Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Research

Third dose of SARS-CoV-2 vaccination in hemato-oncological patients and health care workers: immune responses and adverse events – a retrospective cohort study

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KEYWORDS
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Abstract ***Background:*** Due to potentially immune-escaping virus variants and waning immunity, a third SARS-CoV-2 vaccination dose is increasingly recommended. However, data in patients with cancer are limited.
Patients and methods: We measured anti-SARS-CoV-2 spike protein antibody levels after the third vaccination dose in 439 patients with cancer and 41 health care workers (HCW) at an academic centre in Austria and a rural community hospital in Italy. Adverse events were retrieved from questionnaires.

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Results: Overall, 439 patients and 41 HCW were included. SARS-CoV-2 infections were observed in 62/439 (14.1%) patients before vaccination and in 5/439 (1.1%) patients after ≥1 dose. Longitudinal analysis revealed a decrease of antibody levels between 3 and 6 months after second vaccination in patients with solid tumours ($p < 0.001$) and haematological malignancies without anti-B cell therapies ($p < 0.001$). After the third dose, anti-S levels increased compared to the first/second dose. Patients receiving B cell-targeted agents had lower antibody levels than patients with haematological malignancies undergoing other treatments ($p < 0.001$) or patients with solid tumours ($p < 0.001$). Moreover, anti-S levels correlated with CD19+ (B cell) and CD56+ (NK cell) counts in peripheral blood. The most frequent adverse events after the third dose were local pain (75/160, 46.9%), fatigue (25/160, 15.6%) and fever/chills (16/160, 10.0%). Patients with cancer had lower anti-S levels than HCW ($p = 0.015$).
Conclusions: This study in patients with cancer shows improved antibody levels after the third vaccination dose at an acceptable side-effect profile. Lower antibody levels than in controls underline the need for further follow-up studies and dedicated trials.

1. Introduction

Patients with cancer are particularly affected by the COVID-19 pandemic. They are not only prone to adverse outcomes and severe COVID-19 when infected with SARS-CoV-2 but also at risk of disruptions of anticancer treatment or monitoring visits because of SARS-CoV-2 infections [1–4]. Therefore, large oncological societies recommend SARS-CoV-2 vaccination for all patients with cancer [5].

Overall, SARS-CoV-2 vaccines are highly effective and well tolerated [6–8]. Although SARS-CoV-2 vaccination shows immunogenicity in patients with cancer, seroconversion rates and antibody levels are lower than healthy cohorts, especially in patients undergoing antineoplastic treatment [9–14]. Similar results were observed in patients with immunosuppression due to organ transplantation [15].

With the emergence of variants of concern with increased immune evasion abilities, expanding the overall vaccination coverage and administration of a third booster vaccination is needed to avoid prolonging the pandemic [16]. A third vaccination dose shows the ability to lower the rates of SARS-CoV-2 infection and severe COVID-19 in comparison to non-boostered elderly populations [17]. Studies in immunosuppressed transplant recipients report improved antibody responses after the third dose [18,19]. Similarly, first data after the booster dose in patients with cancer show higher antibody titers, especially in patients with minimal to moderate responses after the second dose [20–22].

However, the existing data are limited by small sample sizes, and large-scale real-life data assessing the immune response after the third dose in patients with haemato-oncological diseases are scarce. Therefore, we aimed to assess clinical factors impacting humoral immune responses after the third SARS-CoV-2 vaccination dose in a large real-life cohort of patients with haemato-oncological malignancies.

2. Materials and methods

2.1. Patient cohorts

In this retrospective cohort study, we included samples from two cohorts of patients with haemato-oncological malignancies undergoing antineoplastic treatment and/or regular follow-up visits as well as from one control group of health care workers (HCWs) as described previously [9]. This study was reviewed and approved by the ethics committees of the Medical University of Vienna (protocol no. 1164/2019, 1296/2020, 1349/2020, 1073/2021) and the Südtiroler Sanitätsbetrieb (South Tyrolean Healthcare Service, amended protocol no. 35/2020, 139/2021). The study has been conducted according to the Declaration of Helsinki, all its later amendments and in compliance with local and institutional guidelines. All individuals provided informed consent prior to study inclusion.

2.1.1. Vienna patient cohort

The Vienna patient cohort includes patients with solid tumours undergoing systemic treatment, who participate in the Biobanking Program at the Division of Oncology, Department of Medicine I (Medical University of Vienna). Regular SARS-CoV-2 testing prior to outpatient visits was performed as previously published and according to institutional practice [23]. Blood samples were stored by the 'MedUni Wien Biobank' facility in accordance with Standard Operating Procedures in an ISO 9001:2015-certified environment [24]. Patients were included if blood samples after the third SARS-CoV-2 vaccination dose were available. Sampling

was performed at 15.5 days after vaccination in the median (range: 1–70). Anti-SARS-CoV-2 nucleocapsid (anti-NC) and anti-SARS-CoV-2 spike protein (anti-S) antibodies were measured using Roche Elecsys assays at the Department of Laboratory Medicine as outlined previously and according to institutional practice [9].

2.1.2. Meran patient cohort

The Meran patient cohort includes patients with haematological diseases and solid tumours who underwent systemic treatment and/or regular follow-up visits between 24/09/2021 and 03/12/2021 at the haemato-oncological day hospital ward of the 'Franz Tappeiner' Hospital in Meran/Merano, Italy. All patients in this cohort received the BNT162b2 vaccine as first, second and third doses. According to national guidelines, the second dose was considered as booster dose in patients with previous SARS-CoV-2 infection. Anti-NC/-S antibodies were measured 21 days after the first dose, while a further analysis was performed 21 days after the second dose in patients who did not show seroconversion (anti-S <50 AU/ml) after the first dose. Moreover, to assess the timely variations of antibody levels, repeated blood sampling at pre-defined timepoints (in median 3, 4.5 and 6 months after the second vaccination) was performed in a longitudinal cohort. Furthermore, lymphocyte subset counts were assessed 6 months after the second vaccination in this cohort. Antibody measurements after the third dose were performed at a median of 18 days (range: 3–66) after vaccination. Anti-NC and anti-S levels were determined using the Abbott SARS-CoV-2 IgG assays on the Abbott Alinity system as published previously [9]. Patient-reported adverse events (AEs) after vaccination were collected using a standardised questionnaire.

2.1.3. HCWs cohort

A cohort of HCWs was included as control group. This cohort included physicians, nurses as well as scientific and administrative staff employed at the Division of Oncology, Department of Medicine I (Medical University of Vienna). Blood biobanking was performed as described previously [9, 25], and antibody levels were measured as outlined for the Vienna patient cohort.

2.2. Statistical analysis

To compare distributions between metric variables, the Mann-Whitney-U, Kruskal–Wallis and Wilcoxon signed-rank tests were used as appropriate, supplemented by non-parametric methods for longitudinal data [26]. A two-sided $p < 0.05$ was considered as a significance threshold. Due to the exploratory and hypothesis-generating design of the present study, no adjustment for multiple testing was applied [27].

Table 1
Baseline characteristics of the patient cohorts.

	Vienna cohort (n = 26)	Meran cohort (n = 413)
Age (median, range)	**63 (28–85)**	**70 (24–90)**
Gender		
- Male	17 (65.4%)	196 (47.5%)
- Female	9 (34.6%)	217 (52.5%)
Solid tumours	**26 (100.0%)**	**240 (58.1%)**
- Lung cancer	6 (23.1%)	32 (13.3%)
- Breast cancer	5 (19.2%)	51 (21.3%)
- Head and neck cancer	3 (11.5%)	1 (0.1%)
- Pancreatic cancer	4 (15.4%)	8 (3.3%)
- Colorectal cancer	0 (0.0%)	29 (12.1%)
- Upper gastrointestinal cancer	3 (11.5%)	10 (4.2%)
- Renal cancer	0 (0.0%)	14 (5.8%)
- Ovarian cancer	0 (0.0%)	22 (9.2%)
- Prostate cancer	0 (0.0%)	31 (12.9%)
- *Other*	*5 (19.2%)*	*42 (17.5%)*
Haematological malignancy		**173 (41.9%)**
- Essential thrombocythemia	–	32 (18.5%)
- Chronic lymphatic leukaemia	–	26 (15.0%)
- Multiple myeloma	–	22 (12.7%)
- Chronic myeloid leukaemia	–	15 (8.7%)
- Polycythemia vera	–	11 (6.4%)
- Follicular lymphoma	–	11 (6.4%)
- Myelodysplastic syndrome	–	11 (6.4%)
- Diffuse large B cell lymphoma	–	10 (5.8%)
- *Other*	–	*35 (20.2%)*
Ongoing treatment		
- Chemotherapy	8 (30.8%)	151 (36.6%)
- Targeted therapy	3 (11.5%)	96 (23.2%)
- Immune checkpoint inhibition (ICI)	8 (30.8%)	32 (7.7%)
- Chemotherapy + targeted therapy	2 (7.7%)	44 (10.7%)
- Chemotherapy + ICI	5 (19.2%)	4 (0.1%)
- No ongoing antineoplastic treatment	0 (0.0%)	58 (14.0%)
- *Other*[a]	*0 (0.0%)*	*28 (6.8%)*
- B cell-targeted agent (rituximab, obinutuzumab, ibrutinib)	**0 (0.0%)**	**39 (9.4%)**
Used vaccine		
- 3x BNT162b2	19 (73.1%)	413 (100.0%)
- 3x mRNA-1273	3 (11.5%)	
- 2x BNT162b2 → 1x mRNA-1273	1 (3.8%)	
- 2x mRNA-1273 → 1x BNT162b2	2 (7.7%)	
- 2x AZD1222 → 1x mRNA-1273	1 (3.8%)	
Confirmed SARS-CoV-2 infections	0 (0.0%)	62 (15.0%)
- Prior to vaccination	–	57 (91.9%)
- Between 1st and 2nd dose	–	2 (3.2%)
- After 3rd dose	–	3 (4.8%)

Statistical analysis was performed using GraphPad Prism 9.3.0 (La Jolla, CA, USA) and R 4.1.2 (The R Project for Statistical Computing, Vienna, Austria) with RStudio 2021.09.1 (RStudio Inc., Boston, MA, USA).

3. Results

3.1. Patients' characteristics

In total, 26 patients were included in Vienna, while 413 patients were enrolled in Meran. In the Vienna cohort, the median age was 63 years (range: 28–85) and all patients were treated for solid tumours. The most frequently applied treatments were chemotherapy and immune checkpoint inhibitors (ICI) in 8/26 (30.8%) patients each.

In the Meran cohort, the median age was 70 years (range: 24–90). Overall, 240/413 (58.1%) patients were diagnosed with a solid tumour, while 173/413 (41.9%) patients with haematological malignancies were included. In Meran, chemotherapy was the most frequently applied treatment modality (151/413, 36.6%), while 39/413 (9.4%) received a B cell-targeted agent. Detailed patient characteristics are given in Table 1.

3.2. Used vaccinations and COVID-19 infections

In Vienna, 19/26 (73.1%) patients received three doses of the BNT162b2 vaccine, while 3/26 (11.5%) were vaccinated three times with mRNA-1273. A heterologous vaccination regimen was applied in 4/26 (15.4%) patients. Of note, there were no documented previous SARS-CoV-2 infections as verified by RT-PCR of respiratory specimens until 30/11/2021 (Table 1).

In Meran, all patients were vaccinated with three doses of the BNT162b2 vaccine. Notably, 62/413 (15.0%) patients had a confirmed SARS-CoV-2 infection; however, 57/62 infections (91.9%) occurred prior to vaccination (Table 1). Still, breakthrough infections could be observed in 5 patients. Two patients with confirmed SARS-CoV-2 infection between the first and second dose had a mild clinical course and could be managed in an outpatient setting. In total, three patients were infected after the third dose (3 days, 3 weeks and 4 weeks after vaccine administration, respectively). One patient suffered from acute myeloid leukaemia and received 5-azacytidine treatment, another individual was under active ibrutinib treatment for CLL. Both were admitted to the hospital but did not need admission to the intensive care unit (ICU). In the third patient, rituximab maintenance therapy due to follicular lymphoma had been stopped 6 months prior to infection. Still, the patient had no detectable SARS-CoV-2 antibodies after vaccination and experienced a severe course with ICU admission.

Bold and italics were used to emphasize important subgroups. Other (in italics) is defined as footnote, B cell-targeted agent is in bold as this is a subgroup where the text repeatedly refers to.

[a] Other including hormonal therapy, intravenous immunoglobulins, radiotherapy and bisphosphonates.

3.3. Humoral immune responses after the third vaccination in patients with cancer

In the Vienna patient cohort, the median anti-S level after the second vaccination was 236 U/ml (range: 0.0–2500 U/ml; below the detection range (0.4 U/ml): 2/24 patients, 8.3%). After the third vaccination, the anti-S concentrations of these patients increased to a median of 2500 U/ml (range: 2–2500 U/ml; <0.4 U/ml: 0/26 patients, 0.0%; $p < 0.001$, Wilcoxon signed-rank test, Fig. 1A).

In the Meran cohort, median anti-S levels after the first vaccination were 222.8 AU/ml (range: 0–40000 AU/ml; <50 AU/ml: 115/411, 28.0%). Sampling after the second vaccination was only performed in patients with anti-S values < 50 AU/ml. Median anti-S level after the second dose reached 48.35 AU/ml (range: 0–40000; <50 AU/ml: 56/112, 50.0%). After the third vaccination, antibody levels increased (median levels 12924 AU/ml, range: 0–40000; <50 AU/ml: 39/413, 9.4%) compared to the first and second dose ($p < 0.001$, Wilcoxon signed-rank test, Fig. 1B). Antibody levels after the third vaccination were lower in patients with haematological malignancies receiving anti-B cell therapies (median: 4 AU/ml, range: 0–40000) than those receiving other treatments (median: 11124 AU/ml, range: 1.7–40000, $p < 0.001$, Mann-Whitney-U) or patients with solid tumours (median: 18624 AU/ml, range: 3.2–40000, $p < 0.001$, Fig. 1C). Of note, 26/39 (66.7%) patients with ongoing anti-B cell treatment did not develop anti-S antibodies, whereas this was the case in 10/134 (7.5%) patients with haematological cancers without anti-B cell therapy and 3/240 (1.3%) patients with solid tumours. In the latter, no difference according to applied treatments could be detected overall ($p = 0.199$, Kruskal Wallis); still, in uncorrected pairwise comparisons, patients receiving chemotherapy had somewhat lower levels (median 13383 AU/ml, range: 32–40000, <50 AU/ml: 1/98, 1.0%) than those with no active antineoplastic treatment (median: 34288 AU/ml, range: 7112–40000, <50 AU/ml: 0/17, 0.0%, $p = 0.022$, Fig. 1D). There were no differences in time between the third vaccination and blood sampling between these subgroups (pairwise $p > 0.999$, Mann-Whitney-U).

3.4. Longitudinal analysis of antibody levels after SARS-CoV-2 vaccination

In 178/413 patients of the Meran cohort, longitudinal measurements of anti-S levels after the second vaccination were performed. Patients' characteristics of this subcohort are given in Supplementary Table 1. In 58/178

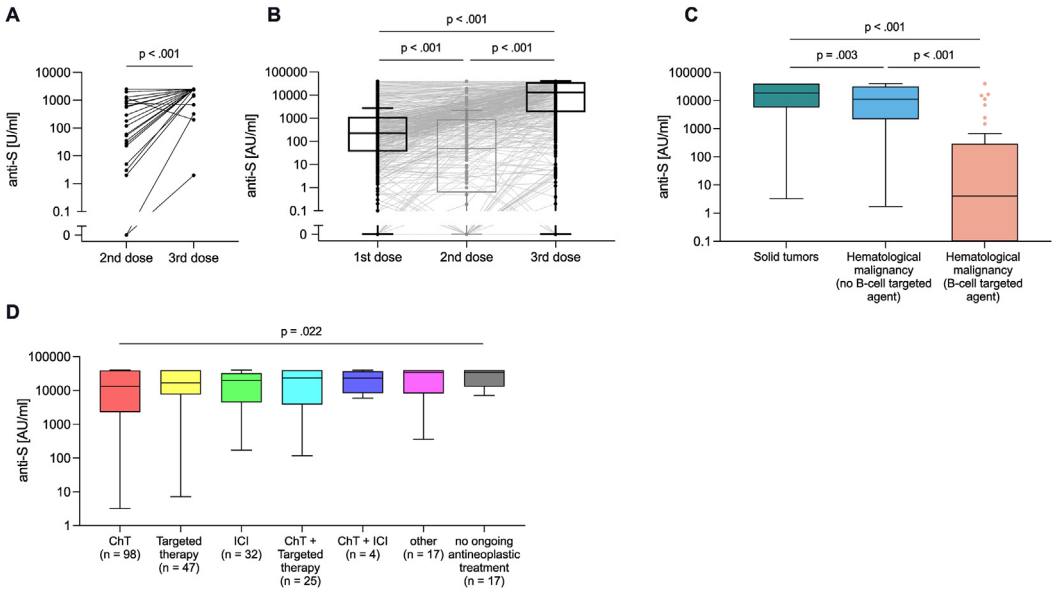

Fig. 1. (**A**) Anti-S levels after the second and third vaccination dose in the Vienna cohort. (**B**) Anti-S levels after the first, second and third vaccination dose in the Meran cohort. Anti-S levels after the second dose were only determined if no seroconversion was seen after the first dose. P-values as determined by Wilcoxon signed-rank test. (**C**) Anti-S levels after the third dose in patients with solid tumours and haematological malignancies with/without B cell-targeted treatment in the Meran cohort. (**D**) Anti-S levels in patients with solid tumours of the Meran cohort according to applied treatment modalities. P-values as determined by Mann-Whitney-U/Kruskal–Wallis test.

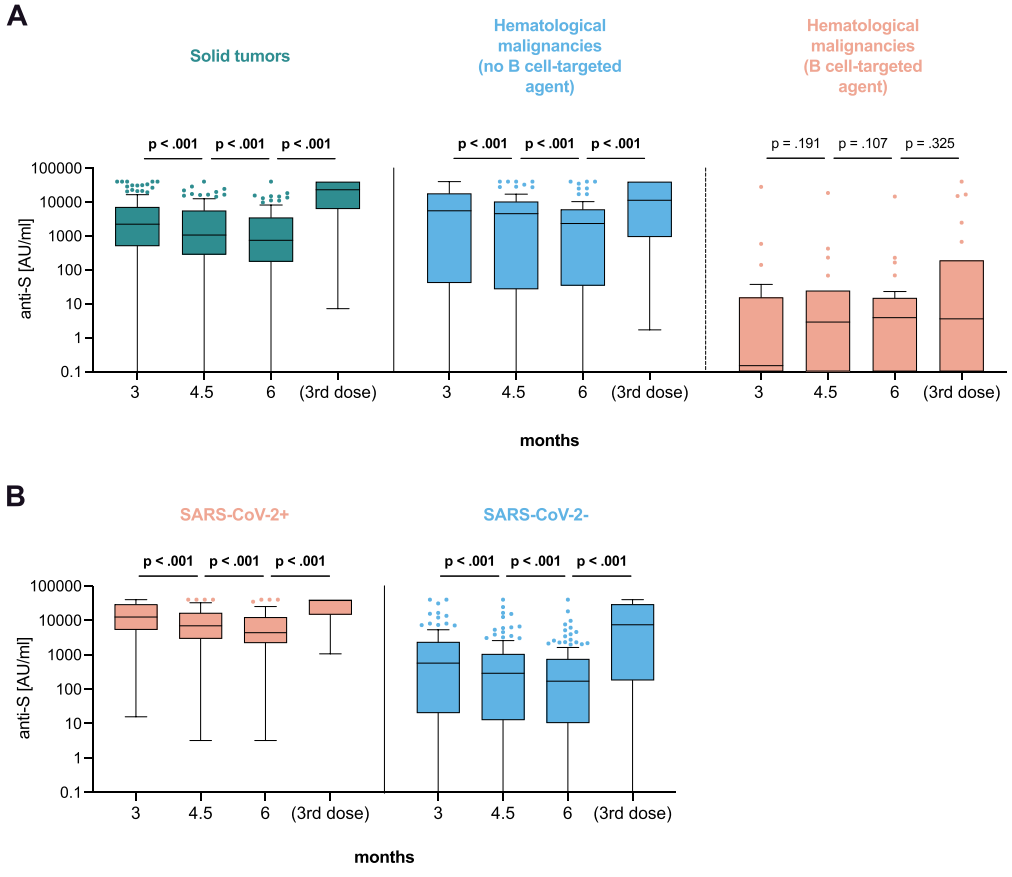

Fig. 2. Anti-S levels 3, 4.5 and 6 months after the second as well as after the third dose in patients with solid tumours and haematological malignancies with/without B cell-targeted therapy (**A**) and patients with/without prior SARS-CoV-2 infection (**B**). P-values as determined by Wilcoxon signed-rank test.

(32.6%) of these patients, a SARS-CoV-2 infection was observed prior to vaccination.

Overall, antibody levels decreased from 3 months to 4.5 and 6 months in the Meran cohort (non-parametric relative effects 0.556, 0.497, 0.464; $p < 0.001$), with time profiles not differing between the cohorts ($p = 0.062$). In patients with solid tumours, antibody levels decreased from 3 months (median 2220 AU/ml, range: 0–40000) to 4.5 (median: 1070, range: 0–40000) and 6 months (median 743.5, range: 0–40000) after the second vaccination ($p < 0.001$, Wilcoxon signed-rank, Fig. 2A). Similarly, in patients with haematological malignancies and no ongoing B cell-targeted treatment, antibody levels decreased (3 months: median 5537 AU/ml, range: 0–40000; 4.5 months: median 4559 AU/ml, range: 0–40000; 6 months: median 2328 AU/ml, range: 0–40000; $p < 0.001$). In contrast, there was no time-dependent change in patients with haematological disease under anti-B cell treatment (3 months: median 0.15 AU/ml, range: 0–28102; 4.5 months: median 2.9 AU/ml, range: 0–18428; 6 months: median 3.9 AU/ml, range: 0–14470; $p > 0.05$) who had lower antibody levels after the second vaccination as reported previously [9]. In these patients, the third vaccination dose did not result in higher antibody levels (median: 3.6 AU/ml, range: 0–40000, $p = 0.325$). In contrast, antibody levels increased in solid tumours (median: 23074 AU/ml, range: 7.2–40000, $p < 0.001$) and haematological patients without B cell-targeted therapy (median: 11261 AU/ml, range: 1.7–39998) after the third vaccination. In both patient cohorts with and without prior SARS-CoV-2 infection, antibody levels decreased over time and increased after the third shot. In addition, patients with prior COVID-19 overall reached higher antibody levels after the third dose (median: 37620.9 AU/ml; range: 1969.6–40000; <50 AU/ml: 0/58, 0.0%) than patients with no documented COVID-19 (median: 7426.95, range: 0–40000; <50 AU/ml: 24/120, 20.0%, Fig. 2B). There was no difference in time between the third vaccination and blood sampling between patients with and without prior COVID-19 ($p = 0.494$, Mann-Whitney-U).

3.5. Correlation of lymphocyte subtype counts with humoral immune responses

In 149/178 (83.7%) patients of the longitudinal cohort, lymphocyte subtype analyses were performed 6 months after the second vaccination dose. Of these patients, 56/149 (37.6%) patients had previously been infected with SARS-CoV-2. These individuals had higher total lymphocyte counts ($p = 0.031$, Mann-Whitney-U) and CD19+ counts ($p < 0.001$) as well as numerically higher CD56+ cell counts ($p = 0.051$) than their counterparts who had not previously been tested positive for SARS-CoV-2 (Fig. 3). Overall, antibody levels 6 months after the second vaccination weakly correlated with CD19+ counts (Spearman's $r = 0.325$, $p < 0.001$) and CD56+ counts (Spearman's $r = 0.220$, $p = 0.008$), as did antibody levels after the third dose (CD19+: $r = 0.288$, $p < 0.001$; CD56+: $r = 0.250$, $p = 0.002$). This association remained significant in patients who were not infected, while there was no correlation in previously infected patients (detailed correlation plots are given in Supplementary Figure 1).

3.6. Reported AEs after SARS-CoV-2 vaccination in patients with cancer

Possibly vaccination-associated AEs were reported in 413 patients of the Meran cohort after the first dose as well as in 361/413 (87.4%) patients after the second

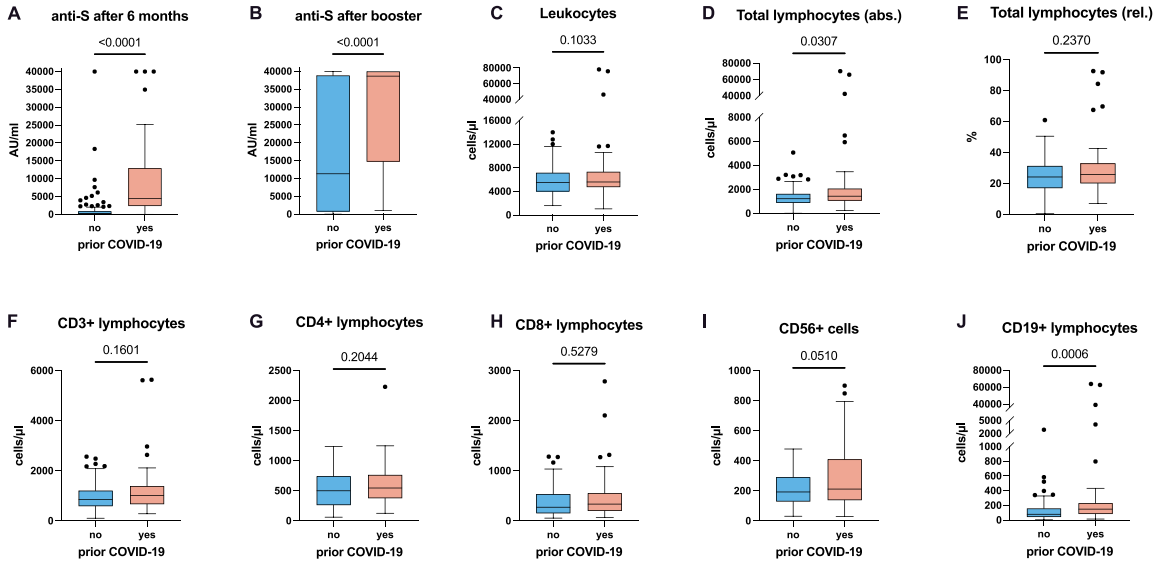

Fig. 3. Anti-S levels 6 months after the 2nd vaccination dose (**A**) and after the 3rd vaccination dose (**B**), as well as total leucocyte (**C**), absolute lymphocyte (**D**), relative lymphocyte (**E**), CD3+ (**F**), CD4+ (**G**), CD8+ (**H**), CD56+ (**I**) and CD19+ (**J**) cell counts.

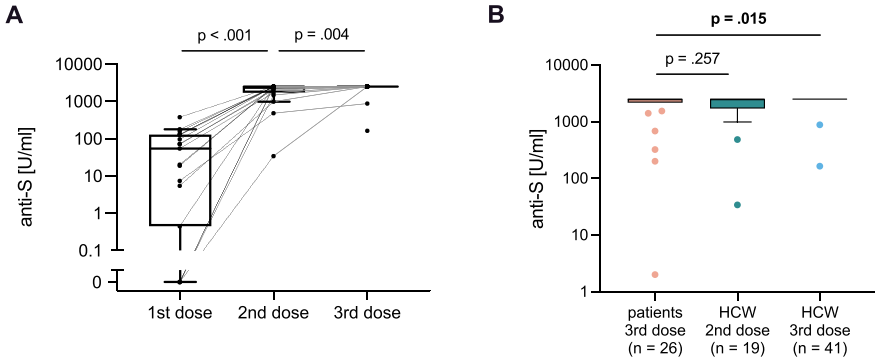

Fig. 4. (**A**) Anti-S levels in HCWs after the first, second and third dose. P-values as determined by Wilcoxon signed-rank test. (**B**) Anti-S levels in HCWs and patients with cancer after the second/third dose. P-values as determined by Mann-Whitney-U test.

and 160/461 (34.7%) patients after the third dose. Higher-grade AEs were overall rare, with only 9 Grade 3 AE after the first, 6 Grade 3 AE after the second and 5 Grade 3 AE after the third dose. Most patients experienced local pain after the first (Grade 1–3: 150/413, 36.3%), second (131/361, 36.3%) and third (75/160, 46.9%) dose, followed by fatigue (first dose: 60/413, 14.5%; second dose: 52/361, 14.4%; third dose: 25/160, 15.6%) and myalgia (first dose: 20/413, 4.8%, second dose: 28/361, 7.8%, third dose: 13/160, 8.1%). Further details on reported AEs are given in Table 2.

3.7. Humoral immune responses after the third vaccination in patients with cancer versus HCW

In the HCW cohort, 41 samples after the third vaccination dose were available, with full longitudinal follow-up after all vaccination doses in 19 HCWs. Baseline characteristics of the HCW cohort are given in Supplementary Table 2. One confirmed SARS-CoV-2 infection was reported, 2/41 (4.9%) HCW had anti-NC antibodies without a positive SARS-CoV-2 RT-PCR.

In HCW, antibody levels increased between the first (median: 54.2 U/ml, range: 0–376, <0.4 U/ml: 4/19, 21.1%) and second (median: 2500 U/ml, range: 34.1–2500, <0.4 U/ml: 0/19, 0.0%; $p < 0.001$) as well as between the second and third (median: 2500 U/ml, range: 164–2500, <0.4 U/ml: 0/41, 0.0%; $p = 0.004$) vaccination dose (Fig. 4A).

Due to different assays used in Vienna and Meran, a comparison between patients with cancer and HCW as control group was only feasible in the Vienna cohort. Notably, patients with cancer had lower anti-S levels after the third dose (median: 2500 U/ml, range: 2–2500, <0.4 U/ml: 0/26, 0.0%) as compared to HCW (median: 2500, range: 164–2500, <0.4 U/ml: 0/41, 0.0%; $p = 0.015$). Indeed, antibody levels in patients after the third dose were comparable with those in HCW after the second dose (median: 2500 U/ml, range: 34.1–2500, <0.4 U/ml: 0/19, $p = 0.257$, Fig. 4B). However, blood sampling was performed somewhat later in HCW (median: 22 days, range: 15–62) than in patients with cancer (median: 15.5 days, range: 1–70; $p = 0.01$, Mann-Whitney-U).

4. Discussion

Previous research has shown that patients with cancer show immune responses after the first and second SARS-CoV-2 vaccination doses, albeit to a lesser extent than healthy individuals [9–14]. However, with the emergence of novel SARS-CoV-2 variants such as the recent B.1.1.529 ('Omikron') variant, the efficacy of the available vaccines may be further impaired [28,29]. Early reports suggest that three doses of the BNT162b2 vaccine result in sufficient amounts of antibodies neutralising the B.1.1.529 variant, whereas levels of these antibodies are markedly lower in individuals who had only received two doses [29,30]. These results underscore the importance of a third 'booster' vaccination dose. However, respective data after the third dose are limited in immunosuppressed patients such as those undergoing cancer treatments.

Here, we show in one of the largest published cohorts so far that anti-S levels increased after the third vaccination in patients with cancer. These results are in line with recent publications of smaller cohorts, where a meaningfully strengthened humoral immune response after the third vaccination dose was suggested [20–22,31,32]. However, and in accordance with other published data, patients with haemato-oncological diseases still show lower antibody levels than controls [20]. In fact, antibody concentrations after the third dose in our cohort of patients with cancer were comparable to those after the second vaccination in the HCW control group. Further follow-up studies will be needed to evaluate whether the administration of additional vaccination doses will be necessary in the further course of the pandemic, especially in immunocompromised patients at high risk for severe clinical courses of COVID-19.

Once again, haematological patients receiving anti-B cell therapies showed impaired humoral immune responses compared to patients undergoing other treatment modalities. This is particularly concerning as one

Table 2
Reported possibly vaccination-related adverse events in patients with cancer.

	First dose (n = 413)			Second dose (n = 361)			Third dose (n = 160)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Local pain	141 (34.1%)	16 (3.9%)	3 (0.7%)	120 (33.2%)	10 (2.8%)	1 (0.3%)	69 (43.1%)	5 (3.1%)	1 (0.6%)
Local redness	12 (2.9%)	1 (0.2%)	1 (0.2%)	6 (1.7%)	1 (0.3%)	0 (0.0%)	5 (3.1%)	1 (0.6%)	0 (0.0%)
Local swelling	16 (3.9%)	1 (0.2%)	0 (0.0%)	8 (2.2%)	1 (0.3%)	0 (0.0%)	4 (2.5%)	1 (0.6%)	0 (0.0%)
Local itching	9 (2.2%)	0 (0.0%)	0 (0.0%)	4 (1.1%)	0 (0.0%)	0 (0.0%)	3 (1.9%)	0 (0.0%)	0 (0.0%)
Allergic reaction	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fever/chills	13 (3.1%)	1 (0.2%)	0 (0.0%)	25 (6.9%)	2 (0.6%)	2 (0.6%)	14 (8.8%)	2 (1.3%)	0 (0.0%)
Flushing	6 (1.4%)	2 (0.5%)	0 (0.0%)	5 (1.4%)	3 (0.8%)	0 (0.0%)	3 (1.9%)	1 (0.6%)	0 (0.0%)
Dizziness	10 (2.4%)	3 (0.7%)	0 (0.0%)	4 (1.1%)	2 (0.6%)	0 (0.0%)	3 (1.9%)	1 (0.6%)	0 (0.0%)
Fatigue	54 (13.1%)	4 (1.0%)	2 (0.5%)	48 (13.3%)	3 (0.8%)	1 (0.3%)	21 (13.1%)	2 (1.3%)	2 (1.3%)
Insomnia	8 (1.9%)	1 (0.2%)	0 (0.0%)	3 (0.8%)	1 (0.3%)	0 (0.0%)	3 (1.9%)	1 (0.6%)	0 (0.0%)
Sweating	7 (1.7%)	1 (0.2%)	0 (0.0%)	5 (1.4%)	1 (0.3%)	0 (0.0%)	5 (3.1%)	0 (0.0%)	0 (0.0%)
Rash	1 (0.2%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sore throat	3 (0.7%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Headache	21 (5.1%)	8 (1.9%)	1 (0.2%)	18 (5.0%)	4 (1.1%)	1 (0.3%)	6 (3.8%)	3 (1.9%)	1 (0.6%)
Myalgia	17 (4.1%)	3 (0.7%)	0 (0.0%)	22 (6.1%)	6 (1.7%)	0 (0.0%)	10 (6.3%)	3 (1.9%)	0 (0.0%)
Arthralgia	17 (4.1%)	0 (0.0%)	0 (0.0%)	8 (2.2%)	12 (3.3%)	0 (0.0%)	9 (5.6%)	1 (0.6%)	0 (0.0%)
Lymphadenopathy	3 (0.7%)	1 (0.2%)	0 (0.0%)	4 (1.1%)	0 (0.0%)	0 (0.0%)	2 (1.3%)	0 (0.0%)	0 (0.0%)
Decreased appetite	9 (2.2%)	0 (0.0%)	0 (0.0%)	10 (2.8%)	0 (0.0%)	0 (0.0%)	4 (2.5%)	0 (0.0%)	0 (0.0%)
Nausea	6 (1.4%)	2 (0.5%)	0 (0.0%)	5 (1.4%)	2 (0.5%)	0 (0.0%)	3 (1.9%)	0 (0.0%)	0 (0.0%)
Diarrhea	3 (0.7%)	0 (0.0%)	1 (0.2%)	3 (0.8%)	0 (0.0%)	1 (0.3%)	4 (2.5%)	0 (0.0%)	1 (0.6%)
Cough	1 (0.2%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	0 (0.0%)	0 (0.0%)	2 (1.3%)	0 (0.0%)	0 (0.0%)
Dyspnea	1 (0.2%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Chest pain	3 (0.7%)	0 (0.0%)	1 (0.24%)	2 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.6%)	0 (0.0%)
Tachycardia	5 (1.2%)	1 (0.2%)	0 (0.0%)	2 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anosmia	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypesthesia	2 (0.5%)	0 (0.0%)	0 (0.0%)	2 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)

patient in our study experienced a breakthrough infection with severe course and ICU admission 6 months after prior rituximab treatment for follicular lymphoma. Of note, no anti-S antibodies were observed in this patient after the third vaccination. Still, cellular immunity may be preserved in many of these patients receiving anti-B cell agents. Reassuringly, previous reports have shown that T cell priming and reactivity are still preserved in patients with rheumatic diseases or multiple sclerosis [33,34]. In a recent publication, the correlation between neutralising antibodies and spike protein-specific T cell responses was weak in patients with cancer, indicating that cellular immunity against SARS-CoV-2 may mount independently from humoral immune responses [20]. In addition, a correlation between cellular immunity and disease severity was postulated in individuals who recovered from COVID-19 [35]. These results suggest that patients under anti-CD20 treatment may still be protected to some extent from severe courses of COVID-19, even if SARS-CoV-2 infection *per se* cannot be prevented in the absence of neutralising antibodies. Moreover, although our data and a previously published report [36] showed that antibody levels diminished in the months after the second dose in patients with cancer, data from other vaccinations imply that vaccination-specific memory T cells may persist for decades after immunisation [37]. Along these lines, a long-acting monoclonal antibody was recently approved for the use as pre-exposure prophylaxis in patients with compromised immune systems due to immunosuppressive medications who are not able to mount an adequate immune response to the COVID-19 vaccination [38]. Further monoclonal antibodies for post-exposure prophylaxis and early outpatient treatment in patients with risk factors have been studied [39,40].

Notably, we found correlations between antibody levels and lymphocyte subset counts, specifically CD19+ B cells and CD56+ natural killer (NK) cells. In line, patients with prior SARS-CoV-2 infection (and subsequently higher antibody levels) had higher B cell and NK cell counts. Still, the correlation of CD19+ and CD56+ cell counts with antibody levels remained also significant in patients who had not been infected. These data confirm previous findings where a link between CD56+ NK cell counts and immune responses towards mRNA-based vaccines has been postulated [41,42]. However, the underlying immunological mechanisms remain elusive and further investigations including antigen-specific T cell assays would be needed to obtain deeper insights into vaccination-induced immunity in patients with cancer.

In our cohorts, 14% of the included patients were infected before vaccination, while breakthrough infections were seen in only ~1%. Although the inferences of our retrospective observations on vaccine efficacy have to be taken cautiously, these data underline that the combination of SARS-CoV-2 vaccination with general protective measures (including personal, institutional and governmental safety measures [23,43]) helps to limit

uncontrolled viral spread in patients with cancer. To add further, AE rates after vaccine administration in our cohort were comparable to those observed in the general population [7]. Overall, our data corroborate the favourable safety profile of the available vaccines in patients with haemato-oncological diseases, confirming the beneficial risk-benefit ratio of SARS-CoV-2 vaccination.

4.1. Limitations

Clearly, our study has important limitations. As in our previous report [9], pooled analyses between both patient cohorts were not feasible due to different assays used in both centres. Again, only patients who were seronegative after the first dose underwent antibody measurements after the second dose in the Meran cohort. Consequently, the increase in antibody levels between the second and third cohort could not be evaluated in all patients. Moreover, anti-S antibody levels are a mere surrogate parameter for humoral immunity, whereas a further investigation on the levels of neutralising antibodies could more precisely reflect the actual anti-SARS-CoV-2 immune responses, especially in the light of emerging virus variants potentially hampering vaccination-induced immunity. In addition, further studies on cellular immune responses could provide a more comprehensive picture on immune responses after vaccination, particularly in patients undergoing anti-B cell therapies. Furthermore, differences in national vaccination regulations between Austria and Italy limit the comparability of both cohorts. While the administration of the third dose is endorsed in both countries, these recommendations were issued earlier in Austria than in Italy, and current or future vaccination mandates may impact the vaccination behaviour of the general population and patients with cancer. Lastly, our study has the inherent shortcomings of a retrospective real-life study such as incompleteness of data and heterogeneous cohorts. In line, the validity of data on possibly vaccination-induced AEs as collected by a questionnaire is limited by a reporting bias.

5. Conclusion

Taken together, our real-life data support the timely administration of the third SARS-CoV-2 vaccination dose in patients with cancer. Our results based on two independent cohorts of patients with haemato-oncological malignancies treated at an academic tertiary care centre in Austria and a communal hospital in a rural area in Italy show that antibody levels considerably increase after the third vaccination dose. Moreover, our data suggest that humoral immune responses do not only correlate with CD19+ (B cell) but also CD56+ (NK cell) counts in peripheral blood. The combination of diminishing antibody levels in the months following the second vaccination and the emergence of viral variants further underscores the necessity of a 'booster' dose in this vulnerable cohort. As antibody levels are still lower than controls and particularly low in specific subgroups such as patients receiving anti-B cell therapies, dedicated trials on SARS-CoV-2 vaccinations and, potentially, additional vaccination doses will be needed.

Authors contributions

Contribution to study design and its implementation: MJM, JMB, MM, MG, ACB, WT, ASB, TP, HH, WWL, MR, ST, TF, TB, DF, MP; data analysis and interpretation: MJM, JMB, MM, MG, ACB, TT, DF, MP; Manuscript writing and editing: MJM, JMB, MM, MP. All authors read and approved the final version of the manuscript. MJM and JMB as well as DF and MP contributed equally and should be regarded co-first/co-last authors.

Access to data statement

MJM and MP had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical approval

This study was approved by the ethics committee of the Medical University of Vienna (protocol no. 1164/2019, 1296/2020, 1349/2020 and 1073/2021) and the Südtiroler Sanitätsbetrieb (South Tyrolean Healthcare Service, amended protocol no. 35–2020, 139/2021).

Data availability

Data are available from the corresponding author/lead contact (Matthias Preusser, matthias.preusser@meduniwien.ac.at) upon reasonable request and necessary regulatory approvals.

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Conflict of interest statement

Anna Sophie Berghoff has received research support from Daiichi Sankyo, Roche, and honoraria for

lectures, consultation or advisory board participation from Roche, Bristol-Meyers Squibb, Merck, Daiichi Sankyo as well as travel support from Roche, Amgen and AbbVie.

Thorsten Fuereder has received honoraria for lectures, consultation or advisory board participation from the following for-profit companies: MSD, Merck Darmstadt, Roche, Bristol-Myers Squibb, Accord, Sanofi, Boehringer Ingelheim as well as travel support from Roche, MSD and Bristol-Myers Squibb. The following for-profit companies have supported clinical trials and contracted research conducted by TF with payments made to his institution: MSD, Merck Darmstadt, Bristol-Myers Squibb.

Matthias Preusser has received honoraria for lectures, consultation or advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen. The following for-profit companies have supported clinical trials and contracted research conducted by MP with payments made to his institution: Boehringer-Ingelheim, Bristol-Myers Squibb, Roche, Daiichi Sankyo, Merck Sharp & Dome, Novocure, GlaxoSmithKline, AbbVie.

All other authors declare that they have no conflict of interest related to the present study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.01.019.

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