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Long-term prognosis at 1.5 years after infection with wild-type strain of SARS-CoV-2 and Alpha, Delta, as well as Omicron variants

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ABSTRACT

Objectives: Knowledge is limited on how changing SARS-CoV-2 variants may translate into different characteristics and affect the prognosis of patients with long COVID, especially following Omicron variants. We compared long-term prognosis of patients in a Danish Post-COVID Clinic infected with wild-type strain, Alpha, Delta, or Omicron variants as well as the pre-Omicron compared to the Omicron period.

Methods: At enrollment, a Post-COVID symptom Questionnaire (PCQ), and standard health scores, were registered and repeated four times until 1.5 years after infection. PCQ was the primary outcome to assess the severity of long COVID, and Delta PCQ to assess failure to improve.

Results: A total of 806 patients were enrolled. Patients infected with Omicron and Delta variants presented with more severe long COVID (median PCQ 43 in Delta vs 38 in wild-type, $P = 0.003$) and health scores (EuroQol five-dimension five-level-index was 0.70 in Omicron vs 0.76 in wild-type, $P = 0.009$ and 0.78 pre-Omicron, $P = 0.006$). At 1.5 years after infection, patients had no clinically meaningful decline in severity of long COVID, and 57% (245/429) of patients failed to improve 1.5 years after infection, with no differences between variants.

Conclusion: More than half of patients referred to a Post-COVID Clinic failed to improve in long COVID severity 1.5 years after infection regardless of variants of SARS-CoV-2.

Introduction

More than 3 years after the first COVID-19 cases, several patients suffer from post-infectious health effects called long COVID [1,2]. These sequelae have been defined as symptoms persisting more than 3 months after initial COVID-19 [3]. Fatigue, concentration difficulties, shortness of breath, and myalgia are among the numerous symptoms associated with long COVID [1,4,5]. It was early documented, that Omicron infection resulted in a milder acute course compared to previous variants [6], and understanding the risk and the characteristics of long COVID symptoms following changing variants has been of great interest for planning prevention and rehabilitation strategies. Overall, studies have documented long COVID following all variants, with a lower risk after infection in the Omicron period [4,7–12], although definitions of long COVID and study populations vary [11,13]. Three large European studies showed significantly reduced risk of long COVID among Omicron compared to Delta-infected individuals [7], or to previous variants in both vaccinated as well as unvaccinated individuals [14], as well as comparing patients who received a long COVID diagnosis between variants [8].

Comparing long COVID symptoms across variant periods is not unambiguous. A systematic review from 2022 suggested individuals may have fever symptoms following Omicron compared to infection with previous variants [9], while a meta-analysis by Du et al. found no significant differences in long COVID symptoms among different variants, except for general symptoms and sleep problems [5]. Diexer et al. [14] show equal severity grade of 24 individual symptoms in participants with long COVID except for a lower risk of smell and taste disorders following Omicron infection compared to previous variants, and Magnusson et al. [12] found equal burden of long COVID symptoms following Omicron and

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Delta infection, except for myalgia. A cluster analysis of 308 individuals with long COVID also showed similar symptom patterns across variants [13], while the RECOVER study found milder long COVID symptoms following Omicron compared to the pre-Omicron period, with similar symptom frequencies but differences in brain fog, GI symptoms, and palpitations [4].

Long COVID may improve gradually over time as documented in population prevalence and cohort studies [1,15,16], but the estimated risk of failure to improve and outcome measures of persisting long COVID differs. A prospective study found that 17% of individuals infected with wild-type SARS-CoV-2 had not recovered after 24 months [15]. However, in a patient cohort, recovery rate of long COVID was only 8% during a period of 23 months [16]. A meta-analysis previously estimated that collectively 15% of patients would have long COVID after 1 year [17].

In Denmark, patients with complex and prolonged long COVID are referred to multidisciplinary regional clinics [18,19]. Risk developing long COVID in all variants was documented, but in these more severely affected patients, we need to establish the prognosis beyond 1 year and the risk of failure to improve, particularly following the most recent occurring variants of concern. Prognostic data are needed to target research, and treatment, as well as information to patients with long COVID.

We investigated the long-term prognosis of long COVID throughout the pandemic among patients referred to a regional Post-COVID Clinic, and reported characteristics and trajectories of long COVID in these more severely affected patients with long COVID during a period of 1.5 years after being infected with either the wild-type strain, Alpha, Delta, or Omicron variants of SARS-CoV-2. We used a Post-COVID symptom Questionnaire (PCQ) score [18] as the primary outcome measure and standardized health scores as the secondary measures of long COVID severity.

Methods

Setting

The Post-COVID Clinic at Aarhus University Hospital (AUH) covers an uptake area of 1 million people. Patients with complex and prolonged symptoms following COVID-19 were referred to the clinic by their general practitioner (GP). The diagnosis long COVID was based on a history of probable or confirmed SARS-CoV-2 infection, with symptoms persisting at least 12 weeks from onset of COVID-19, which could not be explained by an alternative diagnosis in accordance with the World Health Organization definition and Danish guidelines [3,19].

Data collection and analyses

Patients were included in a Post-COVID cohort previously described [18]. Demography and medical history were entered from the patient file into the Research Electronic Data Capture (REDCap) database, along with PCQ and health scores registered at the first clinic visit at a median of 7 (interquartile range [IQR] 4-11) months after infection, which were repeated online 6, 12, 24, and 48 weeks later at a median of 8 (IQR 6-12), 10 (IQR 7-14), 12 (IQR 10-16) and 18 (IQR 15-22) months after SARS-CoV-2 infection, hereafter referred to as 7, 8, 10, 12 and 18-month follow-up after infection, respectively. The upper range of follow-up was 35 months after infection. The PCQ score was constructed from 31 individual symptoms and used as the primary measure of severity of long COVID. PCQ has previously been shown to correlate with severity in standardized health scales [18]. Individual and organ-specific symptom scores were calculated as previously described, and standardized health scores were used as the secondary measures of long COVID severity: functional disability (Post-COVID Functional Status Scale [PCFS]); fatigue (Fatigue Assessment Scale [FAS]); as well as health-related quality of life (EQ-VAS 1-100 and EQ-5D-5L-index) [18]. At the first clinic visit, at 7 months after infection, symptoms during the acute phase were registered as present or not present, which did not yield a score for comparison with the PCQ during follow-up.

Patients were grouped according to time periods with transmission of predominant SARS-CoV-2 variants. After an emerging variant had been detected in the population, this new variant soon became the almost exclusively occurring variant [20]. Date of symptom onset was registered at the first clinic visit, and verification was made that symptom onset and date of SARS-CoV-2 positive polymerase chain reaction (PCR) test were consistent. Patients were grouped in variant groups according to symptom onset in time periods with transmission of predominant SARS-CoV-2 variant, decided by the date the variant accounted for more than 50% of the SARS-CoV-2 PCR positive test results in Denmark. Thus, the wild-type period occurred before 13 February 2021, followed by the Alpha period until 28 June 2021, and then the Delta period until 17 December 2021, ending with the Omicron period until 3 months before the end of study inclusion on 31 August 2022. End of study period was decided by the epidemic curve of Omicron in Denmark [20] plus the 12-week time period after infection; the 12-week period was defined as a criterion for referral to the Post-COVID Clinic [19]. The patient groups will hereafter be referred to as wild-type, Alpha, Delta, and Omicron period, respectively. Comparison of variant periods was made by comparing each variant to the wild-type period and comparing Omicron to pre-Omicron (wild-type, Alpha, and Delta) variant periods. A PCQ above the median of 35 was considered severe long COVID. In explorative analyses, the most severely affected patients had a PCQ score above the median (PCQ >35), moderately/severely affected functional level (PCFS 3-4), extreme fatigue (FAS ≥ 35), and health-related quality of life below the median (EQ-VAS <50, EQ5D index <0.76) [18].

For evaluation of the prognosis of long COVID, we calculated Delta values of symptom and health scores as the difference between scores at 7 and 18 months after infection. For evaluation of "failure to improve" we used the minimal clinically important difference (MCID) as the cut-off value. An MCID for PCQ has not previously been determined, but we used an MCID of 7 based on standardized scores with totals above 100 [21]. Standard MCDIs in secondary outcome measures were 1 in PCFS, 4 in FAS [22], 7 in EQ-VAS [21], and 0.08 in EQ5D-index [23].

Data were analyzed using Stata/MP 18. Frequency and median (interquartile ranges [IQR]) were reported, and results were compared using univariate logistic regression analyses with the wild-type period as the reference group and comparing Omicron with pre-Omicron. Bonferroni corrections of significance level were calculated due to multiple comparisons. Risk factors for "failure to improve" were evaluated in univariate as well as multivariate analyses. Adjustment was made for demographic variables which differed significantly between periods with the different variants.

Results

Demographic characteristics

In total, 936 patients were referred to the Post-COVID Clinic; and 806 (86%) patients were enrolled in this study. In total, 70% of the patients were females with a median age of 48 (IQR 37-56) years. Patients had a positive SARS-CoV-2 test in 97% of cases (90% PCR positive and 8% only SARS-CoV-2 spike Immunoglobulin G antibody positive). In the study cohort, 69% (556/804) of patients were infected during the wild-type period, whereas 9% (73/804), 7% (59/804), and 15% (118/804) were infected in the Alpha, Delta, and Omicron periods, respectively. Patients had their

Table 1
Characteristics of patients infected in time periods of predominant SARS-CoV-2 variants.

	All patients N = 806	Wild-type n = 556	Alpha n = 73	Delta n = 59	Omicron n = 118
Time from symptom onset, median (IQR)	7 (4-11)	9 (5-11)	7 (6-9)	**4 (3-6)**[c]	**4 (3-5)**[c]
Positive test [a], %	97	96	99	100	**100**
Positive PCR test, %	9	89	90	92	**97**
Sex (male), %	30	30	36	31	27
Age in years, median (IQR)	48 (37-56)	48 (38-56)	47 (35-59)	44 (35-55)	46 (36-56)
Another ethnicity than Danish, %	10	9	15	17	8
Hospitalized[b], %	10	12	14	5	**4**
Charlson comorbidity index >1, %	16	16	19	17	14
Previous depression, %	15	15	7	14	19
Body mass index ≥25, %	66	66	69	64	61
Smoking, %	8	8	3	14	6
Alcohol intake >7 units/week, %	6	6	6	4	8

IQR: interquartile range; PCR, polymerase chain reaction.
Univariate logistic regression analyses were used to compare each variant to wild-type strain. Bold: Significance level P <0.05.
[a] SARS-CoV-2 PCR or SARS-CoV-2 spike immunoglobulin G antibody test.
[b] Hospitalized in the acute phase of COVID-19.
[c] Significant difference after Bonferroni correction (P <0.004) and after adjustment for time since infection and hospitalization.

first clinic visit earlier after infection in the Delta and Omicron periods (both with a median at 4 months) compared to the wild-type period, where patients attended their first clinic visit at a median 9 months after infection (P <0.001). Fewer patients were hospitalized during the acute phase in the Omicron (4%) compared to the wild-type period (12%; P = 0.02). Age, sex, comorbidity level, body mass index, previous depression, smoking, and alcohol intake did not differ between patients during the variant of concern periods compared to the wild-type period (Table 1). Compared to the pre-Omicron period patients were seen for their first clinic visit earlier after infection and were less often hospitalized in the Omicron period (Supplementary Table 1).

Symptoms and health scores at the first clinic visit: 7 months after infection

Patients infected in the Delta period presented with significantly more severe long COVID with a mean PCQ of 43 (IQR 31-55) compared to patients infected in the wild-type period with a mean PCQ of 38 (IQR 28-49), P = 0.003. Patients infected in the Omicron period did not differ in PCQ (median 40 [IQR 29-52]) compared to wild-type patients (median 38 [IQR 28-49], P = 0.55) or to pre-Omicron patients (median 38 [IQR 28-49], P = 0.82), but patients infected with Omicron had significantly more impaired functional level (PCFS moderate to severe limitations in 49% vs 32% in the wild-type, P = 0.001, and vs 32%, P = 0.029 in the pre-Omicron period). Patients infected with Omicron had a lower health-related quality of life compared to the patients infected with wild-type (VAS score below 50 in 61% vs 39%, P ≤0.001; EQ5D-index of 0.70 [IQR 0.56-0.81] vs 0.78 [IQR 0.65-0.85], P = 0.009) (Table 2), and compared to patients infected in the pre-Omicron period (VAS score in pre-Omicron was below 50 in 40%, P <0.001; and EQ5D-index median was 0.78 [IQR 0.64-0.86], P = 0.006, although non-significant after adjusting for hospitalization and time since symptom onset) (Supplementary Table 2).

Organ-specific symptom scores did not significantly differ when comparing Alpha, Delta, or Omicron to the wild-type period (Table 2) or comparing Omicron to pre-Omicron period (Supplementary Table 2). The 31 individual symptom scores in patients infected in the different variant periods are compared to the wild-type and pre-Omicron period in Supplementary Figures 1-6. Compared to patients infected with the wild-type and to patients infected with pre-Omicron variants, patients in the Omicron period reported lower scores of disturbed sense of smell in the acute phase and at 7 months but not at 18 months follow-up. Omicron, as well as Delta patients, tended to report higher physical exhaustion at 7 months, and patients infected with Omicron compared to pre-Omicron had lower scores of chest pain and higher scores of joint pain at 18 months follow-up, but these, as well as other individual symptom scores, did not differ between variants after Bonferroni correction (Supplementary Figures 1-6).

Trajectory of long COVID during long-term follow-up (1.5 years after infection)

Of the 806 patients completing a questionnaire at their first clinic visit, at 7 months after infection, 551 (68%), 463 (57%), 466 (57%), and 443 (55%) patients, respectively completed the questionnaire 8, 10, 12, and 18 months after SARS-CoV-2 infection.

Overall, there was a significant reduction in median PCQ score from 7 to 10 months after infection (Figure 1, Supplementary Figure 7), but the PCQ score then plateaued from 10 over 12 to 18 months after SARS-CoV-2 infection. The overall median PCQ score declined from 38 (IQR 28-49) at 7 months to 36 (IQR 23-38) at 8 months, 33 (IQR 22-35) at 10 months, 33 (IQR 22-46) at 12 months, and 33 (IQR 22-46) at 18 months of follow-up. When comparing the trajectory of Alpha, Delta, or Omicron to the wild-type strain there were no differences in median PCQ score during follow-up (Table 2, Figure 1), and comparing Omicron to pre-Omicron confirmed similar trajectory in patients infected with Omicron compared to previous variants (Supplementary Figure 7).

Failure to improve during long COVID

In Figures 2 and 3, we present the Delta PCQ and health scores as a marker of improvement in long COVID from 7 to 18 months after infection. In total, 57% of individuals failed to improve above the MCID of 7 in PCQ (Figure 2) with 58%, 67%, 46%, and 54% in wild-type, Alpha, Delta, and Omicron variants, respectively (Table 2). Similar results were seen in the standardized health scores in which 64%, 58%, 54%, and 62% of all patients failed to improve their PCFS, FAS, EQ-VAS, and EQ5D-index scores during follow-up, respectively (Figure 3, Table 2).

Comparing failure to improve between variants using standardized health scores, we found no significant differences comparing Alpha, Delta, or Omicron variants to the wild-type strain (Table 2). During Omicron compared to pre-Omicron periods, failure to improve functional level (PCFS) was 61% vs 65%; failure to improve fatigue (FAS) was 59% vs 57%; failure to improve health-related quality of life was 44% vs 55% in EQ-VAS and 47% vs 65% in EQ5D-index (Supplementary Table 2).

Table 2
Symptom and health scores during follow-up of patients infected 1.5 years previously, in time periods of predominant SARS-CoV-2 variants.

	All patients N = 806	Wild-type n = 556	Alpha n = 73	Delta n = 59	Omicron n = 118
Seven months after infection					
CNS score, median (IQR)	9 (7-12)	9 (6-12)	9 (7-12)	**10 (7-13)**	**10 (8-12)**
CP score, median (IQR)	5 (3-9)	5 (3-9)	5 (3-8)	5 (3-9)	6 (2-10)
MS score, median (IQR)	8 (4-11)	8 (4-11)	6 (4-9)	**10 (6-13)**	9 (5-12)
PCQ, median (IQR)	38 (28-49)	38 (28-49)	35 (25-48)	**43 (31-55)**[b]	40 (29-51)
PCFS >2, %	35	32	26	44	**49**
FAS ≥35, %	58	57	57	62	62
EQ-VAS <50, %	43	39	32	**55**	**61**[b]
EQ5D index, median (IQR)	0.76 (0.62-0.85)	0.78 (0.65-0.85)	0.80 (0.66-0.89)	0.72 (0.57-0.80)	**0.70 (0.56-0.81)**
18 months after infection					
CNS score, median (IQR)	7 (4-10)	7 (4-10)	7 (4-9)	7 (5-9)	8 (4-11)
CP score, median (IQR)	4 (1-6)	4 (2-7)	3 (1-5)	2 (0-5)	3 (1-6)
MS score, median (IQR)	7 (4-11)	8 (4-11)	**5 (3-9)**	6 (3-11)	8 (5-12)
PCQ, median (IQR)	33 (22-46)	32 (22-47)	29 (18-38)	36 (20-41)	33 (23-45)
PCFS >2, %	29	29	16	29	39
FAS ≥35, %	44	42	41	33	**63**
EQ-VAS <50, %	28	29	14	25	35
EQ5D index, median (IQR)	0.81 (0.69-0.89)	0.81 (0.69-0.89)	0.87 (0.76-0.94)	0.80 (0.70-0.86)	0.79 (0.58-0.87)
Failure to improve[a]					
Delta-CNS score<0, %	36	38	36	21	32
Delta-CP score<0, %	36	38	44	33	**22**
Delta-MS score<0, %	51	53	46	46	44
Delta-PCQ<7, %	57	58	67	46	54
Delta-PCFS<1, %	64	65	69	58	61
Delta-FAS<4, %	58	58	60	46	59
Delta-EQ-VAS<7, %	54	58	**39**	42	44
Delta-EQ5D-index<0.08, %	62	64	74	54	**47**

Central nervous system (CNS) score was the sum of headache, dizziness, short-term memory problems, concentration difficulties, and paresthesia scores. Cardiopulmonary (CP) score was the sum of dyspnea at rest, dyspnea at exercise, cough, chest pain, palpitation scores. Musculoskeletal (MS) score was the sum of joint pain, joint swelling, myalgia, muscle exhaustion, physical fatigue scores. PCQ: Post-COVID symptom Questionnaire. PCFS: Post-COVID-19 Functional Status Scale, FAS: Fatigue Assessment Scale. EQ-VAS: EuroQol visual analogue scale. EQ5D-index: EuroQol five-dimension five-level index.

[a] Delta: Difference from 7 to 18 months after infection. Minimal clinically relevant difference: CNS-score<0, CP score<0, MS-score<0, PCQ<7, PCFS<1, FAS<4, EQ-VAS<7, EQ5D-index<0.08. IQR: inter quartile range. Univariate logistic regression analyses were used to compare each variant to wild-type strain. Bold: Significance level p<0.05.

[b] Significant difference after Bonferroni correction (p<0.006) and after adjustment for time since infection and hospitalization.

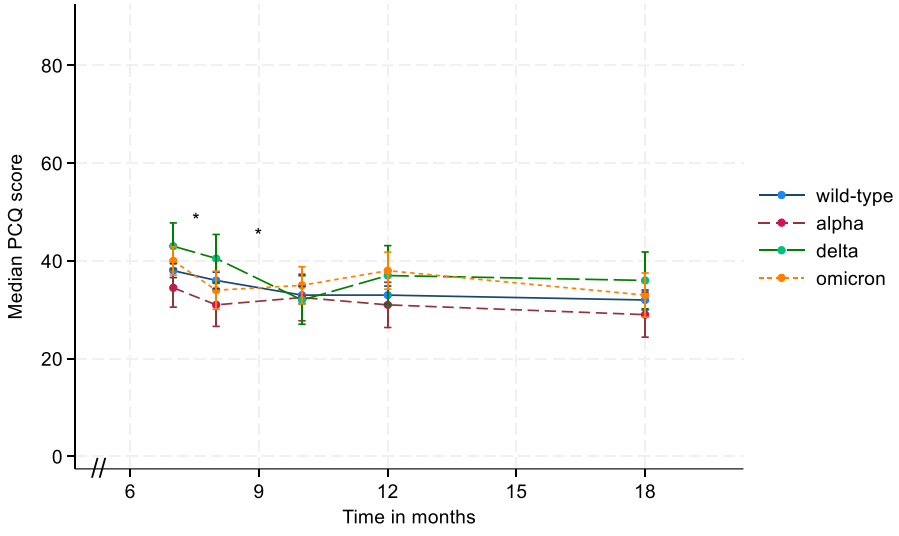

Figure 1. Trajectory of long COVID in variants.
Median Post-COVID Questionnaire symptom (PCQ) score in long COVID patients infected in wild-type, Alpha, Delta, and Omicron variant dominated time periods, during follow-up at 7, 8, 10, 12, and 18 months after SARS-CoV-2 infection, compared using t-test and confirmed in non-parametric test, *P <0.001.

Exploratively, we conducted analyses including only patients with the most severe long COVID at baseline (PCQ >35, PCFS 3-4, FAS ≥35, EQ-VAS <50, EQ5D-5L <0.76). Failure to improve was seen in 47%, 48%, 52%, 39%, and 43% of these patients in PCQ, PCFS, FAS, EQ-VAS, and EQ5D-5L, respectively.

Regression analyses found no effect of potential risk factors for failure to improve including sex, age, ethnicity, time since infection, hospitalization during the acute phase, comorbidity, fever during the acute phase, weight loss during the acute phase, previous depression, body mass index, smoking, and alcohol intake (Supplementary Table 3).

Patients who dropped out of the study prior to 18 months of follow-up were more often younger (48% vs 65% >45 years) and males (37% vs 24%). However, they did not differ in symptoms,

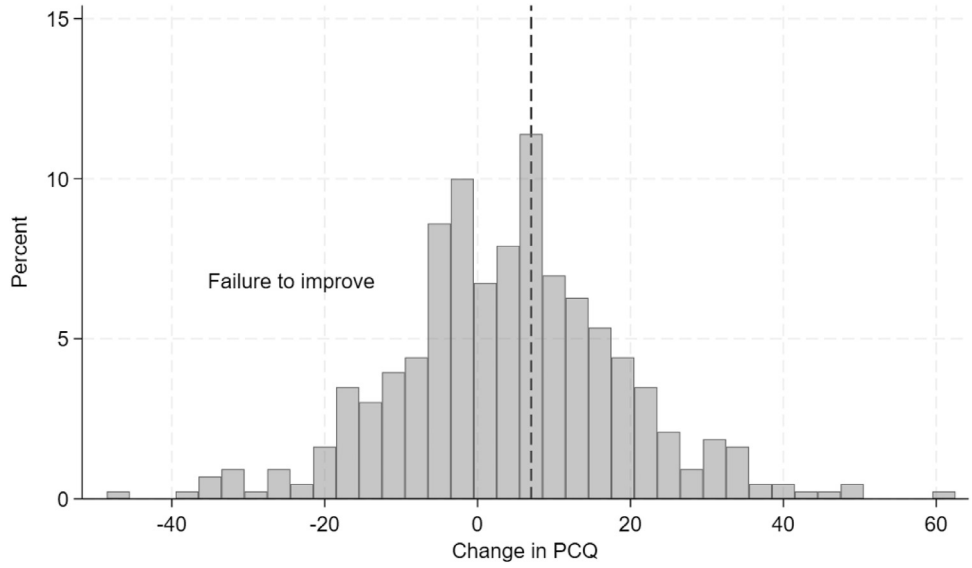

Figure 2. Failure to improve in patients with long COVID.
Change in Post-COVID symptom Questionnaire (PCQ) score during follow-up in patients infected 1.5 years previously. Change in PCQ score: PCQ at clinical evaluation 7 months after infection minus PCQ at 18 months of follow-up. Vertical dashed line: cut-off indicating failure to improve above the minimal clinically important difference of 7.

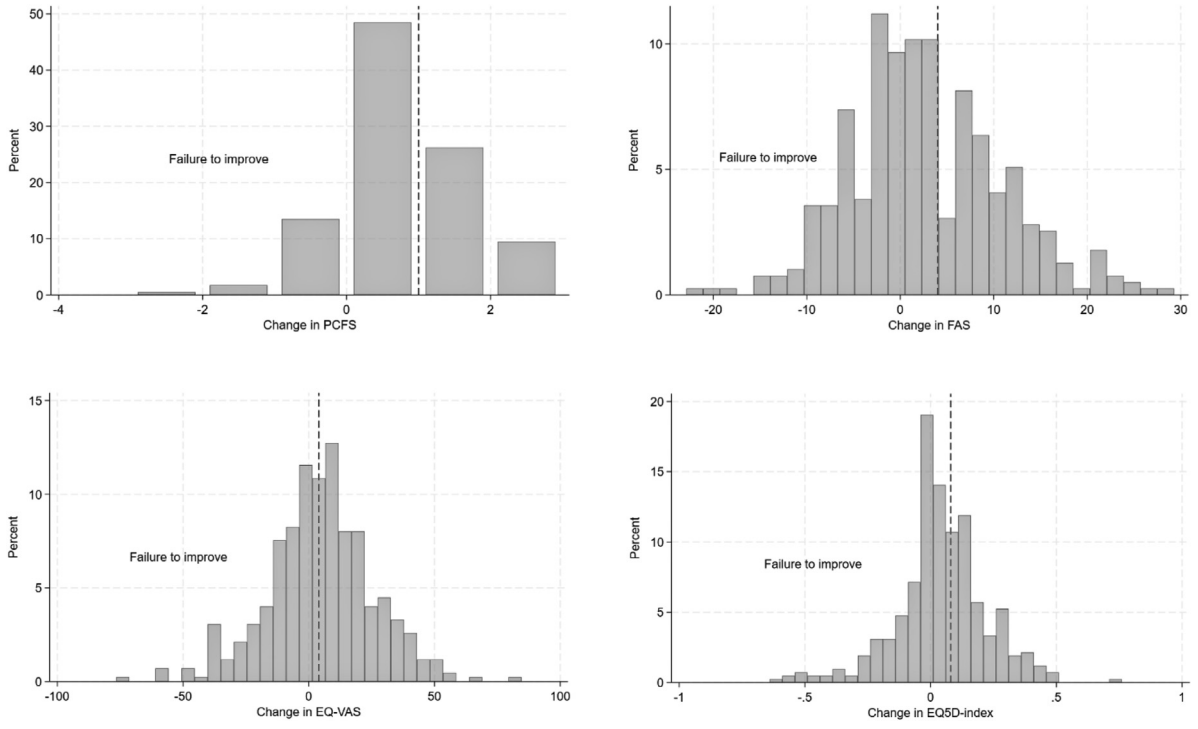

Figure 3. Failure to improve long COVID, using standardized health scores.
Change in standardized health scores of functional disability, fatigue, and health-related quality of life during follow-up in patients infected with SARS-CoV-2 1.5 years previously. Change in PCFS score: PCFS at clinical evaluation (7 months) minus PCFS at 18 months after infection. Change in FAS score: FAS at 7 months minus FAS at 18 months. Change in EQ-VAS score: EQ-VAS at 18 months minus EQ-VAS at 7 months. Change in EQ5D-index: EQ5D-index at 18 months minus EQ5D-index at 7 months. Vertical dashed line: cut-off indicating failure to improve above the minimal clinically important difference.
EQ-VAS: health-related quality of life VAS score, EQ5D-index: health-related quality of life EQ-5D-5L index. FAS: Fatigue Assessment Scale, PCFS: Post-COVID Functional Scale.

time since symptom onset, or health scores compared to participants completing the 18-month questionnaire (Supplementary Table 4).

Discussion

A post-COVID cohort of 806 patients with complex and prolonged long COVID, infected during different waves of SARS-CoV-2 variants, were followed 1.5 years after initial SARS-CoV-2 infection. The demographics of patients with long COVID did not change across the SARS-CoV-2 variant periods, except for patients infected with Omicron and Delta who were evaluated earlier after infection compared to patients infected with the wild-type strain. The patients had similar severity of long COVID when comparing Alpha, Delta, and Omicron periods to the wild-type period. Overall, mean PCQ declined from the first questionnaire at 7 until 10

months after infection. However, this was not a clinically meaningful drop, and no further decline was seen until end of follow-up at 18 months. Additionally, we found no differences in PCQ during follow-up when comparing variants of concern to the wild-type strain or Omicron to pre-Omicron variants. More than 50% of patients with long COVID did not improve during follow-up regardless of variants of SARS-CoV-2 including Omicron, and whether PCQ or any other outcome measure were used to evaluation severity.

Characteristics of complex and prolonged long COVID during waves of SARS-CoV-2 variants

This study documents that severe long COVID develops following infection with different SARS-CoV-2 variants—even the Omicron variant, which might be unexpected given the milder acute phase in this variant [6]. We found that patients infected in the Omicron period had equally severe long COVID, with no difference in PCQ score and more severely affected health-related quality of life compared to patients infected in the wild-type period and compared to the pre-Omicron period. Of note, patients from the Alpha or Delta period reported similar long COVID severity. Various studies support a lower risk of developing long COVID following Omicron infection persisting at more than 28 days [7], at 90-126 days after acute disease [12], at 112 days after infection [8], and at 6 months after acute infection [4]; although the reduced risk following Omicron infection compared to previous variants may disappear after adjusting for vaccine status [11,13]. However, while the risk of developing long COVID [7,12] and of getting a long COVID diagnosis following Omicron is reduced [8], as well as milder cases are seen [9,10], this study documents that some individuals were diagnosed with long COVID and experienced long COVID of the same severity following Omicron infection compared to previous variants, which are potentially not captured in population studies and studies including milder cases.

In Denmark, more than half of the population was infected with the Omicron variant (based on estimates from seroprevalence studies and PCR testing [24]). A smaller percentage of individuals in Denmark were infected with the original wild-type, Alpha or Delta variants [24], and it seems that a lower percentage of Omicron-infected individuals were referred with complex and prolonged long COVID compared to the other variants (Table 2), though we may not have seen all Omicron long COVID patients yet. Considering the high percentage of the population infected with the Omicron variant, and Omicron constituting 15% in our present cohort, a substantial number of patients infected with the Omicron variant may develop long COVID [7,8,11,12].

Looking into individual long COVID symptoms, we found that patients infected in the Delta and Omicron period tended to be more physically exhausted. This is in accordance with other studies reporting more prevalent myalgia comparing Omicron and wild-type infection [5]. Disturbed sense of smell was significantly less commonly reported in patients infected in the Omicron period compared to previous variants, which was not surprising given the less frequent loss of smell during the acute [25] and 3-month follow-up phase, respectively [11]. Thus, results from this study support similar long COVID individual symptoms in different strains as reported previously [5,12,14].

Prognosis of complex and prolonged long COVID during waves of SARS-CoV-2 variants

In various studies, the prevalence of long COVID is reportedly reduced over time [15,16,26,27]. However, the trajectory of symptoms in patients presenting with complex and prolonged long COVID is less clear. A review reports that 15% of patients still have long COVID at year 1 [17], and a recent paper reports little improvement over time in most patients infected in wild-type, Alpha, and Delta variants in the ComPaRe cohort [27]. It was therefore surprising that, in our cohort, half of the patients failed to experience any improvement until 1.5 years after infection, regardless of SARS-CoV-2 variants and outcome measures. There was a statistically significant drop in long COVID severity from 7 to 10 months after infection, during which patients participated in rehabilitative treatment, which may have relieved some symptoms [28]. However, the median PCQ score of long COVID severity dropped less than 7 points, which was considered the MCID, and there was no further decline until 18 months after infection. Explorative analyses of the most severely affected long COVID patients confirmed that 50% failed to improve. In the ComPaRe cohort, 94 patients were registered with highly persistent symptoms, who may resemble our cohort, although this group included patients who were more often hospitalized, had more comorbidity and included no patients infected with Omicron [27]. In patients diagnosed with long COVID recovery may be limited and primarily seen in less symptomatic patients [16]. Collectively, it is important to distinguish results that are from studies on mild to those on severe long COVID.

In some patients, long COVID may last for more than 2 years after infection [15,16,27], which is supported by our data. Neurological sequelae [29] and indications of brain damage have been shown 3 months after infection among patients with long COVID [30]. We previously reported myopathy and muscle histopathology in patients with long COVID [31]. Thus, it seems that in some patients, long COVID is a chronic debilitating disease. In accordance with previous studies [5], we did not find different patterns of long COVID comparing variants of concern to the wild-type strain, suggesting a systemic disease with a common underlying pathophysiological mechanism.

Strengths and limitations

Referral patterns from the GP to the Post-COVID Clinic may have influenced the results. The availability of SARS-CoV-2 tests, patients´health literacy, and the GP as well as the patients´evaluation of whether symptoms were due to long COVID may have affected referral patterns. Patients in this study may only present a fraction of patients affected by long COVID, as information about this condition has not been systematically disseminated within the healthcare system. A longer duration of symptoms was an unavoidable fact among patients infected during the wild-type period, as long COVID services were only officially established in February 2021 at AUH. However, adjusting for the duration of symptoms did not change interpretation of results (Table 2, Supplementary Table 2). Patient characteristics (sex, age, education) may influence patient-reported information, but despite younger males, and patients of another ethnicity than Danish more frequently dropping out, baseline symptoms and health scores did not differ when comparing these dropouts with participants. Recall bias may have been introduced as patients were asked to report symptoms over the past 4 weeks when completing the online questionnaire. However, we found no reason to suspect that this recall bias varied between the questionnaire administered at 7 to the one administered at 18 months. Sample sizes of Alpha and Delta variant groups were small, possibly limiting statistical significance of comparisons. We conducted analyses comparing patients infected with Omicron to pre-Omicron variants to account for this.

COVID-19 vaccination reduces the risk of long COVID [2,4,32]. We do not report vaccine status, but Denmark had a 90% vaccine coverage (two doses) before the Omicron period in age groups included in this study [33]. Despite this, Omicron cases with severe long COVID were observed. Vaccinations during follow-up may have temporarily affected symptom and health scores, but long-

term beneficial or adverse effects of vaccines on long COVID symptoms have not been established [2,32] reducing the likelihood of vaccine-related impacts on the 1.5-year prognosis.

Reinfection increases long COVID risk, with cumulative risk for repeated infections [32,34]. In this study we did not register reinfections. Few in Denmark were infected before the Omicron epidemic, as mentioned above, and most experienced their primary infection during that period [24]. Further, in this study, patients were grouped according to symptom onset. However, while the infecting variant at the symptom onset was registered, we cannot rule out that previous or subsequent infections may have worsened symptoms.

Medical treatment might have alleviated some symptoms, but no treatment with proven effect on long COVID symptoms was provided. Paxlovid, which may prevent long COVID [35], became available in Denmark after inclusion in the present study and is prescribed for risk patients only.

The wild-type strain period consisted of several sub-lineages, whereas the Alpha and Delta variant periods consisted almost exclusively of sub-lineages B.1.1.7 and AY.122, respectively. In the Omicron period, we included patients from time periods where BA.1 and BA.2 subtypes were predominant in Denmark [20]. In this study, we do not compare sub-lineages and cannot exclude that some of these may have accounted for an increased number of referred patients and different manifestations of long COVID.

Varying definitions of long COVID and study populations make it difficult to conclude characteristics and prognosis during waves of SARS-CoV-2 variants. However, we systematically collected data from a large patient cohort of the more severely affected patients, with a high participation rate (86%), and we have documented severe long COVID 1.5 years after infection and failure to improve from long COVID among all SARS-CoV-2 variants.

Conclusion

During the different waves of SARS-CoV-2 variants, patients referred to a Danish Post-COVID Clinic at a university hospital presented with similar characteristics, symptoms, and severity of long COVID. In all variants, more than half of patients failed to improve during follow-up 1.5 years after SARS-CoV-2 infection. We suggest the search for long COVID treatment options focus on these severely affected patients to develop future new treatments, which we believe will be effective across all SARS-CoV-2 variants.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval

The study was approved by the Data Protection Authorities in Central Denmark Region (# 1-16-02-4-21). Written informed consent was obtained from all participants.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.10.022.

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