Number of symptoms during the acute phase of SARS-CoV-2 infection in athletes is associated with multi-organ involvement: AWARE III

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The authors have no competing interest to declare.

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ABSTRACT

Objective

Acute respiratory infections (ARinf), including SARS-CoV-2 infection, can affect multiple organ systems which may influence return to sport (RTS) in athletes. Factors associated with multi-organ involvement in athletes with ARinf is lacking. The aim of this study was to explore if factors such as demographics, sport participation, history of comorbidities/allergies and number of acute symptoms, are associated with multi-organ involvement in athletes with recent SARS-CoV-2 infection.

Design

Prospective cohort study with cross-sectional analysis

Setting

Institutional clinical research facilities

Participants

95 Athletes (18-60 years) underwent a comprehensive medical assessment 10-28 days after SARS-CoV-2 infection

Independent factors

Demographics, sport participation, history of comorbidities/allergies and the number of acute symptoms (in three subgroups:1=≤5, 2=6-9, or 3≥10)

Main outcome measure

Number of organs involved in athletes with recent SARS-CoV-2

Results

The number of organ systems involved was not associated with demographics (age, sex), sport participation (level and type), or history of comorbidities and allergies. However, the number of organ systems involved was significantly higher in athletes with 6-9 symptoms (subgroup 2) compared with those with ≤5 (subgroup 1) and this was more pronounced when comparing athletes with ≥10 symptoms (subgroup 3) with those with ≤5 symptoms (subgroup 1) ($p<0.0001$).

Conclusions

Total number of acute symptoms of SARS-CoV-2 infection is related to number of organ systems involved, which is a measure of disease severity, and could therefore influence RTS decision making. Future studies should explore if this observation holds for athletes with ARinf caused by other pathogens.

Keywords

Covid-19, return to sport, assessment, severity, illness, acute respiratory infection

INTRODUCTION

Acute respiratory infections (ARinf) are a common cause of illness in athletes[1 2] with approximately 20% of ARinf resulting in time loss in training or competition.[3] Time loss (number of days lost to training/competition), is the suggested parameter to estimate severity of illness in athletes.[4] The sport and exercise medicine (SEM) physician regularly makes important decisions when athletes can safely return to sport (RTS) after ARinf. RTS after ARinf is a continuum[5] starting with the decision to return to training (RTT), ongoing decisions to progress with training load, and ends with the final decision to return to full performance (RTFP), thus full RTS. An International Olympic Committee (IOC) consensus group recently proposed an algorithm for RTS decisions after ARinf in athletes.[6] The first step is to determine the severity of the infection based on two important parameters: 1) symptom characteristics during the acute phase of the infection, and 2) evidence of multi-organ involvement.[6] Acute symptoms and evidence of multi-organ involvement, are therefore potential tools for the sports physician to determine severity of ARinf.

Early data on symptom characteristics of SARS-CoV-2 infection showed acute symptom clusters/types can influence RTT.[7 8] There is some evidence that, in the general population, ≥5 acute symptoms of SARS-CoV-2 infection is associated with residual "long-COVID".[9] Recent evidence shows that total number of acute symptoms of SARS-CoV-2 infection in athletes is an indicator of both prolonged RTT[10] and RTFP,[11] and is also associated with a greater rating of perceived exertion (RPE) during exercise after recent SARS-CoV-2 infection.[12] These findings collectively suggest that the total number of acute symptoms of SARS-CoV-2 infection in athletes may be an important predictor of more severe illness and prolonged RTS.

SARS-CoV-2 infection was initially regarded primarily as a respiratory disease, but evidence in the general population indicates that multiple organ systems can be affected.[13] In the general population, older age, male sex, high body mass index (BMI) and history of comorbidities are factors associated with greater risk of multi-organ involvement.[14 15] Studies in athletes with SARS-CoV-2 infection, mostly focused on cardiovascular system involvement.[16 17] Data on the frequency of other organ

involvement and factors associated with multi-organ involvement of recent SARS-CoV-2 infection in athletes are few.

The aim of this study was to explore if factors such as demographics, sport participation, history of comorbidities/allergies and number of acute symptoms are associated with multi-organ involvement in athletes with recent SARS-CoV-2 infection. A secondary aim is to describe the frequency (%) of organ system involvement.

METHODS

Study design and setting

This is a prospective cohort study that is part of the **A**thletes **W**ith **A**cute **R**espiratory Inf**E**ctions (AWARE) studies. During the COVID-19 pandemic, the Sport, Exercise Medicine and Lifestyle Institute (SEMLI), at the University of Pretoria, South Africa, established a COVID-19 Recovery Clinic to medically assess athletes with recent SARS-CoV-2 infections. The study was conducted from July 2020 to October 2021. During this period, a 10-14-day period of self-isolation was advised and the most prevalent SARS-CoV-2 variants were the Ancestral virus, Beta and Delta variants.

Study participants

A total of 95 athletes were deemed eligible to participate, fulfilling the inclusion criteria: 1) aged 18-60 years, 2) confirmed SARS-CoV-2 infection (10-28 days since onset of symptoms), 3) competitive athletes (varying participation levels and sport types), and 4) gave written informed consent. Most athletes (94%) were unvaccinated against SARS-CoV-2, as vaccination was rolled out in phases (early 2021) and not accessible to all age groups during the study period.

Data collection

Data were collected by means of an online questionnaire, and during a medical assessment performed by a sport and exercise medicine (SEM) physician (principal investigator).

Demographics and medical history

Athletes completed a standardised online questionnaire,[7] captured on the Research Electronic Data Capture (REDCap) system,[18 19] with the following sections:

Demographics: Age, sex, weight, and height (for BMI calculation).

Sport participation: Level of sport (professional or amateur) participation and type of sport.[20]

History of comorbidities and allergies: History of comorbidities in ten organ systems: cardiovascular disease (CVD) or CVD risk factors, respiratory, nervous, psychological, gastrointestinal, endocrine, renal, immune/blood system, and cancer. History of allergies were also collected.

Acute symptoms: 26 Self-reported symptoms during the acute phase of infection were grouped and recorded by organ system/anatomical region.[7] We also categorized the athletes into three subgroups based on total number of acute symptoms as follows: subgroup 1 (asymptomatic or ≤ 5 acute symptoms), subgroup 2 (6 – 9 acute symptoms), and subgroup 3 (≥ 10 acute symptoms).

Clinical assessment and selected laboratory investigations

The clinical assessment (Supplementary File A) was performed 10-28 days after the onset of symptoms or positive test (asymptomatic athletes) and was divided into:

Residual symptoms: Residual symptoms (categorized by organ system) were documented by CS and defined as those symptoms still present at the time of the medical assessment.

Abnormal clinical signs on physical examination

Abnormal clinical signs were recorded, by organ system (cardiovascular, respiratory, neurological, gastrointestinal, musculoskeletal, immunologic/hematologic, ocular, skin and systemic), during a standardized physical examination.

Laboratory investigations

Laboratory investigations were performed on all athletes and grouped by organ system as follows:

<u>Cardiovascular</u>

Resting electrocardiogram (ECG): A 12-lead resting ECG was performed and exercise-related adaptive changes ('athlete's heart') were considered normal.

Sub-maximal exercise ECG: A sub-maximal exercise test (modified Bruce protocol up to stage 5) were done on all participants after contraindications for exercise were excluded.[21] Interpretation of all ECG findings followed published guidelines[22] and abnormalities were confirmed by a cardiologist (MM).

Resting echocardiogram (ECHO): Transthoracic ECHO evaluation included left ventricular ejection fraction (LVEF),[23] ventricular wall motion abnormalities and pericardial effusions.

High sensitivity cardiac troponin T (hs-cTnT): hs-cTNT was analyzed on venous blood samples.

Cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE): CMR with LGE, was performed on a subset of 65 athletes, regardless of clinical presentation or other cardiac investigations. The main reasons for not conducting CMR on all athletes were: 1) that CMR was not available for research purposes in the early stage of the COVID-19 pandemic, and 2) although CMR was offered to all athletes once it became available, some athletes did not consent to having a CMR performed. CMR findings were reported by 2 radiologists experienced in CMR (LS, ADP). Myocarditis was diagnosed by CMR, based on the modified Lake Louise criteria.[24]

Respiratory

Pulmonary function tests (PFT): Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were recorded at rest. Results below the lower limit of normal (LLN)[25] of calculated values were regarded as abnormal.

Other organ systems

Evidence of other organ system involvement was determined by abnormalities in the following blood tests:

Gastrointestinal: Aspartate transaminases (AST), alanine transaminases (ALT)

Musculoskeletal: Creatine kinase (CK)

Immunologic/hematologic: Total white cell count (WCC), neutrophil/lymphocyte counts and C-Reactive Protein (CRP)

Definition of organ system involvement and calculation of the number of organ systems involved

We defined organ system involvement as the presence of any of the following abnormalities in an organ system: 1) residual symptoms, or 2) abnormal clinical signs on physical examination, or 3) abnormal laboratory investigations at the time of the medical assessment. Organ systems evaluated were: cardiovascular, respiratory, neurological, gastrointestinal, musculoskeletal, ocular and systemic.

The number of organ systems involved per assessment was calculated as the total number of organ system abnormalities, e.g. if an athlete assessment revealed a residual respiratory symptom, and two abnormalities in the cardiovascular system e.g. chest pain (residual symptom) and an abnormal resting ECG (abnormal laboratory investigation), the number of organs involved was calculated as 2 (organ system counted once, despite number of abnormalities in an organ system).

Patient and public involvement (PPI)

Athletes, as well as medical practitioners treating ARinf, were requested to give feedback on the questionnaire in the developing stages.

Measures of outcome

The main measure of outcome was to determine the number of organ systems involved in athletes after a recent SARS-CoV-2 infection. Potential factors associated with the number of organs involved included demographics, sport participation, history of comorbidities/allergies and the number of acute symptoms (in three subgroups). We also describe the frequency (%) of organ involvement (residual symptoms, abnormal clinical signs on physical examination, or abnormal laboratory investigations) and in three subgroups by number of symptoms.

Statistical analysis of data

Data were analysed using SAS (v 9.4). Demographics, sport participation, history of comorbidities and allergies were described for the 95 athletes using n (%) or mean (SD). One participant had a re-infection. Models were adjusted for duplicate assessments. Variables were reported for 96 athlete

assessments with the exception of CMR (n=65). Missing data were reported on in each variable. Data on missing CMR data (n=31), are reported for both lower (all missing CMR counted as "normal") and upper bound (all missing CMR counted as "missing'). Acute symptom number subgroups (1=≤5, 2=6-9, 3=≥10 symptoms) were compared for demographics, sport participation, history of comorbidities/allergies and organ involvement (number of organ systems involved). The following methods were used for: categorical variables (exact logistic regression), continuous variables (linear regression), number of comorbidities (negative binomial distribution) and number of organ systems involved (Poisson distribution). In the linear regression model, global p-values for the F-statistic and pair-wise differences for the difference between the subgroups were reported. In the exact logistic regression model, global exact p-values for the subgroup differences and exact odds ratios were reported. The negative binomial distribution was used for analysis of number of comorbidities involved. Chi-Square p-value for Type 3-analysis were reported for global test. For the pair-wise differences, the p-values for the z-statistic were reported. The Poisson distribution with error estimator (log link function) was used for analysis of any organ system involvement. The reference category for pair-wise comparisons between subgroups is subgroup 1 (≤5 symptoms). Statistical significance was accepted at $p<0.05$.

Ethical Considerations

All participants gave written informed consent. Ethical clearance was obtained from the Research Ethics Committee of the Faculty of Health Sciences at the University of Pretoria (REC 409/2020 and REC 751/2019).

RESULTS

Ninety-five athletes were included in the study. One athlete had a recurrent SARS-CoV-2 re-infection (8 weeks apart) and both assessments were included; thus 96 athlete assessments were recorded. No athletes were hospitalized and 4 (4.2%) were asymptomatic. The median (interquartile range-IQR) days from onset of symptoms (or positive test if asymptomatic) to the medical assessment was 17 (Q1;Q3=14.5;21) days.

Demographics, sport participation and history of comorbidities and allergies for the study participants

The demographics, sport participation and history of comorbidities and allergies for the study participants (n=95) are depicted in the Supplementary Table A. The mean age of the athletes was 25 years, 63% were male, 46% were professional athletes and 55% competed in mixed sports. A history of comorbidities was reported by 52%, mostly related to the respiratory tract (26%), specifically asthma (15%) and hay fever (16%). Other allergies (plant/animal material or medication) were reported by 23% of participants.

Factors associated with number of organ system involvement

The mean number of organ systems involved per athlete assessment was 2.0 (95%CI: 1.8-2.3; range: 0 to 5).

Demographics, sport participation, and history of comorbidities and allergies

The mean (SE) number of organ systems involved per athlete assessment by demographics, sport participation, and history of comorbidities and allergies is shown in Table 1.

Table 1: The estimated mean number (SE) of organ systems involved per athlete assessment by demographics, sport participation, and history of comorbidities and allergies

Variables	n	Mean (SE)	p-values
Demographics			
Age by category			
< 30 years	78	2.00 (0.14)	0.390
30-39 years	12	1.83 0.33)	
≥ 40 years	6	2.67 (0.57)	
Sex			
Male	61	1.89 (0.15)	0.144
Female	35	2.26 (0.21)	
Body mass index (BMI)	96	24.38 (0.40)	0.850
Sport participation			
Level of sport			
Professional	44	1.96 (0.18)	0.619
Amateur	51	2.08 (0.17)	
Type of sport			
Endurance †	43	2.26 (0.19)	0.083
Mixed ‡ (including skills § n=2 and power ¤ n=7)	53	1.83 (0.16)	
History of comorbidities			
Number of comorbidities			
0	46	1.96 (0.17)	0.229
1	20	1.7 (0.25)	
2	15	2.13 (0.32)	

3 or more	15	2.53 (0.35)	
Allergies			
Yes	22	2.01 (0.14)	0.91
No	74	2.05 (0.26)	

† Cycling, mid/long distance swimming/running, triathlon
‡ Rugby, field hockey, soccer, tennis
§ Golf
▫ Short distance running, shot put, javelin, discus, gymnastics, judo

Number of organ systems involvement was not significantly associated with demographics (age, sex, BMI), sport participation (level and type), or history of comorbidities and allergies.

Number of acute symptoms

The estimated mean number (95% CI) of organ systems involved per athlete assessment in three different subgroups based on total number of acute symptoms (n=96) is depicted in Table 2.

Table 2: The estimated mean number (95%CI) of organ systems involved per athlete assessment in three different subgroups based on total number of acute symptoms (n=96)

Subgroups for number of acute symptoms	**n**	**Mean (SE)**	
		Mean estimate number (95% CI)	**p-value †** **(Differences between subgroups)**
Subgroup 1 (asymptomatic athletes or those with ≤5 symptoms)	30	1.3 (1.0-1.6)	**<0.0001**
Subgroup 2 (6-9 symptoms)	34	2.2 (1.8-2.6)	
Subgroup 3 (≥10 symptoms)	32	2.6 (2.2-3.1)	

† Global test
n, number of athlete assessments; CI, confidence interval

The number of organ systems involved were significantly higher in athletes with 6-9 symptoms (subgroup 2) compared to those with ≤5 (subgroup 1) (p=0.0004). The significance was even more pronounced when comparing athletes with ≥10 symptoms (subgroup 3) with those with ≤5 symptoms (subgroup 1) (p<0.0001). We performed a similar additional analysis using only the subgroup of 65 participants where we had complete CMR data, and this confirmed the results in Table 2 (data not shown).

The relationship between number of any organ systems involved and the total number of symptoms during the acute phase of the infection is shown in Figure 1.

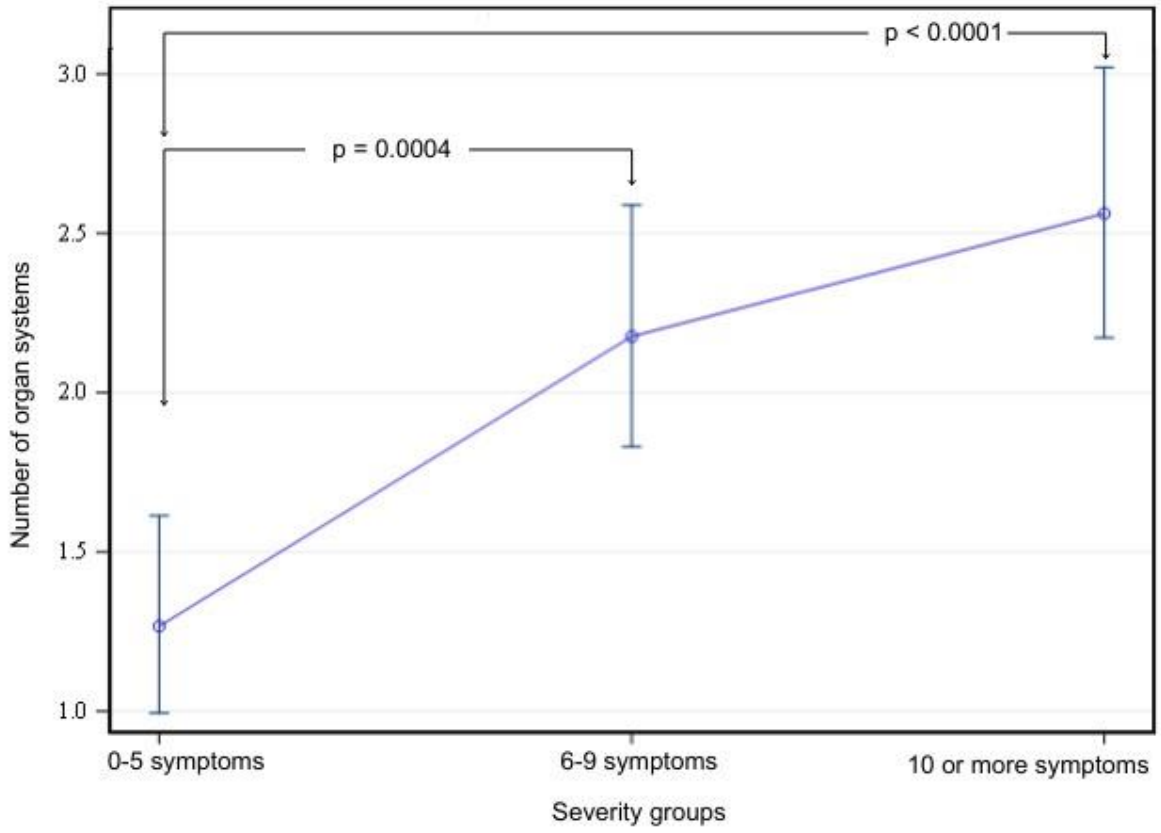

Figure 1: The relationship between the number of organ systems involved per athlete assessment (mean estimate: 95% CI) and the total number of acute symptoms

CI, confidence interval

Frequency of any organ system involvement according to number of acute symptoms

The frequency (% athletes) of any organ system involvement (residual symptoms, abnormal clinical signs and laboratory investigations) in the three different subgroups based on total number of acute symptoms is shown in Table 3.

Table 3: The frequency (% athletes) of any organ system involvement (residual symptoms, abnormal clinical signs and laboratory investigations) in three different subgroups based on total number of acute symptoms (n=96)

Evidence of multiorgan involvement per organ system	**Subgroup 1 (asymptomatic or ≤5 acute symptoms) (n=30)**	**Subgroup 2 (6-9 acute symptoms) (n=34)**	**Subgroup 3 (≥10 acute symptoms) (n=32)**	**p-value (2 vs. 1)**	**p-value (3 vs. 1)**	**p-value (difference between subgroups)**
Any organ involvement [†]	25 (26.0)	32 (33.3)	32 (33.3)	0.223	0.068	0.179
Any residual symptoms [a]	21 (72.4) [b]	30 (90.9) [b]	31 (96.9)	0.116	**0.017**	**0.011**
Cardiovascular (Any)	1 (3.3)	11 (33.3) [b]	13 (40.6)	-	-	-
Respiratory (Any)	16 (55.2) [b]	25 (73.5)	29 (90.6)	0.208	**0.004**	**0.007**
Upper respiratory (Any)	12 (40.0)	10 (29.4)	24 (75.0)	0.531	**0.011**	**0.001**
Lower respiratory (Any)	11 (39.3) [a]	22 (66.7) [b]	22 (68.8)	0.059	**0.042**	**0.040**
Neurological (Any)	12 (40.0)	17 (50.0)	23 (71.9)	0.583	**0.022**	**0.032**
Gastrointestinal (Any)	3 (10.0)	6 (18.2) [b]	7 (21.9)	-	-	-
Musculoskeletal (Any)	0	3 (8.8)	7 (21.9)	-	-	-
Ocular (Any)	0	3 (9.1) [b]	2 (6.5) [b]	-	-	-
Systemic (Any)	0	0	0			
Any abnormal clinical signs [d]	8 (34.8) [e]	11 (39.3) [f]	18 (60.0) [a]	-	-	-
Cardiovascular (Any) [f]	0	0	0			

Respiratory (Any)	8 (29.6) [c]	8 (26.7) [g]	15 (50.0) [a]	-	-	-
Upper respiratory	8 (29.6) [c]	8 (26.7) [g]	15 (50.0) [a]	-	-	-
Lower respiratory	0	0	0			
Neurological (Any)	0	0	0			
Gastrointestinal (Any)	0 [c]	3 (9.1) [b]	6 (19.4) [b]	-	-	-
Skin (Any)	0	1 (2.9)	1 (3.1)	-	-	-
Ocular (Any)	0	2 (6.1) [b]	1 (3.2) [a]	-	-	-
Any abnormal laboratory investigations [a] [†]	15 (15.79)	23 (24.2)	19 (20)	0.181	0.627	0.295
Cardiovascular (Any) [b] [†]	8 (8.42)	13 (13.68)	8 (8.42)	-	-	-
Respiratory (Any)	0 [b]	4 (12.2) [b]	2 (6.7) [a]	-	-	-
Gastrointestinal (Any)	4 (13.3)	7 (20.6)	11 (34.4)	-	-	-
Musculoskeletal (Any)	3 (10.0)	3 (9.4) [a]	4 (12.9) [b]	-	-	-
Immune/blood system (Any)	5 (16.7)	2 (5.9)	3 (9.4)	-	-	-

The frequency of any residual symptoms (p=0.011), respiratory symptoms (p=0.007) and neurological symptoms (p=0.032) differed between subgroups. Specifically, in subgroup 3 vs. 1, there was a higher frequency of overall residual symptoms (p=0.017), residual respiratory (p=0.004) [upper (p=0.011) and lower (p=0.042)] and neurological symptoms (p=0.022). There were no significant differences between subgroups 1 and 2. Numbers were too few to determine statistical differences between all subgroups, but we noted a general increase in frequency of residual symptoms from subgroup 1 to 3.

Although there was no statistically significant difference in the frequency of abnormal clinical signs by organ system between the subgroups (probably due to small sample sizes in the subgroups), the frequency of abnormal clinical signs generally increased from subgroup 1 to 3. The frequency of abnormal laboratory investigations, including CMR, did not differ significantly between the subgroups.

Details on individual residual symptoms, clinical signs and laboratory investigations (including CMR) are depicted in Supplementary Table B.

DISCUSSION

The main findings of this study were that 1) there was no association between number of organ systems involved and demographic variables, sport participation, history of comorbidities or allergies and 2) greater total number of acute symptoms in mainly unvaccinated athletes was associated with greater number of organ systems involved in athletes with recent SARS-CoV-2 infection. Specifically, athletes with >5 acute symptoms, had a significantly higher risk of multi-organ involvement. This association held when the analysis was performed in the subgroup of 65 participants with complete data (CMR subgroup).

These data are the first to provide evidence in support of the recent IOC Consensus recommendation[6] that fewer acute symptom (<5 symptoms) indicates a lower risk of multi-organ involvement, i.e. milder illness severity. Conversely, ≥10 acute symptoms are associated with increased frequency and number of organ systems involved, indicating more severe illness. Therefore, the greater number of symptoms during the acute phase of SARS-CoV-2 infection is associated with a greater risk of multi-organ involvement.

The three organ systems with more frequent residual symptoms were upper respiratory (predominantly blocked nose and sinus pressure), lower respiratory (mostly shortness of breath, dry cough, chest tightness and dyspnea), neurological (excessive fatigue and headache) and the cardiovascular systems (racing heart). A high frequency of residual upper respiratory symptoms and positive clinical signs were reported. The frequency of residual lower respiratory symptoms was also high, but the clinical examination was normal in all cases and PFT's at rest were only abnormal in 6% of athletes. The high prevalence of lower respiratory symptoms may indicate exacerbation of underlying respiratory disorders e.g. asthma, which is commonly underdiagnosed in athletes.[26] In

athletes with residual neurological and cardiovascular symptoms, clinical examinations were all normal.

In exploring abnormalities in laboratory investigations, the 'cardiac triad' had a low yield of abnormalities; resting ECG (2%), ECHO (3%) and hs-cTnT (0%). This was similar to a study in which 2820 athletes underwent ≥1 element of cardiac triad screening with a yield of <1% abnormalities.[27] Although the 'cardiac triad' has been widely used as a screening tool for cardiac pathology,[16 28] the reliability of ECHO[16 29] and elevated hs-cTnT[30 31] to diagnose SARS-CoV-2-specific cardiac involvement, has been questioned. Our data highlight the importance of performing an exercise ECG, with a >3-fold increase in revealing abnormalities compared with a resting ECG. Exercise ECG testing was also advised by other authors[31 32] and should be considered if clinically indicated.

In our study, myocarditis, as defined by the modified by Lake Louise criteria,[24] was diagnosed in only 1 athlete (1.5% of participants with CMR). This frequency of CMR-diagnosed myocarditis in athletes after SARS-CoV-2, is in keeping with a frequency of 0-5% that is reported in several studies[17 28 33] and confirmed in a recent systematic review.[34]

It is therefore apparent that although residual symptoms are prevalent after a recent SARS-CoV-2 infection, the yield of abnormal findings on physical examination and special investigations is low. However, our data suggest that athletes with >5 acute symptoms, should be have a thorough physical examination with selected special investigations (if indicated) as the likelihood of multi-organ involvement is higher.

Recent studies showed that the number of acute symptoms is also associated with prolonged RTT[10], prolonged return to full performance (RTFP)[11] and greater RPE during exercise[12] after recent SARS-CoV-2 infection. Increased time loss (prolonged RTFP), can serve as an indicator of more severe illness in athletes.[4] Number of acute symptoms can thus serve as an indication for the athlete and

coach, on when the athlete can return to training and when full performance can be expected as well as training load adjustment to accommodate for increase RPE.

We recognize that our data are collected on a unique population of predominantly unvaccinated (immune naïve) athletes with SARS-CoV-2 infection. However, these findings are still very important and relevant because they can be compared to findings in future studies on e.g. vaccinated athletes (immune modulated), different SARS-CoV-2 variants, or other respiratory pathogens. Furthermore, our study methods can also serve as a basis for a standardized approach to clinical reporting and assessment of ARinf (including SARS-CoV-2) in athletes so that research findings can be compared. Other strengths are that all clinical assessments were standardised and were performed in one clinic, by the same person, thus minimizing inter-person interpretation differences.

This study also has several limitations. Firstly, findings could not be compared to age-matched, non-infected controls and abnormal clinical and laboratory findings could not be attributed solely to recent SARS-CoV-2 infection (cause-effect). Our study population was self-selected and findings on frequency of organ involvement cannot be generalized to all athletes with SARS-CoV-2 infection. Additionally, we could only perform CMR on 68% of our study participants. In the analysis where we compared subgroups 1, 2 and 3, we did perform an additional analysis only the subgroup of 65 participants with CMR to determine if the relationship between subgroups by acute symptoms (frequency and number of organs involved) held, and found that this analysis confirmed our main finding. Finally, we recognize that small sample size was a limitation, specifically when comparing subgroups by organ systems.

CONCLUSION

The number of symptoms (especially more than 5 symptoms) during the acute phase of SARS-CoV-2 infection in athletes, is associated with multi-organ involvement. Factors including demographic, sport participation, history of comorbidities or allergies is not associated with multi-organ involvement. Multi-organ involvement may serve as an indicator of infection severity.

Practical applications

- We suggest obtaining a thorough history of the symptoms (types and number) during the acute phase of ARinf in an athlete, as this is an important clinical tool to assess disease severity, and can influence decisions to perform further investigations for multi-organ involvement.
- Specifically, in athletes presenting with >5 acute symptoms of ARinf, a comprehensive physical examination and selected laboratory investigations, are indicated to determine multi-organ system involvement.

Author contributions

Carolette Snyders: Conceptualization, methodology, writing - original draft preparation, investigation, writing- reviewing and editing

Marlise Dyer: Methodology, writing- reviewing and editing, formal analysis

Esme Jordaan: Methodology, writing- reviewing and editing, formal analysis

Leonie Scholtz: Investigation, writing- reviewing and editing

Andre Du Plessis: Investigation, writing- reviewing and editing

Martin Mpe: Investigation, writing- reviewing and editing

Kelly Kaulback: Conceptualization, investigation, writing- reviewing and editing

Martin Schwellnus: Conceptualization, methodology, writing - original draft preparation, investigation, supervision, resources, writing- reviewing and editing

Data availability

Data are not publicly available due to ethical restrictions.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, no generative AI or AI-assisted technologies were used.

Submission declaration

The work described in this manuscript has not been published previously and is not under consideration for publication elsewhere.

Supplemental Digital Content

Supplemental Digital File A.docx: Standardized clinical assessment of an athlete with acute respiratory infection

Supplemental Digital Table A.docx: Demographics, sport participation and history of comorbidities and allergies for study participants (n=95)

Supplemental Digital Table B.docx: The frequency (% athlete assessments) of residual symptoms, abnormal clinical signs/laboratory investigations and cardiac magnetic resonance imaging for participants in three different subgroups based on total number of symptoms during the acute phase of the infection (individual variables)

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