (16.5%)	18 (18.2%)	
ICU admission during acute COVID	19 (13.1%)	10 (10.1%)	
Married	90 (62.1%)	64 (64.6%)	
Common Law	3 (2.1%)	0 (0.0%)	
Divorced or separated	22 (15.2%)	16 (16.2%)	
Widow/Widower	2 (1.4%)	2 (2.0%)	
Single	26 (17.9%)	16 (16.2%)	
Marital status not disclosed	2 (1.4%)	1 (1.0%)	
Some high school	8 (5.5%)	3 (3.0%)	
High school equivalence	30 (20.7%)	16 (16.2%)	
Diploma/Trade	52 (34.9%)	41 (41.2%)	
Bachelor	38 (26.2%)	27 (27.3%)	
Graduate	12 (8.3%)	8 (8.1%)	
Education not disclosed	5 (3.4%)	4 (4.0%)	
<25 K	5 (3.4%)	4 (4.0%)	
25–49 K	15 (10.3%)	10 (10.1%)	
50–99 K	50 (34.5%)	30 (30.3%)	
100–149 K	29 (20.0%)	22 (22.2%)	
>150 K	25 (17.2%)	18 (18.2%)	
Household income not disclosed	21 (14.5%)	12 (12.1%)	
Urban	126 (86.9%)	84 (84.8%)	
Rural	19 (13.1%)	15 (15.2%)	

PCCSQ: Post COVID-19 Condition Stigma Questionnaire.

Table 1: **Participant characteristics: PCCSQ evaluation cohort and PCC-related follow-up cohort.**

Measures of central tendency and variability appropriate to the distributions were calculated, including means, modes, standard deviations, and ranges. To explore the relationships between TSS and other variables for which data was collected, we utilized Pearson coefficients to estimate the strength and direction of the relationship between variables, the paired t-test to determine statistical significance, and Cohen's d to estimate effect size. To examine the relationship between the stigma and the five indices of health measures at two points in time, we created a multivariate multiple regression model with delta stigma (delta TSS) serving as the independent variable and total symptoms (ESAS-r), depression score (PHQ-9 total), functional status (PCFS total), and quality of life (EQ5D5L total) as the dependent variables. This approach allowed for analysis of the multiple dependent variables simultaneously, thereby accounting for potential correlations among the variables and guarding against type-1 errors. Model assumptions, including linearity, homoscedascity, and absence of multicollinearity, were assessed using standard procedures and were deemed to be met.

Role of funding source

The funding agency had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Results

Participants

Between May 12 and August 13, 2023, informed consent was obtained from 112 (77%) of the 145 original PCCSQ evaluation participants. Ninety-nine (68%) completed useable questionnaires and were included in the follow-up cohort. The corresponding enrollment data for these participants was collected between June 11, 2021 and April 27, 2022.

The mean (range; SD) age of the study cohort was 48.9 (21.8–79.9; 12.5) years at the time of enrollment into the original PCCSQ evaluation study. The mean (range, SD) age had increased to 50.6 (23.4–81.3; 12.5) by the time of follow-up. Seventy-five (75.8%) identified as a woman; 81.0% were white; 11.1% were a non-white, non-indigenous; 6.1% were indigenous. The mean interval between completion of enrollment and follow-up questionnaires was 595 (411–746; 95.3) days or 1.6 (1.1–2.0; 0.26) years. See Table 1.

Within the follow-up cohort, the earliest documented acute COVID-19 infection (as determined by the date of PCR positivity for SARS-CoV-2) occurred on March 12, 2020 while the most recent occurred on October 29, 2021. Repeat COVID-19 infections were not tracked.

Change in stigma from enrollment to follow-up

Individual participants demonstrated marked heterogeneity in estimated stigma between enrollment and follow-up. While some participants reported improvement, others experienced minimal-to-no change, and others yet described a worsening of stigma. See Fig. 1.

Within the entire 99-member cohort, enrollment stigma (TSS-1) ranged from 45 to 174/200, with a mean (SD) of 105.0 (30.3). Follow-up stigma (TSS-2) ranged from 41 to 178/200, with a mean (SD) of 104.8 (34.5). The change in mean TSS from enrollment to follow-up was negligible at −0.2 ($p = 0.97$). There was a positive correlation between TSS-1 and TSS-2 ($r = 0.77$, $t = 12.0$, $df = 97$, $p < 0.001$). See Fig. 2.

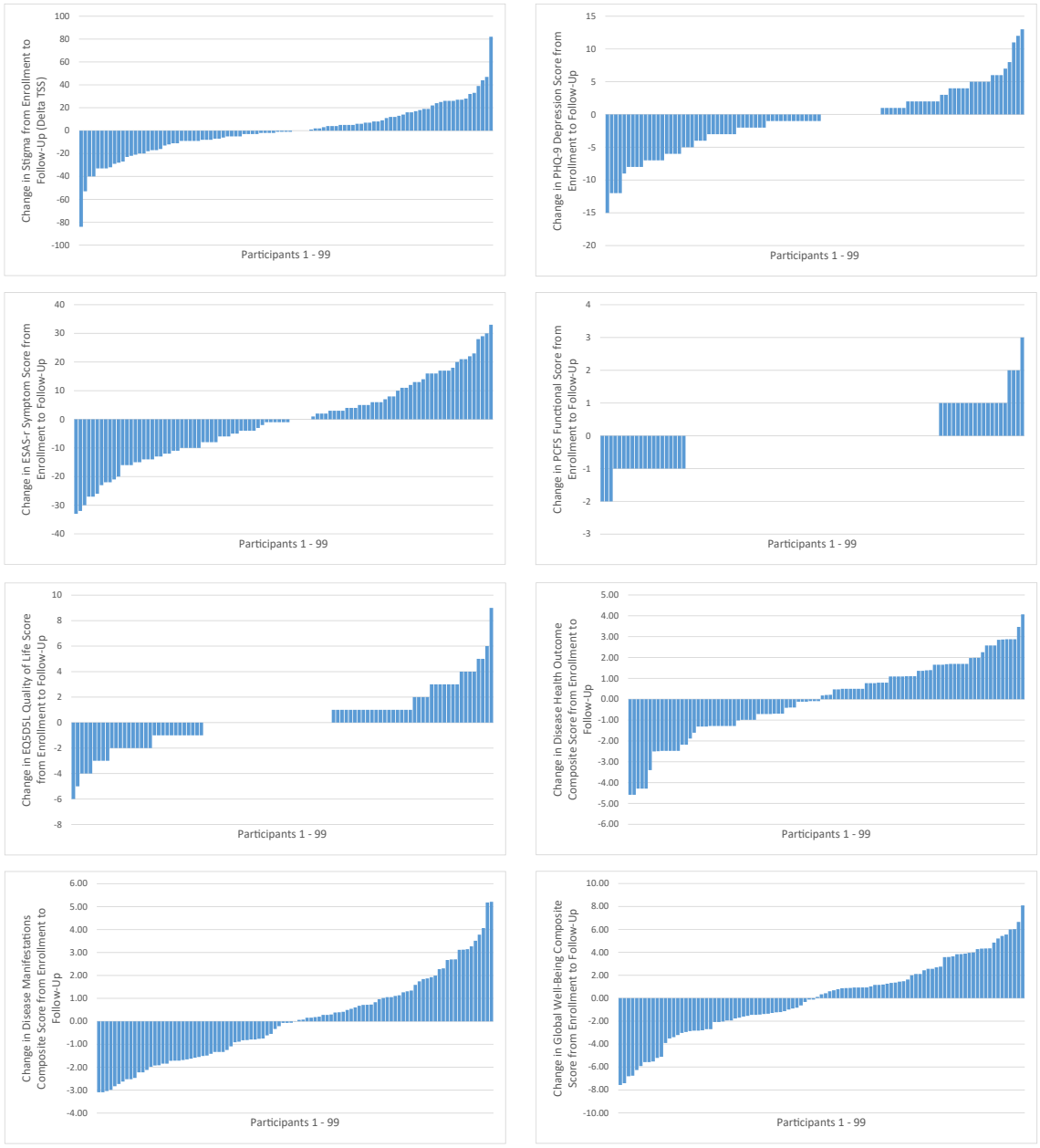

Fig. 1: Change in study metrics from enrollment to follow-up for each of the 99 participants (PCCSQ: Post COVID-19 Condition Stigma Questionnaire; ESAS-r: Edmonton Symptom Assessment System, revised; PHQ-9: Patient Health Questionnaire-9; PCFS: Post COVID Functional Scale; EQ5D5L: European Quality of Life 5-Dimensions 5-Levels).

Change in symptoms, depression, function, and quality of life from enrollment to follow-up

As was the case with stigma scores, participants demonstrated marked individual variability in the progression of ESAS-r, PHQ-9, PCFS, and EQ5D5L index scores over time. See Fig. 1.

Mean scores for the above parameters were not statistically different from enrollment to follow-up. However, statistically significant correlations between enrollment and follow-up were identified. See Table 2.

Stigma, symptoms, depression, function, and quality of life at enrollment

Statistically significant correlations were noted between TSS-1 and *enrollment* metrics, including symptom score (ESAS-r: $r = 0.67$, $t = 8.8$, $df = 97$, $p < 0.001$), depression (PHQ-9: $r = 0.57$, $t = 6.3$, $df = 97$, $p < 0.001$), functional status (PCFS: $r = 0.54$, $t = 12.0$, $df = 97$, $p < 0.001$), quality of life (EQ5D5L index: $r = 0.57$, $t = 6.9$, $df = 97$, $p < 0.001$), work status ($r = -0.27$, $t = -2.8$, $df = 97$, $p < 0.007$), and disability ($r = 0.29$, $t = 3.1$, $df = 97$, $p < 0.003$). See Fig. 3.

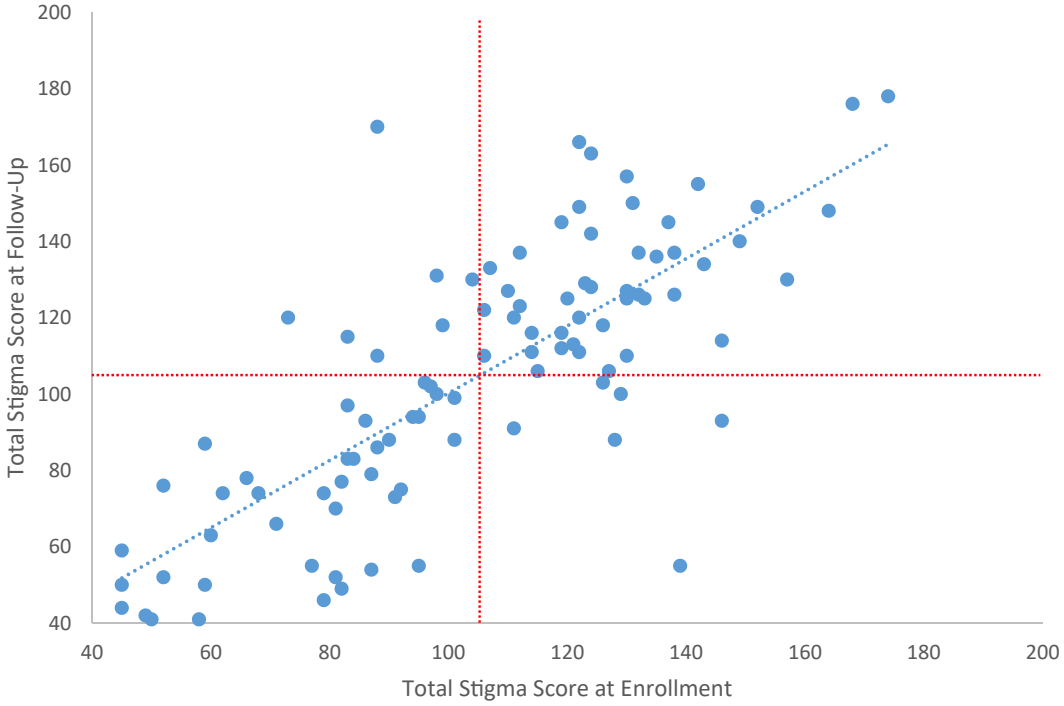

Fig. 2: Correlation between total stigma score at enrollment (TSS-1) and total stigma score at follow-up (TSS-2). Dashed red lines indicate mean stigma scores at enrollment and follow-up.

Stigma, symptoms, depression, function, and quality of life at follow-up

A similar pattern of correlations was noted between TSS-2 and *follow-up* metrics, including symptom score (ESAS-r: r = 0.73, t = 10.5, df = 97, p < 0.001), depression (PHQ-9: r = 0.68, t = 9.1, df = 97, p < 0.001), functional status (PCFS: r = 0.63, t = 7.9, df = 97, p < 0.001), quality of life (EQ5D5L index: r = 0.62, t = 7.9, df = 97, p < 0.001), and disability (r = 0.23, t = 2.2, df = 97, p < 0.05). The correlation between TSS-2 and work status at follow-up was not statistically significant. See Fig. 4.

Enrollment stigma vs. disease manifestation and health outcome metrics at follow-up

Enrollment stigma (TSS-1) demonstrated statistically significant correlations with individual and composite disease manifestation and health outcomes metrics measured at *follow-up*: symptom score (ESAS-r: r = 0.55, t = 6.4, df = 97, p < 0.001); depression (PHQ-9: r = 0.48, t = 5.5, df = 97, p < 0.001); functional status (PCFS: r = 0.45, t = 5.0, df = 97, p < 0.001); quality of life (EQ5D5L index: r = 0.49, t = 5.5, df = 97, p < 0.001); work status (r = –0.21, t = –2.1, df = 97, p = 0.05); disease manifestations composite score (r = 0.54, t = 6.4, df = 97, p < 0.001); health outcome composite score (r = 0.39, t = 4.2, df = 97, p < 0.001); and, global well-being composite score (r = 0.52, t = 6.0, df = 97, p < 0.001). The correlation between TSS-1 and disability at follow-up was not statistically significant. See Fig. 5.

Metric	Mean value at enrollment	Mean value at follow-up	Difference in means	p	Coefficient of correlation between enrollment and follow-up	p
ESAS-r	32.29	31.31	−0.9811	=0.71	0.69	<0.001
PHQ-9	10.51	9.66	−0.85	=0.37	0.72	<0.001
PCFS	1.97	1.99	0.02	=0.90	0.72	<0.001
EQ5D5L index	9.57	9.79	0.22	=0.63	0.75	<0.01

Table 2: Difference and correlation between symptoms (ESAS-r), depression (PHQ-9), functional status (PCFS), and quality of life (EQ5D5L index) at enrollment and follow-up in the 99-member stigma follow-up cohort.

Delta stigma vs. symptoms, depression, function, and quality

Participants with stable or increased stigma trajectory (delta TSS ≥0) had significantly worse symptom, depression, composite disease manifestation, functional status, quality of life, work status, health outcome, and global well-being scores compared to those with a decrease in stigma over time (delta TSS <0). See Table 3.

Multivariate multiple regression analysis of delta stigma vs. symptoms, depression, function, and quality

A multivariate multiple regression analysis to explore the simultaneous association of delta TSS with PCFS,

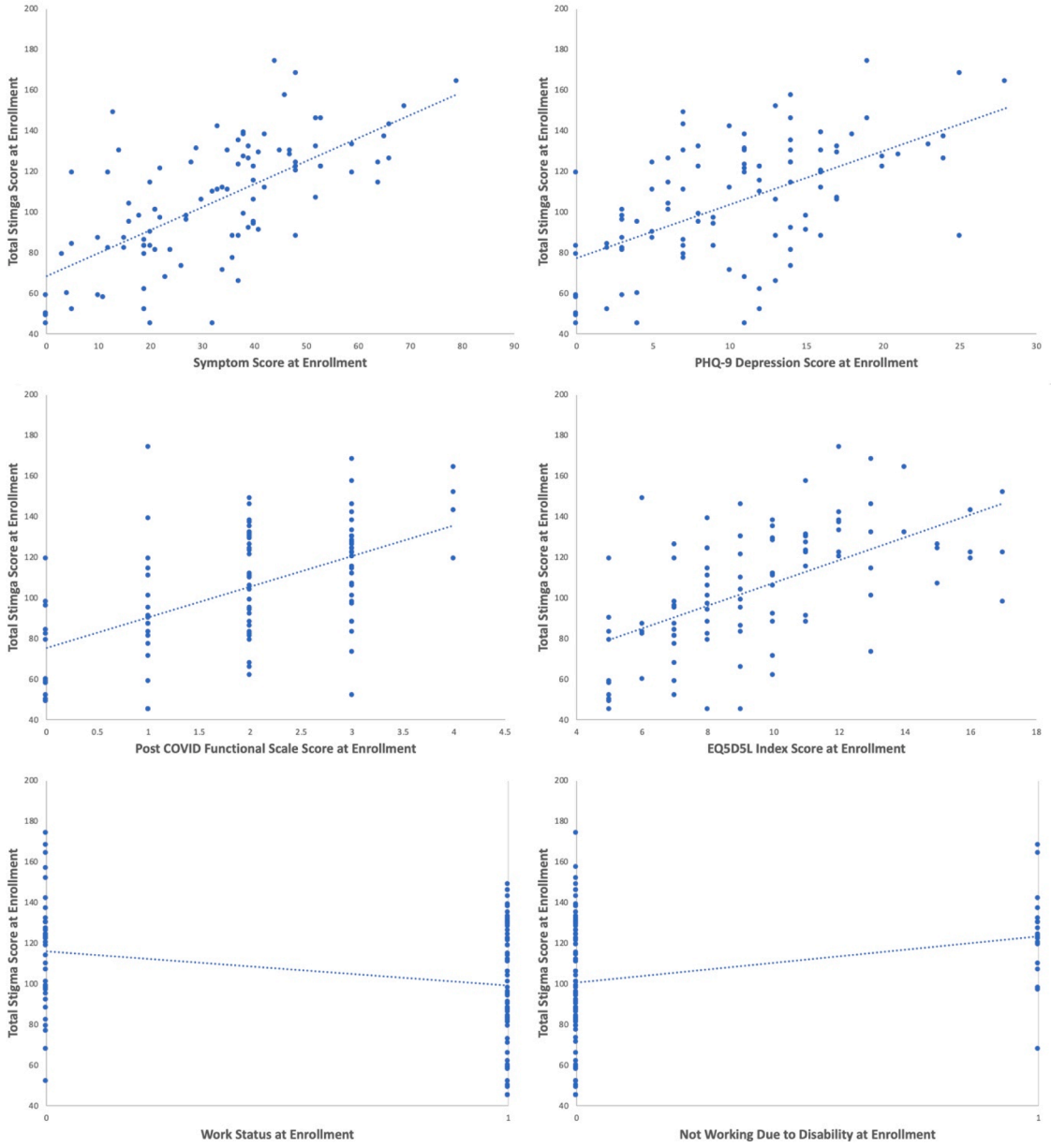

Fig. 3: Enrollment: stigma vs. disease manifestations (ESAS-r symptom score, PHQ-9 depression score), health outcomes (PCFS function score, EQ5D5L index score, work status), and disability status (0 = condition not present; 1 = condition present).

PHQ-9, ESAS-r, and EQ5D5L was undertaken. The overall model was statistically significant (Wilks' Lambda = 0.827, F (4, 93) = 4.88, p = 0.001) indicating that Delta Stigma predicted the combined set of dependent variables.

Delta TSS was significantly associated with lower scores on each of the four patient reported measures at follow-up: ESAS-r (B = –0.28, 95% CI: –0.43 to –0.14, p < 0.001); PHQ-9 (B = –0.11, 95% CI: –0.17 to –0.06, p < 0.001); PCFS (B = –0.18, 95% CI: –0.28 to –0.08, p < 0.001); EQ5D5L (B = –0.45, 95% CI: –0.80 to –0.02, p < 0.001).

Stigma, occupational status, and disability

Eighty-three percent of participants described their pre-pandemic occupational status as "working". This decreased to 66% by the time of enrollment (early PCC) and remained at 66% at follow-up (later PCC). During these three phases, the percentage of participants who self-reported as "not working due to disability" were 3%, 19%, and 14% respectively while percentage of participants in the "retired" or "prefer not to disclose" category was 9%, 8%, and 16% respectively.

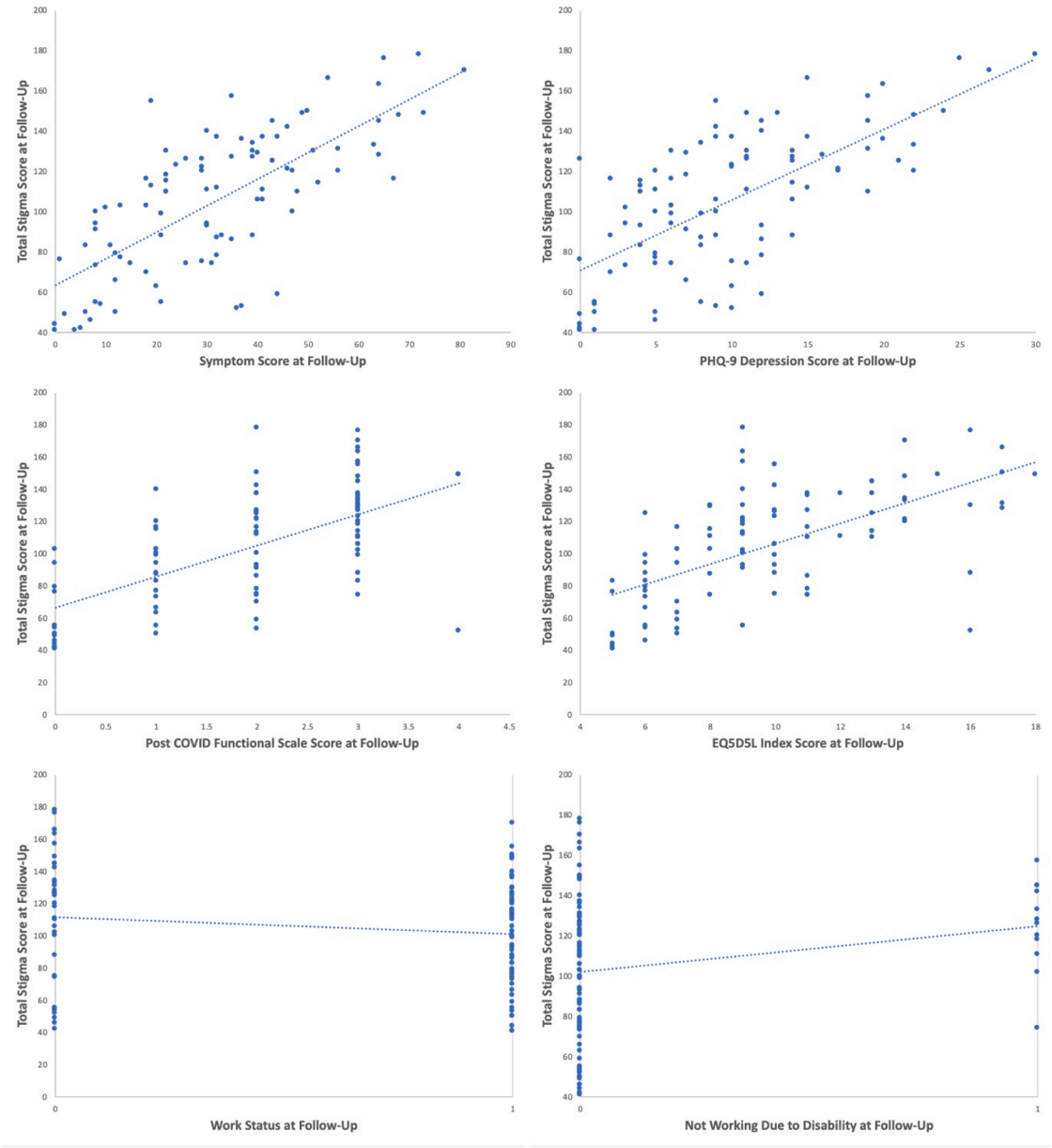

Fig. 4: Follow-up: stigma vs. disease manifestations (ESAS-r symptom score, PHQ-9 depression score) and stigma vs. health outcomes (PCFS function score, EQ5D5L index score, work and disability status (0 = condition not present; 1 = condition present)).

The mean TSS-1 among participants with an occupational status of "working" at the time of follow-up was significantly lower than that those who were "not working" (working vs. not working: 100.5 vs. 113.6, $p < 0.05$), with a moderate effect size (Cohen $d = -0.45$). Similarly, TSS-1 was significantly lower in participants who were "working" at follow-up compared to those self-classified as "not working due to disability" (working vs. disabled: 100.5 vs. 115.1, $p = 0.05$), with a moderate effect size (Cohen $ds = 0.59$).

Discussion

This study provides several insights into the temporal relationship between stigma and patient-centered outcomes in a cohort with well-documented PCC. More specifically, our findings support this study's two hypotheses: that is, changes in PCC-related stigma over time appear to be associated with corresponding changes in symptom burden, levels of depression, functional status, quality of life, and occupational status; and, PCC-related stigma measured early in the course of long COVID is potentially predictive of future

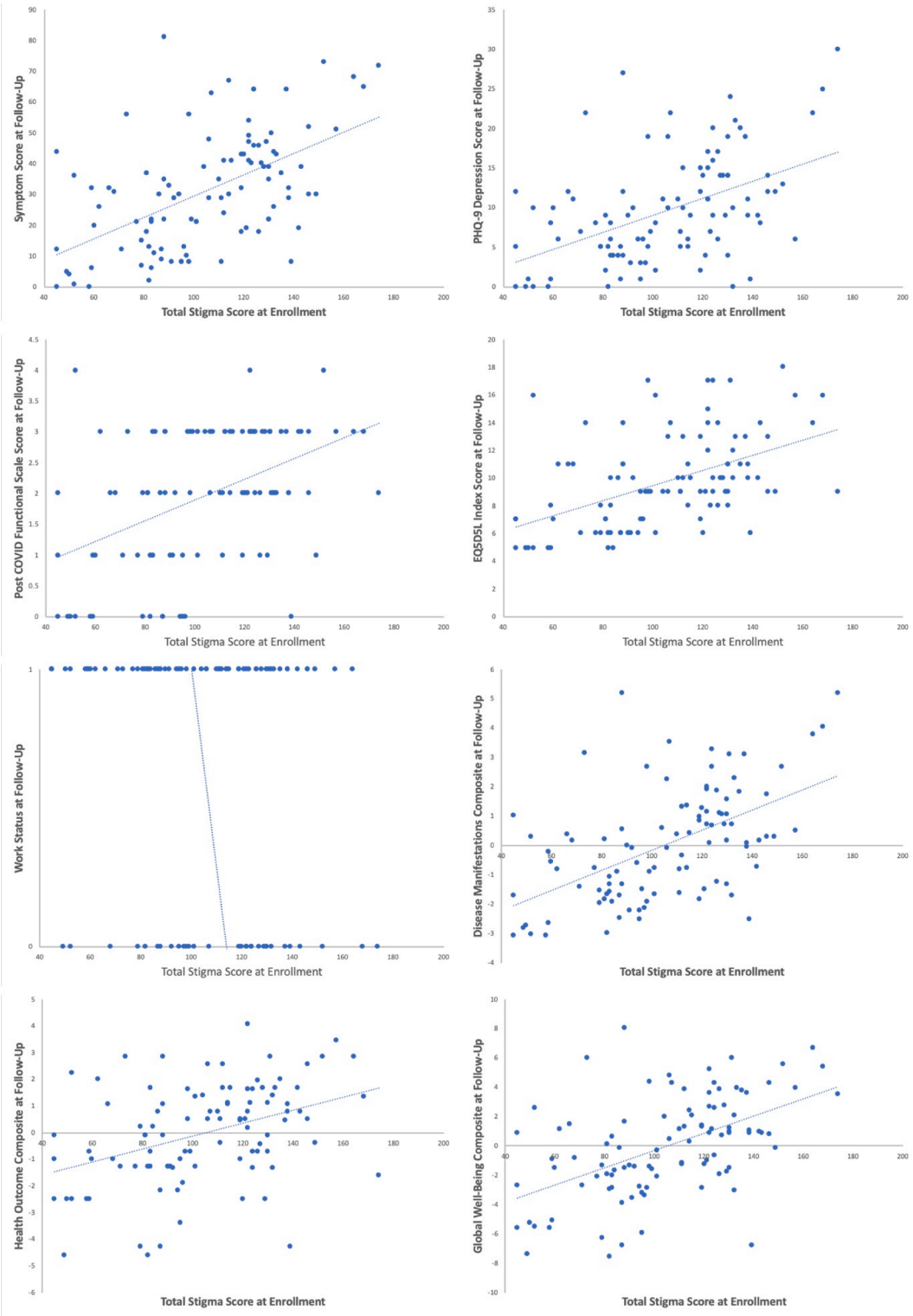

Fig. 5: Associations between enrollment stigma (TSS-1) and study metrics measured at follow-up on average 1.6 years later: ESAS-r symptom score, PHQ-9 depression, PCFS score, EQ5D5L index score, work status, disability affecting work status, composite disease manifestations score, and composite health outcomes score.

Follow-up survey metric	Follow-up instrument	Mean score among participants reporting a decrease in stigma (delta TSS <0)	Mean score among participants reporting no change or an increase in stigma (delta TSS ≥0)	Cohen's d	p
Symptoms	ESASr-2	25.6	37.9	−0.69	<0.001
Depression	PHQ-9-2	7.4	12.0	−0.73	<0.001
Function	PCFS-2	1.7	2.3	−0.58	=0.004
Quality of life	EQ5D5Li	9.0	10.5	−0.43	=0.035
Disease manifestations	DM Composite	−0.68	0.68	−0.76	<0.001
Health outcomes	HO Composite	−0.51	0.52	−0.56	=0.006
Global well-being	GWB Composite	−1.16	1.29	−0.77	<0.001

Delta TSS was categorized as decreasing (delta TSS <0) or unchanged/increasing (delta TSS ≥0). Note that this comparison does not adjust for multiple comparisons: p values should be interpreted with caution.

Table 3: **Relationship between stigma trajectory (delta TSS) and follow-up study metrics.**

disease burden, health outcomes, overall well-being, and occupational status.

Mean estimates of PCC-related stigma, symptom burden, depression, functional status, and quality of life did not change significantly from the time of enrollment through follow-up. At first glance, this might indicate that PCC, once established, is a static, unchanging condition. More detailed analysis, however, demonstrated marked heterogeneity of individual experience: approximately one third of our cohort demonstrated minimal change in over the course of the study; another third of participants reported improvements in study metrics while a final third described a worsening during this interval of time. The combined effect of these contrasting experiences resulted in no significant change across the mean values of the entire cohort.

This heterogeneity of experience is consistent with the reports from patients, patient groups, clinicians, and researchers. It aligns with the concept of PCC as a chronic condition of complex pathogenesis, protean manifestations that wax and wane asynchronously over time, and varying illness trajectories impacted by disease phenotypes, social determinants, levels of support or neglect within the health system, and other factors.[14,23,24] As a result, measures of central tendency on their own may be insufficient for purposes of providing advice to individual patients or tracking the progress of groups over time. These factors, and the lack of universally effective treatment modalities for PCC, contribute to the substantial prognostic uncertainty encountered by patients and clinicians alike.[25]

Moderate-to-strong correlations were noted between stigma estimates and both disease manifestation (ESASr-1, PHQ-9-1) and health outcome metrics (PCFS, ED5D5L index, work status) at both *enrollment* and *follow-up*. Clearly, the associations between stigma, disease manifestations, and health outcomes persisted over our follow-up interval of 1.6 (1.1–2.0) years. Coincidentally, recruitment into our study straddled the World Health Organization's declaration of an end to the pandemic (March 11, 2020–May 23, 2023).[26] Even at this late stage, characterized by "a move past the events of the pandemic", PCC-related stigma/stigmatization was found to persist. This finding is consistent with existing frameworks describing (health-related) stigma as a deeply-ingrained psychosocial construct resistant to short-term or superficial cultural changes and policy interventions.[27]

Estimates of *enrollment* stigma (TSS-1), gathered early on in the pandemic, were found to correlate significantly with *follow-up* disease burden and health outcome metrics collected during the later stages of the pandemic. This was the case for each of the five individual metrics used to in this study (ESAS-r, PHQ-9, PCFS, EQ5D5L, occupational status). It also applied to the three composite measures employed to estimate disease manifestations, health outcomes, and overall well-being. These observations bring up the possibility that stigma, measured at an early stage of PCC, could be predictive of disease persistence and/or reduced health outcomes into the future.

Stigma trajectory (stable or increased stigma vs. decreased stigma from enrollment to follow-up) also appeared to be potentially predictive of symptom, depression, functional status, quality of life, and composite scores at follow-up. Estimated effect sizes were moderate-to-large.

Multivariate multiple regression modelling demonstrated statistically significant associations between the change in stigma (delta TSS or stigma trajectory) from enrollment to follow-up and the set of dependent variables, including symptoms, depression, functional status, and quality of life measured at follow-up. In other words, variations in stigma measurements over time appear to be independently associated with corresponding changes in symptoms, depression, functional status, and quality of life within our cohort.

Between the pre-pandemic and early pandemic (enrollment) phases of this study, the percentage of participants self-described as "working" decreased from 83% to 66%. This remained at 66% by late pandemic (follow-up). During the same three time periods, the percentage of patients not working due to disability was 3%, 19%, and 14%, respectively. These observations suggest that PCC imposes a persistent, negative effect on the ability to work. Early on, PCC sufferers reported an inability to work due to "disability". Over time, those not able to return to work appear to be transitioning to a status of "retired" or "not disclosed".

Stigma estimates from the time of *enrollment* were significantly higher among individuals with a *follow-up* status of "not working" compared to those who were "working". It is enticing to speculate that PCC-related

stigma was one of the factors undermining some participants' ability to return to work. Alternatively, the inability to return to work could be stigmatizing in and of itself, regardless of the specific underlying cause. In many cases, both dynamics could be occurring.

The observation of a relatively strong relationship between stigma measured at an *early* phase of PCC and disease manifestations, health outcomes, works status, and global well-being at a substantially *later point in time* is consistent with existing stigma frameworks. While not conclusively demonstrating stigma as an independent risk factor for poor health outcomes, this association does support the concept of stigma as a potentially targetable social determinant of health for purposes of screening, prognostication, or therapeutic/policy interventions at both individual and population levels.

The participants recruited into this study met strict diagnostic criteria for PCC. We were able to recruit 99/145 (68%) of the original cohort into the follow-up study. Study participants completed *enrollment* questionnaires just before, on average, the first anniversary of their first-ever COVID-19 infection. They went on to complete *follow-up* instruments an average of 1.6 years later. This interval constitutes a substantial period of time, equivalent to about half the duration of the entire SARS-CoV-2 pandemic as declared be the World Health Organization.[26] Questionnaire completion rates among the 99 participants included in the analysis was 100%.

Although based on previously described research methodologies, the definitions of our composite measurements were somewhat arbitrary, with a possibility that the individual scales used to define the composite scores could be overlapping into more than one domain.[20] Nevertheless, these composite measures give some sense of the potential relationship between PCC-related stigma and the ensuing consequences of long COVID, including disease manifestations, health outcomes, and global well-being. Importantly, the patterns noted in our findings align with existing stigma frameworks and prediction models.[2,3]

The sample size of 99 participants was relatively small. Seventy-five percent of participants identified as women. Eighty percent self-reported to be White. The majority (84.8%) lived in an urban setting. These factors limit the generalizability of our results.

Co-morbid conditions, repeat COVID-19 infections, vaccination status, and PCC-related treatment interventions were not tracked. These and other confounding factors could have contributed to unaccounted variations in stigma scores, disease manifestations, and health outcomes over the study interval.

Our design—a longitudinal non-randomized descriptive study—was exploratory in nature, and not able to mitigate the distorting effects of confounding. For example, the analysis of stigma trajectory (delta TSS) and follow-up study metrics as outlined in Table 3 did not adjust for multiple comparisons. Although the results of multivariate regression analysis demonstrated statistically significant relationships between stigma trajectory and the dependent variables, suggesting that the risk of type I error is within reasonable limits, conclusions must be subject to caution.

If replicated, our finding add weight to the emerging picture of PCC as a complex polyphenotypic illness with substantial potential to negatively impact multiple aspects of health and well-being. Importantly, this study suggests that PCC-related stigma is a likely contributor to increased disease burden and poor health outcomes, with an impact that persists over significant periods of time.

These observations, congruent with decades of work in the social sciences and medical literature, are of potential value to patients, clinicians, employers, insurers, policy makers, and others. In addition to highlighting the importance of a supportive, non-judgemental, expert approach to the management of people with PCC (and other stigmatizing health conditions), these insights could serve as a foundation for screening, improved prognostication, mitigation of stigmatizing behaviors such as "gaslighting" and dismissal, and enhanced patient and population well-being in the post-pandemic era.[28–30]

Contributors

RD and LR conceptualisation. RD, LR, and YC development of methodolody. RD and DF database develeopment. RD and LR data collection and curation. RD, LR, JW, and YC data analysis. RD, LR, GL, MPS, JW, CL, MKS, and GF review and editing. GL, MPS, MKS, and GF resources for study. RD and LR had access to and verified the underlying data. All authors read and approved the final version of the manuscript.

Ronald Damant participated in the conceptualisation of the study; the collection, curation, and analyses of data; the development of the methodology; project administration; and the preparation and revisions of the manuscript.

Data sharing statement

The study protocol is presented in the methods section of this article, and the complete set of data collected in this study, along with the data dictionary defining each field in the data file are available upon any reasonable request from Ron Damant (rdamant@ualberta.ca) for a period of five-years following the publication of this article. Participant data will be deidentified prior to circulation.

Declaration of interests

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GF: University of Alberta startup grant; Alberta Innovates grant; honoraria for educational events sponsored by AstraZeneca, Boehringer Ingelheim, Fondazione Menarini, and Roche; safety data monitoring and advisory board work with Boehringer Ingelheim and Roche.

JW: grants and contracts from Astra Zeneca, Janssen, 35 Pharma, Merck, and Sanofi; consulting fees from Apollo Therapeutics, Janssen, and Marck; payments and honoraria for speaking events from Janssen, Merck, and United Therapeutics; payment for expert testimony from Sprigings Intellectual Property Law; support for meetings and/or travel from Janssen and Merck.

All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103531.

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