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Nadia Khan Date

# Exploring the Effects of Comorbidities on COVID-19 Vaccine Response in Patients Receiving Hemodialysis

By

Nadia Khan

Master of Public Health

Epidemiology

_____

Dr. Scott Fridkin

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# Exploring the Effects of Comorbidities on COVID-19 Vaccine Response in Patients Receiving Hemodialysis

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## ABSTRACT

Exploring the Effects of Comorbidities on COVID-19 Vaccine Response in Patients Receiving Hemodialysis

By Nadia Khan

**Background:** Patients undergoing hemodialysis have a higher risk of infection as well as an immunocompromised state due to kidney disease. This makes them more likely to be impacted by infection due to SARS-CoV-2. In addition to risk of infection, dialysis patients have historically shown a reduced immune response to vaccination. Therefore, it is of great importance to examine immune response to SARS-CoV-2 vaccination and identification of risk factors for impaired immunologic response among hemodialysis patient populations.

**Methods:** The SARS-CoV2 Serosurveillance in Hemodialysis Patients (SHEP) study is a prospective surveillance study that began on September 1st, 2020, during the first two waves of the SARS-CoV-2 pandemic in the United States. Around 800 outpatient hemodialysis patients across four Emory Dialysis Clinics had serum tested monthly for SARS-CoV-2 antibodies. This analysis uses serology data collected from November 1st, 2020, until May 31st, 2021, and focuses on a cohort of 303 people based on vaccination and serology test criteria. Logistic regression was used to assess the impacts of age and other biological covariates on COVID-19 vaccine response, measured by DiaSorin LIAISON® SARS-CoV-2 S1/S2 IgG assay.

**Results:** In multivariable regression, weighted Elixhauser Score had a statistically significant inverse association with the likelihood of response to the COVID-19 vaccine (OR 0.97, 95% CI 0.93-1.00, p=0.03). Meanwhile, older patients had lower odds of seroconversion compared to younger patients, but the difference was not statistically significant. Similarly, immunosuppression and albumin level did not have significant associations with COVID-19 vaccine response.

**Conclusions:** Patients receiving hemodialysis do undergo seroconversion after the COVID-19 vaccine. However, the more comorbid conditions present the more likely it was that the patient didn't respond to the vaccine, demonstrated by the significant inverse association between weighted Elixhauser Score and post-vaccine response. Therefore, it could benefit dialysis providers to monitor the serologic status of certain subsets of patients, such as those with comorbidities outlined in the Elixhauser Score. These results can be used to customize vaccine booster dose protocols, keeping in mind these risk factors for seroconversion.

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# INTRODUCTION

Patients undergoing hemodialysis have a higher risk of infections due to frequent use of catheters or needles to access the bloodstream as well as an immunocompromised state due to kidney disease (1). Infection due to Severe Acute Respiratory Syndrome Coronavirus – 2 (SARS-CoV-2) is associated with increased morbidity and mortality among patients on hemodialysis (2). This may be partly due to prevalent underlying comorbidities in this population and their relative immune compromise. These patients also experience a reduced immune response to vaccines, as has been well described for hepatitis B vaccines (3, 4). Therefore, it is of great importance to examine immune response to SARS-CoV-2 vaccination and identification of risk factors for impaired immunologic response among dialysis patient populations to inform COVID-19 vaccine recommendations and policies.

Despite being at a higher risk of serious outcomes from infection, dialysis patients were often overlooked during the COVID-19 pandemic, especially when setting policy for vaccine distribution or in mRNA vaccine clinical trials (5). In Georgia, Phase A priority distribution went mainly to healthcare workers, first responders, and residents of long-term care facilities and nursing homes (6). The next phase included people 65 years and older as well as other frontline workers (6). People undergoing hemodialysis were not specifically mentioned. While there is some overlap between the specified groups and dialysis patients, not all dialysis patients fall in these categories. To guide vaccine policy as the country continues to deal with COVID-19 variants and reoccurring outbreaks, it is important to examine the higher risk of COVID-19 infection faced by dialysis patients and the potential lack of protection they receive from the vaccine.

Existing research suggests that dialysis patients do demonstrate adequate response to the COVID-19 vaccine, but it is lower than people not receiving dialysis, particularly after just the first dose (7). However, there are conflicting results regarding predictors of this lower response. Early studies cite diabetes, age, or immunosuppression as key risk factors of decreased immune response, but populations studied may not be generalizable to the dialysis community in Georgia (7, 8, 9). Even in healthy individuals, age is a known factor of decreased immunity (10), therefore we hypothesized it could be the main predictor of immune response in dialysis patients. To further clarify role of certain key predictors of vaccine response, this study focuses on the impact of age and other biological factors on COVID-19 vaccine response among patients undergoing outpatient intermittent hemodialysis in Atlanta, GA.

## METHODS

### Study Design and Population

The SARS-CoV2 Serosurveillance in Hemodialysis Patients (SHEP) study is a prospective surveillance study that began on September 1st, 2020, during the first two waves of the SARS-CoV-2 pandemic in the United States and ended in June 2021. Around 800 outpatient hemodialysis patients across four Emory Dialysis Centers had serum tested monthly for SARS-CoV-2 antibodies. All adult (age >18 years) patients undergoing hemodialysis at the four centers (Candler, Greenbriar, Northside, and North Decatur) were included in the study apart from people undergoing home (nocturnal) or peritoneal dialysis. Further exclusion criteria included pregnant women, prisoners, cognitively impaired or individuals with impaired decision-making capacity, and individuals who do not speak English.

Current analyses utilize serological data collected from November 1st, 2020, until May 31st, 2021. Most SHEP study patients received first and second doses of the COVID-19 vaccine in March and April 2021. Seventy five percent of the population received the Moderna COVID-19 vaccine and 24% received the Pfizer-BioNTech vaccine. There were four linked sources of data available for analysis. First, dialysis clinic logs were used to define eligible patients and capture demographic and clinical information such as race, age, gender, COVID-19 vaccine dose, time on dialysis, timing of dialysis sessions, vaccine type and administration dates, and any testing for SARS-CoV-2 antigen or PCR. The dialysis clinic vaccine administration data was augmented with vaccine records received from the Georgia Registry of Immunization Transactions and Services (GRITS). Second, clinical data were electronically captured from the Emory Healthcare Clinical Data Warehouse including ICD-10 codes as proxy metrics for comorbidities. Third were laboratory values for periodic tests performed during January-March of 2021. Fourth were all serologic test results and specimen collection dates from the Emory Laboratory testing monthly serum samples from dialysis patients.

We defined an analytic cohort to address the primary hypothesis that adequate vaccine response (seroconversion) was dependent upon patient age; this analytic cohort was defined as individuals within the SHEP study population with at least one COVID-19 vaccine dose, at least one serology test before vaccination and at least one serology test after vaccination. A subset of patients in this analytic cohort were chosen for the primary analysis of seroconversion, those patients with a negative serology result prior to vaccination. After excluding patients who were seropositive prior to vaccination, we were left with 303 patients for primary analysis (Supplementary Table 1).

**Comorbidity Measurement**

Comorbidities of dialysis patients were represented by comorbidity scores, using both the Charlson Comorbidity Index and the Elixhauser Comorbidity Index. The Charlson Comorbidity Index includes 17 chronic conditions used to predict an individual's one-year mortality risk (11). The Elixhauser Comorbidity Index works similarly but uses 31 chronic conditions and is used to predict 1-year mortality, length of hospital stay, adverse events and hospital discharges (12, 13). Both indices were produced by the R package "comorbidity" which uses ICD-10 codes to generate binary variables for certain comorbidities as well as an overall weighted and unweighted comorbidity score, indicative of the burden of disease and associated 1-year mortality risk. ICD-10 codes were obtained from participants' diagnoses records. Upon comparison, the Elixhauser Comorbidity Index has slightly better predictive capabilities overall and in dialysis patients (14); therefore, we chose to use only this measurement of comorbidity moving forward in our analysis.

**Covariates**

The main covariates included demographic data and markers of underlying illnesses. Various markers of dialysis efficiency, overall well-being, infection, nutrition, and inflammation were included (levels of neutrophils, lymphocytes, Kt/V (a measurement of dialysis efficiency), albumin, calcium, ferritin, hemoglobin A1C, phosphorous, normalized protein catabolic rate, parathyroid hormone, AST, ALT, total iron binding capacity, transferrin saturation, white blood cell count, and neutrophil to lymphocyte ratio). Specifically, albumin and ferritin were included in initial analyses as markers of inflammation and overall health.

Binary indicator variables were created for each comorbidity used by the Elixhauser Comorbidity Index. Immunosuppression was defined by ICD-10 codes for "immunosuppression due to medication" (D84.821) and "unspecified immunosuppression" (D84.90). One variable using both ICD-10 codes was created since the number of people in both categories were low. The same was done for "liver disease" and "mild liver disease." Due to ambiguity in the coding for diabetes with complications and diabetes without complications, those variables were also combined into one binary diabetes variable.

**Outcome Measurement**

To measure COVID-19 vaccine response, we defined seroconversion (i.e., response) as a positive post-vaccine serology test, done at least two weeks after first dose of vaccination. Serology tests were administered until May 2021 and some patients received their first vaccination in April, rendering us unable to capture their response at least 2 weeks after the second dose. Therefore, we chose to study response at least 2 weeks after the first dose administration.

Serology was performed using two types of tests. A commercially available assay, the DiaSorin LIAISON® SARS-CoV-2 S1/S2 IgG, was used first on all patients. The DiaSorin assay detects IgG antibodies against the SARS-CoV-2 spike protein. The minimum level of detection, reported as <3.8 AU/mL, was considered negative and any value above that was considered a positive response, with the maximum value being reported as >400 AU/mL. If the DiaSorin result was positive, a second assay developed by Emory Medical Laboratories was conducted to confirm the results. The Emory assay also detects IgG antibodies for the spike

protein, but specifically targets the receptor binding domain (RBD) which allows the spike protein to bind to host cells (15). An optical density of > 0.175 was considered positive, < 0.1 was considered negative, and samples between 0.1 and 0.175 were classified as indeterminate (16). An individual was given an overall positive qualitative result if the DiaSorin assay and the Emory RBD assay were both positive. Quantitative results were examined with box and whisker plot, using DiaSorin results only.

**Statistical Analyses**

To look at differences within the population, we created comparison groups based on the most recent serology test done before vaccination (pre-vaccine serology test) and the most recent serology test done at least 2 weeks after vaccination (post-vaccine serology test). The groups were defined as follows:

| **Patient Category** | **n=405** | **Pre-vaccine Serology** | **Post-vaccine Serology** |
|---|---|---|---|
| Responder | 250 | Negative | Positive |
| Non-responder | 53 | Negative | Negative |
| Persistently positive | 102 | Positive | Positive |

The persistently positive group were those patients with serologic evidence of prior infection with positive pre-vaccination serology; thus, any antibody response would resemble a boosted response to subsequent vaccine administration. Therefore, we included this group in initial descriptive analysis, but excluded it for the main analysis of predictors for adequate response to vaccine. All study demographic, lab, and dialysis related variables were compared between Responders and Non-responders using either the Chi-Square or Wilcoxon Rank Sum test.

Logistic regression models were constructed to examine bivariate associations between each risk factor and vaccine response. Those with a p-value $< 0.05$ were used in the multivariate model.

Multivariate logistic regression was used to assess the impacts of age and other covariates (immunosuppression, weighted Elixhauser Comorbidity Score, and albumin level) on COVID-19 vaccine response in the dialysis cohort. The primary exposure was age, categorized into tertiles, with the lowest age group used as a reference category. The results of the logistic regression analyses were expressed as adjusted odds ratios (aOR) and corresponding 95% confidence intervals (95% CI). Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and an $\alpha < 0.05$ was considered statistically significant.

## RESULTS

The baseline characteristics of the seroconversion analytic cohort (n=303) are outlined in Table 1. In the cohort, 92.7% of patients were Black or African American, the median age was 63 (IQR 18.5) years, 45.2% were women and median time on dialysis was 61 (IQR 63.1) months (Table 1). Ten people had a previous COVID-19 infection confirmed by PCR, occurring between April 2020 and March 2021. They remained in the study cohort because their pre-vaccine serology was negative; all 10 seroconverted post-vaccine (Table 1).

Univariate comparisons of covariates were similar between responders and non-responders for all demographic factors and lab values except for age, immunosuppression, liver disease, Elixhauser Comorbidity Score, weighted Elixhauser Comorbidity Score, and albumin (Table 3). The most significant differences were noted among mean age in the responders (61.3

years) compared to non-responders (66.2 years) as well as weighted Elixhauser Score (11.6 in responders, 15.7 in non-responders (Table 3).

Quantitative results of the DiaSorin test illustrate a robust response to the vaccine among persistently positive individuals (n=102), with 95% of all patients reaching maximum antibody response (>400 AU/mL), while only about 5% of seroconverts (responders, n=250) reached antibody levels of >400 AU/mL (Figure 1). Non-responders (n=53) had a median DiaSorin value of <3.8 AU/mL before and after vaccination. Responders had a median DiaSorin value of <3.8 AU/mL before vaccination and a median of 90.85 AU/mL after vaccination, indicating an immune response to the vaccine.

In multivariable regression, comorbidities, measured by weighted Elixhauser Scores, had a statistically significant inverse association with the likelihood of response to the COVID-19 vaccine (OR 0.97, 95% CI 0.93-1.00, p=0.03). Immunosuppression was also associated with non-response although the association was not significant (OR 0.21, 95% CI 0.04-1.22). Those above the median albumin level had a non-significantly greater likelihood of seroconversion compared to those below the median (OR 1.69, 95% CI 0.89-3.21). After adjusting for comorbidities, the association between older age and vaccine response was diminished and although the aOR suggested an increased risk of non-response, the risk in older people compared to younger people was not statistically significant (Table 2).

## DISCUSSION

Response to the COVID-19 vaccine occurred in 83% of the dialysis patient cohort that were seronegative prior to vaccination. This is a lower response rate compared to previous

literature that found a 96.4% response rate among their dialysis cohort (8). However, waning immunity and timing between vaccination and serology testing could impact response. Our response rate is similar to an 81% response rate found among a different hemodialysis cohort, tested 36 days after first vaccine dose (17).

Upon examining key predictors of vaccine response, our analysis found that only weighted Elixhauser Comorbidity Score had a statistically significant impact on vaccine response in our cohort. Age did have an inverse relationship with the odds of seroconversion but the difference in seroconversion between age groups was not statistically significant. Immunosuppression was a significant predictor of vaccine response in other studies (9) but in our study cohort the association was not significant. It is important to note that only 2% of our cohort were categorized as being immunosuppressed, making the effect difficult to capture. In studies where 10% of the population was immunosuppressed, the condition was prevalent enough to see a significant difference in vaccine response (18).

Also of note is the robust post-vaccine immune response among the persistently positive individuals who were not included in analysis. They had higher post-vaccine response levels than patients who were negative pre-vaccine and seroconverted (responders). This is because earlier infection elicited an initial immune response, and the first vaccine dose is acting as a booster dose of vaccine to augment the existing antibody levels. It would be of interest to examine quantitative serology results in the analytic cohort two weeks after the second vaccine dose to see if the levels of response in responders and persistently positive people are similar.

**Limitations**

This study lacks the racial diversity needed to generalize results to populations in other regions of the United States. Most of the cohort were Black or African American and the racial distribution seen in the Southern United States is likely to be different than other regions.

Over time, we have seen that immune response to the COVID-19 vaccine wanes. Although that is a relevant concern in dialysis populations, our study was not equipped to examine waning immunity since serology collection did not extend far enough after vaccination. The vaccine was introduced in the second half of the serology collection period, so there are only a couple of months of serology tests after vaccination. Additionally, there were reports of high rates of early seroconversion (14-30 days) after vaccination in hemodialysis populations (8), which could have been missed in our study due to the varying number of days between vaccination and post-vaccine serology measurement (median: 29 days, min: 15 days, max: 80 days).

Ideally, our study would have measured response 2 weeks after the second vaccine dose, but serology tests were only administered until May 2021 and some patients received their first doses in April, rendering us unable to capture their response at least 2 weeks after the second dose.

A potential confounder of our results is the second vaccination dose. The second dose was administered 28 days after the first dose, and our response measurement included serology tests at least 14 days after the first dose. The median time between vaccination and response measurement was 29 days, indicating that our serology measurements could have quantified

responses to the second vaccine dose if they were done more than 27 days after the first vaccine dose.

## CONCLUSIONS

Patients receiving hemodialysis do undergo seroconversion after the COVID-19 vaccine; around 83% responded in our cohort. Given the low prevalence of immunosuppression in the analytic cohort, patients had a higher likelihood of seroconversion. However, the more comorbid conditions present the more likely it was that the patient did not respond to the vaccine, demonstrated by the significant association between weighted Elixhauser Score and post-vaccine response. Hypertension and diabetes were the top two most prevalent comorbid conditions affecting the cohort. Although not individually tested in our model, these conditions factor into the Elixhauser Score, which was predictive of vaccine response. Therefore, it could benefit dialysis providers to monitor serologic status of certain subsets of patients, such as people with hypertension or diabetes. In addition, customized vaccine booster dose protocols can be created keeping in mind these risk factors for seroconversion.

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**Table 1. Demographic and Clinical Characteristics of Emory Dialysis Clinic Analytic Cohort Stratified by Response Group (n=303)**

| | Nonresponder (N=53) | Responder (N=250) | Overall (N=303) |
|---|---|---|---|
| **Race** | | | |
| Asian | 1 (1.9%) | 4 (1.6%) | 5 (1.7%) |
| Black or African American | 49 (92.5%) | 232 (92.8%) | 281 (92.7%) |
| White | 3 (5.7%) | 14 (5.6%) | 17 (5.6%) |
| **Age** | | | |
| Mean (SD) | 66.2 (13.8) | 61.3 (13.9) | 62.2 (13.9) |
| Median [Min, Max] | 67.0 [25.0, 94.0] | 62.0 [21.0, 94.0] | 63.0 [21.0, 94.0] |
| **Age (tertiles)** | | | |
| 21-57 | 15 (28.3%) | 91 (36.4%) | 106 (35.0%) |
| 58-69 | 18 (34.0%) | 86 (34.4%) | 104 (34.3%) |
| 70-94 | 20 (37.7%) | 73 (29.2%) | 93 (30.7%) |
| **Gender** | | | |
| F | 23 (43.4%) | 114 (45.6%) | 137 (45.2%) |
| M | 30 (56.6%) | 136 (54.4%) | 166 (54.8%) |
| **Total Time on Dialysis (months)** | | | |
| Mean (SD) | 76.9 (53.9) | 71.9 (56.8) | 72.8 (56.2) |
| Median [Min, Max] | 70.0 [8.11, 247] | 58.9 [8.31, 470] | 61.0 [8.11, 470] |
| **Elixhauser Comorbidity Score** | | | |
| Mean (SD) | 6.24 (3.76) | 5.29 (3.45) | 5.45 (3.52) |
| Median [Min, Max] | 6.00 [1.00, 16.0] | 5.00 [1.00, 19.0] | 5.00 [1.00, 19.0] |
| Missing | 3 (5.7%) | 5 (2.0%) | 8 (2.6%) |
| **Weighted Elixhauser Comorbidity Score** | | | |
| Mean (SD) | 15.7 (11.5) | 11.6 (8.38) | 12.3 (9.08) |
| Median [Min, Max] | 14.5 [1.00, 46.0] | 9.00 [-2.00, 42.0] | 10.0 [-2.00, 46.0] |
| Missing | 3 (5.7%) | 5 (2.0%) | 8 (2.6%) |
| **Immunosuppression** | | | |
| No | 47 (88.7%) | 242 (96.8%) | 289 (95.4%) |
| Yes | 3 (5.7%) | 3 (1.2%) | 6 (2.0%) |

| | Nonresponder (N=53) | Responder (N=250) | Overall (N=303) |
|---|---|---|---|
| Missing | 3 (5.7%) | 5 (2.0%) | 8 (2.6%) |
| **Diabetes** | | | |
| No | 26 (49.1%) | 131 (52.4%) | 157 (51.8%) |
| Yes | 24 (45.3%) | 114 (45.6%) | 138 (45.5%) |
| Missing | 3 (5.7%) | 5 (2.0%) | 8 (2.6%) |
| **Liver Disease** | | | |
| No | 44 (83.0%) | 231 (92.4%) | 275 (90.8%) |
| Yes | 6 (11.3%) | 14 (5.6%) | 20 (6.6%) |
| Missing | 3 (5.7%) | 5 (2.0%) | 8 (2.6%) |
| **Kidney Transplant** | | | |
| No | 47 (88.7%) | 227 (90.8%) | 274 (90.4%) |
| Yes | 3 (5.7%) | 18 (7.2%) | 21 (6.9%) |
| Missing | 3 (5.7%) | 5 (2.0%) | 8 (2.6%) |
| **Previous COVID-19 Infection** | | | |
| No | 53 (100%) | 240 (96.0%) | 293 (96.7%) |
| Yes | 0 (0%) | 10 (4.0%) | 10 (3.3%) |
| **Albumin (g/dL)** | | | |
| Mean (SD) | 3.77 (0.308) | 3.87 (0.296) | 3.85 (0.300) |
| Median [Min, Max] | 3.80 [3.10, 4.50] | 3.90 [2.80, 4.70] | 3.90 [2.80, 4.70] |
| **Ferritin (µg/L)** | | | |
| Mean (SD) | 781 (405) | 678 (348) | 696 (360) |
| Median [Min, Max] | 710 [23.0, 2090] | 691 [5.00, 1750] | 697 [5.00, 2090] |

Values are n(%) unless otherwise stated (mean (SD) or median [min, max])

**Table 2. Estimated odds of COVID-19 Vaccine Response Among Dialysis Patients, Based on Age, Adjusting for Various Predictors**

| Covariate | | Adjusted OR (95% CI) | P-value |
|---|---|---|---|
| Age (years) | 21-57* | - | - |
| | 58-69 | 0.724 (0.321, 1.632) | 0.80 |
| | 70-94 | 0.621 (0.274, 1.408) | 0.36 |
| Weighted Elixhauser Comorbidity Score | | 0.965 (0.934, 0.996) | **0.03** |
| Albumin (g/dL) | Below Median* | - | - |
| | Above Median | 1.687 (0.887, 3.209) | 0.11 |
| Immunosuppressed | No* | - | - |
| | Yes | 0.209 (0.036, 1.219) | 0.08 |

* Indicates Reference Group
Median albumin was 3.9 g/dL
Bolded text corresponds to a significant p-value

**Table 3. Univariate Comparisons of Significant Covariates Between Response Groups**

| Covariate | Total (n=303) | Response (n=250) | No Response (n=53) | P-value |
|---|---|---|---|---|
| Age | 62.2 (13.9) | 61.3 (13.9) | 66.2 (13.8) | 0.02 |
| Immunosuppression, n (%) | 6 (2.0) | 3 (1.2) | 3 (5.7) | 0.10 |
| Liver Disease, n (%) | 20 (6.6) | 14 (5.6) | 6 (11.3) | 0.19 |
| Elixhauser Comorbidity Score | 5.45 (3.52) | 5.29 (3.45) | 6.24 (3.76) | 0.10 |
| Weighted Elixhauser Score | 12.3 (9.08) | 11.6 (8.38) | 15.7 (11.5) | 0.06 |
| Albumin, mg/ml | 3.85 (0.30) | 3.87 (0.296) | 3.77 (0.31) | 0.02 |

Comparisons conducted using Chi-Squared or Wilcoxon Rank Sum Tests
Values written as mean (SD) unless otherwise noted
P-values considered significant if $p<0.2$

**Figure 1. Pre-vaccine (left graph) and Post-vaccine (right graph) DiaSorin Quantitative Test Results Stratified by Response Group**

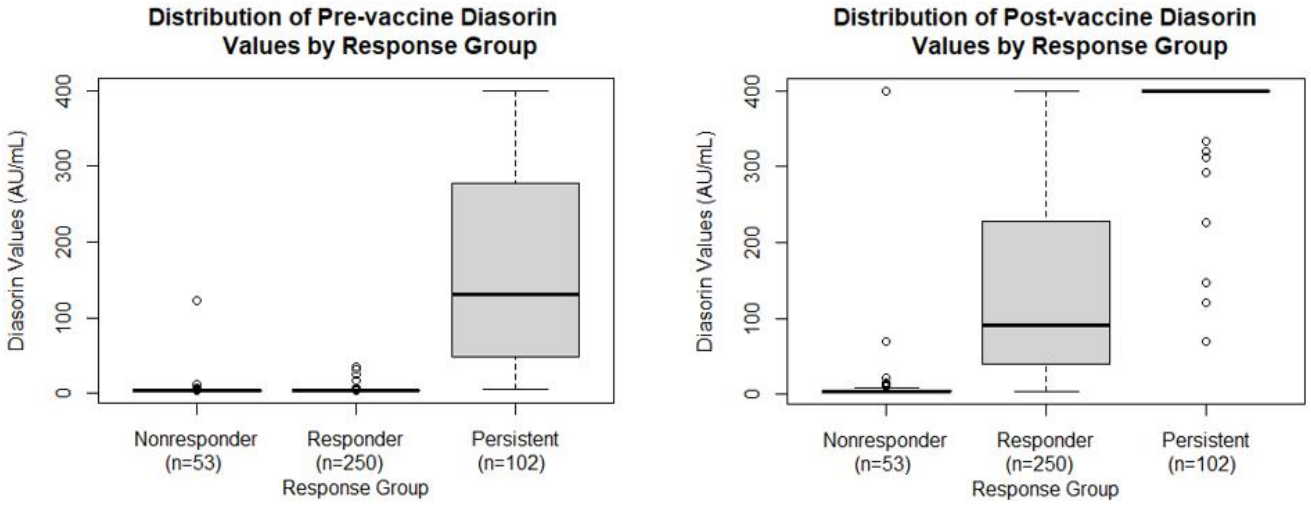



**Figure 2. Post-Vaccine DiaSorin Quantitative Test Results Stratified by Age Group**

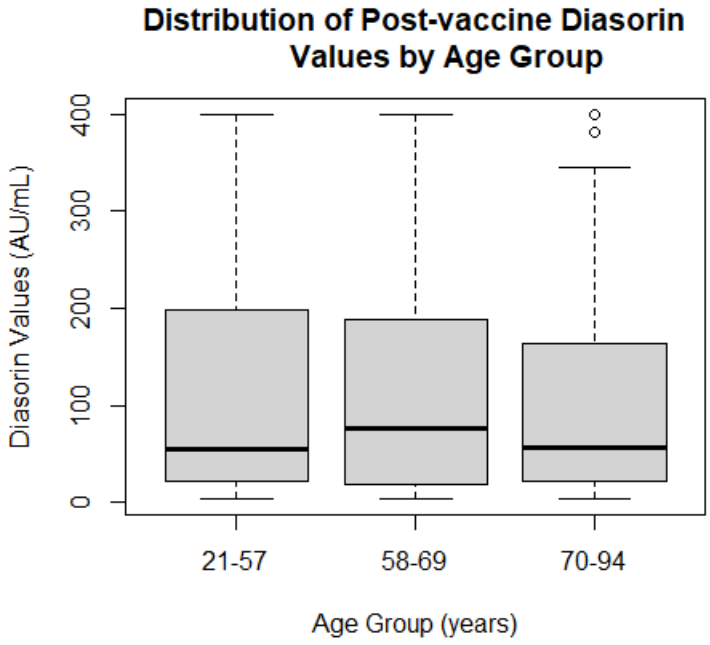
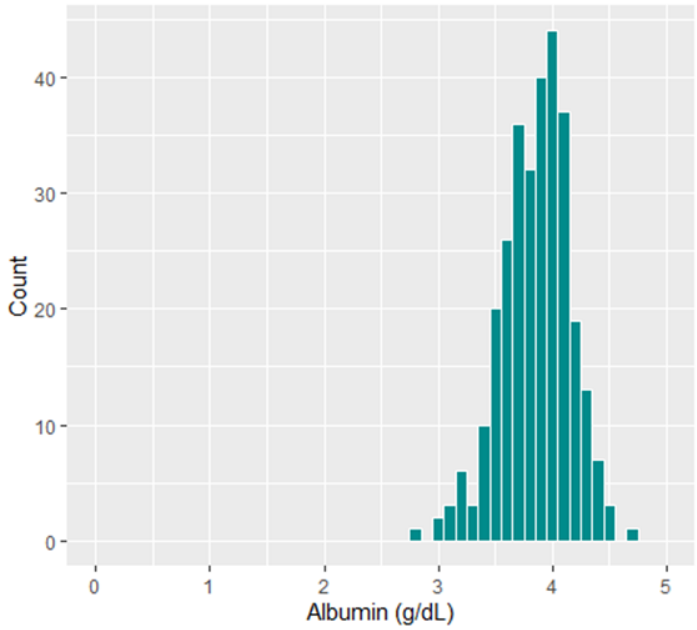


**Figure 3. Distribution of Albumin values (g/dL) among study cohort, from samples in January-March 2021**




**Supplementary Table 1. Number of hemodialysis patients cared for by study clinics eligible for analytic cohort, by exclusion criteria**

| **Eligible Patients** | |
|---|---|
| All patients , Emory Dialysis Clinics (November 2020 – May 2021) | n=728 |
| Exclude those on other types of dialysis (not hemodialysis) | n=10 |
| Exclude those without at least one serology test | n=44 |
| Exclude unvaccinated individuals | n=224 |
| Exclude those without at least one test before vaccination | n=19 |
| Exclude those without at least one test after vaccination | n=26 |
| Remove persistent group | n=102 |
| Final analytic cohort | n=303 |