Ther Adv Respir Dis

2021, Vol. 15: 1–7

DOI: 10.1177/17534666211025221

Does pre-existent physical inactivity have a role in the severity of COVID-19?

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Abstract

Background and Aims: Physical inactivity is considered an important lifestyle factor for overweight and cardiovascular disease. We aimed to investigate the association between pre-existent physical inactivity and the risk of severe coronavirus disease 2019 (COVID-19).

Methods: We included 164 (61.8 ± 13.6 years) patients with COVID-19 who were admitted between 15 February and 14 March 2020 in this retrospective study. We evaluated the association between pre-existent physical inactivity and severe COVID-19 using a logistic regression model.

Results: Of 164 eligible patients with COVID-19, 103 (62.8%) were reported to be physically inactive. Univariable logistic regression analysis showed that physical inactivity was associated with an increased risk of severe COVID-19 [unadjusted odds ratio (OR) 6.53, 95% confidence interval (CI) 1.88–22.62]. In the multivariable regression analysis, physical inactivity remained significantly associated with an increased risk of severe COVID-19 (adjusted OR 4.12, 95% CI 1.12–15.14) after adjustment for age, sex, stroke, and overweight.

Conclusion: Our data showed that pre-existent physical inactivity was associated with an increased risk of experiencing severe COVID-19. Our findings indicate that people should be encouraged to keep physically active to be at a lower risk of experiencing a severe illness when COVID-19 infection seems unpredicted.

The reviews of this paper are available via the supplemental material section.

Keywords: coronavirus disease 2019, physical inactivity, prognosis

Received: 27 February 2021; revised manuscript accepted: 20 May 2021.

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Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has posed a significant threat to the public.[1] It is critical to identify characteristics of people who may be at a high risk of experiencing severe SARS-CoV-2 infection to inform timely intervention. Some factors such as older age, hypertension, diabetes, or a previous history of pulmonary disease increase the severity of COVID-19.[2,3] Previous studies also showed that overweight and cardiovascular disease were associated with a poor outcome in patients with COVID-19.[4,5] Physical inactivity is considered an important lifestyle factor for overweight and cardiovascular disease. Several studies have shown that patients who took regular physical activity had a lower incidence, severity, and mortality from viral infections.[6–8] Physical inactivity might be associated with poor immune response *via* the vicious cycle between inactivity and obesity,[9,10] exerting a negative impact on immune function and host defense. Exercise may affect susceptibility to infection by modifying monocyte and lymphocyte distribution, phenotype, and cytokine release.[11] A previous large-scale general population study showed that physical inactivity [relative risk 1.32, 95% confidence interval (CI) 1.10–1.58] was associated with an increased risk of COVID-19 hospital admission;[12] however, whether pre-existent physical inactivity has a role in the severity of COVID-19 remains unclear. Since regular physical activity reduces the risk of systemic inflammation, a main contributor to pneumonia due to SARS-CoV-2 infection, we hypothesized that physical inactivity may play an important role in mitigating the severity of COVID-19. We therefore investigated the association between pre-existent physical inactivity and severe COVID-19 in this retrospective study.

Methods

Standard protocol approvals, registrations, and patient consent

The ethics committee of Fujian Medical University Union Hospital approved this study. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was waived due to the nature of our retrospective study of routine clinical data.

Data collection and outcome measures

We analyzed the data of 164 consecutive patients with COVID-19 at the Tumor Center of Union Hospital (Wuhan, China) between 15 February 2020 and 14 March 2020 in this study. The epidemiological, demographic, clinical, laboratory, and radiological data were extracted from a digital database using a standardized data collection form. If data were missing or uncertain from the medical records, we obtained and clarified data by direct communication with attending doctors and other healthcare providers. To assess the pre-existent physically active status, we employed a well-validated Exercise Vital Sign evaluation method.[13] Briefly, we asked participants or their caregivers two questions: "On average, how many days (0–7) per week does the patient engage in moderate to strenuous exercise?" and "On average, how many minutes does the patients engage in exercise at this level?". We recorded minutes in blocks of 10: 0, 10, 20, 30, 40, 50, 60, 90, 120, and 150 or greater. Physical inactivity was defined as <150 min/week of moderate activity or <75 min/week of vigorous activity.[13] Laboratory confirmation of COVID-19 infection was performed as previously described.[14] Our primary outcome was severe COVID-19 defined as fever or suspected respiratory infection, plus one of: respiratory rate >30 breaths/min; severe respiratory distress; Peripheral capillary oxygen saturation (SPO_2) $\leqslant 93\%$ on room air based on World Health Organization clinical management of severe acute respiratory infection when COVID-19 is suspected: interim guidance.[15] Our second outcome was death, which was limited by the end of our observation (14 March 2020).

Statistical analysis

Data were summarized with mean value with standard deviations or median value with interquartile range and categories data as counts with percentages. We used the *t*-test or Mann–Whitney U test to compare the differences in continuous variables, and the chi-square test or Fisher's exact test to compare the differences in categorical variables as appropriate. We used univariable and multivariable logistic regression analysis to evaluate the association between physical inactivity and 30-day severe COVID-19. For multivariable analysis, we chose the variables based on previous findings and clinical constraints to avoid overfitting the logistic regression model.[16] We therefore included hypertension, chronic obstructive pulmonary disease (COPD), coronary heart disease, tumor, renal impairment, decreased leucocytes, decreased lymphocytes, increased lactate dehydrogenase and chest computed tomography (CT) findings as potential confounders each in turn along with age and sex in the regression model. We also included the pre-existent comorbidity with $p < 0.05$ in the univariable regression analysis along with age and sex into the final multivariable regression model. All analyses were performed using SPSS for Windows (SPSS 25.0, IBM).

Data available statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Of 164 eligible patients with COVID-19, 103 (62.8%) were reported to be physically inactive. The demographics and clinical and radiological characteristics of patients with and without physical inactivity are shown in Table 1. Patients with physical inactivity were similar to those without physical inactivity in comorbidities (except the previous stroke), exposure to wet seafood market, onset symptoms, and laboratory and radiological findings. Patients who were physically inactive were older (63.6 ± 18.8 years *versus* 58.7 ± 13.9 years), and more likely to have had a previous

Table 1. Demographic, clinical, laboratory, radiological characteristics, treatment, and outcome between patients with and without physical inactivity.

	Total (*n* = 164)	Inactivity (*n* = 103)	Activity (*n* = 61)	*p*
Age, (years) mean ± SD	61.8 ± 13.6	63.6 ± 13.8	58.7 ± 13.9	0.023
Male, *n* (%)	84 (51.2)	54 (52.4)	30 (49.2)	0.688
Current smoker, *n* (%)	17 (10.4)	9 (8.7)	8 (13.1)	0.374
Regular drinker, *n* (%)	3 (1.8)	2 (1.9)	1 (1.6)	>0.999
Hypertension, *n* (%)	52 (31.7)	37 (35.9)	15 (24.6)	0.132
Diabetes, *n* (%)	31 (18.9)	19 (18.4)	12 (19.7)	0.846
Dyslipidemia, *n* (%)	63 (38.4)	39 (37.9)	24 (39.3)	0.851
Atrial fibrillation, *n* (%)	10 (6.1)	8 (7.8)	2 (3.3)	0.410
Overweight, *n* (%)	55 (33.5)	37 (35.9)	18 (29.5)	0.400
Previous stroke, *n* (%)	6 (3.7)	6 (5.8)	0 (0.0)	0.085
Chronic obstructive pulmonary disease, *n* (%)	12 (7.3)	10 (9.7)	2 (3.3)	0.223
Coronary heart disease, *n* (%)	18 (11.0)	14 (13.6)	4 (6.6)	0.257
Renal impairment, *n* (%)	25 (15.2)	21 (20.4)	4 (6.6)	0.031
Digestive disease, *n* (%)	15 (9.1)	8 (7.8)	7 (11.5)	0.426
Immunosuppressives, *n* (%)	3 (1.8)	1 (1.0)	2 (3.3)	0.643
Tumor, *n* (%)	13 (7.9)	11 (10.7)	2 (3.3)	0.163
Wet market exposure, *n* (%)	2 (1.2)	2 (1.9)	0 (0.0)	0.530
Clinical symptoms				
Fever, *n* (%)	115 (70.1)	70 (68.0)	45 (73.8)	0.432
Dry cough, *n* (%)	104 (63.4)	65 (63.1)	39 (63.9)	0.915
Productive cough, *n* (%)	23 (14.0)	13 (12.6)	10 (16.4)	0.501
Fatigue, *n* (%)	57 (34.8)	34 (33.0)	23 (37.7)	0.542
Muscle or joint ache, *n* (%)	21 (12.8)	15 (14.6)	6 (9.8)	0.381
Thoracalgia, *n* (%)	31 (18.9)	21 (20.4)	10 (16.4)	0.528
Sore throat, *n* (%)	23 (14.0)	14 (13.6)	19 (14.8)	0.836
Diarrhea, *n* (%)	13 (7.9)	11 (10.7)	2 (3.3)	0.163
Catarrh, *n* (%)	6 (3.7)	2 (1.9)	4 (6.6)	0.275
Anorexia, *n* (%)	48 (29.3)	27 (26.2)	21 (34.4)	0.264
Shortness of breath, *n* (%)	65 (39.6)	40 (38.8)	25 (41.0)	0.786
Headache, *n* (%)	19 (11.6)	11 (10.7)	8 (13.1)	0.638

(Continued)

Table 1. (Continued)

	Total ($n = 164$)	Inactivity ($n = 103$)	Activity ($n = 61$)	p
Total symptoms (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	0.935
Routine blood examinations				
Decreased leucocytes, *n* (%)	11 (6.7)	6 (5.8)	5 (8.2)	0.792
Decreased lymphocytes, *n* (%)	55 (33.5)	37 (35.9)	18 (29.5)	0.400
Decreased hemoglobin, *n* (%)	42 (25.6)	25 (24.3)	17 (27.9)	0.610
Decreased platelets, *n* (%)	14 (8.5)	11 (10.7)	3 (4.9)	0.324
Increased ALT or AST, *n* (%)	58 (35.4)	35 (34.0)	23 (37.7)	0.630
Increased LDH, *n* (%)	50 (30.7)	32 (31.4)	18 (29.5)	0.803
Complications				
Acute stroke, *n* (%)	3 (1.8)	3 (2.9)	0 (0.0)	0.295
Shock, *n* (%)	3 (1.8)	3 (2.9)	0 (0.0)	0.295
CT findings, *n* (%)				0.338
Unilateral pneumonia, *n* (%)	26 (15.9)	13 (12.6)	13 (21.3)	
Bilateral pneumonia, *n* (%)	86 (52.4)	56 (54.4)	30 (49.2)	
Multiple mottling and ground-glass opacity, *n* (%)	52 (31.7)	34 (33.0)	18 (29.5)	
Treatment				
Oxygen therapy, *n* (%)				0.214
Nasal cannula, *n* (%)	79 (48.2)	48 (46.6)	31 (50.8)	
Medical mask, *n* (%)	5 (3.0)	4 (3.9)	1 (1.6)	
High solution, *n* (%)	5 (3.0)	5 (4.9)	0 (0.0)	
Invasive ventilation, *n* (%)	3 (1.8)	3 (2.9)	0 (0.0)	
Glucocorticoid, *n* (%)	20 (12.2)	13 (12.6)	7 (11.5)	0.828
Antibacterial, *n* (%)	117 (71.8)	76 (74.5)	41 (67.2)	0.317
Antivirus, *n* (%)	158 (96.3)	99 (96.1)	59 (96.7)	>0.999
Chinese traditional medicine, *n* (%)	156 (95.1)	99 (96.1)	157 (93.4)	0.694
Outcomes				
Cured at discharge, *n* (%)	103 (62.8)	67 (65.0)	36 (59.0)	0.440
Death, *n* (%)	6 (3.7)	6 (5.8)	0 (0.0)	0.085
Severe COVID-19	29 (17.4)	26 (25.2)	3 (4.9)	0.002

Decreased means below the lower limit of the normal range: leucocytes ($\times 10^9$/L; normal range 3.5–9.5); lymphocytes ($\times 10^9$/L; normal range 1.1–3.2); platelets ($\times 10^9$/L; normal range 125.0–350.0); hemoglobin (g/L; normal range 130.0–175.0). ALT: U/L; normal range 0–40; AST: U/L; normal range 0–40; LDH: U/L; normal range 109–245, data available in 163 patients.
ALT, alanine transaminase; AST, alanine aminotransferase; COVID-19, coronavirus disease 2019; CT, computed tomography; IQR, interquartile range; LDH, lactate dehydrogenase; SD, standard deviation.

Table 2. Association between physical inactivity and severe COVID-19.

	OR	95% CI	*p* value
Unadjusted	6.53	1.88–22.62	0.003
Age and sex adjusted	4.98	1.38–17.964	0.014
Age, sex, and hypertension adjusted	4.99	1.38–18.06	0.014
Age, sex, and diabetes adjusted	5.05	1.39–18.27	0.014
Age, sex, and CHD adjusted	5.03	1.39–18.19	0.014
Age, sex, and tumor adjusted	4.82	1.32–17.54	0.017
Age, sex, and renal impairment adjusted	4.40	1.21–16.03	0.025
Age, sex, and current smoker adjusted	4.89	1.35–17.65	0.015
Age, sex, and overweight adjusted	4.77	1.31–17.30	0.018
Age, sex, and stroke adjusted	4.47	1.23–16.24	0.023
Multivariable	4.12	1.12–15.14	0.033

Multivariable = adjustment for age, sex, stroke, and overweight.
CHD, coronary heart disease; CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio.

stroke [6 (5.8%) *versus* 0 (0.0%)]. Patients who were physical inactive had more severe COVID-19 [26 (25.2%) *versus* 3 (4.9%)] and mortality [6 (5.8%) *versus* 0 (0.0%)].

A total of 29 patients (17.7%) experienced severe COVID-19 during our observations. In the univariable logistic regression analysis, physical inactivity was associated with an increased risk of severe COVID-19 [unadjusted odds ratio (OR) 6.528, 95% CI 1.88–22.62]. This association remained after adjustment for age and sex (Table 2). Additional adjustment for coronary heart disease, COPD, and tumor or renal impairment separately as confounders in addition to age and sex did not change the relationship between physical inactivity and severe COVID-19. In the multivariable regression analysis, physical inactivity remained significantly associated with an increased risk of severe COVID-19 (adjusted OR 4.12, 95% CI 1.12–15.14).

Discussion

Our main finding was that patients with physical inactivity who had a SARS-CoV-2 infection were at an increased risk of experiencing severe COVID-19, indicating that physical inactivity might be a hazardous behavior for COVID-19 severity. Our findings were in line with a large sample observational study ($n = 48,440$) that showed patients with COVID-19 who were consistently physically inactive had a higher risk of admission to the intensive care unit (OR 1.73; 95% CI 1.18–2.55) and mortality (OR 2.49; 95% CI 1.33–4.67) than patients who were consistently meeting physical activity guidelines.[17] Several physiological processes might explain the relationship between physical activity and improved immune and respiratory function, supporting the association between physical inactivity and higher risk of severe COVID-19. Regular physical exercise can increase immune cells and improve immune health. Prolonged moderate aerobic exercise has been previously proven to contribute some positive benefits on influenza (or pneumonia) immunization. Possible mechanisms of exercise-induced benefits may include the role of endogenous opioids, inflammatory biomarkers, or memory to naïve T lymphocyte ratio.[18] Moreover, regular physical exercise could upregulate the expression of antiviral immunity markers, lead to higher activation and proliferation of T cells, and proper balance of T-helper responses, enhancing natural killer cell activity that optimizes the systemic immune response.[19] Some researchers proposed that even a small increase in baseline maximal oxygen uptake across the population may have the effect of shifting a significant proportion of high-risk patients into a lower risk category.[20] Further investigations are needed to determine whether physical exercise would confer immune protection to patients with COVID-19 with cardiovascular and metabolic disorders.[11]

During the COVID-19 pandemic, people worldwide were encouraged to stay at home to avoid contact with individuals outside to minimize the spread of SARS-CoV-2. People therefore had very limited access to physical and sports facilities due to lockdowns, so the risk of physical inactivity increased. Our findings suggest physical inactivity is a modifiable risk factor for severe COVID-19 outcomes. We therefore propose that people should keep structured activity as a critical strategy for optimizing the immune system's functional integrity to prevent severe COVID-19 infection. Indoor or home-based physical exercise is a low-cost approach to maintaining appropriate immune responsiveness that might contribute to prevention or remediation of COVID-19.[20]

The main limitation of our study was that it was a retrospective study conducted at a single-centered hospital with a limited sample size. Moreover, physical inactivity was assessed by two simple questions, so their prevalence may be misestimated. However, data from a previous study supported the use of this self-reported exercise assessment in diverse patient populations in clinical practice.[13] Notably, this approach can be finished within 1 min, without additional staff and medical resources, and can generally be used in most medical institutions worldwide, even under the unprecedented COVID-19 pandemic conditions. Lastly, we only included Chinese patients with COVID-19 during the first wave of the pandemic in the present study; caution should be taken about generalizing our findings to other COVID-19 populations.

Conclusion

Pre-existent physical inactivity seems to influence the course of COVID-19 infection. Our findings indicated that adopting simple lifestyle changes could lower the risk of severe COVID-19; people should keep physical active to be at a lower risk of experiencing severe illness if a COVID-19 infection occurs.

Acknowledgements

We thank all the patients for their data for this analysis. We thank the medical workers who are on the front line of caring for patients.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Fujian Natural Science Foundation (2018J01309) and the Fujian Provincial Natural and Science Innovation Project (No. 2016B014).

On behalf of the Fujian Medical Team Support Wuhan for COVID-19.

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Supplemental material

The reviews of this paper are available via the supplemental material section.

References

1. Zhou F, Yu T, Du R, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054–1062.
2. Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497–506.
3. Wang D, Hu B, Hu C, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; 323: 1061–1069.
4. Cai Q, Chen F, Wang T, *et al.* Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. *Diabetes Care* 2020; 43: 1392–1398.
5. Pranata R, Huang I, Lim MA, *et al.* Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19 – systematic review, meta-analysis, and meta-regression. *J Stroke Cerebrovasc Dis* 2020; 29: 104949.

6. Nieman DC and Wentz LM. The compelling link between physical activity and the body's defense system. *J Sport Health Sci* 2019; 8: 201–217.
7. da Silveira MP, da Silva Fagundes KK, Bizuti MR, *et al.* Physical exercise as a tool to help the immune system against COVID-19: an integrative review of the current literature. *Clin Exp Med* 2021; 21: 15–28.
8. Burtscher J, Millet GP and Burtscher M. Low cardiorespiratory and mitochondrial fitness as risk factors in viral infections: implications for COVID-19. *Br J Sports Med* 2021; 55: 413–415.
9. Laddu DR, Lavie CJ, Phillips SA, *et al.* Physical activity for immunity protection: inoculating populations with healthy living medicine in preparation for the next pandemic. *Prog Cardiovasc Dis* 2021; 64: 102–104.
10. Pietiläinen KH, Kaprio J, Borg P, *et al.* Physical inactivity and obesity: a vicious circle. *Obesity* 2008; 16: 409–414.
11. Jesus I, Vanhee V, Deramaudt TB, *et al.* Promising effects of exercise on the cardiovascular, metabolic and immune system during COVID-19 period. *J Hum Hypertens* 2021; 35: 1–3.
12. Hamer M, Kivimäki M, Gale CR, *et al.* Lifestyle risk factors, inflammatory mechanisms, and COVID-19 hospitalization: a community-based cohort study of 387,109 adults in UK. *Brain Behav Immun* 2020; 87: 184–187.
13. Coleman KJ, Ngor E, Reynolds K, *et al.* Initial validation of an exercise "vital sign" in electronic medical records. *Med Sci Sports Exerc* 2012; 44: 2071–2076.
14. Du HW, Chen JN, Pan XB, *et al.* Prevalence and outcomes of re-positive nucleic acid tests in discharged COVID-19 patients. *Eur J Clin Microbiol Infect Dis* 2021; 40: 413–417.
15. World Health Organization. *Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance*, 28 January 2020 (accessed 5 March 2020).
16. Wu C, Chen X, Cai Y, *et al.* Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; 180: 934–943.
17. Sallis R, Young DR, Tartof SY, *et al.* Physical inactivity is associated with a higher risk for severe COVID-19 outcomes: a study in 48440 adult patients. *Br J Sports Med*. Epub ahead of print 13 April 2021. DOI: 10.1136/bjsports-2021-104080.
18. Song Y, Ren F, Sun D, *et al.* Benefits of exercise on influenza or pneumonia in older adults: a systematic review. *Int J Environ Res Public Health* 2020; 17: 2655.
19. Furtado GE, Letieri RV, Caldo-Silva A, *et al.* Sustaining efficient immune functions with regular physical exercise in the COVID-19 era and beyond. *Eur J Clin Invest* 2021; 51: e13485.
20. Ahmed I. COVID-19 – does exercise prescription and maximal oxygen uptake (VO_2 max) have a role in risk-stratifying patients? *Clin Med (Lond)* 2020; 20: 282–284.

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