Original Article

Persisting Symptoms After COVID-19

Prevalence and Risk Factors in a Population-Based Cohort

Christian Förster, Miriam Giovanna Colombo, Anna-Jasmin Wetzel, Peter Martus, Stefanie Joos

Summary

Background: After recovering from coronavirus disease 2019 (COVID-19), a considerable number of patients report long-term sequelae. The epidemiologic data vary widely in the studies published to date, depending on the study design and the patient cohorts analyzed. Using a population-based approach, we report symptoms and clinical characteristics following COVID-19 (long COVID), focusing on symptoms ≥ 12 weeks (post-COVID-19).

Methods: In three German administrative districts, all adult patients with a diagnosis of COVID-19 confirmed by polymerase chain reaction (PCR) between March and September 2020 (n = 4632) were invited to complete a questionnaire. Predictors for post-COVID-19 were identified by multiple ordinal regression analysis. Study registration: DRKS00023069.

Results: A total of 1459 patients were included in the study, 175 (12%) of whom had been hospitalized for treatment of the acute phase of COVID-19. The prevalence of post-COVID-19 was 72.6% (n = 127) and 46.2% (n = 588) for hospitalized and non-hospitalized patients, respectively. The most frequently occurring long-term symptoms were fatigue (41.5% of all symptoms ≥ 12 weeks, n = 297), physical exhaustion (40.8%, n = 292), difficulty in concentrating (30.6%, n = 219), and loss of the senses of taste (25.9%, n = 185) and smell (25.5%, n = 182). Quality of life was significantly impaired in patients with post-COVID-19. The strongest risk factors for post-COVID-19 were female sex, overall severity of comorbidities, and severity of acute COVID-19.

Conclusion: Patients who are not hospitalized also frequently experience continued symptoms following COVID-19. The heterogeneity of symptoms calls for a multidisciplinary stepped-care approach, for which identification of patients at risk is crucial. A limitation of the study is the lack of a control group.

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A considerable proportion of patients infected with the novel coronavirus-2 (SARS-CoV-2) continue to experience symptoms after recovery from the acute phase of coronavirus disease 2019 (COVID-19). These long-term conditions manifest in a wide range of symptoms, such as fatigue, dyspnea, and cognitive dysfunction (1–4). There is ongoing discussion on the definition and terminology of sequelae after COVID-19 (long COVID). In the present study, the term post-COVID-19 refers to all symptoms persisting at least 12 weeks after COVID-19, irrespective of the etiology. The 12-week duration was defined by the National Institute for Health and Care Excellence (NICE) and a consensus conference of the World Health Organization (WHO), and has been adopted in the the German clinical practice guideline (5–7).

The reported prevalences differ by study design, the definition of post-COVID-19 applied, and the sample analyzed (8). The literature and systematic reviews report a prevalence of 33–87% in cohorts hospitalized for treatment of acute COVID-19, whereas studies with non-hospitalized patients report lower prevalences of between 2% and 53% (1, 9, 10). However, most studies have investigated small (11, 12) or non-representative samples (13, 14) or included participants without positive SARS-CoV-2 test results (15). Due to the heterogeneity in the existing evidence, the Long-COVID Forum and other groups recently defined as a research priority the identification of clinical characteristics, comorbidities, and potential risk factors of post-COVID-19, particularly in non-hospitalized or population-based cohorts (3, 16, 17).

The aims of this study were:

- To report the prevalence of symptoms following COVID-19
- To describe the clinical characteristics
- To identify potential predictive factors in a population-based retrospective cohort in Germany

Methods

The study was conducted as a total population survey in three German administrative districts (Reutlingen, Tübingen, Enzkreis) with a total of 715 268 inhabitants. In Germany, every person who tests positive for infection with SARS-CoV-2 is registered by the local

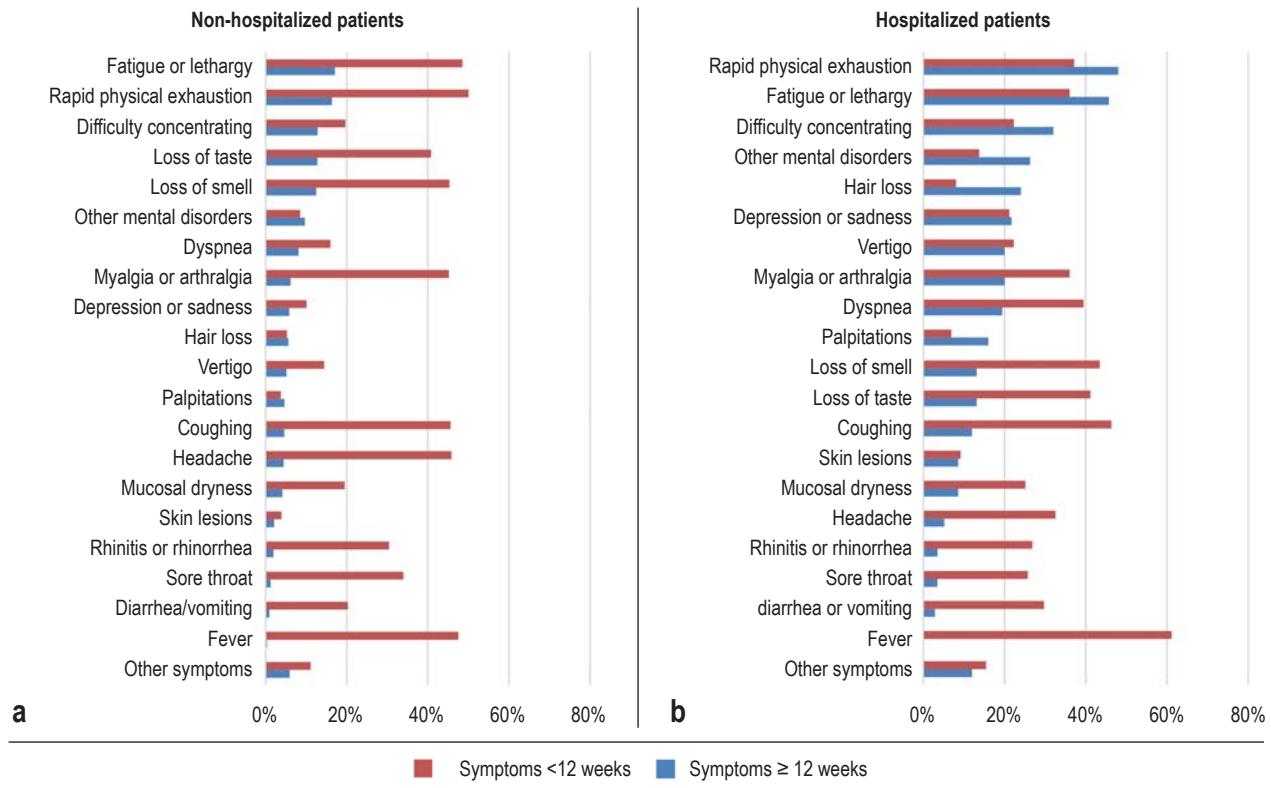
TABLE 1

Sociodemographic data, lifestyle factors and health-related quality of life of the study population (n = 1459)

	Total study population		p-value[*1]	Post-COVID-19 (symptom duration ≥ 12 weeks)		p-value[*1]
	No symptoms/ symptoms < 12 weeks n = 739	Symptoms ≥ 12 weeks (post-COVID-19) n = 720		Not hospitalized n = 588	Hospitalized n = 127	
Age (years)						
Median (IQR)	50 (33–60)	54 (42–64)	< 0.001[*2]	52 (37–61)	69 (57–80)	< 0.001[*2]
Sex						
Male	361 (48.8)	226 (36.1)	< 0.001	196 (33.3)	62 (48.8)	0.004[*3]
Female	369 (49.9)	455 (63.2)		388 (66.0)	65 (51.2)	
Missing value	9 (1.2)	5 (0.7)		4 (0.7)	0 (0)	
Education level						
No qualifications	16 (2.2)	8 (1.1)	< 0.001	3 (0.5)	5 (3.9)	< 0.001[*3]
School certificate	211 (28.6)	179 (24.9)		142 (24.1)	36 (28.3)	
Vocational training diploma	243 (32.9)	290 (40.3)		228 (38.8)	61 (48.0)	
University degree	261 (35.3)	233 (32.4)		207 (35.2)	24 (18.9)	
Missing value	8 (1.1)	10 (1.4)		8 (1.4)	1 (0.8)	
Administrative district						
Enzkreis	166 (22.5)	147 (20.4)	0.608	108 (18.4)	38 (29.9)	0.012
Reutlingen	267 (36.1)	272 (37.8)		231 (39.3)	40 (31.5)	
Tübingen	306 (41.4)	301 (41.8)		249 (42.3)	49 (38.6)	
Smoking status						
Current smoker or ex- smoker	470 (63.6)	424 (57.5)	0.044	220 (37.4)	60 (47.2)	0.004
Never smoker	245 (33.2)	284 (39.4)		354 (60.2)	59 (46.5)	
Missing value	24 (3.2)	22 (3.1)		14 (2.4)	8 (6.3)	
diet						
Conventional	661 (89.4)	634 (88.1)	0.652	511 (86.9)	119 (93.7)	0.074[*3]
Vegetarian/vegan	67 (9.1)	72 (10.0)		65 (11.1)	6 (4.7)	
Missing value	11 (1.5)	14 (1.9)		12 (2.0)	2 (1.6)	
Nursing home resident						
Yes	34 (4.6)	13 (1.8)	0.010	9 (1.5)	4 (3.1)	0.414[*3]
No	697 (94.3)	700 (97.2)		574 (97.6)	122 (96.1)	
Missing value	14 (1.1)	7 (1.0)		5 (0.9)	1 (0.8)	
Cumulative duration of sick leave (days)						
Median (IQR)	14 (14–20)	20 (14–28)	< 0.001[*2]	18 (14–26)	45 (28–77)	< 0.001[*2]
Health-related quality of life						
EQ5D-5L, median (IQR)	1.00 (0.94–1.00)	0.93 (0.84–1.00)	< 0.001[*2]	0.94 (0.87–1.0)	0.85 (0.62–0.92)	< 0.001[*2]
EQ5D-VAS, median (IQR)	90 (80–95)	80 (65–85)	< 0.001[*2]	80 (70–90)	70 (50–75)	< 0.001[*2]

Absolute and relative frequencies are presented as n (%) unless otherwise indicated.
Information on hospitalization was missing for five participants in the post-COVID-19 group.
EQ5D-5L, EuroQoL 5-dimension 5-level; EQ5D-VAS, EuroQoL 5-dimension visual analog scale; IQR, interquartile range
[*1] Chi-square tests were used to calculate p-values unless otherwise indicated.
[*2] Mann–Whitney U test.; [*3] Fisher's exact test.

FIGURE



Prevalence of symptoms following COVID-19 in a population-based cohort. Proportions of participants who had the respective symptom for less than 12 weeks (acute and ongoing COVID-19) or for at least 12 weeks (post-COVID-19) after the infection. a) symptoms of non-hospitalized patients (n = 1273); b) symptoms of hospitalized patients (n = 175)

health office. These offices sent out a questionnaire to all adult patients with a positive polymerase chain reaction (PCR) test between 1 March and 30 September 2020 (n = 4632).

We asked participants retrospectively to recall the symptoms they experienced due to COVID-19 and to specify symptom duration. Based on the NICE guideline, patients were divided into the following groups:

- Acute COVID-19 (symptoms for 0–4 weeks)
- Ongoing COVID-19 (4–12 weeks)
- Post-COVID-19 (≥ 12 weeks)

For reasons of clarity, patients without symptoms and symptoms < 12 weeks are presented in the same column of the relevant *Tables*. For the multiple ordinal logistic regression, we combined participants with acute and ongoing COVID-19 into one category, resulting in an outcome variable with three categories (no symptoms, symptom duration < 12 weeks, symptom duration ≥ 12 weeks). Goodness of fit was assessed by means of a likelihood ratio test comparing the fitted model to a model with varying location parameters. We conducted multiple imputation to replace missing values. Backward selection was used to select variables, taking account of p-values between 0.05 and 0.10. Age and sex were included in all models. More detail can be found in the *eMethods*.

Results

Study population

By 31 January 2021, a total of 1907 questionnaires (41%) had been returned. Of those, 448 were excluded (*eMethods*), so the final study population comprised 1459 participants.

The median age of the participants was 53 years (interquartile range [IQR] 37–62); n = 824 (56.5%) of the participants were women. This is in line with the total 4632 confirmed COVID-19 cases in the districts (median age 48 years, 52.7% women; *eTable 1*). The mean duration of follow-up was 219 days (standard deviation [SD] 32.6). A total of 175 (12%) participants received hospital treatment for COVID-19. Further details are shown in *Table 1*.

Prevalence of symptoms following COVID-19

No symptoms during or after COVID-19 were reported by 8.3% (n = 121), while 33.0% (n = 481) had at least one COVID-19-related symptom for < 4 weeks (acute COVID-19), 9.4% (n = 137) had at least one symptom that lasted for 4 to < 12 weeks (ongoing COVID-19), and 49.3% (n = 720) had at least one symptom ≥ 12 weeks after the infection (post-COVID-19). Among hospitalized and non-hospitalized participants,

TABLE 2

Time of onset of symptoms*

	Post-COVID-19 (symptoms ≥12 weeks after infection)			
	Not hospitalized n = 588		Hospitalized n = 127	
	Immediate onset n (%)	Delayed onset n (%)	Immediate onset n (%)	Delayed onset n (%)
Fever	4 (0.7)	0 (0)	0 (0)	0 (0)
Diarrhea/vomiting	8 (1.3)	3 (0.5)	4 (3.1)	1 (0.8)
Sore throat	15 (2.6)	0 (0)	5 (3.9)	1 (0.8)
Rhinitis or rhinorrhea	23 (3.9)	1 (0.2)	6 (4.7)	0 (0)
Skin lesions	12 (2.0)	14 (2.3)	6 (4.7)	9 (7.0)
Headache	45 (7,7)	11 (1.9)	7 (5.5)	2 (1.6)
Mucosal dryness	36 (6.1)	13 (2.2)	10 (7.8)	5 (3.9)
Coughing	51 (8.7)	6 (1.0)	19 (15.0)	2 (1.6)
Palpitations	32 (5.4)	27 (4.6)	21 (16.5)	7 (5.5)
Vertigo	42 (7.1)	22 (3.7)	24 (18.9)	11 (8.7)
Depression or sadness	38 (6.4)	36 (6.1)	24 (18.9)	14 (11.0)
Other mental disorders	72 (12.2)	50 (8.5)	30 (23.6)	15 (11.8)
Myalgia or arthralgia	65 (11.0)	13 (2.2)	25 (19.7)	10 (7.8)
Hair loss	17 (2.9)	54 (9.2)	14 (11.0)	28 (22.0)
Dyspnea	60 (10.2)	42 (7.1)	29 (22.8)	5 (3.9)
Loss of taste	133 (22.6)	29 (4.9)	16 (12.5)	7 (5.5)
Loss of smell	124 (21.1)	35 (5.9)	20 (15.7)	3 (2.3)
Difficulty concentrating	95 (16.1)	68 (11.6)	44 (34.6)	12 (9.4)
Fatigue or lethargy	174 (29.6)	41 (7.0)	68 (53.5)	11 (8.6)
Rapid physical exhaustion	170 (28.9)	35 (5.9)	72 (56.7)	11 (8.6)

*Symptoms with immediate onset (within 2 weeks of infection) or late onset (at least 2 weeks after infection) in non-hospitalized and hospitalized participants with symptoms persisting for at least 12 weeks (post-COVID-19).

the prevalence of post-COVID-19 was 72.6% (n = 127) and 46.2% (n = 588), respectively.

The most frequently occurring symptoms among patients with post-COVID-19 were:

- Fatigue or lethargy (41.5%, n = 297)
- Physical exhaustion (40.8%, n = 292)
- Difficulty concentrating (30.6%, n = 219)
- Loss of sense of taste (25.9%, n = 185)
- Loss of sense of smell (25.5%, n = 182)

Figure 1 displays the percentage occurrence of all symptoms reported for a duration of < 12 weeks or ≥ 12 weeks.

Table 2 shows the post-COVID-19 symptoms with immediate onset (within the first 2 weeks of the infection) versus delayed onset (at least 2 weeks after infection). Most symptoms were present from the beginning of the infection. The only symptoms that often had delayed onset were skin lesions and hair loss.

Characteristics of patients with post-COVID-19

Patients with post-COVID-19 were older, more often female, had a significantly lower health-related quality of life (HrQoL), and had more days of sick leave *(Table 1)*. The overall burden of comorbidity correlated with a higher risk of post-COVID-19, as did most of the specific chronic conditions such as hypertension, heart and lung disease, and depression *(Table 3, eTable 2)*. Polypharmacy and intake of most of the long-term medications also correlated with a higher risk of post-COVID-19 *(eTable 3)*.

Patients with post-COVID-19 more often took medication such as antibiotics, anticoagulants, or analgesics during the acute phase of acute COVID-19 *(eTable 4)*.

Predictors of post-COVID-19

Univariate ordinal logistic regression identified only a small number of variables that proved to be potential predictors for long-term sequelae *(Table 4)*. The strongest predictors for post-COVID-19 identified here were:

- Female sex (odds ratio [OR] 1.81, 95% confidence interval [1.45; 2.24])
- The overall burden of comorbidity with an OR of 1.10 per point in the Self-Administered Comorbidity Questionnaire (SCQ-D; maximum 45 points) [1.06; 1.14)
- Hospitalization for acute COVID-19 (OR 2.01 [1.54; 2.64)
- The need for analgesics during acute COVID-19 (OR 1.70 [1.19; 2.45)

The last two points are surrogates for a severe course of the acute infection.

Nursing home residents had a lower risk of post-COVID-19 (OR 0.09 [0.05; 0.17]). No positive or negative association was found for smoking, specific comorbidities, regular medication, other specific medication for COVID-19, polypharmacy, or age.

Discussion

Prevalence and symptoms

The present study is one of the largest so far to investigate the prevalence of symptoms following COVID-19 in a population-based cohort. A total of 1273 (87.3%) participants were not hospitalized for treatment of their acute COVID-19.

While previous studies mostly described mixed cohorts with varying proportions of non-hospitalized and hospitalized participants, we present data for non-hospitalized and hospitalized patients separately. At least one post-COVID-19 symptom was reported by 46.2% (n = 588) of the non-hospitalized and 72.6% (n = 127) of the hospitalized patients. Compared with previous smaller studies that were also based on the NICE and WHO definition of post-COVID-19, there is good agreement (e1–e4).

The most frequently mentioned symptoms in the post-COVID-19 group were fatigue or lethargy (n = 297, 41.5%) and rapid physical exhaustion

TABLE 3

Comorbidities

	Total study population		p-value*1	Post-COVID-19 (symptom duration ≥ 12 weeks)		p-value*1
	No symptoms/ symptoms < 12 weeks n = 739	Symptoms ≥ 12 weeks (post-COVID-19) n = 720		Not hospitalized n = 588	Hospitalized n=127	
Body mass index (kg/m^2), median (IQR)	25 (22–28)	25 (22–29)	0.646*2	25 (22–28)	27 (24–31)	< 0.001*2
SCQ-D score, median (IQR)	2 (0–3.25)	3 (1–6)	< 0.001*2	2.37 (0–5)	6 (4–9)	< 0.001*2
Heart problems	69 (9.3)	116 (16.1)	< 0.001	65 (11.1)	51 (40.2)	< 0.001
Hypertension	174 (23.5)	222 (30.8)	0.002	148 (25.2)	74 (58.3)	< 0.001
Lung problems	58 (7.8)	114 (15.8)	< 0.001	72 (12.2)	41 (32.3)	< 0.001
Diabetes/blood sugar	37 (5.0)	63 (8.8)	0.007	34 (5.8)	29 (22.8)	< 0.001
Gastrointestinal problems	62 (8.4)	108 (15.0)	< 0.001	83 (14.1)	25 (19.7)	0.126
Kidney problems	17 (2.3)	27 (3.8)	0.126	9 (1.5)	18 (14.2)	< 0.001
Liver problems	3 (0.4)	14 (1.9)	0.007	7 (1.2)	7 (5.5)	< 0.003
Anemia/other blood problems	26 (3.5)	37 (5.1)	0.156	25 (4.3)	12 (9.4)	0.026
Cancer	36 (4.9)	38 (5.3)	0.812	25 (4.3)	13 (10.2)	0.020
Depression	48 (6.5)	85 (11.8)	< 0.001	63 (10.7)	22 (17.3)	0.027
Osteoarthritis	91 (12.3)	167 (23.2)	< 0.001	117 (19.9)	49 (38.6)	< 0.001
Back pain	191 (25.8)	283 (39.3)	< 0.001	219 (37.2)	63 (49.6)	< 0.001
Rheumatism	19 (2.6)	39 (5.4)	0.007	26 (4.4)	13 (10.2)	0.017
Polypharmacy*3	30 (4.1)	87 (12.1)	< 0.001	48 (8.2)	39 (30.7)	< 0.001

Absolute and relative frequencies are presented as n (%) unless otherwise indicated. Information on hospitalization was missing for five patients in the post-COVID-19 group.
IQR, Interquartile range; SCQ-D, Self-Administered Comorbidity Questionnaire, German version
*1 Chi-square tests were used to calculate p-values unless otherwise indicated. *2 Mann–Whitney U test
*3 Polypharmacy was defined as five or more medications taken on a regular basis.

(n = 292, 40.8%), followed by difficulty concentrating (n = 219, 30.6%). Although the reported frequency of these symptoms varies very widely between studies, recent reviews confirm that fatigue is a predominant symptom (2, 3). Considering the heterogeneity of symptoms, however, it should be discussed whether these conditions represent phenotypes of one and the same entity or whether they result from different pathophysiology. In contrast, loss of the sense of taste and/or smell is thought to be a rather specific symptoms of COVID-19 and was reported to persist ≥ 12 weeks by n = 185 (25.9%) and n = 182 (25.5%), respectively. In the general population, the self-reported frequency of problems with taste and smell is 0.4% and 1.6%, respectively (e5).

Considerations on pathophysiology

Most participants in our study reported that their long-term symptoms had been present since the beginning of the infection. However, skin lesions and hair loss were mostly reported with a delay in symptom onset. Whether these differences in time of onset are due to different pathophysiological causes is currently a matter for discussion. Persistence of symptoms from the onset could support the hypothesis of residual viral particles to which the organism reacts as in the acute phase (18, 19), while delayed symptom onset could indicate immunological dysregulation (20). Moreover, direct viral toxicity the severity of the acute illness might also influence the underlying pathophysiology, the latter potentially causing hair loss and skin lesions (21).

On the other hand, some symptoms following COVID-19 may not be specific for SARS-CoV-2 but could be caused by another etiology and/or triggered by social effects of the pandemic; this is particularly likely for fatigue and mental health problems (22, 23). Some conditions reported by hospitalized patients could also be caused by post-intensive care syndrome (PICS) or post-traumatic stress disorder (PTSD) following an ICU stay (e6, e7). The lack of a control group in this study means it is not possible to differentiate between post-COVID-19 and symptoms with other causes.

Implications for health care

The quality of life was lower in the post-COVID-19 group, particularly in hospitalized participants. This is consistent with previous reports (e1, e2). Periods of sick leave were longer in patients with

TABLE 4

Parsimonious model of the multiple ordinal logistic regression[*1]

	Level	OR	[95% CI]	p-value
Age	Continuous	1.003	[0.996; 1.010]	0.45
Sex	Female	1.805	[1.454; 2.241]	< 0.001
	Male	Reference		
Education level[*2]	Metric	1.147	[1.057; 1.245]	0.001
Nursing home resident	Yes	0.087	[0.046; 0.165]	< 0.001
	No	Reference		
SCQ-D[*3]	Continuous	1.096	[1.058; 1.137]	< 0.001
Hospitalized during acute COVID-19[*4]	Yes	2.014	[1.538; 2.637]	< 0.001
	No	Reference		
Need for analgesics during acute COVID-19[*5]	Yes	1.704	[1.186; 2.446]	0.004
	No	Reference		

[*1] Parsimonious model after stepwise backward selection of the potential predicting variables for post-COVID-19. The outcome variable comprised three categories (1, no symptoms; 2, symptom duration < 12 weeks; 3, symptom duration ≥ 12 weeks) with post-COVID-19 (symptom duration ≥ 12 weeks) as response (n = 1459; imputed data set with 500 imputations).

[*2] Only one parameter was estimated in a linear coding of the six different educational levels.

[*3] Interpretation of the OR: with each increase of one point on the 45-point scale of the SCQ-D, the likelihood of developing post-COVID-19 rises by 9.6%. In other words, the higher the overall burden of comorbidities (measured on the SCQ-D), the greater the likelihood of developing post-COVID-19.

[*4] Interpretation of the OR: Study participants who had to be hospitalized for treatment during the acute phase of COVID-19 have a 2.01 times greater likelihood of developing post-COVID-19 than those who were not hospitalized. In other words, their risk of developing post-COVID-19 is 101% higher.

[*5] Interpretation of the OR: Study participants who had to take analgesics during the acute phase of COVID-19 had a 1.7 times greater likelihood of developing post-COVID-19 than those who did not have to take analgesics. In other words, their risk of developing post-COVID-19 is 70% higher. This does not mean that the consumption of analgesics causes the higher risk; rather, it is a surrogate for the severity of the acute disease.

95% CI, 95% confidence interval; OR, odds ratio;
SCQ-D, Self-Administered Comorbidity Questionnaire, German version

post-COVID-19, presumably reflecting the disabling character of the symptoms. Studies from the USA and other countries report that 40% of patients had not returned to regular work by 60 days after discharge and that 22.3% were still not back to work after a median of 7 months (15, 24). Considering the still growing number of infections, this could have a major economic impact.

The heterogeneity of symptoms calls for multidisciplinary management, coordinated by primary care specialists (5, 25). Referrals to specialists should be limited to patients with specific needs (stepped-care approach). Local cross-specialty networks with multidisciplinary boards, supplemented by specialty units from the inpatient sector, could improve the care of these patients (26–28). In addition, the identification of patients at risk for developing post-COVID-19 will help to set the course of treatment and develop structured management strategies.

Predictors of post-COVID-19

The regression analysis revealed that hospitalization for COVID-19 and the need for analgesics during the acute phase of COVID-19 were risk factors for post-COVID-19. This suggests an association of acute infection severity with the risk of developing post-COVID-19, as previously reported by other study groups (29, 30). It is therefore plausible that convalescence is prolonged in patients who were immobilized during the acute infection or had severe pulmonary pathology resulting in post-critical illness, persisting dyspnea, PTSD, or PICS (31–33).

Another strong predictor for post-COVID-19 was the overall burden of comorbidity. Patients with post-COVID-19 were more likely to have chronic concomitant diseases, were more often on regular medication, and had a higher rate of polypharmacy. This is in line with other studies that also show an association between preexisting comorbidity and the risk of developing post-COVID-19 (13, 34).

Consistent with previous studies, we found that female sex was associated with an increased risk of developing post-COVID-19 (4, 14, 35, 36). Other studies also reported more advanced age as an independent risk factor for post-COVID-19 (35), which was not confirmed by our multiple regression analysis.

Interestingly, we found that higher educational qualifications were also a predictor for post-COVID-19. This could not attributed to age differences and may therefore be in line with a study showing that persons with higher education levels develop depressive symptoms and a greater decline in life satisfaction during the pandemic more often than others (37). However, this could indicate that these symptoms are not specific for COVID-19.

Living in a nursing home seemed to protect against developing post-COVID-19. This may be due to a healthy patient effect, since those nursing home residents who survive COVID-19 presumably possess greater resilience (38).

Strengths and limitations

A major limitation of this study is the lack of a control group. This means that it is not possible to distinguish between symptoms specific for COVID-19 and symptoms arising from other causes.

Reports of prevalence vary substantially among previous studies owing to differences in study design. In the present study, we therefore chose a population-based approach and found an overall post-COVID-19 prevalence of 49.3% in hospitalized and non-hospitalized patients. After standardization for age, gender, and district with the data known for all of the 4632 patients contacted *(eTable 1)*, this sensitivity analysis yielded only a slight reduction in prevalence to 47.4%. Nonetheless, sampling bias is very likely and could have led to an overestimation of the prevalence of post-COVID-19, since patients with long-term sequelae would be more likely to participate than those without. The most conservative estimation would count all of the non-responders as not having post-COVID-19, resulting in a post-COVID-19 prevalence of 14.6% for non-hospitalized and 22.9% for hospitalized patients,

given that 31.5% of the questionnaires distributed were included for statistical analysis.

Growing media attention to post-COVID-19 may influence both patients and medical staff and could also have led to overestimation of symptoms (39). All data derived from patients' self-reports and may have been biased by patients having to recall their symptoms and duration of illness retrospectively. Another possible bias is the number of persons with higher educational status.

Conclusion

The data from a large population-based cohort indicate that long-term health consequences are a frequent burden even after a moderate acute course of COVID-19. Health care professionals can take advantage of these findings to improve their understanding of these patients' symptoms and care needs and to identify patients at risk. Within the spectrum of post-COVID-19 symptoms, further studies are needed with a focus on the most disabling sequelae and should include a control group in order to distinguish between post-COVID-19 and symptoms from other causes.

Major medical and socio-economic challenges are posed when some patients are unable to attain their previous state of health or return to work owing to functional impairment and reduced quality of life (40). Interdisciplinary local networks based on a stepped-care approach will be key to the treatment strategy for this complex disease.

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Conflict of interest statement
All authors declare that no conflict of interest exists.

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► **Supplementary material**
eReferences, eMethods, eTables:
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Supplementary material to:

Persisting Symptoms After COVID-19

Prevalence and Risk Factors in a Population-Based Cohort

by Christian Förster, Miriam Giovanna Colombo, Anna-Jasmin Wetzel, Peter Martus, and Stefanie Joos

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eMETHODS

Study design and study population

This retrospective cohort study was conducted as a total population survey in three administrative districts (Reutlingen, Tübingen, Enzkreis) located in southwest Germany with a total of 715 268 inhabitants. In Germany, every person who tests positive for infection with SARS-CoV-2 is registered by the local health authorities. We contacted all patients who met the inclusion criteria (a positive polymerase chain reaction [PCR] test for SARS-CoV-2 between 1 March and 30 September 2020 and age at least 18 years. A total of 4632 persons with a confirmed SARS-CoV-2 infection met these inclusion criteria. They were invited via mail by the respective local health authorities to anonymously complete a questionnaire and return it to the Institute of General Practice and Interprofessional Care using a prepaid envelope. The questionnaires were sent out on 26 October (Reutlingen, n = 1781), 12 November (Tübingen, n = 1476), and 2 December (Enzkreis, n = 1375) 2020, respectively. Two hundred forty questionnaires could not be delivered due to incorrect mailing addresses.

Of all returned questionnaires, 448 were excluded from analysis because the study participants were < 18 years of age (n = 1), had a positive test result outside of the study period (n = 17) or in the 12 weeks prior to the date the questionnaires were sent out (n = 158), did not provide information on the date of the positive test (n = 115) or symptom duration (n = 152), or returned blank questionnaires (n = 5). The final study population comprised 1459 participants.

The study was conducted in accordance with the Declaration of Helsinki, participation was voluntary, and all responses were anonymous. The study was approved by the ethics committee of the university hospital Tuebingen (reference 698/2020BO) and registered in the German Clinical Trials Registry (reference DRKS00023069).

Data collection and questionnaire

The self-developed questionnaire assessed the following categories: self-reported symptoms of COVID-19, including onset and duration of these symptoms, need for hospitalization and intubation, comorbidities, medications taken during acute COVID-19 and medications taken on a regular basis, health-related quality of life (HrQoL), lifestyle factors, and sociodemographic data.

Participants were asked retrospectively to recall symptoms they experienced due to COVID-19 and to specify whether the onset of symptoms was “immediate” or “delayed.” The latter was defined as first occurrence of symptoms 2 weeks or longer after the positive test result for SARS-CoV-2. Furthermore, for each symptom participants were asked to either specify the duration in weeks or to confirm that the symptom persisted up to the time the questionnaire was filled out. For ongoing symptoms, the duration was calculated by subtracting the date the questionnaire was sent from the date of the positive test result for SARS-CoV-2. If the onset of a symptom was marked as “delayed,” 2 weeks were subtracted from the overall symptom duration. The main outcome of this study, post-COVID-19, was defined as at least one symptom persisting for 12 weeks or longer after the initial positive test result (5).

Hospitalization for COVID-19 was defined as at least one night in the hospital. Medications for COVID-19 could be selected from a list of frequently prescribed drugs; other medications could be entered in an optional text field.

Comorbidity was ascertained using the German version of the Self-Administered Comorbidity Questionnaire (SCQ-D), a validated

inventory to assess the presence of chronic conditions such as heart disease, hypertension, and diabetes from the patient's perspective (e9, e10). The SCQ-D consists of 12 predefined medical problems with the option of specifying up to three further problems in a text field. Each condition is then rated in three categories:

1) Presence of the medical problem (yes/no)
2) Treatment for the medical problem (yes/no)
3) Functional limitation due to the medical problem (yes/no).

The minimum score of the SCQ-D is zero (all conditions absent), and the maximum score is 45 points (all conditions present, requiring treatment, and causing functional limitation). Participants were asked to provide information solely about diseases that existed before the infection with SARS-CoV-2.

The patients were asked to provide information on the medications they had been taking regularly for at least 12 months. A list of frequently prescribed drugs was provided with optional text fields. Polypharmacy was defined as five or more pharmaceuticals.

Smoking status distinguished current smokers, ex-smokers (quit smoking at least 12 months ago), and never smokers. Dietary preferences were categorized into conventional, vegetarian, or vegan diets. The body mass index (BMI) was calculated as kg/m^2. To assess their education level, the patients were asked to specify whether they had a graduation certificate from a lower, intermediate, or upper secondary school, a diploma in vocational training, or a university degree. They were also asked to indicate the cumulative days of sick leave if they were not able to work because of COVID-19-related symptoms.

HrQoL was assessed using the EQ5D-5L (e11). The validated instrument consists of a visual analogue scale (VAS), ranging from zero (worst imaginable health) to 100 (best imaginable health), and a descriptive part comprising five dimensions, each with five levels of severity. We calculated the value for these dimensions based on the comparative data set for the German standard population, which ranges from –0.661 (poor health) to 1 (full health) (e12).

Data analysis

According to the indicated duration of symptoms and based on the NICE guidelines (5), patients were categorized as "no symptoms" if they had no COVID-19-related symptoms, as "acute COVID-19" if they had at least one symptom for <4 weeks, as "ongoing COVID-19" if they had at least one symptom that lasted between 4 and < 12 weeks, or as "post-COVID-19" if they reported at least one symptom ≥ 12 weeks after the infection. Differences between groups in terms of categorical variables were determined using the Pearson chi-square test and Fisher's exact test. The Kruskal–Wallis test was used for non-normally distributed continuous variables (age, BMI, SCQ-D). The significance level was set at $\alpha < 0.05$ (two-sided).

A multiple ordinal regression model was used to identify predictors of post-COVID-19. For the regression analysis, the study participants with symptom durations of < 4 weeks and 4 to < 12 weeks were amalgamated into one category, creating an outcome variable with three categories (no symptoms, symptom duration of < 12 weeks, symptom duration of ≥ 12 weeks). Potential predictors for post-COVID-19 were identified from the literature and their association with the outcome was investigated by means of univariate regression analyses. All predictors that showed an association with the outcome were entered into the full model. Stepwise backward selection was used to identify those predictors that contributed to the final parsimonious model in a statistically significant way. Age was included in the parsimonious model regardless of variable selection. The majority of predictors entered into the full regression model exhibited only few missing values; the SCQ-D was the predictor

with the highest proportion of missing values (23%). We conducted multiple imputation to replace missing values (number of imputation-based data sets n = 500). To test the validity of the results determined by the ordinal logistic regression, two binary logistic regression models (no symptoms and symptom duration < 12 weeks vs. symptom duration of ≥ 12 weeks; no symptoms vs. symptom duration < 12 weeks and symptom duration of ≥ 12 weeks) were calculated as a sensitivity analysis. The assumption of proportional odds was not met (chi-square [7] between 48.2 and 83.7, mean 68.7, $p<0.001$ for each imputation). Therefore, we present in the sensitivity analysis the two separate binary logistic regression models which are combined in the proportional odds model.

All analyses were performed using IBM SPSS Statistics for Windows, version 27.

eTABLE 1

Confirmed cases of SARS-CoV-2 in the participating districts from 1 March to 30 September 2020, age 18 years or older[*1]

Administrative district (inhabitants)	Total number of cases	Returned questionnaires	Gender	Age (years), n										Reported deaths among positive cases
				0–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99	100+	
Tübingen (228 678)			Female	10	155	105	122	163	91	51	75	34	2	
			Male	13	129	105	74	148	83	52	54	9	0	
			Other	0	1	0	0	0	0	0	0	0	0	
	1476[*2]	756 (51.2%)		23	285	210	196	311	174	103	129	43	2	23
Enzkreis (199 556)			Female	8	126	101	121	125	56	34	48	29	1	
			Male	17	162	124	109	124	52	27	22	4	0	
			Other	0	1	0	1	0	0	0	0	0	0	
	1292[*3]	423 (32.7%)		25	289	225	231	249	108	61	70	33	1	60
Reutlingen[*5] (287 034)	1781[*4]	728 (40.9%)		334		227	240	385	218	135	170	72		82

[*1] All 4632 persons were contacted by mail and invited to participate in the study. Reported deaths during this period by district (e8). Numbers of inhabitants as of 31 December 2019 (www.wikipedia.org).
[*2] Including 73 letters that were returned undelivered
[*3] Excluding 83 letters that were returned undelivered
[*4] Including 84 letters that were returned undelivered
[*5] No information on gender available

eTABLE 2

Additional chronic conditions that were stated in the optional text boxes

	Total study population		p-value*1	Post-COVID-19 (symptom duration ≥ 12 weeks)		p-value*1
	No symptoms/ symptoms < 12 weeks n = 739	Symptoms ≥ 12 weeks (post-COVID-19) n = 720		Not hospitalized n = 588	Hospitalized n = 127	
Allergies	16 (2.2)	16 (2.2)	1.0	16 (2.7)	0 (0)	0.090*2
Thyroid disorder	20 (2.7)	42 (5.8)	0.004	36 (6.1)	6 (4.7)	0.679
Skin lesions	5 (0.7)	17 (2.4)	0.009	15 (2.6)	1 (0.8)	0.329*2
Orthopedic symptoms	11 (1.5)	18 (2.5)	0.191	12 (2.0)	6 (4.7)	0.110*2
Neurological symptoms	7 (0.9)	9 (1.3)	0.623	5 (0.9)	4 (3.1)	0.058*2
Headache	8 (1.1)	11 (1.5)	0.453	11 (1.9)	0 (0)	0.228*2
Other chronic conditions	28 (3.8)	30 (4.2)	0.789	21 (3.6)	9 (7.1)	0.086

Absolute and relative frequencies are presented as n (%) unless otherwise indicated. Information on hospitalization was missing for five patients in the post-COVID-19 group.
*1 Chi-square tests were used to calculate p-values unless otherwise indicated. *2 Fisher's exact test.

eTABLE 3

Medications taken on a regular basis (for at least 12 months)

	Total study population		p-value*1	Post-COVID-19 (Symptom duration ≥ 12 weeks)		p-value*1
	No symptoms/ symptoms < 12 weeks n = 739	Symptoms ≥ 12 weeks (post-COVID-19) n = 720		Not hospitalized n = 588	Hospitalized n = 127	
ACE-I and ARB	108 (14.6)	172 (23.9)	< 0.001	108 (18.4)	63 (49.6)	< 0.001
Other antihypertensives	118 (16.0)	159 (22.1)	0.011	98 (16.7)	61 (48.0)	< 0.001
Metformin	20 (2.7)	40 (5.6)	0.008	21 (3.6)	19 (15.0)	< 0.001
Other antidiabetics	18 (2.4)	30 (4.2)	0.077	16 (2.7)	14 (11.0)	< 0.001
Diuretics	51 (6.9)	79 (11.0)	0.023	39 (6.5)	41 (32.3)	< 0.001
Lung inhalers	33 (4.5)	71 (9.9)	< 0.001	47 (8.0)	22 (17.3)	< 0.001
Cholesterol-reducing drugs	53 (7.2)	90 (12.5)	0.002	53 (9.0)	37 (29.1)	< 0.001
ASA 100	51 (6.9)	83 (11.5)	0.006	49 (8.3)	33 (26.0)	< 0.001
Anticoagulants	36 (4.9)	44 (6.1)	0.584	16 (2.7)	28 (22.0)	< 0.001
Opiates and morphines	11 (1.5)	16 (2.2)	0.498	9 (1.5)	7 (5.5)	< 0.001
Other analgesics	59 (8.0)	83 (11.5)	0.041	58 (9.9)	25 (19.7)	< 0.001
Vitamin D	104 (14.1)	157 (21.8)	< 0.001	118 (20.1)	38 (29.9)	0.018
Antidepressants*3	12 (1.6)	38 (5.3)	< 0.001	28 (4.8)	10 (7.9)	0.156
Thyroid medications*3	68 (9.2)	119 (15.3)	< 0.001	93 (15.8)	16 (12.6)	0.360
Homeopathic preparations*3	7 (0.9)	19 (2.6)	0.015	14 (2.4)	5 (3.9)	0.323
Proton pump inhibitors*3	15 (2.0)	25 (3.5)	0.092	20 (3.4)	5 (3.9)	0.766
Contraceptives*3	16 (2.2)	21 (2.9)	0.407	20 (3.4)	1 (0.8)	0.149*2
Vitamins and supplements*3	26 (3.5)	35 (4.9)	0.200	27 (4.6)	8 (6.3)	0.419
Other medications*3	57 (7.7)	86 (11.9)	0.007	59 (10.0)	27 (21.3)	< 0.001

Absolute and relative frequencies are presented as n (%). Information on hospitalization was missing for five patients in the post-COVID-19 group.
ACE-I, Angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ASA 100, acetylsalicylic acid 100 milligram
*1 Chi-square tests were used to calculate p-values unless otherwise indicated. *2Fisher's exact test. *3 Information from the optional text boxes

eTABLE 4

Treatment during the acute phase of COVID-19.

	Total study population		p-value*1	Post-COVID-19 (Symptom duration ≥ 12 Wochen)		p-value*1
	No symptoms/ symptoms < 12 weeks n = 739	Symptoms ≥ 12 weeks (post-COVID-19) n = 720		Not hospitalized n = 588	Hospitalized n = 127	
Hospitalization for acute COVID-19						
Not hospitalized	685 (92.7)	588 (81.7)	< 0.001	588	n. a.	n.d.
Hospitalized*2	48 (6.5)	127 (17.6)		n.d.	127	
Intensive care unit	6 (0.8)	25 (3.5)	< 0.001	n.d.	25	
Mechanical ventilation	5 (0.7)	20 (2.8)		n.d.	20	
Medication for acute Covid-19						
No	576 (77.9)	412 (57.2)	< 0.001	386 (65.6)	21 (16.7)	< 0.001
Yes	156 (21.1)	295 (41.0)		196 (33.3)	99 (78.0)	
Antibiotics	54 (7.3)	100 (13.9)	< 0.001	43 (7.3)	57 (44.9)	< 0.001
Zinc/selenium/vitamin D	25 (3.4)	61 (8.5)	< 0.001	49 (8.3)	12 (9.4)	0.726
Anticoagulation	20 (2.7)	63 (8.8)	< 0.001	22 (3.7)	41 (32.3)	< 0.001
Cortisone	9 (1.2)	39 (5.4)	< 0.001	26 (4.4)	13 (10.2)	0.012
Analgesics *3	58 (7.8)	85 (11.8)	0.013	75 (12.8)	10 (7.9)	0.133
Common cold remedies *3	10 (1.4)	18 (2.5)	0.128	16 (2.7)	2 (1.6)	0.554*4
Homeopathic preparations *3	3 (0.4)	3 (0.4)	1.000*4	3 (0.5)	0 (0)	1.000*4
Other vitamins/trace elements *3	5 (0.7)	10 (1.4)	0.202	10 (1.7)	0 (0)	0.223*4
Lung inhalers *3	5 (0.7)	18 (2.5)	0.006	15 (2.6)	3 (2.4)	1.000*4
Others *3	17 (2.3)	41 (5.7)	< 0.001	24 (4.1)	17 (13.4)	< 0.001

Absolute and relative frequencies are presented as n (%). Information on hospitalization was missing for five patients in the post-COVID-19 group.
*1 The chi-square test was used to calculate p-values unless otherwise indicated. *2 Including intensive care unit and mechanical ventilation.
*3 Information from the optional text boxes. *4 Fisher's exact test
n.a., not applicable

eTABLE 5

Sensitivity analysis of regression*[1]

	Level	No symptoms vs. any duration			Post-COVID-19 vs. no symptoms or duration <12 weeks		
		OR	95% CI	p-value	OR	95% CI	p-value
Age	Continuous	0.988	[0.975; 1.001]	0.070	1.006	[0.999; 1.014]	0.105
Sex	Female	1.556	[1.028; 2.355]	0.037	1.921	[1.529; 2.414]	< 0.001
	Male	Reference			Reference		
Educational level*[2]	Metric	1.356	[1.182; 1.556]	< 0.001	1.112	[1.019; 1.214]	< 0.017
Nursing home resident	Yes	0.145	[0.068; 0.309]	< 0.001	0.156	[0.072; 0.334]	< 0.001
	No	Reference			Reference		
SCQ-D	Continuous	1.012	[0.955; 1.073]	0.68	1.110	[1.069; 1.153]	< 0.001
Hospitalized during acute COVID-19	Yes	3.432	[1.587; 7.422]	0.002	1.839	[1.407; 2.404]	< 0.001
	No	Reference			Reference		
Need for analgesics during acute COVID-19	Yes	n.d.*[3]	n.d.*[3]	n.d.*[3]	1.528	[1.059; 2.205]	0.024
	No	n.d.*[3]			Reference		

*[1] As sensitivity analysis, binary logistic regression models were calculated by combining two out of three categories that were also used in the multiple ordinal logistic regression (1, no symptoms; 2, symptom duration < 12 weeks; 3, symptom duration ≥ 12 weeks) (n = 1459; imputed data set with 500 imputations)

*[2] Only one parameter was estimated in a linear coding of educational status with six different levels.

*[3] The predictor "need for analgesics during acute COVID-19" was excluded from the analysis of no symptoms vs. any duration, because all patients who took analgesics also had symptoms (of any duration).

CI, Confidence interval; n.d., no data; OR, odds ratio; SCQ-D, Self-Administered Comorbidity Questionnaire, German version