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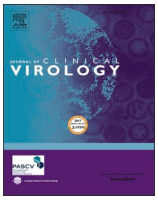

High rate of RNAemia and impaired immunity in patients with immunodeficiency in the vaccination era

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ABSTRACT

Background: Immunocompromised individuals, hemato-oncologic diseases or post-transplantation included, are, due to impaired immune response, at increased risk for severe and prolonged COVID-19. Observational Studies showed that SARS-CoV-2 RNAemia has been associated with poorer prognosis and higher disease severity.
Objective: The aim of this study was to investigate the occurrence of RNAemia and its association with anti-SARS-CoV-2 antibodies in immunocompromised COVID-19 patients. Risk factors for RNAemia were included in the analysis.
Study design: A retrospective study was conducted in 55 immunocompromised patients tested positive for SARS-CoV-2, who received treatment with monoclonal antibodies (mAb) between December 2021 and March 2022. Serological and virological tests were performed before mAb administration and clinical data were collected from electronic health records.
Results: Out of 55 patients, 35 % showed SARS-CoV-2 RNAemia. RNAemia was present in the 2 reported fatal cases. It was associated with negative testing for anti-receptor binding domain (RBD) IgG, anti-S2 domain of spike protein (S2) IgG and a lower leukocyte count. No association was found between previous COVID-19 vaccinations and the risk for RNAemia in immunocompromised patients.
Conclusion: The study underscores the importance of humoral response in controlling SARS-CoV-2 replication. RNAemia can serve as a potential biomarker for disease severity in immunocompromised individuals. Therefore, it should be considered in clinical settings for appropriate therapy decisions. Further research is needed to evaluate the pathophysiology and implications of RNAemia in immunodeficient patients with COVID-19.

1. Background

Immunocompromised patients, including patients with hemato-oncological diseases and solid organ transplant recipients, have been reported to have an increased risk for severe COVID-19, primarily as consequence of their impaired immune responses to natural infection as well as vaccination [1–4]. Although the Omicron variants have been associated with reduced hospitalization rates and mortality in the normal population, vulnerable patients still show a relevant higher incidence of severe course of SARS-CoV-2 infection in comparison to immunocompetent individuals [5,6].

Therefore, tailored immunization strategies and identification of

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parameters for early identification of individuals at higher risk for severe disease still represent an important need for opportune management of SARS-CoV-2 infections in immunocompromised patients [7–10].

In the precedent waves, the detection of SARS-CoV-2 RNAemia was identified as a marker of disease severity and associated to an impaired immune response [11–14].

However, the clinical relevance of SARS-CoV-2 RNAemia in the context of dominating omicron variants and broadly applied active immunization strategies has been poorly investigated [15–17].

2. Objectives

Based on these observations, the present study aimed to investigate the occurrence of RNAemia in association with specific anti-SARS-CoV-2 antibodies in a cohort of immunocompromised patients tested positive for SARS-CoV-2 between December 2021 and March 2022 before treatment with monoclonal antibodies. Risk factors potentially associated with RNAemia were analyzed.

3. Study design

3.1. Patients and data collection

This retrospective study included immunocompromised patients with molecular laboratory-confirmed SARS-CoV-2 infection, who presented at the University Hospital of Cologne for specific antiviral treatment with monoclonal antibodies (mAb) between December 2021 and March 2022 [18]. Patients presented shortly, with a mean of four days after onset of symptoms.

At this time point, Omicron variants BA.1/BA.2 were dominantly circulating in Germany [19]. Patients who had previously received prophylactic mAb (in the context of pre- or post- exposure prophylaxis) were excluded from subsequent analyses as exogenous antibodies might have influenced the serologic assays. Clinical data were collected from electronic health records. Clinical severity of COVID-19 was characterized according to WHO Clinical Progression Scale [20]. The study was conducted according to the declaration of Helsinki. All included participants gave written informed consent for use of their biomaterial and clinical data in scientific research (ethics committee reference no. 20-1157).

Virological testing was performed as part of our clinical routine before mAb administration. Serum samples were tested for IgA targeting the S1 domain of SARS-CoV-2 spike protein, anti-RBD (receptor binding domain) IgG, and anti-trimeric spike IgG by commercial assays, according to manufacturer's recommendations. IgG targeting the S2 domain of spike protein (anti-S2-IgG) were measured by an in-house ELISA according to previous described method [21,22]. Respiratory and serum specimens were tested for the detection of SARS-CoV-2 RNA by real-time PCR and viral loads were expressed as cycle threshold (ct) values. Additional information about serological and molecular assays are reported in supplements.

3.2. Statistical analysis

Continuous variables were expressed as median (interquartile range, IQR) and compared using the Wilcoxon-rank sum test. Categorical variables were compared using either the $\chi 2$ test or the Fisher exact test, as appropriate. Multiple logistic regression models were applied to assess associations between relevant baseline parameters and the occurrence of RNAemia. Two-sided p-values were presented, and a α of <0.05 was determined as significant. All statistical analyses were performed using R (version 4.3.0, R Foundation for Statistical Computing, Vienna, Austria).

4. Results

4.1. Cohort characteristics

Between December 2021 and March 2022, a total of 62 COVID-19 patients with immunodeficiency were treated with monoclonal antibodies in our outpatient's clinic after being tested positive for SARS-CoV-2 RNA in respiratory swab. Out of them, seven patients were excluded from the present analysis due to previous mAB administration.

Of the remaining 55 patients, 47 % ($n = 26$) were female and the mean age was 50 years. Main underlying conditions were hemato-oncological diseases in 40 % ($n = 22$) or history of solid organ transplantation (SOT) in 35 % ($n = 19$) of participants. An active immunization with three or more COVID-19 vaccine doses was documented in 61 % ($n = 33$) of the patients. Anti-RBD and anti-trimeric spike IgG response was missing in 33 % ($n = 18$) of our cohort (Supplement Table 1). During the disease 15 % of patients ($n = 8$) was hospitalized. Of them, four required (non)invasive ventilation/O2-therapy and two patients were known to have had a fatal outcome (Table 1).

Table 1
Demographic and clinical characteristics of patients according to SARS-CoV-2 RNA detection in blood. Bold values express statistical significance at p-value. ct = cycle threshold; CRP = *c*-reactive protein; IQR = interquartile range; ETI = endotracheal intubation; NIV = non-invasive ventilation; O2 = oxygen; RBD = receptor binding domain of spike protein; S1 = S1 domain of spike protein; S2 = S2 domain of spike protein; SOT = solid organ transplant; WHO = World Health Organization.

Patients	Full cohort, $n = 55$	Presence of RNAemia, $n = 19$	No detection of RNAemia, $n = 36$	P value
Age in years, median (IQR)	50 (35–62)	59 (49–71)	47 (34–56)	**0.018**
Female, n (%)	26 (47.3)	7 (36.8)	19 (52.8)	0.400
Medical history				
Hemato-oncological, n (%)	22 (40.0)	8 (42.1)	14 (38.9)	0.482
SOT, n (%)	19 (34.6)	8 (42.1)	11 (30.6)	
Other immunodeficiency disorders, n (%)	14 (25.5)	3 (15.8)	11 (30.6)	
COVID-19 mRNA vaccine with ≥3 doses, n (%)	33 (61.1)	13 (68.4)	20 (55.6)	0.603
Days after onset of symptoms (IQR)	4 (3–6)	3 (2–4)	4 (3–6)	**0.021**
Baseline ct-value nasopharyngeal, median (IQR)	21 (19–23)	20 (18–22)	22 (20–24)	0.085
Baseline ct in serum median (IQR)	37 (35–38)	NA	NA	NA
Anti-S1 IgA negative, n (%)	32 (58.2)	5 (26.3)	18 (50.0)	0.160
Anti-RBD IgG negative, n (%)	18 (33.3)	11 (57.9)	7 (19.4)	**0.010**
Anti-trimeric spike IgG negative, n (%)	18 (33.3)	9 (47.4)	9 (25.0)	0.126
Anti-S2 IgG negative, n (%)	15 (27.3)	8 (42.1)	7 (19.4)	0.140
Leucocytes (x/nl), median (IQR)	5.2 (4.0–8.2)	4.5 (3.0–7.9)	5.5 (4.3–8.2)	0.111
CRP (mg/dl), median (IQR)	7.4 (2.5–27.5)	19.9 (5.1–56.5)	4.7 (2.2–14.4)	**0.022**
Hospitalization, n (%)	8 (14.6)	5 (26.3)	3 (8.3)	0.109
ETI/NIV/O2 required, n (%)	4 (7.3)	4 (21.1)	0 (0.0)	**0.011**
Clinical severity of COVID-19 (WHO clinical progression scale)				
1–3 (mild), n (%)	46 (83.6)	13 (68.4)	33 (91.7)	**0.028**
4,5(moderate), n (%)	6 (10.9)	3 (15.8)	3 (8.3)	
6–9 (severe), n (%)	3 (5.5)	3 (15.8)	0 (0.0)	

SARS-CoV-2 RNAemia was detected in 35 % ($n = 19$) of our patients. Individuals with RNAemia were significantly older than those with non-detected SARS-CoV-2 RNA in plasma ($p = 0.018$). In addition, they showed significant higher c-reactive protein (CRP) values ($p = 0.022$) and a longer time since symptom onset ($p = 0.021$). Before administration of mAb, 57.9 % ($n = 11/19$) of RNAemia positive patients were tested negative for anti-RBD IgG in comparison to 19.4 % ($n = 7/36$) of patients without RNAemia ($p = 0.010$). Other antibodies as well as vaccine status, sex, underlying disease were not found to be significantly different between patients with and without RNAemia (Table 1).

Grade of disease severity was differently distributed between patients with and without RNAemia ($p = 0.028$). A larger portion (31.6 %; $n = 6/19$) of RNAemia positive patients were assigned to a worse clinical classification (moderate or severe) at the time of diagnosis in comparison to patients without RNAemia. All documented cases requiring (non) invasive ventilation/O2-therapy ($n = 4$) as well as known fatal outcomes ($n = 2$) belonged to the SARS-CoV-2 RNA positive group. The two reported fatal cases, in addition to being viremic, were not reactive for anti-RBD and anti-trimeric spike IgG. Both patients were male and had a history of solid organ transplantation (SOT).

4.2. Factors associated with detectable RNAemia in serum samples

In the multiple logistic regression model adjusting for covariates, absent anti-RBD IgG (OR 5.93 (1.15–38.22 95 %CI)) was significantly associated with the presence of RNAemia (Fig. 1a). A similar association was found in case of negative anti-S2 IgG (OR 6.81 (1.11, 52.87)) (Fig. 1b). In both models, the leukocyte count was identified as a risk factor for SARS-CoV-2 RNAemia. No significant associations were found between the other analyzed antibodies and detectable RNAemia (Supplement Fig. 1a and 1b). A trend observable in all tested models identified a condition of SOT as a potential risk factor for SARS-CoV-2 RNAemia in comparison to hemato-oncological diseases.

5. Discussion

Aim of the present study was to provide more insights into SARS-CoV-2 RNAemia occurring due to infections with omicron variant in immunocompromised patients.

More than one-third-of patients included in the present cohort were tested positive for SARS-CoV-2 RNAemia at a median of four days after onset of symptoms. A similar detection rate was reported in the pre-vaccine period in a cohort of immunocompetent patients seven days after symptoms began [12].A higher proportion of detectable RNAemia up to 44 % was observed at the beginning of the pandemic in a cohort of hospitalized patients in the early stage of infection [15]. According to previous data, the detection of SARS-CoV-2 RNAemia was associated with an impaired immune response, including missing anti-RBD-IgG, anti-S2-IgG and lower leukocyte count [13,23,24,25]. So far, the detection of SARS-CoV-2 RNAemia in vaccinated cohorts, including immunosuppressed individuals, has been poorly investigated. The high detection rate observed in the present cohort suggests that immunocompromised patients remain susceptible to a more severe course of infection, despite an apparently less pathogenic variant and vaccine

a

Variable		N	Odds ratio	p-value
Age in years		52	1.03 (0.97, 1.09)	0.327
Sex	Male	27	Reference	NA
	Female	25	0.81 (0.17, 3.89)	0.789
Vaccine status	<3 doses mRNA vaccine	20	Reference	NA
	≥3 doses mRNA vaccine	32	1.29 (0.18, 9.69)	0.794
Medical history	Hemato-oncological	21	Reference	NA
	SOT	18	3.48 (0.43, 43.38)	0.273
	Other immunodeficiency disorders	13	0.80 (0.08, 8.09)	0.848
Days after onset of symptoms		52	0.75 (0.54, 1.01)	0.060
Leukocytes (x/nl)		52	0.77 (0.57, 0.97)	0.048
CRP (mg/dl)		52	1.03 (1.00, 1.07)	0.054
Anti-RBD IgG	Positive	34	Reference	NA
	Negative	18	5.93 (1.15, 38.22)	0.041

b

Variable		N	Odds ratio	p-value
Age in years		52	1.02 (0.97, 1.08)	0.447
Sex	Male	27	Reference	NA
	Female	25	0.62 (0.12, 2.98)	0.553
Vaccine status	<3 doses mRNA vaccine	20	Reference	NA
	≥3 doses mRNA vaccine	32	1.51 (0.25, 10.08)	0.656
Medical history	Hemato-oncological	21	Reference	NA
	SOT	18	2.07 (0.24, 21.81)	0.516
	Other immunodeficiency disorders	13	0.79 (0.09, 6.97)	0.825
Days after onset of symptoms		52	0.73 (0.52, 0.97)	0.045
Leukocytes (x/nl)		52	0.75 (0.55, 0.95)	0.034
CRP (mg/dl)		52	1.03 (1.01, 1.07)	0.039
Anti-S2 IgG	Positive	37	Reference	NA
	Negative	15	6.81 (1.11, 52.87)	0.046

Fig. 1. Multiple logistic regression model adjusting for covariates, testing for anti-RBD IgG (**a**) und for anti- S2 IgG (**b**). SOT = solid organ transplant; CRP = *c*-reactive protein; RBD = receptor binding domain of spike protein; S2 = S2 domain of spike protein.

availability [1,5,6,17,26].

Despite Important limitations, including the heterogeneity of underlying conditions, the small size of the analyzed cohort as well as missing follow-up information for all patients, the present study reinforces the importance of serological testing to identify patients without an antibody response against the SARS-CoV-2 spike protein [14,27].

To our knowledge, this is one of the first studies investigating SARS-CoV-2 RNAemia since the emergence of the Omicron variant and the beginning of the vaccination campaign.

Differently from immunocompetent individuals, immunocompromised patients might benefit from more intense booster vaccination strategies, as seen for other vaccine preventable infectious diseases [8,10,28–31]. The routine assessment of SARS-COV-2 RNAemia and antibody status among this vulnerable population might improve the management of these patients, including early initiation of appropriate therapies and more intense monitoring of infection.

CRediT authorship contribution statement

Anne Thierbach: Writing – original draft, Methodology, Data curation, Conceptualization. **Veronica Di Cristanziano:** Writing – original draft, Methodology, Data curation, Conceptualization. **Kirsten A. Eberhardt:** Writing – original draft, Visualization, Formal analysis. **Martin Pirkl:** Writing – review & editing, Formal analysis. **Gertrud Steger:** Methodology. **Eva Heger:** Writing – review & editing. **Rolf Kaiser:** Writing – review & editing. **Manuel Koch:** Writing – review & editing. **Florian Klein:** Writing – review & editing. **Dominic Rauschning:** Writing – review & editing, Data curation. **Jakob J. Malin:** Writing – original draft, Supervision, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcv.2025.105774.

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