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RESEARCH ARTICLE

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Quantifying the impact of post-acute sequelae of coronavirus on the cardiopulmonary endurance of athletes

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Abstract

Post-acute sequelae of Coronavirus (PASC), or Long COVID, has emerged as a critical health concern. The clinical manifestations of PASC have been described, but studies have not quantified the cardiopulmonary effects. The goal of this study was to quantify PASC cardiopulmonary changes among endurance athletes. Endurance athletes were recruited via social media; 45 met inclusion criteria, 32 had PASC and 13 were asymptomatic at 3 months (control). Comprehensive interviews were conducted to assess: cardiopulmonary symptoms at 3 months; quantitative and qualitative changes in cardiovascular endurance; exercise hours per week at baseline and 3 months; and Modified Oslo, Dyspnea, and EQ-5D-5L scales. All collected data was based on self-reported symptoms. Wilcoxon rank sum compared PASC with control to distinguish the effects of PASC vs effects of COVID infection/lockdown. PASC subjects were more likely to be female (Table). The most common 3-month symptoms in PASC were fatigue and shortness of breath. Based on self-reported data, subjects endorsed a median decrease of 27% in cardiopulmonary endurance levels compared with 0% in controls ($p = 0.0019$). PASC subjects exercised less hours and had worse self-reported health as compared with controls. PASC subjects also had significantly worse Modified Oslo, Dyspnea, and EQ-5D-5L scores. Of the 32 PASC patients, 10 (31%) reported a complete inability to engage in any cardiovascular endurance exercise at 3 months. PASC leads to a significant, quantifiable decrease in cardiopulmonary health and endurance.

KEYWORDS
cardiopulmonary health, endurance, long Covid, PASC

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has severely impacted healthcare around the world. Although the acute phase pulmonary and extrapulmonary symptoms are well described, the long-term effects of COVID-19, also known as post-acute sequalae of SARS-COV-2 infection (PASC), are only starting to be understood. According to the World Health Organization, PASC is

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defined as the persistence of symptoms 3 months from the onset of COVID-19, with symptoms that last for at least 2 months and cannot be explained by an alternate diagnosis.[1]

The underlying pathogenesis of PASC is not well understood. Potential mechanisms include virus specific pathophysiologic changes, immunologic aberrations, and inflammatory damage in response to the acute infection.[2] Mechanisms for lasting cardiopulmonary impairment following acute COVID-19 also require further investigation. Some investigators hypothesize that PASC-related heart dysfunction is a result of chronic inflammation evoked by viral reservoirs following acute infection, leading to chronic tissue damage and impaired myocardial function.[3] Another proposed mechanism is a prolonged autoimmune response to COVID-19 antigens, leading to molecular mimicry, resulting in sustained myocardial inflammation.[4] Investigators have also proposed neurohormonal activation, stress mediated responses, and acute direct injury to ACE2-receptors leading to tissue damage as potential contributors underlying PASC symptoms.[5] Similarly, a variety of mechanistic drivers of pulmonary vascular dysfunction among PASC patients have been proposed, including but not limited to host factors, metabolic and inflammatory changes to the vascular smooth muscle and intima post-viral insult, and alterations to the surrounding matrix.[6]

A recent review examining 194 studies showed that 45% of COVID-19 survivors experienced a range of unresolved cardiopulmonary and other symptoms at 4 months. The symptoms of PASC can vary widely and most commonly affect the respiratory, cardiovascular, gastrointestinal, and nervous systems. Systematic reviews have reported common clinical manifestations such as fatigue (31%), dyspnea (25%), weakness (41%), reduced quality of life (37%), and general malaise (33%) in patients with PASC.[7]

While PASC has emerged as a critical health concern, and its clinical manifestations have been well described, studies have not yet been able to quantify its cardiopulmonary effects. A lack of baseline testing, particularly baseline treadmill testing, or a matched control arm limits understanding of the prevalence of cardiopulmonary symptomatology among those with PASC. Studying athletes allows an internal control of background cardiopulmonary symptoms and performance, given that many athletes keep detailed performance records. We hypothesized that athletes with PASC would have frequent cardiopulmonary symptoms and quantifiable reduction in both exercise performance and athlete-reported outcomes regarding quality of life compared to post-COVID athletes who did not develop PASC.

METHODS

Enrollment

Athletes ≥18 years old were recruited via social media platforms (Twitter and Facebook) and advertisements in various clinics at Vanderbilt University Medical Center. Inclusion criteria were: 1) prior history of COVID-19; 2) endurance athletes, defined as those participating in greater than 6 h of intense aerobic activity per week (including badminton, basketball, boxing, canoeing/kayaking, cross-country skiing, cycling, decathlon, field hockey, handball, ice hockey, lacrosse, orienteering, race walking, racquetball/squash, rowing, running, soccer, speed skating, swimming, tennis, triathlon, and CrossFit). This population was felt to be the most likely to have quantifiable measures of their performance/endurance, which would allow direct comparison of cardiopulmonary symptoms before and after PASC. Athletes were excluded if diagnosed with COVID-19 within 3 months, as this would not allow assessment of PASC. After enrollment, athletes were assigned a diagnosis of PASC or no-PASC based on their responses to the survey questions and the published definition. A total of 296 patients were initially recruited via social media. A total of 104 patients ultimately began but did not complete the consent document associated with participation in the study and a total of 72 participants did not proceed to complete the screening survey (Supporting Information S1: Data S1); 75 did not meet inclusion/exclusion criteria, with the most common exclusion due to athletes not meeting the requirement of 6 h of activity per week before SARS-CoV-2 infection. Ultimately 45 patients were included in the study (Figure 1). This study was approved by the Vanderbilt Institutional Review Board, IRB# 210720. Informed consent was obtained from all individual participants included in the study.

Data collection

Once recruited, athletes underwent comprehensive telephone interviews to assess baseline cardiopulmonary status and symptoms at 1- and 3- months post-COVID. This included a comprehensive assessment of symptoms, including fatigue, shortness of breath, difficulty breathing, chest pain, palpitations, tachycardia, myalgias (see Supporting Information S1: Data S1 for full list of questions performed at baseline). Athletes were asked to document their weekly exercise hours. In addition, athletes indicated qualitative changes in their cardiovascular endurance at baseline

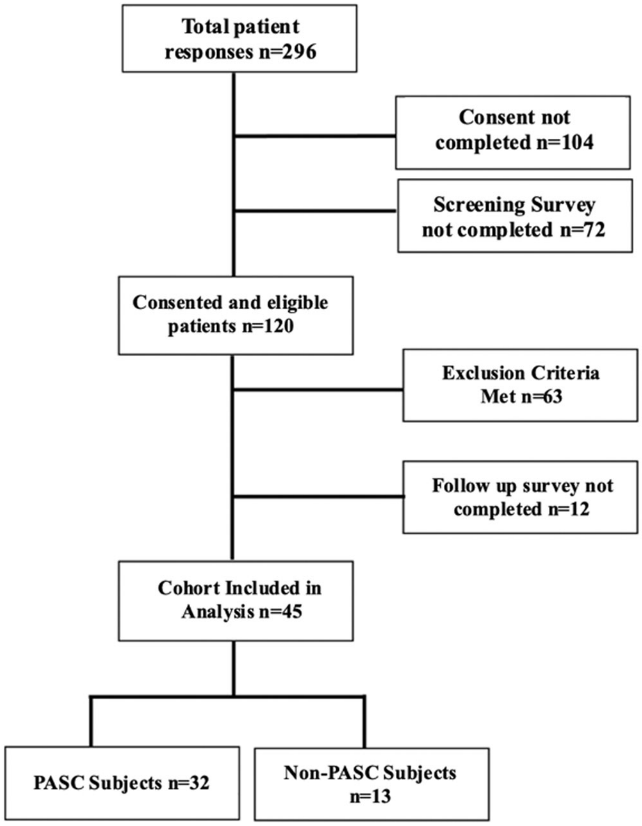

FIGURE 1 Flow chart of study identification, inclusion, and exclusion criteria.

compared to at 3 months following COVID diagnosis. When asked to quantify their own ability to engage in aerobic activity, subjects were asked to indicate which aerobic activity they most frequently participated in and provide a numerical measure that could be tracked at 3 months as compared to baseline. Examples included time it took to run a mile, CrossFit output, swimming times, marathon times, and cycling times. For example, an athlete with PASC noted that before their COVID-19 diagnosis they were able to consistently run a mile in 6 min, but the same athlete reported 7 min as their fastest mile time 3 months after SARS-CoV-2 infection. This was recorded as a 15.3% decrease in endurance performance.

In addition, athletes completed three validated questionnaires to further quantify the degree of symptomatic change at 3 months from baseline. The three scales included were the Modified Oslo Scale (Modified Oslo), Modified British Medical Research Council Dyspnea Scale (Dyspnea Scale), and the 5 level version of the EuroQol 5 dimension scale (EQ-5D-5L) (Supporting Information S1: Data S1).[8–10] The Modified Oslo scale consists of four questions that capture the burden of sport-related health problems using standard sports injury data collection. The Dyspnea Scale, used to stratify the severity of dyspnea in respiratory distress, is scored out of 5 points. Lastly, athletes were asked to complete the EQ-5D-5L scale, a widely used tool to measure health related quality of life. The scale focuses on mobility, quality of life, daily activities, pain and discomfort, anxiety and depression, and self-related health. The EQ-5D-5L values were then indexed based on values published for the United States, with a value of 1 being full health and values less than 1 representing decreased health. The EQ-VAS was also assessed, where a sliding scale is presented to the subject with "100" representing the best imaginable health and "0" the worst imaginable health.

Twelve monthly follow up questionnaires were emailed to participants asking if symptoms had changed since the prior survey. If symptoms had changed, more detailed questions were asked to discern how the symptoms had changed. Finally, participants filled out a comprehensive survey 1-year post entry in the study.

Statistical analysis

Demographic variables were compared using either a Wilcoxon rank-sum (continuous variables) or a Chi-square or Fisher's exact test (categorical variables). A Wilcoxon Rank Sum was used to evaluate the difference in continuous variables between groups and a Chi-square or Chi-square for trend were used to evaluate differences in categorical and ordinal variables between groups. Analyses were performed using STATA SE 15.1 (StataCorp). Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Vanderbilt.

RESULTS

Thirty-two athletes met criteria for PASC and 13 athletes did not (Table 1). The average age for PASC athletes was 34.5 years old (y/o), while the average age of Non-PASC athletes was 29 years. There was no significant difference between the distribution of athlete's races between the groups. Between the two groups there were significantly more females in the PASC group as compared to the Non-PASC group.

The three most common symptoms following infection at any time in both groups were fatigue, shortness of breath, and muscle aches (Table 2). At 3-months, the most common symptoms in the PASC group were fatigue (69%) and shortness of breath (63%). In addition, over

TABLE 1 Control and post-acute sequalae of SARS-COV-2 infection demographics.

	PASC Athletes *N*=32	Non-PASC Athletes *N*=13	p-value
Age (mean)	34.5 (23.5, 40)	29 (22, 32)	0.35
Race			
White	30 (93.8%)	12 (92%)	0.45
Black	1 (3.1%)	1 (8%)	
Asian	1 (3.1%)	0	
Gender			
Male	8 (25%)	10 (77%)	0.001
Female	24 (75%)	3 (23%)	
COVID-19 Diagnosis			
Nasal swab	28 (87.5%)	12 (92%)	0.74
Blood test	3 (9.4%)	1 (8%)	
No-testing (symptoms c/w COVID-19)	0	0	
Positive testing but cannot remember what type	1 (3.1%)	0	

TABLE 2 Self-reported cardiopulmonary symptoms.

	PASC		Non-PASC	
Symptoms	At Any Time (Diagnosis - 3 Months)	At 3 Months	At Any Time (Diagnosis – 3 Months)	At 3 Months
Fatigue	100%	69%	92%	0%
SOB	65%	63%	54%	0%
Difficulty Breathing	44%	9%	31%	0%
Chest Pain	40%	34%	15%	0%
Palpitations	47%	25%	15%	0%
Tachycardia	46%	44%	15%	0%
Muscle Aches	78%	13%	77%	0%

30% of PASC subjects endorsed chest pain and over 40% endorsed tachycardia. As expected, Non-PASC subjects did not endorse any symptoms at 3 months following acute infection.

PASC subjects exercised fewer hours than non-PASC subjects at 3-months post COVID ($p = 0.003$) (Table 3). Of note, while non-PASC subjects continued to exercise over 6 h each week, 14/32 (44%) of PASC subjects reported less than 3 h of exercise per week. Of the 32 PASC subjects, 10 (31%) reported a complete inability to engage in any cardiovascular endurance exercise at 3 months. Overall, PASC subjects endorsed a median decrease of 27% in cardiopulmonary endurance levels compared with 0% in controls ($p = 0.0019$).

There was a significant difference in scores for the Modified Oslo, Dyspnea, and 5Q-5D-5L scales between PASC and non-PASC subjects (Table 3). On the Modified Oslo, the median score of PASC subjects was 43.5, as

TABLE 3 Quantitative symptomatic change from baseline.

		PASC Athletes N=32	Non-PASC Athletes N=13	p-value
Activity Hours/Week 3 Months Post COVID Diagnosis		4–5 h (2–3,>6)	>6 h (>6,>6)	0.003
Athlete Reported Difference in Quantifiable Endurance Levels (%)		0.73 (0,0.89)	1 (1,1)	0.0019
Modified Oslo Severity Scores		43.5 (3,61)	0 (0,0)	0.0071
Dyspnea Scale		2 (1,2)	1 (1,1)	0.003
EQ-5D-5L Scale	*EQ Index Questionnaire Score*	80 (66,85)	90 (80,92)	0.07
	EQVAS Self-Reported change from baseline	−3.5 (−5, −2)	0 (−1,5)	0.0032

compared to 0 in non-PASC subjects ($p = 0.0071$). On the Dyspnea Scale sixteen PASC subjects (50%) reported getting short of breath when hurrying or walking up a slight hill, and 4/32 (12.5%) reported walking more slowly than people on flat ground because of breathlessness. In total, the median score for PASC subjects was 2 points on the scale, as compared to the Non-PASC group, whose median was 1 point ($p = 0.003$). On the 5Q-5D-5L scale, PASC subjects reported less exercise hours and had worse self-reported health as compared with controls. PASC subjects reported worse but not statistically significant scores on the EQ Index with a median score of 80 as compared to a median score of 90 in Non-PASC athletes ($p = 0.07$). Lastly, PASC subjects also reported significantly lower scores on the EQVAS self-reported change from baseline as compared to non-PASC patients ($p = 0.0032$).

DISCUSSION

This study was the first of which we are aware to use self-reported patient symptoms in an attempt to quantify the impact of PASC on athletes' endurance and exercise levels. The results of our study suggests that PASC leads to a significant, quantifiable decrease in self-reported cardiopulmonary health and endurance.

As expected, the PASC group reported a significant symptom burden compared with the non-PASC group, with fatigue, chest pain, and SOB as the most common reported symptoms. These findings are consistent with previous reports in the literature that have attempted to gauge the prolonged symptom burden following acute infection. In a retrospective observational study of patients 6 months following hospitalization with PCR confirmed SARS-COV-2, 5.8% of patients reported presence of sequelae or persistent cardiovascular symptomatology with 3.1% reporting arrythmia or palpitations and 2.9% reporting syncope.[11] Carvalho-Schneider et al. performed a descriptive clinical follow up of 150 patients following PCR infection and found chest pain to be persistent in 13.1% of patients on day 60 from infection, with 10.9% experiencing palpitations and 7.7% experiencing shortness of breath.[12] Additionally, in a prospective, case-control study based out of the UK with over 4000 patients, and an average duration of reporting of 180 days following a positive COVID-19 test, 16.3% reported chest pain and 7.2% self-reported irregular heartrate.[13] The lower prevalence in these studies is due to the selection criteria and these studies are likely suboptimal comparators for our study, which sought to determine the prevalence and severity of symptoms in patients with PASC. Indeed, the numbers from our study are more comparable to those focused on patients with PASC. In an observational study of 126 patients presenting to a comprehensive post-COVID center at Yale at a mean follow up of 5 months, Wang et al. reported up to 30% of patients reporting three or more cardiovascular symptoms (dyspnea, chest pain, fatigue), with up 48% of patients reporting persistent chest pain.[14] A similar retrospective analysis of patients presenting to a Post-COVID cardiology clinic at Washington University at an average of 90 days following initial diagnosis reported a range of symptoms with 66% of patients reporting persistent chest pains, 59% with palpitations, and 56% with dyspnea on exertion.[15]

Along with demonstrating a high symptomatic burden, our study revealed that PASC subjects have issues with mobility, self-care, an impaired ability to engage in their usual activities and, in some cases, are prevented from participating in sports and exercise entirely. Furthermore, across multiple activities, PASC athletes reported an overall 25% decrease in cardiopulmonary endurance as compared to baseline, with 30% unable to participate in any activities. This finding shows that the true impact of PASC on athletes may be underestimated, and that some athletes may suffer extremely debilitating effects. In addition to the negative effects on an athlete's quality of life, persistent symptoms associated with PASC may contribute to the significant burden of anxiety and depression that is often seen concurrently with the disease.[16] This symptom persistence also places a significant burden on the healthcare system with frequent follow up appointments, increased hospital admissions, and further athlete de-conditioning.[17]

We are unaware of other studies quantifying the effects of PASC, but prior studies have evaluated symptoms in patients with PASC and have demonstrated similar changes in the scoring systems analyzed as part of this manuscript. Mastrorosa used the EQ-5D-3L but used only EQ-VAS score, demonstrating decreased health when compared with normative data in Italy.[18] Tak used the EQ-5D-5L and demonstrated low indexed and EQ-VAS values in patients with PASC, though they did not compare the responses to a control group.[19] Ahmad also evaluated the EQ-5D-5L and the dyspnea scale in patients after COVID-19 and found that hospitalized patients were more likely to have worse scores for the categories of "usual activities" and "pain and discomfort," as well as worse EQ-VAS scores.[20] They also found higher scores on the dyspnea scale. Similarly, Huang demonstrated that patients with more severe acute illness had worse scores on the Dyspnea Scale.[21] That group also demonstrated worse EQ-5D-5L scores for athletes with PASC for "mobility," "pain or discomfort," and "anxiety or depression." In comparison to these studies, our data demonstrated a lower indexed EQ-5D-5L, worse dyspnea scores, and a lower EQ-VAS in athletes with PASC, though the latter did not reach statistical significance.

Limitations

While over 250 athletes initially responded to the study, only 45 completed consent, all study materials, and met inclusion criteria (as seen in Figure 1). Unfortunately, as there was no way to contact the respondents who did not complete these sections, it is unclear why a large percentage chose not to proceed. Although the sample size is small, we believe that the novel findings regarding PASC severity warrant reporting and advance our current understanding of the disease's impact on our athletes. The methods used in this study, while quantifiable, relied on patient-recall. Objective methods before and after SARS-CoV-2 infection would provide the optimal assessment of PASC, but these are unavailable. In addition, while patient enrollment via social media allows for broad geographic recruitment, there is inherent selection bias, with younger athletes and athletes with more severe disease likely to respond. This selection bias may have led to an increase in the severity of symptoms in athletes with PASC. There was also a lower than expected response rate, with many respondents not completing the initial consent or screening form; unfortunately, as there was no way to contact the respondents who did not complete these sections, it is unclear why a large percentage chose not to proceed. Furthermore, primarily subjective, self-reported data used in data analysis could lead to reporting bias and make distinguishing between cardiopulmonary versus potential psychological limitations to activity more difficult. Future studies using objective testing such as cardiopulmonary exercise testing would allow for more concrete physiologic measurements of cardiopulmonary endurance, but these are difficult to obtain before and after SARS-CoV-2 infection and even more difficult to obtain in patients who eventually develop PASC.

Our data analysis occurred between 2021 and 2022, during the COVID pandemic. To maximize generalizability, we included all athletes 18 years old or older, which includes a range of athlete participation (college athletes, master athletes, etc.). With ever-changing contact and quarantine guidelines, shelter in place policies, and business closures, there is possibility that inherent deconditioning due to lack of access to exercise facilities and a prolonged time spent at home without exercise could have impacted our participants conditioning levels. We believe that the possible deconditioning was controlled for by including a control group after SARS-CoV-2 infection without PASC; there were multiple statistically significant differences between groups across several validated scales. Lastly, endurance athletes may not be representative of society as a whole, as they may recover more quickly from PASC or be more sensitive to its impacts. Future investigations comparing athletes to non-athletes with PASC will be necessary to understand similarities and differences in response to PASC.

CONCLUSION

This study is the first to report the quantifiable, persistent cardio-pulmonary impacts of PASC on endurance athletes long after an initial acute COVID diagnosis. PASC not only leads to a significant symptomatic burden for several months following acute infection, but also impacts athletes' ability to engage in exercise as a whole, leads to worse dyspnea with everyday activities, and impairs athletes' 'mobility and ability to engage in usual activities such as work, study, and housework. Nearly one-third of high performing athletes with PASC experienced debilitating symptoms resulting in a complete inability to engage in any cardiovascular endurance exercise at 3 months post-COVID.

AUTHOR CONTRIBUTIONS

All authors have contributed in a significant and meaningful way deserving of authorship. Jonathan H. Soslow, Eric D. Austin, Daniel E. Clark, and Daniel Lubarsky were involved in the conception and design of the study. Jonathan H. Soslow, Eric D. Austin, Kimberly Crum, Ashley Karpinos, Daniel Lubarsky were involved in the conduct of the study, analysis, and interpretation of the results. Daniel Lubarsky, Jonathan H. Soslow, and Eric D. Austin drafted the manuscript and Daniel E. Clark, Kimberly Crum, and Ashley Karpinos critically revised the manuscript. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

This material is the authors' own original work, which has not been previously published elsewhere. The paper is not currently being considered for publication elsewhere. The paper reflects the authors' own research and analysis in a truthful and complete manner. The paper properly credits the meaningful contributions of co-authors and co-researchers. The results are appropriately placed in the context of prior and existing research.

GUARANTOR

Jonathan H. Soslow, Eric D. Austin, Daniel E. Clark are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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