

# Prognostic Value of SARS-CoV-2 Anti-RBD IgG Antibody Quantitation on Clinical Outcomes in Hospitalized COVID-19 Patients

Luai Madanat<sup>1</sup>, Melinda Sager<sup>1</sup>, Daniel O'Connor<sup>1</sup>, Bijaya Thapa<sup>1</sup>, Nishant Aggarwal<sup>1</sup>, Bipin Ghimire<sup>1</sup>, Carl Lauter<sup>1-4</sup>, Gabriel N Maine<sup>5,6</sup>, Matthew Sims<sup>1,2,4</sup>, Alexandra Halalau<sup>1,4</sup>

<sup>1</sup>Internal Medicine, William Beaumont Hospital, Royal Oak, MI, USA; <sup>2</sup>Infectious Diseases, William Beaumont Hospital, Royal Oak, MI, USA; <sup>3</sup>Allergy and Immunology, William Beaumont Hospital, Royal Oak, MI, USA; <sup>4</sup>Oakland University William Beaumont School of Medicine, Rochester, MI, USA; <sup>5</sup>Pathology and Laboratory Medicine, William Beaumont Hospital, Royal Oak, MI, USA; <sup>6</sup>Pathology, Oakland University William Beaumont School of Medicine, Rochester, MI, USA

Correspondence: Luai Madanat, Internal Medicine, William Beaumont Hospital, Royal Oak, MI, USA, Tel +1 248-551-3000, Email Luai.madanat@beaumont.org

**Background:** Antibody levels against SARS-CoV-2 can be used as an indicator of recent or past vaccination or infection. However, the prognostic value of antibodies targeting the receptor binding protein (anti-RBD) in hospitalized patients is not widely reported.

**Purpose:** Determine prognostic impact of SARS-CoV-2 antibody quantitation at the time of admission on clinical outcomes in hospitalized COVID-19 patients.

**Methods:** We conducted a pilot observational study on patients hospitalized with SARS-CoV-2 infection to determine the prognostic impact of antibody quantitation within the first two days of admission. Anti-nucleocapsid IgG (anti-N) and Anti-RBD levels were measured. Anti-RBD level of 500 AU/mL was used as a cutoff to stratify patients. Spearman's rank Coefficient ( $r_s$ ) was used to demonstrate association.

**Results:** Of the 26 patients included, those who were vaccinated more frequently tested positive for Anti-RBD (100% vs 46.2%,  $P = 0.005$ ) with higher median titer level (623 vs 0,  $P = 0.011$ ) compared to unvaccinated patients. Anti-N positivity was more frequently seen in unvaccinated patients (53.9% vs 7.7%,  $P = 0.03$ ). Anti-RBD levels  $>500$  were associated with lower overall hospital length of stay (LOS) (5 vs 10 days,  $P = 0.046$ ). The analysis employing a Spearman Rank coefficient demonstrated a strong negative correlation between anti-S titer and LOS ( $r_s = -.515$ ,  $p = 0.007$ ) and a moderate negative correlation with oxygen needs ( $r_s = -.401$ ,  $p = 0.042$ ).

**Conclusion:** Anti-RBD IgG levels were associated with lower LOS and oxygen needs during hospitalization. Further studies are needed to determine if levels on admission can be used as a prognostic indicator.

**Keywords:** SARS-CoV-2, anti-RBD IgG, anti-nucleocapsid IgG, hospitalized patients, prognosis, outcomes

## Introduction

The SARS-CoV-2 pandemic continues to negatively impact the healthcare system globally despite the availability of vaccination since late 2020.<sup>1</sup> In fall 2021, the worldwide health system experienced another exponential rise in case volume, which was attributed to several factors including a more virulent strain of SARS-CoV-2, B.1.617.2 (Delta), incomplete global vaccine uptake, and potentially waning vaccine-induced immunity.<sup>2</sup> The SARS-CoV-2 virus is made up of four major structural proteins which include the spike (S), membrane (M), envelope (E) and nucleocapsid (N) proteins. The S protein which is responsible for recognition of the host cellular receptor to initiate virus entry is divided into S1 and S2 domains. The S1 domain determines receptor recognition via the receptor binding domain (RBD) while the S2 protein plays a role in fusion and entry.<sup>3,4</sup> Three vaccines against SARS-CoV-2 were made widely available to the US population: BNT162b2 (mRNA, Pfizer-BioNTech), mRNA-1273 (mRNA, Moderna), and Ad26.COV2.S (adenoviral vector, J&J) which showed initial efficacy of 95%, 94%, and 67%, respectively, in multicenter randomized trials.<sup>5-7</sup> SARS-CoV-2 vaccines, induce both humoral and T-cell mediated responses to the virus by mainly targeting the S protein

of the virus, particularly the S1 domain.<sup>4</sup> This results in the production of IgG antibodies against the S1 domain of the SARS-CoV-2 spike protein, including the RBD which is found within this protein.<sup>8</sup> However, antibody levels following vaccinations have been shown to wane over time.<sup>9,10</sup> It has been established that vaccinations reduce the severity of SARS-CoV-2 infection.<sup>11</sup> The prognostic value of anti-RBD quantitation on clinical severity in hospitalized patients is unclear.

Our pilot study aims at reporting the correlation between the level of SARS-CoV-2 antibodies and clinical outcomes, including mortality, major adverse cardiovascular events (MACE), intensive care unit (ICU) admission, and maximum oxygen support needs.

## Materials and Methods

### Study Design and Setting

We conducted a prospective observational study on patients hospitalized with SARS-CoV-2 infection at William Beaumont Hospital in Royal Oak, Michigan, from November 1–November 22, 2021. The Beaumont Health Institutional Review Board approved the current study (IRB # 2021–277). The study complies with the Declaration of Helsinki of ethical principles for medical research involving human subjects. Electronic medical records (EMR) of all patients hospitalized with SARS-CoV-2 infection were screened for enrollment based on inclusion/exclusion criteria. Eligible patients were contacted via phone to explain the study and obtain consent using the standard operating procedure at our institution to limit exposure and SARS-CoV-2 transmission during the pandemic. From those enrolled, we obtained data regarding COVID vaccine status, immunization dates, symptom onset and previous COVID diagnosis. Remnant blood samples obtained for routine clinical care from the first two days of admission were used to assess the presence of two SARS-CoV-2 antibodies, anti-RBD IgG and anti-nucleocapsid IgG (anti-N). Patients were followed 28 days post admission to collect data regarding clinical outcomes.

### Participants

All patients  $\geq 18$  years of age who were hospitalized and diagnosed with a SARS-CoV-2 infection by a positive RT-PCR test were potentially eligible for the study and were approached to provide consent for antibody testing. Enrollment had to occur within three days of hospital admission for blood samples from the first 48 hours of admission to be available for testing. Patients were excluded if: they were on mechanical ventilation given their inability to provide consent, had symptom duration greater than two weeks prior to presentation, were unable to provide vaccination history without documentation in the EMR, were previously treated with monoclonal antibodies, and if they were immunosuppressed and unlikely to be able to mount an antibody response. Patients considered immunosuppressed were those with an active solid tumor or hematologic malignancy, recipient of solid-organ or hematopoietic stem cell transplant, past medical history of a severe primary immunodeficiency, living with HIV, or active treatment with immunosuppressive medications such as cancer chemotherapeutic agents, TNF blockers, certain biologic agents (eg, rituximab), or high-dose corticosteroids.

### Variables and Data Collection

Responses to the questionnaire as well as demographic information (age, sex, race, BMI, tobacco use), comorbid conditions (diabetes, renal disease, hypertension, coronary artery disease, stroke, COPD, asthma, myocardial infarction and congestive heart failure), and SARS-CoV-2 antibody determination on admission were collected. Outcomes of interest included ICU stay, overall length of stay (LOS), need for and duration of mechanical ventilation, highest fraction of inspired oxygen (FiO<sub>2</sub>) needs, venous thromboembolism (VTE) events, MACE defined as composite of stroke, myocardial infarction, congestive heart failure exacerbation, and all-cause mortality. All outcomes were collected at 28 days after admission. Study outcomes were antibody positivity rates in patients hospitalized with SARS-CoV2 infection, clinical outcomes between vaccinated and unvaccinated individuals hospitalized with SARS-CoV2 infection, and clinical outcomes based on SARS-CoV2 anti-RBD IgG quantitation.

## Data Sources/Measurements

SARS-CoV-2 testing specimens were obtained via nasopharyngeal swab and the same NAAT testing system was used. For SARS-CoV-2 antibody levels, we used the Abbott Architect chemiluminescent microparticle immunoassay test system (AdviseDx SARS-CoV-2 IgG II) which has demonstrated excellent linearity compared to other available assays.<sup>12</sup> Oxygen requirements and FiO<sub>2</sub> needs were collected from EMR and verified with respiratory therapist's notes.

## Bias

Clinical outcomes and covariates were obtained by two independent reviewers without knowledge of antibody status. Researcher bias was controlled by strict adherence to the study protocol. All patients who presented to the hospital during the study period were screened for eligibility regardless of vaccination status and disease severity at presentation to avoid selection bias.

## Study Size

The number of cases during the study period and available funding determined the sample size. This was a pilot study that included 26 patients.

## Statistical Analysis

We compared patient outcomes based on two sub-groups based on vaccination status and anti-RBD IgG level. For antibody levels, we chose 500 AU/mL as the cutoff value, with a test reportable range of Range 50–50,000 AU/mL. Patients that yield a result of  $\geq 50$  AU/mL are considered seropositive for SARS-CoV-2 anti-RBD IgG. Categorical variables are provided as frequencies and percentages. They were examined with chi-square tests when appropriate (expected frequency  $>5$  in 80% of cells), otherwise Fisher's Exact tests were used. All continuous variables were provided as either the mean ( $\pm$  SD) or median (25th and 75th) percentiles, depending on the normality of the data. Continuous data were examined with Mann–Whitney *U*-tests. SAS for Windows<sup>®</sup> version 9.4, Cary, NC was used for all analysis.

With 26 patients, it was difficult to determine statistically significant differences. The purpose of this pilot study was to detect associations and was not powered to provide statistical significance.

## Results

### Participants

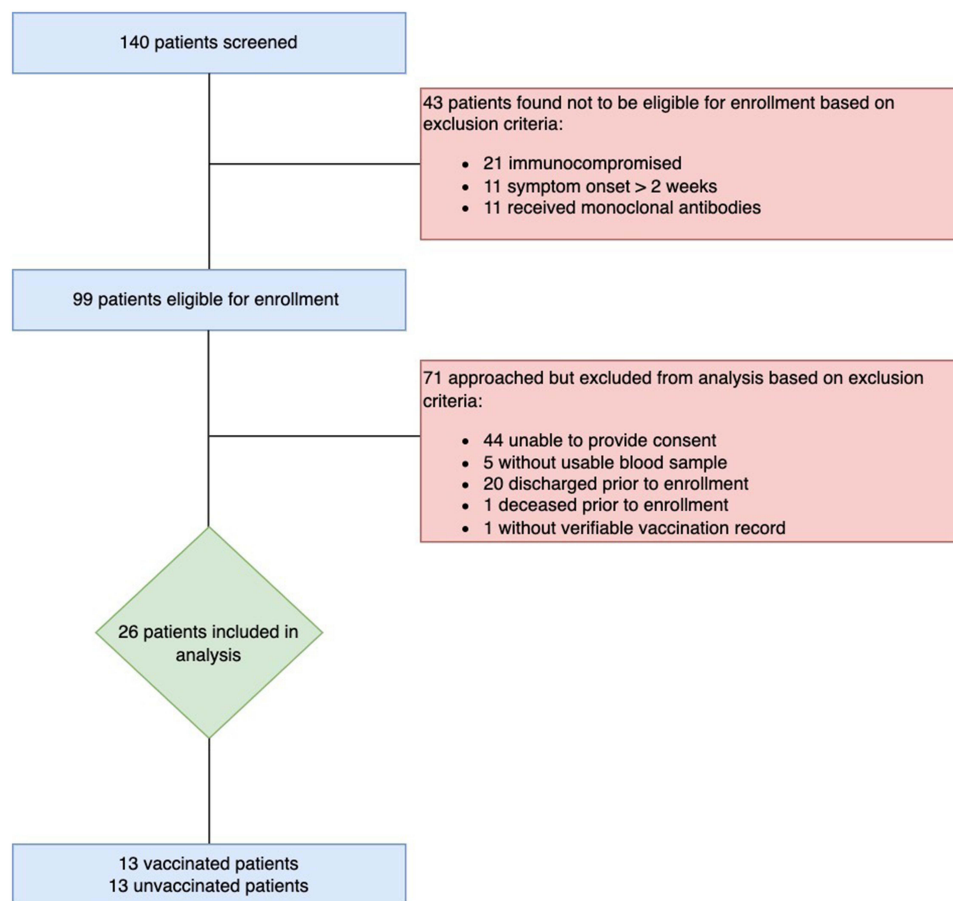
Twenty-six patients were included in the analysis. Patient selection process is demonstrated in (Figure 1).

### Descriptive Data

Of the total sample population, 73.1% were identified as White, 19.2% as African American, and 7.7% as other ethnicities. Males represented 50% of the sample. None of the patients had known prior SARS-CoV-2 infection. Out of the 13 patients who were vaccinated, six received Pfizer (BNT162b2), six received Moderna (mRNA-1273) and one received J&J (Ad26.COV2.S). All individuals who were vaccinated with Pfizer or Moderna received two doses, and none had received a booster dose. Patient's demographics and baseline characteristics based on subgrouping are demonstrated in Table 1.

### Outcome Data

Of the 26 patients who were included, 50% were vaccinated. Median time from COVID-19 infection to first and second dose of vaccine was 233 days and 209 days, respectively. Twenty-three patients (88.5%) were symptomatic with a median onset of symptoms five days prior to presentation (range 2–14). Irrespective of vaccination status, 19 patients (73.1%) were positive for anti-RBD with a median level of 623. Eight patients (30.8%) had positive anti-N. Three patients were mechanically ventilated and required ICU level of care and 23.1% had MACE. Overall mortality occurred in 15.4% of patients. Results of the granular data of participants are demonstrated in [Supplementary Table 1](#).



**Figure 1** Flow Chart demonstrating patient selection process.

## Main Results

### Outcomes Based on Anti-RBD Antibody Quantitation

Patients were divided into two groups according to anti-S titer:  $>500$  AU/mL ( $n = 12$ ) and  $<500$  AU/mL ( $n = 14$ ). Outcomes are demonstrated in Table 2. Of the 12 patients with antibody levels  $>500$ , 75% were vaccinated as opposed to 28.6% in those  $<500$  ( $p = 0.049$ ). Patients with antibody titers  $>500$  had shorter overall hospital stay (5 vs 10 days,  $p = 0.046$ ). Although not statistically significant, for antibody levels  $>500$ , we observed a lower percentage of ICU admissions and mechanical ventilations (MV) (8.3% vs 14.3%); decreased FiO<sub>2</sub> need (32% vs 37%,  $P = 0.14$ ); and need for supplemental oxygen (41.7% vs 14.3%,  $P = 0.26$ ).

Patients who tested positive for anti-N trended toward having a longer duration of symptoms prior to testing (Median of 10 vs 4 days,  $P = 0.08$ ), compared to those who tested negative.

Spearman's rank-order correlation ( $r_s$ ) analysis was conducted between anti-RBD level and outcomes of interest. A strong negative correlation was observed between anti-RBD titer and overall LOS ( $r_s = -0.515$ ,  $P = 0.007$ ) and a moderate negative correlation with FiO<sub>2</sub> ( $r_s = -0.401$ ,  $p = 0.042$ ). Anti-RBD level trended towards statistically significant moderate correlation with oxygen flow rate ( $r_s = -0.345$ ,  $p = 0.160$ ). Results are summarized in Table 3

### Outcomes Based on Vaccination Status

Vaccinated patients were more likely to test positive for anti-RBD compared to unvaccinated individuals (100% vs 46.2%, respectively,  $P = 0.0052$ ). In contrast, more patients that were unvaccinated tested positive for anti-N compared to

**Table 1** Baseline Characteristics of Included Patients Based on Anti-RBD IgG Titer Subgrouping

Characteristics	Overall	Anti-RBD IgG <500 AU/mL (N=14)	Anti-RBD IgG >500 AU/mL (N=12)	p-value
<b>Age</b> (Years)	59 (±17)	58 (±17.6)	60 (±17.4)	0.96
<b>Male Gender</b>	13 (50%)	5 (35.7%)	8 (66.7%)	0.24
<b>Race</b>				
White	19 (73.1%)	9 (64.3%)	10 (83.3%)	0.55
AA	5 (19.2%)	-	-	
Other	2 (7.7%)	-	-	
<b>BMI</b>	33 (±7)	34.5 (±7.1)	31.5 (6.3%)	0.46
<b>Tobacco Use</b>	10 (38.4%)	5 (35.7%)	5 (41.7%)	1.00
<b>Diabetes</b>	8 (30.8%)	5 (35.7%)	3 (25.0%)	0.87
<b>Hypertension</b>	17 (65.4%)	8 (57.1%)	9 (75.0%)	0.59
<b>COPD</b>	2 (7.7%)	2 (14.3%)	0	—
<b>Asthma</b>	6 (23.1%)	3 (21.4%)	3 (25%)	1.00
<b>Coronary Artery Disease</b>	8 (30.8%)	4 (28.6%)	4 (33.3%)	1.00
<b>Stroke</b>	3 (11.5%)	1 (7.1%)	2 (16.7%)	0.89
<b>Prior Myocardial Infarction</b>	5 (19.2%)	3 (21.4%)	2 (16.7%)	1.00
<b>Congestive Heart Failure</b>	4 (15.4%)	2 (14.3%)	2 (16.7%)	1.00
<b>Chronic Kidney Disease</b>	8 (30.8%)	4 (28.6%)	4 (33.3%)	1.00

**Table 2** Clinical Outcomes According to Vaccination Status and Anti-RBD IgG Level

Outcome	Anti-RBD <500 AU/mL (N=14)	Anti-RBD >500 AU/mL (N=12)	P-value
Mortality	2 (14.3%)	2 (16.7%)	1.00
MACE	3 (21.4%)	3 (25.0%)	1.00
DVT/PE	0	1 (8.3)	0.46
ICU admission	2 (14.3%)	1 (8.3%)	1.00
Need for mechanical ventilation	2 (14.3%)	1 (8.3%)	1.00
Need for supplemental oxygen	12 (85.7%)	7 (58.3%)	0.26
FIO <sub>2</sub> needs (%)	37 (30, 100)	32 (21, 39)	0.14
Onset of symptoms prior to presentation (Days)	6 (4, 9)	5 (4, 6)	0.92
Overall LOS (Days)	10 (6, 11)	5 (3, 9)	0.046*
	<b>Unvaccinated (N=13)</b>	<b>Vaccinated (N=13)</b>	
Anti-RBD Ab positive	6 (46.2%)	13 (100%)	0.0052*
Anti-RBD titer (AU/mL)	0 (0, 416)	623 (298, 1345)	0.011*
Anti-nucleocapsid Ab positive	7 (53.9%)	1 (7.7%)	0.03*
Mortality	2 (15.4%)	2 (15.2%)	1.00
MACE	2 (15.4%)	4 (30.8%)	0.64
DVT/PE	1 (7.7%)	0	1.00
ICU admission	2 (15.4)	1 (7.7)	1.00
Need for mechanical ventilation	2 (15.4%)	1 (7.7%)	1.00
Need for supplemental oxygen	11 (84.6%)	8 (61.5%)	0.376
Onset of symptoms prior to presentation (Days)	8 (6, 8)	4 (3, 4)	0.006*
FIO <sub>2</sub> needs (%)	37 (37, 100)	31 (21, 45)	0.08
Overall LOS (Days)	9 (4, 11)	8 (4, 9)	0.45

**Note:** \*Denotes significant p-value.

**Table 3** Spearman's Rank Order Correlation Between Anti-RBD IgG Titer and Outcomes of Interest

Spearman Correlation Coefficients Prob >  r  Under H0: Rho=0 Number of Observations	
Outcome	Anti-RBD IgG Level
FIO2 needed	-0.401 0.042 26
Oxygen flow rate needed	-0.345 0.160 18
Overall LOS	-0.515 0.007 26

those that were vaccinated (53.9% vs 7.7%, respectively,  $P = 0.030$ ). Median anti-S level was higher in vaccinated patients (623 vs 0,  $P = 0.011$ ). Mortality was similar between vaccinated (15.2%) and unvaccinated patients (15.4%). Outcomes are summarized in [Table 2](#).

## Discussion

In this pilot study, we have found that anti-RBD level on admission was linked to clinical outcomes. Patients with anti-RBD IgG levels  $>500$  AU/mL had lower overall hospital length of stay and trended towards less need to require supplemental oxygen and had lower FiO2 needs and oxygen flow rates during hospitalization. In addition, when considered as a continuous variable, there was a statistically significant negative linear correlation between anti-RBD level and overall hospital length of stay and FiO2 needs. Anti-RBD titers were also negatively correlated with oxygen flow rates during hospitalization with a p-value reaching towards statistical significance. In our population, vaccinated patients were more likely to test positive for anti-RBD and have a higher antibody level compared to those who were unvaccinated. Seroconversion after natural infection with SARS-CoV-2 is shown to occur within 1–3 weeks, with peak antibody levels achieved around one month.<sup>13–16</sup> Vaccinated patients presented earlier at a median of four days following onset of symptoms and thus higher anti-RBD titers were likely the result of prior vaccination.<sup>8–10</sup>

Conversely, unvaccinated individuals were more likely to test positive for anti-N. Our low rate of positivity in vaccinated patients is similar to the report by Colavita et al, which demonstrated that only 6% of vaccinated patients were positive for anti-N at the time of diagnosis of a breakthrough infection.<sup>17</sup> Nucleocapsid protein is the first to undergo translation after infection and anti-N assays have been shown to be more sensitive in detecting infection compared to anti-Spike IgG.<sup>18–20</sup> Patients who tested positive for anti-N had a longer onset of symptoms prior to presentation compared to patients who tested negative (median of 10 vs 4 days) and could explain our observation. While it has been shown that vaccines do not induce the production of anti-N,<sup>21</sup> recent studies have demonstrated lower anti-N sensitivity among vaccinated patients.<sup>22</sup> In a randomized placebo-controlled trial involving 1789 patients, those who were vaccinated with mRNA – 1273, had seroconversion to anti-N occur in only 40% compared to 93% of unvaccinated patients ( $p < 0.001$ ).<sup>22</sup> Therefore, the prognostic impact of anti-N positivity is not clear and provides an area of future research.

It has been established that antibodies directed specifically against the receptor binding domain (RBD) region of the spike protein correlate with neutralizing antibodies and play a role in immunity and protection from symptomatic infection.<sup>23</sup> In one study including twenty one unvaccinated patients hospitalized with COVID-19, higher levels of anti-spike IgG indicated worse outcomes. However, antibody levels were measured approximately one week after hospital admission.<sup>24</sup> Conversely, in another report involving unvaccinated COVID-19 patients, neither the presence nor the levels of SARS-CoV-2 antibodies served as prognostic markers.<sup>25</sup> In vaccinated patients however, antibody levels are



well known to be correlates of protection against several SARS-CoV-2 variants.<sup>26–28</sup> IgG antibody levels specifically against the RBD region of the spike protein have also been associated with favorable outcomes in patients who mount a higher antibody response in the first week after symptoms.<sup>29</sup> In our study, we have used the AdviseDx SARS-CoV-2 IgG II immunoassay which has been shown to be feasible in predicting neutralizing antibody titer.<sup>30</sup>

There remains to be limited data on the prognostic impact of anti-RBD IgG antibody levels on clinical outcomes in patients who required hospitalization with SARS-CoV-2. To our knowledge, this is the first report to demonstrate a negative linear relationship between anti-RBD levels with oxygen needs and overall hospital length of stay. Further studies are needed to determine the prognostic impact of anti-RBD IgG levels relative to symptom onset on clinical outcomes.

## Limitations

There were several limitations to our study. This was a pilot study and our sample size was small due to limited funding needed for measuring the SARS-CoV-2 antibodies. Subsequently, nearly all data points are underpowered. We only enrolled patients who were able to provide consent and thus might have inadvertently excluded patients who were sicker at presentation.

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## Disclosure

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