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Antibodies against SARS-CoV-2 after natural infection in healthcare workers and clinical characteristics as putative antibody production prediction

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ABSTRACT

Introduction: There is a need for detailed data on early antibody responses against SARS-CoV-2 as this may contribute to the prediction of the clinical course of COVID-19 and the optimization of convalescent plasma treatment. This study aims to gain insight into developing antibodies to SARS-CoV-2 in health care workers (HCWs) infected in the first wave of the SARS-CoV-2 pandemic in the Netherlands.

Materials and methods: In this retrospective analysis, sera from PCR-confirmed COVID-19 positive HCWs are included at the time of the initial PCR ($T = 0$, $n = 95$) and at least 21 days after the initial serum ($T \geq 21$, $n = 133$). This study assesses correlations between qualitative total Ig, IgM, IgA, IgG, and quantitative anti-S-RBD antibody responses and participant characteristics.

Results: Higher Ct values were associated with higher antibody positivity rates for total Ig (OR 1.261 (95% CI 1.095–1.452)), IgM (OR 1.373 (95% CI 1.125–1.675)), and IgA (OR 1.222 (95% CI 1.013–1.475)). Gender was predictive of IgM and IgA antibody positivity rates at $T = 0$ (OR 0.018 (95% CI 0.001–0.268)) and (OR 0.070 (95% CI 0.008–0.646)). At $T \geq 21$, a substantial proportion of HCWs developed IgM (103/133; 77.4%) and total Ig (128/133; 96.2%) antibodies. IgA and IgG seroconversions were observed in only 51.1% (67/131) and 55.7% (73/131) of HCWs. Anti-S-RBD responses were higher when the interval between onset of symptoms and sampling was longer.

Conclusion: The findings of this study give insight into early antibody responses and may have implications for the selection of convalescent plasma donors and the further development of monoclonal antibody treatment.

1. Introduction

Humoral immune responses play a critical role in the defense against SARS-CoV-2. Upon infection, naïve or pre-existing memory B-cells produce several subclasses of antibodies with T-cell-dependent and T-cell-independent mechanisms. In the early phase of disease, T-cell-independent production of antibodies by extra-follicular short-lived plasma cells is of utmost importance in containing the infection in the first weeks [1]. These early appearing antibodies are mainly of the IgM and IgA isotype [1–2]. After the initial phase of infection, a T-cell-dependent immune response follows. More differentiated germinal center-derived long-lived plasma cells produce high-affinity antibodies, reflecting all isotypes, including IgM, IgA, and IgG [1,3]. Antibodies against the receptor-binding domain (RBD) are associated with virus neutralization, and research has mainly focused on these neutralizing antibody responses [4–7].

Recent research indicates a benefit of convalescent plasma therapy and the use of synthetic monoclonal antibodies in SARS-CoV-2 patients [8–9]. Neutralizing antibodies are the presumed active component of these treatments. However, there is less data on the contribution of early appearing subtypes of antibodies on the effect of convalescent plasma and monoclonal antibody treatment. To optimize these treatments, it is essential to understand which subtypes of antibodies aid in the early containment of infection [10]. Furthermore, insight into early antibody responses might be of value for predicting the clinical course of COVID-19 disease.

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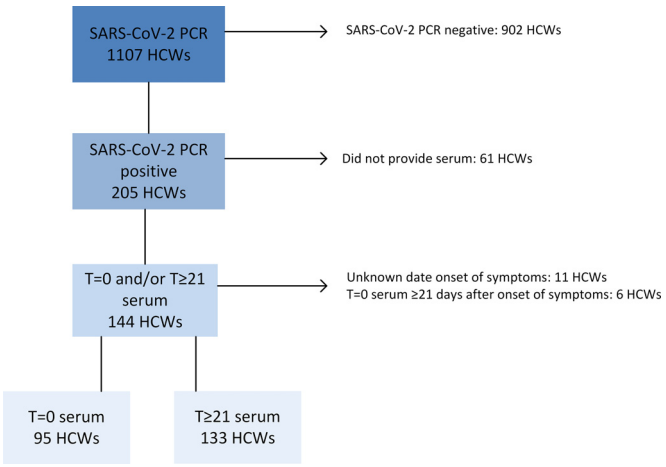

Fig 1. Inclusion of participants.

In the present study, initial and follow-up samples are analysed within the first two months after infection to gain insight into qualitative IgM, IgA, IgG, and total Ig responses and quantitative anti-S-RBD responses to SARS-CoV-2 in infected healthcare workers (HCWs). Clinical characteristics as predictors of antibody responses are explored. This study was executed during the first wave of the SARS-CoV-2 pandemic in the Netherlands, before vaccination and the emergence of variants of concern.

2. Methods

2.1. Study design

Between April 1st and July 1st 2020, all HCWs with suspected COVID-19 disease were tested by SARS-CoV-2 PCR on combined nasopharyngeal throat swabs. Sampled HCWs were invited to participate voluntarily in this study. Blood samples were collected at the moment of the first PCR ($T = 0$) and at least 21 days after the initial serum ($T \geq 21$).

The present study included PCR confirmed SARS-CoV-2 positive HCWs. Of 1107 tested HCWs, 18.5% (205/1107) had a positive PCR result. 144 HCWs provided a serum at $T = 0$ or $T \geq 21$. For 11 HCWs, the date of onset of symptoms was unknown and were excluded from analyses. Six female HCWs had experienced symptoms >21 days before sample collection and were excluded for analyses of the $T = 0$ samples. Sera from 133 participants were available for inclusion in the study. 95 HCWs provided a $T = 0$ serum, and 133 HCWs provided a $T \geq 21$ serum (Fig. 1). Questionnaires including HCWs characteristics and symptoms were collected at the time of initial PCR. The questionnaire included the following symptoms: fever, cough, throat soreness, headache, and rhinorrhea. None of the HCWs were hospitalized for COVID-19 and were thus considered to have mild or moderate disease.

The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local institutional review board, the Medical Ethical Committee, of the MUMC+ (registration number 2020–2280).

2.2. Testing policy of HCWs

HCWs were requested to stay at home until fever had passed and were invited for the initial PCR test and serum sampling. If the SARS-CoV-2 PCR cycle threshold (Ct) value was ≥30, HCWs were allowed to return to work. If the Ct value was <30, HCWs were invited for a second PCR test after two days. PCR testing was repeated until the follow-up PCR was negative.

2.3. Diagnostic tests

2.3.1. SARS-CoV-2 PCR

RT-qPCR was performed amplifying the E gene [11] and mCMV-ie as internal control as described previously [12]. Amplification was performed using TaqPath 1-Step RTqPCR Master Mix (Thermofisher) on Quantstudio 5 systems (Thermofisher). RNA extraction was performed using the MagNA Pure 96 DNA and Viral NA Small Volume Kit (Roche Diagnostics) according to the manufacturer's instructions and was eluted in 100 µl. Any valid amplification signal of SARS-CoV-2 RNA above the validated threshold was considered a positive result.

2.3.2. Antibody tests

The Wantai SARS-CoV-2 Ab (Ig), Wantai SARS-CoV-2 IgM (Beijing Wantai Biological Pharmacy Enterprise Co., Ltd., Beijing, China), Euroimmun IgA, and Euroimmun IgG ELISA (EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany) were used to determine qualitative antibody responses using the Virion/Serion Immunomat (Virion/Serion, Würzburg, Germany) [13–16]. The Wantai total Ig ELISA detects total antibodies binding the SARS-CoV-2 spike RBD. The Euroimmun IgA and IgG ELISAs use the recombinant spike protein (S1 domain) as antigen. Antibody titers tested with the Wantai and Euroimmun tests are expressed as Optical density (OD) ratios. The OD ratios for both tests were calculated according to the manufacturer's instructions. The Elecsys anti-SARS-CoV-2 S (Roche Diagnostics GmbH, Mannheim, Germany) test was performed on the $T \geq 21$ sera using the Cobas 8000 (Roche Diagnostics GmbH, Mannheim, Germany) [17]. This test is an electrochemiluminescence assay (ECLIA) and detects total antibodies quantitatively against the SARS-CoV-2 spike RBD (anti-S-RBD). The test is standardized against an internal anti-RBD monoclonal antibody mixture and is expressed as units/mL (U/mL). Serological tests were performed according to the manufacturer's instructions. The Wantai total Ig and IgM ELISAs are considered positive in case of an OD value ≥1.1. An OD value ≥0.9 to <1.1 is considered borderline. For Euroimmun IgA and IgG, OD values of ≥1.1 are positive. Values of ≥0.8 to <1.1 are considered borderline. Values of ≥0.8 U/mL are considered reactive for the Elecsys anti-SARS-CoV-2 S test. Samples with values ≥250 U/mL were retested in a dilution of 1:4 with diluent buffer (Roche Diagnostics GmbH, Mannheim, Germany).

2.3.3. Statistical analysis

Statistical analysis was performed using SPSS version 25.0. Differences between males and females were analysed with the Mann-Whitney U test. Total Ig, IgM, IgA, and IgG results were dichotomized into positive and negative, and used as outcomes in four different logistic regression models to assess associations between patient characteristics and antibody responses. Borderline results were excluded from the analysis. Patient characteristics with $p<0.2$ in the univariable models were included in multivariable models. Antibody responses for which the positive or negative results contained <10 cases were not analysed, i.e. IgA in females at $T = 0$ and total Ig at $T \geq 21$.

The anti-S-RBD results at $T \geq 21$ were transformed to normally distributed data using Box-Cox transformation with the following formula: $(x^{0.2} - 1)/0.2$. Multivariable linear regression with backward stepwise selection was used to assess the ability of variables to predict antibody levels at $T \geq 21$. A preliminary analysis was conducted to ensure no violation of linearity, multi-collinearity, and homoscedasticity assumptions. A 2-sided $p \leq 0.05$ was considered to be statistically significant.

3. Results

3.1. Characteristics of the study population

Characteristics of HCWs are summarized in Table 1. The median interval between onset of symptoms and sampling was for $T = 0$ 6 days (IQR 3–11) and for $T \geq 21$ 35 days (IQR 31–42). Males provided the first

Table 1
Characteristics of the study population.

	Total	Males (n = 50)	Females (n = 83)	Mann-Whitney U
Age, median years (IQR)	40 (28–53)	46 (29–54)	35 (27–49)	0.079
Ct[a] value T = 0, median (IQR)	27 (22–33)	26 (20–33)	28 (23–34)	0.183
Interval between onset of symptoms and serum/PCR, median days (IQR)	6 (3–11)	7 (4–13)	4 (3–10)	0.032*
Onset of symptoms until early serum	35 (31–42)	34 (31–41)	36 (31–43)	0.266
Onset of symptoms until late serum	12 (9–17)	14 (10–17)	11 (8–16)	0.210
Onset of symptoms until CT≥30	24 (18–30)	24 (18–29)	24 (17–30)	0.954
Onset of symptoms until negative PCR				
Positive/reactive antibody response T = 0, n/total tested (%)	41/95 (43.2)	20/41 (48.8)	21/54 (38.9)	
total Ig	30/95 (31.6)	19/41 (46.3)	11/54 (20.4)	
IgM	19/94 (20.2)	13/40 (32.5)	6/54 (11.1)	
IgA	7/94 (7.4)	6/40 (15.0)	1/54 (1.9)	
IgG	26/92 (28.3)	14/38 (36.8)	12/54 (22.2)	
anti-S-RBD				
Positive/reactive antibody response $T \geq 21$, n/total tested (%)	128/133 (96.2)	49/50 (98.0)	79/83 (95.2)	
total Ig	103/133 (77.4)	43/50 (86.0)	60/83 (72.3)	
IgM	67/131 (51.1)	29/50 (58.0)	38/81 (46.9)	
IgA	73/131 (55.7)	28/50 (56.0)	45/81 (55.6)	
IgG	124/128 (96.9)	47/48 (97.9)	77/80 (96.3)	
anti-S-RBD				

[a] Ct value = Cycle treshold value. * p<0.05.

serum later than females: 7 days (IQR 4–13) compared to 4 days (IQR 3–10), p<0.05.

3.2. Qualitative and quantitative antibody responses

Qualitative and quantitative antibody responses are summarized in Table 1. The percentage of total Ig positive HCWs increased from 43.2% (41/95) at T = 0 to 96.2% (128/133) at $T \geq 21$. 3.8% of HCWs (2/53) with a negative total Ig result at T = 0 had a negative total Ig result in the $T \geq 21$ serum.

At T = 0, 31.6% (30/95) of HCWs had a positive IgM result. This percentage increased to 77.4% at $T \geq 21$. The IgM result at $T \geq 21$ remained negative in 23.4% (15/64) of HCWs with a negative IgM result at T = 0. Of 31 participants with borderline or positive IgM results at T = 0, one seroreversion was observed (3.2%).

For IgA, seropositivity increased from 20.2% (19/94) at T = 0 to 51.1% (67/131) at $T \geq 21$. The IgA result at $T \geq 21$ remained negative in 36.7% (25/68) of HCWs with a negative IgA result at T = 0. Seroreversions for IgA were observed in 8,3% (2/24) of HCWs who had borderline or positive responses at T = 0.

IgG seropositivity increased from 7.4% (7/94) at T = 0 to 55.7% (73/131) at $T\geq$. Of all HCWs 27.7% remained seronegative (23/83).

Seropositivity for anti-S-RBD antibodies increased from 28.3% (26/92) at T = 0 to 96.9% (124/128) at $T \geq 21$. The median values of the reactive samples at T = 0 and $T \geq 21$ were 9,67 U/ml (IQR 2,75–21,42), and 60,71 U/ml (IQR 23,82–139,13). For 4.9% (3/61) HCWs with a negative anti-S-RBD result at T = 0, the test remained negative in the $T \geq 21$ serum.

The kinetics of the responses are displayed in supplementary figures 2 and 3.

3.2.1. Clinical predictors of semi-quantitative total Ig, IgM, IgA, and IgG antibody responses

Results of the analysis of clinical predictors for the total Ig, IgM, and IgA ELISA at T = 0 are presented in Table 2. Less than 10 participants tested positive for IgG at T = 0, and therefore logistic regression analysis was not performed.

At T = 0, the initial Ct value was predictive of total Ig, IgM, and IgA positivity. Higher Ct values were significantly associated with higher antibody positivity rates; OR 1.261 (95% CI 1.095–1.452), OR 1.373 (95% CI 1.125–1.675), and OR 1.222 (95% CI 1.013–1.475), respectively. Second, an increasing interval between the onset of symptoms and the T = 0 serum was predictive of higher IgM positivity rates at T = 0; OR 1.309 (95% CI 1.034–1.658). Third, throat soreness was associated with lower IgM positivity rates at T = 0; OR 1.373 (95% CI 0.009–0.778). Finally, gender was identified as predictor for IgM and IgA positivity rates at T = 0; OR 0.018 (95% CI 0.001–0.268), and OR 0.070 (95% CI 0.008–0.646), respectively. Females had lower IgM and IgA positivity rates at T = 0 than males. The interval between onset of symptoms and the T = 0 serum was significantly different between males and females, 7 days (IQR 4–13) and 4 (IQR 3–10), respectively. However, gender was still identified as independent predictor for IgM and IgA responses in the multivariable model. Furthermore, a sub-analysis focusing on gender could not identify variables predictive for the IgM response (supplementary Table 3).

No participant characteristics were identified as a predictor for antibody positivity rates at $T \geq 21$ (supplementary Table 4).

3.2.2. Clinical predictors of quantitative anti-S-RBD antibody responses

A multivariable linear regression model was performed to predict the anti-S-RBD response at $T \geq 21$. Only the interval between the onset of symptoms and the $T \geq 21$ serum was predictive for the anti-S-RBD response at $T \geq 21$; β 1.234 (95% CI 1.044–1.452), R^2 = 0.046.

4. Discussion

This study analysed developing antibodies of different classes to SARS-CoV-2 in HCWs after natural infection with only mild to moderate disease severity and explored possible clinical predictors of early antibody responses. The main findings of this study are the association between higher Ct values of the initial SARS-CoV-2 PCR and positive total Ig, IgM, and IgA antibody responses and difference in IgM and IgA responses between males and females at T = 0.

The association between the Ct value and IgM and IgA responses may reflect the detection of early T-cell independent produced antibodies, aiming to contain the infection. Verkerke et al. reported significant clinical improvement in an infant with remdesivir refractory COVID-19 disease after convalescent plasma treatment with high IgA antibody levels. They speculated that IgA antibodies could be associated with viral clearance and infection resolution [10]. Although we found an association between the initial Ct value and total Ig, IgM, and IgA antibody responses, we did not observe an association between these early isotype

Table 2
Univariable and multivariable logistic regression analyses, $T = 0$.

	total Ig		IgM			IgA	
	Univariable OR (95% CI)	Multivariable OR (95%CI)	Univariable OR (95% CI)	Multivariable OR (95% CI)		Univariable OR (95% CI)	Multivariable OR (95% CI)
Gender (female) Female: $n = 54$ Male: $n = 40$	0.636 (0.278–1.455)		0.283 (0.114–0.701)*	**0.018 (0.001–0.268)***	**Gender (female)** Female: $n = 52$ Male: $n = 37$	0.241 (0.081–0.713)*	**0.070 (0.008–0.646)***
Age $n = 94$	1.027 (0.994–1.061)	1.008 (0.955–1.064)	1.032 (0.997–1.069)	0.970 (0.902–1.004)	**Age** $n = 89$	1.030 (0.989–1.073)	1.003 (0.911–1.104)
Fever Yes: $n = 28$ No: $n = 58$	2.303 (0.897–5.909)	1.980 (0.460–8.517)	4.210 (1.542–11.492)*	5.031 (0.775–32.640)	**Fever** Yes: $n = 26$ No: $n = 56$	4.312 (1.326–14.024)*	2.131 (0.211–21.563)
Throat soreness Yes: $n = 47$ No: $n = 52$	0.442 (0.192–1.020)	0.399 (0.100–1.581)	0.511 (0.210–1.244)	**0.082 (0.009–0.778)***	**Throat soreness** Yes: $n = 44$ No: $n = 45$	0.900 (0.326–2.484)	
Headache Yes: $n = 63$ No: $n = 31$	0.507 (0.212–1.211)	0.611 (0.128–2.915)	0.977 (0.389–2.454)		**Headache** Yes: $n = 60$ No: $n = 29$	0.786 (0.272–2.268)	
Ct[a] value initial PCR $n = 94$	1.259 (1.150–1.379)#	**1.261 (1.095–1.452)***	1.300 (1.168–1.446)#	**1.373 (1.125–1.675)***	**Ct[a] value initial PCR** $n = 89$	1.217 (1.098–1.348)#	**1.222 (1.013–1.475)***
Days onset of symptoms until negative PCR $n = 97$	1.014 (0.973–1.055)		1.014 (0.972–1.057)		**Days onset of symptoms until negative PCR** $n = 87$	1.096 (1.025–1.172)*	1.034 (0.884–1.210)
Days onset of symptoms until $T = 0$ serum $n = 92$	1.335 (1.178–1.513)#	1.155 (0.974–1.371)	1.386 (1.215–1.580)#	**1.309 (1.034–1.658)***	**Days onset of symptoms until $T = 0$ serum** $n = 87$	1.309 (1.153–1.486)#	1.197 (0.954–1.503)
Multi-variable model		Cox R^2 0.451 $n = 92$		Cox R^2 0.538 $n = 80$			Cox R^2 0.395 $n = 74$

Multivariable significant results are shown in bold. aCt = Cycle threshold value. * $p<0.05$. # $p<0.001$. Cough, rhinorrhea and the number of days between onset of symptoms and Ct≥30 were not predictive for total Ig, IgM or IgA antibody responses in univariable analysis and where thus not presented in this table. For total Ig and IgM, participant numbers were equal.

responses and clearance of infection. Future proof-of-principle studies are needed to analyze the effect of early appearing antibodies on viral clearance.

Gender was identified as a predictor for IgM and IgA positivity rates at $T = 0$. This difference between males and females might be explained by the number of days between the onset of symptoms and the moment of first sampling ($T = 0$). In the multivariable model, gender was still a predictor for early IgM and IgA responses. A possible hypothesis of higher IgM and IgA positivity rates in males early in the infection may be the difference in mounted immune responses between males and females in the acute phase of infections [18]. Females show a more pronounced T-cell response than males during the early phase of SARS-CoV-2 disease, particularly a more robust CD8 T-cell response [19]. We hypothesize that more robust first-line cellular immune responses to SARS-CoV-2 infection in women in the early phase might contribute to faster successful control of infection, resulting in less pronounced antibody responses generated by short-lived, low-affinity antibody-secreting plasmablasts [20–21]. However, in the $T \geq 21$ sera, no association between gender and IgM or IgA positivity was found, which might be explained by the detection of high-affinity antibodies in the later stages of infection.

Antibodies directed against SARS-CoV-2 appear around 12–14 days PSO, which may explain the observed low IgG response at $T = 0$ in the present study [4, 22-23]. Interestingly, IgA and IgG seroconversions were detected in only 51.1% (67/131) and 55.7% (73/131) of the HCWs, at $T \geq 21$. This may be explained by the study population, including HCWs with mild or moderate disease, none of which were hospitalized for COVID-19. A recent study found seroconversions of IgG and IgA of 86% and 94% in patients with severe disease within 2–4 weeks PSO, and modest responses of 81% and 68% in patients with mild SARS-CoV-2 infections [24]. Likewise, more studies have shown less pronounced antibody responses in patients with mild disease and higher antibody responses in patients with severe disease [7] [20] [22] [24–28]. Respiratory symptoms limited to the upper respiratory tract symptoms may reflect milder disease, which may explain the association between throat soreness and lower IgM positivity rates at $T = 0$.

The observation that higher anti-S-RBD responses were detected when the interval between onset of symptoms and the sampling of the $T \geq 21$ serum was longer, may reflect the detection of high-affinity antibodies as a result of maturation of the antibody response. Future extensive studies are warranted to fully comprehend the role of cellular immune responses and early produced antibody isotypes in the early stage of infection.

Limitations of this study are that donation of serum samples was voluntary, making the study design prone to selection bias. However, 70.2% (144/205) of HCWs with a positive SARS-CoV-2 PCR donated a serum sample. Further, HCWs were asked when symptoms of COVID-19 started, and recall bias might have occurred. And last, the study sample size was limited, and the group of females with a positive IgA antibody response at $T = 0$ was too small to perform logistic regression analysis adequately. This was also the case for the total Ig responses at $T \geq 21$ since most HCWs had positive or borderline total Ig responses.

In conclusion, the present study found an association between higher Ct values and early total Ig, IgM, and IgA antibody responses. Second, gender was associated with early IgM and IgA antibody responses. Finally, higher anti-S-RBD antibodies were detected when the interval between onset of symptoms and sampling was longer. These findings might have implications for the selection of convalescent plasma donors and needs to be confirmed in more extensive proof-of-principle studies.

Authors' contributions

I.H.M. van Loo and P.H.M. Savelkoul conceived the idea to write this manuscript. D.A.T. Hanssen, K. Heijgele, L.E.A. Bank, M. Mulder and M.H.C. Slaats collected the data. D.A.T. Hanssen, K. Heijgele and S. de Leede performed the data analysis in consultation with I.H.M. van Loo and J. Penders. D.A.T. Hanssen, K. Heijgele and S. de Leede wrote the

manuscript in consultation with J. Penders, I.H.M. van Loo and P.H.M. Savelkoul.

Declaration of Competing Interest

None of the manufacturers was involved in any stage of this study.

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Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by our local institutional review board, the Medical Ethical Committee, of the Maastricht UMC+ (registration number 2020–2280).

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Supplementary materials

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