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MAJOR ARTICLE

Severe Acute Respiratory Syndrome Coronavirus 2 Plasma Antibody and Nucleocapsid Antigen Status Predict Outcomes in Outpatients With Coronavirus Disease 2019

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Background. Reliable biomarkers of coronavirus disease 2019 (COVID-19) outcomes are critically needed. We evaluated associations of spike antibody (Ab) and plasma nucleocapsid antigen (N Ag) with clinical outcomes in nonhospitalized persons with mild-to-moderate COVID-19.

Methods. Participants were nonhospitalized adults with mild-to-moderate COVID-19 enrolled in ACTIV-2 between January and July 2021 and randomized to placebo. We used quantitative assays for severe acute respiratory syndrome coronavirus 2 spike Ab and N Ag in blood and determined numbers of hospitalization/death events within 28 days and time to symptom improvement.

Results. Of 209 participants, 77 (37%) had quantifiable spike Ab and 139 (67%) quantifiable N Ag. Median age was 50 years; 111 (53%) were female, 182 (87%) White, and 105 (50%) Hispanic/Latino. Higher risk of hospitalization/death was seen with unquantifiable (22/132 [16.7%]) versus quantifiable (1/77 [1.3%]) spike Ab (risk ratio [RR], 12.83 [95% confidence interval {CI}, 1.76–93.34]) and quantifiable (22/139 [15.8%]) vs unquantifiable (1/70 [1.4%]) N Ag (RR, 11.08 [95% CI, 1.52–80.51]). Increasing risk of hospitalizations/deaths was seen with increasing N Ag levels. Time to symptom improvement was longer with unquantifiable versus quantifiable spike Ab (median, 14 [interquartile range {IQR}, 8 to >27] vs 8 [IQR, 4–22] days; adjusted hazard ratio [aHR], 0.66 [95% CI, .45–.96]) and with quantifiable versus unquantifiable N Ag (median, 12 [7 to >27] vs 10 [5–22] days; aHR, 0.79 [95% CI, .52–1.21]).

Conclusions. Absence of spike Ab and presence of plasma N Ag predicted hospitalization/death and delayed symptom improvement in COVID-19 outpatients.

Keywords. COVID-19; SARS-CoV-2; biomarker; nucleocapsid; spike antibody.

Reliable biomarkers of coronavirus disease 2019 (COVID-19) severity and outcomes are critically needed to identify individuals who are at the highest risk for complications. Early in the pandemic, several characteristics and comorbidities (eg, old age, high body mass index [BMI]), and certain underlying conditions (eg, cardiovascular or pulmonary disease) were identified as being associated with unfavorable outcomes [1–3]. However, laboratory predictors of severe disease have been elusive. Several studies have evaluated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA levels in the upper respiratory tract of persons with COVID-19 as a measure of clinical severity and outcomes [4–7]. RNA concentrations in blood have also been proposed as a potentially more sensitive and accurate predictor of COVID-19 disease severity, as they may reflect viral dissemination and systemic consequences of infection [4]. SARS-CoV-2 antibodies provide a functional measure of host immunity against SARS-CoV-2. The presence of SARS-CoV-2–specific antibody early in infection may be associated with faster resolution of disease and more favorable outcomes. Both plasma viral nucleocapsid antigen (N Ag) and antibodies against SARS-CoV-2 spike protein (spike Ab) have been studied in COVID-19 [8–11]. They have been well characterized in inpatients, for example, in the Accelerating COVID-19 Therapeutic Interventions and Vaccines 3: Therapeutics for Inpatients With COVID-19 (ACTIV-3/

Received 22 May 2024; editorial decision 29 May 2024; published online 17 July 2024

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https://doi.org/10.1093/cid/ciae324

TICO) study and others [12, 13], where the majority of hospitalized individuals with COVID-19 showed detectable N Ag in plasma at enrollment. From both individual and public health perspectives, reliable biomarkers are particularly important for outpatients to (1) enable early identification of individuals who are at the highest risk for complications and progression to severe disease; (2) tailor medical care to individual risk; (3) target antiviral therapy and other interventions to the most vulnerable; and (4) allow more reliable risk stratification for clinical and translational research, which may provide insight into the pathways associated with severe COVID-19.

We evaluated spike Ab and SARS-CoV-2 N Ag in plasma as candidate biomarkers to predict clinical outcomes in nonhospitalized adults with mild-to-moderate COVID-19 enrolled in the ACTIV-2/AIDS Clinical Trials Group (ACTG) A5401 trial, a randomized controlled platform trial that evaluated investigational agents for the treatment of acute COVID-19 (NCT04518410) [14, 15].

METHODS

Participants

ACTIV-2/A5401 is a randomized, placebo-controlled platform trial that evaluated the safety and efficacy of investigational agents for the treatment of mild-to-moderate COVID-19. Eligible participants included adults (aged >18 years) at high risk for progression to severe COVID-19 with a documented positive respiratory tract SARS-CoV-2 polymerase chain reaction or antigen test within 10 days and no more than 10 days of symptoms at enrollment. The population for this report included study participants who (1) were enrolled at US sites, (2) consented to future use of their stored samples, (3) received blinded placebo for amubarvimab plus romlusevimab, a combination monoclonal antibody [14], and (4) did not have a history of having received a vaccine for COVID-19.

Samples and Assays

Spike Ab and N Ag were measured by the quantitative Simoa SARS-CoV-2 immunoglobulin G (IgG) antibody assay (lower limit of quantification [LLoQ], 0.77 μg/mL) and the quantitative Simoa SARS-CoV-2 N Protein Advantage (LLoQ, 3 pg/mL) (both from Quanterix, Billerica, Massachusetts) from available plasma samples. All samples were collected at the time of study entry. The assays were conducted as per the manufacturer's instructions and as previously described [16, 17].

Outcome Measures

The primary clinical outcome measures were all-cause hospitalization/death through day 28 and time to symptom improvement through day 28. Hospitalization was defined as ≥24 hours of acute care in a hospital or similar acute care facility. Time to symptom improvement was defined as days from study entry (day 0) to the first of 2 consecutive days with all symptoms improved from their status at day 0. Participants who were hospitalized without previously achieving symptom improvement were retained in the risk set for the outcome and could not achieve improvement any longer on the symptom improvement analyses. Symptom measurement was based on a daily symptom diary completed by participants through day 28 [14]. There were 13 targeted symptoms, each recorded as absent, mild, moderate, or severe by the participant: feeling feverish, cough, shortness of breath or difficulty breathing at rest with activity, sore throat, body pain or muscle pain/aches, fatigue (low energy), headache, chills, nasal obstruction or congestion (stuffy nose), nasal discharge (runny nose), nausea, vomiting, and diarrhea.

Statistical Analysis

The analysis was conducted using a data cut from September 2023. Plasma spike Ab levels at day 0 were dichotomized into 2 categories, unquantifiable (<0.77 μg/mL) and quantifiable (≥0.77 μg/mL). Plasma SARS-CoV-2 N Ag levels at day 0 were grouped into 2 categories (unquantifiable, <3 pg/mL; quantifiable, ≥3 pg/mL) and, for additional analyses, into 4 categories (<3 pg/mL, 3 to <100 pg/mL, 100 to <1000 pg/mL, ≥1000 pg/mL).

The Kaplan-Meier estimator method was used to estimate time to hospitalization/death and time to symptom improvement across spike Ab and SARS-CoV-2 N Ag categories. Associations between spike Ab and SARS-CoV-2 N Ag levels at day 0 and hospitalization/death through day 28 were assessed using log-binomial regression models (or Poisson regression [18] if convergence issues occurred) with robust variance estimates. Risk ratios (RRs) and 95% confidence intervals (CIs) are reported. Associations with time to symptom improvement were estimated using Cox proportional hazards regression adjusting for age (<60 vs ≥60 years), race (White/non-White), ethnicity (Hispanic/Latino or non-Hispanic/Latino), sex (male or female), COVID-19 variant (Alpha, Delta, other, result not available), and days of symptoms prior to enrollment (≤5 vs >5 days). Adjusted hazard ratios (HRs) and 95% CIs are reported, with HRs <1 indicating longer (worse) time to symptom improvement relative to the reference group.

To explore if the strength of associations could be improved by looking at markers in tandem, we descriptively compared hospitalization/death rates and time to symptom improvement across combinations of day 0 spike Ab and N Ag categories.

All statistical tests used a 2-sided 5% significance level. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

Role of the Funding Source

The funding source (National Institutes of Health) had representatives as members of the study team and they were involved

in protocol development, conduct of the study, sample analysis, and interpretation of analyses.

Institutional Review Board Approval

The ACTIV-2/A5401 protocol was approved by a central institutional review board, Advarra (Pro00045266), with additional local institutional review board approval as required. The procedures followed were in accordance with the Helsinki Declaration of the World Medical Association. All participants of ACTIV-2/A5401 provided written informed consent before undergoing study procedures and all participants of the current study consented to secondary use of their samples for additional analyses.

RESULTS

Participant Characteristics

Of 422 ACTIV-2 participants enrolled to the placebo arm for amubarvimab and romlusevimab between January and July 2021, 209 met criteria for inclusion in this analysis. Reasons for exclusions were enrollment at ex-US sites (n = 129), nonconsent to future research (n = 29), unavailability of analyzable specimens or data or data integrity concerns (n = 36), receipt of a COVID-19 vaccine prior to study entry (n = 7), and no receipt of placebo study product (n = 12).

The median age was 50 (interquartile range [IQR], 40–59) years, with 159 participants (76%) <60 years of age (Table 1); 111 (53%) were female and 100% were cisgender; 182 (87%) identified as White and 16 (8%) as Black or African American, and 105 (50%) reported Hispanic or Latino ethnicity. Median BMI was 31.0 (IQR, 26.6–36.7) kg/m^2. The median time between symptom onset and enrollment was 6 (IQR, 3–7) days; 96 participants (46%) experienced symptom onset within 5 days of enrollment.

Seventy-seven participants (37%) had quantifiable plasma spike Ab levels (≥0.77 μg/mL) at day 0. The maximum spike Ab level was 413 μg/mL. The majority of participants, 139 (67%), had quantifiable plasma N Ag levels (≥3 pg/mL) at day 0, with a median of 20 (IQR, <3 to 195) pg/mL. The maximum N Ag level was 16 135 pg/mL. Seventy (33%) had unquantifiable N Ag (<3 pg/mL), and 76 (36%) had N Ag from 3 to <100 pg/mL, 35 (17%) from 100 to <1000 pg/mL, and 28 (13%) ≥1000 pg/mL.

Plasma Spike Ab and Risk for Hospitalization/Death

Twenty-three participants (11.0%) were hospitalized or had died by 28 days, with all 23 reaching the primary endpoint by hospitalization prior to day 28 and 3 who subsequently died (on days 6, 28, and 80). The proportion of hospitalizations/deaths was higher among participants with unquantifiable (<0.77 μg/mL) day 0 spike Ab levels (22/132 [16.7%]; ie, positive predictive value [PPV], 16.7%) than those with quantifiable

Table 1. Baseline Characteristics (N = 209)

Characteristic	No. (%)
Age, y	
Median (IQR)	50 (40–59)
<60	159 (76)
Female sex	111 (53)
Cisgender	209 (100)
Race	
Asian	6 (3)
Black or African American	16 (8)
White	182 (87)
Multiracial or other	5 (2)
Hispanic or Latino ethnicity	105 (50)
BMI, kg/m^2, median (IQR)	31.0 (26.6–36.7)
Risk factor for progression	
Hypertension[a]	85 (41)
Current smoker[b]	58 (28)
Obesity (BMI >35 kg/m^2)	63 (30)
Age ≥60 y	50 (24)
Diabetes mellitus	33 (16)
Chronic lung disease[c]	38 (18)
Cardiovascular disease	16 (8)
Immunosuppressed[d]	3 (1)
Active cancer (other than localized skin)	4 (2)
History of cirrhosis	0 (0)
Chronic kidney disease[e]	1 (<1)
COVID-19 variant	
Alpha	25 (16)
Beta	0 (0)
Delta	36 (23)
Epsilon	25 (16)
Gamma	6 (4)
Iota	1 (1)
Lambda	2 (1)
Mu	6 (4)
Other	56 (36)
Missing	52
Spike Ab, μg/mL	
Median (IQR)	<LLoQ[f] (<LLoQ—3.14)
Min, max	<LLoQ[f], 413.33
≥0.77[f]	77 (37)
N Ag, pg/mL	
Median (IQR)	20.0 (<LLoQ[f]—195.0)
Min, max	<LLoQ[f], 16 135
≥3[f]	139 (67)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: Ab, antibody; BMI, body mass index; COVID-19, coronavirus disease 2019; IQR, interquartile range; LLoQ, lower limit of quantification; N Ag, nucleocapsid antigen.

[a]Hypertension was defined as requiring at least 1 medication for hypertension recommended or prescribed.

[b]Current smoker was defined as anyone who currently inhaled a nicotine product.

[c]Chronic lung disease was defined as chronic lung disease or asthma requiring daily prescribed therapy.

[d]Immunosuppression was defined as any of the following: human immunodeficiency virus infection with CD4 count <200 cells/μL, receiving corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days within 30 days prior to study entry, treatment with biologics (eg, infliximab, adalimumab, ustekinumab), immunomodulators (eg, methotrexate, 6-mercaptopurine, azathioprine), or cancer chemotherapy within 90 days prior to study entry.

[e]Chronic kidney disease was defined as requiring hemodialysis or peritoneal dialysis.

[f]LLoQ: 0.77 μg/mL for spike Ab and 3 pg/mL for N Ag.

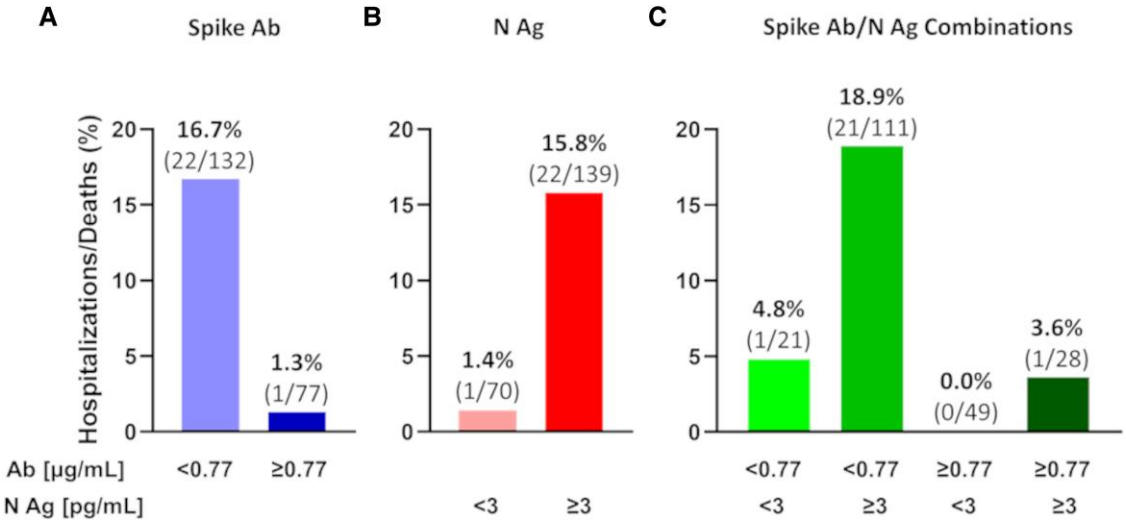

Figure 1. Hospitalizations/deaths through day 28 for nucleocapsid antigen (N Ag) and spike antibody (Ab) values below vs equal to or above lower limit of quantification (LLoQ) at day 0. Evaluating spike Ab (LLoQ, 0.77 µg/mL) (*A*), N Ag (LLoQ, 3 pg/mL) (*B*), and combinations of spike Ab and N Ag (*C*).

day 0 spike Ab (1/77 [1.3%]; negative predictive value [NPV] of nonhospitalization with quantifiable spike Ab, 98.7%; RR, 12.83 [95% CI, 1.76–93.34]) (Figure 1*A* and Supplementary Table 1).

Plasma N Ag and Risk for Hospitalization/Death

The proportion of those who were hospitalized or died was also higher among participants with quantifiable day 0 plasma N Ag (22/139; PPV, 15.8%) versus unquantifiable day 0 plasma N Ag (1/70; ie, 1.4%; NPV 98.6%, RR, 11.08 [95% CI, 1.52–80.51]) (Figure 1*B* and Supplementary Table 1).

The proportion of participants who were hospitalized or died through day 28 increased across increasing categories of day 0 N Ag levels: 1.4% (1/70) for <3 pg/mL, 5.3% (4/76) for 3 to <100 pg/mL, 8.6% (3/35) for 100 to <1000 pg/mL, and 53.6% (15/28) for ≥1000 pg/mL. Among those with quantifiable day 0 N Ag, the RR of hospitalization/death was 3.79 per 1 $\log_{10}$ pg/mL increase in day 0 levels of N Ag (95% CI, 2.38–6.04) (Supplementary Table 1). The 1 participant with unquantifiable N Ag at baseline who was hospitalized had reported 2 days of symptoms at enrollment.

Combination of Plasma Spike Ab and N Ag and Risk for Hospitalization/Death

When spike Ab and N Ag levels at day 0 were considered simultaneously, the proportion of those who were hospitalized or died through day 28 was highest among participants with unquantifiable spike Ab and quantifiable N Ag (21/111; ie, PPV 18.9%, NPV 98.0%) (Figure 1*C*). The risk for hospitalization/death in our analysis was 0% (0/49) for participants with quantifiable spike Ab and unquantifiable N Ag, 4.8% (1/21) in those who had unquantifiable levels of both spike Ab and N Ag, and 3.6% (1/28) in those with quantifiable levels of both. The combination of unquantifiable spike Ab and quantifiable N Ag as a predictor of hospitalization or death through day 28 was less sensitive (91.3%) but more specific (51.6%) than unquantifiable spike Ab alone (sensitivity 95.7%, specificity 40.9%) or quantifiable N Ag alone (95.7%, specificity 37.1%).

Among the 132 participants with unquantifiable spike Ab at day 0, the observed rate of hospitalizations/deaths increased with increasing day 0 N Ag levels: 5% (1/21) in those with N Ag <3 pg/mL, 7% (4/56) with N Ag 3 to <100 pg/mL, 10% (3/31) with N Ag 100 to <1000 pg/mL, and 58% (14/24) with N Ag ≥1000 pg/mL (Figure 2 and Supplementary Table 2). Among the 77 participants with quantifiable spike Ab at day 0, there were no hospitalizations in those who had day 0 N Ag levels <1000 pg/mL (0/73 [0%]), and 1 hospitalization in the 4 participants (25%) with day 0 N Ag level ≥1000 pg/mL.

Plasma Spike Ab and Time to Symptom Improvement

Participants with unquantifiable day 0 spike Ab levels had a significantly longer time to symptom improvement compared to those with quantifiable day 0 spike Ab levels (median, 14 vs 8 days; adjusted HR [aHR], 0.66 [95% CI, .45–.96]) (Figure 3*A* and Supplementary Table 3).

Plasma N Ag and Time to Symptom Improvement

Median time to symptom improvement for participants with quantifiable N Ag at day 0 was 12 (IQR, 7 to >27) days versus 10 (IQR, 5–22) days for those with unquantifiable N Ag (Figure 3*B*). The median time to symptom improvement increased in higher categories of N Ag levels at day 0: 10 (IQR, 5–22) days for <3 pg/mL, 11 (IQR, 6 to >27) days for 3 to <100 pg/mL, 11 (IQR, 6 to >27) days for 100 to <1000 pg/mL, and 25 (IQR, 13 to >27) days for ≥1000 pg/mL

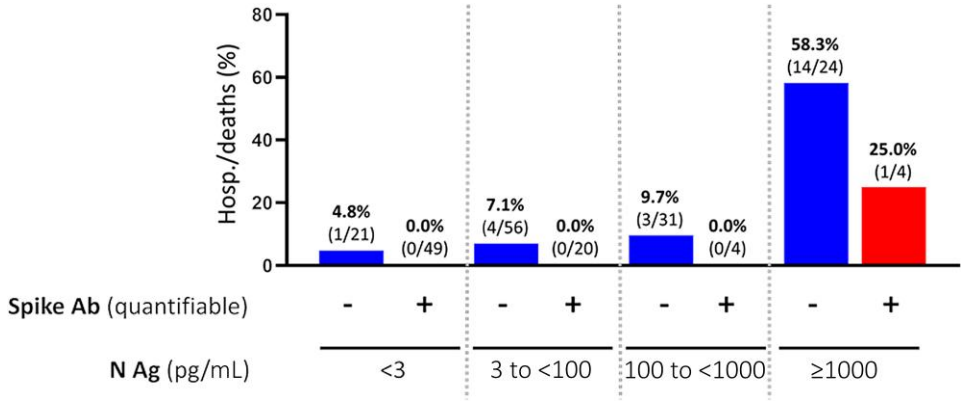

Figure 2. Hospitalizations/deaths through day 28 by nucleocapsid antigen (N Ag) categories and serostatus at day 0. Lower limit of quantification (LLoQ) for N Ag is 3 pg/mL; LLoQ for spike antibody (Ab) is 0.77 μg/mL.

(Figure 3C and Supplementary Table 3). There was a significant association between day 0 N Ag levels and time to symptom improvement among participants with quantifiable levels, suggesting that participants with higher day 0 N Ag levels had a longer time to symptom improvement (aHR, 0.78 per 1 $\log_{10}$ pg/mL higher day 0 levels [95% CI, .62–.98]).

Combination of Plasma Spike Ab and N Ag and Time to Symptom Improvement

When spike Ab and N Ag levels at day 0 were considered simultaneously, the time to symptom improvement was shortest among those with quantifiable spike Ab and unquantifiable N Ag (median, 7 [IQR, 4–14] days) and longest among those with N Ag ≥1000 pg/mL, regardless of whether the spike Ab levels were unquantifiable (median, 25 [IQR, 10 to >27]) or quantifiable (median, >27 [IQR, 22 to >27]) (Supplementary Table 4).

DISCUSSION

We evaluated plasma spike Ab and N Ag as biomarkers for clinical outcomes in symptomatic outpatients with acute COVID-19 who were rigorously characterized in the ACTIV-2/A5401 trial [14]. Both absence of spike Ab and presence of N Ag at enrollment were associated with increased risk of subsequent hospitalizations/deaths. We further demonstrated that higher levels of N Ag correlated with these unfavorable outcomes, as individuals with plasma N Ag levels ≥1000 pg/mL demonstrated the highest frequency of hospitalizations/deaths and prolonged time to symptom improvement compared to those with unquantifiable N Ag levels. Additional explorative analyses suggested that the combination of these 2 biomarkers may increase their value in the prediction of clinical outcomes of COVID-19, showing the lowest risk of hospitalization/death with quantifiable spike Ab and unquantifiable N Ag. Our study provides evidence that both spike Ab and N Ag are associated with disease progression in the outpatient setting.

Clinical risk factors for unfavorable outcomes were identified early in the COVID-19 pandemic, such as increasing age, high BMI, and several comorbidities, including cardiovascular disease or pulmonary disease and others [1–3]. However, laboratory-based predictors of severe COVID-19 disease are still needed. Our results highlight 2 laboratory parameters (spike Ab and plasma N Ag) as predictive biomarkers of outcomes in COVID-19 that could be used to stratify individual risk.

These biomarkers offer a direct assessment of the host immune response and the extent of viral dissemination, and thus have the potential to better predict the subsequent clinical course. This is supported by the ACTIV-3/TICO study of the monoclonal antibody bamlanivimab for inpatients, which showed in >2500 hospitalized participants that a high plasma N Ag level was strongly associated with worsening pulmonary disease and with longer time to hospital discharge [12], and by data from the Adaptive COVID-19 Treatment Trial 1 (ACTT-1) in inpatients in which measures of viral load, including plasma N Ag and plasma SARS-CoV-2 RNA, were associated with recovery and mortality [19]. In addition, the ACTIV-3/TICO study team described a signal of clinical benefit from monoclonal antibody treatment detected in those with both unquantifiable neutralizing antibody and high levels of antigenemia, but not in the overall bamlanivimab-treated population [16]. This aligns with the notion that passive anti-SARS-CoV-2 antibody therapy may be particularly effective in a setting of inadequate endogenous humoral responses to COVID-19 and/or if high viral replication is present. In addition to the results in hospitalized patients, our data suggest that these unfavorable markers are relevant for the prediction of poor outcomes in nonhospitalized individuals and may be useful to anticipate subsequent clinical deterioration.

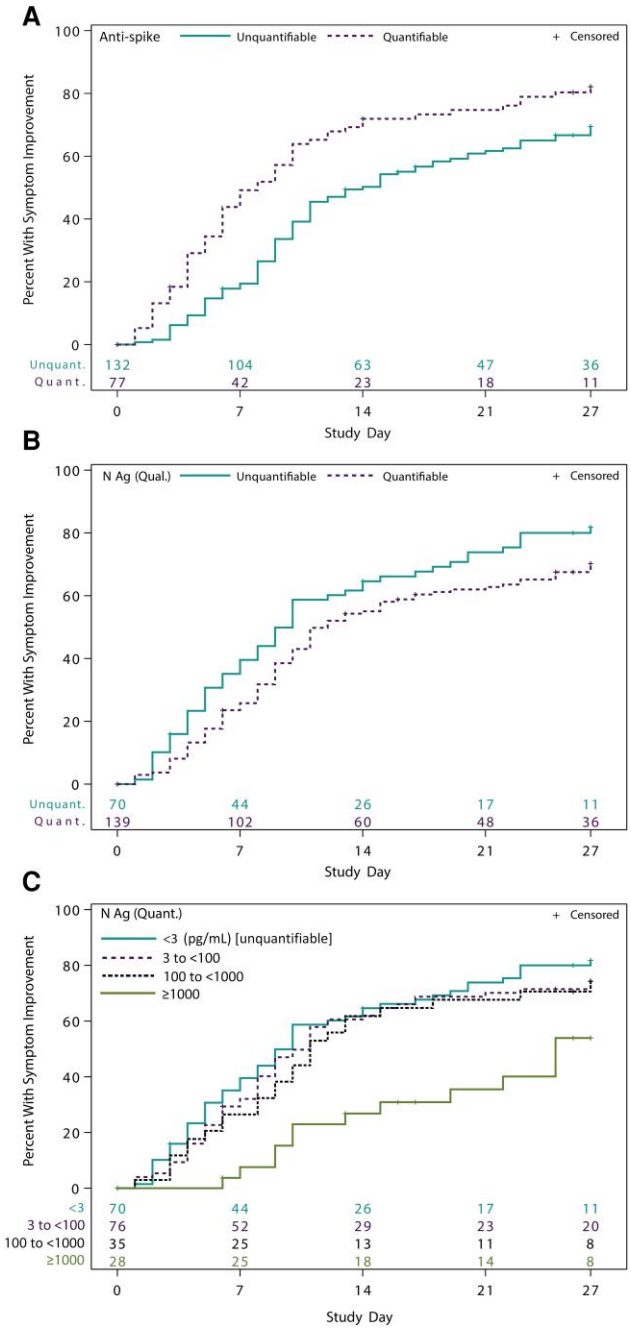

Figure 3. Time to improvement of all targeted symptoms for 2 consecutive days for spike antibody (Ab) (below lower limit of quantification [LLoQ] vs ≥LLoQ) (*A*); for nucleocapsid antigen (N Ag), qualitative analysis, ie, unquantifiable (<LLoQ) vs quantifiable (≥LLoQ) (*B*); and for N Ag by 4 categories: <LLoQ, ≥LLoQ to <100, ≥100 to <1000, ≥1000 (pg/mL) (*C*). LLoQ is 0.77 µg/mL for spike Ab and 3 pg/mL for N Ag. Number of participants still at risk for symptom improvement over time are provided at the bottom of each panel.

In the current unvaccinated cohort, 37% of participants had a quantifiable antibody response at study enrollment. The threshold to quantify IgG to SARS-CoV-2 spike with the ultrasensitive digital technology that was used for this study is likely substantially lower than with traditional enzyme-linked immunosorbent assays. Given that inclusion criteria allowed enrollment up to 10 days after symptom onset and/or a positive COVID-19 test, it is possible that in some individuals, the time since infection was sufficient to develop a primary antibody response that was quantified in the assay. Another likely possibility is that for some participants the current COVID-19 episode was a reinfection and that there was a preexisting antibody titer and/or an anamnestic response leading to much more rapid emergence of antibodies compared to a primary antibody response. We hypothesize that in both cases, quantifiable spike Abs are a correlate of preexisting immunity or of an effective immune response and may therefore be associated with protection from severe COVID-19. In contrast, absence of an antibody response at enrollment and presence of a correlate of high viral replication by quantification of nucleocapsid in plasma may in some participants be manifestations of a poor, late, or absent antibody response and occur, for example, in the setting of advanced age, other forms of immunosuppression, or with waning immunity after previous infection.

It is important to note that the enrolled population is not reflective of subsequent and the current population levels of SARS-CoV-2 immunity [20, 21] and the resultant lower risk of progression to hospitalizations or deaths from COVID-19 compared to the earlier phases of the pandemic [22]. However, even though the vast majority of the population has received SARS-CoV-2 vaccinations, has experienced prior infection, or both, waning immunity and immunosuppression may result in low plasma spike Ab levels in a subset of individuals who may be at particular risk of severe disease. In addition, a relevant proportion of immunosuppressed individuals has an undetectable antibody response to COVID-19 vaccination [23]. Risk stratification of these patients by standardized biochemical markers that can be measured with rapid tests could facilitate decisions on monitoring and treatment. This may be especially helpful in the current environment, where the uptake of nirmatrelvir-ritonavir is relatively low [24] despite the recommendation that it be prescribed for individuals at high risk of disease progression. The identification of individuals who are at highest risk of severe outcomes could help target our efforts to identify and prescribe antiviral therapy to those who may benefit the most. While the assays used in this study are not clinically available, the results provide proof-of-principle that plasma antibody and antigen testing could be clinically useful and deserve further evaluation as a clinical assay. Other limitations of this study include the infection with pre-Omicron variants and the numbers of individuals with hospitalizations/deaths such that we focused our multivariable analysis to the timing of symptom improvement. Additional studies confirming the predictive utility of the spike Ab and N Ag biomarkers within the context of the current population immune profile and COVID-19 variants are needed.

In summary, SARS-CoV-2 spike Ab and plasma SARS-CoV-2 N Ag may serve as informative biomarkers for

risk stratification in the evaluation of outpatients with COVID-19. These biomarkers should be evaluated in a larger, independent, and more contemporary vaccinated cohort of nonhospitalized individuals with COVID-19. Further studies are needed to assess how SARS-CoV-2 antigenemia plays a mechanistic role in the systemic manifestations of COVID-19.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Conception and design: N. J., H. C. L., K. W. C., R. D., D. M. S., J. Z. L., and M. D. H. Obtaining of funding: K. W. C., J. S. C., D. M. S., and M. D. H. Administrative, technical, or logistic support: K. W. C., J. S. C., J. J. E., and D. M. S. Provision of study materials or patients: K. W. C., T. H. E., E. S. D, J. J. E., J. S. C., and D. M. S. Statistical expertise: M. J. G., J. R., C. M., and M. D. H. Collection and assembly of data: R. D., K. S.-S., H. C. L., M. J. G., J. R., and M. D. H. Analysis and interpretation of the data: M. J. G., N. J., J. R., M. D. H., C. M., K. W. C., D. M. S., and J. Z. L. Drafting of the article: N. J., M. J. G., K. W. C., J. R., R. D., D. M. S., and J. Z. L. Critical revision of the article for important intellectual content: K. S.-S., C. M., T. H. E., E. S. D., J. J. E., J. S. C., M. D. H., and H. C. L. Final approval of the article: All authors.

Acknowledgments. The authors thank the study participants, the ACTIV-2/A5401 study team including site staff and site investigators, and the ACTIV-2 Community Advisory Board; the AIDS Clinical Trials Group (ACTG), including Lara Hosey, Jhoanna Roa, and Nilam Patel; the ACTG laboratory center, including Grace Aldrovandi and William Murtaugh; Frontier Science, including Marlene Cooper, Howard Gutzman, and Kevin Knowles; the Harvard Center for Biostatistics in AIDS Research and ACTG Statistical and Data Analysis Center; the National Institute of Allergy and Infectious Diseases/Division of AIDS, including Peter Kim, Bill Erhardt, Lorraine Waring, and Diane Hessinger, the Foundation for the National Institutes of Health (NIH) and the ACTIV partnership, including Stacey Adams; and the PPD clinical research services of Thermo Fisher Scientific.

Data availability. Data are available under restricted access due to ethical restrictions. Access can be requested by submitting a data request at https://submit.mis.s-3.net/ and will require the written agreement of the AIDS Clinical Trials Group (ACTG). Requests will be addressed as per ACTG standard operating procedures. Completion of an ACTG Data Use Agreement may be required.

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Financial support. This work was supported by the National Institute of Allergy and Infectious Diseases of the NIH (grant numbers UM1AI068634 to M. D. H., UM1AI068636 to J. S. C., UM1AI106701 and 1K08AI15573 to N. J., Harvard University Center for AIDS Research [HU-CFAR] 5P30AI060354 to N. J., and University of California, Los Angeles–Charles Drew University Center for AIDS Research [UCLA-CDU CFAR] P30AI152501 to K. W. C.).

Potential conflicts of interest. N. J. received salary support to the institution from Sagent Pharmaceuticals. D. A. W. has received funding to his institution to support research and honoraria for advisory boards and consulting from Gilead Sciences. T. H. E. serves as a consultant for Tonix Pharmaceuticals. E. S. D. receives consulting fees from Gilead Sciences, Merck, and GSK/ViiV and research support through his institution from Gilead Sciences and GSK/ViiV. J. Z. L. has received research funding from Merck. J. J. E. is an ad hoc consultant to GSK/VIR, data monitoring committee chair for Adagio Phase 3 studies. J. S. C. has consulted for Merck and Company. D. M. S. has consulted for Fluxergy, Kiadis, Linear Therapies, Matrix BioMed, Arena Pharmaceuticals, VxBiosciences, Model Medicines, Bayer Pharmaceuticals, Signant Health, and Brio Clinical. K. W. C. received research funding to the institution from Merck Sharp & Dohme and is a consultant for Pardes Biosciences. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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