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Key Predictors of IgG Seropositivity in Individuals Exposed to SARS-CoV-2 Prior to Vaccine Rollout

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Abstract

Introduction: The COVID-19 pandemic has highlighted the need to understand factors influencing the immune response to SARS-CoV-2. Immunoglobulin G (IgG) antibodies serve as indicators of prior exposure and potential immunity. This study aims to identify demographic, clinical, and exposure-related predictors of IgG positivity in individuals exposed to SARS-CoV-2 before the initiation of vaccination programs.

Materials and Methods: A cross-sectional study was conducted among 944 participants recruited from healthcare facilities. Eligible participants were aged 18 years or older, presented with COVID-19 symptoms or known exposure to confirmed SARS-CoV-2 cases, and had not received a COVID-19 vaccine. Data were collected via structured questionnaires, including demographics, clinical symptoms, and exposure history, and analyzed using logistic regression. IgG antibodies were detected using the SARS-CoV-2 IgG ELISA method.

Results: IgG antibodies were detected in 75.0% of participants. Younger age ($B = -0.026$, $p < 0.001$), divorced marital status ($B = 0.973$, $p = 0.021$, $Exp(B) = 2.65$), recent international travel ($B = 0.953$, $p = 0.047$, $Exp(B) = 2.594$), and symptoms such as runny nose ($B = 2.561$, $p = 0.012$, $Exp(B) = 12.96$), nausea ($B = 1.614$, $p = 0.048$, $Exp(B) = 5.025$), and lack of appetite ($B = 1.366$, $p = 0.049$, $Exp(B) = 3.918$) were significant predictors of IgG positivity. Each additional year of age was associated with a 2.6% reduction in the likelihood of IgG positivity. The model achieved 75.4% classification accuracy with an AUC of 0.640, indicating moderate predictive performance.

Conclusion: This study demonstrates the importance of demographic, clinical, and exposure-related factors in predicting IgG positivity. The findings enhance understanding of immune responses to SARS-CoV-2 and provide insights that can guide public health strategies in mitigating the pandemic's impact.

Keywords: COVID-19, SARS-CoV-2, IgG antibodies, Immune response, Logistic regression

1. Introduction

The COVID-19 pandemic has posed unprecedented challenges to global health systems, necessitating a comprehensive understanding of the factors influencing the immune response to SARS-CoV-2. Among these factors, the presence of IgG antibodies serves as a critical indicator of prior exposure to the virus and potential immunity. Notably, recent studies have revealed that individuals who are IgG-positive can still exhibit COVID-19 symptoms, suggesting that the relationship between seropositivity and clinical presentation is more intricate than previously understood [1]. This phenomenon raises important questions about the persistence of the virus, the dynamics of the immune response, and the implications for public health strategies.

Identifying the demographic, clinical, and exposure-related variables associated with IgG positivity is essential for informing public health strategies and vaccination efforts. Factors such as age, sex, and pre-existing health conditions may confound the relationship between exposure to SARS-CoV-2 and IgG positivity. For instance, older individuals and those with pre-existing health conditions may exhibit different immune responses, potentially leading to persistent symptoms despite the presence of IgG antibodies [2]. Therefore, it is imperative to employ robust methodologies to identify and adjust for these confounders to ensure accurate conclusions.

This study aims to elucidate these associations within a diverse cohort of patients potentially exposed to SARS-CoV-2. By systematically adjusting for identified confounders, the study employs a cross-sectional design utilizing logistic regression analysis to explore the factors associated with IgG positivity among participants. The findings are expected to contribute to the growing body of literature on COVID-19 and inform public health strategies aimed at mitigating the impact of the pandemic. This research seeks to address the critical gaps in understanding the factors associated with IgG positivity in a diverse population potentially exposed to SARS-CoV-2. By employing rigorous methodologies to adjust for confounding variables, the study aims to yield insights that can guide future public health interventions and enhance our understanding of the immune response to COVID-19.

2. Materials and Methods

Participant Selection

A total of 944 patients were recruited from various healthcare facilities. Inclusion criteria included individuals aged 18 years and older who presented with symptoms suggestive of COVID-19 or had known exposure to a confirmed SARS-CoV-2-positive individual. Exclusion criteria encompassed individuals with severe immunocompromised conditions or those receiving immunosuppressive therapy, as these factors could significantly influence antibody responses, as well as those who had been vaccinated against Covid-19. Recruitment was facilitated through collaboration with healthcare providers to ensure a diverse demographic representation.

Data Collection

Data were collected using a structured questionnaire that included demographic information (age, sex, marital status), clinical symptoms (fatigue, fever, respiratory symptoms, gastrointestinal symptoms), exposure history (contact with confirmed cases, location of exposure, recent travel), and serological testing results for IgG antibodies. The serological testing for IgG antibodies was performed using a SARS-CoV-2 IgG ELISA, following the established protocol. Briefly, serum/plasma samples were added to antigen-coated wells, incubated with a secondary antibody conjugated to an enzyme, and the reaction was developed using a substrate solution. The optical density was measured at 450 nm, and results were interpreted based on a standard curve or cutoff value. The questionnaire was pilot-tested to ensure clarity and comprehensiveness, and trained research assistants administered the questionnaires and collected biological samples to minimize variability in data collection procedures.

Management of Confounders and Bias

To address potential confounders and biases, several strategies were implemented throughout the study design and analysis phases:

Identification of Confounders: Confounders were identified based on established guidelines, which suggest that confounders must be associated with both the exposure and the outcome, and must not lie on the causal pathway between them. A directed acyclic graph (DAG) approach was utilized to visualize relationships among variables and to guide the selection of confounders for adjustment. This method is preferred over traditional statistical modeling strategies, as it helps avoid biased estimates due to omitted variable bias.

Statistical Adjustment: Multivariable logistic regression was employed to adjust for identified

confounders, including demographic factors (age, sex, marital status), clinical symptoms, and exposure history. This approach allows for the estimation of the independent effect of each variable on IgG positivity while controlling for the influence of confounders. The selection of variables for adjustment was based on known associations with the outcome and exposure, ensuring that potential confounding variables were adequately controlled.

Bias Minimization: To minimize selection bias, the study employed a comprehensive recruitment strategy that included diverse healthcare settings and patient demographics. This approach aimed to ensure that the sample was representative of the broader population potentially exposed to SARS-CoV-2. Additionally, informed consent was obtained from all participants, ensuring that they understood the study's purpose and their right to withdraw at any time.

Statistical Analysis

Descriptive statistics summarized the demographic and clinical characteristics of participants. Logistic regression analysis identified factors significantly associated with IgG positivity, with a significance level set at $p < 0.05$ for all analyses. Model fit and accuracy were assessed using the Omnibus Tests of Model Coefficients and the Hosmer-Lemeshow test. The classification accuracy of the logistic regression model was evaluated through a classification table, providing insights into the model's predictive capabilities regarding IgG positivity. The Area Under the Curve (AUC) was calculated to assess the discriminative ability of the model, with an AUC value indicating moderate predictive accuracy.

3. Results

Descriptive Analysis

A total of 944 participants were included in the study, with a mean age of 37.56 years (SD = 10.64). Most participants were female (66.2%, *n* = 625), while 33.8% (*n* = 319) were male. The majority were single (58.6%, *n* = 553), followed by married individuals (37.2%, *n* = 351), and divorced individuals (4.2%, *n* = 40). Commonly reported symptoms included fatigue (31.5%, *n* = 297), fever ≥ 39.0°C (23.6%, *n* = 223), and respiratory symptoms such as sore throat (12.7%, *n* = 120) and cough (11.9%, *n* = 112). Gastrointestinal symptoms were also notable, with nausea (13.8%, n = 130) and vomiting (13.0%, *n* = 123) frequently reported.

Regarding exposure history, 28.6% (*n* = 270) of participants reported contact with a confirmed SARS-CoV-2-positive individual in the past four days. Hospital settings accounted for 55.0% (*n* = 519) of exposures, while 9.9% (*n* = 93) had recent domestic or international travel. Overall, 75.0% (*n* = 708) of participants tested positive for IgG antibodies, suggesting prior exposure to SARS-CoV-2 in the majority of the cohort.

Logistic Regression Analysis

The logistic regression model identified significant predictors of IgG positivity. Age showed a statistically significant negative association with IgG positivity (B = -0.026, $p < 0.001$), indicating a 2.6% decrease in likelihood of IgG positivity with each additional year of age. Marital status was significant for divorced individuals (B = 0.973, p = 0.021, Exp(B) = 2.65), suggesting they were 165% more likely to test IgG-positive compared to single individuals. Among symptoms, runny nose (B = 2.561, p = 0.012, Exp(B) = 12.96), nausea (B = 1.614, p = 0.048, Exp(B) = 5.025), and lack of appetite (B = 1.366, p = 0.049, Exp(B) = 3.918) were all positively associated with IgG positivity. Exposure history showed that recent international travel in the past 10 days was significantly associated with IgG positivity (B = 0.953, p = 0.047, Exp(B) = 2.594).

Table 1. Logistic Regression Output: IgG Positivity Predictors

Variables in the Equation									
Parameters		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Age	-0.026	0.007	16.193	1	0.000	.974	0.962	0.987
	Female	0[b]	-	-	-	-	-	-	-
	Male	-0.142	0.174	.661	1	0.416	.868	0.617	1.221
	Single			5.188	2	0.075			
	Married	-0.630	0.422	2.226	1	0.136	.532	0.233	1.219
	Divorced	0.973	0.466	4.354	1	0.037	.378	0.152	.943
	Fatigue	0.070	0.222	.099	1	0.753	1.072	0.694	1.658
	Fever ≥38.0°C	-0.228	0.271	.708	1	0.400	.796	0.469	1.354
	Sore throat	-0.531	0.659	.649	1	0.420	.588	0.161	2.141
	Loss of smell	0.148	0.754	.039	1	0.844	1.160	0.265	5.079
	Loss of taste	-0.682	0.758	.810	1	0.368	.506	0.114	2.233
	Runny nose	2.561	1.019	6.317	1	0.012	.077	0.010	0.569
	Cough	-0.210	0.600	.123	1	0.726	.810	0.250	2.627
	Shortness of breath	0.283	0.735	.148	1	0.700	1.327	0.314	5.605
	Vomiting	0.971	0.759	1.636	1	0.201	2.639	0.597	11.678
	Nausea	1.614	0.817	3.901	1	0.048	5.025	1.012	24.938
	Diarrhoea	-0.722	0.656	1.211	1	0.271	.486	0.134	1.758
	Lack of appetite	1.366	0.693	3.884	1	0.049	3.918	1.008	15.237
	Constipation	-0.315	0.647	.237	1	0.626	.730	0.205	2.594
	Early satiety	0.274	0.432	.404	1	0.525	1.316	0.565	3.065
	Hyper active bowel sensation	0.086	0.433	.039	1	0.843	1.089	0.466	2.546
	Abdominal pain	-0.862	0.487	3.134	1	0.077	.422	0.163	1.097
	Gastro esophageal reflux	0.382	0.362	1.114	1	0.291	1.465	0.721	2.979
	Headache	0.547	0.425	1.657	1	0.198	1.729	0.751	3.978
	Muscle ache	0.168	0.484	.120	1	0.729	1.182	0.458	3.051
	Travelled (domestically) in the last 10	-0.908	0.515	3.112	1	0.078	.403	0.147	1.106
	Travelled (internationally) in the last 10 days	0.953	0.479	3.953	1	0.047	2.594	1.014	6.639
	Had contact with patient with COVID 19 symptoms in the last 4 days	0.233	0.225	1.076	1	0.300	1.263	0.813	1.961
	Attended festival or mass gathering in the last 10 days	0.026	0.361	.005	1	0.942	1.027	0.506	2.085
	Exposed to person with similar illness	-0.358	0.242	2.175	1	0.140	.699	0.435	1.125
	Was visited or was admitted to inpatient health facility in the last 10 days	0.467	0.291	2.582	1	0.108	1.595	0.902	2.819
	Visited outpatient treatment facility in the last 10 days	-0.552	0.283	3.795	1	0.051	.576	0.331	1.003
	Were you isolated after exposure	0.059	0.172	.119	1	0.731	1.061	0.757	1.488
	Constant	3.356	0.683	24.119	1	0.000	28.678		

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Model fit and accuracy were assessed using the Omnibus Tests of Model Coefficients, which demonstrated that the predictors collectively had a significant impact on IgG positivity ($\chi^2 = 56.815$, df = 32, p = 0.004). The Hosmer-Lemeshow test ($\chi^2 = 11.507$, df = 8, p = 0.175) indicated a good model fit, as there was no significant difference between observed and predicted outcomes. The model's classification accuracy was 75.4%, with 98.1% of IgG-positive cases correctly predicted. However, 7.7% of IgG-negative cases were misclassified as positive. Significant predictors of IgG positivity included younger age, symptoms such as nausea and lack of appetite, and recent international travel.

Table 2.Omnibus Tests of Model Coefficients Assessing the Model's Ability to Predict the Outcome Variable.

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	56.815	32	.004
	Block	56.815	32	.004
	Model	56.815	32	.004

Table 3.Classification Table Evaluating the Model's Predictive Accuracy for IgG Test Results.

Classification Tablea

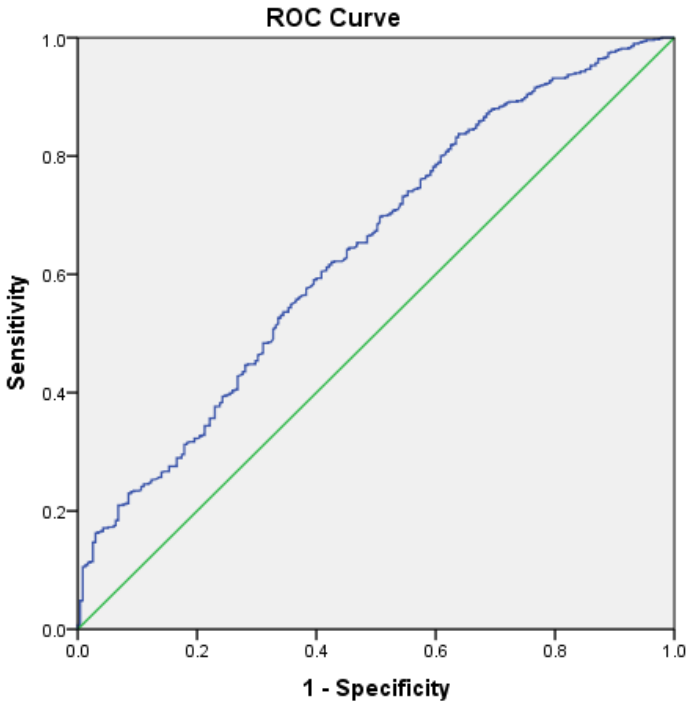
			Predicted		
			IgG		Percentage Correct
			NEGATIVE	POSITIVE	
Step 1	IgG	NEGATIVE	18	217	7.7
		POSITIVE	13	688	98.1
	Overall Percentage				75.4

Table 4. Hosmer and Lemeshow Goodness-of-Fit Test Results

Hosmer and Lemeshow Test

Step	Chi-square	df	Sig.
1	11.507	8	0.175

Area Under the Curve (AUC) analysis was conducted to evaluate the model's discriminative ability. The AUC for the model was 0.640 (SE = 0.021, $p < 0.001$, 95% CI = 0.600 to 0.681), indicating moderate predictive accuracy.



Diagonal segments are produced by ties.

Table 5. Area Under the Curve
Test Result Variable(s): Predicted probability

Area	Std. Errora	Asymptotic Sig.b	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.640	0.021	0.000	0.600	0.681

The test result variable(s): Predicted probability has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

4. Discussion

The results of the study on 944 patients provide a comprehensive overview of demographic characteristics, clinical symptoms, exposure history, and antibody testing related to SARS-CoV-2. The mean age of participants was 37.56 years, with a significant majority being female (66.2%). This gender distribution aligns with previous studies indicating a higher prevalence of COVID-19 among females in certain populations, potentially due to biological and social factors influencing exposure and immune response [3]. The marital status of participants revealed that the majority were single (58.6%), which may reflect the demographic trends in urban settings where the study was conducted, as single individuals often have different social behaviors and exposure risks compared to married individuals [4].

The symptomatology reported by participants is particularly noteworthy. Fatigue was the most common symptom, affecting 31.5% of the cohort, followed by fever (23.6%) and respiratory symptoms such as sore throat and cough (12.7% and 11.9%), respectively. These findings are consistent with the clinical presentations documented in other studies, where fatigue and fever were frequently reported among COVID-19 patients [5]. The presence of gastrointestinal symptoms, such as nausea and vomiting, in 13.0% and 13.8% of participants, respectively, underscores the diverse clinical manifestations of SARS-CoV-2 infection, which have been increasingly recognized in the literature [6].

Exposure history is a critical aspect of understanding the transmission dynamics of SARS-CoV-2. The study found that 28.6% of participants had been in contact with a confirmed SARS-CoV-2-positive individual within the preceding four days, while 26.6% had been exposed to someone with similar symptoms. This level of exposure is reflective of the high transmissibility of the virus, particularly in healthcare settings, where 55.0% of participants reported exposure [7]. The association between exposure in hospital settings and increased risk of infection has been documented in various studies, emphasizing the need for stringent infection control measures in these environments [8].

The serological analysis revealed that 75.0% of participants tested positive for IgG antibodies, indicating a significant level of prior exposure to SARS-CoV-2 within this population. This finding is corroborated by other research that highlights the prevalence of IgG antibodies in populations with high exposure risk, such as healthcare workers and individuals in densely populated areas [8]. The presence of IgG antibodies is crucial for understanding the immune response to SARS-CoV-2 and can inform public health strategies aimed at managing the pandemic.

Logistic regression analysis was employed to identify factors associated with IgG positivity. The results indicated a statistically significant negative relationship between age and IgG positivity,

suggesting that younger individuals are more likely to test positive for antibodies. This finding is consistent with existing literature that posits age as a critical factor influencing immune response, where younger individuals often exhibit a more robust antibody response compared to older adults [9]. The lack of significant association between sex and IgG positivity suggests that both genders have similar immune responses to SARS-CoV-2, which aligns with findings from other studies [3].

Marital status also emerged as a significant predictor, with divorced individuals being more likely to test positive for IgG antibodies compared to their single counterparts. This could reflect differences in social interactions and exposure patterns, as divorced individuals may have different lifestyle choices that affect their risk of exposure [4].

Interestingly, specific clinical symptoms were also associated with IgG positivity. Runny nose, nausea, and lack of appetite were positively correlated with IgG positivity, indicating that respiratory and gastrointestinal symptoms may serve as important indicators of SARS-CoV-2 infection [6]. The analysis of exposure history revealed that recent international travel was significantly associated with a higher likelihood of IgG positivity. This finding underscores the importance of travel history in assessing exposure risk, particularly in the context of global pandemics where international travel can facilitate the spread of infectious diseases [9].

The model's overall fit and accuracy were assessed, demonstrating a classification accuracy of 75.4%, which is indicative of a robust model capable of identifying IgG-positive individuals effectively [10]. The Area under the Curve (AUC) analysis further evaluated the model's discriminative ability, yielding an AUC of 0.640, which indicates moderate predictive accuracy. While this suggests that the model performs better than random chance, it also highlights the need for further refinement to enhance sensitivity and specificity [10].

In the present study, we observed a notable phenomenon: individuals who had COVID-19 symptoms tested positive for IgG antibodies, despite the established understanding that IgG typically indicates past infection. This finding suggests a more complex interplay between seropositivity and symptomatology than previously recognized.

One potential explanation for this discrepancy is the possibility of viral persistence or reactivation in IgG-positive individuals. Research indicates that while IgG antibodies are markers of past infection, they do not guarantee complete viral clearance [11] (Butterfield et al., 2020). For instance, some studies have reported that patients who are IgG positive can still harbor viral particles, which may lead to ongoing symptoms [12]. This aligns with findings that demonstrate a correlation between high IgG levels and the presence of viral RNA, suggesting that these individuals may still be experiencing active infection or a reactivation of the virus [13].

Moreover, the timing of antibody response can vary significantly among individuals. It has been documented that IgG levels can peak at different times based on the severity of the initial infection and the individual's immune response [14]. In some cases, IgG may be present while IgM levels are still low, indicating that the immune response is still developing [15]. This variability can result in symptomatic individuals who are IgG positive, as their immune systems may not have mounted a sufficiently robust response to eliminate the virus entirely [16].

Additionally, the emergence of SARS-CoV-2 variants may complicate the relationship between IgG positivity and symptomatology. Variants may exhibit mutations that allow them to partially evade the immune response generated by previous infections, leading to reinfection even in those with detectable IgG levels [17]. This highlights the importance of ongoing surveillance and research to understand the implications of seropositivity in the context of evolving viral strains.

5. Conclusion

This study provides valuable insights into the factors associated with IgG antibody positivity against SARS-CoV-2. Younger age, gastrointestinal symptoms such as nausea and loss of appetite, along with recent international travel, were identified as significant factors associated with IgG antibody positivity against SARS-CoV-2. These findings emphasize the importance of considering both demographic characteristics and clinical presentations when assessing exposure risks and immune responses. The logistic regression model used in this study showed promise as a screening tool for SARS-CoV-2 IgG antibody positivity; though it's moderate accuracy highlights the need for further refinement to improve its sensitivity and specificity. Future research should aim to enhance this model and explore additional factors, such as genetic predispositions and population-level variations in immune responses. By advancing our understanding of SARS-CoV-2 seropositivity, this study supports more targeted public health strategies. Further longitudinal studies tracking

antibody levels, clinical symptoms, and viral RNA in symptomatic individuals will provide deeper insights into the dynamics of immune responses and guide better clinical management for affected populations.

Ethical Considerations

Compliance with ethical guidelines

This study was conducted in accordance with the Declaration of Helsinki, and all participants provided informed consent. Ethical approval for the study was granted by the ethical committee board of Federal University Teaching Hospital, Owerri, Imo State. Informed consent was obtained from all participants prior to their inclusion in the study.

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Author's contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors have no conflicts of interest to declare.

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