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The clinical spectrum of COVID-19 complications in young adults: combined analysis of the American Heart Association COVID-19 Cardiovascular Disease Registry and the Outcomes Registry for Cardiac Conditions in Athletes

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ABSTRACT

Background: While young adults 18-24 years old bear a significant proportion of COVID-19 diagnoses, the risk factors for hospitalization and severe COVID-19 complications in this population are poorly understood.

Objective: The objective of this study was to identify risk factors for hospitalization and other COVID-19 complications across the health spectrum of young adults diagnosed with SARS-CoV-2 infection.

Study Design: Retrospective cohort study

Particpants: Young adults (ages 18-24) with confirmed SARS-CoV-2 infection from the American Heart Association (AHA) COVID-19 Cardiovascular Disease registry of hospitalized patients and the Outcomes Registry for Cardiac Conditions in Athletes (ORCCA) study of collegiate athletes.The AHA registry included 636 young adults from 152 hospitals. The ORCCA registry consisted of 3653 competitive college athletes from 42 colleges and universities.

Intervention: None (exposure to SARS-CoV-2)

Primary and Secondary Outcome Measures: Main outcomes included hospitalization, death, major adverse cardiovascular events and other severe clinical events.

Results: In comparison to the ORCCA registry, patients in the AHA registry were more likely to be female (59% vs 33%); have higher average BMI (32.4 vs. 25.6); and have increased prevalence of diabetes (10% vs. 0.4%), hypertension (7% vs. 0.6%), chronic kidney disease (2% vs. 0%), and asthma (14% vs. 8%), all with $p<0.01$. There were 8 (2%) deaths in the AHA hospitalized registry compared to zero in the ORCCA cohort. BMI was a statistically significant predictor of death in the hospitalized cohort (OR: 1.05, 95% CI: 1.00, 1.10). No significant predictors of MACE or other severe clinical events were identified.

Conclusions: The risk of cardiac events in young adults ages 18-24 diagnosed with SARS-CoV-2 infection is low. Risk factors for hospitalization include pre-existing medical comorbidities and elevated

BMI. Once hospitalized, elevated BMI is associated with increased mortality although other drivers of MACE and other severe clinical events remains unclear.

Strengths and Limitations

- Through a comparison between two large independent cohorts, cardiac and other severe complications of COVID-19 in young adults between the ages of 18 to 24 were able to be identified
- Cross-comparisons between cohorts is limited as these are two independent cohorts with two different criteria for entry
- The low prevalence of basic cardiovascular testing in the AHA cohort likely leads to under-ascertainment of major adverse cardiac events.

INTRODUCTION

Coronavirus disease 19 (COVID-19) infection has manifested in a wide array of clinical complications including but not limited to respiratory failure, systemic inflammation, thromboembolic events, and cardiovascular events. [1-3] While older age and comorbidities have been identified as a significant risk factors for increased morbidity and mortality in patients infected with COVID-19, severe complications of COVID-19 have been reported across all age groups including young adults ages 18-24. [4-6] Although these individuals bear a significant proportion of COVID-19 infections, the spectrum and risk of COVID-19 complications in this age group remain understudied.

The issue of cardiovascular complications and the necessity of screening following COVID-19 infection in young adults has been the source of significant debate.[7,8] While the vast majority of young adults recover with minor or no cardiovascular injury, several case reports and case series have demonstrated the potential cardiac impact of COVID-19 in healthy young adults. [9] Reported sequelae include myocardial infarction, myocarditis, sudden onset biventricular heart failure requiring mechanical support, and sudden cardiac death. [10-12] Multi-inflammatory response syndrome with multi-organ failure has also been noted in young adults. [13,14] The reasons why certain individuals have such devastating cardiovascular consequences of COVID-19 infection are not known.

Our study aims to better define the clinical spectrum of COVID-19 cardiac and non-cardiac complications in young adults by utilizing two registries representing the 'bookends' of health: the American Heart Association (AHA) COVID-19 Cardiovascular Disease registry of hospitalized patients and the Outcomes Registry for Cardiac Conditions in Athletes (ORCCA) study of previously healthy collegiate athletes. Through a combined analysis and comparison of these two registries, our primary aim is to evaluate both the prevalence of serious cardiac and non-cardiac complications and the risk factors for hospitalization and severe complications in these young adults. Our secondary aim is to

examine the utility of diagnostic testing for cardiac involvement along the health spectrum of young adults diagnosed with COVID-19.

METHODS

Data Sources

The AHA COVID-19 Cardiovascular Disease registry is a retrospective registry of consecutive patients collected by 152 hospitals and centers participating in this quality improvement registry. Eligible patients are all patients hospitalized with a diagnosis of COVID-19. All aduts 18-24 years of age were included from the AHA registry between the dates of March 1st, 2020 and April 19, 2021. The registry captures baseline demographics, testing, laboratory results, and health outcomes.

The ORCCA study consists of National Collegiate Athletic Association athletes with confirmed SARS-CoV-2 infection from September 1, 2020 to June 1, 2021. Eligibility criteria and data collection methods have been described previously. [15] Patient demographics, COVID-19 symptoms, cardiac evaluations, and cardiac outcomes were captured in the registry. Evaluations were performed per the discretion of local institutions and included a clinical assessment with or without cardiac testing such as a 12-lead electrocardiogram (ECG), cardiac troponin assay, trans-thoracic echocardiogram (TTE), and cardiac magnetic resonance (CMR) imaging.

Definition of Primary Outcomes

Primary outcomes included hospitalization, death, major adverse cardiovascular events (MACE), and other severe clinical events. A MACE was defined as the occurrence of one or more of the following events: ischemic stroke, myocardial infarction, sustained ventricular arrythmias, cardiogenic shock, new onset heart failure, myocarditis/myocardial involvement, requirement of permanent pacemaker (PPM) or pulmonary embolism/deep vein thrombosis. Other severe clinical events included new hemodialysis or continuous renal replacement therapy (CRRT), requirement of mechanical

ventilation, or non-cardiogenic shock. SARS-CoV-2 myocardial involvement was defined in the current study as probable or definitive myocardial or myopericardial involvement per previous definitions.[15] Follow-up was requested from participating institutions periodically throughout the study period by the ORCCA investigators. There was no follow-up beyond the initial hospitalization in the AHA COVID-19 registry. Because hospitalization was an entry criterion for the AHA registry, hospitalization rates were assessed only for ORCCA study participants.

Statistical Analysis

Standard descriptive statistics were used to describe patient characteristics, symptoms, cardiac testing, and incidence of MACE and other severe clinical complications in both cohorts. Asymptomatic patients, including female patients admitted for labor and delivery, were removed from the AHA cohort as COVID-19 likely was an incidental finding and not the cause of hospitalization. Means and standard deviations (SD) summarize continuous variables. Frequencies and percentages summarize categorical variables. Two sample t-tests were used for continuous comparisons, while chi-square tests or Fisher's exact tests were used for categorical comparisons, as appropriate. To account for the small number of observed events, univariable firth logistic regression models were created to assess potential predictors of death, MACE, and other severe clinical events. Odds ratios and 95% confidence intervals are provided for all models. We followed the STROBE Checklist for reporting of cohort studies. [16]The American Heart Association Precision Medicine Platform (https://precision.heart.org/) was used for data analysis. IQVIA (Parsippany, New Jersey) serves as the data collection and coordination center. All statistical analyses were conducted in SAS v9.4 (SAS Institutes, Cary, NC).

RESULTS

Baseline Characteristics

Baseline characteristics of participants in the AHA and ORCCA registries are shown in Table 1. 3653 individuals were included in the ORCCA cohort with mean age of 19.9 (SD=1.42) years with 33%

women and 28% Black. 636 individuals were included in the AHA cohort with mean age of 21.4 (SD=1.91) years with 59% women and 27% Black. BMI was significantly higher in the hospitalized AHA registry (32.4 kg/m^2, SD= 10.6) compared to the ORCCA registry (25.6 kg/m^2, SD=4.7) p <0.001. The frequencies of diabetes mellitus (10% vs 0.4%), hypertension (7% vs 0.6%), chronic kidney disease (2% vs 0.0%), obesity (51% vs 13%), and asthma (14% vs 8%) were greater in the AHA cohort compared to ORCCA cohort, all with p<0.01. Participants in the ORCCA cohort were more likely to have no significant past medical history compared to the AHA cohort (70% vs 62%, p< 0.01). In those participants with no medical history, participants in the ORCCAA study were more likely to be non-obese (BMI <30 kg/m2) compared to the AHA registry (87% vs 52%, p <0.01%).

Initial Symptoms

The initial symptoms of both groups are shown in Table 2. The AHA cohort had greater proportions of fever/chills (43%), cough (41%), shortness of breath (38%), nausea/vomiting or diarrhea (32%), and chest pain (7%) compared to the ORCCA cohort (19%, 17%, 6%, 5%, and 3% respectively), all p-values <0.01. In contrast, the ORCCA cohort had greater proportions of headache (23%), loss of sense of smell/taste (23%), sore throat (18%), and nasal congestion (18%) compared to the AHA cohort (12%, 6%, 8%, and 5%, respectively), (all p-values <0.01)

Cardiac testing

Cardiac testing for the AHA and ORCCA cohorts is depicted in Table 2 and Figure 1. There was significantly more cardiac testing including CMR (cardiac magnetic resonance imaging) (14% vs 0.3%), electrocardiogram (95% vs 52%), troponin assay (87% vs 33%), and transthoracic echocardiogram (82% vs 7%) in the ORCCA cohort compared to the AHA cohort (all p-values <0.001).

Death, MACE, and Other Severe Clinical Events

Clinical Outcomes

Table 3 depicts the incidence of death, MACE, and secondary clinical events in the ORCCA cohort and AHA cohort. There were 12 (2%) deaths in the AHA cohort compared to 0 deaths in the ORCCA cohort. Characteristics of patients who died in the AHA registry are shown in supplemental Table 1. With respect to MACE, there were 22 (0.6%) overall events in the ORCCA cohort,- with 1 (0.03%) case of pulmonary embolism and 21 (0.6%) cases of SARS CoV-2 myocardial involvement. The range of the events occurred from 8/2020 to 2/2021. In the AHA cohort, 22 (3.5%) patients experienced a MACE. There were 6 (1%) cases of ischemic stroke, 4 (0.6%) cases of pulmonary embolism, 5 (0.8%) cases of new onset heart failure, 3 events (0.5%) of sustained ventricular arrythmias, 3 (0.5%) cases of myocarditis, and 1 (0.2%) myocardial infarction. There were no other severe clinical events in the ORCCA group. There were 83 (13.1%) other severe clinical events in the AHA registry with 60 (9%) young adults requiring ventilation, 19 (3%) meeting criteria for shock, and 4 (0.6%) requiring hemodialysis or CRRT.

There were 4 (0.1%) hospitalizations for COVID-19 in the ORCCA cohort, while all patients in the AHA cohort by definition were hospitalized. The median follow-up for the ORCCA cohort was 411 [IQR: 387, 447] days; given the cross-sectional design of the AHA registry, no follow-up was conducted on those patients.

Univariable analysis

Results of univariable analyses to identify predictors for death, MACE, and other severe clinical events in the AHA cohort are provided in Table 4. A higher BMI was associated with death (OR: 1.05, 95% CI: 1.00, 1.10; p=0.04). No significant predictors of MACE or other severe clinical events were identified.

DISCUSSION

The purpose of this study was to define the clinical spectrum of disease and identify cardiac and other severe complications of COVID-19 in young adults between the ages of 18 to 24 from two

established registries on potentially opposite sides of the disease severity continuum. The patients in the AHA registry were more likely to have medical comorbidities including diabetes mellitus, hypertension, chronic kidney disease, and asthma compared to patients in the ORCCA study. It should be noted that the ORCCA study does not represent the general 18-24-year-old population but rather a young, athletic population. This is the first analysis of health outcomes in young adults hospitalized with COVID-19 from the AHA COVID-19 CVD registry. Importantly, we observed: 1) more pre-existing comorbidities in hospitalized patients, 2) a mortality rate of 2%, and 3) a higher risk of death with higher BMI. This study also highlights the low rate of cardiac testing in the AHA hospitalized patient cohort, in contrast with frequent cardiac testing and high resource utilization in the ORCCA study collegiate athlete cohort. Unlike initial studies of older adults hospitalized with COVID-19, this study did not find a similarly high rate of myocardial injury or MACE. [17-19]

Prior studies of young adults demonstrate low mortality rates for patients hospitalized with COVID-19, though point estimates range from 0.2% for 18 to 29-year-olds in a large academic health system to 2.7% in a large series of 18 to 34-year-olds derived from insurance data.[20,21] Our findings confirm that obesity is a risk factor for COVID-19 related mortality in young adults. [20] While heterogeneity exists for mortality in younger individuals hospitalized with COVID-19, the mortality rate in the young is strikingly lower than that of elderly individuals, estimated by Nguyen *et al.* to be 26.6% in individuals 80 and older. [22]

Comparison to data from the National Health and Nutrition Examination Survey (NHANES) puts the prevalence of co-morbidities found in the AHA hospitalized COVID-19 cohort in context. [23] While prevalence of asthma (14%) in young adults hospitalized with COVID-19 seems high, this is similar to the 18% prevalence seen in the overall population of 18 to 24-year-olds. [23] In contrast, the incidences of diabetes mellitus (10%) and hypertension (7%) are higher than those seen in the overall population according to NHANES data (0.5% and 4%, respectively). [23] Despite the high co-morbidity

burden compared to non-hospitalized collegiate athletes, 62% of patients in the AHA hospitalized cohort still had no remarkable past medical history, highlighting that COVID-19 adverse outcomes can affect any patient and that risk factors are hard to predict and incompletely understood.

Our analysis juxtaposing an athletic young adult cohort with a hospitalized young adult cohort highlights the heterogenous nature of BMI as a risk predictor. BMI has been identified as a risk factor for hospitalization and mortality following hospitalization across all age groups. [24-26] However, in the ORCCA dataset involving collegiate athletes, BMI was not found to be associated with SARS-CoV-2 myocardial involvement.[15] Notably, however, the elevated BMI of an elite athlete is different than the elevated BMI of a non-athlete as the traditional BMI metric does not take into account muscle mass, body composition, and bone density. [27] Therefore, the limitations of using BMI should be considered before extrapolating the risks of elevated BMI in the general population to athletes with COVID-19. A more detailed assessment of adiposity in conjunction with BMI is an important area of future study.

The utilization of cardiac testing was starkly different between the ORCCA cohort and the AHA cohort. Initial concerns for myocardial inflammation from SARS-CoV-2 infection and an elevated risk of sudden death in competitive athletes drove initial consensus recommendations to err on the side of early detection with the potential for over-diagnosis.[28] Thus, institutions participating in the ORCCA study used protocols aimed at sensitivity, with 93.4% of athletes receiving at least one of troponin, ECG, or TTE, and 6.6% of participants receiving mandatory CMR screening.[15] In the AHA cohort, cardiac diagnostic testing was likely to be more specific, driven by clinical suspicion and the need to minimize healthcare worker exposure or the transport of critically ill patients. For hospitalized patients, there was a lower-than-expected rate of cardiac testing with only 49% of patients receiving ECG, 35% troponin testing, 7% TTE, and 0.2% CMR. With over 42% of patients in the AHA cohort experiencing shortness of breath or chest pain, the use of TTE in only 7% of patients is significantly lower than in previous studies of hospitalized patients with similar symptoms. [29,30] Similarly, an ECG in less than 50% of

patients is much lower than previously described in hospitalized patients given patient comorbidities, symptom description, early concerns around myocarditis, and the frequency with which QT_C prolonging medications were used for the treatment of COVID-19. [31-33] A desire to minimize patient contact and the scarcity of personal protective equipment early in the pandemic likely limited cardiac testing in the hospital. These lower rates of cardiac testing also may have been due to an underappreciation of the cardiac manifestations of COVID-19, or errors and discrepancies in reporting cardiac testing in the AHA registry. Our findings raise the possibility that under-utilization of cardiac testing in hospitalized patients may have led to under-diagnosis of cardiac involvement, while over-utilization of cardiac testing in competitive athletes may have led to over-diagnosis.

There are several important limitations to this study. First, this is a comparison of two independent cohorts with two different criteria for entry: participation in NCAA athletics for the ORCCA cohort versus hospitalization for COVID-19 in the AHA cohort. These differences limit cross-comparisons between cohorts. Second, the AHA cohort relies on registry abstraction, and may be overweighted towards hospitals and hospital systems with resources sufficient to populate these registries. Thus, outcomes in the AHA cohort may not fully reflect the outcomes experienced for young adult patients hospitalized with COVID-19 across all hospitals in the United States. Third, in contrast to the ORCCA study with greater than 1 year of follow-up, there is no follow-up beyond the initial hospitalization in the AHA COVID-19 registry. This limits accurate assessment of the true incidence of severe events, MACE, and mortality related to COVID-19 hospitalization. Fourth, registry capture in the AHA cohort was incomplete, with 27% of patients not having documented presenting symptoms. Fifth, the low prevalence of basic cardiovascular testing in the AHA cohort likely leads to under-ascertainment of MACE. Last, with the relatively low prevalence of mortality, MACE, and severe COVID-related adverse events, and the relatively small sample size of 18- to 24-year-old patients hospitalized for

COVID-19, our study is underpowered for detailed modeling of risk factors associated with poorer outcomes in the setting of COVID-19 illness.

In conclusion, this study compared clinical outcomes in young adults patients across the health spectrum with SARS-CoV-2 infection. We found a significantly higher burden of comorbidities and lower rates of cardiac testing in hospitalized patients as compared to competitive athletes with COVID-19. Nine percent of hospitalized young adults with COVID-19 required mechanical ventilation, 3.5% suffered a MACE, and 2% died. Importantly, elevated BMI predicted mortality in hospitalized patients. Additional research is needed to better elucidate risk factors for severe health outcomes in young adults afflicted with COVID-19.

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Data sharing statement: Technical appendix, statistical code and dataset available from the AHA

Precision Medicine Platform

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FIGURE LEGENDS

Figure 1. Abbreviations: AHA, American Heart Association; ECG, electrocardiogram; MRI- magnetic resonance imaging; ORCCA, Organized Registry for Cardiac Conditions in Athletes

TABLES

Initial Result Tables

Table 1: Baseline Characteristics in the AHA and ORCCA Cohorts of Young Adults with COVID-19

	ORCCA (N=3653)	AHA (N=636)	p-value
Age, mean (SD)	19.91 (1.42)	21.43 (1.91)	<0.001
Female, n(%)	1209 (33%)	376 (59%)	<0.001
Race			<0.001
Black, n (%)	992 (28%)	172 (27%)	
Hispanic, n (%)	112 (3%)	205 (32%)	
White-Non Hispanic	2334 (65%)	195 (31%)	
Other*	166 (5%)	64 (10%)	
Medical History†			
Unremarkable Medical History	2540 (70%)	397 (62%)	<0.001
BMI kg/m^2, mean (SD)	25.64 (4.74)	32.40 (10.57)	<0.001
Obesity (BMI > 30 kg/ m$^{2)}$			
Normal weigh or other com			
Atrial Fibrillation	1 (0.03%)	3 (0.5%)	0.01
Stroke/Transient Ischemia Attack	0	8 (1%)	<0.001
Diabetes Mellitus	12 (0.4%)	63 (10%)	<0.001
Dyslipidemia	11 (0.3%)	9 (1%)	0.001
Heart Failure		5 (0.8%)	
Hypertension	20 (0.6%)	47 (7%)	<0.001
Peripheral Artery Disease	0	1 (0.2%)	0.15
Chronic Kidney Disease	0	**11 (2%)**	<0.001
Deep Vein Thrombosis	0	**5 (0.8%)**	<0.001
Pulmonary Embolism	1 (0.03%)	**6 (1%)**	<0.001
eCigarette (vaping)		10 (2%)	
Smoking		**48 (8%)**	
Immune Disorders	0	**12 (2%)**	<0.001
Congenital heart Disease	18 (0.5%)	**3 (0.5%)**	0.99
Asthma	265 (8%)	**90 (14%)**	<0.001
Other Pulmonary Disease	0	**5 (0.8%)**	<0.001
Pulmonary Arterial Hypertension	0	**3 (0.5%)**	0.003

†Fisher's exact test used for all categorical comparisons due to small expected cell counts

*Other race includes mixed, Asian, American-Indian, native-Hawaiian, Pacific Islander (ORCCA) and Asian, Pacific Islander, Unknown, Native American (AHA)

Abbreviations: AHA (American Heart Association); ORCCA (Outcomes Registry for Cardiac Conditions in Athletes)

Table 2: Initial Symptoms and Cardiac Testing Performed

	ORCCA (N=3653)	AHA (N=636)	p-value
Initial Symptoms[a]			
Fever/Chills	683 (19%)	269 (43%)	<0.001
Cough	612 (17%)	258 (41%)	<0.001
Shortness of Breath	226 (6%)	236 (38%)	<0.001
Fatigue	553 (16%)	90 (14%)	0.55
Headache	853 (23%)	75 (12%)	<0.001
Myalgia	604(17%)	97 (15%)	0.45
Sore Throat	674 (18%)	49 (8%)	<0.001
Nasal Congestion	644 (18%)	34 (5%)	<0.001
Nausea, Vomiting or Diarrhea	182 (5%)	198 (32%)	<0.001
Loss of Sense of Smell/Taste	834 (23%)	36 (6%)	<0.001
Chest Pain	121 (3%)	44 (7%)	<0.001
Not Documented	381 (11%)	172 (27%)	<0.001
Asymptomatic	1078 (30%)	N/A	
Cardiac Testing			
MRI	516 (14%)	1 (0.33%)	<0.001
EKG	3486 (95%)	327 (52%)	<0.001
Troponin	3166 (87%)	232 (33%)	<0.001
Echo	2999 (82%)	47 (7%)	<0.001
Myocardial Injury (troponin elevation)	27 (0.9%)	173(77%)	
Hospitalization Characteristics			
Hospitalized	4	731 (100%)	--
Ventilated	0	60 (9%)	--

[a] Initial Symptoms for ORCCA and symptoms at the time of admission for AHA

Abbreviations: AHA (American Heart Association); ORCCA (Outcomes Registry for Cardiac Conditions in Athlete

Table 3: Incidence of Major Adverse Cardiovascular Events and other Severe Clinical Events in Young Adults with COVID-19

	ORCCA	AHA
Death, n (%)	0	12 (2%)
Major Adverse Cardiovascular Events (MACE)		
Total Events	22 (0.6%)	22 (3.5%)
Ischemic Stroke/Intracranial Hemorrhage, n (%)	0	6 (1%)
Pulmonary embolism, n (%)	1 (0.03%)	4 (0.6%)
New onset heart failure, n (%)	0	5 (0.8%)
Sustained Ventricular Arrythmias, n (%)	0	3 (0.5%)
Requirement of PPM, n (%)	0	0
Acute Myocardial Infarction, n (%)	0	1 (0.2%)
Myocarditis, n (%)	21 (0.6%)	3 (0.5%)
Cardiogenic Shock, n (%)	0	0
Other Severe Clinical Events		
Total Events	0 (0.0%)	104(16.4%)
New Hemodialysis or CRRT, n (%)	0	4 (0.6%)
Ventilation	-	60 (9%)
In-hospital Shock, n (%)	0	19 (3%)
Requirement of Mechanical Support, n (%)	-	2 (0.4%)
Requirement of Pressor Support, n (%)	-	19 (3%)

Abbreviations: AHA (American Heart Association); CRRT, continuous renal replacement therapy ; ORCCA (Outcomes Registry for Cardiac Conditions in Athletes)

Table 4: Univariable predictors of Death, MACE and Other Severe Clinical Events in AHA Cohort

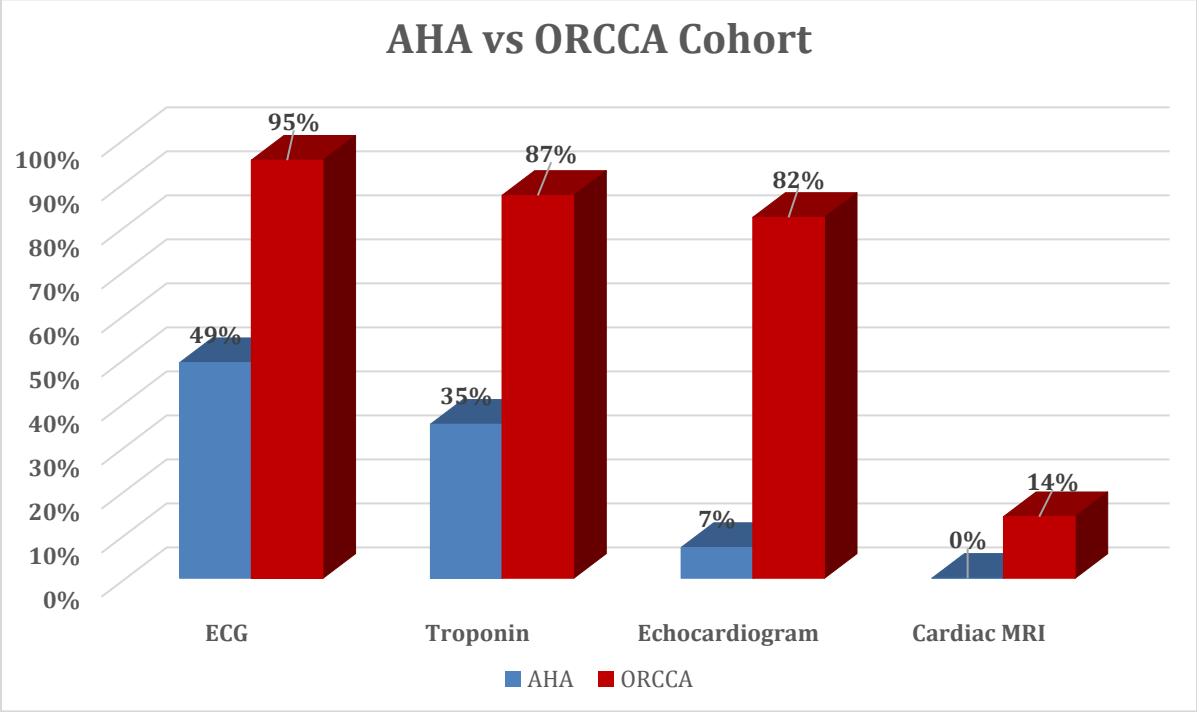
	Death (N=12)		**Major Adverse Cardiac Event (MACE)[a] (N=22)**		**Other Severe Clinical Events[b] (N=63)**	
Variable	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.02 (0.76, 1.36)	0.92	0.93 (0.75, 1.16)	0.53	0.98 (0.85, 1.12)	0.72
Female	0.50 (0.16, 1.52)	0.22	0.47 (0.20, 1.11)	0.08	0.64 (0.38, 1.08)	0.09
Race / Ethnicity		0.75		0.60		0.77
Black	0.62 (0.13, 2.98)	0.37	0.65 (0.22, 1.89)	0.59	0.87 (0.45, 1.68)	0.92
Hispanic	0.95 (0.25, 3.58)	0.90	0.54 (0.18, 1.57)	0.31	0.72 (0.37, 1.38)	0.34
White Non-Hispanic	REF		REF		REF	REF
Other	1.70 (0.35, 8.28)	0.33	1.12 (0.32, 3.97)	0.44	1.01 (0.42, 2.44)	0.69
BMI kg/m^2	1.05 (1.00, 1.10)	0.04	0.98 (0.93, 1.02)	0.31	1.01 (0.98, 1.03)	0.50
Diabetes	1.17 (0.21, 6.65)	0.86	1.10 (0.29, 4.23)	0.89	1.43 (0.66, 3.12)	0.37
Hypertension	0.49 (0.03, 8.59)	0.62	1.53 (0.39, 5.95)	0.54	1.45 (0.60, 3.49)	0.41
Asthma	0.78 (0.14, 4.38)	0.78	0.41 (0.08, 2.20)	0.30	1.05 (0.51, 2.19)	0.89
Smoking	0.48 (0.03, 8.39)	0.61	1.49 (0.38, 5.80)	0.56	0.67 (0.22, 2.08)	0.49

[a] MACE: ischemic stroke, myocardial infarction, sustained ventricular arrythmias, cardiogenic shock, new onset heart failure, myocarditis, requirement of permanent PPM and pulmonary embolism/deep vein thrombosis

[b] Other severe clinical events were new hemodialysis or continuous renal replacement therapy (CRRT), requirement of ventilation, or non-cardiogenic shock

FIGURES

Figure 1: Comparison of Cardiac Testing in the American Heart Association (AHA) Cardiovascular Disease Registry of Hospitalized Patients and the Outcomes Registry for Cardiac Conditions in Athletes (ORCCA)



Abbreviations: AHA, American Heart Association; ECG, electrocardiogram; MRI- magnetic resonance imaging; ORCCA, Organized Registry for Cardiac Conditions in Athletes

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5/6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than	6

		one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	12
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6-7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7
Statistical methods	#12c	Explain how missing data were addressed	7
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	7
Statistical methods	#12e	Describe any sensitivity analyses	7
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	7-8

		confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	7
Participants	#13c	Consider use of a flow diagram	
NA- can provide if needed			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	7/8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
8			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
8/9			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
8/9			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence	9

		interval). Make clear which confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	9
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	#18	Summarise key results with reference to study objectives	9
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	12
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11
Generalisability	#21	Discuss the generalisability (external validity) of the study results	11
Other Information			

Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

Notes:

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BMJ Open

The clinical spectrum of COVID-19 complications in young adults: combined analysis of the American Heart Association COVID-19 Cardiovascular Disease Registry and the Outcomes Registry for Cardiac Conditions in Athletes

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The clinical spectrum of COVID-19 complications in young adults: combined analysis of the American Heart Association COVID-19 Cardiovascular Disease Registry and the Outcomes Registry for Cardiac Conditions in Athletes

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ABSTRACT

Background: While young adults 18-24 years old bear a significant proportion of COVID-19 diagnoses, the risk factors for hospitalization and severe COVID-19 complications in this population are poorly understood.

Objective: The objective of this study was to identify risk factors for hospitalization and other COVID-19 complications across the health spectrum of young adults diagnosed with COVID-19 infection.

Study Design: Retrospective cohort study

Participants: Young adults (ages 18-24) with confirmed COVID-19 infection from the American Heart Association (AHA) COVID-19 Cardiovascular Disease registry of hospitalized patients and the Outcomes Registry for Cardiac Conditions in Athletes (ORCCA) study of collegiate athletes. The AHA registry included 636 young adults from 152 hospitals. The ORCCA registry consisted of 3653 competitive college athletes from 42 colleges and universities.

Intervention: None (exposure to COVID-19)

Primary and Secondary Outcome Measures: Main outcomes included hospitalization, death, major adverse cardiovascular events and other severe clinical events.

Results: In comparison to the ORCCA registry, patients in the AHA registry were more likely to be female (59% vs 33%); have higher average BMI (32.4 vs. 25.6); and have increased prevalence of diabetes (10% vs. 0.4%), hypertension (7% vs. 0.6%), chronic kidney disease (2% vs. 0%), and asthma (14% vs. 8%), all with $p<0.01$. There were 8 (2%) deaths in the AHA hospitalized registry compared to zero in the ORCCA cohort. BMI was a statistically significant predictor of death in the hospitalized cohort (OR: 1.05, 95% CI: 1.00, 1.10). No significant predictors of MACE or other severe clinical events were identified.

Conclusions: The risk of cardiac events in young adults ages 18-24 diagnosed with COVID-19 infection is low. Patients who were hospitalized (AHA registry) were more likely to have pre-existing medical

comorbidities and higher BMI than healthy collegiate athletes (ORCCA registry). Once hospitalized, elevated BMI is associated with increased mortality although other drivers of MACE and other severe clinical events remain unclear.

Strengths and Limitations

- Through a comparison between two large independent cohorts, cardiac and other severe complications of COVID-19 in young adults between the ages of 18 to 24 were able to be identified
- Cross-comparisons between cohorts is limited as these are two independent cohorts with two different criteria for entry
- The low prevalence of basic cardiovascular testing in the AHA cohort likely leads to under-ascertainment of major adverse cardiac events.

INTRODUCTION

Coronavirus disease 19 (COVID-19) infection has manifested in a wide array of clinical complications including but not limited to respiratory failure, systemic inflammation, thromboembolic events, and cardiovascular events. [1-3] While older age and comorbidities including chronic kidney disease have been identified as a significant risk factors for increased morbidity and mortality in patients infected with COVID-19, severe complications of COVID-19 have been reported across all age groups including young adults ages 18-24. [4-6] Although these individuals bear a significant proportion of COVID-19 infections, the spectrum and risk of COVID-19 complications in this age group remain understudied.

The issue of cardiovascular complications and the necessity of screening following COVID-19 infection in young adults has been the source of significant debate.[7 8] While the vast majority of young adults recover with minor or no cardiovascular injury, several case reports and case series have demonstrated the potential cardiac impact of COVID-19 in healthy young adults. [9] Reported sequelae include myocardial infarction, myocarditis, sudden onset biventricular heart failure requiring mechanical support, and sudden cardiac death. [10-12] Multi-inflammatory response syndrome with multi-organ failure has also been noted in young adults. [13 14] The reasons why certain individuals have such devastating cardiovascular consequences of COVID-19 infection are not known.

Our study aims to better define the clinical spectrum of COVID-19 cardiac and non-cardiac complications in young adults by utilizing two registries representing the 'bookends' of health: the American Heart Association (AHA) COVID-19 Cardiovascular Disease registry of hospitalized patients and the Outcomes Registry for Cardiac Conditions in Athletes (ORCCA) study of previously healthy collegiate athletes. Through a combined analysis and comparison of these two registries, our primary aim is to evaluate both the prevalence of serious cardiac and non-cardiac complications and the risk factors for hospitalization and severe complications in these young adults. Our secondary aim is to

examine the utility of diagnostic testing for cardiac involvement along the health spectrum of young adults diagnosed with COVID-19.

METHODS

Patient and Public Involvement

The AHA COVID-19 Cardiovascular Disease registry is a retrospective registry of consecutive patients collected by 152 hospitals and centers participating in this quality improvement registry. Eligible patients are all patients hospitalized with a diagnosis of COVID-19. All adults 18-24 years of age were included from the AHA registry between the dates of March 1st, 2020 and April 19, 2021. The registry captures baseline demographics, testing, laboratory results, and health outcomes.

The ORCCA study consists of National Collegiate Athletic Association athletes with confirmed COVID-19infection from September 1, 2020 to June 1, 2021. Eligibility criteria and data collection methods have been described previously. [15] Patient demographics, COVID-19 symptoms, cardiac evaluations, and cardiac outcomes were captured in the registry. Evaluations were performed per the discretion of local institutions and included a clinical assessment with or without cardiac testing such as a 12-lead electrocardiogram (ECG), cardiac troponin assay, trans-thoracic echocardiogram (TTE), and cardiac magnetic resonance (CMR) imaging. Results were communicated to the patients and if necessary were referred for further evaluation.

Definition of Primary Outcomes

Primary outcomes included hospitalization, death, major adverse cardiovascular events (MACE), and other severe clinical events. A MACE was defined as the occurrence of one or more of the following events: ischemic stroke, myocardial infarction, sustained ventricular arrythmias, cardiogenic shock, new onset heart failure, myocarditis/myocardial involvement, requirement of permanent pacemaker (PPM) or pulmonary embolism/deep vein thrombosis. Other severe clinical events included new hemodialysis or continuous renal replacement therapy (CRRT), requirement of mechanical

ventilation, or non-cardiogenic shock. COVID-19 myocardial involvement was defined in the current study as probable or definitive myocardial or myopericardial involvement per previous definitions.[15] Follow-up was requested from participating institutions periodically throughout the study period by the ORCCA investigators. There was no follow-up beyond the initial hospitalization in the AHA COVID-19 registry. The median duration of hospitalization was 4 days. Because hospitalization was an entry criterion for the AHA registry, hospitalization rates were assessed only for ORCCA study participants.

Statistical Analysis

Standard descriptive statistics were used to describe patient characteristics, symptoms, cardiac testing, and incidence of MACE and other severe clinical complications in both cohorts. Asymptomatic patients, including female patients admitted for labor and delivery, were removed from the AHA cohort as COVID-19 likely was an incidental finding and not the cause of hospitalization. Means and standard deviations (SD) summarize continuous variables. Frequencies and percentages summarize categorical variables. Two sample t-tests were used for continuous comparisons, while chi-square tests or Fisher's exact tests were used for categorical comparisons, as appropriate. To account for the small number of observed events, univariable firth logistic regression models were created to assess potential predictors of death, MACE, and other severe clinical events. Odds ratios and 95% confidence intervals are provided for all models. We followed the STROBE Checklist for reporting of cohort studies. [16]The American Heart Association Precision Medicine Platform (https://precision.heart.org/) was used for data analysis. IQVIA (Parsippany, New Jersey) serves as the data collection and coordination center. All statistical analyses were conducted in SAS v9.4 (SAS Institutes, Cary, NC).

RESULTS

Baseline Characteristics

Baseline characteristics of participants in the AHA and ORCCA registries are shown in Table 1.

Table 1: Baseline Characteristics in the AHA and ORCCA Cohorts of Young Adults with COVID-19

	ORCCA (N=3653)	AHA (N=636)	p-value
Age, mean (SD)	19.91 (1.42)	21.43 (1.91)	<0.001
Female, n(%)	1209 (33%)	376 (59%)	<0.001
Race			<0.001
Black, n (%)	992 (28%)	172 (27%)	
Hispanic, n (%)	112 (3%)	205 (32%)	
White-Non Hispanic	2334 (65%)	195 (31%)	
Other*	166 (5%)	64 (10%)	
Medical History†			
Unremarkable Medical History	2540 (70%)	397 (62%)	<0.001
BMI kg/m^2, mean (SD)	25.64 (4.74)	32.40 (10.57)	<0.001
Obesity (BMI > 30 kg/ m$^{2)}$			
Normal weigh or other com			
Atrial Fibrillation	1 (0.03%)	3 (0.5%)	0.01
Stroke/Transient Ischemia Attack	0	8 (1%)	<0.001
Diabetes Mellitus	12 (0.4%)	63 (10%)	<0.001
Dyslipidemia	11 (0.3%)	9 (1%)	0.001
Heart Failure		5 (0.8%)	
Hypertension	20 (0.6%)	47 (7%)	<0.001
Peripheral Artery Disease	0	1 (0.2%)	0.15
Chronic Kidney Disease	0	**11 (2%)**	<0.001
Deep Vein Thrombosis	0	**5 (0.8%)**	<0.001
Pulmonary Embolism	1 (0.03%)	**6 (1%)**	<0.001
eCigarette (vaping)		10 (2%)	
Smoking		**48 (8%)**	
Immune Disorders	0	**12 (2%)**	<0.001
Congenital heart Disease	18 (0.5%)	**3 (0.5%)**	0.99
Asthma	265 (8%)	**90 (14%)**	<0.001
Other Pulmonary Disease	0	**5 (0.8%)**	<0.001
Pulmonary Arterial Hypertension	0	**3 (0.5%)**	0.003

†Fisher's exact test used for all categorical comparisons due to small expected cell counts

*Other race includes mixed, Asian, American-Indian, native-Hawaiian, Pacific Islander (ORCCA) and Asian, Pacific Islander, Unknown, Native American (AHA)

Abbreviations: AHA (American Heart Association); ORCCA (Outcomes Registry for Cardiac Conditions in Athletes)

3653 individuals were included in the ORCCA cohort with mean age of 19.9 (SD=1.42) years with 33% female, 65% white, 28% Black, and 3% Hispanic. 636 individuals were included in the AHA cohort with mean age of 21.4 (SD=1.91) years with 59% female, 31% white, 27% Black, and 32% Hispanic. BMI was significantly higher in the hospitalized AHA registry (32.4 kg/m^2, SD= 10.6) compared to the

ORCCA registry (25.6 kg/m^2, SD=4.7) p <0.001. The frequencies of diabetes mellitus (10% vs 0.4%), hypertension (7% vs 0.6%), chronic kidney disease (2% vs 0.0%), obesity (51% vs 13%), and asthma (14% vs 8%) were greater in the AHA cohort compared to ORCCA cohort, all with p<0.01. Participants in the ORCCA cohort were more likely to have no significant past medical history compared to the AHA cohort (70% vs 62%, p< 0.01). In those participants with no medical history, participants in the ORCCAA study were more likely to be non-obese (BMI <30 kg/m2) compared to the AHA registry (87% vs 52%, p <0.01%).

Initial Symptoms

The initial symptoms of both groups are shown in Table 2.

Table 2: Initial Symptoms and Cardiac Testing Performed

	ORCCA (N=3653)	AHA (N=636)	p-value
Initial Symptoms[a]			
Fever/Chills	683 (19%)	269 (43%)	<0.001
Cough	612 (17%)	258 (41%)	<0.001
Shortness of Breath	226 (6%)	236 (38%)	<0.001
Fatigue	553 (16%)	90 (14%)	0.55
Headache	853 (23%)	75 (12%)	<0.001
Myalgia	604(17%)	97 (15%)	0.45
Sore Throat	674 (18%)	49 (8%)	<0.001
Nasal Congestion	644 (18%)	34 (5%)	<0.001
Nausea, Vomiting or Diarrhea	182 (5%)	198 (32%)	<0.001
Loss of Sense of Smell/Taste	834 (23%)	36 (6%)	<0.001
Chest Pain	121 (3%)	44 (7%)	<0.001
Not Documented	381 (11%)	172 (27%)	<0.001
Asymptomatic	1078 (30%)	N/A	
Cardiac Testing			
MRI	516 (14%)	1 (0.33%)	<0.001
EKG	3486 (95%)	327 (52%)	<0.001
Troponin	3166 (87%)	232 (33%)	<0.001
Echo	2999 (82%)	47 (7%)	<0.001
Myocardial Injury (troponin elevation)	27 (0.9%)	173(77%)	
Hospitalization Characteristics			
Hospitalized	4	731 (100%)	--
Ventilated	0	60 (9%)	--

[a] Initial Symptoms for ORCCA and symptoms at the time of admission for AHA

Abbreviations: AHA (American Heart Association); ORCCA (Outcomes Registry for Cardiac Conditions in Athlete

The AHA cohort had greater proportions of fever/chills (43%), cough (41%), shortness of breath (38%), nausea/vomiting or diarrhea (32%), and chest pain (7%) compared to the ORCCA cohort (19%, 17%, 6%, 5%, and 3% respectively), all p-values <0.01. In contrast, the ORCCA cohort had greater proportions of headache (23%), loss of sense of smell/taste (23%), sore throat (18%), and nasal congestion (18%) compared to the AHA cohort (12%, 6%, 8%, and 5%, respectively), (all p-values <0.01)

Cardiac testing

Cardiac testing for the AHA and ORCCA cohorts is depicted in Table 2 and Figure 1. There was significantly more cardiac testing including CMR (cardiac magnetic resonance imaging) (14% vs 0.3%), electrocardiogram (95% vs 52%), troponin assay (87% vs 33%), and transthoracic echocardiogram (82% vs 7%) in the ORCCA cohort compared to the AHA cohort (all p-values <0.001).

Death, MACE, and Other Severe Clinical Events

Clinical Outcomes

Table 3 depicts the incidence of death, MACE, and secondary clinical events in the ORCCA cohort and AHA cohort.

Table 3: Incidence of Major Adverse Cardiovascular Events and other Severe Clinical Events in Young Adults with COVID-19

	ORCCA	AHA
Death, n (%)	0	12 (2%)
Major Adverse Cardiovascular Events (MACE)		
Total Events	22 (0.6%)	22 (3.5%)
Ischemic Stroke/Intracranial Hemorrhage, n (%)	0	6 (1%)
Pulmonary embolism, n (%)	1 (0.03%)	4 (0.6%)
New onset heart failure, n (%)	0	5 (0.8%)
Sustained Ventricular Arrythmias, n (%)	0	3 (0.5%)
Requirement of PPM, n (%)	0	0
Acute Myocardial Infarction, n (%)	0	1 (0.2%)
Myocarditis, n (%)	21 (0.6%)	3 (0.5%)
Cardiogenic Shock, n (%)	0	0
Other Severe Clinical Events		
Total Events	0 (0.0%)	104(16.4%)
New Hemodialysis or CRRT, n (%)	0	4 (0.6%)
Ventilation	-	60 (9%)
In-hospital Shock, n (%)	0	19 (3%)

Requirement of Mechanical Support, n (%)	-	2 (0.4%)
Requirement of Pressor Support, n (%)	-	19 (3%)

Abbreviations: AHA (American Heart Association); CRRT, continuous renal replacement therapy ; ORCCA (Outcomes Registry for Cardiac Conditions in Athletes)

There were 12 (2%) deaths in the AHA cohort compared to 0 deaths in the ORCCA cohort.

With respect to MACE, there were 22 (0.6%) overall events in the ORCCA cohort, - with 1 (0.03%) case of pulmonary embolism and 21 (0.6%) cases of COVID-19 myocardial involvement. The range of the events occurred from 8/2020 to 2/2021. In the AHA cohort, 22 (3.5%) patients experienced a MACE. There were 6 (1%) cases of ischemic stroke, 4 (0.6%) cases of pulmonary embolism, 5 (0.8%) cases of new onset heart failure, 3 events (0.5%) of sustained ventricular arrythmias, 3 (0.5%) cases of myocarditis, and 1 (0.2%) myocardial infarction. There were no other severe clinical events in the ORCCA group. There were 104 (16.4%) other severe clinical events in the AHA registry with 60 (9%) young adults requiring ventilation, 19 (3%) meeting criteria for shock, and 4 (0.6%) requiring hemodialysis or CRRT.

There were 4 (0.1%) hospitalizations for COVID-19 in the ORCCA cohort, while all patients in the AHA cohort by definition were hospitalized. The median follow-up for the ORCCA cohort was 411 [IQR: 387, 447] days; given the cross-sectional design of the AHA registry, no follow-up was conducted on those patients.

Univariable analysis

Results of univariable analyses to identify predictors for death, MACE, and other severe clinical events in the AHA cohort are provided in Table 4.

Table 4: Univariable predictors of Death, MACE and Other Severe Clinical Events in AHA Cohort

	Death (N=12)		**Major Adverse Cardiac Event (MACE)[a] (N=22)**		**Other Severe Clinical Events[b] (N=63)**	
Variable	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value

Age	1.02 (0.76, 1.36)	0.92	0.93 (0.75, 1.16)	0.53	0.98 (0.85, 1.12)	0.72
Female	0.50 (0.16, 1.52)	0.22	0.47 (0.20, 1.11)	0.08	0.64 (0.38, 1.08)	0.09
Race / Ethnicity		0.75		0.60		0.77
Black	0.62 (0.13, 2.98)	0.37	0.65 (0.22, 1.89)	0.59	0.87 (0.45, 1.68)	0.92
Hispanic	0.95 (0.25, 3.58)	0.90	0.54 (0.18, 1.57)	0.31	0.72 (0.37, 1.38)	0.34
White Non-Hispanic	REF		REF		REF	REF
Other	1.70 (0.35, 8.28)	0.33	1.12 (0.32, 3.97)	0.44	1.01 (0.42, 2.44)	0.69
BMI kg/m^2	1.05 (1.00, 1.10)	0.04	0.98 (0.93, 1.02)	0.31	1.01 (0.98, 1.03)	0.50
Diabetes	1.17 (0.21, 6.65)	0.86	1.10 (0.29, 4.23)	0.89	1.43 (0.66, 3.12)	0.37
Hypertension	0.49 (0.03, 8.59)	0.62	1.53 (0.39, 5.95)	0.54	1.45 (0.60, 3.49)	0.41
Asthma	0.78 (0.14, 4.38)	0.78	0.41 (0.08, 2.20)	0.30	1.05 (0.51, 2.19)	0.89
Smoking	0.48 (0.03, 8.39)	0.61	1.49 (0.38, 5.80)	0.56	0.67 (0.22, 2.08)	0.49

[a] MACE: ischemic stroke, myocardial infarction, sustained ventricular arrythmias, cardiogenic shock, new onset heart failure, myocarditis, requirement of permanent PPM and pulmonary embolism/deep vein thrombosis

[b] Other severe clinical events were new hemodialysis or continuous renal replacement therapy (CRRT), requirement of ventilation, or non-cardiogenic shock

A higher BMI was associated with death (OR: 1.05, 95% CI: 1.00, 1.10; p=0.04). No significant predictors of MACE or other severe clinical events were identified.

DISCUSSION

The purpose of this study was to define the clinical spectrum of disease and identify cardiac and other severe complications of COVID-19 in young adults between the ages of 18 to 24 from two established registries on potentially opposite sides of the disease severity continuum. The patients in the AHA registry were more likely to have medical comorbidities including diabetes mellitus, hypertension, chronic kidney disease, and asthma compared to patients in the ORCCA study. Importantly, there were racial disparities in the two cohorts with the ORCCA cohort being 65% white and only 3% Hispanic,

while the AHA cohort was 31% white and 32% Hispanic. There were also sex differences which may have a role in COVID-19 outcomes, with 59% of patients in the AHA cohort being female versus 35% in the ORCCA cohort.[17] Initial symptoms differed between the groups, with more severe symptom presentations in hospitalized patients from the AHA cohort such as shortness of breath, fever, and vomiting compared to symptoms in the ORCCA registry, perhaps indicating an eventual more severe illness course. It should be noted that the ORCCA study does not represent the general 18-24-year-old population but rather a young, athletic population. This is the first analysis of health outcomes in young adults hospitalized with COVID-19 from the AHA COVID-19 CVD registry. Importantly, we observed: 1) more pre-existing comorbidities in hospitalized patients, 2) a mortality rate of 2%, and 3) a higher risk of death with higher BMI. This study also highlights the low rate of cardiac testing in the AHA hospitalized patient cohort, in contrast with frequent cardiac testing and high resource utilization in the ORCCA study collegiate athlete cohort. Unlike initial studies of older adults hospitalized with COVID-19, this study did not find a similarly high rate of myocardial injury or MACE. [18-20]

Prior studies of young adults demonstrate low mortality rates for patients hospitalized with COVID-19, though point estimates range from 0.2% for 18 to 29-year-olds in a large academic health system to 2.7% in a large series of 18 to 34-year-olds derived from insurance data.[21 22] Our findings confirm that obesity is a risk factor for COVID-19 related mortality in young adults. [21] While heterogeneity exists for mortality in younger individuals hospitalized with COVID-19, the mortality rate in the young is strikingly lower than that of elderly individuals, estimated by Nguyen *et al.* to be 26.6% in individuals 80 and older. [23]

Comparison to data from the National Health and Nutrition Examination Survey (NHANES) puts the prevalence of co-morbidities found in the AHA hospitalized COVID-19 cohort in context. [24] While prevalence of asthma (14%) in young adults hospitalized with COVID-19 seems high, this is similar to the 18% prevalence seen in the overall population of 18 to 24-year-olds. [24] In contrast, the

incidences of diabetes mellitus (10%) and hypertension (7%) are higher than those seen in the overall population according to NHANES data (0.5% and 4%, respectively). [24] Despite the high co-morbidity burden compared to non-hospitalized collegiate athletes, 62% of patients in the AHA hospitalized cohort still had no remarkable past medical history, highlighting that COVID-19 adverse outcomes can affect any patient and that risk factors are hard to predict and incompletely understood.

Our analysis juxtaposing an athletic young adult cohort with a hospitalized young adult cohort highlights the heterogenous nature of BMI as a risk predictor. BMI has been identified as a risk factor for hospitalization and mortality following hospitalization across all age groups. [25-27] However, in the ORCCA dataset involving collegiate athletes, BMI was not found to be associated with COVID-19 myocardial involvement.[15] Notably, however, the elevated BMI of an elite athlete is different than the elevated BMI of a non-athlete as the traditional BMI metric does not take into account muscle mass, body composition, and bone density. [28] Therefore, the limitations of using BMI should be considered before extrapolating the risks of elevated BMI in the general population to athletes with COVID-19. A more detailed assessment of adiposity in conjunction with BMI is an important area of future study.

The utilization of cardiac testing was starkly different between the ORCCA cohort and the AHA cohort. Initial concerns for myocardial inflammation from COVID-19 infection and an elevated risk of sudden death in competitive athletes drove initial consensus recommendations to err on the side of early detection with the potential for over-diagnosis.[29] Thus, institutions participating in the ORCCA study used protocols aimed at sensitivity, with 93.4% of athletes receiving at least one of troponin, ECG, or TTE, and 6.6% of participants receiving mandatory CMR screening.[15] In the AHA cohort, cardiac diagnostic testing was likely to be more specific, driven by clinical suspicion and the need to minimize healthcare worker exposure or the transport of critically ill patients. For hospitalized patients, there was a lower-than-expected rate of cardiac testing with only 49% of patients receiving ECG, 35% troponin testing, 7% TTE, and 0.2% CMR. With over 42% of patients in the AHA cohort experiencing shortness

of breath or chest pain, the use of TTE in only 7% of patients is significantly lower than in previous studies of hospitalized patients with similar symptoms. [30 31] Similarly, an ECG in less than 50% of patients is much lower than previously described in hospitalized patients given patient comorbidities, symptom description, early concerns around myocarditis, and the frequency with which QT_C prolonging medications were used for the treatment of COVID-19. [32-34] A desire to minimize patient contact and the scarcity of personal protective equipment early in the pandemic likely limited cardiac testing in the hospital. These lower rates of cardiac testing also may have been due to an underappreciation of the cardiac manifestations of COVID-19, or errors and discrepancies in reporting cardiac testing in the AHA registry. Our findings raise the possibility that under-utilization of cardiac testing in hospitalized patients may have led to under-diagnosis of cardiac involvement, while over-utilization of cardiac testing in competitive athletes may have led to over-diagnosis.

There are several important limitations to this study. First, this is a comparison of two independent cohorts with two different criteria for entry: participation in NCAA athletics for the ORCCA cohort versus hospitalization for COVID-19 in the AHA cohort. These differences limit cross-comparisons between cohorts. Second, the AHA cohort relies on registry abstraction, and may be overweighted towards hospitals and hospital systems with resources sufficient to populate these registries. Thus, outcomes in the AHA cohort may not fully reflect the outcomes experienced for young adult patients hospitalized with COVID-19 across all hospitals in the United States. Third, in contrast to the ORCCA study with greater than 1 year of follow-up, there is no follow-up beyond the initial hospitalization in the AHA COVID-19 registry. This limits accurate assessment of the true incidence of severe events, MACE, and mortality related to COVID-19 hospitalization. The rates of CT scanning was not included in the AHA registry which may affect the rates of pulmonary embolism diagnosis. Fourth, registry capture in the AHA cohort was incomplete, with 27% of patients not having documented presenting symptoms. Fifth, the low prevalence of basic cardiovascular testing in the AHA cohort likely

leads to under-ascertainment of MACE. Another important consideration is that data was collected in these registries before widespread availability of the COVID-19 vaccination, which has shown to be effective in reducing severe complications and hospitalization from COVID-19 infection. Last, with the relatively low prevalence of mortality, MACE, and severe COVID-related adverse events, and the relatively small sample size of 18- to 24-year-old patients hospitalized for COVID-19, our study is underpowered for detailed modeling of risk factors associated with poorer outcomes in the setting of COVID-19 illness.

In conclusion, this study compared clinical outcomes in young adults patients across the health spectrum with COVID-19 infection. We found a significantly higher burden of comorbidities and lower rates of cardiac testing in hospitalized patients as compared to competitive athletes with COVID-19. Nine percent of hospitalized young adults with COVID-19 required mechanical ventilation, 3.5% suffered a MACE, and 2% died. Importantly, elevated BMI predicted mortality in hospitalized patients. Additional research is needed to better elucidate risk factors for severe health outcomes in young adults afflicted with COVID-19.

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Data sharing statement: Data are available upon reasonable request. Technical appendix, statistical code and dataset available from the AHA Precision Medicine Platform.

Author Contributions

Aakash Bavishi, Stephanie A. Kliethermes, Bradley Petek, Nathaniel Moulson, Timothy W. Churchill, Kimberly Harmon, Manesh Patel, Aaron L. Baggish, Jonathon A. Drezner, and Kannan Mutharasan participated in study design, data collection, statistical analysis and preparation of manuscript. Prenav Mellacheruvu participated in data collection.

Ethics Approval

This study involves human participants and was approved by an Ethics Committee(s) or Institutional Board(s). The Massachusetts General Hospital Review Board Reference ID is 2020P002667.

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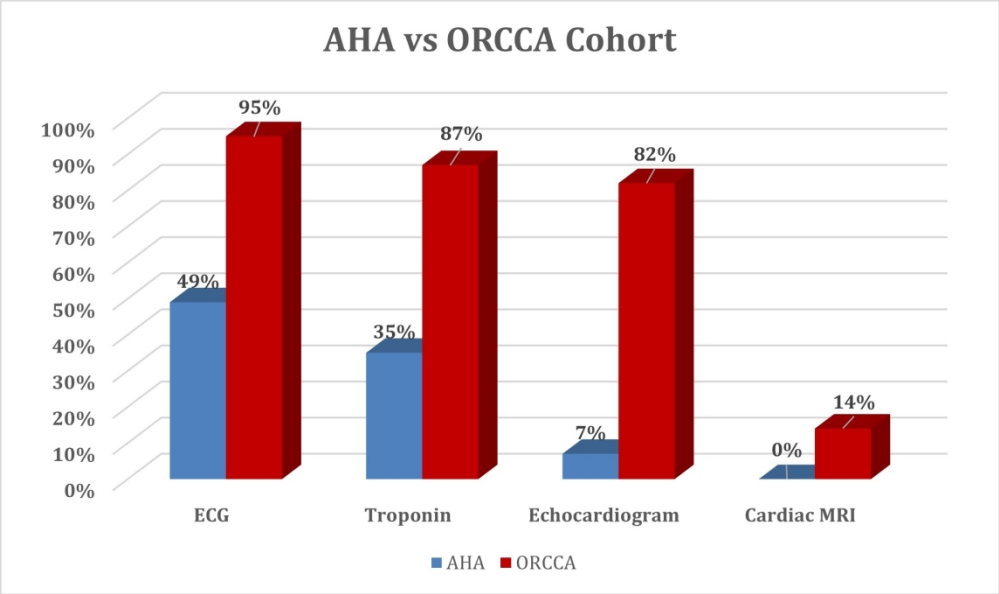
FIGURE LEGENDS

Figure 1. Abbreviations: AHA, American Heart Association; ECG, electrocardiogram; MRI- magnetic resonance imaging; ORCCA, Organized Registry for Cardiac Conditions in Athletes



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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5/6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than	6

		one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	12
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6-7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7
Statistical methods	#12c	Explain how missing data were addressed	7
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	7
Statistical methods	#12e	Describe any sensitivity analyses	7
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	7-8

		confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	7
Participants	#13c	Consider use of a flow diagram	
NA- can provide if needed			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	7/8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
8			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
8/9			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
8/9			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence	9

		interval). Make clear which confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	9
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	#18	Summarise key results with reference to study objectives	9
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	12
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11
Generalisability	#21	Discuss the generalisability (external validity) of the study results	11
Other Information			

Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

Notes:

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BMJ Open

The clinical spectrum of COVID-19 complications in young adults: combined analysis of the American Heart Association COVID-19 Cardiovascular Disease Registry and the Outcomes Registry for Cardiac Conditions in Athletes

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Keywords:	PUBLIC HEALTH, Adult cardiology < CARDIOLOGY, COVID-19

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The clinical spectrum of COVID-19 complications in young adults: combined analysis of the American Heart Association COVID-19 Cardiovascular Disease Registry and the Outcomes Registry for Cardiac Conditions in Athletes

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ABSTRACT

Background: While young adults 18-24 years old bear a significant proportion of COVID-19 diagnoses, the risk factors for hospitalization and severe COVID-19 complications in this population are poorly understood.

Objective: The objective of this study was to identify risk factors for hospitalization and other COVID-19 complications across the health spectrum of young adults diagnosed with COVID-19 infection.

Study Design: Retrospective cohort study

Participants: Young adults (ages 18-24) with confirmed COVID-19 infection from the American Heart Association (AHA) COVID-19 Cardiovascular Disease registry of hospitalized patients and the Outcomes Registry for Cardiac Conditions in Athletes (ORCCA) study of collegiate athletes. The AHA registry included 636 young adults from 152 hospitals. The ORCCA registry consisted of 3653 competitive college athletes from 42 colleges and universities.

Intervention: None (exposure to COVID-19)

Primary and Secondary Outcome Measures: Main outcomes included hospitalization, death, major adverse cardiovascular events and other severe clinical events.

Results: In comparison to the ORCCA registry, patients in the AHA registry were more likely to be female (59% vs 33%); have higher average BMI (32.4 vs. 25.6); and have increased prevalence of diabetes (10% vs. 0.4%), hypertension (7% vs. 0.6%), chronic kidney disease (2% vs. 0%), and asthma (14% vs. 8%), all with $p<0.01$. There were 8 (2%) deaths in the AHA hospitalized registry compared to zero in the ORCCA cohort. BMI was a statistically significant predictor of death in the hospitalized cohort (OR: 1.05, 95% CI: 1.00, 1.10). No significant predictors of MACE or other severe clinical events were identified.

Conclusions: The risk of cardiac events in young adults ages 18-24 diagnosed with COVID-19 infection is low. Patients who were hospitalized (AHA registry) were more likely to have pre-existing medical

comorbidities and higher BMI than healthy collegiate athletes (ORCCA registry). Once hospitalized, elevated BMI is associated with increased mortality although other drivers of MACE and other severe clinical events remain unclear.

Strengths and Limitations

- Through a comparison between two large independent cohorts, cardiac and other severe complications of COVID-19 in young adults between the ages of 18 to 24 were able to be identified
- Cross-comparisons between cohorts is limited as these are two independent cohorts with two different criteria for entry
- The low prevalence of basic cardiovascular testing in the AHA cohort likely leads to under-ascertainment of major adverse cardiac events.

INTRODUCTION

Coronavirus disease 19 (COVID-19) infection has manifested in a wide array of clinical complications including but not limited to respiratory failure, systemic inflammation, thromboembolic events, and cardiovascular events. [1-3] While older age and comorbidities including chronic kidney disease have been identified as a significant risk factors for increased morbidity and mortality in patients infected with COVID-19, severe complications of COVID-19 have been reported across all age groups including young adults ages 18-24. [4-6] Although these individuals bear a significant proportion of COVID-19 infections, the spectrum and risk of COVID-19 complications in this age group remain understudied.

The issue of cardiovascular complications and the necessity of screening following COVID-19 infection in young adults has been the source of significant debate.[7 8] While the vast majority of young adults recover with minor or no cardiovascular injury, several case reports and case series have demonstrated the potential cardiac impact of COVID-19 in healthy young adults. [9] Reported sequelae include myocardial infarction, myocarditis, sudden onset biventricular heart failure requiring mechanical support, and sudden cardiac death. [10-12] Multi-inflammatory response syndrome with multi-organ failure has also been noted in young adults. [13 14] The reasons why certain individuals have such devastating cardiovascular consequences of COVID-19 infection are not known.

Our study aims to better define the clinical spectrum of COVID-19 cardiac and non-cardiac complications in young adults by utilizing two registries representing the 'bookends' of health: the American Heart Association (AHA) COVID-19 Cardiovascular Disease registry of hospitalized patients and the Outcomes Registry for Cardiac Conditions in Athletes (ORCCA) study of previously healthy collegiate athletes. Through a combined analysis and comparison of these two registries, our primary aim is to evaluate both the prevalence of serious cardiac and non-cardiac complications and the risk factors for hospitalization and severe complications in these young adults. Our secondary aim is to

examine the utility of diagnostic testing for cardiac involvement along the health spectrum of young adults diagnosed with COVID-19.

METHODS

Data Sources

The AHA COVID-19 Cardiovascular Disease registry is a retrospective registry of consecutive patients collected by 152 hospitals and centers participating in this quality improvement registry. Eligible patients are all patients hospitalized with a diagnosis of COVID-19. All adults 18-24 years of age were included from the AHA registry between the dates of March 1st, 2020 and April 19, 2021. The registry captures baseline demographics, testing, laboratory results, and health outcomes.

The ORCCA study consists of National Collegiate Athletic Association athletes with confirmed COVID-19 infection from September 1, 2020 to June 1, 2021. Eligibility criteria and data collection methods have been described previously. [15] Patient demographics, COVID-19 symptoms, cardiac evaluations, and cardiac outcomes were captured in the registry. Evaluations were performed per the discretion of local institutions and included a clinical assessment with or without cardiac testing such as a 12-lead electrocardiogram (ECG), cardiac troponin assay, trans-thoracic echocardiogram (TTE), and cardiac magnetic resonance (CMR) imaging. Results were communicated to the patients and if necessary were referred for further evaluation.

In both cohorts, individual participant consent was waived as only deidentified data was used.

Definition of Primary Outcomes

Primary outcomes included hospitalization, death, major adverse cardiovascular events (MACE), and other severe clinical events. A MACE was defined as the occurrence of one or more of the following events: ischemic stroke, myocardial infarction, sustained ventricular arrythmias, cardiogenic shock, new onset heart failure, myocarditis/myocardial involvement, requirement of permanent pacemaker (PPM) or pulmonary embolism/deep vein thrombosis. Other severe clinical events included

new hemodialysis or continuous renal replacement therapy (CRRT), requirement of mechanical ventilation, or non-cardiogenic shock. COVID-19 myocardial involvement was defined in the current study as probable or definitive myocardial or myopericardial involvement per previous definitions.[15] Follow-up was requested from participating institutions periodically throughout the study period by the ORCCA investigators. There was no follow-up beyond the initial hospitalization in the AHA COVID-19 registry. The median duration of hospitalization was 4 days. Because hospitalization was an entry criterion for the AHA registry, hospitalization rates were assessed only for ORCCA study participants.

Statistical Analysis

Standard descriptive statistics were used to describe patient characteristics, symptoms, cardiac testing, and incidence of MACE and other severe clinical complications in both cohorts. Asymptomatic patients, including female patients admitted for labor and delivery, were removed from the AHA cohort as COVID-19 likely was an incidental finding and not the cause of hospitalization. Means and standard deviations (SD) summarize continuous variables. Frequencies and percentages summarize categorical variables. Two sample t-tests were used for continuous comparisons, while chi-square tests or Fisher's exact tests were used for categorical comparisons, as appropriate. To account for the small number of observed events, univariable firth logistic regression models were created to assess potential predictors of death, MACE, and other severe clinical events. Odds ratios and 95% confidence intervals are provided for all models. We followed the STROBE Checklist for reporting of cohort studies. [16] The American Heart Association Precision Medicine Platform (https://precision.heart.org/) was used for data analysis. IQVIA (Parsippany, New Jersey) serves as the data collection and coordination center. All statistical analyses were conducted in SAS v9.4 (SAS Institutes, Cary, NC).

Patient and Public Involvement

No patient involved

RESULTS

Baseline Characteristics

Baseline characteristics of participants in the AHA and ORCCA registries are shown in Table 1.

Table 1: Baseline Characteristics in the AHA and ORCCA Cohorts of Young Adults with COVID-19

	ORCCA (N=3653)	AHA (N=636)	p-value
Age, mean (SD)	19.91 (1.42)	21.43 (1.91)	<0.001
Female, n(%)	1209 (33%)	376 (59%)	<0.001
Race			<0.001
Black, n (%)	992 (28%)	172 (27%)	
Hispanic, n (%)	112 (3%)	205 (32%)	
White-Non Hispanic	2334 (65%)	195 (31%)	
Other*	166 (5%)	64 (10%)	
Medical History†			
Unremarkable Medical History	2540 (70%)	397 (62%)	<0.001
BMI kg/m^2, mean (SD)	25.64 (4.74)	32.40 (10.57)	<0.001
Obesity (BMI > 30 kg/ m$^{2)}$			
Normal weigh or other com			
Atrial Fibrillation	1 (0.03%)	3 (0.5%)	0.01
Stroke/Transient Ischemia Attack	0	8 (1%)	<0.001
Diabetes Mellitus	12 (0.4%)	63 (10%)	<0.001
Dyslipidemia	11 (0.3%)	9 (1%)	0.001
Heart Failure		5 (0.8%)	
Hypertension	20 (0.6%)	47 (7%)	<0.001
Peripheral Artery Disease	0	1 (0.2%)	0.15
Chronic Kidney Disease	0	**11 (2%)**	<0.001
Deep Vein Thrombosis	0	**5 (0.8%)**	<0.001
Pulmonary Embolism	1 (0.03%)	**6 (1%)**	<0.001
eCigarette (vaping)		10 (2%)	
Smoking		**48 (8%)**	
Immune Disorders	0	**12 (2%)**	<0.001
Congenital heart Disease	18 (0.5%)	**3 (0.5%)**	0.99
Asthma	265 (8%)	**90 (14%)**	<0.001
Other Pulmonary Disease	0	**5 (0.8%)**	<0.001
Pulmonary Arterial Hypertension	0	**3 (0.5%)**	0.003

†Fisher's exact test used for all categorical comparisons due to small expected cell counts

*Other race includes mixed, Asian, American-Indian, native-Hawaiian, Pacific Islander (ORCCA) and Asian, Pacific Islander, Unknown, Native American (AHA)

Abbreviations: AHA (American Heart Association); ORCCA (Outcomes Registry for Cardiac Conditions in Athletes)

3653 individuals were included in the ORCCA cohort with mean age of 19.9 (SD=1.42) years with 33% female, 65% white, 28% Black, and 3% Hispanic. 636 individuals were included in the AHA cohort with mean age of 21.4 (SD=1.91) years with 59% female, 31% white, 27% Black, and 32% Hispanic. BMI was significantly higher in the hospitalized AHA registry (32.4 kg/m^2, SD= 10.6) compared to the ORCCA registry (25.6 kg/m^2, SD=4.7) p <0.001. The frequencies of diabetes mellitus (10% vs 0.4%), hypertension (7% vs 0.6%), chronic kidney disease (2% vs 0.0%), obesity (51% vs 13%), and asthma (14% vs 8%) were greater in the AHA cohort compared to ORCCA cohort, all with p<0.01. Participants in the ORCCA cohort were more likely to have no significant past medical history compared to the AHA cohort (70% vs 62%, p< 0.01). In those participants with no medical history, participants in the ORCCAA study were more likely to be non-obese (BMI <30 kg/m2) compared to the AHA registry (87% vs 52%, p <0.01%).

Initial Symptoms

The initial symptoms of both groups are shown in Table 2.

Table 2: Initial Symptoms and Cardiac Testing Performed

	ORCCA (N=3653)	AHA (N=636)	p-value
Initial Symptoms[a]			
Fever/Chills	683 (19%)	269 (43%)	<0.001
Cough	612 (17%)	258 (41%)	<0.001
Shortness of Breath	226 (6%)	236 (38%)	<0.001
Fatigue	553 (16%)	90 (14%)	0.55
Headache	853 (23%)	75 (12%)	<0.001
Myalgia	604(17%)	97 (15%)	0.45
Sore Throat	674 (18%)	49 (8%)	<0.001
Nasal Congestion	644 (18%)	34 (5%)	<0.001
Nausea, Vomiting or Diarrhea	182 (5%)	198 (32%)	<0.001
Loss of Sense of Smell/Taste	834 (23%)	36 (6%)	<0.001
Chest Pain	121 (3%)	44 (7%)	<0.001
Not Documented	381 (11%)	172 (27%)	<0.001
Asymptomatic	1078 (30%)	N/A	
Cardiac Testing			
MRI	516 (14%)	1 (0.33%)	<0.001
EKG	3486 (95%)	327 (52%)	<0.001
Troponin	3166 (87%)	232 (33%)	<0.001
Echo	2999 (82%)	47 (7%)	<0.001

Myocardial Injury (troponin elevation)	27 (0.9%)	173(77%)	
Hospitalization Characteristics			
Hospitalized	4	731 (100%)	--
Ventilated	0	60 (9%)	--

[a] Initial Symptoms for ORCCA and symptoms at the time of admission for AHA
Abbreviations: AHA (American Heart Association); ORCCA (Outcomes Registry for Cardiac Conditions in Athlete

The AHA cohort had greater proportions of fever/chills (43%), cough (41%), shortness of breath (38%), nausea/vomiting or diarrhea (32%), and chest pain (7%) compared to the ORCCA cohort (19%, 17%, 6%, 5%, and 3% respectively), all p-values <0.01. In contrast, the ORCCA cohort had greater proportions of headache (23%), loss of sense of smell/taste (23%), sore throat (18%), and nasal congestion (18%) compared to the AHA cohort (12%, 6%, 8%, and 5%, respectively), (all p-values <0.01)

Cardiac testing

Cardiac testing for the AHA and ORCCA cohorts is depicted in Table 2 and Figure 1. There was significantly more cardiac testing including CMR (cardiac magnetic resonance imaging) (14% vs 0.3%), electrocardiogram (95% vs 52%), troponin assay (87% vs 33%), and transthoracic echocardiogram (82% vs 7%) in the ORCCA cohort compared to the AHA cohort (all p-values <0.001).

Death, MACE, and Other Severe Clinical Events

Clinical Outcomes

Table 3 depicts the incidence of death, MACE, and secondary clinical events in the ORCCA cohort and AHA cohort.

Table 3: Incidence of Major Adverse Cardiovascular Events and other Severe Clinical Events in Young Adults with COVID-19

	ORCCA	AHA
Death, n (%)	0	12 (2%)
Major Adverse Cardiovascular Events (MACE)		
Total Events	22 (0.6%)	22 (3.5%)
Ischemic Stroke/Intracranial Hemorrhage, n (%)	0	6 (1%)
Pulmonary embolism, n (%)	1 (0.03%)	4 (0.6%)

New onset heart failure, n (%)	0	5 (0.8%)
Sustained Ventricular Arrythmias, n (%)	0	3 (0.5%)
Requirement of PPM, n (%)	0	0
Acute Myocardial Infarction, n (%)	0	1 (0.2%)
Myocarditis, n (%)	21 (0.6%)	3 (0.5%)
Cardiogenic Shock, n (%)	0	0
Other Severe Clinical Events		
Total Events	0 (0.0%)	104(16.4%)
New Hemodialysis or CRRT, n (%)	0	4 (0.6%)
Ventilation	-	60 (9%)
In-hospital Shock, n (%)	0	19 (3%)
Requirement of Mechanical Support, n (%)	-	2 (0.4%)
Requirement of Pressor Support, n (%)	-	19 (3%)

Abbreviations: AHA (American Heart Association); CRRT, continuous renal replacement therapy ; ORCCA (Outcomes Registry for Cardiac Conditions in Athletes)

There were 12 (2%) deaths in the AHA cohort compared to 0 deaths in the ORCCA cohort.

With respect to MACE, there were 22 (0.6%) overall events in the ORCCA cohort, - with 1 (0.03%) case of pulmonary embolism and 21 (0.6%) cases of COVID-19 myocardial involvement. The range of the events occurred from 8/2020 to 2/2021. In the AHA cohort, 22 (3.5%) patients experienced a MACE. There were 6 (1%) cases of ischemic stroke, 4 (0.6%) cases of pulmonary embolism, 5 (0.8%) cases of new onset heart failure, 3 events (0.5%) of sustained ventricular arrythmias, 3 (0.5%) cases of myocarditis, and 1 (0.2%) myocardial infarction. There were no other severe clinical events in the ORCCA group. There were 104 (16.4%) other severe clinical events in the AHA registry with 60 (9%) young adults requiring ventilation, 19 (3%) meeting criteria for shock, and 4 (0.6%) requiring hemodialysis or CRRT.

There were 4 (0.1%) hospitalizations for COVID-19 in the ORCCA cohort, while all patients in the AHA cohort by definition were hospitalized. The median follow-up for the ORCCA cohort was 411 [IQR: 387, 447] days; given the cross-sectional design of the AHA registry, no follow-up was conducted on those patients.

Univariable analysis

Results of univariable analyses to identify predictors for death, MACE, and other severe clinical events in the AHA cohort are provided in Table 4.

Table 4: Univariable predictors of Death, MACE and Other Severe Clinical Events in AHA Cohort

	Death (N=12)		**Major Adverse Cardiac Event (MACE)[a] (N=22)**		**Other Severe Clinical Events[b] (N=63)**	
Variable	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.02 (0.76, 1.36)	0.92	0.93 (0.75, 1.16)	0.53	0.98 (0.85, 1.12)	0.72
Female	0.50 (0.16, 1.52)	0.22	0.47 (0.20, 1.11)	0.08	0.64 (0.38, 1.08)	0.09
Race / Ethnicity		0.75		0.60		0.77
Black	0.62 (0.13, 2.98)	0.37	0.65 (0.22, 1.89)	0.59	0.87 (0.45, 1.68)	0.92
Hispanic	0.95 (0.25, 3.58)	0.90	0.54 (0.18, 1.57)	0.31	0.72 (0.37, 1.38)	0.34
White Non-Hispanic	REF		REF		REF	REF
Other	1.70 (0.35, 8.28)	0.33	1.12 (0.32, 3.97)	0.44	1.01 (0.42, 2.44)	0.69
BMI kg/m^2	1.05 (1.00, 1.10)	0.04	0.98 (0.93, 1.02)	0.31	1.01 (0.98, 1.03)	0.50
Diabetes	1.17 (0.21, 6.65)	0.86	1.10 (0.29, 4.23)	0.89	1.43 (0.66, 3.12)	0.37
Hypertension	0.49 (0.03, 8.59)	0.62	1.53 (0.39, 5.95)	0.54	1.45 (0.60, 3.49)	0.41
Asthma	0.78 (0.14, 4.38)	0.78	0.41 (0.08, 2.20)	0.30	1.05 (0.51, 2.19)	0.89
Smoking	0.48 (0.03, 8.39)	0.61	1.49 (0.38, 5.80)	0.56	0.67 (0.22, 2.08)	0.49

[a] MACE: ischemic stroke, myocardial infarction, sustained ventricular arrythmias, cardiogenic shock, new onset heart failure, myocarditis, requirement of permanent PPM and pulmonary embolism/deep vein thrombosis

[b] Other severe clinical events were new hemodialysis or continuous renal replacement therapy (CRRT), requirement of ventilation, or non-cardiogenic shock

A higher BMI was associated with death (OR: 1.05, 95% CI: 1.00, 1.10; p=0.04). No significant predictors of MACE or other severe clinical events were identified.

DISCUSSION

The purpose of this study was to define the clinical spectrum of disease and identify cardiac and other severe complications of COVID-19 in young adults between the ages of 18 to 24 from two

established registries on potentially opposite sides of the disease severity continuum. The patients in the AHA registry were more likely to have medical comorbidities including diabetes mellitus, hypertension, chronic kidney disease, and asthma compared to patients in the ORCCA study. Importantly, there were racial disparities in the two cohorts with the ORCCA cohort being 65% white and only 3% Hispanic, while the AHA cohort was 31% white and 32% Hispanic. There were also sex differences which may have a role in COVID-19 outcomes, with 59% of patients in the AHA cohort being female versus 35% in the ORCCA cohort.[17] Initial symptoms differed between the groups, with more severe symptom presentations in hospitalized patients from the AHA cohort such as shortness of breath, fever, and vomiting compared to symptoms in the ORCCA registry, perhaps indicating an eventual more severe illness course. It should be noted that the ORCCA study does not represent the general 18-24-year-old population but rather a young, athletic population. This is the first analysis of health outcomes in young adults hospitalized with COVID-19 from the AHA COVID-19 CVD registry. Importantly, we observed: 1) more pre-existing comorbidities in hospitalized patients, 2) a mortality rate of 2%, and 3) a higher risk of death with higher BMI. This study also highlights the low rate of cardiac testing in the AHA hospitalized patient cohort, in contrast with frequent cardiac testing and high resource utilization in the ORCCA study collegiate athlete cohort. Unlike initial studies of older adults hospitalized with COVID-19, this study did not find a similarly high rate of myocardial injury or MACE. [18-20]

Prior studies of young adults demonstrate low mortality rates for patients hospitalized with COVID-19, though point estimates range from 0.2% for 18 to 29-year-olds in a large academic health system to 2.7% in a large series of 18 to 34-year-olds derived from insurance data.[21 22] Our findings confirm that obesity is a risk factor for COVID-19 related mortality in young adults. [21] While heterogeneity exists for mortality in younger individuals hospitalized with COVID-19, the mortality rate in the young is strikingly lower than that of elderly individuals, estimated by Nguyen *et al.* to be 26.6% in individuals 80 and older. [23]

Comparison to data from the National Health and Nutrition Examination Survey (NHANES) puts the prevalence of co-morbidities found in the AHA hospitalized COVID-19 cohort in context. [24] While prevalence of asthma (14%) in young adults hospitalized with COVID-19 seems high, this is similar to the 18% prevalence seen in the overall population of 18 to 24-year-olds. [24] In contrast, the incidences of diabetes mellitus (10%) and hypertension (7%) are higher than those seen in the overall population according to NHANES data (0.5% and 4%, respectively). [24] Despite the high co-morbidity burden compared to non-hospitalized collegiate athletes, 62% of patients in the AHA hospitalized cohort still had no remarkable past medical history, highlighting that COVID-19 adverse outcomes can affect any patient and that risk factors are hard to predict and incompletely understood.

Our analysis juxtaposing an athletic young adult cohort with a hospitalized young adult cohort highlights the heterogenous nature of BMI as a risk predictor. BMI has been identified as a risk factor for hospitalization and mortality following hospitalization across all age groups. [25-27] However, in the ORCCA dataset involving collegiate athletes, BMI was not found to be associated with COVID-19 myocardial involvement.[15] Notably, however, the elevated BMI of an elite athlete is different than the elevated BMI of a non-athlete as the traditional BMI metric does not take into account muscle mass, body composition, and bone density. [28] Therefore, the limitations of using BMI should be considered before extrapolating the risks of elevated BMI in the general population to athletes with COVID-19. A more detailed assessment of adiposity in conjunction with BMI is an important area of future study.

The utilization of cardiac testing was starkly different between the ORCCA cohort and the AHA cohort. Initial concerns for myocardial inflammation from COVID-19 infection and an elevated risk of sudden death in competitive athletes drove initial consensus recommendations to err on the side of early detection with the potential for over-diagnosis.[29] Thus, institutions participating in the ORCCA study used protocols aimed at sensitivity, with 93.4% of athletes receiving at least one of troponin, ECG, or TTE, and 6.6% of participants receiving mandatory CMR screening.[15] In the AHA cohort, cardiac

diagnostic testing was likely to be more specific, driven by clinical suspicion and the need to minimize healthcare worker exposure or the transport of critically ill patients. For hospitalized patients, there was a lower-than-expected rate of cardiac testing with only 49% of patients receiving ECG, 35% troponin testing, 7% TTE, and 0.2% CMR. With over 42% of patients in the AHA cohort experiencing shortness of breath or chest pain, the use of TTE in only 7% of patients is significantly lower than in previous studies of hospitalized patients with similar symptoms. [30 31] Similarly, an ECG in less than 50% of patients is much lower than previously described in hospitalized patients given patient comorbidities, symptom description, early concerns around myocarditis, and the frequency with which QT_C prolonging medications were used for the treatment of COVID-19. [32-34] A desire to minimize patient contact and the scarcity of personal protective equipment early in the pandemic likely limited cardiac testing in the hospital. These lower rates of cardiac testing also may have been due to an underappreciation of the cardiac manifestations of COVID-19, or errors and discrepancies in reporting cardiac testing in the AHA registry. Our findings raise the possibility that under-utilization of cardiac testing in hospitalized patients may have led to under-diagnosis of cardiac involvement, while over-utilization of cardiac testing in competitive athletes may have led to over-diagnosis.

There are several important limitations to this study. First, this is a comparison of two independent cohorts with two different criteria for entry: participation in NCAA athletics for the ORCCA cohort versus hospitalization for COVID-19 in the AHA cohort. These differences limit cross-comparisons between cohorts. Second, the AHA cohort relies on registry abstraction, and may be overweighted towards hospitals and hospital systems with resources sufficient to populate these registries. Thus, outcomes in the AHA cohort may not fully reflect the outcomes experienced for young adult patients hospitalized with COVID-19 across all hospitals in the United States. Third, in contrast to the ORCCA study with greater than 1 year of follow-up, there is no follow-up beyond the initial hospitalization in the AHA COVID-19 registry. This limits accurate assessment of the true incidence of

severe events, MACE, and mortality related to COVID-19 hospitalization. The rates of CT scanning was not included in the AHA registry which may affect the rates of pulmonary embolism diagnosis. Fourth, registry capture in the AHA cohort was incomplete, with 27% of patients not having documented presenting symptoms. Fifth, the low prevalence of basic cardiovascular testing in the AHA cohort likely leads to under-ascertainment of MACE. Another important consideration is that data was collected in these registries before widespread availability of the COVID-19 vaccination, which has shown to be effective in reducing severe complications and hospitalization from COVID-19 infection. Last, with the relatively low prevalence of mortality, MACE, and severe COVID-related adverse events, and the relatively small sample size of 18- to 24-year-old patients hospitalized for COVID-19, our study is underpowered for detailed modeling of risk factors associated with poorer outcomes in the setting of COVID-19 illness.

In conclusion, this study compared clinical outcomes in young adults patients across the health spectrum with COVID-19 infection. We found a significantly higher burden of comorbidities and lower rates of cardiac testing in hospitalized patients as compared to competitive athletes with COVID-19. Nine percent of hospitalized young adults with COVID-19 required mechanical ventilation, 3.5% suffered a MACE, and 2% died. Importantly, elevated BMI predicted mortality in hospitalized patients. Additional research is needed to better elucidate risk factors for severe health outcomes in young adults afflicted with COVID-19.

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Author Contributions

Aakash Bavishi, Stephanie A. Kliethermes, Bradley Petek, Nathaniel Moulson, Timothy W. Churchill, Kimberly Harmon, Manesh Patel, Aaron L. Baggish, Jonathon A. Drezner, and Kannan Mutharasan participated in study design, data collection, statistical analysis and preparation of manuscript. Prenav Mellacheruvu participated in data collection.

Ethics Approval

This study involves human participants and was approved by an Ethics Committee(s) or Institutional Board(s). The Massachusetts General Hospital Review Board Reference ID is 2020P002667.

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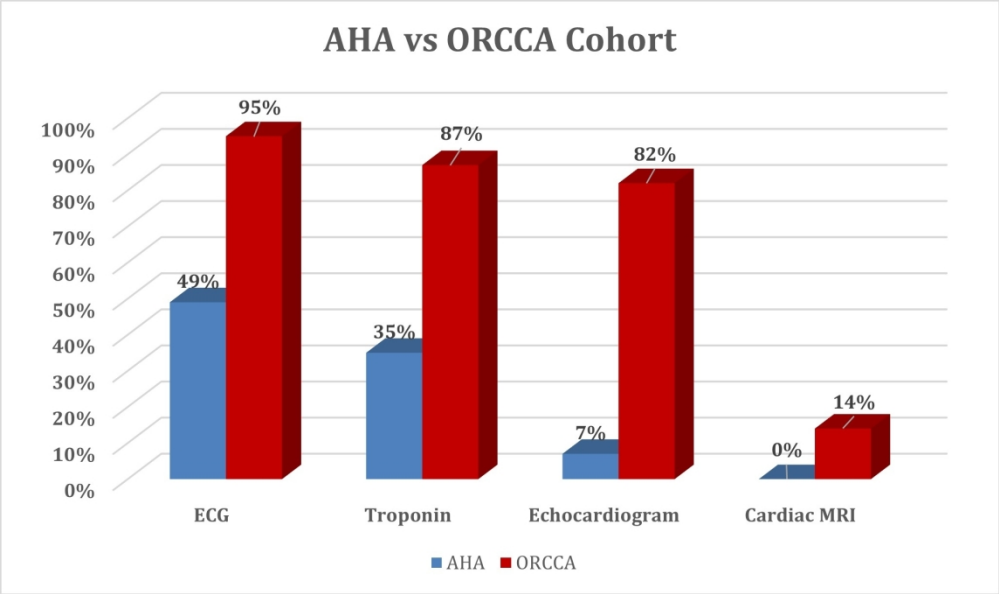
FIGURE LEGENDS

Figure 1. Abbreviations: AHA, American Heart Association; ECG, electrocardiogram; MRI- magnetic resonance imaging; ORCCA, Organized Registry for Cardiac Conditions in Athletes



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Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5/6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than	6

		one group. Give information separately for for exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	12
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6-7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7
Statistical methods	#12c	Explain how missing data were addressed	7
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	7
Statistical methods	#12e	Describe any sensitivity analyses	7
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	7-8

		confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	7
Participants	#13c	Consider use of a flow diagram	
NA- can provide if needed			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	7/8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
8			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
8/9			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
8/9			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence	9

		interval). Make clear which confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	9
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	#18	Summarise key results with reference to study objectives	9
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	12
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11
Generalisability	#21	Discuss the generalisability (external validity) of the study results	11
Other Information			

Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

Notes:

- 13c: NA- can provide if needed The STROBE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 07. November 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai