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Deficient Immune Response following SARS-CoV-2 Vaccination in Patients with Hepatobiliary Carcinoma: A Forgotten, Vulnerable Group of Patients

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Keywords
COVID-19 · Vaccination · SARS-CoV-2 neutralization · Hepatobiliary carcinoma · Chronic liver disease · Liver cirrhosis · Waning immunity

Abstract

Introduction: Data on immune response rates following vaccination for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in patients with hepatobiliary carcinoma (HBC) are rare. However, impaired immunogenicity must be expected due to the combination of chronic liver diseases (CLDs) with malignancy and anticancer treatment. ***Methods:*** In this prospective, longitudinal study, 101 patients were included, of whom 59 were patients with HBC under anticancer treatment. A cohort of patients with a past medical history of gastrointestinal cancer, of whom 28.6% had HBC without detectable active tumor disease having been off therapy for at least 12 months, served as control. Levels of SARS-CoV-2 anti-spike IgG, surrogate neutralization antibodies (sNABs), and cellular immune responses were compared. In uni- and multivariable subgroup analyses, risk factors for impaired immunogenicity were regarded. Data on rates and clinical courses of SARS-CoV-2 infections were documented. ***Results:*** In patients with HBC under active treatment, levels of SARS-CoV-2 anti-spike IgG were significantly lower (2.55 $\log_{10}$ BAU/mL; 95% CI: 2.33–2.76; $p < 0.01$) than in patients in follow-up care (3.02 $\log_{10}$ BAU/mL; 95% CI: 2.80–3.25) 4 weeks after two vaccinations. Antibody levels decreased over time, and differences between the groups diminished. However, titers of SARS-CoV-2 sNAB were for a longer time significantly lower in patients with HBC under treatment (64.19%; 95% CI: 55.90–72.48; $p < 0.01$) than in patients in follow-up care (84.13%; 95% CI:

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76.95–91.31). Underlying CLD and/or liver cirrhosis Child-Pugh A or B (less than 8 points) did not seem to further impair immunogenicity. Conversely, chemotherapy and additional immunosuppression were found to significantly reduce antibody levels. After a third booster vaccination for SARS-CoV-2, levels of total and neutralization antibodies were equalized between the groups. Moreover, cellular response rates were balanced. Clinically, infection rates with SARS-CoV-2 were low, and no severe courses were observed. ***Conclusion:*** Patients with active HBC showed significantly impaired immune response rates to basic vaccinations for SARS-CoV-2, especially under chemotherapy, independent of underlying cirrhotic or non-cirrhotic CLD. Although booster vaccinations balanced differences, waning immunity was observed over time and should be monitored for further recommendations. Our data help clinicians decide on individual additional booster vaccinations and/or passive immunization or antiviral treatment in patients with HBC getting infected with SARS-CoV-2.
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Introduction

In October 2022, over 600 million cases of coronavirus disease-2019 (COVID-19) caused by the newly identified severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were confirmed. By that time, more than 12.5 billion SARS-CoV-2 vaccine doses had been administered [1]. While for all persons – regardless of any comorbidities – three vaccinations were recommended [2], immunocompromised patients were encouraged to receive at least four vaccine doses. Most recently, immunization with vaccines adapted to the SARS-CoV-2 variant of concern (VOC), Omicron, has additionally been recommended for people aged 12 years or older [3].

Patients with chronic liver disease (CLD) are facing higher rates of SARS-CoV-2-associated morbidity and mortality [4, 5]. However, studies on response rates to well-known vaccines in patients with CLD have revealed impaired immune responses and faster antibody decline over time [6–9]. These effects were especially pronounced in cases of decompensated liver cirrhosis or in patients undergoing immunosuppressive therapy due to autoimmune hepatitis [10]. As expected, poor response rates to vaccinations for SARS-CoV-2 have also been found in almost a quarter of patients with CLD in published studies to date [11, 12]. Unfortunately, the group of patients with hepatobiliary carcinoma (HBC), i.e., hepatocellular carcinoma (HCC), cholangiocarcinoma (CCC), and gallbladder cancer (GBC), is underrepresented in these cohorts, leading to incomplete data concerning these patients [13, 14]. One would assume a pronounced impairment of immune responses. First, these patients are frequently confronted with underlying CLD, which is associated with immunodeficiency, resulting in reduced immune responses to vaccines as detailed above [13, 15]. Second, in patients with hematologic and in patients with different solid cancer types, immunogenicity after vaccination for SARS-CoV-2 was worse than in healthy people [16–18], especially under active anticancer treatment [19]. Taking these facts into consideration, patients with HBC were expected to be at high risk for severe COVID-19 due to impaired immune response rates to vaccination for SARS-CoV-2. The question remains whether malignancy per se, anticancer treatment, underlying liver pathologies, or a combination of these factors mainly contribute to this impairment. Here, we present prospective data on humoral and cellular response rates as well as on clinical efficacy and safety in a large cohort of patients with HBC under active anticancer treatment to further clarify the mentioned dubieties concerning immunogenicity following basic and booster vaccination for SARS-CoV-2.

Patients and Methods

Study Design

This prospective, longitudinal, observational study explores humoral and cellular immune response rates to SARS-CoV-2 vaccinations in a cohort of patients with HBC and gastrointestinal (GI) cancer treated at the Department of Internal Medicine I, Gastroenterology Oncology Section at the University Hospital of Bonn, Germany, between January 2021 and July 2022. Blood samples were drawn 4, 12, and 24 weeks after the second (basic vaccination) and third vaccination (first booster vaccination) for SARS-CoV-2. Seroprevalence of SARS-CoV-2 anti-spike antibodies (IgG) was analyzed at all time points, while SARS-CoV-2 surrogate neutralization antibodies (sNABs) were measured 12 weeks after the basic and 4 and 24 weeks after the first booster vaccination. To determine cellular immune response rates, a SARS-CoV-2 interferon gamma release assay (IGRA) was performed 4 and 24 weeks after the third vaccination. In addition, all patients who reported having received a second booster vaccination had their blood drawn again 4 weeks thereafter to re-measure humoral and cellular response rates.

The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Medical Faculty of the University of Bonn (Nos. 341/17 and 023/22). Written informed consent was obtained from all participating patients.

Patient Characteristics and Eligibility Criteria

Patients with HBC (HCC, CCC, or GBC) under any active anticancer treatment or having finished their anticancer treatment

within the last 12 months without detectable cancer disease for the time being were eligible to be included. Those patients who were under best supportive care continuing their treatment in the department of palliative care were not included. Patients with a past medical history of GI cancer without detectable cancer disease for at least 12 months prior to inclusion were included as control group. Additionally, these patients did not receive oncologic treatment during the study period and in the last 12 months prior to inclusion to avoid any effects of active cancer disease and/or of anticancer therapy. Of note, at least 28.6% of the patients in this follow-up group had a past medical history of HBC. The control group features the following additional advantages and is therefore especially matchable. First, patients shared comparable risk factors, both for cancer pathogenesis and for severe COVID-19 (shown in Table 1). Second, all patients were treated in the same center according to standardized procedures. Basic vaccination with one of the SARS-CoV-2 vaccines authorized by the European Medicines Agency was obligatory for inclusion. Patients who refused to receive booster vaccinations were not excluded.

Relevant clinical data regarding risk factors for severe COVID-19, increased immunosuppression (suspected in patients with long-term immunosuppressive medication and chronic HIV infection with impaired immune status), as well as underlying cirrhotic and non-cirrhotic liver diseases (alcoholic liver disease, non-alcoholic fatty liver disease, chronic viral hepatitis, autoimmune hepatitis, primary sclerosing cholangitis, hemochromatosis, Budd-Chiari syndrome) were acquired from standardized medical records. Of note, only patients with liver cirrhosis Child-Pugh A or B (score <8) were included as patients with decompensated liver cirrhosis are not eligible for anticancer treatment. Finally, clinical data on side effects potentially associated with the vaccinations as well as on the course of infections with SARS-CoV-2 despite vaccinations were collected.

Assessment of Humoral and Cellular Response Rates

To quantify antibodies against SARS-CoV-2 spike receptor-binding domain (SARS-CoV-2 anti-spike IgG), SARS-CoV-2 IgG II Quant chemiluminescent microparticle immunoassay (Abbott) was used. SARS-CoV-2 sNABs in relation to all antibodies [%] were identified using a blocking ELISA detection tool (cPass^{TM} SARS-CoV-2 Neutralization Antibody Detection Kit; GenScript). This test detects functional virus neutralization strongly correlating with live-cell neutralization [20, 21]. Of note, its relevance concerning current SARS-CoV-2 (VOCs) is limited as neutralization of the SARS-CoV-2 wild type is identified by this test.

Cellular immune response rates, i.e., SARS-CoV-2 spike-protein-specific T-cell response, were determined by a standardized IGRA (EUROIMMUN Quan-T-Cell SARS-CoV-2 and EUROIMMUN Quan-T-Cell ELISA). For qualitative detection of SARS-CoV-2 anti-nucleocapsid IgG in patients having been infected with SARS-CoV-2, Elecsys Anti-SARS-CoV-2 electrochemiluminescence immunoassay (Roche) was used. All assays were performed according to the manufacturer's instructions.

Statistical Analysis

Statistical analysis was carried out using R version 4.1.1 (R Core Team 2021: R: a language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria). Descriptive analyses included the calculation of medians and interquartile ranges for continuous variables and frequencies (absolute and relative) for categorical variables. The association between levels of SARS-CoV-2 anti-spike IgG and SARS-CoV-2 surrogate NAB was analyzed using Spearman's rank correlation coefficient.

Univariate linear mixed effects models were used to compare ($\log_{10}$ transformed) levels of SARS-CoV-2 anti-spike IgG (at all points of time) with respect to treatment status, tumor type (HCC or CCC), and type of treatment, with time treated as factor variable. Each model contains main effects, interaction terms between risk factor and time, as well as a patient-specific random intercept. To compare antibody levels between the different points of time in each group and between the two groups at each point of time, we performed an additional post hoc pairwise comparison based on these mixed effects models. Moreover, ($\log_{10}$ transformed) levels of SARS-CoV-2 anti-spike IgG were compared with respect to underlying CLD and a compensated liver cirrhosis in the group of patients with HBC under anticancer treatment using univariate linear mixed effects models. Analogously, SARS-CoV-2 surrogate NAB (measurements at 12 weeks after basic as well as 4 and 24 weeks after the first booster vaccination) was compared with respect to the discussed influencing factors. Also, applying univariate linear mixed effects regression, levels of SARS-CoV-2 IGRA (measurements four and 24 weeks after the third vaccination) were compared with respect to treatment status.

Furthermore, multivariable regression analyses (for SARS-CoV-2 anti-spike IgG and SARS-CoV-2 surrogate NAB) were performed to examine a possible effect of age, sex, history of SARS-CoV-2 infection, additional immunosuppression, and diabetes mellitus (DM), respectively. p values ≤ 0.05 were regarded as statistically significant. Bonferroni-Holm adjustments were applied as appropriate.

Results

Baseline Characteristics

In this study, 101 patients were included: 58.4% (n = 59) suffered from active HBC and were under anticancer treatment, while 41.6% (n = 42) had a past medical history of GI cancer being in follow-up care. There were 64.4% patients with HCC (n = 38) and 35.6% patients with CCC/GBC (n = 21) under anticancer treatment. In the follow-up care group, 16.7% of patients had HCC (n = 7), 11.9% had CCC/GBC (n = 5), and 71.4% had other GI cancer types (n = 30) ($p < 0.01$). The different distribution of tumor types as well as higher rates of immunosuppression and CLD in patients with active HBC was related to the different prognosis and pathogenesis of the tumor types. Overall, the groups were well matchable as summarized in Table 1.

Humoral Response Rates, Clinical Efficacy, and Safety after Second Vaccination

Four weeks after the second vaccination for SARS-CoV-2, titers of SARS-CoV-2 anti-spike IgG were significantly lower in patients with HBC under active

Table 1. Baseline characteristics

	Under treatment (n = 59)	Off treatment >1 year (n = 42)	p value
Age, years			
Median	67 (40–84)	65 (31–85)	0.59
IQR			
Sex			
Female	32.2% (19)	47.6% (20)	0.15
Male	67.8% (40)	52.4% (22)	
Tumor type			
Hepatobiliary cancers	100% (59)	28.6% (12)	<0.01
HCC	64.4% (38)	16.7% (7)	
CCC/GBC	35.6% (21)	11.9% (5)	
GI cancers*	–	71.4% (30)	
Type of treatment			
Local therapy	39% (23)	–	
Targeted therapy and/or immune checkpoint inhibition	28.8% (17)	–	
Chemotherapy	27.1% (16)	–	
Off treatment <1 year**	5.1% (3)	–	<0.01
Underlying liver disease	69.5% (41)	19% (8)	
Cirrhotic (Child-Pugh A or B, score <8)	63.4% (26)	62.5% (5)	
ALD	38.5% (10)	40% (2)	
NAFLD	38.5% (10)	60% (3)	
Hepatitis B/C	15.4% (4)	–	
Hemochromatosis	3.8% (1)	–	
Autoimmune	3.8% (1)	–	
Non-cirrhotic	36.6% (15)	37.5% (3)	
NAFLD	46.7% (7)	33.3% (1)	
Hepatitis B/C	20% (3)	33.3% (1)	
PSC	13.3% (2)	–	
Hemochromatosis	13.3% (2)	–	
Budd-Chiari syndrome	–	33.3% (1)	
ALD	6.7% (1)	–	
Additional immunosuppression	16.9% (10)	2.4% (1)	0.02
Co-medication with corticosteroids	50% (5)	100% (1)	
Calcineurin inhibitors	30% (3)	–	
Co-medication with azathioprine	10% (1)	–	
HIV infection (T helper cells <400/μL)	10% (1)	–	
Risk factors for severe COVID-19			
Age >65 years	67.8% (40)	73.8% (31)	0.65
BMI >30 kg/m^2	23.7% (14)	7.1% (3)	0.03
History of smoking	33.9% (20)	31% (13)	0.53
Hypertension	61% (36)	50% (21)	0.31
Chronic respiratory disease	13.6% (8)	19% (8)	0.58
Cardiovascular disease	20.3% (12)	26.2% (11)	0.63
Chronic kidney disease	13.6% (8)	2.4% (1)	0.07
CLD	69.5% (41)	19% (8)	<0.01
Neurological disorder	5.1% (3)	4.8% (2)	1
Autoimmune disease	11.9% (7)	2.4% (1)	0.13
DM	33.9% (20)	14.3% (6)	0.03
SARS-CoV-2 infection before initial vaccination ***	3.4% (2)	2.4% (1)	1
Clinical outcome after vaccination			
SARS-CoV-2 infection after second vaccination ***	5.1% (3)	2.4% (1)	0.64
SARS-CoV-2 infection after third vaccination ***	6.8% (4)	9.5% (4)	0.71

Table 1 (continued)

	Under treatment (n = 59)	Off treatment >1 year (n = 42)	p value
Vaccine			
Initial vaccine			0.79
BNT162b2 (Pfizer & BioNTech)	86.4% (51)	83.4% (35)	
AZD1222 (AstraZeneca)	11.9% (7)	9.5% (4)	
mRNA-1273 (Moderna)	1.7% (1)	7.1% (2)	
Third vaccine			0.21
BNT162b2 (Pfizer & BioNTech)	87.2% (34)	75% (21)	
mRNA-1273 (Moderna)	12.8% (5)	25% (7)	
Fourth vaccine			1
BNT162b2 (Pfizer & BioNTech)	91.7% (11)	100% (7)	
mRNA-1273 (Moderna)	8.3% (1)	–	
Vaccine side effects****			
Initial vaccination			
Local side effects	13.6% (8)	28.6% (12)	
Systemic side effects	16.9% (10)	33.3% (14)	
Third vaccination			
Local side effects	10.2% (4)	7.1% (2)	
Systemic side effects	17.9% (7)	17.9% (5)	
Fourth vaccination			
Local side effects	16.7% (2)	–	
Systemic side effects	25% (3)	33.3% (2)	

Baseline characteristics were compared between treatment and control group using Student's t test for age and Fisher's exact tests for the categorical variables. CCC, cholangiocellular cancer; GBC, gallbladder cancer; HCC, hepatocellular carcinoma; GI cancers, gastrointestinal cancers; CRC, colorectal carcinoma; CUP, cancer of unknown primary; GIST, gastrointestinal stromal tumor; NET, neuroendocrine tumor; NAFLD, non-alcoholic fatty liver disease; ALD, alcoholic liver disease; PSC, primary sclerosing cholangitis; IQR, interquartile range. * Gastrointestinal% (GI) cancers – pancreatic cancer, duodenal cancer, gastric and esophageal cancer, CRC, CUP, GIST, NET. ** Patients who received oncological treatment within the last 12 months currently under no anticancer treatment and without detectable tumor. *** SARS-CoV-2 anti-nucleocapsid IgG positive. **** Local side effects: erythema or swelling of injection side, local pain, lymph node swelling; systemic side effects: fever, nausea/vomiting, diarrhea, headaches, allergic reactions.

treatment (2.55 $\log_{10}$ BAU/mL; 95% CI: 2.33–2.76; $p < 0.01$) than in patients in follow-up care (3.02 $\log_{10}$ BAU/mL; 95% CI: 2.80–3.25). Over time, a decrease in mean antibody levels was observed, which was pronounced in patients under treatment (shown in Tables 2A, 3A; Fig. 1a). At week 12 after the second vaccination, differences between the groups were minor and not significant ($p = 0.20$, shown in Tables 2A, 3B; Fig. 1a). However, levels of SARS-CoV-2 sNAB determined at week 12 after the second vaccination were still significantly lower in patients with active HBC under treatment (64.19%; 95% CI: 55.90–72.48; $p < 0.01$) compared to patients in follow-up care (84.13%; 95% CI: 76.95–91.31) (shown in Tables 2C and 3B; Fig. 1b). Of note, 10.6% ($n = 6$) of patients with active HBC and 4.8% ($n = 2$) of patients in follow-up care failed to develop any SARS-CoV-2 antibody titer after the basic vaccination. Levels of total and neutralization antibodies were associated with a correlation coefficient of 0.93 at week 12 after the second vaccination (shown in Fig. 1c).

From a clinical point of view, infections with SARS-CoV-2 after the second vaccination (either self-reported or validated by PCR test) were found in 5.1% ($n = 3$) of patients with active HBC under treatment and 2.4% ($n = 1$) of patients in follow-up care, all with a mild course and most of them with SARS-CoV-2 VOC B1.617.2 (Delta). No severe adverse side effects related to the vaccinations were reported (shown in Table 1).

Humoral Response Rates, Clinical Efficacy, and Safety after Booster Vaccinations

A total of 66.1% ($n = 39$) of patients with active HBC under treatment and 66.7% ($n = 28$) of patients in follow-up care received a third vaccination 6 months after the second vaccination (shown in Table 1). Prior to that, mean levels of SARS-CoV-2 anti-spike IgG were re-measured (24 weeks after the second immunization), revealing a further decline of antibody levels in patients with active HBC (1.95 $\log_{10}$ BAU/mL; 95% CI: 1.71–2.19;

Table 2. Titers of SARS-CoV-2 antibodies

A SARS-CoV-2 anti-spike IgG following second vaccination

Time after vaccination	4 weeks			12 weeks			24 weeks		
	estimate [log_{10} BAU/mL]	95% CI	*p* value	estimate [log_{10} BAU/mL]	95% CI	*p* value	estimate [log_{10} BAU/mL]	95% CI	*p* value
Treatment									
Off treatment >1 year*	3.02	2.80–3.25		2.48	2.27–2.68	<0.001	2.07	1.85–2.29	<0.001
Under treatment	2.55	2.33–2.76	0.003	2.18	1.99–2.38	0.29	1.95	1.71–2.19	0.06
Tumor type									
Off treatment >1 year*	3.02	2.80–3.25		2.48	2.27–2.68	<0.001	2.07	1.85–2.29	<0.001
HCC	2.58	2.31–2.84	0.01	2.17	1.93–2.40	0.46	2.05	1.75–2.36	0.05
CCC/GBC	2.51	2.13–2.89	0.02	2.26	1.92–2.59	0.24	1.79	1.41–2.16	0.39

B SARS-CoV-2 anti-spike IgG following third vaccination

Time after vaccination	4 weeks			12 weeks			24 weeks		
	estimate [log_{10} BAU/ml]	95% CI	*p*-value	estimate [log_{10} BAU/ml]	95% CI	*p*-value	estimate [log_{10} BAU/ml]	95% CI	*p*-value
Treatment									
Off treatment > 1 year*	3.53	3.25–3.80		3.22	2.92–3.53	0.24	3.18	2.89–3.48	0.33
Under treatment	3.47	3.23–3.71	0.05	3.43	3.13–3.72	<0.01	3.42	3.09–3.75	<0.001
Tumor type									
Off treatment > 1 year*	3.53	3.25–3.80		3.22	2.92–3.53	0.24	3.18	2.89–3.48	0.32
HCC	3.56	3.27–3.85	0.04	3.67	3.27–4.06	<0.01	3.46	3.08–3.84	<0.001
CCC/GBC	3.28	2.86–3.70	0.37	3.09	2.64–3.54	0.24	3.23	2.47–3.99	0.22

C SARS-CoV-2 neutralization antibodies following second and third vaccinations

Time after vaccination	12 weeks after second vaccination			4 weeks after third vaccination			24 weeks after third vaccination		
	estimate [%]	95% CI	*p* value	estimate [%]	95% CI	*p*-value	estimate [%]	95% CI	*p* value
Treatment									
Off treatment > 1 year*	84.13	76.95–91.31		99.36	89.20–100.00	0.02	91.18	79.92–100.00	0.3
Under treatment	64.19	55.90–72.48	<0.001	98.54	89.22–100.00	0.03	94.91	81.37–100.00	0.03
Tumor type									
Off treatment > 1 year*	84.13	76.95–91.31		99.36	89.20–100.00	0.02	91.18	79.92–100.00	0.3
HCC	61.77	52.15–71.39	<0.001	99.39	88.07–100.00	0.03	98.49	83.06–100.00	0.01
CCC/GBC	71.45	54.79–88.11	0.17	96.68	80.02–100.00	0.46	82.40	53.54–100.00	0.83

CI, confidence interval; CCC, cholangiocellular carcinoma; HCC, hepatocellular carcinoma; GBC, gallbladder cancer. The results of linear mixed model analysis for the SARS-CoV-2 anti-spike IgG and neutralization antibodies are shown. Results are reported by mean estimates, 95% confidence intervals, and associated *p* values. *p* values refer to the comparison to patients off treatment >1 year 4 weeks after second vaccination. * Patients with a history of GI cancer in follow-up care being at least 1 year off therapy.

Table 3. Time and group effect on antibody levels

A Comparisons between different points of time for patients under treatment and patients off treatment >1 year		
Regarded points of time	SARS-CoV-2 anti-spike IgG	
	under treatment (*p* value)	off treatment >1 year (*p* value)
2–1	<0.01	0.02
3–1	<0.01	<0.01
4–1	<0.01	<0.01
5–1	1.0	<0.01
6–1	1.0	<0.01
3–2	<0.01	0.58
4–2	<0.01	<0.01
5–2	<0.01	<0.01
6–2	<0.01	<0.01
4–3	<0.01	<0.01
5–3	<0.01	<0.01
6–3	<0.01	<0.01
5–4	0.80	1.0
6–4	0.46	1.0
6–5	1.0	1.0

B Comparison between patients under treatment and patients off treatment >1 year at each point of time						
	Point of time					
	1	2	3	4	5	6
Comparison patients under treatment versus patients off treatment >1 year (*p* value) for SARS-CoV-2 anti-spike IgG	0.02	0.20	1.0	1.0	1.0	1.0
Comparison patients under treatment versus patients off treatment >1 year (*p* value) for SARS-CoV-2 neutralization antibodies	/	<0.01	/	1.0	/	1.0

The results of a post hoc pairwise comparison based on the mixed regression model reported in Table 2 A–C are shown. The numbers are referred to the different points of time as follows: 1–3 = 4, 12, and 24 weeks after second vaccination, respectively; 4–6 = 4, 12, and 24 weeks after third vaccination, respectively.

$p < 0.01$) and patients in follow-up care (2.07 $\log_{10}$ BAU/mL; 95% CI: 1.85–2.29; $p = 0.06$) compared to levels 4 weeks after the second vaccination (shown in Table 2A; Fig. 1a).

Four weeks after the first booster vaccination, predicted mean antibody levels of SARS-CoV-2 anti-spike IgG showed a significant increase in patients with HBC under treatment (3.47 $\log_{10}$ BAU/mL; 95% CI: 3.23–3.71; $p = 0.05$) and in patients in follow-up care (3.53 $\log_{10}$ BAU/mL; 95% CI: 3.25–3.80; $p < 0.01$) compared to patients in follow-up care at week four after the second vaccination. Titers between the groups were almost equal (shown in Table 2B; Fig. 1a). This effect could also be observed for SARS-CoV-2 sNAB in both groups (98.54%; 95% CI: 89.22–100.0; $p = 0.04$ and 99.36%; 95% CI: 89.20–100.0; $p = 0.02$) (shown in Table 2C; Fig. 1b). Importantly, all of the patients who did not develop SARS-CoV-2 antibody titers following the basic vaccination ($n = 8$) showed a positive immune response after the first booster vaccination.

However, levels of total as well as neutralization antibodies decreased again in patients with HBC under treatment and in patients in follow-up care over time (shown in Tables 2B, 2C; Fig. 1a, b). In comparison to the decrease of antibody levels after the first two vaccinations, the decrease after the third vaccination was less pronounced (shown in Tables 2B, C, 3A, B; Fig. 1a, b). Despite official recommendations and our reinforcement, only 20.4% ($n = 12$) of patients under treatment and 16.7% ($n = 7$) of patients in follow-up care opted to receive a fourth vaccination (shown in Table 1). In patients with active HBC under treatment as well as in patients in follow-up care, this second booster vaccination stabilized and, again, improved antibody levels of total (3.75 $\log_{10}$ BAU/mL; 95% CI:

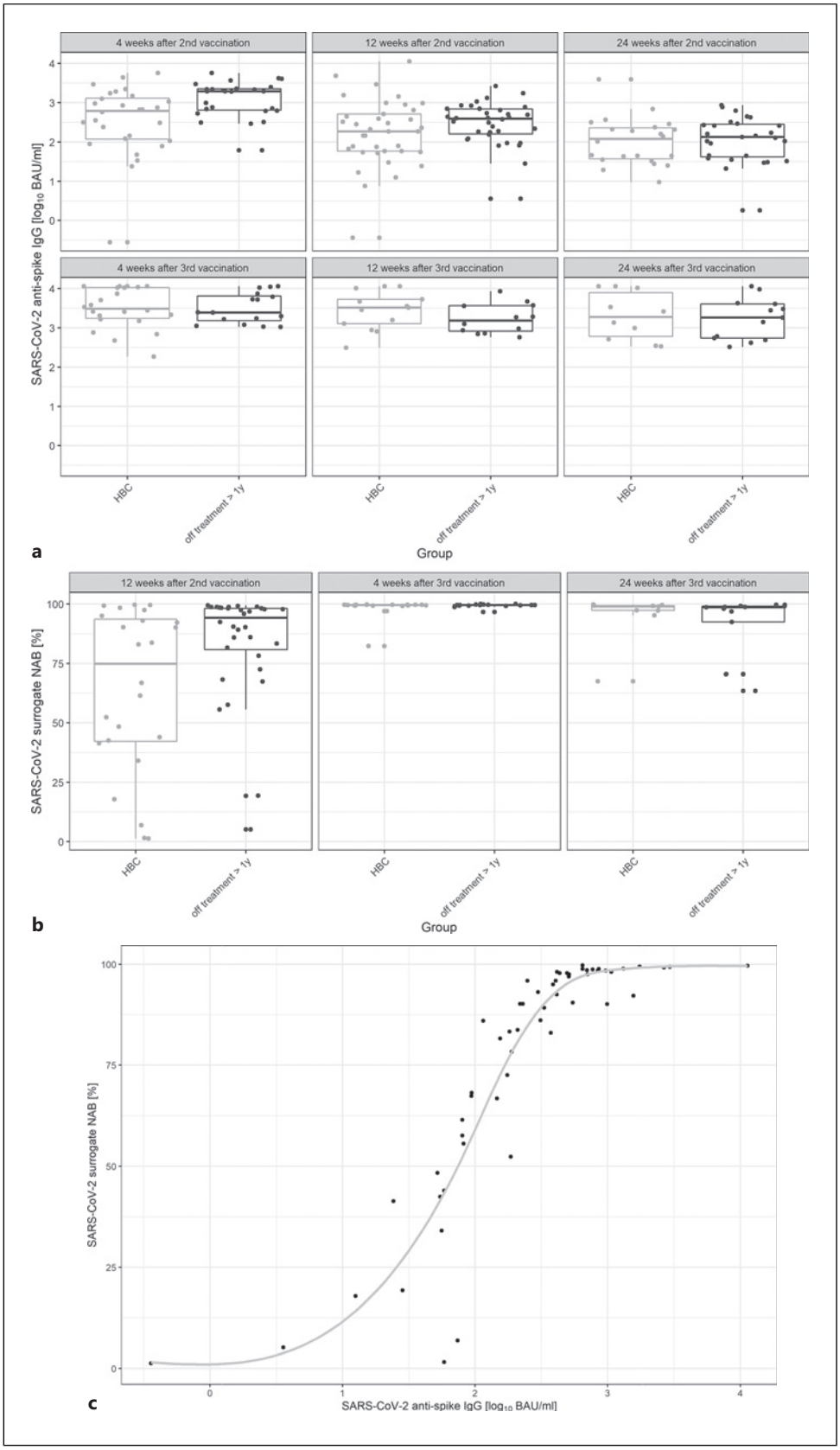

Fig. 1. Comparison of SARS-CoV-2 antibody titer between patients with HBC undergoing active anticancer treatment and patients being off treatment >1 year. **a** log10 SARS-CoV-2 anti-spike IgG titer at weeks 4, 12, and 24 after the second and third vaccinations, respectively. **b** SARS-CoV-2 surrogate neutralization antibody titer at week 12 after the second and at weeks 4 and 24 after the third vaccination, respectively. **c** Association between log10 SARS-CoV-2 anti-spike IgG and SARS-CoV-2 surrogate NAB titer with a correlation coefficient of 0.93. Lower and upper ends correspond to the 25% and 75% quartiles, respectively; length of boxes represents interquartile range; horizontal line shows median log10 SARS-CoV-2 anti-spike and SARS-CoV-2 surrogate neutralization antibody titer. BAU, binding antibody units; NABs, neutralization antibodies; HBC, hepatobiliary cancer.

2.86–4.17 and 3.60 $\log_{10}$ BAU/mL; 95% CI: 2.93–4.10) as well as of neutralization antibodies (99.14%; 95% CI: 97.00–99.70 and 98.88%; 95% CI: 98.40–99.60).

Up until May 2022, infections with SARS-CoV-2 were found in 8 patients of our cohort – all with a mild course. Infections with VOCs BA.1 and BA.2 (Omicron) were documented in 1.7% (n = 1) of patients with active HBC under treatment and 4.8% (n = 2) of patients in follow-up care despite booster vaccination. With VOCs BA.4 and BA.5 (Omicron), 2 patients in follow-up care (4.8%) and 3 patients under anticancer treatment (5.1%) were infected (shown in Table 1). The third and fourth vaccinations in our cohort of patients were also well tolerated with only mild side effects (shown in Table 1).

Cellular Response Rates after Booster Vaccination

In addition, we examined cellular response rates in both groups after the third vaccination for SARS-CoV-2. Levels of SARS-CoV-2-stimulated interferon gamma release were balanced with similar titers in patients with HBC under treatment (1,372.39 mIU/L; 95% CI: 940.69–1,804.08) and in patients in follow-up care (1,248.34 mIU/L; 95% CI: 843.20–1,653.49; p = 0.68) 4 weeks after the third vaccination. At week 24 after the third vaccination, levels of patients in follow-up care were stable (1,341.70 mIU/L; 95% CI: 852.87–1,830.53), while those of patients with HBC under anticancer treatment decreased distinctly (921.98 mIU/L; 95% CI: 349.14–1,494.83) (shown in Table 4).

Subgroups Analyses and Factors Influencing Humoral Immune Response Rates

In the group of patients with active HBC, we analyzed factors potentially impairing immune response rates. Neither underlying CLD nor liver cirrhosis was found to be associated with significantly reduced antibody levels (shown in Fig. 2). Concerning tumor types, no significant differences between patients with HCC and patients with CCC/GBC could be determined at any point of time (shown in Table 2; Fig. 3 A, B). Of note, in the control group, time-averaged mean predicted total (2.74 $\log_{10}$ BAU/mL; 95% CI: 2.41–3.07 vs. 2.77 $\log_{10}$ BAU/mL; 95% CI: 2.57–2.97; p = 0.89) and neutralization SARS-CoV-2 antibody levels (84.91%; 95% CI: 72.87–88.53 vs. 91.17%; 95% CI: 84.29–98.04; p = 0.38) did not differ between patients with a past medical history of HBC and patients with a past medical history of other GI cancer types. In patients under treatment, chemotherapy significantly reduced levels of total (−0.50 $\log_{10}$ BAU/mL; 95% CI: −0.85 to −0.15; p < 0.01) as well as of neutralization antibodies (−15.23%; 95% CI: −28.50 to −1.96; p = 0.03). By contrast, the potential impact of local, targeted, or immune checkpoint therapy was insignificant and minor (shown in Fig. 3c, d).

In a multivariable analysis, we again regarded factors potentially influencing humoral response rates to vaccinations for SARS-CoV-2. Additional immunosuppression was associated with significantly reduced levels of total 0.70 $\log_{10}$ BAU/mL; 95% CI: −1.06 to −0.34; p < 0.01) and neutralization antibodies (26.99%; 95% CI: −42.51 to −11.45; p < 0.01). Of note, immunosuppression was only suspected in patients under co-medication with corticosteroids, calcineurin inhibitors, or azathioprine and/or in patients with an underlying HIV infection and T helper cells <400/μL (shown in Table 1). Thus, in the present model, immunosuppression was not linked to chemotherapy, identifying immunosuppression as an independent risk factor for impaired response rates. Conversely, chemotherapy itself significantly impaired levels of SARS-CoV-2 anti-spike IgG (−0.79 $\log_{10}$ BAU/mL; 95% CI: −1.28 to −0.29; p < 0.01), while its impact on neutralization antibodies was less pronounced (−16.94%; 95% CI: −35.97 to +2.09; p = 0.08). Vice versa, DM as comorbidity reduced levels of neutralization antibodies significantly (−16.75%; 95% CI: −29.06 to −4.45; p < 0.01) with an inferior impact on levels of total antibodies (−0.29 $\log_{10}$ BAU/mL; 95% CI: −0.55 to −0.02; p = 0.04). Being off treatment <1 year without detectable tumor activity and/or a past medical history of COVID-19 prior to vaccinations were linked to distinctly higher levels of total and neutralization antibodies by trend. Other therapy regimes (immune checkpoint therapy, targeted therapy, local therapy), age, sex, CLD, and/or compensated liver cirrhosis (i.e., Child-Pugh A or B) showed no substantial impact on antibody levels (shown in Fig. 4a, b).

Regarding levels of total and neutralization antibodies after the first booster vaccination, negative effects of additional immunosuppression, chemotherapy, and/or DM were minor and insignificant. Moreover, the positive impacts of infections with SARS-CoV-2 on antibody levels and/or of finishing anticancer treatment within 1 year diminished (shown in Fig. 4c, d).

Discussion

In a large cohort of patients with GI cancer, we showed that patients with active HBC under anticancer treatment are facing significantly impaired immune responses to basic vaccination for SARS-CoV-2 without safety concerns. Although response rates could eventually be

Table 4. Cellular response rates after SARS-CoV-2 vaccination

	Estimate, mIU/mL	95% CI	*p* value
Four weeks after third vaccination			
Treatment			
Off treatment >1 year *	1,248.34	843.20–1,653.49	<0.001
Under treatment	1,372.39	940.69–1,804.08	0.68
24 weeks after third vaccination			
Treatment			
Off treatment >1 year *	1,341.70	852.87–1,830.53	0.7
Under treatment	921.98	349.14–1,494.83	0.18

The results of linear mixed model analysis for the SARS-CoV-2 IGRA are shown. Results are reported by mean estimates, 95% confidence intervals, and associated *p* values. *p* values refer to the comparison to patients off treatment >1 year 4 weeks after second vaccination. IGRA, interferon gamma release assay; mIU/mL, milli-international units per milliliter; CI, confidence interval. *Patients with a history of GI cancer in follow-up care being at least 1 year off therapy.

improved by booster vaccinations in our cohort of patients to levels similar to those in patients without active cancer disease in follow-up care, waning immunity over time was again observed and should be taken into consideration for further recommendations.

Patients with CLD and with solid cancer have been shown to develop worse immune responses to basic vaccination for SARS-CoV-2 than healthy people [13, 16]. Unfortunately, differentiated data on patients with active HBC are missing to date. These patients have been suspected to be especially vulnerable during the ongoing COVID-19 pandemic due to the underlying combination of CLD and malignant disease. Thus, in this study, we focused on immune response rates to vaccination for SARS-COV-2 in a relatively large cohort of patients with active HBC receiving anticancer treatment (being or having been under local therapy, chemotherapy, targeted therapy, or immune checkpoint inhibition within the last 12 months). Patients with a past medical history of GI cancer having been at least 1 year without detectable tumor disease and without anticancer treatment were included as control group. Within the control group, there was a proportion of 28.6% of patients with a past medical history of HBC. All patients were well matched as detailed above, particularly as they shared comparable risk factors for cancer development and for severe COVID-19 which could not be found in a cohort of healthy people.

As expected, the present data reveal that patients with active HBC are especially challenged by significantly reduced levels of total and neutralization SARS-CoV-2 antibodies when compared to patients with a past medical history of GI cancer in follow-up care. Levels of total and neutralization antibodies were strongly associated (correlation coefficient of 0.93) as described before [22]. However, while differences in total antibodies diminished over time, significant differences in neutralization antibodies persisted marking a discrepancy in real effectiveness. Previous studies on response rates to vaccinations for seasonal influenza, hepatitis A or B, and *Streptococcus pneumoniae* in patients with CLD revealed impaired immunogenicity compared to healthy controls [6–9]. Recently, these effects could be shown in patients with CLD after having received SARS-CoV-2 vaccines [11, 12].

HBC per se as well as underlying CLD and liver fibrosis/cirrhosis in most patients are associated with augmented immunodeficiency [23, 24], resulting in worse immune responses to vaccines. In order to further dissect the influence of additional underlying hepatological conditions, subgroup analyses were performed. Interestingly, neither underlying CLD nor liver cirrhosis was associated with significantly reduced levels of total and neutralizing antibodies, in our cohort of patients with active HBC. These results were also confirmed in a multivariable analysis. Concerning liver cirrhosis, only patients with compensated liver cirrhosis (Child-Pugh A or B) were included in our cohort, explaining in part the missing effect of cirrhosis on levels of SARS-CoV-2 anti-spike IgG. In general, patients with CLD had positive SARS-CoV-2 anti-spike IgG levels after basic vaccination in >85.0% of cases [25]. The positive titers found in 89.4% of cases after basic vaccination in our cohort of patients are in line with these data. Previously, it has been shown that compensated liver cirrhosis did not impair immune response rates to vaccinations for SARS-CoV-2 in patients with CLD other than HBC [12] which is confirmed here for patients with

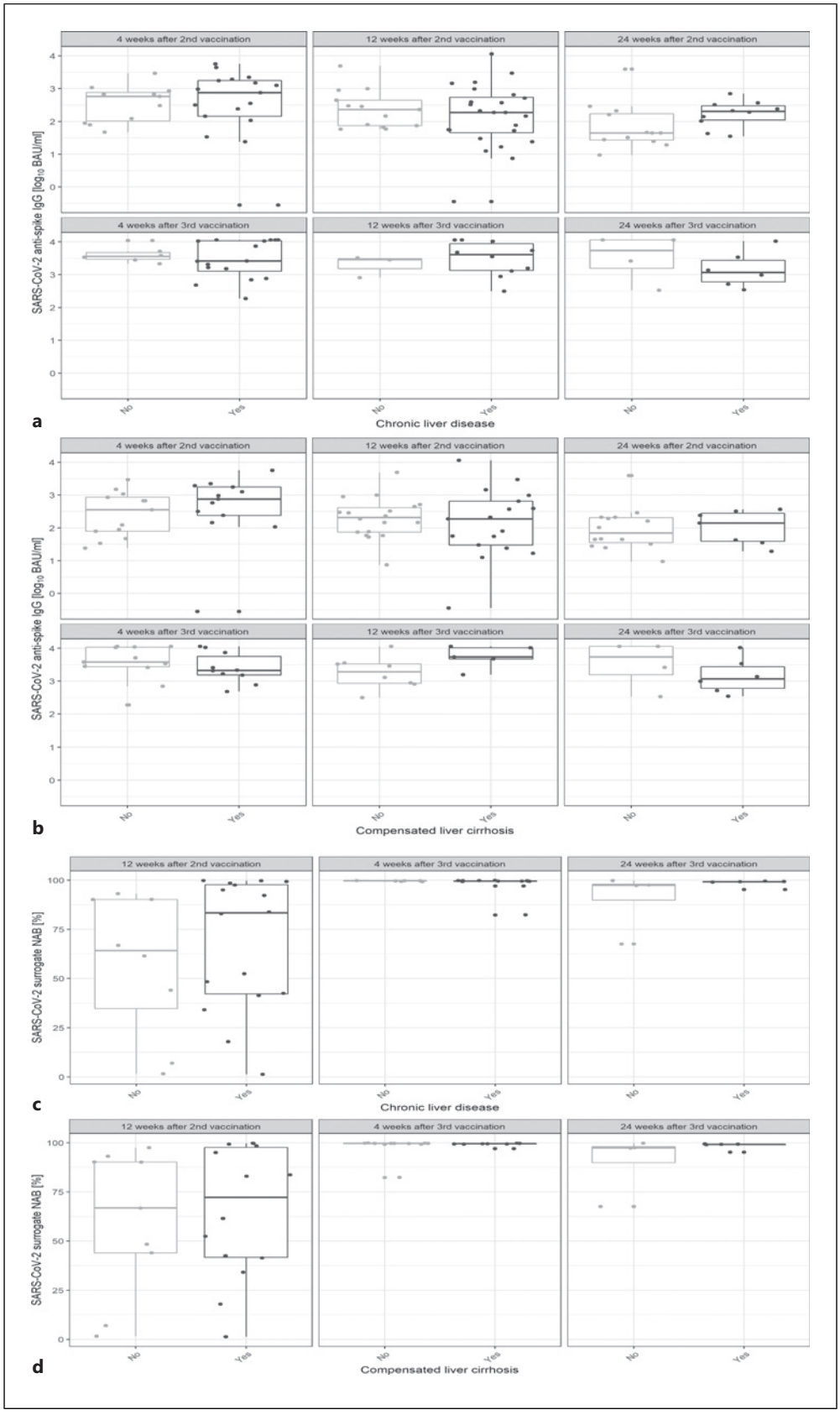

Fig. 2. Comparison of SARS-CoV-2 antibody titer of patients with HBC with and without underlying liver diseases and compensated liver cirrhosis, respectively. **a** log10 SARS-CoV-2 anti-spike IgG titer of patients undergoing active anticancer treatment with and without an underlying liver disease. **b** log10 SARS-CoV-2 anti-spike IgG titer of patients undergoing active anticancer treatment with and without underlying compensated liver cirrhosis. **c** SARS-CoV-2 surrogate neutralization antibody titer of patients undergoing active anticancer treatment with and without an underlying liver disease. **d** SARS-CoV-2 surrogate neutralization antibody titer of patients undergoing active anticancer treatment with and without an underlying compensated liver cirrhosis. Lower and upper ends correspond to the 25% and 75% quartiles, respectively; length of boxes represents interquartile range; horizontal line shows median log10 SARS-CoV-2 anti-spike and SARS-CoV-2 surrogate neutralization antibody titer. Compensated liver cirrhosis was defined as liver cirrhosis Child Pugh A or B with a score less than 8. BAU, binding antibody units; NABs, neutralization antibodies; HBC, hepatobiliary cancer.

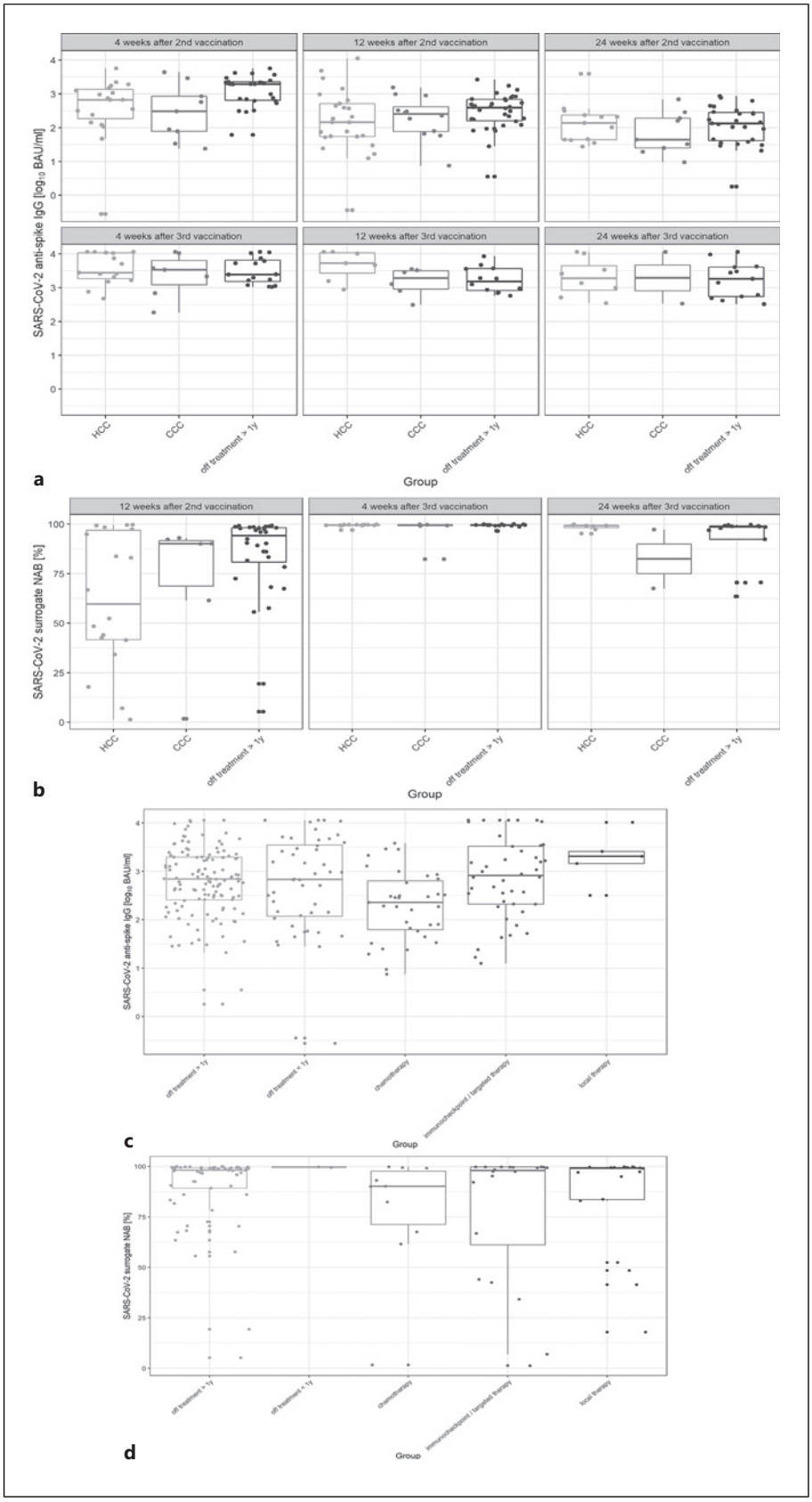

Fig. 3. Comparison of SARS-CoV-2 antibody titer between patients with HCC and CCC undergoing different types of anticancer treatment and patients being off treatment >1 year. **a** log10 SARS-CoV-2 anti-spike IgG titer at weeks 4, 12, and 24 after second and third vaccinations, respectively. **b** SARS-CoV-2 neutralization antibody titer at week 12 after second vaccination and at weeks 4 and 24 after third vaccination, respectively. **c** Comparison of log10 SARS-CoV-2 anti-spike IgG titer of patients with HBC undergoing different types of anticancer treatment. **d** Comparison of SARS-CoV-2 neutralization antibody titer of patients with HBC undergoing different types of anticancer treatment. Lower and upper ends correspond to the 25% and 75% quartiles, respectively; length of boxes represents interquartile range; horizontal line shows median log10 SARS-CoV-2 anti-spike and SARS-CoV-2 surrogate neutralization antibody titer. BAU, binding antibody units; NABs, neutralization antibodies; HCC, hepatocellular cancer; CCC, cholangiocellular cancer; HBC, hepatobiliary cancer.

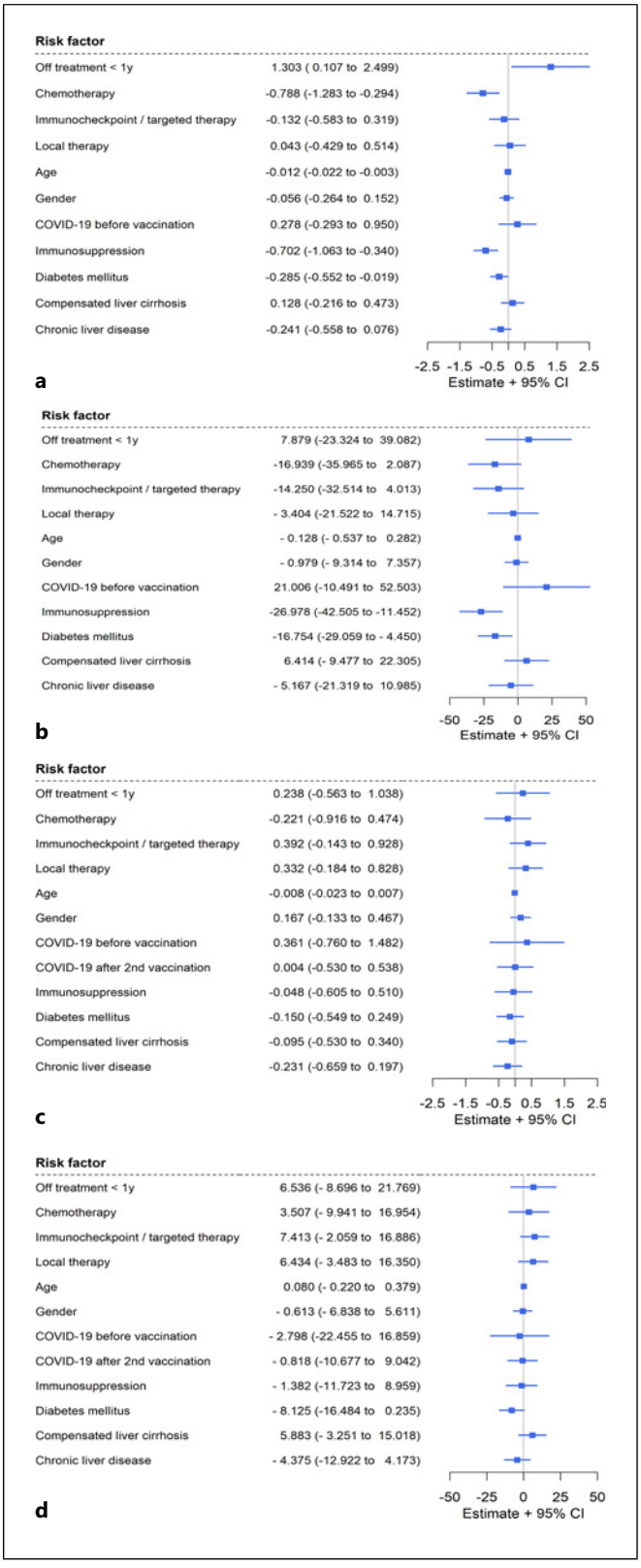

Fig. 4. Effects of suspected factors influencing immunogenicity for SARS-CoV-2 antibody titer. **a** Effects on log10 SARS-CoV-2 anti-spike IgG titer after second vaccination. **b** Effects on SARS-CoV-2 surrogate neutralization antibody titer after the second vaccination. **c** Effects on log10 SARS-CoV-2 anti-spike IgG titer after the third vaccination. **d** Effects on SARS-CoV-2 surrogate neutralization antibody titer after third vaccination. The results of multivariable linear mixed effects analysis for the log10 SARS-CoV-2 anti-spike IgG and SARS-CoV-2 neutralization antibodies are shown. Forest plots are showing point estimates and 95% CIs. Compensated liver cirrhosis was defined as liver cirrhosis Child-Pugh A or B with a score less than 8. CI, confidence interval.

HBC. However, immunogenicity after vaccination for hepatitis A and B was especially impaired in cases of decompensated liver cirrhosis correlating with clearly reduced liver synthesis [10]. One would thus also assume worse levels of SARS-CoV-2 antibodies in patients with HBC in situations of decompensated liver conditions, which were not included as these patients are mostly not eligible for anticancer treatment.

Although no significant differences between solid tumor types could be demonstrated to date [26], differentiated data for several tumor types are still missing. In our own preliminary analysis on efficacy of SARS-CoV-2 vaccinations in patients with GI cancer, we could identify patients with active HBC (n = 39) as especially facing impaired immunogenicity compared to patients with other types of active GI cancer and to patients in follow-up care [27]. Separating HCC from CCC, there were no differences in antibody levels between the 2 groups of patients with HBC in our cohort. Moreover, patients with a past medical history of HBC did not show worse immune responses than patients with a past medical history of other GI cancers. While, as far as studies are comparable, the finding of positive antibody titers in 89.4% of patients with active HBC after basic vaccination in our cohort of patients is worse than in other solid cancer patients (95.0%), it is better than in patients with hematological malignancy (60.0%) [28]. By contrast, 96.2% of patients in follow-up care showed better positive antibody titers, resembling response rates of healthy people. We therefore conclude for our cohort of patients that those with undetectable cancer and without any treatment for at least 12 months are well protected from severe COVID-19.

Moreover, anticancer treatment in general was identified as an outstanding risk factor for significantly reduced levels of SARS-CoV-2 antibodies as shown before by Lee LY et al. [19]. In detail, patients, especially those under chemotherapy, were facing reduced antibody levels, while antibody levels of patients under local or targeted/immunological therapy were not substantially impaired in our cohort of patients. Chemotherapy has previously been identified as an outstanding risk factor for lower antibody levels [29].

According to our multivariable analysis, additional immunosuppression could be identified as a main risk factor for impaired immunogenicity following SARS-CoV-2 vaccination. This is in line with data in patients on immunosuppressive medication following liver transplantation [11, 30]. Of note, this immunosuppression was not linked to anticancer treatment, especially not to chemotherapy. Interestingly, chemotherapy was confirmed as another risk factor which mainly impaired levels of total antibodies with a lesser impact on neutralization antibodies. Moreover, DM as comorbidity showed similar negative effects on SARS-CoV-2 immunogenicity, especially on levels of sNAB. The effects of chemotherapy as well as of DM can be at least partly explained by the underlying immunodeficiency associated with both conditions [31].

A past medical history of COVID-19 was linked to higher levels of total and neutralization antibodies by trend following basic vaccination for SARS-CoV-2. This has previously been revealed for patients with cancer [26] and could here be confirmed for patients with HBC. Natural infections have been shown to possess higher immunogenic potential than vaccinations [32]. Moreover, hybrid immunity, i.e., vaccination after having undergone COVID-19, showed best immune responses compared to natural as well as immunity by vaccination [33]. Higher SARS-CoV-2 antibody levels were also observed in patients who finished their anticancer treatment within 1 year. The formally positive effect of finishing anticancer treatment within 1 year and of a past medical history of COVID-19 on antibody levels in our cohort of patients are though limited in its meaning as only very few patients showed these features.

Differences between antibody levels have eventually been overcome by a third vaccination. Correspondingly, only rare infections with BA.1 and BA.2 were observed in both groups of patients thereafter, highlighting the clinical importance of booster vaccinations, especially for patients at high risk of impaired SARS-CoV-2 immunogenicity. Moreover, cellular response rates were balanced between the groups after the first booster vaccination. It has been shown that the course of COVID-19 was less severe after booster vaccination [34]. In patients with solid as well as blood cancer having been seronegative after the first and the second vaccination for SARS-CoV-2, seropositivity could be traced after the first booster vaccination [35]. This was also true for patients under immunosuppressive treatment after liver transplantation [36] and could also be observed in 8 patients of our cohort. Contrary to our reinforced recommendations, only about two-thirds of patients in our cohort received a third vaccination. Of note, this is in line with the general German booster vaccination rate of 61.95% [1], prompting more intense awareness campaigns, especially for vulnerable groups, such as patients with active HBC.

Despite vaccination, infections with new VOCs (BA.4 and BA.5) were found to increase in our cohort of patients up to about 5.0%, in line with observations of antibody escape of these VOCs from vaccines [37,

38]. Fortunately, no severe courses of COVID-19 were observed. This indicates that the decrease of antibody levels over time was not critical and that the maintained neutralizing capacity still was sufficient to prevent severe COVID-19 from a clinical point of view. Waning immunity over time was confirmed by data from the UK [39], which we also observed in our cohort of patients, making them a vulnerable group concerning infections with SARS-CoV-2. Of note, levels of cellular response were especially diminished in patients with active HBC and must be further monitored. Fortunately, decrease of antibody levels was less pronounced after the third vaccination compared to the same time points after the second vaccination stressing the need for booster vaccinations. However, it is difficult to define a titer effectively preventing infections with SARS-COV-2 and/or a severe course of COVID-19. Titers ≥264.0 BAU/mL were described as being most likely linked to protection from infections with VOC B1.1.7 (alpha) before [40]. Taking the mentioned escape phenomena of new VOCs with increasing infection rates into consideration, for the authors of this study, it is thus speculative to name titers being probably linked to protection for the time being.

The mentioned negative effects of additional immunosuppression, anticancer treatment, particularly of chemotherapy, and DM on immune responses were overcome by the first booster vaccination. Improved immune responses following the third vaccination for SARS-CoV-2 could already be shown for immunocompromised patients, particularly for patients with past medical history of liver transplantation [41, 42].

The overall low rates of infections in our patient cohort reflect that chronically ill patients do stick to hygienic and social distancing rules. As clinical benefits of a fourth vaccine dose have recently been documented [43, 44], which was therefore recommended for immunocompromised patients in the meantime [3], we encouraged our patients to obtain a fourth vaccine for SARS-CoV-2. However, only less than a quarter of the patients in our cohort received a second booster vaccination, resulting in improved and stabilized antibody levels. At least, this vaccination rate is markedly higher than that in the general German population with a vaccination rate of 8.7% [45].

To the best of our knowledge, this is the first report focusing on immune responses to vaccination for SARS-CoV-2 in a large cohort of patients with HBC and with emphasis on underlying hepatological conditions as well as oncological therapy regimes. Due to the limited life expectancy of most of the patients with active HBC, follow-up of all patients was difficult as some patients died and others experienced reduced performance status while continuing their medical treatment in the department of palliative care. Patients under best supportive care were not included. Data on cellular immune response were only evaluated after the first booster vaccination, while data after the second vaccination and thus a longitudinal analysis of this parameter are missing.

In conclusion, patients with HBC are facing significantly impaired immune responses to basic vaccinations for SARS-CoV-2. This seemed to be more related to the malignant disease in general, to therapy regimes (especially chemotherapy), and to any additional immunocompromising circumstances (therapy related or comorbidities) than to underlying cirrhotic or non-cirrhotic CLD or compensated cirrhosis. The currently recommended booster vaccinations effectively overcame discrepancies in effectiveness of vaccination with low infection rates and/or mostly mild courses of COVID-19 thereafter. Patients should be encouraged to receive at least three, better still four, vaccinations according to our data due to waning immunity. Continued monitoring including antibody assessment of the vulnerable group of patients with HBC may help decide on individual extra booster vaccinations, passive immunization, and/or antiviral treatment for patients with active HBC. In future studies, the effects of booster vaccinations on long-term SARS-CoV-2 immunogenicity should be analyzed putting emphasis on new SARS-CoV-2 VOCs, VOC-adapted vaccines, and potential escape phenomena of VOCs from vaccines.

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Statement of Ethics

The study was performed in accordance with the Declaration of Helsinki and approved by the institutional review board of the Medical Faculty of the University of Bonn (Nos. 341/17 and 023/22). Written informed consent was obtained from all participating patients.

Conflict of Interest Statement

M.A.G.C. has contributed to advisory boards for Roche, Eisai, BMS, MSD, and AZ. C.B. received honoraria for lectures and/or consultancies from AbbVie, Gilead, Janssen, MSD, and ViiV as

well as funding from Dt. Leberstiftung, DZIF, Hector Stiftung, and NEAT ID. M.B.M. received travel expenses and honoraria from Gilead, Pfizer, and Virology Education. JKR has received honoraria for lectures and/or consultancies from Abivax, Galapagos, Gilead, Merck, Janssen, Theratechnologies, and ViiV. However, these activities have no potential conflicts of interest with the manuscript. None of the other authors have any potential conflicts (financial, professional, or personal) that are relevant to the manuscript.

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Author Contributions

Malte B. Monin: study concept and design; analysis and interpretation of data; drafting of the manuscript; statistical analysis; administrative, technical, or material support; and study supervision. Leona I. Baier: acquisition of data; analysis and interpretation of data; drafting of the manuscript; and statistical analysis. Jens G. Gorny: acquisition of data; analysis and interpretation of data; and critical revision of the manuscript for important intellectual content. Moritz Berger: analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and statistical analysis. Taotao Zhou, Robert Mahn, Christian Möhring, and Anna-Maria Eis-Hübinger: acquisition of data; critical revision of the manuscript for important intellectual content; and administrative, technical, or material support. Farsaneh Sadeghlar: study concept and design; acquisition of data; critical revision of the manuscript for important intellectual content; administrative, technical, or material support; and study supervision. Christoph Boesecke, Kathrin van Bremen, Jürgen K. Rockstroh, and Christian P. Strassburg: critical revision of the manuscript for important intellectual content and administrative, technical, or material support Matthias Schmid: critical revision of the manuscript for important intellectual content and statistical analysis. Maria A. Gonzalez-Carmona: study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis; administrative, technical, or material support; and study supervision.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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