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Severity Outcomes Associated with SARS-CoV-2 XBB Variants, an observational analysis

Eili Y. Klein[1,2,3,*], **Amary Fall**[4], **Julie M. Norton**[4], **Raghda E. Eldesouki**[4], **Omar Abdullah**[4], **Lijie Han**[4], **Madeline Yunker**[4], **Heba H. Mostafa**[4]

[1]Department of Emergency Medicine, Johns Hopkins School of Medicine, Baltimore, MD

[2]Department of Infectious Diseases, Johns Hopkins School of Medicine, Baltimore, MD

[3]One Health Trust, Washington, DC

[4]Department of Pathology, Division of Medical Microbiology, Johns Hopkins School of Medicine, Baltimore, MD

Abstract

The rapidity with which SARS-CoV-2 XBB variants rose to predominance has been alarming. We used a large cohort of patients diagnosed with Omicron infections between September 2022 and mid-February 2023 to evaluate the likelihood of admission or need for supplemental oxygen in patients infected with XBB variants. Our data showed no significant association between XBB or XBB.1.5 infections and admissions. Older age groups, lack of vaccination, immunosuppression and underlying heart, kidney, and lung disease showed significant associations with hospitalization.

Introduction

Since the Omicron variant of SARS-CoV-2 emerged, new subvariants have continually emerged, with the currently most predominant being XBB.1.5. The XBB variant, first detected in August in Southeast Asia,[1] was followed by further recombination that led to the emergence of XBB.1.5, which includes mutations that improve cell binding and mediate immune escape,[2] that likely contribute to its enhanced transmissibility. Data from the CDC suggests that XBB.1.5, already dominant in the Northeast, is rapidly spreading across the country.[3] Despite rapidly displacing other subvariants, an understanding of disease severity

[*]Corresponding Author: Eili Y. Klein, Associate Professor, Department of Emergency Medicine, Johns Hopkins School of Medicine, 5801 Smith Ave, Davis Suite 3220, Baltimore, MD 21209, Phone: (410) 735-7559, eklein@jhu.edu, Mobile: (732) 266-7732.

Author contributions

EYK and HHM performed study design. AF, JMN, REE, OA, LH, and MY conducted experiments. EYK performed data analysis. HHM and EYK wrote and edited the manuscript. JMN, LH, MY organized samples/experiments. EYK obtained clinical information. HHM and EYK supervised the study.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

of XBB.1.5 infections is lacking. We evaluated the relative severity of XBB infections compared to other circulating subvariants as well as prior variants in a large US hospital center.

Methods

Clinical specimens from patients of the Johns Hopkins Healthcare System (JHHS) across the greater Baltimore-Washington were sequenced after standard of care as previously described.[4] JHHS includes five hospitals, two academic and three community, that together account for ~20% of all hospital beds in the State of Maryland. Data on patient demographics, comorbidities, vaccination status, and clinical course were bulk extracted from the common electronic medical record system (EHR). Multivariable logistic regression was used to evaluate the odds ratio of admission and need for supplemental oxygen. As the outcome of interest was hospital admission, asymptomatic patients were excluded, as were patients whose symptoms started more than 14 days prior to testing or when testing occurred after admission. Symptomatic patients were defined based on whether the test was or was not asymptomatic screening. To account for potential order bias, a more conservative approach that included documentation of symptoms (either in the chief complaint or by the admission diagnosis) was included in a sensitivity analysis. A P-value less than 0.05 was considered significant. We compared the odds of admission or need for supplemental oxygen from patients with XBB infections to patients infected with other Omicron subvariants (Table S1 shows the distribution of Omicron subvariants during the period of the study). To account for potential changes in hospital practices, we also evaluated only sequences collected since September 2022. As the number of XBB infections was relatively small, we used propensity score matching to conduct a sensitivity analysis of similar patients with and without XBB infections.[5] All statistical analyses were conducted in Stata 17 (StataCorp LP, College Station, TX). Research was conducted under a Johns Hopkins IRB-approved protocol IRB00221396, with a waiver of consent.

Results

Between September 2022 and mid-February 2023, a total of 2,189 SARS-CoV-2 specimens were sequenced and matched to clinical data from symptomatic patients, including 403 XBB.1.5 and 499 XBB samples. Patients with XBB/XBB.1.5 strains skewed older and a higher percentage were vaccinated, but overall were fairly similar to the total cohort (Table 1). Notably a lower percentage of patients with XBB/XBB.1.5 strains were admitted (11.8%/11.2% compared to 13.2%). However, multivariable regression failed to find a significant relationship between XBB strains and admission (Odds Ratio [OR] 0.93 [0.61–1.42]) or need for supplemental oxygen (OR 0.78 [0.52–1.18]; Table 2). Qualitatively similar results were found for XBB.1.5 strains and when we matched patients with and without XBB strains (Table 2). Additionally, alternative definitions of admission did not significantly alter the results. The greatest risk-factor for admission and need for supplemental oxygen was age, with older patients, particularly those over 80 having the highest odds of being admitted and needing supplemental oxygen. Lack of vaccination was significantly associated with an increased risk of admission, but having the bivalent booster was not associated

with admission. Immunosuppressed patients or those with kidney, heart or lung disease had higher odds of being admitted or needing supplemental oxygen.

Discussion

The emergence of XBB.1.5 in October 2022 led to heightened concern of potential strain on the hospital system. However, while evidence suggests that XBB strains are more transmissible,[2] our results find no significant association between XBB infection and admission or need for supplemental oxygen after controlling for other factors known to be associated with the likelihood of admission. Given the number of patients within the catchment area of JHHS the results are a fair representative of the likely severity of XBB in Maryland. Differences in exposure and vaccination uptake in other geographic areas may limit the generalizability of the results to other States, however, at the time of the study, uptake of bivalent booster in Maryland was only around 20%, and measures to restrict transmission (e.g., mandatory masking) had been abandoned. Thus, the results are likely generalizable to other geographic areas in the US.

There are limitations to this study. First of all it was a convenience sample of patients presenting with symptoms, though the coverage of the population by JHHS means this is fairly representative of the state, and likely overrepresents the risk of admission as people with mild symptoms were less likely to seek testing. Second, only samples where sequencing was successful were included, which may bias to higher viral loads, but indicates that our cohort, highly likely, represents patients with new or recent infections. Finally, while we attempted to exclude patients without symptoms, the methods rely on accurate documentation, and thus a percentage of patients were likely included even though COVID was not the primary reason for admission. However, a sensitivity analysis using more strict admission criteria found qualitatively similar results, suggesting this was not a significant limitation. Overall, the limitations in the study do not significantly detract from the overall message that the XBB subvariant appears no more virulent than prior Omicron subvariants even if it is potentially more transmissible. Nevertheless, regardless of the strain, older individuals and unvaccinated individuals continue to be the most at risk of adverse outcomes from infection. While we found no significant protective effect of the bivalent booster to-date, the number of patients with a booster presenting with symptoms was low, which may be due to the reported lack of efficacy of the booster to prevent infection[6] or relatively low uptake.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Infection with XBB.1.5 is not associated with higher risk of admission or need for supplemental oxygen compared to other Omicron subvariants
- Lack of vaccination and older age are associated with higher risk of admission

Table 1.

Demogranhics

	All Strains*	XBB	XBB.1.5
N	2,189	499	403
Admitted	467 (21.3%)	85 (17.0%)	66 (16.4%)
COVID-Related Admission	288 (13.2%)	59 (11.8%)	45 (11.2%)
Female	1,201 (54.9%)	266 (53.3%)	208 (51.6%)
Age			
0–17	563 (2 5.7%)	123 (24.6%)	99 (24.6%)
18–44	606 (27.7%)	166 (33.3%)	133 (33.0%)
45–64	455 (20.8%)	97 (19.4%)	81 (20.1%)
65–79	354 (16.2%)	52 (10.4%)	43 (10.7%)
80+	211 (9.6%)	61 (12.2%)	47 (11.7%)
Race/Ethnicity			
Black	861 (3 9.3%)	179 (35.9%)	142 (35.2%)
Hispanic	296 (13.5%)	102 (20.4%)	78 (19.4%)
Other	288 (13.2%)	73 (14.6 %)	59 (14.6%)
White	744 (34.0%)	145 (29.1%)	124 (30.8%)
Comorbidities			
Lung Disease	622 (28.4%)	115 (23.0%)	96 (23.8%)
Kidney Disease	439 (20.1%)	82 (16.4%)	65 (16.1%)
Immuno suppression	534 (24.4%)	92 (18.4%)	70 (17.4%)
Diabetes	424 (19.4%)	76 (15.2%)	65 (16.1%)
Heart Failure	268 (12.2%)	49 (9.8%)	41 (10.2%)
Atrial Fibrillation	221 (10.1 %)	32 (6.4%)	27 (6.7%)
Cerebrovascular Disease	349 (15.9%)	83 (16.6%)	67 (16.6%)
Cancer	750 (34.3%)	176 (35.3%)	135 (33.5%)
Coronary Artery Disease	553 (25.3%)	104 (20.8%)	82 (20.3%)
Smoker	309 (14.1%)	70 (14.0%)	56 (13.9%)
Pregnant	44 (2.0%)	22 (4.4%)	19 (4.7%)
Prior Positive Test	325 (14.8%)	85 (17.0%)	71 (17.6%)
Vaccination Status			
Vaccinated	1,133 (51.8%)	271 (54.3%)	218 (54.1%)
Bivalent Booster	108 (4.9%)	32 (6.4%)	26 (6.5%)
Mean Days since Symptom Onset, (95% CI)	2.2 (2.1–2.3)	1.6 (1.4–1.9)	1.6 (1.3–1.9)
Mean Days from testing to admission, (95% CI)	0.1 (0.0–0.1)	0.1 (0.0–0.2)	0.1 (0.0–0.2)
Year			
2022	1,709 (78.1%)	169 (33.9%)	105 (26.1%)
2023	480 (21.9%)	330 (66.1%)	298 (73.9%)

[*] Includes all strains sequenced and typed since 9/1/2022

[†] Includes only COVID-related admitted patients

Table 2.

Multivariate Regression Results of the Association between Infection with XBB strain and hospital admission

	Admission	Admission Propensity Matched Sensitivity Analysis†	Admission XBB.1.5†,‡	Supplemental Oxygen
XBB	0.93 (0.61–1.42)	0.99 (0.58–1.68)	0.79 (0.49–1.27)	0.78 (0.52–1.18)
Female	0.94 (0.70–1.27)	0.73 (0.47–1.14)	0.94 (0.70–1.26)	1.05 (0.79–1.39)
Age				
0–17	Reference	Reference	Reference	Reference
18–44	1.66 (0.87–3.16)	1.79 (0.69–4.63)	1.67 (0.88–3.19)	1.07 (0.59–1.95)
45–64	3.68 (1.94–6.97)	3.83 (1.57–9.36)	3.68 (1.94–6.99)	2.52 (1.40–4.51)
65–79	4.21 (2.15–8.25)	5.57 (2.09–14.85)	4.23 (2.16–8.28)	3.51 (1.92–6.43)
80+	8.61 (4.33–17.13)	6.89 (2.67–17.79)	8.69 (4.37–17.27)	7.95 (4.25–14.88)
Race/Ethnicity				
Black	Reference	Reference	Reference	Reference
Hispanic	0.64 (0.35–1.20)	0.76 (0.38–1.54)	0.64 (0.34–1.20)	0.59 (0.31–1.14)
Other	0.66 (0.38–1.13)	0.80 (0.39–1.66)	0.66 (0.38–1.13)	1.19 (0.73–1.95)
White	1.12 (0.80–1.56)	1.33 (0.80–2.22)	1.12 (0.80–1.57)	1.99 (1.44–2.76)
Comorbidities				
Lung Disease	1.41 (1.03–1.92)	1.25 (0.78–2.01)	1.41 (1.03–1.92)	1.48 (1.09–2.00)
Kidney Disease	2.66 (1.88–3.77)	2.42 (1.34–4.37)	2.66 (1.88–3.76)	2.45 (1.75–3.43)
Immunosuppression	1.88 (1.36–2.60)	1.81 (1.04–3.15)	1.87 (1.35–2.59)	2.29 (1.68–3.14)
Diabetes	0.99 (0.71–1.39)	1.03 (0.63–1.70)	0.99 (0.70–1.39)	0.98 (0.71–1.37)
Heart Failure	2.31 (1.55–3.43)	1.89 (0.98–3.64)	2.32 (1.56–3.45)	2.05 (1.39–3.00)
Atrial Fibrillation	0.58 (0.38–0.88)	0.69 (0.33–1.46)	0.57 (0.37–0.88)	1.06 (0.71–1.57)
Cerebrovascular Disease	1.35 (0.96–1.91)	2.10 (1.20–3.68)	1.36 (0.96–1.92)	1.03 (0.73–1.44)
Cancer	0.83 (0.60–1.14)	0.98 (0.60–1.60)	0.83 (0.60–1.14)	0.73 (0.54–1.00)
Coronary Artery Disease	1.33 (0.93–1.90)	1.36 (0.77–2.40)	1.32 (0.92–1.89)	1.90 (1.36–2.65)
Smoker	1.15 (0.79–1.68)	0.88 (0.47–1.65)	1.15 (0.79–1.68)	1.21 (0.84–1.75)
Pregnant	3.49 (1.24–9.76)	5.60 (1.66–18.85)	3.55 (1.27–9.97)	1.25 (0.28–5.60)
Prior Positive Test	1.13 (0.76–1.68)	0.94 (0.52–1.70)	1.14 (0.77–1.69)	0.83 (0.56–1.25)
Vaccination Status				
Unvaccinated	1.44 (1.04–1.99)	1.78 (1.11–2.88)	1.43 (1.03–1.98)	1.46 (1.06–2.02)
Bivalent Booster	0.80 (0.43–1.49)	1.18 (0.56–2.50)	0.79 (0.42–1.48)	0.63 (0.35–1.14)
Mean Days since Symptom Onse	0.93 (0.88–0.99)	1.01 (0.95–1.08)	0.93 (0.88–0.99)	1.00 (0.95–1.05)
Year				
2022	Reference	Reference	Reference	Reference
2023	1.05 (0.70–1.59)	1.14 (0.64–2.02)	1.14 (0.75–1.73)	1.87 (1.27–2.76)
XBB	0.93 (0.61–1.42)	0.99 (0.58–1.68)	0.79 (0.49–1.27)	0.78 (0.52–1.18)

[†]Matched on demographics, vaccination status, comorbidities, infection history, and days since symptom onset using psmatch2 with a nearest neighbor of five and a caliper of .03

[‡]Using all strains since 9.1.2022 and classifying other XBB strains as control, all other analyses used all XBB strains as independent variable.