



Antibody Responses to COVID-19 Vaccination in Cancer: A Systematic Review

Deniz C. Guven¹, Taha K. Sahin², Saadettin Kilickap^{1,3} and Fatih M. Uckun^{4,5*}

¹ Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Turkey, ² Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey, ³ Department of Medical Oncology, Istinye University, Istanbul, Turkey, ⁴ Department of Immunology and Inflammatory Disorders, Reven Pharmaceuticals, Westminster, CO, United States, ⁵ Immuno-Oncology Program and COVID-19 Task Force, Ares Pharmaceuticals, St. Paul, MN, United States

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*Correspondence:

Fatih M. Uckun
fatih.uckun@reven.com

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Introduction: After the results of phase III vaccine studies became available, the leading oncology societies recommended two doses of COVID-19 vaccination to all patients with cancer with no specific recommendation for tumor type and active treatments. However, the data on the COVID-19 vaccine efficacy in cancer patients is limited due to exclusion of cancer patients from most vaccine clinical trials. Therefore, we systemically reviewed the available evidence evaluating the antibody responses in cancer patients.

Methods: We conducted a systematic search from the Pubmed database and calculated risk differences (RD) and 95% confidence intervals (CI) to compare seroconversion rates between cancer patients and controls using the Review Manager software, version 5.3.

Results: Our systematic search retrieved a total 27 studies and we included 17 studies with control arms in the analyses. Cancer patients had significantly lower seroconversion rates (37.3%) than controls (74.1%) (RD: -0.44, 95% CI: -0.52, -0.35, $p < 0.001$) with first vaccine dose. After two doses, the seroconversion rates were 99.6% in control arm and 78.3% in cancer patients (RD: -0.19, 95% CI: -0.28, -0.10, $p < 0.001$). The difference in seroconversion rates was more pronounced patients with hematologic malignancies (72.6%) (RD: -0.25, 95% CI: -0.27, -0.22, $p < 0.001$) than patients with solid tumors (91.6%) (RD: -0.09, 95% CI: -0.13, -0.04, $p < 0.003$) and patients in remission (RD: -0.10, 95% CI: -0.14, -0.06, $p < 0.001$).

Conclusion: In conclusion, COVID-19 vaccine seroconversion rates were significantly lower in patients with hematological malignancies and patients under active treatment. Further research focusing on the approaches to improve vaccine efficacy and exploration of novel treatment options is urgently needed for these patients.

Keywords: COVID-19, vaccination, seroconversion, cancer, antibody

INTRODUCTION

The COVID-19 pandemic stormed the World in the last two years and caused more than four million deaths (1). Patients with cancer are among the most susceptible populations for high morbidity and mortality with COVID-19 disease (2). The increased mortality risk was especially prominent in patients with hematologic cancers, patients under active chemotherapy, and advanced age patients with additional comorbidities (3–5). The elements of the adaptive immune system, including B-cells, CD4+ T cells (especially T helper cells) and CD8+ T cells, play pivotal roles for the course, severity and health outcomes in patients with COVID-19 (6) and perturbations of the adaptive immunity have been implicated for the adverse outcomes in cancer patients with COVID-19 (7–10).

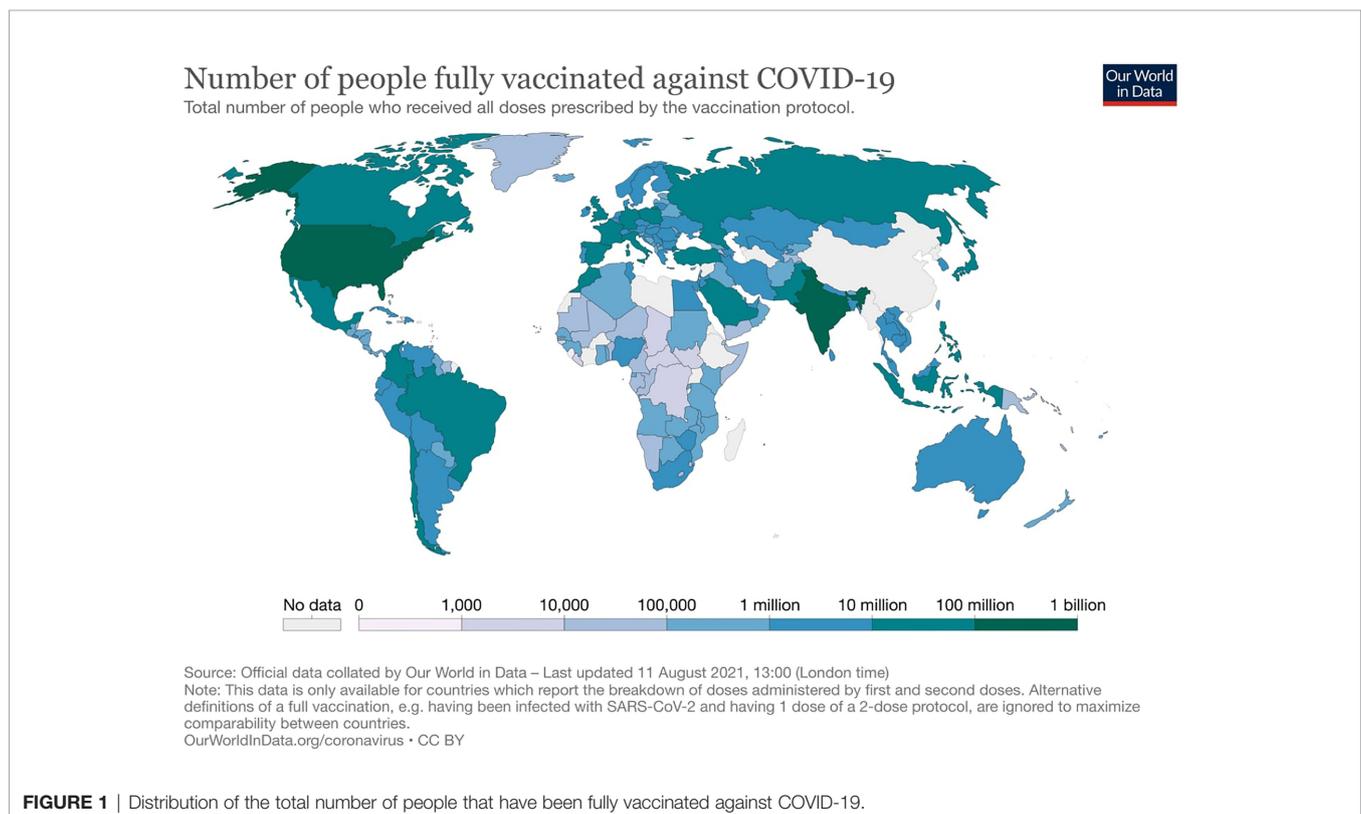
The protection of patients with cancer from COVID-19 disease while continuing optimal cancer care has been an ongoing challenge during the pandemic (11). Hopefully, the vaccination against SARS-CoV-2 showed the light at the end of the tunnel. Several vaccines, including the Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273), exhibited safety and efficacy in large phase II and III clinical trials and received emergency approval by regulatory agencies (12–14). Almost all vaccines generated more than 90% antibody response rates and over 80% prevention rates from severe COVID-19 infection (12–14). These studies provided the foundation of a worldwide mass vaccination campaign, and to date, more than four billion doses of COVID-19 vaccines have been administered (15, 16) (**Figure 1**).

Higher case fatality rates and increased morbidity in cancer patients prompted the leading oncology groups to recommend that cancer patients should receive full COVID-19 vaccination with two doses where applicable (17, 18). However, the data on the vaccine efficacy is limited due to exclusion of cancer patients from most COVID-19 vaccine clinical trials (19). Both cancer and anti-cancer treatments challenge the proper functioning of adaptive immune machinery and could complicate the efficacy of vaccines (20). The previous experience with the influenza vaccination (21) and early reports with SARS-COV-2 vaccines (22) pointed out a decreased vaccine efficacy in patients with cancer due to both cancer and treatment-induced immunosuppression albeit with heterogeneous study populations and limited sample sizes. From these points, we systemically reviewed the available evidence of antibody responses and affecting factors for cancer patients following COVID-19 vaccination.

METHODS

Literature Search

We conducted a systematic review from the Pubmed database per the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidance (23). The MeSH search terms were “vaccine” OR “vaccination” AND “cancer” OR “malignancy” OR “lymphoma” OR “leukemia” OR “myeloma”. The search was limited to studies published between April 1st 2021 and July 26th 2021. We included the original research evaluating the seroconversion rates with



SARS-COV-2 vaccines in patients with cancer and excluded reviews, opinion papers, and commentaries.

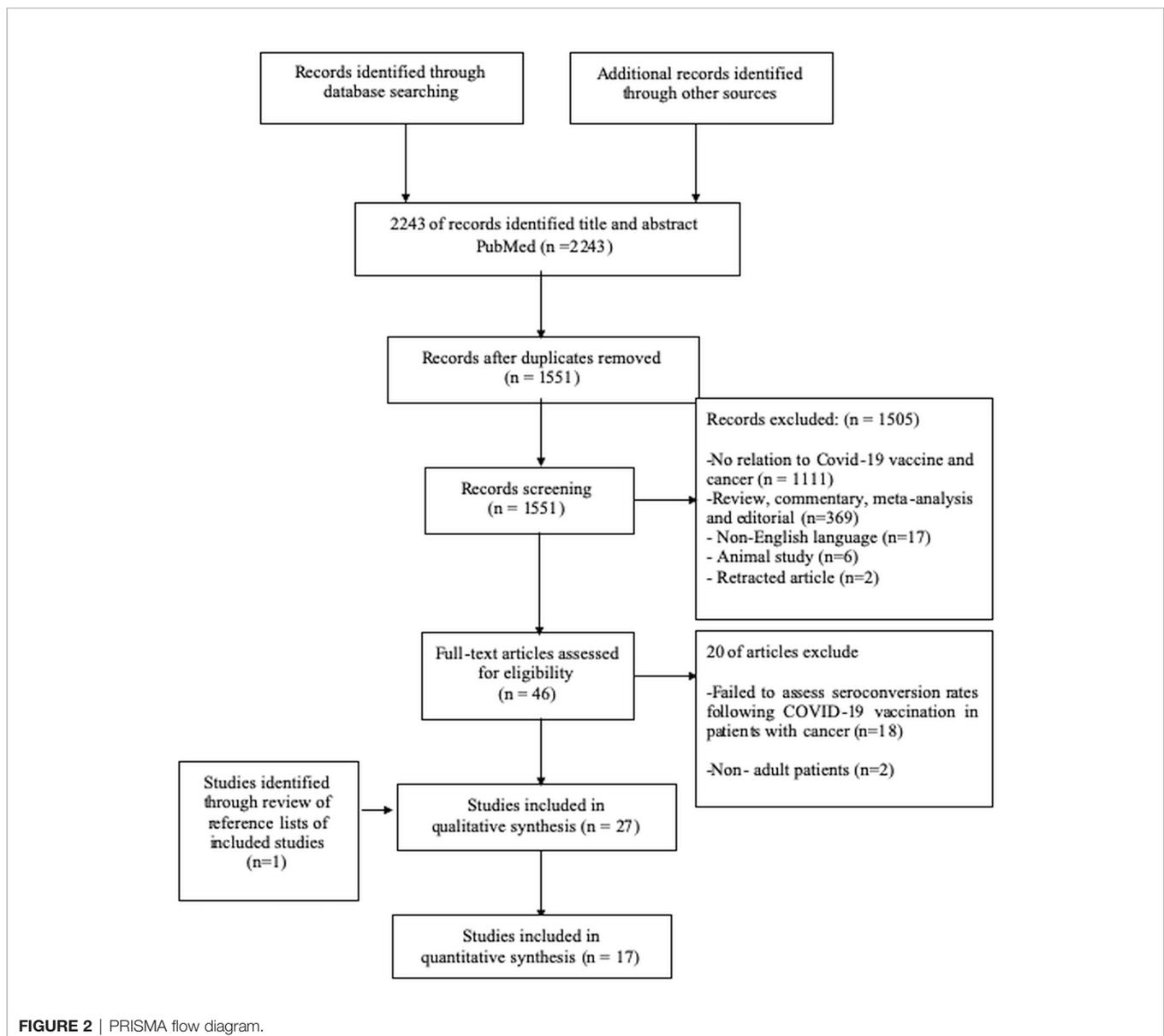
Study Selection and Data Extraction

Our systematic search retrieved a total of 2243 records. After removing duplications (n=692), we screened the remaining 1551 articles. We excluded the 1505 records due to irrelevance (n=1111), reviews, commentaries, and meta-analyses (n=369), articles not in the English language (n=17), animal studies (n=6), and retracted articles (n=2). We further evaluated the remaining 46 articles and excluded 20 more records with absent details on seroconversion rates following COVID-19 vaccination in patients with cancer (n=18) and studies including pediatric patients (n=2) and included 26 records in review. One additional study was added to review from the reference lists of included studies making a total of 27 studies included in the

systematic review. 17 studies with control arms were included in the quantitative synthesis (Figure 2).

Meta-Analysis

We conducted separate meta-analyses to compare seroconversion rates in cancer patients and healthy controls vaccinated with one or two vaccine doses. Additionally, we conducted subgroup analyses for the malignancy type (hematologic vs. non-hematologic) and status of therapy (ongoing active treatment vs. remission off therapy). Two authors (DCG and TKS) independently reviewed and extracted the available data for the meta-analyses, and any disagreements were resolved by the senior authors (SK, FMU). We included the studies reporting seroconversion rates in the meta-analyses, while the studies with missing data for these outcomes and studies using different outcomes (i.e., antibody titers only) were excluded from the meta-analyses.



We recorded lead author names, journals, the total number of patients, seroconversion rates after one or two vaccines for each study. The risk of bias and individual study qualities was assessed independently by the DCG and TKS with Newcastle-Ottawa Scale (NOS) (Table 1). We performed the meta-analysis using the generic inverse-variance method with a random-effects model considering the significant heterogeneity between the studies. We selected principal summary measure as the risk differences with 95% two-sided confidence intervals to better delineate the seronegativity risk for individual patients and to prevent overestimation of seronegativity risk in cancer patients due to almost 100% seropositivity with vaccines in healthy controls. All analyses were done using the Review Manager software, version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). The heterogeneity within each subgroup is reported using the I-square statistics. The p values below 0.05 were considered statistically significant.

RESULTS

Study Characteristics

A total of 27 studies evaluated the seroconversion rates after at least one dose of a COVID-19 vaccine. The sample sizes were very variable (minimum 16- maximum 423). Most studies (18/27) included a control group which involved mostly health care workers. Seven studies included only patients with solid tumors (22, 25, 27, 32, 34, 36, 39), four studies included both solid tumor patients and patients with hematologic malignancies (28, 33, 40, 41) and 16 studies included only patients with hematologic malignancies (24, 26, 29–31, 35, 37, 38, 42–49). Nine studies included both patients in remission and patients under active treatment. Twelve studies measured baseline anti-SARS-CoV-2 antibodies and excluded patients with positive baseline antibody titers (27–30, 33, 37–39, 41, 44, 48, 49). Eight studies used only previous COVID-19 history as the exclusion criteria (24, 25, 31, 34–

36, 43, 46) and 4 studies included patients with previous COVID-19 history (22, 26, 40, 42). The antibody measurement methods were very heterogeneous between the studies and immunoglobulin G (IgG) antibodies against the SARS-CoV-2 spike protein were the most commonly used antibody assay (Table 2).

Seroconversion Rates After First Vaccination

Seroconversion rates after the first dose of vaccination and second dose of vaccination were reported in 17 studies each. Seven studies reported seroconversion rates after both the first and second vaccine doses (27–29, 32–34, 41). Low seroconversion rates after the first vaccine dose were consistent across all studies, and the reported seroconversion rates were only around 20–30% for patients with lymphoid malignancies (Table 2). After the first vaccine dose, the seroconversion rates were quite variable in patients with solid tumors and ranged between 29% to 83%. After the first dose of vaccination, the seroconversion rates of control groups were over 90% in all but 4 studies. The 4 studies with lower seroconversion rates in the control group after the first vaccine dose used mostly octogenarians as control group (29, 36, 38). In the pooled data from 9 studies with control arms, the possibility of seroconversion was significantly lower in cancer patients (268/719, 37.3%) than healthy controls (890/1201, 74.1%) after first dose of vaccination (RD: -0.44%, 95% CI: -0.52%, -0.35%, $p < 0.001$) (Figure 3). Significant variability existed among the studies ($I^2 = 75\%$) (Figure 3). Six studies included only patients vaccinated with the BNT162b2 vaccine, while two studies included both the BNT162b2 or AZD1222 vaccines (35, 37) and one study included patients vaccinated with either of the mRNA vaccines (BNT162b2 and mRNA-1273) and AZD1222 vaccine (36). Further analyses with the exclusion of studies including vaccines other mRNA vaccines (seven studies), demonstrated a consistent risk of seronegativity in cancer patients compared to controls (RD: -0.45%, 95% CI: -0.58%, -0.33%, $p < 0.001$) (Supplement). Similarly, in the pooled analyses of three studies (35–37) including both mRNA and

TABLE 1 | Newcastle-ottawa scores of included studies.

Author, year	Selection	Comparability	Exposure/Outcome	Reference
Herishanu Y, Blood	***	**	***	(24)
Massarweh A, JAMA Oncol	****	**	***	(25)
Palich R, Ann Onc	***	**	***	(22)
Oekelen OV, Cancer Cell	**	**	**	(26)
Barrière J, Ann Onc	**	**	**	(27)
Monin L, Lancet Oncol	****	**	***	(28)
Pimpinell F, J Hematol Oncol	***	**	**	(29)
Avivi I, Br J Haematol	****	**	***	(30)
Tzarfati KH, Am J Hematol	****	**	***	(31)
Shroff RT, MedRxiv	****	**	***	(32)
Addeo A, Cancer Cell	***	*	**	(33)
Goshen-Lago T, Jama Oncol	****	**	***	(34)
Palich R, Ann Onc 2	***	**	**	(22)
Gavriatopoulou M, Clin Exp Med	****	**	***	(35)
Terpos E, Journal of Hematology & Oncology	***	**	**	(36)
Chowdhury O, Br J Haematol	**	**	***	(37)
Terpos E, Blood	***	**	***	(38)

The stars refer to the scores.

TABLE 2 | Summary of studies evaluating antibody responses to SARS-CoV-2 vaccination.

Lead Author, Journal	Patient Cohort	Healthy Control	Number of Participants	Baseline Antibody Measurement	Antibody Assay	Platform	Vaccine	Seroconversion Rate After 1st Dose	Seroconversion Rate After 2nd Dose	Seroconversion Rate of Control Group	Additional Findings	Reference
Massarweh A, JAMA Oncol	Solid Tumors	Y	102 Patient/78 Control	N/A (No History of COVID-19)	SARS-CoV-2 IgG II Quant assay	Abbott (architect i2000sr platform)	BNT162b2	N/A	90%	100%	Lower antibody titers in patients treated with chemotherapy plus immunotherapy (p=0.001)	(25)
Herishanu Y, Blood	CLL	Y	167 Patients (52 Patient and 52 Control for Matched Cohort)	N/A (No History of COVID-19)	Anti-SARS-CoV-2 S	Elecsys (Analyzer: Cobas E 601)	BNT162b2	N/A	39.5%	100%	Lower seroconversion in patients under treatment (16%) vs. patients with clinical remission (79.2%) and treatment-naïve patients (55.2%)/No seroconversion in patients exposed to anti-CD20 treatment in last 12 months (0/22)	(24)
Palich R, Ann Onc	Solid Tumors	Y	110 Patients/25 Controls	N/A (Prior COVID-19 infection in 15 patients as evidenced by positive anti-N IgG)	Serum anti-N IgG and anti-S IgG	Abbott	BNT162b2	55%	N/A	100% after 1 st dose	Lower seropositivity in >65 years (OR: 3.58, 95% CI: 1.40-9.15, p=0.008), and treatment with chemotherapy (OR: 4.34, 95% CI: 1.67-11.30, p=0.003)	(22)
Palich R, Ann Onc	Solid Tumors	Y	223 Patient/49 Control	Negative anti-SARS-CoV-2 anti-nucleoprotein IgG	SARS-CoV-2 immunoglobulin (Ig) G/ SARS-CoV-2 total Ig electrochemiluminescent immunoassay	Abbott Alinity/Roche Elecsys	BNT162b2	N/A	94%	100%	8/13 of the seronegative patients had metastatic disease and 10/13 seronegative patients were treated with chemotherapy	(39)
Barrière J, Ann Onc	Solid Tumors	Y	122 Patients/31 Controls	Negative SARS-CoV-2 S	Anti-SARS-CoV-2 S	Elecsys	BNT162b2	47.5%	95.2%	100%	Patients under active CT lower seroconversion rates after first-dose compared to patients without CT, and patients under targeted therapy alone (42.9% vs. 76.5%, p=0.016)	(27)
Goshen-Lago T, Jama Oncol	Solid Tumors	Y	232 Patients/261 Controls	N/A (No History of COVID-19)	SARS-CoV-2 anti-spike (S) S1/S2 IgG assay	Liaison [®] analyzer	BNT162b2	29%	86%	84% after 1 st dose	Low rates of seropositivity in patients undergoing chemotherapy (OR: 0.41, 95%CI: 0.17-0.98)/Low rate of systemic adverse events	(34)
Shroff RT, medRxiv	Solid Tumors	Y	52 Patients/50 Controls	Neutralizing antibodies (WA1 isolate)	Neutralizing antibodies (WA1 isolate)	ImmunoSpot Versa	BNT162b2	67%	80%	98% after 1 st dose/ 100% after 2 nd dose	Lower overall antibody and T cell responses in cancer cohort compared with control cohorts	(32)
Terpos E, J Hematol Oncol	Cancer patients receiving checkpoint inhibitors	Y	59 Patients/283 Controls	N/A (No History of COVID-19)	Neutralizing antibodies (SARS-CoV-2 NAb Detection Kit)	cPass [™]	BNT162b2 and mRNA-1273	25%	N/A	65.7	None of the patients enrolled had neutropenia or lymphopenia at first vaccination dose	(36)
Addeo A, Cancer Cell	Solid/ Hematologic Malignancies	N	131	Negative anti-SARS-CoV-2 nucleocapsid protein IgG	Anti-SARS-CoV-2 S	Elecsys	BNT162b2 and mRNA-1273	83% in solid tumors/77% in hematological tumors	94%	N/A	Lower seroconversion in hematological malignancy (77% vs. 98%)/Lower seroconversion in patients treated with chemotherapy or immunotherapy (98% vs. 93% and 93%)/No seroconversion under anti-CD20 treatment (0/4)	(33)
Monin L, Lancet Oncol	Solid/ Hematologic Malignancies	Y	151 Patients/54 Controls	Negative SARS-CoV-2 S/Negative rRT-PCR	SARS-CoV-2 S-specific IgG	Local (ELISA)	BNT162b2	38% solid tumor/ 18% hematologic cancer	95% solid tumor/ 60% hematologic cancer	94% after 1 st dose/100% after 2 nd dose	No adverse events in more than 50% of the patients with vaccination/T-cell responses in 82%, 71% and 50% of the controls, solid tumor cohort and hematologic tumor cohort with first vaccine dose	(28)
Thakkar A, Cancer Cell	Solid/ Hematologic Malignancies	N	200	N/A	SARS-CoV-2 IgG II	AdviseDx CIMA (on Abbott)	BNT162b2, mRNA-	N/A	94%	N/A	Lower seroconversion rates in hematologic malignancies (85%), patients treated with anti-CD20 therapies (70%)	(40)

(Continued)

TABLE 2 | Continued

Lead Author, Journal	Patient Cohort	Healthy Control	Number of Participants	Baseline Antibody Measurement	Antibody Assay	Platform	Vaccine	Seroconversion Rate After 1st Dose	Seroconversion Rate After 2nd Dose	Seroconversion Rate of Control Group	Additional Findings	Reference
Fong D, Eur J Cancer	Solid/Hematologic Malignancies	N	154	(*Prior COVID-19 infection in 18 patients) Negative Anti-SARS-CoV-2 nucleocapsid and spike protein IgG	SARS-CoV-2 nucleocapsid and spike protein IgG chemiluminescent immunoassay	i2000SR instrument)	1273 and Ad26	61%	85.7%	N/A	and stem cell transplantation (73%) compared to patients with solid tumors (98%)/Higher seroconversion rates in patients treated with immunotherapy (97%) or hormonal therapies (100%) Higher antibody titres in CoV- <i>positive</i> patients after the first vaccine dose (p<0.001)	(41)
Oekelen OV, Cancer Cell	MM	Y	320 Patients/67 Controls	N/A (Prior COVID-19 infection in 60 patients)	SARS-CoV-2 IgG test	COVID-SeroKlir Kantaro	BNT162b2 and mRNA-1273	N/A	84.2%	100%	Lower seroconversion rates in patients treated with anti-CD38 (HR: 4.258, p=0.005) or BCMA-targeted treatment (HR: 10.269, p<0.001)/Better seroconversion rates in patients with CR (HR: 0.389, p=0.037)	(26)
Bird S, Lancet Haematol	MM	N	93	N/A	Anti-SARS-CoV-2 IgG and AntiSARS-CoV-2 total antibody against S1 spike protein	Ortho Clinical Diagnostics	BNT162b2 and AZD1222	56% (70% total antibody response)	N/A	N/A	Higher seroconversion in responding patients (p=0.0046)/Lower seroconversion rates in patients under treatment (48% vs. 74%, p=0.037)/Similar seroconversion rates with Pfizer and AstraZeneca vaccines	(42)
Pimpinell F, J Hematol Oncol	MM/MPN	Y	92 Patients/36 Controls	SARS-CoV-2 S1/S2 IgG test	SARS-CoV-2 S1/S2 IgG test	Liaison [®] analyzer	BNT162b2	21.4% in myeloma/52% in MPN	78.6% in myeloma/88% in MPN	52.8% after 1 st dose/100% after 2 nd dose	Lower seroconversion rates in daratumumab-treated patients (50% vs. 92.9%, p=0.003)/Low rate of systemic adverse events	(29)
Terpos E, Blood	MM	Y	48 Patients/104 Controls	Neutralizing Antibodies Against SARS-CoV-2	Neutralizing Antibodies Against SARS-CoV-2	cPass [™]	BNT162b2	25%	N/A	54.8% after 1 st dose	All patients with clinically relevant viral inhibition (%4/4) after first dose was in remission without treatment	(38)
Lim SH, Lancet Haematol	Lymphoma	Y	119 Patients/150 Controls	Negative anti-SARS-CoV-2 nucleocapsid protein IgG	Qualified electrochemiluminescent Anti-SARS-CoV-2 S assay	Meso Scale Discovery	BNT162b2 and AZD1222	N/A	N/A	100%	Lower seroconversion rates in patients who received systemic anti-lymphoma therapy after the first vaccine dose (p=0.0002), after the second vaccine dose p<0.001 for BNT162b2 vaccine)	(44)
Avivi I, Br J Haematol	MM	Y	171 Patients/64 Controls	Negative anti-SARS-CoV-2 nucleocapsid protein IgG	Anti-SARS-CoV-2 S	Elecsys	BNT162b2	N/A	78%	98%	Lower seroconversion rates in daratumumab-treated patients (69% vs.81%, p=0.08)	(30)
Chowdhury O, Br J Haematol	CML	Y	59 Patients/232 Controls	Negative anti-SARS-CoV-2 nucleocapsid protein IgG	SARS-CoV-2 IgG II Quant Assay	Abbott	BNT162b2 or AZD1222	58%	N/A	97% after 1 st dose	The highest seroconversion rates in patients with CML (75%)	(37)
Roeker LE, Leukemia	CLL	N	44	N/A	SARS-CoV-2 S1/S2 IgG assay	Liaison [®]	BNT162b2 and mRNA-1273	N/A	52%	N/A	Lower seropositivity in >70 years (OR: 12, 95% CI: 2.9-50.5, p=0.001), and prior-CLL directed therapy (OR: 56.7, 95% CI: 6.2-518, p<0.001)	(45)
Agha M, medRxiv	Hematologic Malignancies	N	67	N/A (No History of COVID-19)	Semi-quantitative SARS-CoV-2 IgG against the Spike protein receptor-binding domain	Beckman Coulter SARS-CoV-2 platform	BNT162b2 and mRNA-1273	N/A	53.7%	N/A	Lower seroconversion in CLL patients compared to patients with other hematological malignancies (23.1% vs 61.1%, p = 0.01)	(46)
Diefenbach C, medRxiv	CLL, HL and NHL	Y	53 Patients/5 Controls	N/A	Multiplex bead-binding IgG spike and receptor binding domain assay for SARS-CoV2	Yeti ZE5 Cell Analyzer	BNT162b2 and mRNA-1273	47.1%	N/A	100%	Lower seroconversion rates in patients treated with anti-CD20 (p<0.001) and BTK inhibitors (p=0.003)/No effect of	(47)

(Continued)

TABLE 2 | Continued

Lead Author, Journal	Patient Cohort	Healthy Control	Number of Participants	Baseline Antibody Measurement	Antibody Assay	Platform	Vaccine	Seroconversion Rate After 1st Dose	Seroconversion Rate After 2nd Dose	Seroconversion Rate of Control Group	Additional Findings	Reference
Gavriatopoulou M, Clin Exp Med.	WM, CLL and NHL	Y	58 Patients/213 Controls	N/A (No History of COVID-19)	Neutralizing antibodies	cPass™	BNT162b2 and AZD1222	14%	N/A	%54	additional boost on antibody titers in most patients (94%) Lower response rates (<30%) in patients under active treatment	(35)
Tzarfati KH, Am J Hematol	Hematologic Malignancies	Y	315 Patients/108 Controls	N/A (No History of COVID-19)	SARS-CoV-2 S1/S2 IgG test	Liaison®	BNT162b2	N/A	75%	99%	Older age (p<0.001), higher lactate dehydrogenase (p=0.02), and number of treatment lines (p<0.001) was correlated with lower seropositivity Absolute lymphocyte count (p 0.001), total globulin level (p=0.002), and time from last treatment to vaccination(p<0.001) correlated with higher seropositivity likelihood and antibody titers	(31)
Harrington P, Leukemia	CML	N	16	Negative anti-SARS-CoV-2 anti-nucleoprotein IgG	SARS-CoV-2 Anti-S IgG ELISA	Local	BNT162b2	81.25%	N/A	N/A	Higher post-vaccine anti-S IgG EC50 and neutralising antibody ID50 titres in myelofibrosis patients (n = 9) compared to patients with other MPN subtypes (p = 0.012)	(48)
Harrington P, Br J Haematol	CML	N	16	Negative Anti-SARS-CoV-2 nucleocapsid and spike protein IgG	SARS-CoV-2 Anti-S IgG ELISA	Local	BNT162b2	87.5%	N/A	N/A	No statistical difference seen between different TKIs in neutralising antibody titres (p=0.68)	(49)
Re D, Leuk Lymphoma	Hematologic Malignancies	N	102	N/A (No History of COVID-19)	Commercially available kit detecting SARS-CoV-2 anti-spike (S)	N/A	BNT162b2 and mRNA-1273	N/A	62.7%	N/A	Lower seroconversion rates after the first vaccine dose in patients who received anti-CD20 treatment beyond the last 12 months (p< 0.0001)	(43)

ALC, Absolute lymphocyte count; BCMA, B cell maturation antigen; BTK, Bruton tyrosine kinase; CML, Chronic myeloid leukemia; CLL, Chronic lymphocytic leukemia; COVID-19, Coronavirus disease 2019; HL, Hodgkin lymphoma; CT, Chemotherapy; MM, Multiple myeloma; MPN, Myeloproliferative neoplasms; N/A, Not available; NHL, Non-Hodgkin lymphoma; RBD, receptor binding domain; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; WM, Waldenstrom macroglobulinemia.

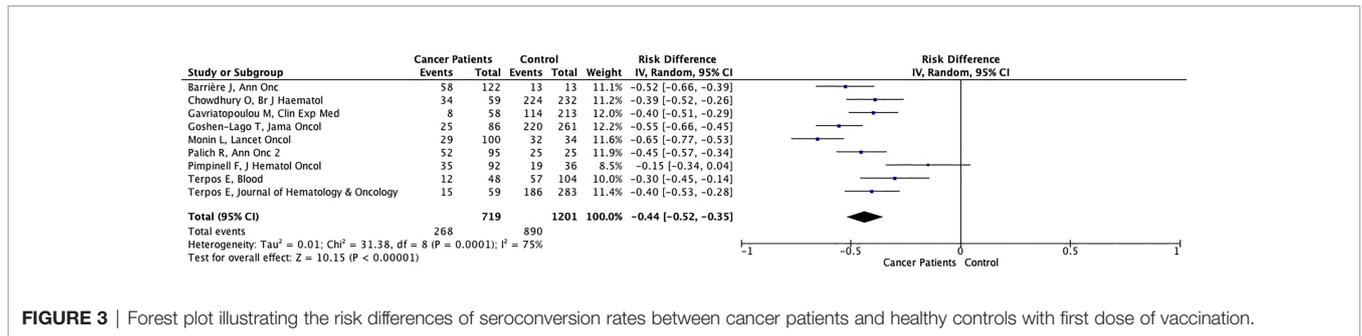


FIGURE 3 | Forest plot illustrating the risk differences of seroconversion rates between cancer patients and healthy controls with first dose of vaccination.

AZD1222 vaccines, the seroconversion rates were significantly lower in cancer patients (RD: -0.40%, 95% CI: -0.47%, -0.33%, p<0.001) (Supplement). The separate data on the seroconversion rates with mRNA and AZD1222 vaccines was only available in one study. The seroconversion rates were similar for AZD1222 (59.5%) and BNT162b2 (54.5%) vaccines in this study after the first dose of vaccination (37).

Seroconversion Rates After Second Vaccination

In contrast to low seroconversion rates after the first dose of vaccination, patients with solid tumors who received their complete vaccination had seroconversion rates greater than 90%. Likewise, patients with hematologic malignancies had over 75% seroconversion rates in all but one study (24). Additionally, anti-CD20 treatments in lymphoma patients and anti-CD38 treatments in multiple myeloma patients were associated with low seroconversion rates in 5 (24, 33, 40, 43, 47) and 3 studies (26, 29, 30), respectively. By comparison, the seroconversion rates almost 100% in the control arms with complete vaccination in all reported studies (538/540, 99.6%).

The possibility of achieving seroconversion was 19% lower in cancer patients (78.3%) compared to controls (99.6%) (RD: -0.19%, 95% CI: -0.28%, -0.10%, p<0.001), in the pooled data of ten studies with available seroconversion rates after complete vaccination (Figure 4). The antibody titers were lower in cancer patients than controls in most studies including control arms (Table 2). In contrast, Goshen-Lago (34) and Addeo et al. (33) reported similar neutralizing anti-SARS-CoV-2 antibody titers in patients with active cancer and patients whose cancer is in

remission, respectively. The difference in seroconversion rates was more pronounced for patients with hematologic malignancies (733/1010, 72.6%) (RD: -0.25%, 95% CI: -0.27%, -0.22%, p<0.001) (Figure 5A) than patients with solid tumors (401/438, 91.6%)

(RD: -0.09%, 95% CI: -0.13%, -0.04%, p<0.003) (Figure 5B). Additionally, six studies (five involving only patients with hematologic malignancies) reported specific outcomes for patients in remission. In the pooled analysis of 5 studies with control arms, the cancer patients in remission had significantly lower seroconversion rates than healthy controls albeit with a smaller risk difference (RD: -0.10%, 95% CI: -0.14%, -0.06%, p<0.001) (Figure 5C). Significant heterogeneity was present in all analyses other than analyses in the solid tumor subgroup (I² = 43%) (Figures 4, 5A–C). Nine of the ten studies included patients vaccinated with the BNT162b2 vaccine, while the study by Oekelen et al. (26) included patients vaccinated with the BNT162b2 or mRNA-1273 vaccine. Due to use of mRNA vaccines in all of the studies, no stratification could be done according to vaccine type.

DISCUSSION

To the best of our knowledge, this was the first meta-analysis on the antibody responses to COVID-19 vaccination in cancer patients. In the pooled analyses of the studies, cancer patients had significantly lower seroconversion rates with one or two doses of vaccination. The seroconversion rates were especially lower in patients with hematologic malignancies, while patients

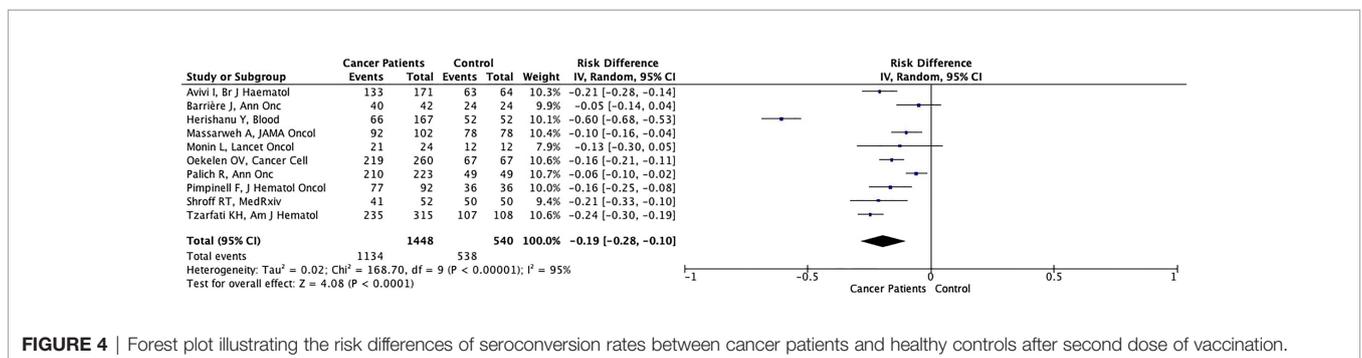
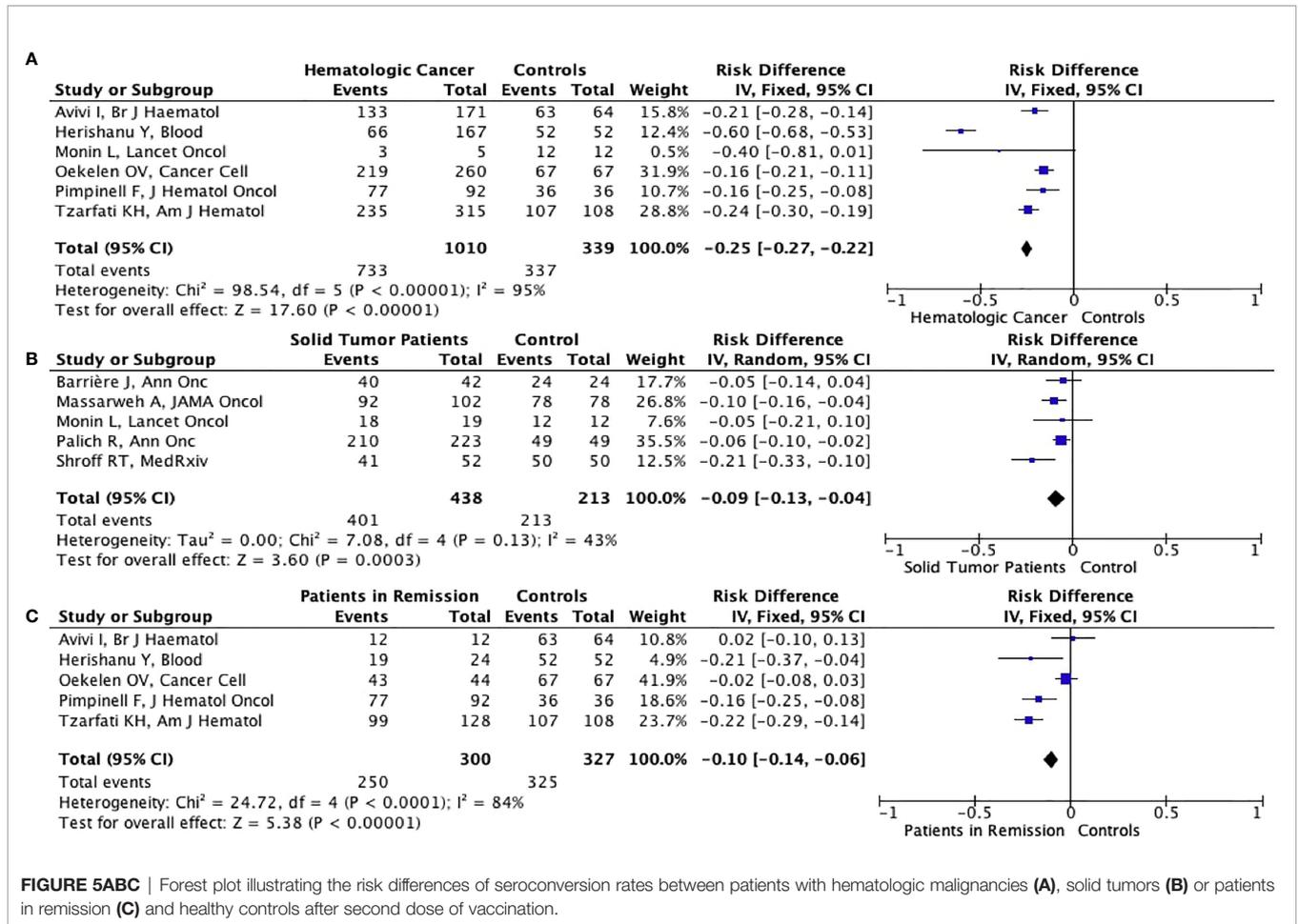


FIGURE 4 | Forest plot illustrating the risk differences of seroconversion rates between cancer patients and healthy controls after second dose of vaccination.



with solid tumors and patients in remission had slightly reduced antibody responses to vaccination.

Vaccination against SARS-CoV-2 is vital for patients with cancer. However, T-cell immunity is severely impaired in most cancer patients which could reduce the immune responses to vaccines (50). The first clue of this problem was evident in the study by Solodky et al. reporting significantly lower seroconversion rates in cancer patients after SARS-CoV-2 infection (30% in cancer patients vs. 71% in health care workers, p=0.04) (51). However, the sample size was very small (n=24) (51). Marra et al. challenged this finding in a larger cohort (n=166) and reported similar seropositivity between cancer patients (80.5%) and health care workers (87.9%) after COVID-19 infection (p=0.39) (52). Later, Takkar and colleagues demonstrated a high seroconversion rate (92%) in the 261 patients with cancer after COVID-19 disease, although significantly lower seroconversion rates in patients with hematological malignancies (82%) and patients who received anti-CD20 treatment (59%) were concerning (53).

Cancer patients were among the prioritized groups of persons for COVID-19 vaccination (18). However, the data on the efficacy of vaccines were limited in cancer patients due to the exclusion of these patients from clinical trials. This issue made studies from real-world evidence settings imperative and led to a

continuous effort in that direction. The earliest studies evaluated the seroconversion rates after the single vaccine dose and focused on the hematological cancers as a susceptible group for low seroconversion rates. Single-dose mass vaccination, generally with a prolonged delay for the second dose, was proposed to provide a broader vaccine coverage due to the limited vaccine supply (15). Initial reports reported over 70% protection from symptomatic COVID-19 disease with a single dose vaccine in the general population (54, 55) and this observation created the foundation of extended interval vaccination in England to vaccinate a larger part of the population with at least one vaccine dose. However, this strategy seems risky and not sustainable for cancer patients considering their already significantly lower seroconversion rates with first vaccine dose (37.3% in cancer patients vs. 74.1% in controls, **Figure 3**). Antibody titers were also significantly lower with a single vaccine dose in seroconverted patients (22, 29, 33), necessitating the application of a second dose vaccine in a time interval recommended in clinical trials.

Although the seroconversion rate for cancer patients was increased after the second dose of the vaccine, the rate was still significantly lower than the controls. Patients with solid tumors had over 90% seroconversion rates, while the patients with hematologic malignancies had significantly lower seroconversion rates

(**Table 2**). The lower seroconversion rates were especially prominent in patients with lymphoid malignancies (**Table 2**). Additionally, patients treated anti-B cell antibodies targeting CD20 or CD38 antigens as part of their standard of care had significantly lower antibody responses after COVID-19 vaccination (26, 33). The negative effect of anti-CD20 therapy appeared to be long-lasting, as evidenced by lack of seroconversion in 22 chronic lymphocytic leukemia patients who were treated with anti-CD20 antibodies within the last 12 months (24). We think that these patients should be prioritized for novel approaches for COVID-19 like anti-SARS-CoV-2 antibody studies (56) and third dose vaccinations (57).

An early report in 30 solid organ transplant recipients with negative or low antibody levels after two vaccination doses, an additional vaccine boost increased antibody titers in all patients with low antibody response (6/6) and created seroconversion in the 6 of 24 seronegative patients. 80% of the study population were received boosts with a different vaccine in the study (58). An anecdotal report by Hill et al. also supported the possible benefit of an additional boost with a heterologous vaccine providing seroconversion in a seronegative lymphoma patient (59). Recently, a phase II study with CoronaVac vaccine in healthy adults reported significantly increased antibody titers with a third dose boost which applied 6-8 months after the second dose in patients became seronegative (60). If further research supports these observations, the seronegative patients with cancer could benefit from a three-dose vaccination schedule similar to strategies with influenza and hepatitis B vaccinations (61, 62). In contrast to those observations, a small study on 18 seronegative CLL, NHL and myeloma patients with two doses of BNT162b2 vaccination demonstrated no seroconversion with a third dose (57). A large phase I study is currently evaluating the benefit of a three-dose vaccination in 1000 patients with cancer (NCT04936997) and hopefully could aid to determine the best strategy in seronegative cancer patients. While the oncology community is eagerly awaiting the results of three-dose vaccination studies, the Centers for Disease Control and Prevention (CDC) recommended a third-dose Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273) vaccine booster in solid organ transplantation patients or who have a similar level of immunosuppression based on the two studies in transplantation patients demonstrating more than a 30% increase in seroconversion rates with a third-dose boost (63, 64). This immunosuppression definition includes cancer patients under active treatment or patients who had stem cell transplantation in the last two years and these patients should have a third-dose booster until further data is available (65). Several other countries including Italy and Turkey also recommended a third-dose booster in older patients and patients with comorbidities creating immunosuppression. However, data on the booster dose efficacy in immunosuppressed patients is not available for other vaccines including inactive whole virus vaccines and viral vector vaccines.

There are still significant knowledge gaps and unanswered questions. The seroconversion is often used as a surrogate laboratory marker of adaptive immunity against vaccination in

immunocompromised cohorts (29, 66). However, the available studies have yet to report any meaningful correlation between measured anti-SARS-CoV-2 antibody titers and T-cell immunity against COVID-19 in cancer patients following vaccination. T-cells are the main actors of the fight against COVID-19 and the creation of the long-lasting immune memory against COVID-19 (67) and could be a better reflector of the immunity against COVID-19. A recent report with the BBIBP-CorV vaccine reported no significant correlation between the serum IgG antibody titers and interferon-gamma concentrations in the peripheral blood mononuclear cells ($p=0.11$) (68) suggesting antibody measurements could be imprecise to detect SARS-CoV-2 specific adaptive immunity. The imprecision of seroconversion as a COVID-19 vaccine efficacy was further supported by the work of Tzarfati and colleagues. The authors reported no COVID-19 cases in 315 patients with hematologic malignancies vaccinated with two doses of BNT162b2 vaccine, albeit with a relatively low seroconversion rate (75%) in the cohort pointing out the limitation of seroconversion rate as the sole denominator of immunity (31). The evaluation of T-cell immunity with vaccination is being addressed in the SOAP-02 study (28) and could be especially important in patients with low or negative antibody responses to vaccination (69). In addition to the one-dimensional nature of antibody measurements as a denominator of vaccine efficacy, the SARS-CoV-2 antibody assays have previously been reported to suffer from moderate concordance and variable sensitivities. These inherent limitations have emerged as an important challenge in accurately diagnosing the SARS-CoV-2 infection during the early phases of pandemic (70–72). Several new strategies including the combined use of ELISA and virus neutralization tests have been proposed to improve the diagnosis of COVID-19 by increasing the sensitivity of detection for SARS-CoV-2 (73). The diagnostic challenges have resolved with the rapid development of assays with significantly improved sensitivity and specificity (74). While several studies have previously evaluated the vaccine seroconversion rates based on antibody assays with lower sensitivities (29, 31) or antibody assays without an FDA authorization developed for research purposes (32), a consistent trend across studies and the use of Elecsys and Abbott spike IgG assays (>95% sensitivity and specificity for both) (**Table 2**), have decreased the possibility of confounding problems due to antibody assay performance during the evaluation of seroconversion rates with COVID-19 vaccination.

Furthermore, B-cell immunity against COVID-19 is hampered by emergence of variants of concern, such as B.1.1.7 (alpha strain from UK), B.1.351 (beta strain from South Africa), B.1.617.2 (delta strain from India) and P.1 (gamma strain from Brazil) characterized by mutant spike proteins, that may not be effectively neutralized by low titers of anti-SARS-CoV-2 spike protein antibodies induced by available COVID-19 vaccine platforms using the ancestral strain of SARS-CoV-2. A recent study from the United Kingdom reported modestly decreased vaccine efficacy against delta variant, especially with a single-dose vaccination (75). The authors including 316 participants from the clinically extremely vulnerable group, including cancer patients. However, a separate dataset was not

available for cancer patients (75). The results of COVIVAC-ID (NCT04844489) and EREVA (NCT04952766) studies are eagerly anticipated to delineate the vaccine efficacy against variants of concern in cancer patients.

Another knowledge gap pertains to the effects of different anti-cancer treatments on antibody responses to COVID-19 vaccination, especially immunotherapy and chemotherapy. Previous studies have demonstrated that cancer patients treated with immune checkpoint inhibitors (ICIs) or precision medicines (e.g. tyrosine kinase inhibitors) who subsequently develop COVID-19, can enjoy survival outcomes that are similar to the survival outcomes of the general population with COVID-19 (3, 76). It's hypothesized that cancer patients treated with ICI or precision medicines have significant T-cell immunity against viral infections (76, 77). The retained T-cell immunity could also orchestrate efficient responses to vaccination (78), similar to the robust antibody responses to COVID-19 vaccination in myeloma patients with treated with immunomodulatory agents (79). However, in part due to a focus on hematological cancers and the lack of separate studies for seroconversion rates, the published information regarding the seroconversion rates for cancer patients treated with ICI or precision medicines is very limited and the data is unequivocal. Addeo et al. reported similar seroconversion rates (93% in both) in ICI- *versus* chemotherapy treated patients. But the median antibody titers (1.116 *vs.* 611 U/mL) and seroconversion rates after the first vaccine dose (85 *vs.* 69%) were significantly higher in ICI-treated patients compared to patients treated with cytotoxic chemotherapy. Additionally, 21 of the 22 patients treated with anti-HER2, anti-VEGF, RANKL inhibitors or kinase inhibitors had reportedly seroconversion after two vaccine doses (33). Similarly, Thakkar et al. reported 97% and 100% seroconversion rates in patients treated with ICI and hormonal therapy, respectively (40). Singer et al. reported higher seroconversion rates in ICI-treated patients compared to patients treated with chemotherapy, targeted therapy or radiotherapy. Additionally, the seroconversion rates were higher with the ICI-chemotherapy combinations than patients treated with chemotherapy only, supporting a possible benefit of ICIs in immune response against vaccination (80). In contrast, Massarweh et al. pointed out a possible adverse synergistic effects of combined ICI + chemotherapy or biotherapy on COVID-19 antibody responses and reported significantly lower median antibody titers in patients treated with combinations of ICI and chemotherapy or biotherapy than patients treated with chemotherapy alone (25). Similarly, Terpos et al. reported significantly lower seroconversion rates after first vaccination dose in 59 ICI-treated patients compared to healthy controls (25 *vs.* 65.7%, $p < 0001$) (36). These unequivocal findings emphasize the need for additional studies focusing on these patients. Similarly, whether antibody responses were impaired in patients treated with radiation therapy remains to be deciphered.

An important point is the paucity of data on the optimal vaccination schedule in cancer patients with COVID-19 history. While these patients are vaccinated with schedules similar to general population as seen in the reported studies (Table 2), Reynolds et al. reported robust T and B-cell responses against

B.1.1.7 variant with a single boost of mRNA vaccine in 25 patients with COVID-19 history (81). Similarly, Fong et al. reported significantly higher seroconversion rates in cancer patients with COVID-19 history ($n=89$) compared to patients without COVID-19 history ($n=154$) (91% *vs.* 61%) (41). Whether a single dose vaccination strategy could be suitable in patients with COVID-19 history should be investigated in larger cohorts. Further, it is unknown whether available vaccines differ in protecting cancer patients from symptomatic or severe COVID-19. The available studies were mostly conducted with mRNA vaccines, and Addeo et al. reported similar seroconversion rates with two different mRNA vaccines (33), while Lim et al. reported similar antibody responses to BNT162b2 and ChAdOx1 vaccines in lymphoma patients (44). While the mRNA and adenovirus vectors attach to different toll-like receptors (TLR7 and TLR9, respectively), after the TLR attachment both vaccines cause the type I interferon secretion and the activation of the CD4-positive T-cells. This mechanism of action suggests both vaccines could have a similar efficacy from a biologic standpoint (82). However, several parts of the World, including China, Russia, and India, use different vaccines. Reports from different parts of the World will be critically important and could direct the optimal vaccination planning for cancer patients in the future. Studies with the different vaccines from these countries, and separate reporting for seroconversion rates with different vaccines is vital for the future studies and vaccination planning in cancer patients.

In conclusion, patients with cancer had significant seroconversion rates with a two-dose vaccination schedule, while seroconversion rates were significantly lower in patients with hematological malignancies and patients under active treatment. Given the life-saving nature of anti-cancer treatments, further research focusing on these patients is urgently needed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

DG and FMU have planned the work. DG, TS, SK and FMU participated in data collection. All authors have made significant and substantive contributions to the reporting of the work, drafting of the manuscript, review and revisions of the final draft. All co-authors qualify the criteria for authorship according to Vancouver protocol.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2021.759108/full#supplementary-material>

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Conflict of Interest: FMU was employed by Ares Pharmaceuticals, LLC and was a consultant for Aptevo Therapeutics and for Reven Pharmaceuticals.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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