The Weekly COVID-19 Literature Surveillance Summary

April 23, 2021

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

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EXECUTIVE SUMMARY

Epidemiology

- Association Between Upper Respiratory Tract Viral Load, Comorbidities, Disease Severity, and Outcome of Patients With SARS-CoV-2 Infection: Epidemiologists and microbiologists from the National Public Health Organization in Athens evaluated factors associated with high upper respiratory tract (URT) viral load in 1122 cases of SARS-CoV-2 infection diagnosed between February 26 and May 3, 2020 (Table 1). They found higher viral load was most often observed in patients with comorbidities (i.e. hypertension, obesity, immunosuppression) and patients with high viral load stayed longer in the ICU and required longer intubation than patients with low or moderate viral load (Table 3). Authors suggest URT viral load is a useful predictor of morbidity and severe outcomes in COVID-19.

Transmission & Prevention

- Identifying COVID-19 Risk Through Observational Studies to Inform Control Measures: Physicians from the COVID-19 Response Team from the United States Centers for Disease Control review observational studies investigating settings and occasions associated with higher risk of SARS-CoV-2 spread. They found dining at restaurants and going to bars or coffee shops were associated with a higher odds of a positive SARS-CoV-2 PCR (Figure). They argue that, alongside vaccination, preventative strategies should target high risk activities and must be continually adapted to the current situation to optimally control the pandemic.

- SARS-CoV-2 Serologic Assays in Control and Unknown Populations Demonstrate the Necessity of Virus Neutralization Testing: Immunologists, infectious disease pediatricians, and statisticians from the University of Washington compared combinations of 4 viral antigens and 5 human antibody isotype enzyme-linked immunosorbent assay (ELISA) platforms with 15 positive and 30 negative SARS-CoV-2 controls followed by viral neutralization assessment (Figure 1) in a clinically-relevant cohort of 114 patients from Seattle (Figure 6). They found that SARS-CoV-2 receptor binding domain (RBD) IgG, spike IgG3, and nucleocapsid protein (NP) IgG were the best-performing virus-specific antibody detection platforms in controls, with spike IgG3 most accurately predicting serologically positive individuals with virus neutralization activity (Table 1). The authors conclude that coupling virus neutralization analysis to a spike IgG3 antibody test can indicate individuals' immune protection status for SARS-CoV-2.

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ADULTS

ASSOCIATION BETWEEN UPPER RESPIRATORY TRACT VIRAL LOAD, COMORBIDITIES, DISEASE SEVERITY, AND OUTCOME OF PATIENTS WITH SARS-COV-2 INFECTION

Maltezou HC, Raftopoulos V, Vorou R, Papadima K, Mellou K, Spanakis N, Kossyvakis A, Gioula G, Exindari M, Froukala E, Martinez-Gonzalez B, Panayiotakopoulos G, Papa A, Mentis A, Tsakris A.. J Infect Dis. 2021 Apr 8;223(7):1132-1138. doi: 10.1093/infdis/jiaa804.
Level of Evidence: 5 - Inception cohort studies

BLUF

Epidemiologists and microbiologists from the National Public Health Organization in Athens evaluated factors associated with high upper respiratory tract (URT) viral load in 1122 cases of SARS-CoV-2 infection diagnosed between February 26 and May 3, 2020 (Table 1). They found higher viral load was most often observed in patients with comorbidities (i.e. hypertension, obesity, immunosuppression) and patients with high viral load stayed longer in the ICU and required longer intubation than patients with low or moderate viral load (Table 3). Authors suggest URT viral load is a useful predictor of morbidity and severe outcomes in COVID-19.

ABSTRACT

BACKGROUND: There is limited information on the association between upper respiratory tract (URT) viral loads, host factors, and disease severity in SARS-CoV-2 infected patients. METHODS: We studied 1,122 patients (mean age: 46 years) diagnosed by PCR. URT viral load, measured by PCR cycle threshold, was categorized as high, moderate or low. RESULTS: There were 336 (29.9%) patients with comorbidities; 309 patients (27.5%) had high, 316 (28.2%) moderate, and 497 (44.3%) low viral load. In univariate analyses, compared to patients with moderate or low viral load, patients with high viral load were older, had more often comorbidities, developed symptomatic disease, were intubated and died; in addition, patients with high viral load had longer stay in intensive care unit and longer intubation compared to patients with low viral load (p-values <0.05 for all). Patients with chronic cardiovascular disease, hypertension, chronic pulmonary disease, immunosuppression, obesity and chronic neurological disease had more often high viral load (p-value<0.05 for all). Multivariate analysis found that a high viral load was associated with COVID-19. The level of viral load was not associated with any other outcome. CONCLUSIONS: URT viral load could be used to identify patients at higher risk for morbidity or severe outcome.

FIGURES

Table 1. Characteristics of Patients With SARS-CoV-2 Infection by URT Viral Load

		URT Viral Load Status			
Characteristic	No. of Cases	High (n = 309)	Moderate (n = 316)	Low (n = 497)	*P* Value
Age, y, mean ± SD	1082	50 ± 22	48 ± 21	43 ± 21	.001
Age group, y, No. (%)					
<18	82	24 (7.9)	22 (7.2)	36 (7.6)	.107
18–64	767	202 (66.9)	224 (73.2)	356 (75.1)	
≥65	233	76 (25.2)	60 (19.6)	82 (17.3)	
Sex male, No. (%)	1122	156 (50.5)	189 (59.8)	274 (55.1)	.064
Comorbidities, No. (%)	1122	124 (40.1)	104 (32.9)	108 (32.1)	<.001
Comorbidities, mean ± SD	1122	0.62 ± 0.89	0.47 ± 0.79	0.32 ± 0.67	<.001

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; URT, upper respiratory tract.

Table 1. Characteristics of Patients With SARS-CoV-2 Infection by URT Viral Load

Table 3. SARS-CoV-2–Associated Morbidity and Outcome by URT Viral Load

Morbidity	No. of Cases	URT Viral Load Status			*P* Value
		High (n = 309)	Moderate (n = 316)	Low (n = 497)	
Asymptomatic infection	274	42 (13.6)	71 (22.5)	161 (32.4)	<.001
COVID-19	848	267 (86.4)	245 (77.5)	336 (67.6)	<.001
Hospitalization	518	153 (49.5)	155 (49.1)	210 (42.3)	.064
Complications	231	88 (28.5)	69 (21.8)	74 (14.9)	.084
Admission to ICU	99	37 (12.0)	27 (8.5)	35 (7.0)	.055
ICU LOS, d, mean ± SD		6.76 ± 12.99	5.13 ± 13.64	3.21 ± 8.30	.011[a]
Intubation	93	35 (11.3)	26 (8.2)	32 (6.4)	.050
Intubation duration, d, mean ± SD		7.53 ± 13.23	5.79 ± 12.54	3.29 ± 8.24	.006[a]
Death	89	35 (11.3)	23 (7.3)	31 (6.2)	.030

Data are No. (%) except where indicated.

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; LOS, length of stay; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; URT, upper respiratory tract.

[a] *P* value only for the comparison between low and high viral load.

Table 3. SARS-CoV-2–Associated Morbidity and Outcome by URT Viral Load

IDENTIFYING COVID-19 RISK THROUGH OBSERVATIONAL STUDIES TO INFORM CONTROL MEASURES

Tenforde MW, Fisher KA, Patel MM.. JAMA. 2021 Apr 13;325(14):1464-1465. doi: 10.1001/jama.2021.1995.
Level of Evidence: 5 - Review / Literature Review

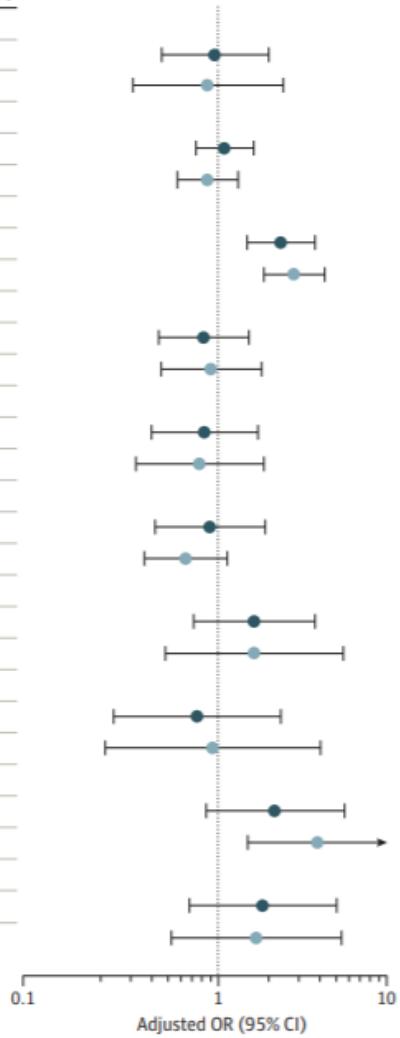
BLUF

Physicians from the COVID-19 Response Team from the United States Centers for Disease Control review observational studies investigating settings and occasions associated with higher risk of SARS-CoV-2 spread. They found dining at restaurants and going to bars or coffee shops were associated with a higher odds of a positive SARS-CoV-2 PCR (Figure). They argue that, alongside vaccination, preventative strategies should target high risk activities and must be continually adapted to the current situation to optimally control the pandemic.

FIGURES

Figure. Community Exposures Associated With Confirmed COVID-19 Among Symptomatic Adults (N = 314) in the US, July 1-29, 2020

	Adjusted OR (95% CI)
Shopping	
Close COVID-19 contact	0.96 (0.46-2.00)
No close COVID-19 contact	0.87 (0.31-2.43)
Home, ≤10 persons	
Close COVID-19 contact	1.09 (0.74-1.63)
No close COVID-19 contact	0.87 (0.57-1.32)
Restaurant	
Close COVID-19 contact	2.37 (1.49-3.76)
No close COVID-19 contact	2.82 (1.86-4.26)
Office setting	
Close COVID-19 contact	0.82 (0.45-1.52)
No close COVID-19 contact	0.91 (0.46-1.80)
Salon	
Close COVID-19 contact	0.83 (0.40-1.71)
No close COVID-19 contact	0.78 (0.32-1.86)
Home, >10 persons	
Close COVID-19 contact	0.89 (0.42-1.89)
No close COVID-19 contact	0.64 (0.37-1.13)
Gym	
Close COVID-19 contact	1.64 (0.71-3.76)
No close COVID-19 contact	1.64 (0.49-5.53)
Public transportation	
Close COVID-19 contact	0.75 (0.24-2.35)
No close COVID-19 contact	0.93 (0.21-4.05)
Bar or coffee shop	
Close COVID-19 contact	2.18 (0.85-5.61)
No close COVID-19 contact	3.88 (1.49-10.05)
Church or religious gathering	
Close COVID-19 contact	1.84 (0.67-5.02)
No close COVID-19 contact	1.68 (0.53-5.38)



Odds ratios (ORs) represent comparison of exposures by symptomatic patients (n = 154) who tested positive for SARS-CoV-2 and a control group (n = 160) who tested negative. ORs were adjusted for race/ethnicity, sex, age, and reporting ≥1 underlying chronic medical condition. ORs were estimated using unconditional logistic regression with generalized estimating equations, which accounted for Influenza Vaccine Effectiveness in the Critically Ill Network site–level clustering. A second model was restricted to participants who did not report close contact to a person known to have COVID-19 (n = 225). Community exposure questions are specified in the *MMWR* publication.[6] Responses were coded as "never" vs "at least once." This figure was adapted from Fisher et al.[6]

SARS-COV-2 SEROLOGIC ASSAYS IN CONTROL AND UNKNOWN POPULATIONS DEMONSTRATE THE NECESSITY OF VIRUS NEUTRALIZATION TESTING

Rathe JA, Hemann EA, Eggenberger J, Li Z, Knoll ML, Stokes C, Hsiang TY, Netland J, Takehara KK, Pepper M, Gale M.. J Infect Dis. 2021 Apr 8;223(7):1120-1131. doi: 10.1093/infdis/jiaa797.
Level of Evidence: 4 - Case-control studies, or "poor or non-independent reference standard

BLUF

Immunologists, infectious disease pediatricians, and statisticians from the University of Washington compared combinations of 4 viral antigens and 5 human antibody isotype enzyme-linked immunosorbent assay (ELISA) platforms with 15 positive and 30 negative SARS-CoV-2 controls followed by viral neutralization assessment (Figure 1) in a clinically-relevant cohort of 114 patients from Seattle (Figure 6). They found that SARS-CoV-2 receptor binding domain (RBD) IgG, spike IgG3, and nucleocapsid protein (NP) IgG were the best-performing virus-specific antibody detection platforms in controls, with spike IgG3 most accurately predicting serologically positive individuals with virus neutralization activity (Table 1). The authors conclude that coupling virus neutralization analysis to a spike IgG3 antibody test can indicate individuals' immune protection status for SARS-CoV-2.

ABSTRACT

BACKGROUND: To determine how serologic antibody testing outcome links with virus neutralization of SARS-CoV-2, we evaluated a unique set of individuals for SARS-CoV-2 antibody level and viral neutralization. METHODS: We compared serum Ig levels across platforms of viral antigens and antibodies with 15 positive and 30 negative SARS-CoV-2 controls followed by viral neutralization assessment. We then applied these platforms to a clinically relevant cohort of 114 individuals with unknown histories of SARS-CoV-2 infection. RESULTS: In controls, the best performing virus-specific antibody detection platforms were SARS-CoV-2 receptor binding domain (RBD) IgG [specificity 87%, sensitivity 100%, positive predictive value (PPV) 100%, negative predictive value (NPV) 93%], spike IgG3 [specificity 93%, sensitivity 97%, PPV 93%, NPV 97%], and nucleocapsid protein (NP) IgG [specificity 93%, sensitivity 97%, PPV 93%, NPV 97%]. Neutralization of positive and negative control sera showed 100% agreement. 20 unknown individuals had detectable SARS-CoV-2 antibodies with 16 demonstrating virus neutralization. Spike IgG3 provided the highest accuracy for predicting serologically positive individuals with virus neutralization activity [Misidentified 1/20 unknowns compared to 2/20 for RBD and NP IgG]. CONCLUSION: The coupling of virus neutralization analysis to a spike IgG3 antibody test is optimal to categorize patients for correlates of SARS-CoV-2 immune protection status.

FIGURES

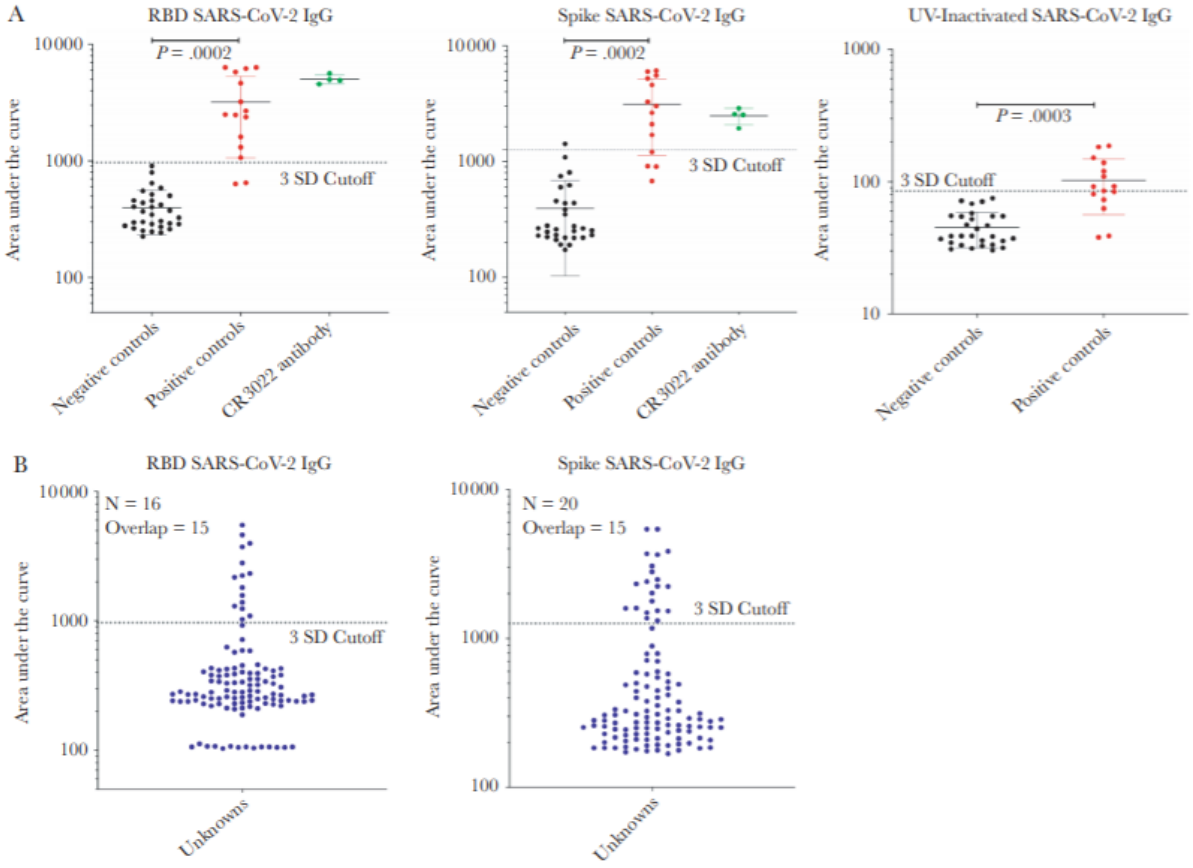


Figure 1. Comparison of ELISA IgG platforms. *A*, Positive and negative control serum sample total IgG antibody recognition of SARS-CoV-2 RBD, spike protein, and UV-inactivated SARS-CoV-2. *B*, Unknown serum samples total IgG RBD and spike assays. Mean ± SD, Student *t* tests for comparisons of mean of groups. Dotted lines represent cutoff of 3 SD from the mean of the negative control samples to designate "positive" antibody samples. Abbreviations: ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

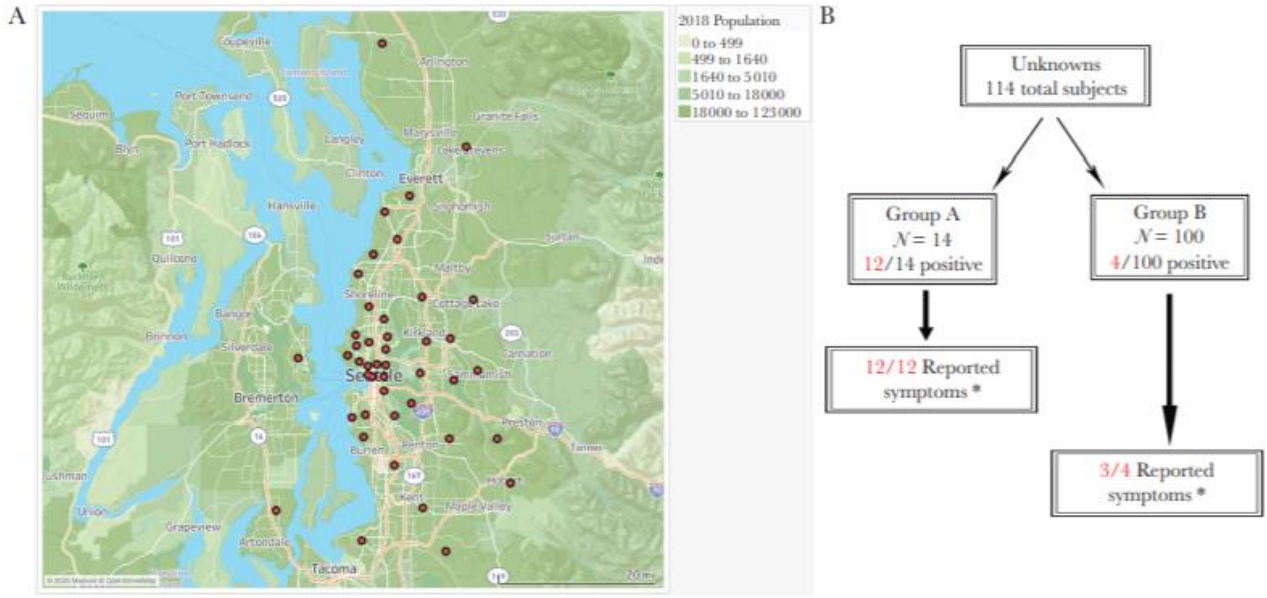


Figure 6. Study subject description and serologic prevalence estimates. *A*, A map of Seattle with circles denoting the zip codes of the subjects involved in the study. Underlying map colors represent the population density for the areas shown. *B*, Number of subjects, exposure status, and reported symptoms for positive subjects. Group A and B unknown subjects had never been diagnosed with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Group A subjects had close contact with a known infected SARS-CoV-2 individual. Group B subjects had no known exposure to SARS-CoV-2 infected individuals. *Subjects reported symptoms within 5 days of exposure to SARS-CoV-2–positive individuals. **Subjects reported symptoms over the possible exposure window in the Seattle area (21 January to 15 April 2020).

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