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Early View

Research letter

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Residual symptoms and lower lung function in patients recovering from SARS-CoV-2 infection

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Take home message: About half of the patients recovering from SARS-CoV-2 have persistent symptoms and reduced lung function as long as two months after infection. This is common even in younger SARS-CoV-2 convalescents with few comorbidities. (224 characters)

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Initial reports of SARS-CoV-2 infection indicate only mild disease in 81% of symptomatic cases [1]. Nearly half of the infected individuals do not seem to develop clinical symptoms at all depending on the cohort investigated [2]. Comorbidities and older age were identified early during the pandemic as predictors for severe or critical disease [3] which is found in about 19% [1]. Independently from disease severity, little is known about longer-term outcomes as well as resolution of symptoms. We therefore set out to systematically evaluate residual symptoms and lung function impairment in patients after SARS-CoV-2 infection.

Patients were prospectively included for cross-sectional follow-up after PCR-confirmed SARS-CoV-2 infection. The protocol was approved by the Ethics Committee of the Medical Faculty Heidelberg (Heidelberg University) as part of an exploratory project and registered at clinicaltrials.gov (NCT04456075).

All subjects underwent spirometry and body-plethysmography between March and June 2020 after written informed consent was obtained. Transfer factor for carbon monoxide (TLCO) was determined in single-breath technique. Clinical information was acquired at follow-up and retrospectively for the time of infection using a structured questionnaire. GLI (spirometry, TLCO) [4] and ECSC (body-plethysmography) [5] reference values were used. Unenhanced chest computed tomography (CT) was performed at follow-up when clinically indicated and within one week of lung function testing.

Mean values are given ±standard deviation (SD) and between-group differences were assessed by Student's t-test. Fisher's exact test was used for categorical data. An alpha error of less than 5% in two-sided testing was considered statistically significant. R Statistical Software (v3.6.1, Foundation for Statistical Computing, Vienna, Austria) was used for all data analysis.

A total of 246 consecutive patients (age 48±15 years) were included with a mean follow-up of 68±16 days after infection (TABLE 1). The majority of patients (n=224, 91%) did neither require hospital admission nor receive specific therapy (n=236, 96%). Inpatients were routinely supplemented with oxygen while only 2 of the 22 hospitalized patients required ICU treatment. No comorbidities were reported in 143 patients (58%) while respiratory (n=24, 10%) and cardiovascular (n=22, 9%) were the most frequently reported diseases. Symptoms were present in 244 patients (99%) at time of infection (range 1-7 symptoms). At follow up, 113 patients (46%) remained symptomatic (range 1-3 symptoms). Olfactory loss was present in n=162 (66%) at infection and n=10 (4%) at follow-up. Corresponding frequencies were cough: 159 (65%) vs 35 (14%), pyrexia 145 (59%) vs 1 (<1%), dyspnoea 76 (31%) vs 79 (32%), sore throat 63 (26%) vs 1 (<1%), rhinitis 61 (25%) vs 2 (1%), thoracic pain 59 (24%) vs. 15 (6%), limb pain 41 (17%) vs 2 (1%), cephalgia 40 (16%) vs 1 (<1%), fatigue 14 (6%) vs 3 (1%), diarrhoea 1 (<1%)

vs. 0 (0%). Significantly more symptoms at time of infection (3.7±1.5) were reported by patients remaining symptomatic as compared to patients being asymptomatic at follow-up (3.1±1.5, $p<0.01$). Symptomatic patients had a significantly lower FEV_1 of 96±17% predicted, VC of 96±15% predicted, and TLCO of 83±15% predicted. FEV_1, VC and TLCO were 103±13% ($p<0.01$), 102±14% ($p<0.01$) and 88±15% ($p<0.05$) in asymptomatic patients, respectively. CT was available in a subgroup of 17 (7%). Any abnormality was present in 71% (n=12) of those patients. The most frequent findings were consolidations (n=12, 71%), followed by ground class opacities (n=11, 64%). Pulmonary embolism and reticulations were detected in n=2 (12%) each.

We were able to demonstrate that about half of the patients recovering from SARS-CoV-2 have persistent symptoms for more than two months after acute infection. Symptomatic patients have significantly reduced lung function, most notably impaired gas transfer, lung volume and central obstruction. To the best of our knowledge, this is the first report to systematically evaluate residual symptoms and lower lung function in convalescents from SARS-CoV-2 infection.

Our findings are especially noticeable as we investigated a cohort with only minor comorbid burden before COVID-19 onset. In the initial phase of the current pandemic, high comorbidity and older age were identified as predictors of severe cases [3]. However, symptoms and reduced lung function seem to be a relevant burden even in younger populations with only few comorbidities. This is in accordance with recent findings obtained from long-term follow-up of mostly healthy medical staff infected with SARS-CoV-1 during the 2002/2003 pandemic. Initial restriction resolved during the follow-up 15 years later whereas the incidence of reduced TLCO and forced expiratory flow 25–75% (FEF_{25-75}) both increased [6]. The latter may correspond to previous findings in seasonal influenza. Small airway obstruction decreased by about 40% during a 5 week's course. after uncomplicated Influenza A. Parameters of central obstruction (FEV_1) and FEF_{25-75} [7] were within normal which can be explained by the well-known insensitivity of spirometry. In our data, this may translate to the lower FEV_1 (central obstruction) and higher sR_{tot} (resistance) in symptomatic patients Therefore, subtle changes in the small airways may be detectable using more sensitive techniques such as oscillometry or imaging [8]. While CT abnormalities are well described in SARS-CoV-2 [9], little is known about their long-term course. In a subgroup, we found pathologies in an overall of 71% with consolidations and ground class opacities being the dominant patterns, which is congruent to the literature [10].

Clinical symptoms at time of presentation are well characterized in both SARS-CoV-1 and SARS-CoV-2. However, little is known about long-term courses. Data from the 2002/2003 pandemic suggest that SARS-CoV-1-induced pulmonary lesions recovered to a greater extent within 1 year after recovery [6].

Reports from Hong Kong and Canada show an increased risk for neuro-psychiatric disorders such as chronic fatigue, depression, pain and sleep disturbances [11, 12].

In SARS-CoV-2 infection, the median time from first symptoms to development of dyspnoea is about 5-8 days [13, 14]. We could demonstrate a shift of the most frequent symptoms from initially olfactory loss to dyspnoea later on. Dyspnoea then persists over a mean of nearly 70 days in about one third of the patients while olfactory loss was still reported by 4%. We did not find statistically significant or clinically meaningful differences for any of the baseline characteristics in univariate analysis. Female patients showed a trend to being more often symptomatic. Respiratory disorders were numerically slightly more frequent in symptomatic as compared to asymptomatic patients (12% vs. 8%) with bronchial asthma being the leading entity. In previous reports, asthma was not associated with more severe outcomes in SARS-CoV-2 infection in general [15, 16]. Although lying within the normal range, we found differences in lung function parameters. The reduction of TLCO can be potentially attributed to structural damage as previously seen during the 2002/2003 pandemic. Likewise, reduction of VC might be an expression of musculoskeletal weakness. Long-term consequences remain unknown. Nevertheless, we believe they may already have clinical relevance. First, these changes were associated with clinical symptoms and may even justify medication. Second, the impact of SARS-CoV-2 infection on small airway function may be larger as previously shown in chronic obstructive lung disease [17]. This can provide a missing link between lung function and clinical presentation requiring further research. Before the approval of remdesivir in the EU in July 2020, no specific therapy was available for severe SARS-CoV-2 infection [18]. With the majority of our patients not requiring hospital admission, they accordingly did not receive treatment during the initial phase of the pandemic. Patients who did not report symptoms at follow-up were more frequently not treated at time of infection. At follow-up, symptomatic patients received inhaled steroids and bronchodilators more often potentially indicating more severe disease.

Our study has several strengths such as the structured clinical work-up and elaborate lung function testing. However, some limitations should also be discussed. Lung function data was not available prior to infection as most patients did not report symptoms requiring diagnostic work-up. No conclusions on health-related quality of life can be drawn and should be investigated in future long-term studies. Selection bias may have been introduced at two points. All patients referred to our hospital participated in the study. However, this may not represent all recovered patients due to the voluntary nature of consulting the medical system. CT was only performed in a small percentage of patients with clinical indication. This may lead to an overrepresentation of symptomatic patients in this subgroup. We do not consider these points as major drawbacks of our study since we intentionally aimed at investigating a

rather healthy and young cohort. Severely ill patients are therefore underrepresented in our study with only 9% of the hospitalized population requiring ICU treatment. While severely ill patients intuitively have greater impairments at discharge as recently demonstrated [19], we believe our findings are valuable in this context. The large proportion of outpatient treatment indicates rather mild disease while entailing persistent symptoms in a population that is currently not being considered at risk.

Taken together, symptoms and lower lung function are common even in younger SARS-CoV-2 convalescents with few comorbidities. The long-term effects remain unknown given the most recent occurrence of the disease. Based on extrapolations from the previous SARS pandemic, careful follow-up is warranted in the current situation. Measures should be designed to detect and appropriately manage any persistent or emerging long-term consequences.

Conflicts of Interest: F. Trinkmann received travel support from Actelion, Berlin Chemie, Boehringer Ingelheim, Chiesi, Novartis, Mundipharma and TEVA as well as speaker or consultation fees from AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, GlaxoSmithKline, Novartis, Roche and Sanofi-Aventis, all outside the submitted work. N. Kahn received travel support from GSK and Berlin Chemie as well as speaker or consultation fees from Berlin Chemie and Roche, all outside the submitted work. F. Trudzinski received travel support from Actelion, Berlin Chemie, Chiesi, Novartis, and speaker or consultation fees from Novartis and Berlin Chemie, all outside the submitted work. M. Eichinger reports consultation fees from Roche, outside the submitted work. C.P. Heussel reports speaker or consultation fees from AstraZeneca, Basilea, Bayer, Bracco, Boehringer Ingelheim, Chiesi, Covidien, Essex, Gilead, Grifols, Intermune, Lilly, MEDA Pharma, MSD, Novartis, Roche, Schering-Plough, Siemens, Pfizer, Pierre Fabre, all outside the submitted work. All other authors have nothing to disclose.

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Data sharing: Individual patient data cannot be made available publicly due to data protection regulations.

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Table 1 Clinical characteristics and lung function

		symptomatic at follow-up (n=113)		asymptomatic at follow-up (n=133)		
	unit	**value**	**range**	**value**	**range**	**p-value**
clinical characteristics						
age	[years]	47±14	19-82	48±16	9-85	0.47
male	[n]	41 (36%)		67 (50%)		0.06
follow up	[days]	66±17	17-110	70±15	9-105#	0.07
symptoms						
at infection	[n]	3.7±1.5	1-7	3.1±1.5	1-6	<0.01*
at follow up	[n]	1.3±0.5	1-3	0	0	<<0.001
clinical course						
outpatient	[n]	97 (86%)		127 (95%)		0.01*
inpatient	[n]	15 (13%)		5 (4%)		<0.01*
intensive care	[n]	1 (<1%)		1 (<1%)		>0.99
comorbidities						
number	[n]	0.3±0.6	0-2	0.2±0.5	0-2	0.49
respiratory	[n]	14 (12%)		10 (8%)		0.28
asthma	[n]	8 (7%)		6 (5%)		0.41
sarcoidosis	[n]	1 (1%)		0		0.46
other	[n]	5 (4%)		4 (3%)		0.74
cardiovascular	[n]	8 (7%)		14 (11%)		0.38
hypertension	[n]	6 (5%)		11 (8%)		0.45
other	[n]	2 (2%)		3 (2%)		>0.99
diabetes	[n]	4 (4%)		2 (2%)		0.41
therapy (at infection)						
none	[n]	105 (93%)		131 (98%)		<0.05*
steroids	[n]	2 (2%)		0		<0.21
antiviral	[n]	2(2%)		2 (2%)		>0.99
antibacterial	[n]	3 (3%)		1 (<1%)		0.33
antifungal	[n]	1 (<1%)		0		0.46
anticoagulation	[n]	1 (<1%)		0		0.46
therapy (at follow-up)						
inhaled steroids	[n]	7 (6%)		1 (<1%)		<0.05*
bronchodilators	[n]	6 (5%)		0		<0.01*
lung function (at follow-up)						
FEV_1/FVC	[%]	85±8	57-111	84±7	66-102	0.26
FEV_1	[%pred]	96±17	34-129	103±13	64-138	<0.01*
MEF_{50}	[%pred]	116±47	22-298	116±43	43-263	0.98
VC	[%pred]	96±15	59-129	102±14	61-136	<0.01*
TLC	[%pred]	103±16	46-135	105±15	56-142	0.51
RV/TLC	[%]	38±10	16-68	36±10	16-88	0.27
sR_{tot}	[%pred]	108±63	19-461	99±47	21-271	0.24

TLCO[§]	[%pred]	83±15	48-116		88±15	48-118	<0.05*

FEV_1: forced expiratory volume in one second, (F)VC: (forced) vital capacity, MEF_{25}: maximum expiratory flow at 50% of FVC, TLC: total lung capacity, RV: residual volume, sR_{tot}: specific total airway resistance, TLCO: transfer factor, %pred: percent of predicted. *statistically significant $p<0.05$ (Student's t-test). [#] one patient underwent body-plethysmography on the day of confirmed SARS-CoV-2 infection. [§] TLCO was available in 159 patients (65%).