ORIGINAL RESEARCH

High Prevalence of Both Previous Infection with SARS-CoV-2 and Persistent Symptoms

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Introduction: **Universities are unique settings with large populations, congregate housing, and frequent attendance of events in large groups. However, the current prevalence of previous COVID-19 infection in university students, including symptomatic and asymptomatic disease, is unknown. Our goal therefore was to determine the prevalence of previous infection, risk factors for infection, and the prevalence of persistent symptoms following infection among university students.**

Methods: **This was a cross-sectional study set in a large public university between January 22 and March 22, 2021. We surveyed students about demographics, risk factors, and symptoms, and simultaneously tested their saliva for IgA antibodies to SARS-CoV-2. To estimate the prevalence of previous infection we adjusted our intentional sample of a diverse student population for year in school and age to resemble the composition of the entire student body and adjusted for the imperfect sensitivity and specificity of the antibody test. Univariate and multiple regression analysis was used to identify independent risk factors for infection, and the proportion of students with persistent symptoms following acute infection was determined.**

Results: **A total of 488 students completed the survey, 432 had a valid antibody result, and 428 had both. The estimated prevalence of previous infection for 432 participants with valid antibody results was 41%. Of 145 students in our sample with a positive antibody test, 41.4% denied having a previous positive polymerase chain reaction (PCR) test for SARS-CoV-2 and presumably had an asymptomatic infection; in our adjusted analysis we estimate that approximately 2-thirds of students had asymptomatic infections. Independent risk factors for infection included male sex, having a roommate with a known symptomatic infection, and having two or fewer roommates. More frequent attendance of parties and bars was a univariate risk factor, but not in the multiple regression analysis. Of 122 students reporting a previous symptomatic infection, 14 (11.4%) reported persistent symptoms consistent with postacute COVID-19 a median of 132 days later.**

Conclusions and Relevance: **Previous COVID-19 infection, both symptomatic and asymptomatic, was common at a large university. Measures that could prevent resurgence of the infection when students return to campus include mandatory vaccination policies, mass surveillance testing, and testing of sewage for antigen to SARS-CoV-2. (J Am Board Fam Med 2022;35:570–578.)**

Keywords: **Adolescent, Asymptomatic Infections, COVID-19, Cross-Sectional Studies, Long-COVID, Prevalence, Regression Analysis, SARS-CoV-2, Students, Universities**

Introduction

It has become clear that many patients infected with SARS-CoV-2 are asymptomatic or minimally symptomatic.[1,2] This is an important factor in the spread of the virus through the human population, as these persons can still spread the disease to others.[3,4] Therefore, understanding the extent of asymptomatic infection is important to inform future disease control efforts.

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Universities are unique settings with large populations, congregate housing, and frequent attendance of events in large groups such as sporting events, classrooms, bars, and other venues. A narrative review of cohort studies found that younger cohorts tended to have higher rates of asymptomatic infection with SARS-CoV-2.[2] This was confirmed by a large cohort study of 5484 quarantined case contacts, which found that younger persons were significantly more likely to experience an asymptomatic infection than older persons. For example, only 22% of individuals 20 to 39 years of age developed a symptomatic infection compared with 65% of people over the age of 80 years.[5]

As of May 26, 2021, a total of 6391 symptomatic cases have been reported at the University of Georgia (UGA) in Athens, Georgia (16.3% of the 39 147-person student body). Of these 6391 symptomatic cases, 4756 occurred during 2020.[6] In a previous study, we used data from reported symptomatic cases and surveillance testing of asymptomatic students to estimate that ~75% of SARS-CoV-2 infections were asymptomatic.[6] However, this estimate requires confirmation via population-based testing for antibodies to SARS-CoV-2.

Typically, serum samples are used for antibody detection via enzyme-linked immunosorbent assays (ELISAs); however, saliva samples have also been used successfully for the detection of SARS-CoV-2 antibodies.[7,8] IgG antibody profiles from plasma and saliva are highly correlated for other pathogens as well.[9] Using IgA antibody-based SARS-CoV-2 serologic tests, the majority of antibodies detected in saliva are mucosal[10,11] We therefore set out to determine the prevalence of previous symptomatic and asymptomatic infection with SARS-CoV-2 in a sample of students at the UGA using detection of IgA antibodies in saliva. We also sought to identify independent predictors of previous infection, as well as the proportion of students who had persistent symptoms.

Methods

This was a cross-sectional study. It was approved by the Human Subjects Committee at the University of Georgia (Version 00000889, Project 00003338). All participants gave written informed consent before participation. Participants were not compensated for participation; internal funding was used to purchase laboratory supplies.

Population

UGA is a large public institution in Athens, Georgia with 29,765 undergraduates and 9382 graduate and professional students enrolled in the fall semester of 2020. Students were required to be on campus during the fall semester, and faculty were encouraged to teach in person unless they obtained an Americans with Disabilities Act exemption approved by Human Resources at the University. Our goal was to identify a sample of 500 students from all levels that was representative of the student body. Because testing for SARS-CoV-2 was not required at any point during the semester, we instead obtained a list of classes that included the names of instructors, the college, the number of students allowed in the class, and the instructional level. We identified classes with at least 20 students from each of the university's 17 colleges, selecting both early undergraduate, late undergraduate, and graduate classes to develop as representative a sample as possible. We then asked instructors whether we could come to their class to identify students who would voluntarily provide saliva samples and who would complete a 1-page survey. Data collection was done by trained student volunteers.

Detection of Antibodies to SARS-CoV-2

We used a locally developed enzyme-linked immunosorbent assay (ELISA) test to detect IgA to SARS-CoV-2 in saliva samples. Detailed information on the laboratory procedures for processing saliva sample and performing the ELISA test can be found in the Appendix.

Determination of Cutoffs for Defining a Positive Antibody Test

The ELISA test for SARS-CoV-2 IgA antibodies was administered simultaneously with a serum test for SARS-CoV-2 IgG antibodies as a reference standard to 18 volunteers. The optimal cutoff that maximizes sensitivity and specificity at 89% was based on Youden's J statistic.[13] The cutoff between positive and negative saliva samples was determined to be > 61.85 ng/mL, and that threshold was used to define a positive or negative test for the univariate and multiple regression analysis.

Survey

We developed a brief survey and pilot tested it in a group of 10 graduate students, modifying it based

on their feedback. The survey was completed during each class period, and included questions about year of study, age, sex, race, ethnicity, type of housing, and number of room or housemates. Students were also asked whether they had experienced a previous confirmed COVID-19 infection, whether they were ever symptomatic, and whether they were still symptomatic. Finally, they were asked about adherence to face coverings and distancing, frequency of attendance of bars and parties, and whether someone they lived with had tested positive. All samples and surveys were identified by a code number only. Surveys were administered from approximately January 22 through March 22 of 2021. Data collection was halted as vaccination began among students to avoid confounding results (students were also asked to not provide a sample if they had been vaccinated).

Analysis to Estimate Prevalence

Sample prevalence was weighted by gender and year in school to reflect an appropriate distribution among UGA students (UGA Factbook: https://oir.uga.edu/_resources/files/factbook/pages/UGAFactBook_p20.pdf). The weighted prevalence was then further adjusted using the approach proposed by Diggle,[14] as the saliva test had imperfect sensitivity. A cutoff of >68.21 ng/mL was chosen for estimation of prevalence because it had a specificity of 100%, therefore requiring only adjustment for sensitivity rather than for both sensitivity and specificity (see Appendix Table). We also chose a slightly higher cutoff of >72.82 ng/mL (also 100% specific) as a sensitivity analysis for the estimation of prevalence.

Analysis for Predictors of Positive Antibody Test

A logistic regression model was used to assess the association between student characteristics such as demographics and behaviors and COVID-19 infection. Because of skewed distributions for some variables and small sample sizes for some categories, categories for race, year in school, and number of people sharing a household were combined for the analysis. The antibody test result was the dependent variable with age, sex, race, year in school, housing, number of people sharing a household, mask-wearing off campus, numbers of parties and bars, and roommates positive as independent variables. Results for univariate and multiple logistic regression are presented as unadjusted and adjusted odds ratios with 95% confidence intervals (CIs). We used a correlation matrix and variance inflation factors to identify potential collinearity, and then removing potentially correlated variables to examine their effect on the remaining predictors.

Descriptive Analysis of Participants with History of Confirmed Symptomatic COVID-19

A descriptive analysis was done to look at students reporting symptoms for a previous laboratory-confirmed positive viral test for SARS-CoV-2 infection as well as the presence of persistent symptoms at the time of survey. The length of time participants had persistent symptoms was estimated using the reported date of their positive COVID-19 test and the midpoint of our survey data collection (February 22, 2021).

Results

A total of 497 participants were enrolled between January 20 and March 22, 2021, of whom eight did not submit a survey, one submitted a survey but no saliva sample, and 62 who provided indeterminate or inadequate saliva samples. This left a total of 488 participants who completed the survey, 432 participants with a valid antibody result. and 428 who provided both (Table 1). The mean age of our study population was 20.6 years, 68.7% were female, and 85.3% identified as white. A previous laboratory-confirmed positive viral test for COVID-19 was reported by 140 of 488 students (28.7%).

Estimate of Overall Prevalence

Among all 432 participants who provided saliva samples and had a deterministic measure of IgA titers, the raw prevalence estimate was 30.0% (95% CI 26.0%–34.6%) using the cutoff for prevalence estimation of >68.21 ng/mL. Most of these participants were undergraduate students (n = 392), and they had a raw prevalence of 30.4% (95% CI 26.0%–35.1%). After weighting by their gender and year in school, the weighted prevalence was 31.9% (95% CI 24.4%–39.4%). Finally, with adjustment to account for the imperfect sensitivity of the saliva test, the estimated adjusted prevalence was 41.0% (95% CI 31.4%–50.7%). The analysis was repeated using a cutoff of >72.82 ng/mL as a sensitivity analysis and the adjusted prevalence was estimated to be 42.2% (95% CI 31.4%–52.9%). Of 145 students in our sample with a positive antibody test, 41.4% denied having a previous positive

Table 1. Characteristics of Study Participants with Both Valid Antibody Result and Completed Survey (n = 428)

		Antibody Result (> 61.85 ng/mL)	
	Total (n = 428)	Positive (n = 145)	Negative (n = 283)
Age			
Mean (SD)	20.6 (2.28)	20.4 (2.20)	20.7 (2.32)
Sex			
Male	133 (31.1%)	54 (37.2%)	79 (27.9%)
Female	294 (68.7%)	91 (62.8%)	203 (71.7%)
Other	1 (0.2%)	0 (0%)	1 (0.4%)
Race			
Alaska Native/Native American	1 (0.2%)	0 (0%)	1 (0.4%)
Asian/Pacific Islander	21 (4.9%)	10 (6.9%)	11 (3.9%)
Black/African American	21 (4.9%)	4 (2.8%)	17 (6.0%)
White	365 (85.3%)	125 (86.2%)	240 (84.8%)
Multiracial	18 (4.2%)	5 (3.4%)	13 (4.6%)
Not Reported	2 (0.5%)	1 (0.7%	1 (0.4%)
Year in School			
Undergraduate Year 1/2	177 (41.4%)	64 (44.1%)	113 (39.9%)
Undergraduate Year 3/4/5	216 (50.5%)	70 (48.3%)	146 (51.6%)
Graduate or Professional	35 (8.2%)	11 (7.6%)	24 (8.5%)
Housing			
UGA Dormitory	117 (27.3%)	43 (29.7%)	74 (26.1%)
Fraternity/Sorority House	42 (9.8%)	13 (9.0%)	29 (10.2%)
Apartment/Condo	185 (43.2%)	59 (40.7%)	126 (44.5%)
Living at Home with Parents/Guardians	21 (4.9%)	8 (5.5%)	13 (4.6%)
Rental or Other Home	63 (14.7%)	22 (15.2%)	41 (14.5%)
Number Sharing Household			
0–2 Roommates	197 (46.0%)	77 (53.1%)	120 (42.4%)
>2 Roommates	217 (50.7%)	64 (44.1%)	153 (54.1%)
Missing	14 (3.3%)	4 (2.8%)	10 (3.5%)
Mask-Wearing Off Campus			
Almost Always	230 (53.7%)	78 (53.8%)	152 (53.7%)
Sometimes	148 (34.6%)	53 (36.6%)	95 (33.6%)
Rarely or Never	49 (11.4%)	14 (9.7%)	35 (12.4%)
Number of Parties/Bars Attended During Fall Semester			
0–1 Time	180 (42.1%)	53 (36.6%)	127 (44.9%)
2–5 Times	109 (25.5%)	35 (24.1%)	74 (26.1%)
6–10 Times	50 (11.7%)	18 (12.4%)	32 (11.3%)
11 or More Times	89 (20.8%)	39 (26.9%)	50 (17.7%)
At Least One Roommate Positive			
Yes	195 (45.6%)	79 (54.5%)	116 (41.0%)
No	228 (53.3%)	63 (43.4%)	165 (58.3%)
Missing	5 (1.2%)	3 (2.1%)	2 (0.7%)

Abbreviations: SD, standard deviation.

polymerase chain reaction (PCR) test for COVID-19 and presumably had an asymptomatic infection.

Univariate and Multiple Regression Analysis of Risk Factors for Infection

In the univariate analysis, a positive antibody test was significantly more likely in male students (40.6% vs 30.8%, P = .048), in students reporting more than 5 attendances at bars or parties during the semester (41.0% vs 30.5%, P = .03), in those with at least one roommate who had been diagnosed with COVID-19 (40.5% vs 27.6%, P = .01), and in those reporting two or fewer people sharing their residence (39.1% vs 29.5%, P = .04). There

Table 2. Results of Logistic Regression with Presence of Antibodies (> 61.85 ng/mL) as the Dependent Variable

Risk Factor	Univariate OR (95% CI)	Adjusted OR (95% CI)	P*
Age (years)	0.95 (0.87–1.05)	0.97 (0.84–1.13)	0.698
Male sex	1.53 (1.00–2.34)	1.66 (1.03–2.67)	0.036
Non-White race	0.93 (0.47–1.82)	1.05 (0.49–2.26)	0.896
Year in School			
Undergraduate year 1/2	Ref	Ref	
Undergraduate year 3/4/5	0.85 (0.56-1.29)	0.92 (0.46 – 1.82)	0.803
Graduate	0.81 (0.37-1.76)	0.62 (0.18 – 2.17)	0.453
Housing			
Dormitory	Ref	Ref	
Greek	0.77 (0.36-1.64)	1.08 (0.38 – 3.04)	0.884
Apartment	0.81 (0.50–1.31)	1.57 (0.70 – 3.50)	0.273
At Home	1.06 (0.41-2.76)	2.68 (0.87 – 8.22)	0.085
Rental Home	0.92 (0.49-1.75)	2.24 (0.82 – 6.11)	0.117
Mask-Wearing Off Campus			
Almost always	Ref	Ref	
Sometimes	1.09 (0.70–1.68)	1.01 (0.61 – 1.67)	0.968
Rarely or Never	0.78 (0.40–1.53)	0.56 (0.26 - −1.20)	0.134
Number of Parties/Bars Attended During Fall Semester			
0–1	Ref	Ref	
2–5	1.13 (0.68–1.89)	1.11 (0.63–1.99)	0.708
6–10	1.35 (0.70–2.61)	1.19 (0.55–2.55)	0.658
11+	1.87 (1.10–3.17)	1.65 (0.86–3.15)	0.130
At Least One Roommate Positive	1.78 (1.19–2.68)	1.92 (1.18–3.12)	0.009
Number Sharing Housing >2	0.65 (0.43–0.98)	0.41 (0.23–0.72)	0.002

* For adjusted multiple variable logistic regression.
Abbreviations: OR, odds ratio; CI, confidence interval.

was no significant association of a positive antibody test with mask-wearing off campus, type of housing, race, or year in school.

The multiple regression analysis showed that sharing housing with more than two roommates during the fall 2020 semester was associated with receiving a positive COVID-19 antibody test, OR 0.43 (95% CI 0.24–7.74). Living with roommates that had also received a confirmed COVID-19 diagnosis was associated with being positive for COVID-19 antibodies, OR 2.01 (95% CI 1.23–3.32). Social activities that include mask-wearing off campus and the number of parties or bars attended did not have a significant association with a positive antibody result. Analyses removing potentially collinear variables did not affect the strength of association for the remaining predictors.

Prevalence of Persistent Symptoms

Of the 488 participants who returned a survey, 140 participants had received a previous laboratory confirmed diagnosis of COVID-19 (Table 3). Additional analysis of these patients showed that 122 (87.1%) of the participants were experiencing symptoms at the time of diagnosis, and 14 (11.4%) of participants with laboratory confirmed symptomatic COVID-19 reported still having symptoms from their infection at the time that the survey was taken. The median

Table 3. Characteristics of Participants with Previous Confirmed COVID-19 Infection

	Confirmed COVID-19 (n = 140)
Symptoms	
Yes	122 (87.1%)
No	18 (12.9%)
Persistent Symptoms	
Yes	14 (10.0%)
No	126 (90.0%)
Number of Days with Persistent Symptoms (n = 14)	
Mean (SD)	132 (22.5)
Median [Min, Max]	131 [12, 253]

Abbreviations: SD, standard deviation.

duration of persistent symptoms in these 14 patients was 132 days, with a range of 12 to 253 days; 13 of 14 reported symptoms for more than 1 month, and 10 for more than 2 months.

Comparison of Previous Viral Testing and Antibody Results

In the 428 students with both survey and antibody results, 85 of 112 (75.9%) reporting a previous laboratory confirmed positive viral test also were positive for salivary IgA antibodies. Of 316 students without a previous laboratory confirmed positive viral test, 60 (18.9%) were positive for salivary IgA antibodies.

Discussion

We estimate that 41% of students had experienced a previous symptomatic or asymptomatic COVID-19 infection at our university. Since it takes approximately 2 weeks for IgA to become detectable in saliva,[15] the previous infections detected by our study represent infections from the beginning of the pandemic until approximately early February. Based on published data there were 5160 symptomatic cases reported during that period,[16] whereas we estimate that the total number of cases was approximately 16,050 (95% CI 12 292–19 847) in the student population of 39 147 persons. Therefore, over two thirds of infections in university students were asymptomatic.

Several seroprevalence surveys of previous COVID-19 infection on college and university campuses have recently been published. A study tested 790 university students in Los Angeles, CA in April and May of 2020 for SARS-CoV-2 antibodies and found a prevalence of 4.0%.[17] In June 2020 a serosurvey of 762 students, staff and In September, 2020 researchers randomly sampled students at Indiana University for antibodies to SARS-CoV-2, and found only a 4.6% prevalence of previous infection.[18] A third cross-sectional seroprevalence survey in December, 2020 found a 17.8% seroprevalence among students at five English universities.[19] The prevalence in our sample was the highest reported, and we also sampled most recently, between late January and early March of 2021. When examining the data from all four studies, despite having been done in three different regions of the United States and in England, a clear progression of seroprevalence is seen: 4.0% in April–May, 2021; 4.6% in September 2020; 17.8% in December 2020; and 41% in January–March 2021.

We observed a very large surge in infections on our campus, with more reported symptomatic cases than any university in the world at one point and hypothesize that similar surges have occurred at other universities. Another reason for our high prevalence is that Georgia has never had a statewide mask mandate other than in health care settings. Whereas a mask mandate was implemented on campus for fall 2020, students and faculty were encouraged to teach in person as much as possible. Bars and restaurants were open and large groups of students in Athens, Georgia visited these establishments throughout the fall and winter of 2020/2021; local mask ordinances were largely ignored by students off-campus. Vaccine mandates were forbidden by the University System of Georgia's Board of Regents.

We found a high rate of asymptomatic cases among young adults, as has been found by others.[2] The extent of asymptomatic transmission has important policy and public health implications. Measures like temperature checks and apps that ask about symptoms are very unlikely to have an impact when so many infected and infectious persons at a university are asymptomatic. Measures like mandatory vaccination for students, faculty and staff,[20] testing of sewage for antigen to SARS-CoV-2,[21] and regular testing of the entire population[22] are more likely to be effective. While many students have antibodies due to previous infection, it is not clear how durable that immunity is. For that reason, the American College Health Association recently recommended requiring COVID-19 vaccination for all students on campus in the fall 2021.[23]

Independent predictors of infection in our study include male sex, having a roommate who had a confirmed symptomatic infection, and having fewer than two roommates. While the number of parties and bars attended during fall semester was linearly and significantly associated with the likelihood of infection, it was not an independent predictor in the multiple regression analysis. It is not clear why having fewer roommates increased the risk of previous infection. While we speculated that perhaps those with more roommates had larger "pods" and therefore felt less need to go to parties and bars, that was not the case (percentage attending more than five parties or bars in the semester was 34%

for those with two or fewer roommates and 30% for those with two or more, P = .43). It is possible that those with less than two roommates lived in smaller, less well-ventilated dorm rooms, although there was no significant difference between dormitories and other living situations in the multiple regression.

Tilley and colleagues saw a trend toward more cases in males.[17] Kianersi and colleagues reported that risk factors for previous COVID-19 included Greek membership, hanging out with more than five persons when drinking alcohol, multiple romantic partners, and having someone in your living environment who had COVID-19. In their sample male sex was not associated with previous infection.[18]

It is concerning that 11% of students who reported a previous symptomatic infection also reported persistent symptoms a median of 131 days after their initial diagnosis. Based on the total symptomatic reported infections (n = 6391), that suggests that approximately 700 students may be experiencing persistent symptoms. This is a new and important finding that has not been previously reported in a population of young adults. It requires further study to assess the longitudinal course of illness, the type of symptoms, and their severity in these patients with what is now called postacute COVID-19.[24] A study in health care workers found that the prevalence of symptoms declined slowly over time in those with persistent symptoms, but that 15% were still experiencing symptoms 8 months later.[25]

A limitation of our study is the fact that this was not a random sample of students. However, we did deliberately sample a broad range of classes, levels, and colleges to a diverse sample, and we also adjusted our estimate to year and sex distribution of the university as a whole. While the saliva test is less accurate than serology, it was more practical for rapid data collection in a classroom setting, and our analysis was able to adjust for the lack of sensitivity using a validated approach. Assessment of risk factors was by self-report and there may be a degree of social desirability bias to some of the questions, such as adherence to mask-wearing and attending parties or bars. Finally, we did not assess the type or severity of persistent symptoms.

Conclusions

We estimate that over 40% of students at our university were infected with SARS-CoV-2 by the spring of 2021, and that many were asymptomatic. Risk factors for infection include having an infected roommate and male sex, and approximately 11% with a symptomatic infection were experiencing persistent symptoms consistent with postacute COVID-19 months later. Given low vaccination rates among young people, and the increasing prevalence of more contagious variants, mandating vaccination before return to campus is needed to prevent resurgence of the infection and harm to students, staff and faculty, especially as many universities have abandoned other protective measures.

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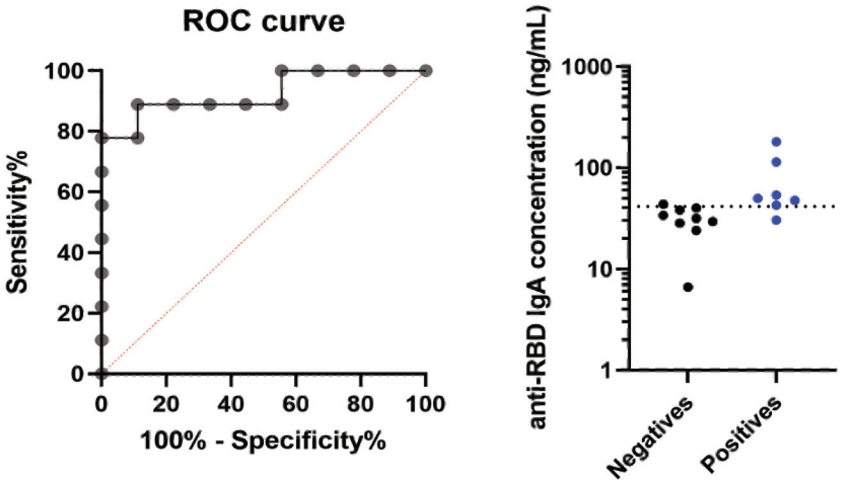
Appendix. Determination of Cutoffs for Abnormal Tests and for Prevalence Estimates

Appendix Figure 1. Receiver Operating Characteristic (ROC) Curve and Dot Plot for Saliva Assay.



Appendix Table 1. Sensitivity and Specificity of Different Antibody Titer Cutoffs for the Diagnosis of Previous Infection With SARS-CoV-2

Antibody Titer	Sensitivity (%)	95% CI	Specificity (%)	95% CI
> 22.90	100	70.09%–100.0%	11.11	0.5699%–43.50%
> 39.16	100	70.09%–100.0%	22.22	3.948%–54.74%
> 43.22	100	70.09%–100.0%	33.33	12.06%–64.58%
> 44.62	100	70.09%–100.0%	44.44	18.88%–73.33%
> 46.34	88.89	56.50%–99.43%	44.44	18.88%–73.33%
> 49.06	88.89	56.50%–99.43%	55.56	26.67%–81.12%
> 53.95	88.89	56.50%–99.43%	66.67	35.42%–87.94%
> 58.57	88.89	56.50%–99.43%	77.78	45.26%–96.05%
> 61.85	88.89	56.50%–99.43%	88.89	56.50%–99.43%
> 64.45	77.78	45.26%–96.05%	88.89	56.50%–99.43%
> 68.21	77.78	45.26%–96.05%	100	70.09%–100.0%
> 72.82	66.67	35.42%–87.94%	100	70.09%–100.0%
> 77.32	55.56	26.67%–81.12%	100	70.09%–100.0%
> 95.59	44.44	18.88%–73.33%	100	70.09%–100.0%
> 140.6	33.33	12.06%–64.58%	100	70.09%–100.0%
> 220.4	22.22	3.948%–54.74%	100	70.09%–100.0%
> 319.4	11.11	0.5699%–43.50%	100	70.09%–100.0%

Abbreviations: CI, Confidence interval.