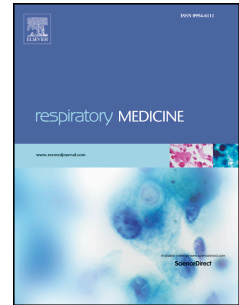


# Journal Pre-proof

Pulmonary function and health-related quality of life after COVID-19 pneumonia

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## TITLE PAGE

### **Title: Pulmonary function and health-related quality of life after COVID-19 pneumonia**

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## **ABSTRACT**

### **Background**

The COVID-19 pandemic has led to many cases of pneumonia with extensive lung abnormalities on CT-scans. The consequences of COVID-19 pneumonia on survivors' pulmonary function and quality of life are unknown. The purpose of this study is to examine the impact of COVID-19 pneumonia on pulmonary function, health-related quality of life (HRQoL) and perceived dyspnoea.

### **Methods**

A prospective longitudinal cohort study regarding patients discharged from our hospital after PCR-proven, non-critical COVID-19 pneumonia was conducted. Cases were classified as moderate or severe pneumonia according to WHO definitions. Six weeks post-discharge subjects underwent interviews and pulmonary function tests, and completed questionnaires to assess their HRQoL, perceived dyspnoea (Borgscale and mMRC), and symptoms of depression and anxiety (HADS).

### **Results**

101 patients were included. Twenty-eight (27.7%) pneumonias were classified as moderate cases of COVID-19 pneumonia and 73 (72.3%) were classified as severe cases. Diffusion limitation ( $\text{DLCOc} < 80\%$  of predicted value) was found in 66 (71.7%) of 92 cases, obstruction in 26 (25.7%) of 101, and restriction in 21 (21.2%) of 99. Diffusion capacity was significantly lower in cases after severe pneumonia. In the entire group, HADS scores  $\geq 8$  for depression were found in 16.6% and in 12.5% for anxiety. Across all SF-36 domains, except for bodily pain, significant impairment was found. FEV1 and DLCOc showed significant positive correlations with mMRC scores and multiple SF-36 domains, especially physical functioning.

### **Conclusion**

COVID-19 non-critical pneumonia survivors have significant impairment in diffusion capacity and HRQOL six weeks after being discharged from hospital.

## INTRODUCTION

The consequences of COVID-19 pneumonia for surviving patient's pulmonary function and health-related quality of life (HRQoL) are not yet known. In other Coronavirus outbreaks, such as SARS in 2003, a negative long-term impact on pulmonary function and HRQoL was reported.[1,2] The importance of respiratory follow-up of patients with COVID-19 pneumonia was already stated, however limited data are known.[3] In Chinese studies limited diffusion capacity was observed in almost half of all non-critical COVID-19-pneumonia cases on the day of discharge and after 30 days.[4,5]

In addition to the physical consequences, hospitalization with COVID-19 infection can lead to mental health complications, such as depression and/or anxiety.[6] Assessment of HRQoL can improve understanding of the consequences of COVID-19 pneumonia, and may provide opportunities to apply tailored interventions.

This observational study was performed to examine the impact of COVID-19 pneumonia on pulmonary function and HRQoL.

## METHODS

A prospective longitudinal study was conducted regarding patients discharged between March 16<sup>th</sup> and April 15<sup>th</sup> 2020 from Amphia Hospital (Breda, the Netherlands) after RT-PCR confirmed, non-critical COVID-19 pneumonia.

According to the WHO-definition, moderate cases of pneumonia did not require supplemental oxygen (WHO ordinal scale for clinical improvement score 3), whereas cases with severe pneumonia did (WHO ordinal scale 4).[7,8] Patients with critical pneumonia necessitating non-invasive ventilation or ICU admission were excluded.

At the visit six weeks post-discharge, subjects were interviewed, underwent physical examination and performed pulmonary function testing (PFT), according to ERS standards (VyaireMasterscreen PFTpro, bodyplethysmograph). Patients completed questionnaires assessing HRQoL (SF-36), perceived dyspnoea (Borg, mMRC), and symptoms of depression and anxiety (HADS). The study was approved by the Dutch medical research ethics committees united (registration-number W20.151).

### Analysis of data

Descriptive statistics were used for clinical parameters and PFT. Comparison between moderate and severe pneumonias was performed by independent sample *t*-test for continuous variables, Mann-Whitney U test for non-parametric data and Chi square test for categorical variables. Lower limit of normal (LLN) was defined as the 5<sup>th</sup> percentile of distribution by calculated z-score of -1.64.

All statistical tests were two-tailed. Statistical significance was taken as  $p < 0.05$ .

SF-36 outcomes were compared to normative data from a random, nationwide sample of 1742 Dutch adults.[9] Correlations were assessed according to Spearman. SPSS version 25 was used for statistical analysis.

## RESULTS

We included 101 COVID-19 pneumonia survivors. Demographic data, comorbidities and PFT results are summarised in Table 1. All patients were able to perform spirometry testing. In 99 out of 101 patients measurement TLC was successfully obtained, and measurement of diffusion capacity succeeded in 92 patients. Diffusion capacity (DLCOc) was most often affected. DLCOc was below 80% in 78.5% of patients (severe pneumonia) and 55.6% (moderate pneumonia), and under 60% in 27.7% (severe pneumonia) and 18.5 % (moderate pneumonia). Restriction ( $TLC < 80\%$ ) was found in 21.2% and obstruction ( $FEV1/FVC < 0.70$ ) in 25.7%.

Of 26 patients with obstruction, 13 had a medical history of COPD, four had asthma, 22 were current or former smokers, and two had no known pulmonary disease and never smoked. Six patients with COPD in their medical history had  $FEV1/FVC > 0.70$ , which was inconsistent with their previous diagnosis. Comparison of DLCO in (ex-) smokers versus never-smokers revealed no significant difference (67% pred for (ex-) smokers, 73% for never-smokers,  $p = 0.130$ ).

### Symptom scores

Borgscale was  $\geq 4$  in 19.8% for dyspnoea with mMRC score  $\geq 2$  in 23.8% ( $n=96$ ). Median HADS scores were 4.0 (IQR 2.0 -7.0) for anxiety and 3.0 (1.0 -6.0) for depressive symptoms ( $n=86$ ). Remarkably, the depression score was significantly higher in after moderate pneumonia in contrast to severe pneumonia (5.00 vs 3.00;  $p$ -value 0.048). HADS scores  $\geq 8$  were found in 16.6% of patients for depression and in 12.5% for anxiety ( $n= 96$ ).

### HRQoL and correlation with pulmonary function

Significant impairment across all SF-36-domains, except for bodily pain (figure 1) was found. The domains with the largest impairment were physical role limitation, physical functioning (PF) and vitality. FEV1 and DLCOc showed significant positive correlations with mMRC scores and multiple SF-36-domains, especially PF ( $r = 0.255$ ;  $p < 0.05$  for DLCOc and PF)

## DISCUSSION

In this study, the majority of COVID-19 pneumonia survivors had abnormal diffusion capacity six weeks after discharge. Table 1 shows a significant impairment in DLCO ( $< 80\%$ ) in 71.7% of patients, with a severe limitation ( $< 60\%$  predicted) in 25% of all cases. When using the lower limit of normal for DLCO 59.7% of patients were affected. There were less anomalies in KCO, with mean KCOc of 89.0% in the moderate group and 83.8% in the patients with a severe pneumonia. This is in accordance with the findings in COVID-19 survivors at time of hospital discharge. [4] KCOc measurement can be normal in the presence of reduced DLCO if alveolar volume is low, reflecting loss of complete acini with alveoli and surrounding blood vessels.[10] TLC was below LLN in 21.8% of patients, compatible with reduced alveolar volume. When TLC is within normal limits, alveolar volume may still be reduced due to inhomogeneous ventilation and perfusion, because measurement of alveolar volume by single breath method only samples the better ventilated and perfused areas of the lungs. [11]

In SARS pneumonia survivors, also limitation of diffusion capacity, expressed by DLCO, was reported in a high percentage of patients.[1,2] Our findings show that COVID-19 may have similar consequences. In a study from China, most patients had abnormalities in gas exchange while restriction was less common.[4] This may reflect damage to the alveolar membrane, rather than advanced fibrosis. The inclusion of only non-ICU cases means abnormalities cannot be attributed to mechanical ventilation but may be caused by COVID-19 related inflammation. However, also smoking status may have contributed to the impaired diffusion capacity since 56 patients (55.4%) of our population were current (three) or former (53) smokers, even though no significant difference in diffusion capacity was found in our population. As data on pre-illness lung function were not available, conclusions on causality can not be drawn from this study.

The importance of PFT was recently emphasized, but very limited data have been reported so far.[3,12] Our study shows that PFT is feasible after COVID-19 pneumonia and can reveal abnormalities even after



non-critical course of disease , we recommend inclusion of PFT in follow up care of COVID19 pneumonia.

All domains of HRQoL, except for bodily pain, were significantly lower than the norm, and a significant correlation with diffusion capacity was found. This correlation (0.255,  $p < 0.05$ ) is weak, indicating that quality of life is determined by more aspects than physical functioning only. Isolation and social distancing may have contributed to these results, especially to the remarkably low score on the SF-36 domain score for physical role limitation.

Screening for anxiety and depression in this COVID-19 cohort demonstrated that 12% of patients were affected by anxiety and 16% by symptoms of depression. These results are similar to results of a Chinese population study which observed a higher risk of depression in patients suspected of COVID-19-infection.[6] A limitation of our study is the relatively small size of the single-center cohort. Furthermore, follow up after six weeks is short and further recovery of pulmonary function and HRQoL can be expected. Long term studies are needed to assess persistent lung damage after COVID-19 and direct research into future treatment options, for both medical and supportive interventions.

## CONCLUSION

The majority of non-critical COVID-19 pneumonia survivors have impaired diffusion capacity six weeks after discharge and HRQoL is reduced. Follow-up for COVID-19 pneumonia patients should include PFT and assess quality of life.

**Table 1.** Characteristics and pulmonary function of COVID-19 pneumonia survivors

	<b>Total (n = 101)</b>	<b>Moderate pneumonia WHO Ordinal scale 3 (n= 28)</b>	<b>Severe pneumonia WHO Ordinal scale 4 (n=73)</b>	<b>p-value mod vs severe</b>
Age in years, mean (SD)	66.4 (12.6)	62.8 (13.7)	67.7 (12.0)	0.08 #
Males	58 (57.4 %)	15 (46.4%)	43 (58.9%)	0.66 #
BMI, median (IQR)	26.5 (24.1 – 29.9)	27.2 (25.0 – 30.4)	26.3 (24.0 – 29.9)	0.24 \$
Never smoker	45 (44.5%)	15 (53.5%)	30 (41.1%)	0.49 ^
Former smoker	53 (52.5%)	12 (42.9%)	41 (56.1%)	0.49 ^
Current smoker	3 (3.0%)	1 (3.6%)	2 (2.7%)	0.49 ^
<b>Comorbidity</b>				
Diabetes mellitus	18 (17.8%)	5 (17.9%)	13 (17.8%)	0.68 ^
Cardiovascular disease	29 (28.7%)	10 (35.7%)	19 (26.0%)	0.34 ^
Pulmonary disease	35 (34.7%)	10 (35.7%)	25 (34.2%)	0.89 ^
Malignancy	14 (13.9%)	3 (10.7%)	11 (15.1%)	0.57 ^
<b>Pulmonary function</b>				
FVC, liters	3.46 (1.01)	3.67 (1.06)	3.38 (0.99)	0.19 #
FVC%pred	90.8 (1.17)	93.4% (15.9)	89.7 (17.6)	0.33 #
FEV1, liters	2.58 (0.83)	2.82 (0.77)	2.49 (0.84)	0.08 #
FEV1%pred	87.9% (20.4)	92.6% (16.0)	86.1% (21.7)	0.15 #
FEV1/FVC	74.7 (11.6)	76.8 (6.90)	73.8 (12.93)	0.29 #
TLC, liters*	5.92 (1.37)	6.03 (1.40)	5.87 (1.37)	0.62 #
TLC % predicted&	95.5 (17.8)	97.0 (14.1)	94.9 (19.1)	0.43 #
DLCOc % predicted&	70.3 (18.0)	76.0 (16.8)	68.0 (18.1)	0.10 #
KCOc % predicted&	85.4% (20.2)	89.0% (17.7)	83.8 (21.1)	0.26 #
<b>Pulmonary function categorized</b>				
DLCOc < 80%, No (%)&	66 (71.7%)	15 (55.6%)	51 (78.5%)	0.03 ^
DLCOc < 60%, No (%)&	23 (25.0%)	5 (18.5%)	18 (27.7%)	0.36 ^
DLCOc < LLN No (%)&	55 (59.7%)	14 (51.8%)	41 (63.1%)	0.15 ^
TLC < 80%, No (%)*	21 (21.2%)	4 (14.8%)	17 (23.6%)	0.34 ^
TLC < LLN No (%)*	22 (21.8%)	5 (18.5%)	17 (23.6%)	0.36 ^
FEV1/FVC < 0.70, No (%)	26 (25.7%)	6 (21.4%)	20 (27.4%)	0.54 ^

Values are numbers (%), unless stated otherwise.

# unpaired t-test

\$ Mann Whitney U test

^ X2 test

&For DLCOc and KCOc: n= 92 (27 moderate pneumonia, 65 severe pneumonia);

\* For TLC: n= 99 (27 moderate pneumonia, 72 severe pneumonia )

LLN = lower limit of normal (defined as 5<sup>th</sup> percentile of distribution by calculated z-score of -1.64)

IQR = interquartile range; BMI = body mass index;

VC=vital capacity; FEV1=forced expiratory volume in 1 second; TLC=total lung capacity; DLCOc=diffusion capacity for carbon monoxide corrected for hemoglobin; hemoglobin KCOc=Carbon monoxide transfer coefficient corrected for hemoglobin

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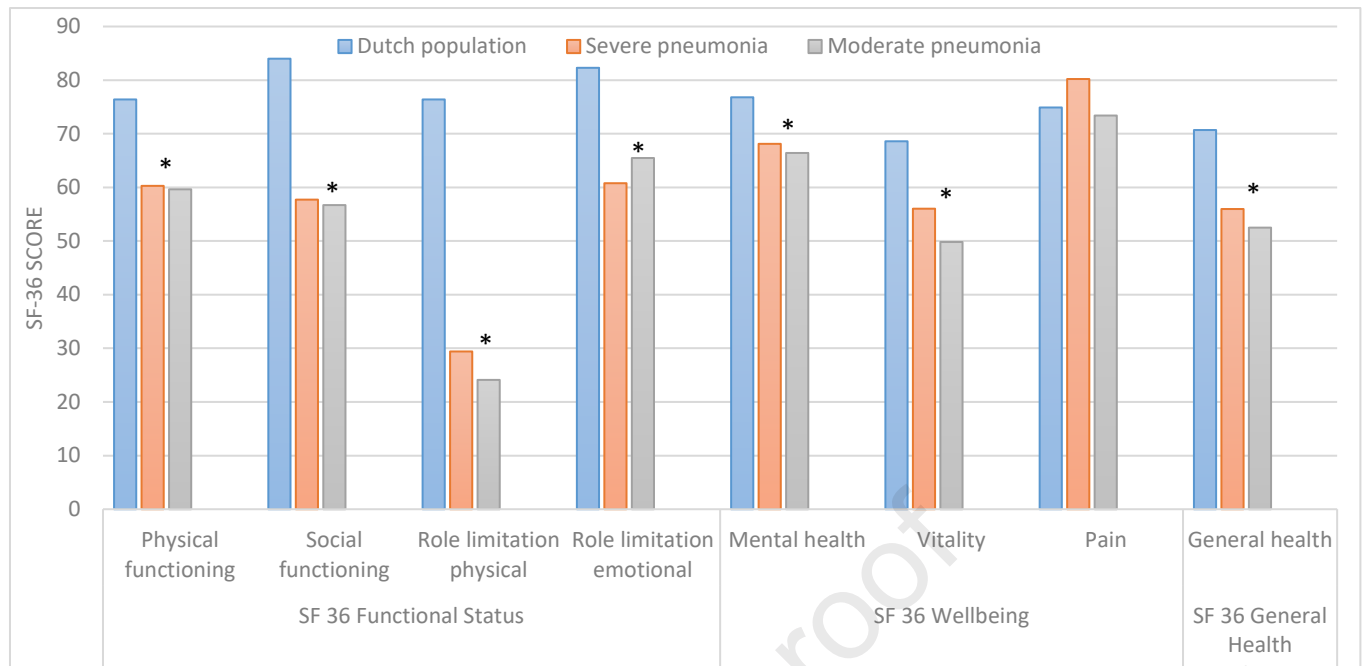
**DECLARATION OF INTEREST:** none

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**Figure 2.** SF-36 domain outcomes. The differences between the general healthy population and COVID pneumonia groups at the domains marked with \* are significant at the level  $p=0.0001$

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Highlights:

- Diffusion capacity is often abnormal six weeks after non-severe COVID 19 pneumonia
- Restriction is found in a minority (21%) of non-severe COVID 19 pneumonia survivors
- Quality of life is reduced in COVID19 pneumonia survivors six weeks after discharge



**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: