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Safety and immunogenicity of inactivated SARS-CoV-2 vaccines in people with gastrointestinal cancer

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ABSTRACT

Objectives: This study aimed to evaluate the safety and immunogenicity of inactivated COVID-19 vaccines in patients with gastrointestinal cancer (GI) cancer. The role of memory B cells (MBCs) in the humoral response to COVID-19 vaccination was also investigated.

Methods: In this prospective observational study, GI cancer patients and healthy individuals who had received 2 doses of inactivated COVID-19 vaccines were included. The data regarding adverse effects, serum anti-receptor binding domain (RBD)-IgG, neutralizing antibodies (NAbs), and frequencies of MBCs were collected prospectively.

Results: The inactivated COVID-19 vaccines were safe and well tolerated. Serum anti-RBD-IgG and NAbs were lower for cancer patients. Old age, high ASA score, and receiving active chemotherapy were risk factors for lower antibody titers. The frequencies of activated and resting MBCs decreased in (17.45% vs 38.11%, $P = 0.002$; 16.98% vs 34.13%, $P = 0.023$), while the frequencies of intermediate and atypical MBCs increased in cancer patients (40.06% vs 19.87%, $P = 0.010$; 25.47% vs 16.61%, $P = 0.025$). The serum antibody titer decreased gradually during follow-up but increased when a booster vaccine was given.

Conclusion: The inactivated COVID-19 vaccines were well tolerated in patients with GI cancer but with lower immunogenicity. The subpopulations of MBCs were disordered in cancer patients, and a booster vaccine may be prioritized for them.

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Introduction

The COVID-19 pandemic has spread worldwide, with over 500 million confirmed cases and over 6 million deaths as of July 2022. It is the most unprecedented public crisis in nearly two hundred

years (Kudhail *et al.*, 2022; Lyudoviyk *et al.*, 2022; Ntagereka *et al.*, 2022).

Cancer patients are at a higher risk of acquiring COVID-19 due to immunosuppression and a higher explosion rate with frequent hospital visits (Cortés *et al.*, 2022). Javadinia (Javadinia *et al.*, 2022a) reported that almost 20% of cancer patients might suffer from asymptomatic COVID-19. Moreover, cancer patients were reported to have a higher rate of COVID-19-induced mortality and the need for mechanical ventilation. (Shahidsales *et al.*, 2021; Taghizadeh-Hesary *et al.*, 2021). Vaccination is the most convenient and economical way to decrease the impact of COVID-19 (Mattiuzzi and Lippi, 2022). However, COVID-19 vaccines might be less effective for cancer patients, older patients, those suffering from hematologic malignancies, or those receiving chemotherapies (Ariamanesh *et al.*, 2022; Javadinia *et al.*, 2022b;

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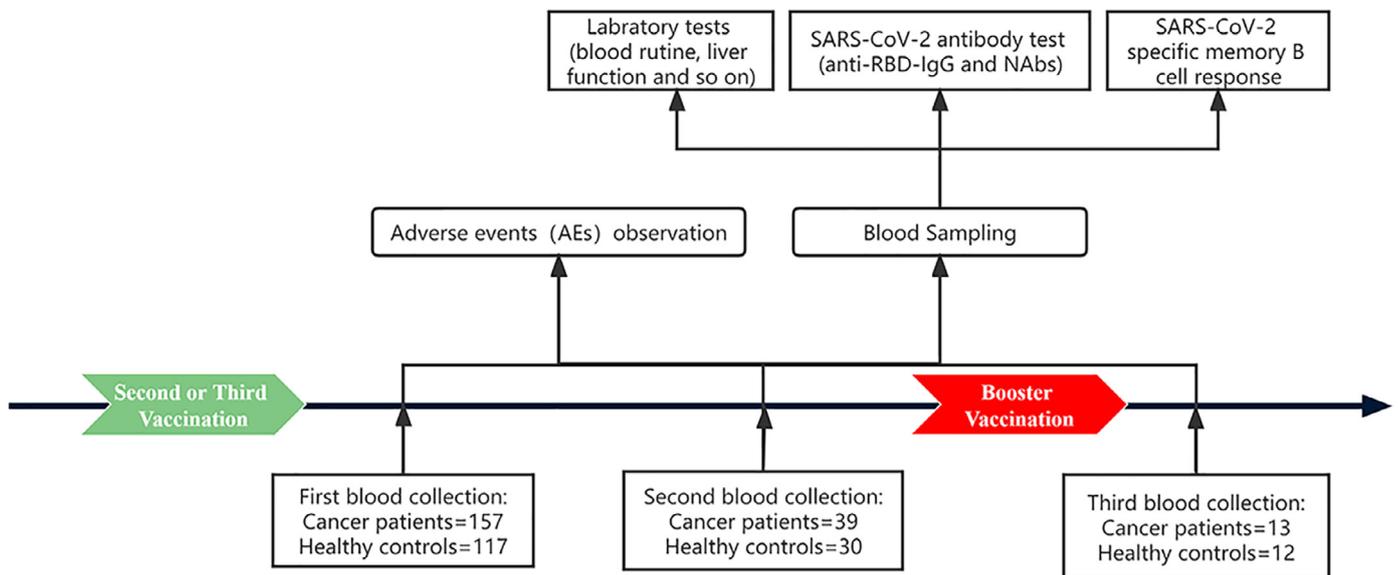


Figure 1. Flowchart of the study.

Table 1
The demographic characteristics of participants.

Variables	GI cancer patients (n = 157)	Healthy controls (n = 117)	P-value
Age, (years)	47, (32-79)	53, (44-61)	0.727
Gender, male, n (%)	106, (67.52)	78, (66.67)	0.882
Days after 2nd dose vaccination, (days)	47, (32-79)	54, (34-75)	0.706
BMI	22.00 (20.70-24.49)	22.86 (21.22-25.39)	0.209
Vaccine type			
BBIBP-CorV, n (%)	50, (31.85)	43, (36.75)	
CoronaVac, n (%)	81, (51.59)	51, (43.59)	0.831
Mixed vaccination, n (%)	2, (1.27)	6, (5.13)	
Zhifei Longcom, China, n (%)	24, (12.74)	17, (14.53)	
Cancer type			
Gastric cancer, n (%)	15, (9.55)	/	/
Liver cancer, n (%)	78, (49.68)	/	/
Intestinal cancer, n (%)	64, (40.76)	/	/
Anticancer therapy			
Active treatment ^a , n (%)	107, (68.15)	/	/
Previous treatment, n (%)	28, (17.83)	/	/
Treatment naïve, n (%)	22, (14.02)	/	/
Therapy type (active)			
Chemotherapy naïve, n (%)	52, (48.60)	/	/
Chemotherapy (+other therapy(ies)), n (%)	55, (51.40)	/	/

BMI = body mass index; GI = gastrointestinal.

^a Patients undergoing anticancer therapy within 6 months before the first dose vaccination.

Joudi et al., 2022). However, the opposite results also exist. The vaccination against COVID in cancer trial showed non-inferiority of two mRNA vaccines in patients receiving immunotherapy, chemotherapy, or chemoimmunotherapy for solid tumors compared with healthy individuals (Oosting et al., 2021). The role of COVID-19 vaccination remains a challenging issue, and minimal data exist on the safety and immunogenicity of inactivated COVID-19 vaccines.

Memory B cells (MBCs) play an essential role in the humoral response to vaccination. When the first dose of vaccine is administered, the receptor binding domain (RBD)-specific MBCs are generated that differentiate into antibody-secreting plasma cells upon administration of the second dose (Oliviero et al., 2020a). Our previous study found that a decrease in the frequency of RBD-specific MBCs in immunocompromised patients might lead to a lower seroprevalence of anti-RBD-IgG (Ao et al., 2022). However, the frequency of MBCs and their correlation with antibody titer have not been thoroughly studied in cancer patients.

In this study, we recruited 157 GI cancer patients and 117 healthy controls to study the safety and immunogenicity of inactivated COVID-19 vaccines. The response of MBCs and their four subpopulations was also detected.

Methods

Participants and study design

Patients diagnosed with GI cancer, mainly gastric cancer, colorectal cancer, and liver cancer (including patients with metastatic diseases) in the Second Affiliated Hospital of Chongqing Medical University and healthy controls from the health management center of the same hospital were recruited consecutively between October 2021 and March 2022 (approximately 800,000 people were infected with COVID-19 in China during the time of the study). The inclusion criteria were as follows: (i) 7-120 days after complete vaccination (BBIBP-CorV/Corona VAC/CHO, all inactivated COVID-

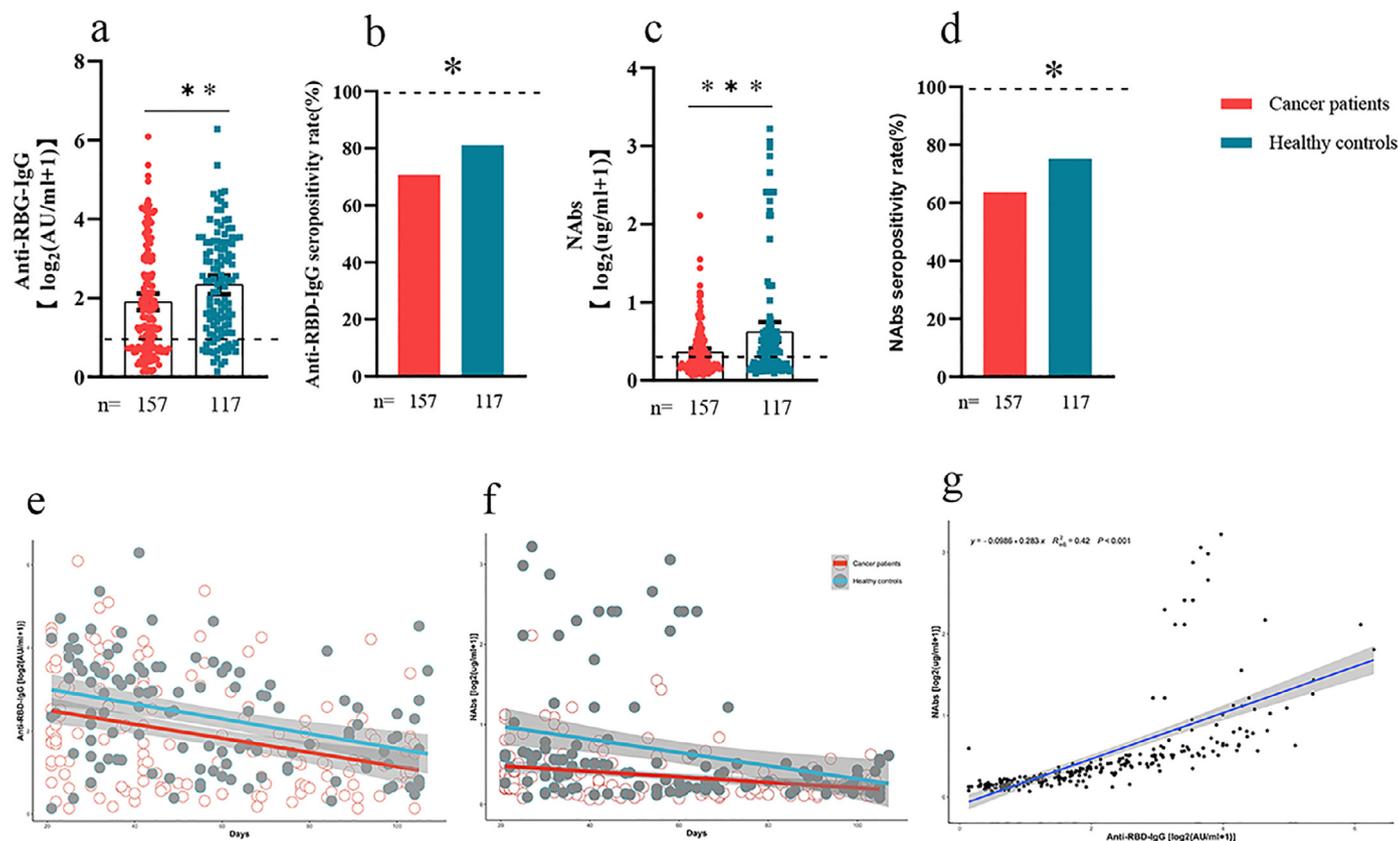


Figure 2. Antibody responses to inactivated SARS-CoV-2 vaccines in patients with gastrointestinal cancer and healthy controls. The titers and seropositivity rate of anti-RBD-IgG (a-b) and NAbs (c-d) in cancer patients and healthy controls. The anti-RBD-IgG (e) and NAbs (f) titers are presented according to different numbers of days post vaccination. The trendlines were generated using a single linear model fit, and the shaded area represents the confidence interval for each fit with a 95% level of confidence. The correlation between the two antibodies (g) The horizontal dotted lines represent the limit of detection. The error bars represent the median (IQR). * $P < 0.05$, ** $P < 0.01$. IQR = interquartile range; Nabs = neutralizing antibodies; RBD = receptor binding domain.

Table 2
Adverse events of COVID-19 vaccination in enrolled participants

AES WITHIN 7 DAYS	GI CANCER PATIENTS (N = 157)	HEALTHY CONTROLS (N = 117)	P-VALUE
OVERALL AES	35, (22.29%)	20, (17.09%)	0.288
LOCAL AES			
PAIN	31, (19.75%)	24, (20.52%)	0.875
SWELLING	5, (3.18%)	2, (1.71%)	0.705
REDNESS	0	0	-
ITCH	6, (3.82%)	0	0.085
INDURATION	0	0	-
SYSTEMIC AES			
MUSCLE PAIN	8, (5.10%)	2, (1.71%)	0.249
PRURITUS	1, (0.64%)	0	1.000
RASH	1, (0.64%)	0	1.000
FATIGUE	16, (10.20%)	4, (3.42%)	0.249
DROWSINESS	1, (0.64%)	2, (1.71%)	0.797
DIZZINESS	5, (3.18%)	0	0.136
HEADACHE	5, (3.18%)	0	0.136
RHINORRHEA	0	0	-
LARYNGEAL PAIN	0	0	-
FEVER	0	0	-
CHILL	0	0	-
COUGH	0	0	-
INAPPETENCE	5, (3.18%)	0	0.136
ABDOMINAL PAIN	4, (2.54%)	0	0.219
ABDOMINAL DISTENSION	4, (2.54%)	0	0.219
DIARRHEA	1, (0.64%)	0	1.000
HEPATALGIA	2, (1.27%)	0	0.509
NAUSEA	3, (1.91%)	0	0.359
CHEST DISTRESS	1, (0.64%)	0	1.000
CONSTIPATION	0	0	-

AE = adverse event; GI = gastrointestinal

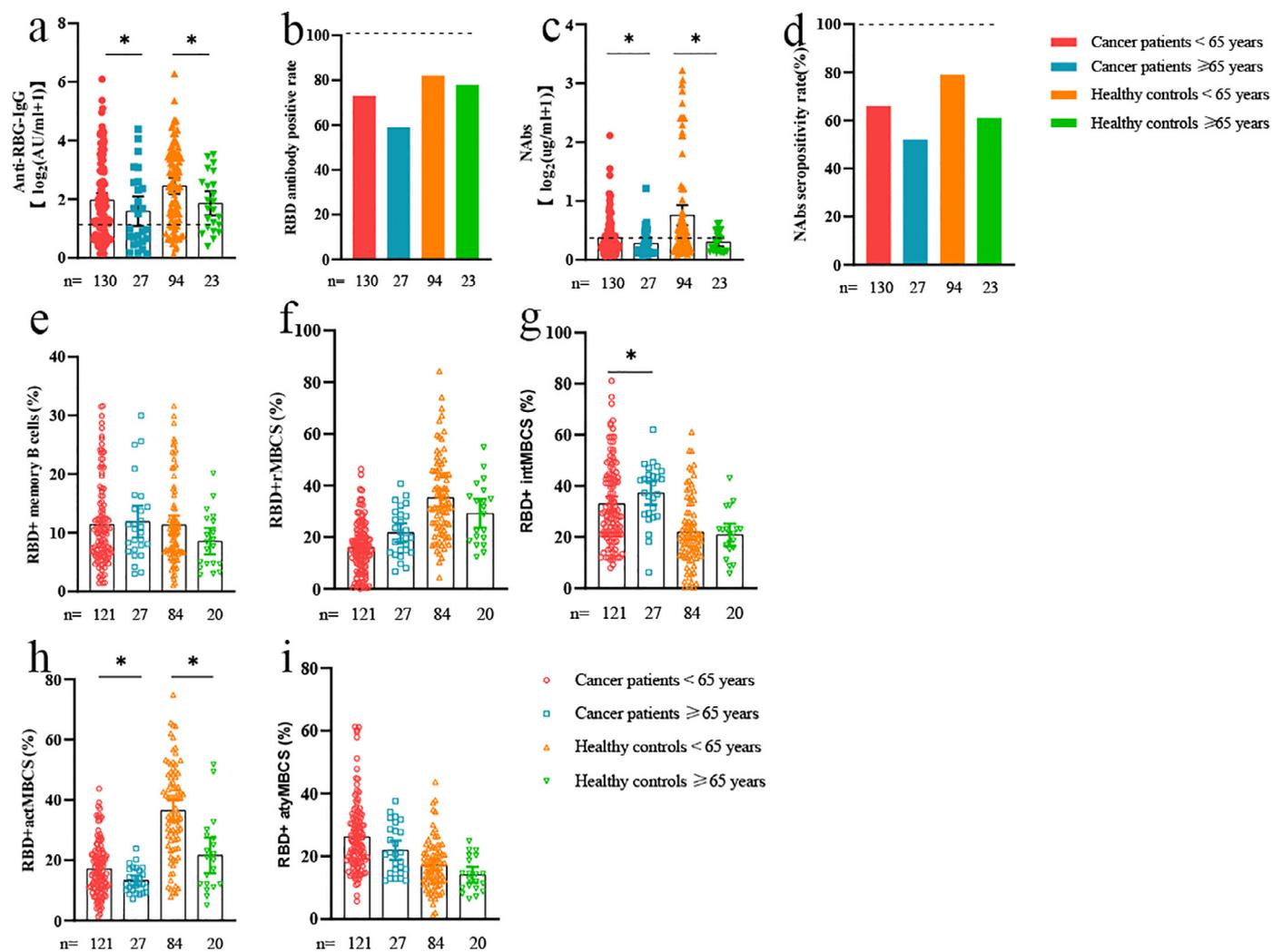


Figure 3. Antibody and specific MBC responses to inactivated SARS-CoV-2 vaccines in participants of different ages. Subgroup analysis of the titers and seropositivity rate of anti-receptor binding domain (RBD)-IgG (a-b) and NAbs (c-d) in participants according to age. The frequencies of RBD-specific MBCs (e), resting MBCs (f), intermediate MBCs (g), activated MBCs (h), and atypical MBCs (i) in participants of different ages. The horizontal dotted lines represent the limit of detection. The error bars represent the median (IQR). **P* < 0.05. MBCs = memory B-cell; Nabs = neutralizing antibodies; RBD = receptor binding domain.

19 vaccines produced in China) and (ii) age >18 years. Individuals with the following conditions were excluded: (i) history of COVID-19 infection, (ii) pregnancy, and (iii) autoimmune diseases.

The minimum sample size for the evaluation of COVID-19 vaccine effectiveness using the WHO sample size calculator was estimated to be 172 people (<https://apps.who.int/iris/handle/10665/340303>). We set the predicted vaccine effectiveness to 90%, the desired precision width to 20%, and the attack rate to 30%, according to previous studies (Joudi et al., 2022).

A cross-sectional analysis was conducted first, and the serum anti-RBG-IgG and neutralizing antibodies (Nabs) levels, as well as the frequency of MBCs and their four subpopulations were evaluated for all the participants 21–105 days after the full course of vaccination. The dynamic changes in the serum antibody titer and the frequency of MBCs were studied during the follow-up. Finally, we collected the antibody titer of those who had received a booster vaccine (see flowchart in Figure 1).

Adverse events (Aes) at 7 days and 30 days were collected using a questionnaire in the outpatient center or by phone call. The classification of Aes was based on the scale issued by the National Medical Products Administration of China (version 2019). Chemotherapy, radiotherapy, molecularly targeted therapy, or immunotherapy within 6 months after or before vaccination was con-

sidered active anticancer therapy. Other clinical data were collected from the electronic medical database.

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University and conformed with the ethical guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants.

SARS-CoV-2 antibody test

Plasma samples were collected for the detection of IgG antibody against the RBD of SARS-CoV-2 spike protein (anti-RBD-IgG) and NAbs using capture chemiluminescence immunoassays performed using MAGLUMI™ X8 (Snibe, Shenzhen, China) according to the manufacturer’s instructions. According to the kit, anti-S-RBD-IgG tests have 100% sensitivity and 99.6% specificity, while NAb tests have 100% sensitivity and 100% specificity for the diagnosis of COVID-19. The cutoff value for NAbs was 0.15 ug/ml, while the cutoff value for anti-RBD-IgG was 1.0 AU/ml.

SARS-CoV-2-specific memory B-cell responses

Biotinylated SARS-CoV-2 spike RBD protein (Sino Biological, 40592-V08H2-B) was mixed with streptavidin BV421 (Biolegend,

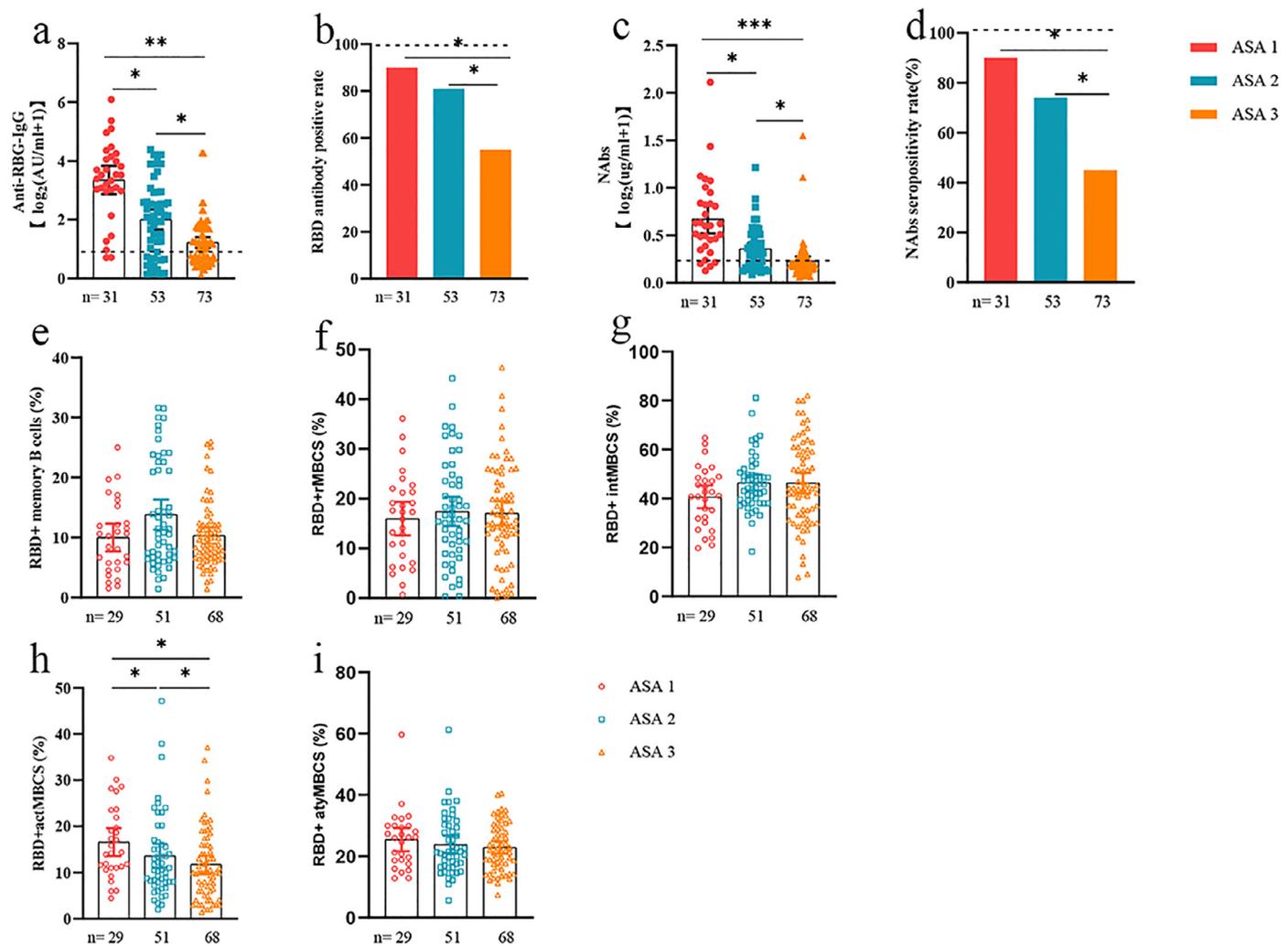


Figure 4. Antibody and specific MBC responses to SARS-COV-2 vaccines in GI cancer patients with different ASA stages. Subgroup analysis of the titers and seropositivity rate of anti- RBD-IgG (a-b) and Nabs (c-d) in cancer patients with different ASA stages. The frequencies of RBD-specific MBCs (e), resting MBCs (f), intermediate MBCs (g), activated MBCs (h), and atypical MBCs (i) in cancer patients with different ASA stages. The horizontal dotted lines represent the limit of detection. The error bars represent the median (IQR). **P* < 0.05, ***P* < 0.01, ****P* < 0.001. MBCs = memory B-cell; Nabs = neutralizing antibodies; IQR = interquartile range; RBD = receptor binding domain.

405225) at a 4:1 molar ratio for 1 hour at 4°C to generate the antigen probe. According to the manufacturer's instructions, peripheral blood mononuclear cells (PBMCs) were extracted from heparinized whole blood by density gradient centrifugation with Histopaque (Sigma–Aldrich, 10771). After rinsing with FACS buffer (PBS+2% FBS), PBMCs were stained at 4°C for 30 minutes with an antigen probe (1:33.3), and the subsequent conjugated antibodies, namely anti-human CD3 (300430, Biolegend, 1:50), anti-human CD19 (302212, Biolegend, 1:50), anti-human CD21 (354918, Biolegend, 1:50), and anti-human CD27 (356406, Biolegend, 1:50). FACS cells were resuspended in 200 µm of FACS buffer after staining. The samples were subjected to flow cytometric evaluation (Beckman Coulter, CytofLEX) and FlowJo analysis (Treestar, 10.0.7r2).

Statistical analysis

The Chi-square and Fisher's exact test were used to compare categorical variables. The Mann–Whitney U test and Kruskal–Wallis test were used to compare continuous variables. The Geomsmooth [ggplot2 package] of a single-term linear model was used to present changes in antibody titers and frequency of MBCs over time. Using simple and multivariate regression analysis, clinical parameters associated with antibody titers were identified. A *P*-value

less than 0.05 was considered statistically significant. Statistics were analyzed using SPSS (IBM, version 24.0.0). GraphPad Prism (GraphPad Software Inc, 9.2.0) and R software (version 4.0.1) were used to create graphs.

Results

Characteristics of the enrolled participants

In total, 274 participants were enrolled in this study from October 2021 to January 2022, of which 157 participants were included in the GI cancer group, and 117 were included in the healthy control group. Of the 274 participants, 184 were male, and 90 were female. The median age was 47 (interquartile range [IQR]: 32–79 years) for the cancer patients and 53 (IQR: 44–61 years) for the healthy individuals. The median number of days post-vaccination was 47 days (IQR: 32–79 days) for the cancer patients and 52 days (IQR: 34–75 days) for the healthy participants (Table 1). Of 157 cancer patients, 78 (49.6%) had liver cancer, 64 (40.8%) had colorectal cancer, and 15 (9.6%) had gastric cancer. A total of 107 patients received active anticancer therapies, 28 had a history of anticancer therapy, and 22 had never received anticancer therapy (most of them had poor general conditions). The chemother-

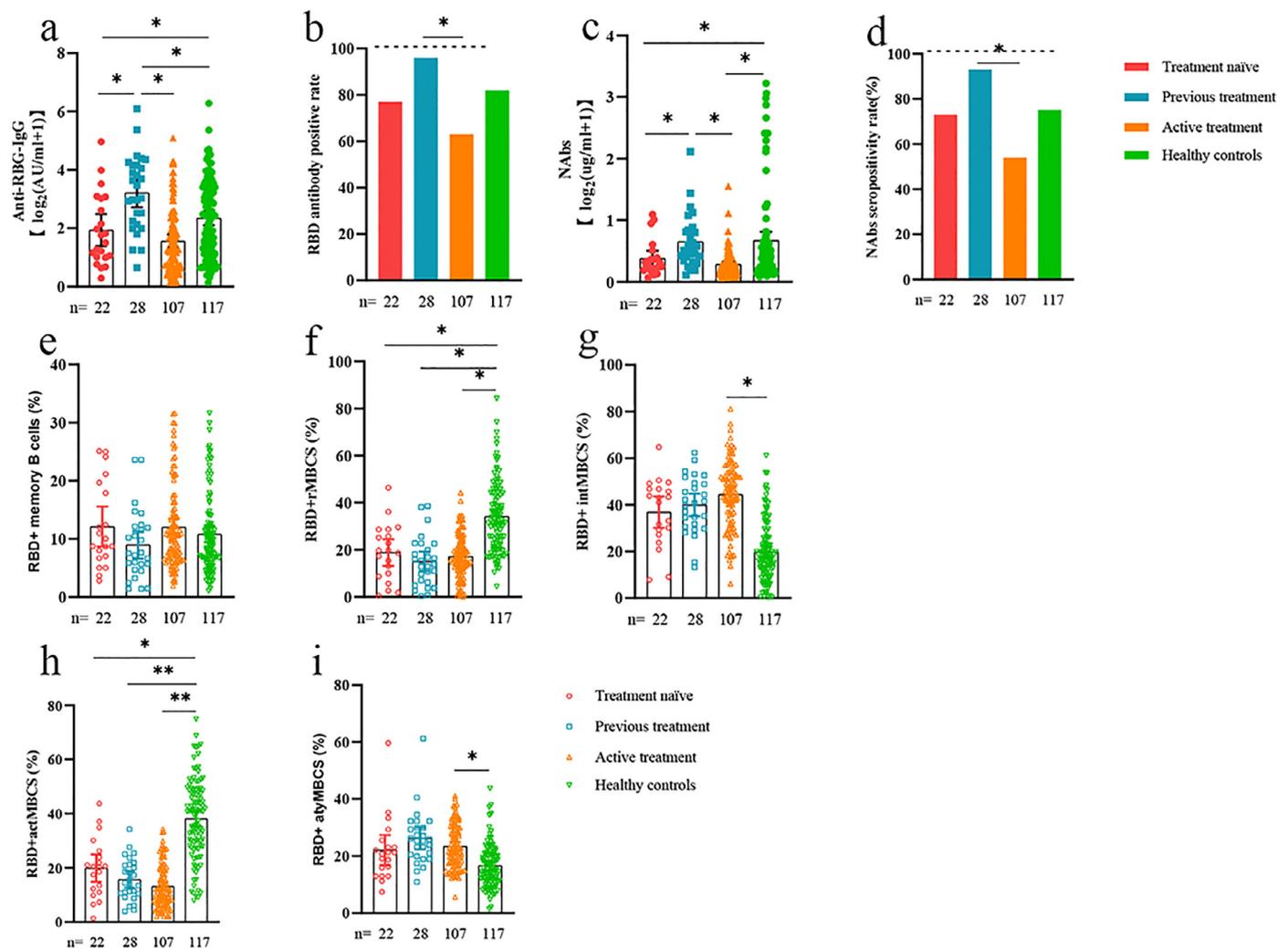


Figure 5. Antibody and specific MBC responses to SARS-COV-2 vaccines in GI cancer patients with different treatments.

The titers and seropositivity rate of anti-RBD-IgG (a-b) and NAbs (c-d) in cancer patients with different treatment statuses. The frequencies of RBD-specific MBCs (e), resting MBCs (f), intermediate MBCs (g), activated MBCs (h), and atypical MBCs (i) in cancer patients with different treatment statuses. The horizontal dotted lines represent the limit of detection. The error bars represent the median (IQR). * $P < 0.05$, ** $P < 0.01$.

GI = gastrointestinal; MBCs = memory B-cell; NAbs = neutralizing antibodies; IQR = interquartile range; RBD = receptor binding domain.

apy regimens are shown in **Supplementary Table 1**. Other clinical characteristics are shown in **Table 1**, and they did not differ between the two groups.

Safety of the inactivated SARS-COVID-2 vaccines

We did not find any severe AEs during the follow-up period. Pain at the injection site was the most common local nonserious AE (19.75% in the cancer group vs 20.52% in the healthy group, $P = 0.875$). Fatigue and headache were the most commonly occurring systemic AEs (**Table 2**). The incidence of these AEs did not differ between the cancer group and healthy controls (**Table 2**). After 30 days of observation, no new AEs occurred in either group (**Supplementary Table 2**).

Antibody responses to inactivated SARS-COVID-2 vaccines

The serum anti-RBD-IgG titers were significantly lower in the cancer patients compared with healthy controls (2.18 [IQR: 0.67–5.05] vs 4.36 [1.31–9.64], $P = 0.004$). The seroprevalence of anti-RBD-IgG was also lower in cancer patients (70.7% vs 80.2%, $P = 0.047$) (**Figure 2**) in addition to the NAbs titers and the seroprevalence of NAbs (0.19 [0.13–0.05] vs 0.31 [0.15–0.54], $P = 0.001$;

63.7% vs 75.2%, $P = 0.042$) (**Figure 2**). In subgroup analysis, we found that patients aged >65 years, with comorbidities, higher ASA scores, diagnosed with colorectal cancer, or recipients of active anticancer therapy (especially chemotherapy) had significantly lower antibody titers (**Figure 3–6**, **Supplementary Figures 1, 2**). Next, we conducted linear regressions to identify risk factors for a lower anti-RBD-IgG titer. Both simple and multiple linear regression found that age >65 years, higher ASA scores, and administration of active chemotherapy were risk factors for a lower antibody titer (**Table 3**). Similar results were found regarding the NAbs (**Supplementary Table 3**). During the follow-up, no participant in this study was infected with COVID-19.

Memory B-cell responses to inactivated SARS-COVID-2 vaccines

MBCs are considered to play an essential role in durable humoral immunity (Ao et al., 2022), and we next evaluated the frequency of RBD-specific MBCs in each group. The gating strategy and representative results are shown in **Supplementary Figure 3**. To our surprise, we did not find a statistically significant difference in the total frequency of RBD⁺ MBCs between the two groups (**Figure 7**). The MBCs had four subpopulations, namely resting MBCs (rMBCs), intermediate MBCs (intMBCs), activated MBCs

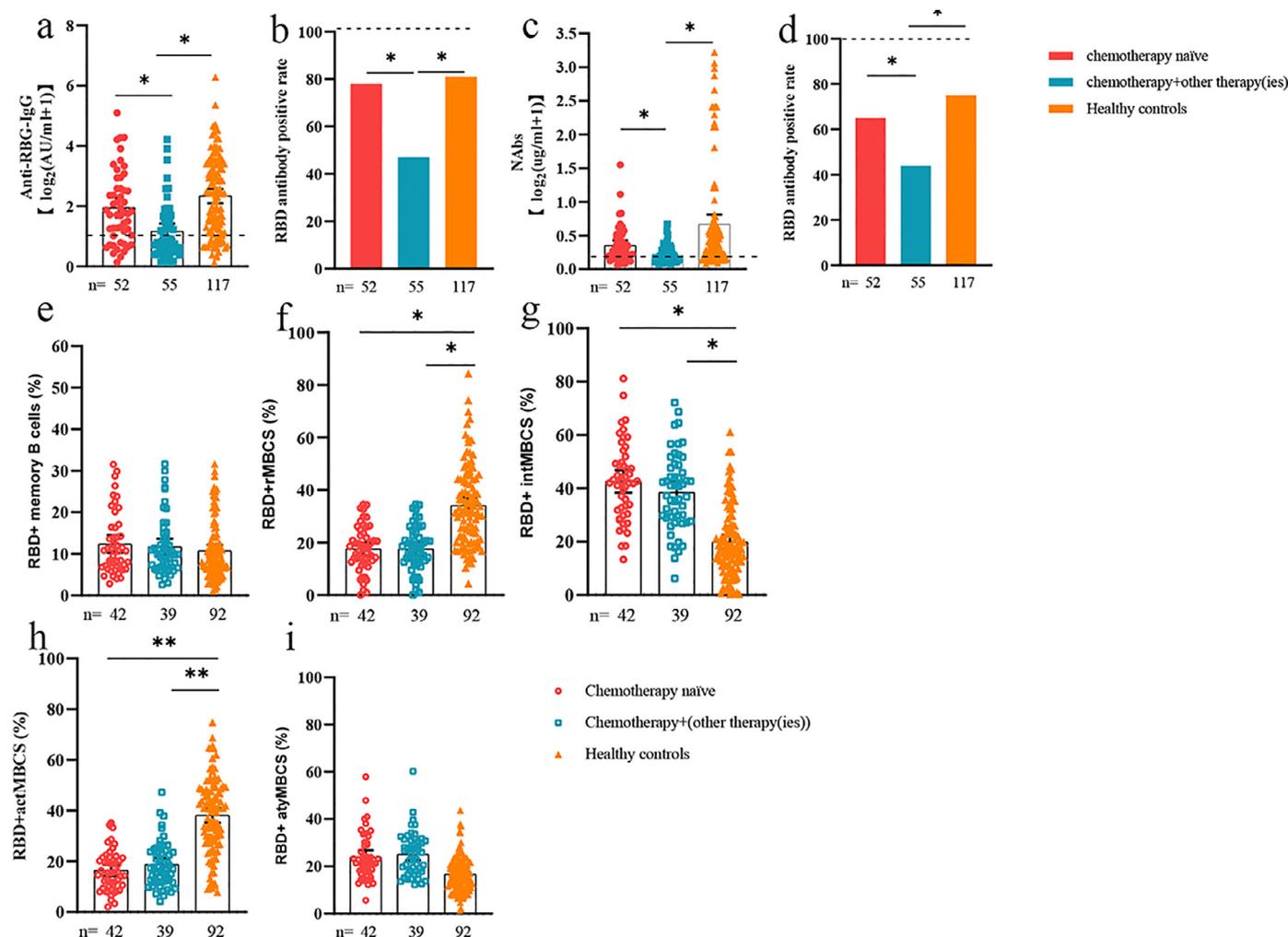


Figure 6. Antibody and specific MBC responses to SARS-CoV-2 vaccines in GI cancer patients with or without chemotherapy. The titers and seropositivity rate of anti-RBD-IgG (a-b) and Nabs (c-d) in cancer patients with or without chemotherapy. The frequencies of RBD-specific MBCs (e), resting MBCs (f), intermediate MBCs (g), activated MBCs (h), and atypical MBCs (i) in cancer patients with or without chemotherapy. The horizontal dotted lines represent the limit of detection. The error bars represent the median (IQR). **P* < 0.05, ***P* < 0.01. GI = gastrointestinal; MBCs = memory B-cell; Nabs = neutralizing antibodies; IQR = interquartile range; RBD = receptor binding domain.

Table 3
Simple and multiple regression analyses to identify risk factors to lower anti-RBD titers in GI cancer patients.

Variables	Simple linear regression		Multiple linear regression	
	β value (95% CI)	<i>P</i> -value	β value (95% CI)	<i>P</i> -value
Age (years)	-0.016 (-0.019, -0.008)	0.018	-0.017 (-0.121, -0.011)	0.018
Gender (female)	-0.677 (-0.990, 1.105)	0.315		
Comorbidity(ies) (no)	-0.016 (-0.022, 0.002)	0.115		
TNM (TNM 4)	0.236 (0.363, 2.249)	0.178		
ASA (ASA 3)	1.226 (1.533, 2.249)	0.035	1.207 (1.503, 2.279)	0.033
Active treatment (no)	0.277 (0.363, 2.249)	0.052		
Active chemotherapy (no)	-0.926 (-1.021, -0.119)	0.000	-0.829 (-1.001, -0.109)	0.000

CI = Confidence interval; GI = gastrointestinal; RBD = receptor binding domain

(actMBCs) and atypical MBCs (atyMBCs), and each subtype had its own characteristics. We next identified whether the frequency of these subpopulations differed between groups. Interestingly, we found that the frequencies of rMBCs and actMBCs were lower (16.98% vs 34.13%, *P* = 0.023; 17.45% vs 38.11%, *P* = 0.002), while the frequencies of intMBCs and atyMBCs were higher in cancer patients (40.06% vs 19.87%, *P* = 0.010; 25.47% vs 16.61%, *P* = 0.025) (Figure 7). In the subgroup analysis, we found that participants of older age with higher ASA scores and those receiving active anti-cancer therapy had a significantly lower frequency of actMBCs and a higher frequency of intMBCs (Figure 3-6).

Follow-up and booster vaccine

Sixty-nine participants completed the follow-up in this study. Although it is far from satisfactory, we still present the results here. Our results showed that the anti-RBD-IgG and NAb titers decreased significantly over time in both cancer patients and healthy individuals (Figure 8). However, if a booster vaccine was given, most participants experienced a sharp increase in antibody titers (Figure 8). We also detected changes in the frequency of MBCs, and found that the frequency of both the total and subpopulations

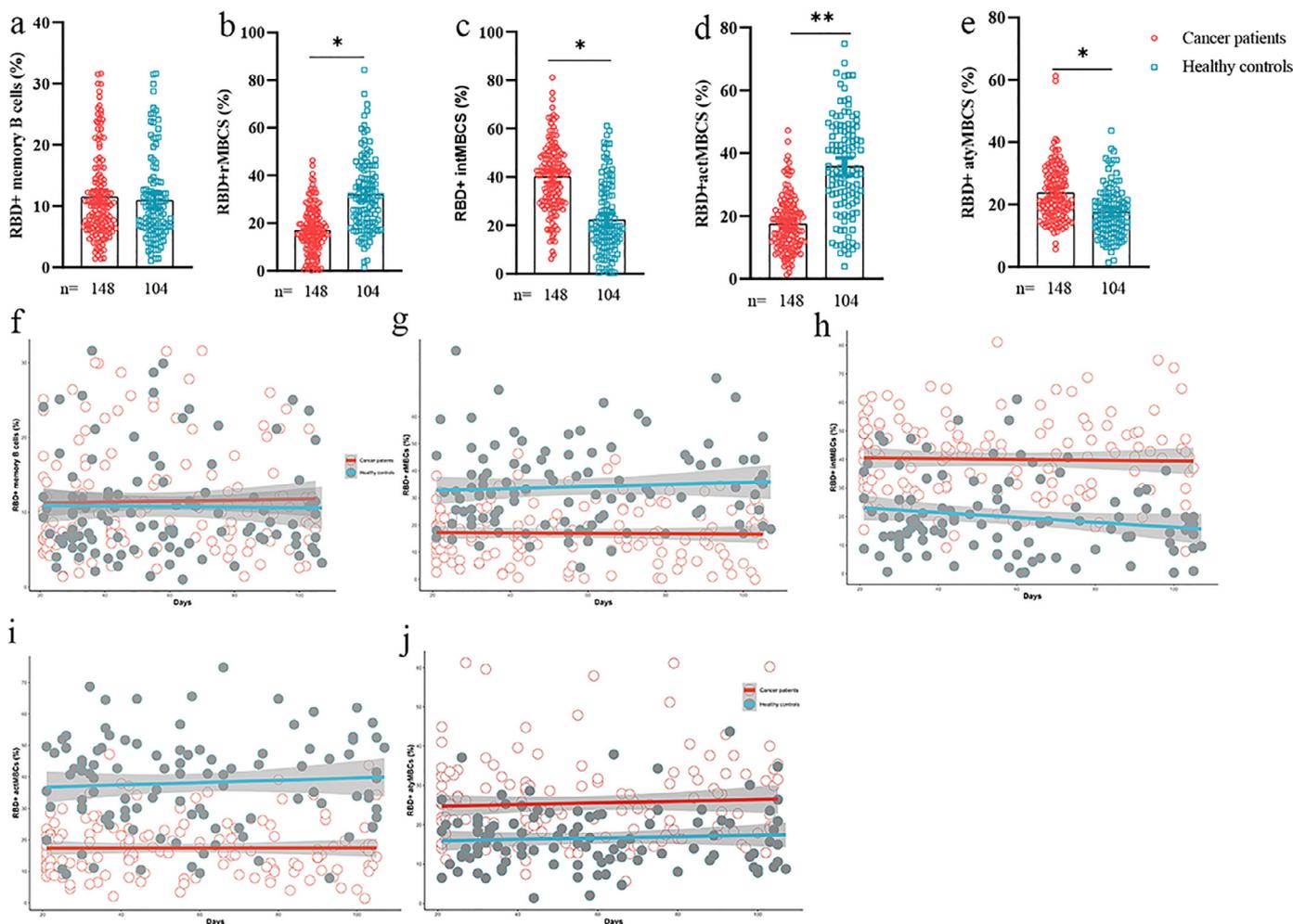


Figure 7. Specific MBC responses to SARS-CoV-2 vaccines in GI cancer patients and healthy controls. The frequencies of RBD-specific MBCs (a), rMBCs (b), intMBCs (c), actMBCs (d), and atyMBCs (e) in cancer patients and healthy controls. The change in frequencies of RBD-specific MBCs (f), rMBCs (g), intMBCs (h), actMBCs (i), and atyMBCs (j) over time in cancer patients and healthy controls. The error bars represent the median (IQR). The trendlines were generated using a single linear model fit, and the shaded area represents the confidence interval for each fit with a 95% confidence level of confidence. * $P < 0.05$, ** $P < 0.01$. actMBCs = activated MBCs; atyMBCs = atypical MBCs; GI = gastrointestinal; Nabs = neutralizing antibodies; IQR = interquartile range; intMBCs = intermediate MBCs; MBCs = memory B-cell; RBD = receptor binding domain; rMBCs = resting MBCs.

of MBCs remained relatively stable in both cancer and healthy individuals (Figure 9).

Discussion

We present the results of a prospective observational study investigating the safety and immunogenicity of inactivated SARS-CoV-2 vaccines in patients with GI tumors and healthy controls. We also evaluated the RBD-specific MBC responses in these people.

Our results were consistent with previous studies (Jara et al., 2022; Joudi et al., 2022; Kang et al., 2022) and showed that inactivated vaccines were safe and well tolerated in GI cancer patients. The most common adverse effect was local pain. Thromboembolic events, myocardial infarction, convulsion, erythema multiforme, and Stevens-Johnson syndrome, which were reported in previous studies, did not occur in this study (Hippisley-Cox et al., 2021; Jabagi et al., 2022; Oosting et al., 2021; Peeters et al., 2021; See et al., 2022). It is worth emphasizing that although 107 patients received active anticancer therapies (chemotherapy, molecular-targeted therapy, and immunotherapy), no serious ad-

verse effects were observed, which further demonstrated the safety of inactivated vaccines.

Consistent with previous studies (Amatu et al., 2022; Goshen-Lago et al., 2021; Ariamanesh et al., 2022), we found that cancer patients had significantly lower serum anti-RBG-IgG and NAb levels after a complete course of vaccination. The seroconversion rate was also lower for cancer patients; approximately 23.98% of cancer patients failed to develop an adequate immune response after vaccination compared to 16.24% of the healthy controls. These results suggested that cancer patients had low immunogenicity to inactivated SARS-CoV-2 vaccines.

In multiple linear regression, we found that old age, high ASA scores, and administration of active chemotherapy were risk factors for a lower antibody titer. Older patients often have a weakened immune system (Korayem et al., 2022). Their B and T cells are less responsive to outside stimuli. They are more likely to have a severe course of COVID-19 and with higher mortality rate (Bubar et al., 2021; Ramasamy et al., 2020; Shapiro et al., 2022). Previous studies have also reported that patients aged >65 years had significantly lower serum antibody titers after vaccination (Ariamanesh et al., 2022; Erdoğan et al., 2022). The ASA score is widely used to evaluate the clinical condition of a patient and to assess the

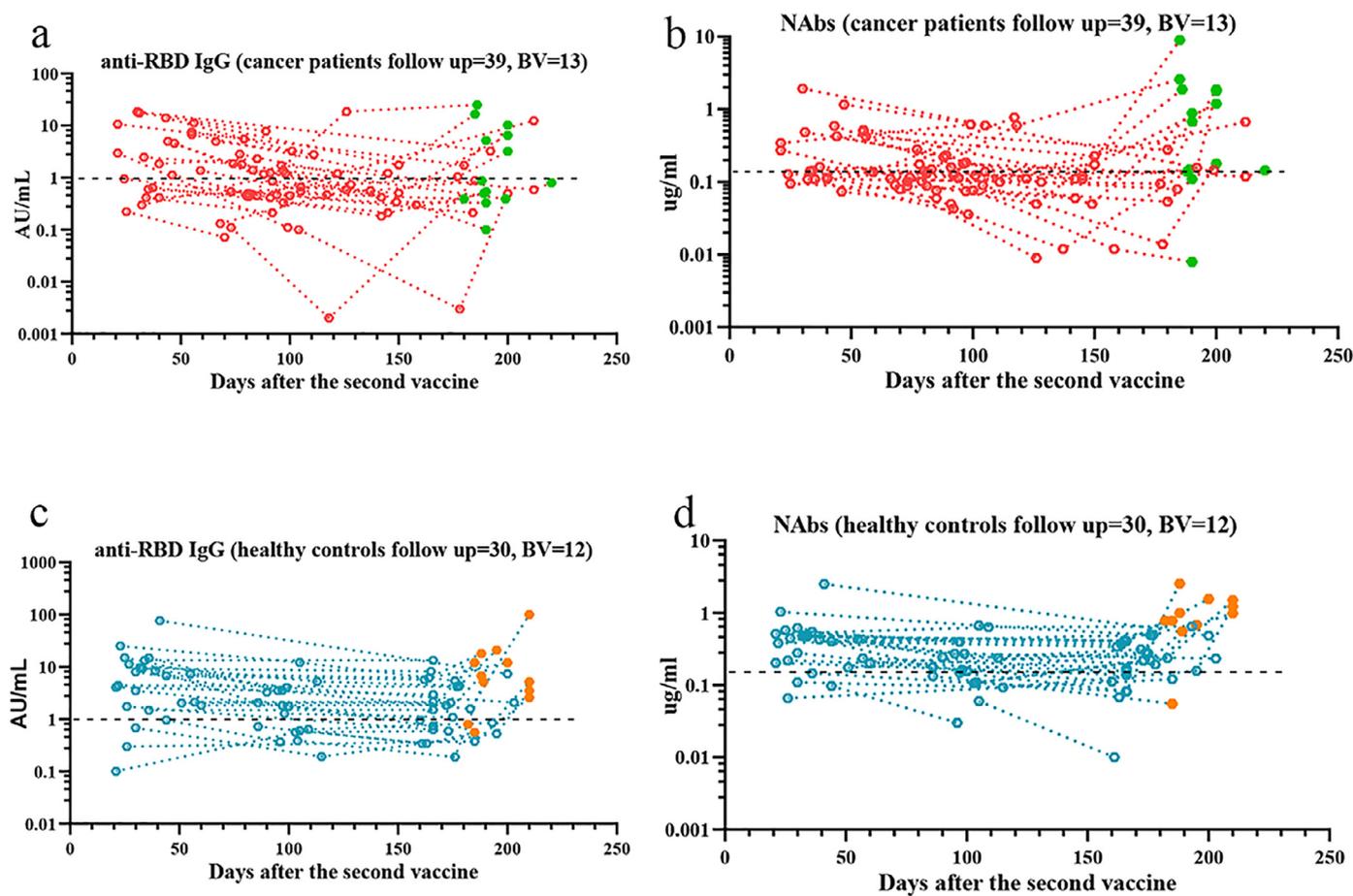


Figure 8. Antibody responses to SARS-CoV-2 vaccines in GI cancer patients and healthy controls during follow-up.

The concentrations of anti-RBD-IgG (a, c) and NAbs (b, d) during follow-up. The red dots indicate samples collected before the BV, and the green dots indicate samples collected after BV (a-b). The blue dots indicate samples collected before BV, and the orange dots indicate samples collected after BV (c-d). The horizontal dotted lines represent the limit of detection.

GI = gastrointestinal; BV = booster vaccine; NAbs = neutralizing antibodies; RBD = receptor binding domain.

risks of receiving anesthesia. A higher ASA score indicates poorer clinical conditions and higher risks of anesthesia. Our results were similar to previous studies that reported that people with a poor ECOG PS (>2) had a higher risk of lacking seroconversion (Amatu et al., 2022). NCCN and other oncological societies recommended that all cancer patients, especially those receiving active treatment, should be vaccinated as a priority (Addeo et al., 2021; Eyu et al., 2022; Yasin et al., 2022). Ruggeri (Ruggeri et al., 2022) reported that drugs interfering with DNA synthesis, multiple-agent chemotherapy, TKIs, and mTOR inhibitors might hamper the humoral response. Other researchers have also reported similar results (Ariamanesh et al., 2022; Erdoğan et al., 2022; Javadinia et al., 2022b). In accordance with these studies, our data showed that receiving active chemotherapy was independently associated with a significantly reduced humoral response to vaccination. As few patients had received targeted therapy and immunotherapy in this study, we did not analyze the impact of these treatments on the effectiveness of the vaccines. In summary, our data indicated that people with old age, high ASA scores, and those receiving active chemotherapy therapy may have decreased immunogenicity to inactivated COVID-19 vaccines. Regular testing of the serum anti-RBD-IgG and NAbs levels may be needed, and a booster vaccine may be required for those with negative seroconversion.

MBCs are terminally differentiated cells that result from a previous immune response due to antigen exposure (Lau et al., 2017;

Sosa-Hernández et al., 2020). When a secondary infection occurs, MBCs differentiate into antibody-secreting cells (ASCs) and protect against the disease (Terrerri et al., 2022; Wang et al., 2022). MBCs have four subpopulations; the actMBCs are primed to become ASCs, and their frequency has a close positive relationship with serum antibody levels. IntMBCs and atyMBCs are often derived from rMBCs, and they can either differentiate into actMBCs or remain unchanged and refractory to further activation by antigens or other stimuli (Salinas et al., 2021). The frequencies of intMBCs and atyMBCs were found to be elevated during chronic inflammation, and several studies have reported their negative relationship with the serum antibody level (Oliviero et al., 2020b; Portugal et al., 2017; Terreri et al., 2022; Wildner et al., 2021). In this study, although no changes in the total numbers of MBCs could be seen, there was a decrease in the frequency of actMBCs and a significant increase in the frequencies of intMBCs and atyMBCs in cancer patients. Similar results were found for patients with old age, high ASA scores, and those receiving active chemotherapy. This may partially explain why cancer patients had a compromised humoral response to the inactivated COVID-19 vaccines.

During the follow-up after the full course of vaccination, the serum anti-RBD-IgG and NAbs levels decreased gradually over time. When a booster vaccine was given, the serum antibody titer increased sharply again. Our data showed that the frequency of

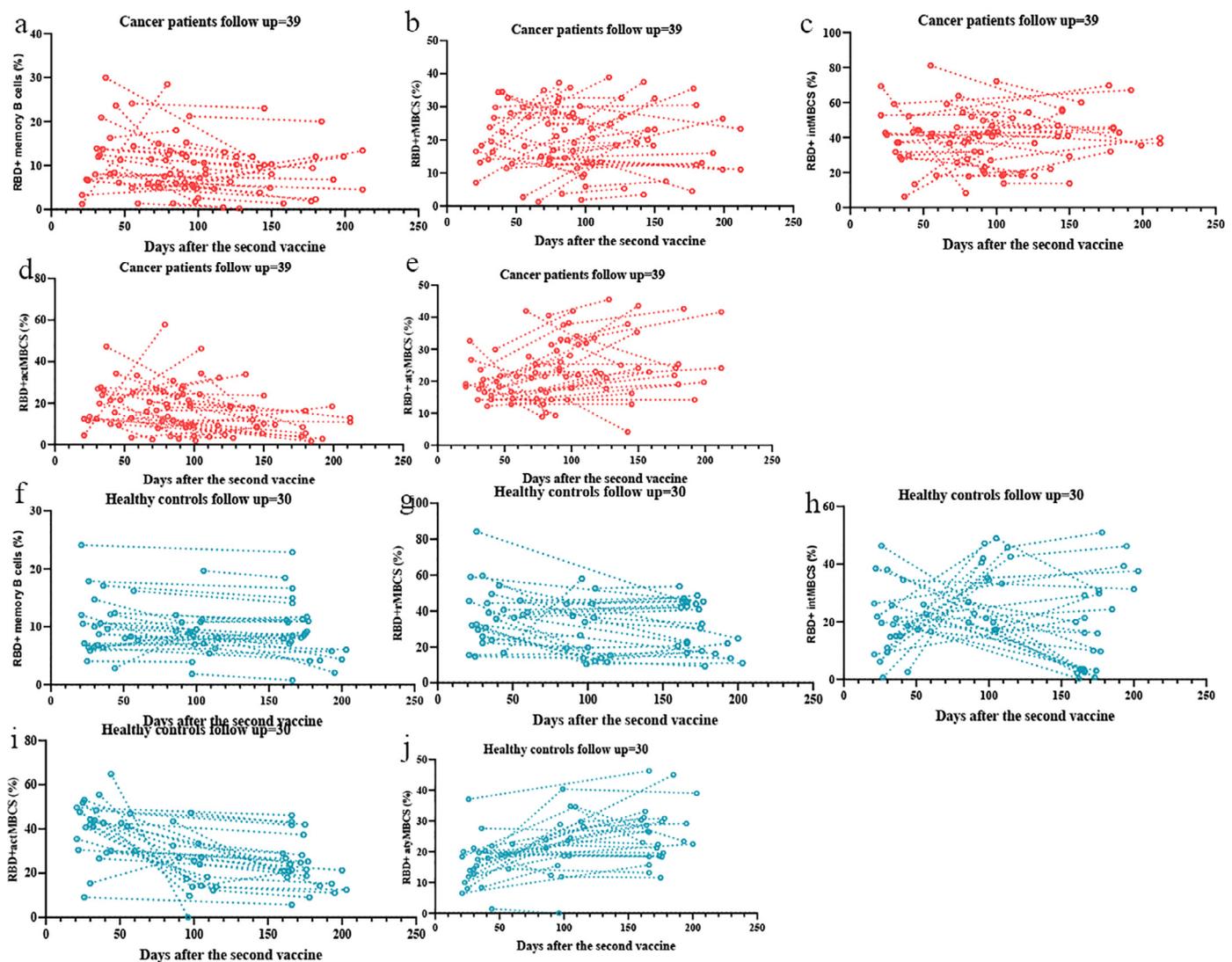


Figure 9. Specific MBC responses to SARS-CoV-2 vaccines in GI cancer patients and healthy controls during follow-up. The frequencies of RBD-specific MBCs (a, f), resting MBCs (b, g), intermediate MBCs (c, h), activated MBCs (d, i), and atypical MBCs (e, j) during follow-up. GI = gastrointestinal; MBCs = memory B-cell; RBD = receptor binding domain

MBCs remained relatively stable after vaccination. However, it decreased slightly among cancer patients. The stable frequency of MBCs may be an important precondition for a functional booster vaccine.

The limitations of this study include the following: (1) only 69 participants completed the follow-up in this study, which weakened the strength of the conclusions regarding the effectiveness of the vaccines during follow-up. (2) Only 25 participants received the booster vaccine; thus, further investigation is needed to determine the safety and immunogenicity of the booster vaccine. (3) T cells and other immune cells also contributed to the humoral response to the vaccines, and the functions of these cells should be studied in future research. Nonetheless, we believe this study provides essential information to clinicians and policymakers.

In conclusion, inactivated SARS-CoV-2 vaccines are safe and well tolerated in GI cancer patients. The antibody response is weak in cancer patients, especially for those with old age, high ASA scores, and those receiving active chemotherapy. The frequency of actMBCs decreased, while the frequencies of intMBCs and atyMBCs increased in cancer patients. During follow-up, the frequency of MBCs remained relatively stable for GI cancer patients. A booster vaccine may be effective and should be prioritized for GI cancer patients.

Ethical approval

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University and conformed with the ethical guidelines of the Declaration of Helsinki.

Author contributions

Tong Li, Rui Song, and Jingjie Wang were responsible for the draft writing and data collection and contributed equally to this study. Jianbo Zhang, Hongxing Cai, Hongmei He, Wei Hu, Dajun Yu, Chuanhu Wang, Qingbo Pan and Mingli Peng were responsible for the data collection, data analysis and follow-up of the patients. Peng Zhu and Hong Ren were responsible for the design and supervision of this study.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ijid.2022.07.050](https://doi.org/10.1016/j.ijid.2022.07.050).

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