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Changes in Lung Diffusion Capacity after SARS-CoV-2 Infections in Highly Trained Athletes

Veränderungen der pulmonalen Diffusionskapazität nach SARS-CoV2-Infektion bei hochtrainierten Sportlern

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Summary

- **Objectives:** By now, many long-term symptoms after COVID-19 are described, mostly concerning hospitalized patients. Our aim was to investigate the long-term effect of COVID-19 on the lung function with focus on the diffusion capacity of athletes.
- **Methods:** 99 athletes (34.17±11.94 years, 56% female) after COVID-19 and 36 athletes (25.80±6.70 years, 65% female) without COVID-19 as controls were included. Symptom severity and lung function were assessed. Lung function of controls were compared with athletes after COVID-19 and changes in patients with dyspnea (during infection and at time of appointment) and changes over time between infection and examination on lung function were examined.
- **Results:** Exertional dyspnea during the infection was reported by 51% of athletes after COVID-19, respectively 27% at the time of examination (158±137 days after infection). 30% of athletes after COVID-19 showed a reduced Diffusion Capacity of the Lungs for Carbon Monoxide (DLCO <80% of the predicted value). Athletes after COVID-19 showed a significant reduced forced vital capacity ($p<0.01$) and forced expiratory volume at 1s ($p<0.01$) compared to controls. Dyspnea during infection was associated with a significant reduction in DLCO ($p<0.05$). There was no significant difference in lung function parameters depending on dyspnea at examination or depending on the duration between infection and examination.
- **Conclusion:** In athletes after COVID-19-Infection, static and dynamic lung volumes seem to be slightly reduced. Furthermore, athletes reporting dyspnea have lower than predicted DLCO. Factors could be reduced alveolar membrane function and lung perfusion. In the follow-up of athletes with dyspnea during infection, evaluation of diffusion capacity seems to be important.

KEY WORDS:
COVID-19, Pulmonary Sequalae, Pulmonary Function, Post-COVID

Zusammenfassung

- **Hintergrund und Ziele:** Es sind bereits zahlreiche Langzeitfolgen bei hospitalisierten COVID-19 Erkrankten bekannt. Momentan sind potenzielle Langzeitfolgen von COVID-19 bei Athleten noch unklar. Daher war es Ziel dieser Arbeit, Langzeitfolgen von COVID-19 auf die Lungenfunktion von Sportlern zu untersuchen.
- **Methode:** 99 Sportler (34.17±11.94 Jahre, 56% weiblich) nach COVID-19 und 36 Kontrollathleten (25.80±6.70 Jahre, 65% weiblich) wurden eingeschlossen. Die COVID-19 Symptomatik wurde durch einen Fragebogen erfasst. Zudem wurde eine Lungenfunktionstestung durchgeführt. Die Lungenfunktionstestung der Athleten nach COVID-19 und der Kontrollathleten wurde miteinander verglichen. Zusätzlich wurden Veränderungen der Lungenfunktion in Abhängigkeit von Dyspnoe und dem Zeitintervall zwischen Infektion und Erhebung untersucht.
- **Ergebnisse:** Belastungsdyspnoe wurde von 51% der Sportler während COVID-19 berichtet, zum Zeitpunkt der Untersuchung (158±137 Tage nach der Infektion) von 27%. 30% der Athleten nach COVID-19 erreichten <80% des vorhergesagten Wertes der DLCO. Im Vergleich zu den Kontrollathleten zeigte sich eine signifikant reduzierte forcierte Vitalkapazität ($p<0,01$) und Einsekundenkapazität ($p<0,01$). Berichtete Dyspnoe während der Infektion war mit einer signifikanten Reduktion der DLCO ($p<0,05$) assoziiert. Keine Unterschiede konnten für anhaltende Dyspnoe und den Zeitraum zwischen Infektion und Untersuchung gezeigt werden.
- **Fazit:** Diese Arbeit legt nahe, dass Athleten nach COVID-19 leicht reduzierte statische und dynamische Lungenvolumina haben. Zusätzlich weisen Athleten mit Dyspnoe eine reduzierte DLCO auf. Ursächlich könnten eine reduzierte alveolare Membranfunktion und Lungenperfusion sein. In Follow-Up Untersuchungen nach COVID-19 sollte bei Athleten mit Dyspnoe während der Infektion ein besonderes Augenmerk auf die Untersuchung der Diffusionskapazität gelegt werden.

SCHLÜSSELWÖRTER:
COVID-19, pulmonale Folgeschäden, Lungenfunktion, Post-COVID

Introduction

Since the beginning of the SARS-CoV-19 pandemic in 2019, potential persisting and long-term sequelae after acute SARS-CoV-19 infection are getting more and more attention. First reports of persisting symptoms were published by patients and patient advocacy groups (9). By now, many long-term symptoms are described, concerning mostly persisting symptoms of hospitalized COVID-19 cases (35, 39). Most frequently reported symptoms include shortness of breath or dyspnea, fatigue and sleep disorders (39, 44, 45). Organ specific sequelae of COVID-19 are commonly described, in particular pulmonary sequelae like reduced diffusion capacity and fibrotic changes on imaging (5, 7, 13, 17, 18, 31, 41, 44, 52, 55, 61, 64, 69). These findings are consistent with long term sequelae of previous corona virus induced infections like MERS (middle east respiratory syndrome) and SARS (severe acute respiratory syndrome) (1). ›

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Table 1

Characteristics of the study population. BMI=Body Mass Index, BGA=Blood gas analysis, sO_2=Oxygen saturation in %, pO_2=partial pressure of Oxygen in mmHg, pCO_2=partial pressure of Carbon dioxide in mmHg.

	ATHLETES WITHOUT COVID-19 (N= 32)	ATHLETES AFTER COVID-19 (N= 72)
	M (SD)	M (SD)
Age	25.80 (6.70)	34.17 (11.94)
Female	65%	56%
BMI	23.10 (3.27)	24.02 (3.74)
Training load		
3-5h/w	3	12
5-10h/w	3	9
10-15h/w	3	7
>15h/w	14	2
unknown	9	42
sO2	-	97.67 (4.02)
BGA		
pO2	70.07 (16.39)	76.16 (8.83)
pCO2	41.65 (10.02)	37.92 (3.85)
Blood pH	7.42 (0.02)	7.44 (0.03)

In addition to the acute infection, patients report increased psychosocial distress like depression and sleep disturbance as a result of home confinement (2, 3). The resumption of physical activity (PA) and exercise can counteract these psychological disorders (66). However, it must be clarified which and how long after infection individual symptoms are still measurable.

Furthermore, PA is well known to be associated with a lower risk of contracting infections of the upper respiratory tract, less illness severity and less missing days at work due to sickness (6, 11, 16, 21, 27, 37, 49, 56, 70). Additionally, pneumonia seems to be less prevalent in physical active adults (29). Moreover, it was shown that PA attenuates the increased risk of pneumonia by higher inflammation markers (20), and first studies suggest that PA is protective against contracting SARS-CoV-2, severe COVID-19 courses, hospitalization due to COVID-19 and COVID-19 related death (8, 30, 54). PA is also associated with a reduced likelihood of getting COVID-19 like symptoms (47). Consistently, a former study showed that most young high performance athletes have asymptomatic or mild-symptomatic infections accompanied with loss of taste and smell, headache and/or sore throat (42). Although the acute course of COVID-19 is asymptomatic or initially milder in physical active adults, there is evidence that persisting symptoms and long-term sequelae are also common in healthy adults with mild courses (60, 63, 65).

Only few studies evaluated pulmonary impairment after COVID-19 in competitive athletes so far (26, 40) and little is known about potential long-term consequences in highly trained athletes with COVID-19. Therefore, this study aimed to examine whether athletes after COVID-19 show a reduction in lung functioning, with special focus on diffusion capacity after infection. Additionally, long-term differences depending on the severity of symptoms during the infection and at time of the examination were studied.

Methods

Study Population

Inclusion Criteria

Athletes aged ≥18 years with a past SARS-CoV-2 infection were included. As proof of infection 1) positive SARS-CoV-2 PCR, or 2) Antibody detection against SARS-CoV-2 with typical symptoms was accepted. Athletes were defined by exercising at least three times per week with a metabolic equivalent >20 hours/week (e.g. cycling with 20 km/h = 7.1 metabolic equivalents (22)). As a control group highly trained national and international athletes, aged ≥14 years, without SARS-CoV-2 infection were included (figure 1). In both groups athletes with a positive SARS-CoV-2 PCR within the last two weeks, insufficient German language skills, refusal of venous blood collection and diseases (acute and chronic) that did not allow admission as estimated by the study physician were excluded (51).

Recruitment

Patients were primarily recruited while attending physical examination after COVID-19 for evaluation of their exercise capacity and physical resilience in the Department of Sports and Rehabilitation Medicine, University Ulm (488 meters above sea level), during November 2020 and January 2022. Some patients were enrolled as a part of the COSMO-S study (51). Subjects of the control group were recruited during presentation for the annual routine check-up.

Ethical Approval

All participating athletes took part voluntarily and gave informed consent prior to inclusion. The study was performed in accordance with the Declaration of Helsinki. The study was approved by the ethics committee of Ulm University (EK 408/20).

Measurements

Spirometry and diffusion capacity were determined with a whole-body plethysmograph (COSMED, Italy). Total lung volume (TLC), forced vital capacity (FVC), forced expiratory volume in one second (FEV1), the ratio of FEV1/FVC, diffusion capacity of carbon monoxide (DLCO), alveolar volume (VA) and Krogh-Index K (DLCO/VA) were assessed and examined. Individual results were compared to predicted values adjusted for hemoglobin from capillary blood gas analysis. A cut-off was set at 80% of individual predicted value, values >80% were defined as normal range (18, 36, 41, 57). In addition, a cut off was set at the 5th percentile, representing the lower limit of normal (58).

COVID-19 symptoms were assessed by a standardized medical history questionnaire, which was supplemented by the CFS Score according to the Canadian Consensus Criteria (24).

Subgroups

For statistical analysis, subgroups were formed based on the presence of dyspnea (during infection and at time of examination). Since dyspnea is associated with at least a moderate course and has already been discussed as a predictor for long-lasting symptoms (12, 48, 67). Persistent dyspnea could indicate fibrotic remodeling of the lungs. Furthermore, subgroups were formed based on the time period between infection with SARS-CoV-2 and enrolment in our study. The division into time periods was carried out in accordance with the National Institute for Health and Care Excellence (NICE) statement (40). Two different groups were defined: time between illness and examination 4-12 weeks or >12 weeks.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics Version 28.0 (Armonk, NY, USA). Normal distribution of the data was verified by Kolmogorov-Smirnov test. Group comparisons were evaluated by independent-sample two-tailed t tests. If data was not normally distributed Mann-Whitney-U-Tests were performed. Chi^2 tests were conducted for comparison of proportions. All data are presented as Mean±Standard deviation (SD). A p≤0.05 was assumed to be significant.

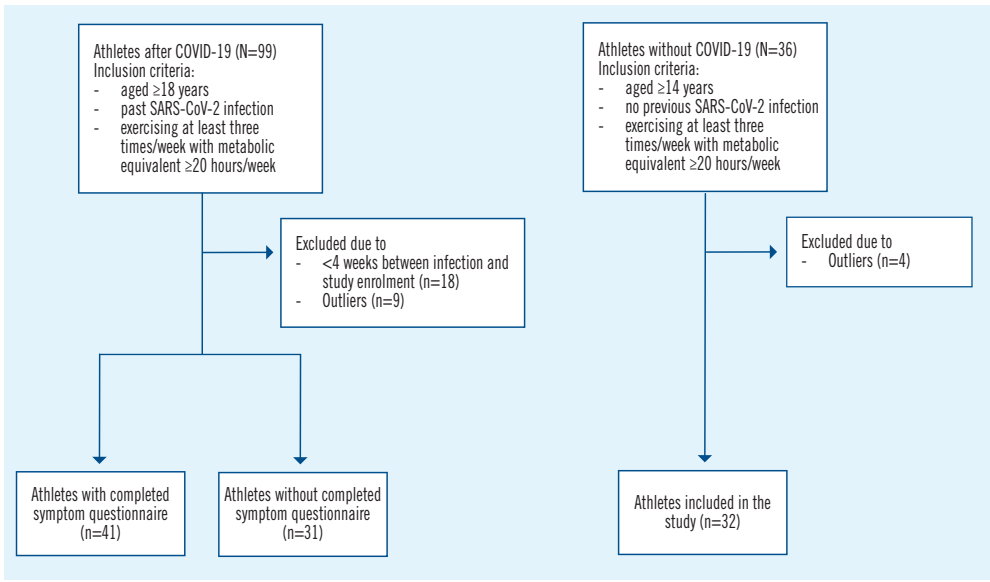

Figure 1

Flow Chart and Inclusion criteria.

Results

Characteristics of the Study Population

99 athletes with a SARS-CoV-2 infection (158±137 days after infection) participated in the study. 18 participants were excluded due to less than four weeks between measurement and infection or missing information about the date of infection. 9 outliers were excluded (figure 1). 41 participants completed the symptom questionnaire. One participant was hospitalized during infection. 36 controls without COVID-19 were enrolled into the study. 4 outliers were excluded. The characteristics of the study population are summarized in table 1.

Symptoms

All athletes reported at least two COVID-19 associated symptoms during infection. The largest number of reported symptoms during COVID-19 in athletes were headache (81%), cough (78%), coryza (73%), sore throat (71%), loss of taste/smell (71%), exertional dyspnea (51%), fever (46%), resting dyspnea (34%) and diarrhea (31%) (figure 2).

At the time of examination, 55% of post COVID-19 athletes reported at least 1 persisting symptom. 42.5% reported more than 2 persisting symptoms. The most reported symptoms were limited performance (44%), concentration problems (40%), sleep disturbances (34%), mood changes (27%), exertional dyspnea (27%) and dizziness (27%) (figure 3).

Lung Function

Table 4 (see supplemental material online) represents results of pulmonary function test between athletes after COVID-19 and controls. Significant differences in FVC (p<0.01) and FEV1 (p<0.01) were observed. The athletes after COVID-19 reached an average 98% of their predicted FVC, respectively 95% of FEV1. The number of participants with less than 80% of predicted value did not differ between the two groups. Comparable results were found with a Cutoff at the 5th percentile (see table 5 and 6, supplemental material online). Around one third of participants in both groups showed a DLCO below the normal range (DLCO< 80% of predicted value; table 4). The average oxygen saturation in athletes after COVID-19 was 97.67±4,02% and the average capillary pO_2 was 76.16±8.83 mmHg in rest. The average capillary pO_2 in controls was 70.07±16.39 mmHg in rest, the difference was not significant (Mann-Whitney-U-Test, p=0.27). However, the lower pCO_2 after COVID-19 indicates some degree of hyperventilation.

21 athletes after COVID-19 reported that they had dyspnea during infection, compared to 11 at time of examination (table 2). Athletes with dyspnea during infection showed a significantly reduced DLCO compared to athletes without dyspnea (p<0.05) and more frequently a DLCO below the normal range, although not statistically significant (p=0.12).

There was no significant difference resting pO_2 between the two groups (Dyspnea during infection: 77.65±7.36; No Dyspnea during infection: 75.18±7.75; p=0.34) and resting sO_2 (Dyspnea: 98.13±2.56; No Dyspnea: 97.5±5.83; p=0.53 (Mann-Whitney-U-Test)). There was no significant difference between athletes after COVID-19 with reported dyspnea at the time of examination and those who have not reported dyspnea in parameters of diffusion capacity. Athletes with dyspnea during examination showed a slightly reduced DLCO (p=0.10, table 2). There was no significant difference resting pO2 between the two groups (Dyspnea during examination: 76.45±8.23; No Dyspnea during examination: 76.45±7.39; p=0.99) and in rest sO_2 (Dyspnea: 98.25±2.66; No Dyspnea: 97.67±4.93; p=0.76 (Mann-Whitney-U-Test)).

There were no significant differences in lung function between the different time periods defined as time between infection and examination in our outpatient clinic (table 3).

Discussion

The ongoing pandemic is leading to an enlarging number of COVID-19 survivors. Increasing evidence suggests a reduction in diffusion parameters after SARS-CoV-2 infection persisting for months (7, 13, 52, 55, 62, 69). To the best of our knowledge, there are currently no data available about long-term sequalae of COVID-19 regarding lung function variables in athletes.

Significant differences between controls and athletes after COVID-19 were shown in FVC and FEV1, but the athletes after COVID-19 achieved an average of 98%, respectively 95% of their individual target. In comparison, participants of the control group achieved an average of 107% and 104%, respectively. Higher values in lung functioning parameters are often observed in athletes (15, 38, 53), therefore it remains unclear whether the significant difference is driven by a decrease in athletes after COVID-19 or an increase in controls. In addition, group ›

Table 2

Comparison of pulmonary function test between athletes after COVID-19 with dyspnea and athletes without dyspnea, during the infection (left columns) and at the time of the examination (right columns). DLCO=diffusion capacity for carbon monoxide; FVC=forced vital capacity; FEV1=forced expiratory volume at 1s; VA=alveolar volume; TLC=total lung volume, pred=predicted value; [a]=Chi²-test; [b]=t-test.

	DURING INFECTION					AT TIME OF EXAMINATION				
	ATHLETES AFTER COVID-19 WITH DYSPNEA (N=21)		ATHLETES AFTER COVID-19 WITHOUT DYSPNEA (N=20)			ATHLETES AFTER COVID-19 WITH DYSPNEA (N=11)		ATHLETES AFTER COVID-19 WITHOUT DYSPNEA (N=30)		
	N (%)	M (SD)	N (%)	M (SD)	P	N (%)	M (SD)	N (%)	M (SD)	P
DLCO <80% of pred	9 (42%)		4 (20%)		0.12[a]	5 (45%)		8 (27%)		0.25[a]
VA <80% of pred	2 (10%)		2 (10%)		0.96[a]	1 (9%)		3 (10%)		0.93[a]
DLCO/VA <80% of pred	6 (29%)		4 (20%)		0.52[a]	2 (18%)		8 (27%)		0.57[a]
FVC <80% of pred	1 (5%)		0 (0%)		0,32[a]	0 (0%)		1 (3%)		0.54[a]
FEV1 <80% of pred	5 (24%)		4 (20%)		0.77[a]	2 (18%)		7 (23%)		0.72[a]
DLCO (% of pred)		0.82 (0.15)		0.91 (0.12)	0.04[b]		0.80 (0.13)		0.88 (0.14)	0.10[b]
VA (% of pred)		0.91 (0.09)		0.96 (0.11)	0.08[b]		0.89 (0.09)		0.95 (0.10)	0.16[b]
DLCO/VA		4.66 (0.62)		4.78 (0.69)	0.83[c]		4.62 (0.45)		4.76 (0.71)	0.47[b]
FVC (% of pred)		0.94 (0.11)		0.99 (0.12)	0.14[b]		0.92 (0.11)		0.99 (0.11)	0.13[b]
TLC (dlco) (% of pred)		0.91 (0.09)		0.97 (0.10)	0.07[b]		0.90 (0.09)		0.95 (0.10)	0.17[b]
FEV1/FVC%		0.81 (0.08)		0.79 (0.07)	0.33[b]		0.82 (0.09)		0.79 (0.06)	0.21[b]
FEV1 (% of pred)		0.92 (0.12)		0.95 (0.14)	0.42[b]		0.91 (0.13)		0.94 (0.13)	0.51[b]

differences (age, amount of training hours per week) could be partly responsible for the significant differences.

All participating athletes reported symptoms during COVID-19. Most common symptoms were headache, cough, coryza, sore throat and loss of taste/smell. The common reported symptoms are comparable to previous research (42), although the frequencies in this study were higher. Accordingly half of athletes reported exertional dyspnea during infection compared to 10% in previous research (42) (cough: 78% of athletes compared to 28% (42)). Furthermore, in contrast to our study previous research has shown a higher proportion of asymptomatic courses in athletes (33%) (42).

Persisting exertional dyspnea at the time of examination was reported by 27% of participants. The most reported symptoms at the time of examination were reduced performance ability (44%) and concentration problems (40%). These findings are consistent with previous research. It has already been shown that between two to seven months after infection shortness of breath (8-21%), fatigue (14-30%), myalgia (6,3-17%) and memory problems (16%) were frequently reported in outpatients (10, 19, 25, 34, 46).

Dyspnea during infection had already been identified as a predictor for ongoing symptoms after SARS-CoV-2 infection (12, 59, 67). Consistent with previous research, we were able to show a significant reduction of DLCO five months after COVID-19 in athletes with dyspnea during their infection. 42% of these athletes showed a DLCO below the normal range (DLCO<80% of predicted value). These effects were more pronounced in women than in men, although the group sizes were quite small. A reduced DLCO with slightly reduced DLCO/VA could be explained through vascular or interstitial changes of the lung (4), since both were found in post-mortem examinations of COVID-19 death victims (33, 68).

Lung membrane alterations (thickening) could a main contributing factor in diffusion capacity of the lung. However, in lung biopsies of COVID-19 survivors without residual symptoms the lung parenchyma was not involved (14). Other possible causes for the observed changes can be structural or function alterations of erythrocytes (28) and / or the pulmonary vascular volume.

Despite the reduction in diffusion capacity in athletes after COVID-19 with dyspnea, no reduction in resting oxygen saturation and oxygen partial pressure in capillary blood gas analysis could be demonstrated despite hyperventilation. Gas exchange in rest was normal in COVID-19 patients after intensive care unit treatment (13, 31), but this may be expected, as during resting conditions, the gas exchange capacity is not stressed. A first study suggests a decrease of pO_2 upon exercise in patients with mild COVID-19 course and mild DLCO impairment at rest (43). Therefore, measuring pO_2 during exercise in athletes after COVID-19 should be considered in further research.

Dyspnea at the time of examination was also associated with a reduction of DLCO below the normal range in 45% of participants. They reached on average 80% of their individual predicted value, but due to a small number of participants (n=11), the level of significance could not be reached (p=0.10). Further research with more participants is needed to clarify whether long lasting dyspnea is associated with a reduced diffusion capacity of the lung or if other mechanisms are involved.

There were no significant differences between athletes examined more than 12 weeks post infection and athletes with 4-12 weeks between infection and examination. Nevertheless, previous research indicates a recovery of DLCO over time (57), especially for patients that are involved in a pulmonary rehabilitation program (32). Therefore, further monitoring of the participants and evaluation over time is in progress.

Restrictions in lung function are particularly relevant for highly trained athletes in everyday life, as these restrictions lead to a reduced athletic performance and a forced break, which could be associated with a reduced quality of life. Actual recommendations for the return to sports after COVID-19 are based on the presence of symptoms, pneumonia and myocarditis (50). Measurement of diffusion parameters should be especially recommended in athletes with dyspnea, to be able to make individual training recommendations and avoid potential long-term

consequences like the development of persisting lung fibrosis and right-heart load (50). Surprisingly, the age-adjusted standard values of the pO_2 in the capillary BGA were not reached in the control group. Therefor no explanation could be found.

Limitations

This study has several limitations. 1. There is no information regarding lung functioning before infection, pre-therapy, infection therapy or comorbidities. Therefore, confounders cannot be ruled out. Further longitudinal studies should be conducted. 2. The study population was quite heterogeneous (e.g., training hours per week, strength and endurance athletes, large variation in the time differences between infection and examination, age). 3. The sample size was quite small as only 41 patients completed the whole procedure and therefore sample selection cannot be ruled out. A larger sample size would be preferable. 4. Selection Bias: Athletes after COVID-19 were recruited attending physical examination after COVID-19 for evaluation of their exercise capacity and physical resilience. Athletes with symptoms might have been more likely to attend physical examination after COVID-19 than asymptomatic individuals. 5. Athletes after COVID-19 were on average almost ten years older than controls, so age may have an influence.

Conclusion

This study demonstrated that many athletes with mild course of infection still suffer from long term sequalae of COVID-19 many weeks after infection (e.g., limited performance, concentration problems and exertional dyspnea). Follow-up care before return to sports after COVID-19 should be considered especially in athletes with dyspnea, due to higher prevalence of reduced DLCO and potential negative long-term consequences. Current recommendations advise to start slowly with light physical activity after COVID-19 and then gradually build in strength training (23). First studies indicate an improvement through structured rehabilitation in elderly (32) (e.g., respiratory muscle training, diaphragmatic training, stretching exercises) but further investigations, especially in athletes, are needed.

Conflict of Interest
The authors have no conflict of interest.

Clinical Trial
Clinical trial has been registered: 00023717 (DRKS)

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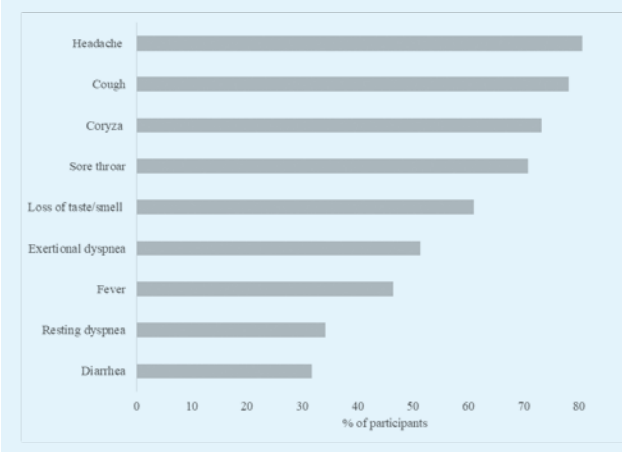

Figure 2
Reported symptoms of athletes during COVID-19.

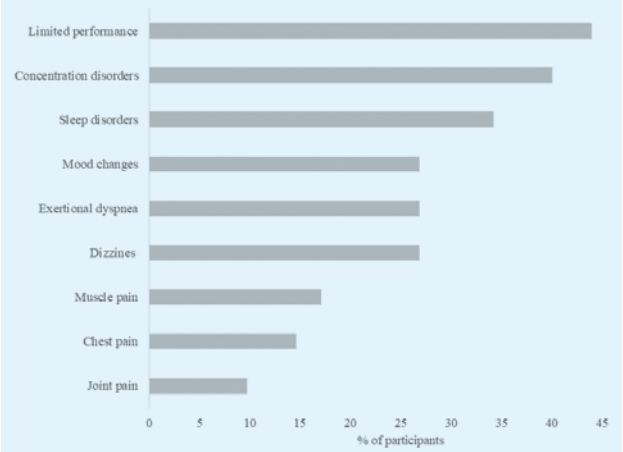

Figure 3
Reported symptoms of athletes after COVID-19.

Table 3
Comparison of pulmonary function test between athletes depending on the time between infection and examination. DLCO=diffusion capacity for carbon monoxide; FVC=forced vital capacity; FEV1=forced expiratory volume at 1s; VA=alveolar volume; TLC=total lung volume, pred=predicted value; b=t-test; c=Mann-Whitney-U-Test.

	4-12 WEEKS (N=28)		>12 WEEKS (N=44)		
	M	SD	M	SD	P
DLCO (% of pred)	0.89	0.14	0.83	0.15	0.12[b]
VA (% of pred)	0.95	0.13	0.92	0.11	0.28[b]
DLCO/VA	4.80	0.71	4.62	0.80	0.35[b]
FVC (% of pred)	1.00	0.14	0.96	0.11	0.13[c]
TLC	0.96	0.12	0.93	0.10	0.25[b]
FEV1/FVC%	0.80	0.07	0.80	0.07	0.92[b]
FEV1 (% of pred)	0.96	0.13	0.94	0.14	0.29[c]

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