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Research Article

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Characterising Humoral Immune Signatures: IgG and IgM Reactivity Patterns in Post-COVID-19 Pandemic Cohort in the UK

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Abstract

The persistence of SARS-CoV-2-specific antibodies, particularly Immunoglobulin G (IgG) and Immunoglobulin M (IgM), is fundamental for understanding long-term immunity, informing public health policy, and optimizing vaccination strategies. IgM generally appears early during infection and declines within weeks, whereas IgG is linked to sustained immune memory and protection. This study characterizes post-COVID-19 serological profiles in a volunteer cohort, revealing several notable immunological phenomena. First, despite documented prior exposure to SARS-CoV-2, 2% of individuals lacked detectable IgG antibodies, indicating seronegative immune responses. These profiles may reflect impaired humoral immunity, rapid antibody decline, or a predominance of cellular immune responses, as previously described in cohorts where T-cell immunity compensates for absent humoral markers. Elevated IgM in IgG-negative individuals suggests recent antigenic stimulation or delayed class switching, consistent with reports of non-standard immune trajectories. Second, the cohort demonstrated near-universal IgG positivity (98%) and persistent IgM reactivity in 47% of participants. While IgG seropositivity aligns with durable immune memory, sustained IgM presence months after infection suggests ongoing immune activation, incomplete viral clearance, or dysregulated B-cell maturation, as increasingly recognized in the literature. Third, females exhibited higher overall IgM levels, whereas males showed lower baseline IgM with occasional high outliers. Both groups had broadly similar IgG averages, reflecting established sex-based differences in immune responses. These findings challenge traditional models of humoral resolution and emphasize the complexity of SARS-CoV-2 immunodynamics. Collectively, these observations highlight the necessity for integrated serological and cellular profiling in post-infection surveillance. Such approaches have implications for vaccine responsiveness, diagnostic interpretation, and identification of individuals at risk for prolonged immune perturbation or autoimmune sequelae.

Keywords: SARS-CoV-2, IgG, IgM, Seronegative Response, Immune Memory, Post-COVID Immunity, Humoral Kinetics, Autoimmune Risk, Antibody Persistence, Immunological Profiling.

Introduction

The persistence of SARS-CoV-2–specific antibodies, particularly Immunoglobulin G (IgG) and Immunoglobulin M (IgM), is central to understanding long-term immunity, informing public health policy, and refining vaccination strategies. IgM typically emerges early in infection and wanes within weeks, whereas IgG is associated with longer-term immune memory and protection.

IgM seroconversion generally begins around 7–10 days after symptom onset, with titres continuing to rise by day 20. Between 23- and 28-days post-infection, elevated IgM levels have been reported in 51% of individuals, and IgM remained detectable in 68.8% of patients at 40 days. In a cohort assessed 40–93 days after infection, 28% continued to exhibit elevated IgM levels, while by nine months post-infection, IgM antibodies persisted in only 0.5% of individuals. IgM antibodies are generally expected to increase only upon re-infection and have not been extensively characterised years after the epidemic. In contrast, IgG seroconversion typically begins around 11 days after symptom onset and continues to rise by day 20. In the same cohort as-

sessed 40–93 days post-infection, 100% of individuals exhibited elevated IgG levels, with IgG responses sustained for up to 100 days. Longer-term follow-up has demonstrated that 92% of cases retain IgG-S antibodies at six months, while IgG-N antibodies remain detectable for up to 18 months, declining from 90% at three months to 79% at 12 months and 72% at 18 months [1-9]. Large-scale serological surveillance from the UK Office for National Statistics (ONS) further supports widespread antibody persistence, with 97–98% of adults across all four nations testing antibody-positive by January 2022 [10]. This study aims to investigate the long-term persistence of IgG and IgM antibodies in individuals years after SARS-CoV-2 infection and vaccination.

Materials & Methods

In a recent study, IgM and IgG antibody levels were measured using the Boditech iCHROMA™ COVID-19 IgG/IgM immunoassay [11, 12] on a fluorescence-based point-of-care system designed for rapid, semi-quantitative detection of SARS-CoV-2-specific antibodies in a cohort of healthy volunteers (19 females and 30 males) attending a health screening day. Results were classified as positive, indeterminate, or negative based on manufacturer-defined cut-off (CO) values and IgG and IgM positivity thresholds were determined by signal-to-cutoff ratios (CO) ≥1.0. Indeterminate results were defined as CO values between 0.9 and 1.0, and negative results corresponded to S/CO <0.9. Statistics were performed using GraphPad Prism.

Results

IgG positivity was observed in 98% of the cohort, with no indeterminate results and only 2% testing negative, indicating widespread seroconversion. In contrast, IgM reactivity was more heterogeneous: 47% tested positive, 8% indeterminate, and 45% negative.

The distribution of serological reactivity is summarized in Figure 1. IgG positivity was observed in 48 of 49 individuals (98%), while one individual (2%) did not exhibit strong IgG reactivity. Notably, the two individuals (numbers 16 and 45) with the lowest IgG reactivity (0 and 2.5) had the highest IgM values (17.3 and 28.2, respectively). IgM reactivity remained variable, with 47% testing positive, 8% indeterminate, and 45% negative.

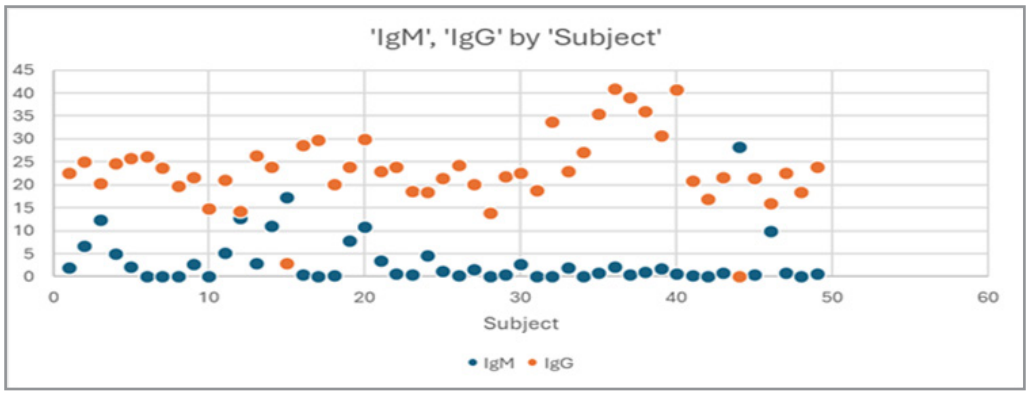

Figure 1: Distribution of IgG and IgM Antibody Test Results in a Post-COVID Cohort (n = 49)

IgM (early antibody response): Females exhibited higher overall IgM levels compared to males, with a mean value of 4.47 in females versus 2.68 in males. The range was broader in females (0–28.2) than in males (0–17.3), and variation was also greater in females (standard deviation 6.75) compared to males (4.47). The increased variability and higher average IgM responses in females were statistically significant (p = 0.0456) (Figure 2).

IgG (longer-term antibody response): Both sexes demonstrated relatively high IgG levels with similar averages; the mean was 23.8 in females and 22.99 in males. The ranges were broad for both groups: females (0–41.0) and males (2.9–40.8). Variation was slightly higher in females (standard deviation 9.0) than in males (7.17). Overall, IgG responses were robust and comparable between sexes, with no significant difference, although females again exhibited slightly greater variability (Figure 2).

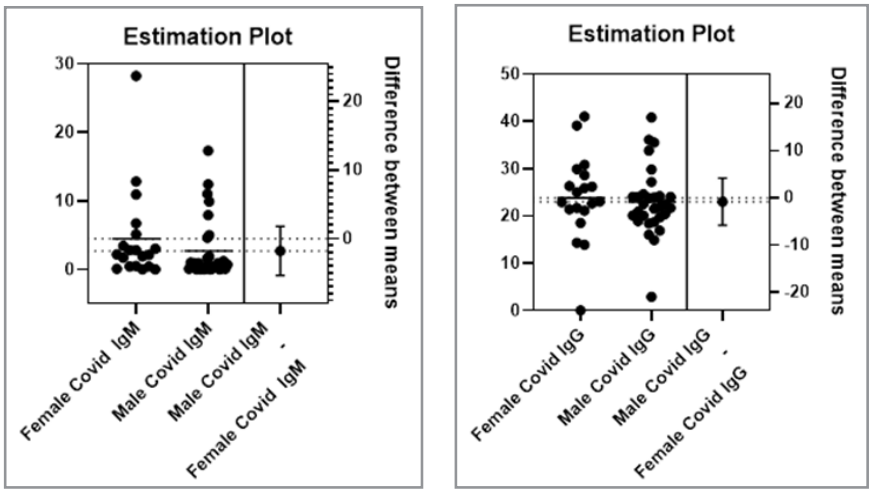

Figure 2: Estimation Plots of IgG and IgM Antibody Test Results in a Post-COVID Cohort (n = 49) Male and Females

Discussion

The serological patterns observed in this post-COVID cohort reveal two notable immunological phenomena. Firstly, the absence of IgG antibodies in a small minority of individuals despite documented prior exposure to SARS CoV 2 raises important questions about seronegative immune responses. Several studies have demonstrated that exposure does not invariably lead to detectable IgG seroconversion, with a subset of individuals mounting robust cellular immunity in the absence of measurable humoral responses [13]. This phenomenon challenges the assumption that IgG detection is a universal marker of prior infection and highlights the role of T cell–mediated immunity in seronegative individuals. Evidence from healthcare worker cohorts further confirms that some previously infected individuals remain IgG negative despite confirmed exposure or PCR positive illness [14]. In addition, rapid waning of IgG below assay detection thresholds has been documented, particularly following mild or asymptomatic infection. Together, these findings support the interpretation that seronegativity does not exclude prior infection and may reflect either a failure to mount a measurable humoral response or non standard immune trajectories dominated by cellular rather than antibody mediated immunity. These findings underscore the need for integrated serological and cellular profiling in post-infection surveillance and raise considerations for vaccine responsiveness, diagnostic interpretation, and risk stratification in immunologically diverse populations.

Secondly, the serological profile of this post COVID cohort characterised by near universal IgG positivity (98%) and persistent IgM reactivity in nearly half of participants (47%) raises important questions about the long term immunological consequences of SARS CoV 2 infection. While IgG seropositivity is expected and typically interpreted as evidence of immune memory and resolution of acute infection, the sustained presence of IgM antibodies months after exposure suggests ongoing immune activation or delayed humoral resolution in a substantial subset of individuals. Classical immunological models describe IgM as a transient early phase antibody that declines within weeks as class switching to IgG occurs; however, Persistent IgM responses have been documented well beyond the acute phase of SARS-CoV-2 infection, with one study reporting detectable IgM in 28% of individuals up to 93 days and in 0.5% at nine months post-infection, while a recent meta-analysis found IgM seropositivity in 17% of recovered patients at 12 months [15, 16]. The persistence of IgM observed here may therefore reflect prolonged antigenic stimulation, incomplete viral clearance, or dysregulated B cell maturation. Alternative explanations include residual viral antigens in tissue reservoirs, episodes of subclinical reinfection, or immune system reprogramming following severe or repeated exposures mechanisms increasingly recognised in post acute COVID 19 immunology.

Females exhibited higher overall IgM concentrations, accompanied by substantial inter-individual variability. In contrast, males generally demonstrated lower baseline IgM levels, with occasional high outliers. IgG levels were broadly comparable between sexes, with similar mean values and overlapping distribution ranges. These patterns align with established sex-based differences in immune regulation, wherein females typically mount stronger humoral responses and display greater variability due to hormonal, genetic, and immunoregulatory factors [17-21]. The slightly higher mean IgM values in females, along with wide variability in both sexes, likely reflect a complex interplay of immune activation thresholds, infection history, and differential susceptibility to autoimmune or inflammatory processes.

Conclusion

This post-COVID-19 serological study identified two principal immunological patterns. First, a small subset of individuals (2%) lacked detectable IgG antibodies despite confirmed prior exposure to SARS-CoV-2, indicating seronegative immune responses potentially resulting from impaired humoral function, rapid antibody waning, or predominant cellular immunity. Second, while IgG positivity was nearly universal (98%), persistent IgM reactivity was observed in 47% of participants, suggesting prolonged immune activation or delayed resolution of the humoral response. These atypical patterns challenge conventional models of post-infection immunity and highlight the necessity for integrated serological and cellular profiling to inform vaccine strategies, diagnostic interpretation, and risk assessment in immunologically diverse populations.

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