Review

Immunogenicity and risk of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection after Coronavirus Disease 2019 (COVID-19) vaccination in patients with cancer: a systematic review and meta-analysis

Andrea Becerril-Gaitan [a,1], Bryan F. Vaca-Cartagena [a,1], Ana S. Ferrigno [a], Fernanda Mesa-Chavez [a], Tonatiuh Barrientos-Gutiérrez [b], Marco Tagliamento [c,d], Matteo Lambertini [d,e], Cynthia Villarreal-Garza [a,*]

[a] *Breast Cancer Center, Hospital Zambrano Hellion TecSalud, Tecnologico de Monterrey, San Pedro Garza Garcia, Nuevo Leon, Mexico*
[b] *National Institute of Public Health, Center for Population Health Research, Cuernavaca, Mexico*
[c] *Department of Medical Oncology, Medical Oncology 2, IRCCS Ospedale Policlinico San Martino, Genova, Italy*
[d] *Department of Internal Medicine and Medical Specialties (DiMI), University of Genova, Genova, Italy*
[e] *Department of Medical Oncology, UOC Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy*

Abstract *Background:* Patients with cancer are considered a priority group for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccination given their high risk of contracting severe Coronavirus Disease 2019 (COVID-19). However, limited data exist regarding the efficacy of immunisation in this population. In this study, we assess the immunologic response after COVID-19 vaccination of cancer versus non-cancer population.
Methods: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science databases were searched from 01st March 2020 through 12th August 12 2021. Primary end-points were anti-SARS-CoV-2 spike protein (S) immunoglobulin G (IgG) seroconversion rates, T-cell response, and documented SARS-CoV-2 infection after COVID-19

* *Corresponding author*: Batallon de San Patricio 112, Real de San Agustin, 66278, San Pedro Garza Garcia, Nuevo Leon, Mexico.
  E-mail address: cynthia.villarreal@tecsalud.mx (C. Villarreal-Garza).
  @Dra_CVillarreal (C. Villarreal-Garza).
[1] Co-first authors.

breakthrough infections

immunisation. Data were extracted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Overall effects were pooled using random-effects models.

Results: This systematic review and meta-analysis included 35 original studies. Overall, 51% (95% confidence interval [CI], 41–62) and 73% (95% CI, 64–81) of patients with cancer developed anti-S IgG above the threshold level after partial and complete immunisation, respectively. Patients with haematologic malignancies had a significantly lower seroconversion rate than those with solid tumours after complete immunisation (65% vs 94%; $P < 0.0001$). Compared with non-cancer controls, oncological patients were less likely to attain seroconversion after incomplete (risk ratio [RR] 0.45 [95% CI 0.35–0.58]) and complete (RR 0.69 [95% CI 0.56–0.84]) COVID-19 immunisation schemes. Patients with cancer had a higher likelihood of having a documented SARS-CoV-2 infection after partial (RR 3.21; 95% CI 0.35–29.04) and complete (RR 2.04; 95% CI 0.38–11.10) immunisation.

Conclusions: Patients with cancer have an impaired immune response to COVID-19 vaccination compared with controls. Strategies that endorse the completion of vaccination schemes are warranted. Future studies should aim to evaluate different approaches that enhance oncological patients' immune response.

1. Introduction

Since the Coronavirus Disease 2019 (COVID-19) was first declared pandemic by the World Health Organization on 11th March 2020, the world has faced an unprecedented socioeconomic and health crisis. By 24th September 24, 2021, confirmed COVID-19 cases surpassed 230 million, and more than 4.7 million deaths have been reported worldwide [1]. Patients with cancer are a vulnerable group at increased risk of infection and COVID-19-related morbidity and mortality compared with the non-cancer population [2,3]. A 30-day mortality rate of 20–25% has been documented in this group [4], which is substantially higher than the estimated 3–4% among the general population [5].

Although several therapies in the general population such as dexamethasone, azithromycin, convalescent plasma, antivirals, Janus kinase 1/2 inhibitor and monoclonal antibodies have been explored in the 'Randomised Evaluation of COVID-19 Therapy' "RECOVERY"and 'COV-BARRIER' studies, the vast majority did not show a decrease in mortality rate or length of hospitalisation [6,7]. A substantial proportion of patients who were hospitalised died even when receiving one of the few treatments that have shown an improvement in the overall survival rate (i.e. dexamethasone, tocilizumab and baricitinib) [6,8,9]. Thus, the development and widespread application of COVID-19 vaccines represent the most effective strategy for overcoming the current crisis [10]. Because cancer itself is an independent risk factor for poor COVID-19 prognosis [11], international organisations such as the National Comprehensive Cancer Network (NCCN), the Asian Oncology Society and the European Society for Medical Oncology have urged the prioritisation of oncological patients for COVID-19 immunisation [12–14].

Even though robust data confirm the safety and efficacy of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccines' in preventing COVID-19 among the general population [15,16], data about their performance in oncological patients remain scarce. Recent studies reporting on COVID-19 immunogenicity using anti-SARS-CoV-2 spike protein (S) immunoglobulin G (IgG) titres, a surrogate of humoral response that has been correlated with neutralising antibodies [3,17], have shown a suboptimal response after immunisation in patients with cancer [18–20]. However, owing to the exclusion and underrepresentation of patients with cancer in most COVID-19 vaccines' clinical trials [21], several gaps in knowledge persist regarding vaccines' effectiveness, best timing for administration, extent and durability of the attained immune response and safety profile in this high-risk population [21]. To refine the existing evidence, a systematic review and meta-analysis were performed to assess seroconversion rates based on anti-S IgG titres after partial and complete COVID-19 immunisation among oncological patients compared with non-cancer participants.

2. Methods

This systematic review and meta-analysis were conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [22]. The complete protocol is available at the International Prospective Register of Systematic Reviews (PROSPERO) website (ID CRD42021261974) [23].

2.1. Search strategy and selection criteria

A comprehensive literature search was performed for abstracts and full-text articles published from 01st

March 2020 through 12th August 2021 in PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science databases, using the following search strategy: *(neoplasm* OR oncolog* OR cancer OR malign*) AND (COVID-19 OR SARS-CoV-2 OR coronavirus) AND (vaccin*) AND (immun* OR sero* OR humoral)*. Retrieved articles were cross-referenced to confirm that all eligible records were identified.

Studies needed to satisfy the following inclusion criteria: (1) assess the immune humoural response rate in patients with cancer based on anti-S SARS-CoV-2 IgG; (2) report original findings (3) be in English, Spanish or French language.

The following variables were recorded: first author; year of publication; study design and methodology; participants' median/mean age; number of controls and patients with cancer; type of malignancy (i.e. solid vs haematological); proportion of patients with cancer undergoing active treatment; type and number of COVID-19 vaccine doses administered; type of anti-S IgG immunoassay and threshold value used to define 'vaccine responders'; proportion of cancer and non-cancer participants classified as 'vaccine responders' and 'vaccine non-responders' and their mean/median IgG titres; participants' T-cell response and number of documented COVID-19 cases after vaccination. Two reviewers extracted the data in duplicate, and disagreements were solved by a third author. For studies with ≥1 publication or having a superimposable population, only the largest study was included in the quantitative analysis.

To assess the risk of bias, two reviewers independently assessed the methodological quality of each study using the Risk of Bias in Non-randomized Studies − of Interventions (ROBINS-I) tool. Disagreements among reviewers were solved by consensus.

2.2. Study objectives

The primary aim was to assess the proportion of oncological patients classified as vaccine responders, defined as the number of patients with anti-S SARS-CoV-2 IgG levels above each individual study's threshold value versus controls. We hypothesised that patients with haematological malignancies and those with partial immunisation regimens would achieve inferior immunogenicity after COVID-19 immunisation; thus, subgroup analyses assessing seroconversion rates between patients with solid versus haematologic malignancies, as well as partial and complete COVID-19 vaccination regimens, were conducted. As secondary outcomes, the proportion of documented SARS-CoV-2 infection and T-cell response after COVID-19 immunisation in oncological and control subjects was assessed.

2.3. Statistical analysis

The proportion of oncological patients who achieved seroconversion and detectable T-cell response as well as the percentage of patients diagnosed with SARS-CoV-2 infection after receiving at least one COVID-19 vaccine were assessed using generalised linear mixed-effects models of the logit-transformed proportions of individual studies. Confidence intervals (CIs) of individual studies were calculated with the Clopper-Pearson method, whereas the Hartung-Knapp adjustment was used to calculate the CI around the pooled effect. Between-study variability (τ^2) was estimated by the restricted maximum likelihood.

The effect size for binary outcomes is presented as risk ratios (RRs) calculated with the Mantel-Haenszel method, with a corresponding 95% CI as forest plots. The method by Hartung-Knapp was used to adjust test statistics and 95% CI. The corresponding prediction intervals are also reported. Between-study variance was estimated using the Paule-Mandel estimator for τ^2, and heterogeneity between studies was assessed using the Higgins's I^2 and Cochran's Q tests. The relationship between effect estimates and study precision was assessed visually using funnel plots and the Harbord score test. In case asymmetry was detected, a limit meta-analysis was conducted to adjust for small-study effects.

Bivariate metaregressions were used to assess type of COVID-19 vaccine (messenger ribonucleic acid [mRNA] vs mRNA/viral vector), immunisation scheme (incomplete vs complete) and time from the last vaccine dose to the serologic test (<3 vs ≥ 3 weeks from the last dose) as explanatory variables, in terms of the studies' effect size (outcome variable) when determining the pooled RR of seroconversion rates. Sensitivity analyses were conducted to assess studies evaluating only mRNA vaccines and for studies with low-to-moderate risk of bias. All statistical analyses were conducted using R statistical software (version 4.1.0, R Project for Statistical Computing) and RStudio software (version 1.4.1717, R Foundation for Statistical Computing). A two-tailed P-value of <0.05 was considered significant.

3. Results

3.1. Systematic review and characteristics of the studies

The systematic literature search yielded 1821 records, of which 1287 remained after duplicates were excluded. After title and abstract review, 1233 records were excluded given that they reported non-original findings, did not include patients with cancer or did not assess COVID-19 vaccines' immunogenicity. Of the 54 articles that underwent full-text review, 35 articles [17−20,24−46] were considered eligible and were included in the meta-analysis (Fig. 1).
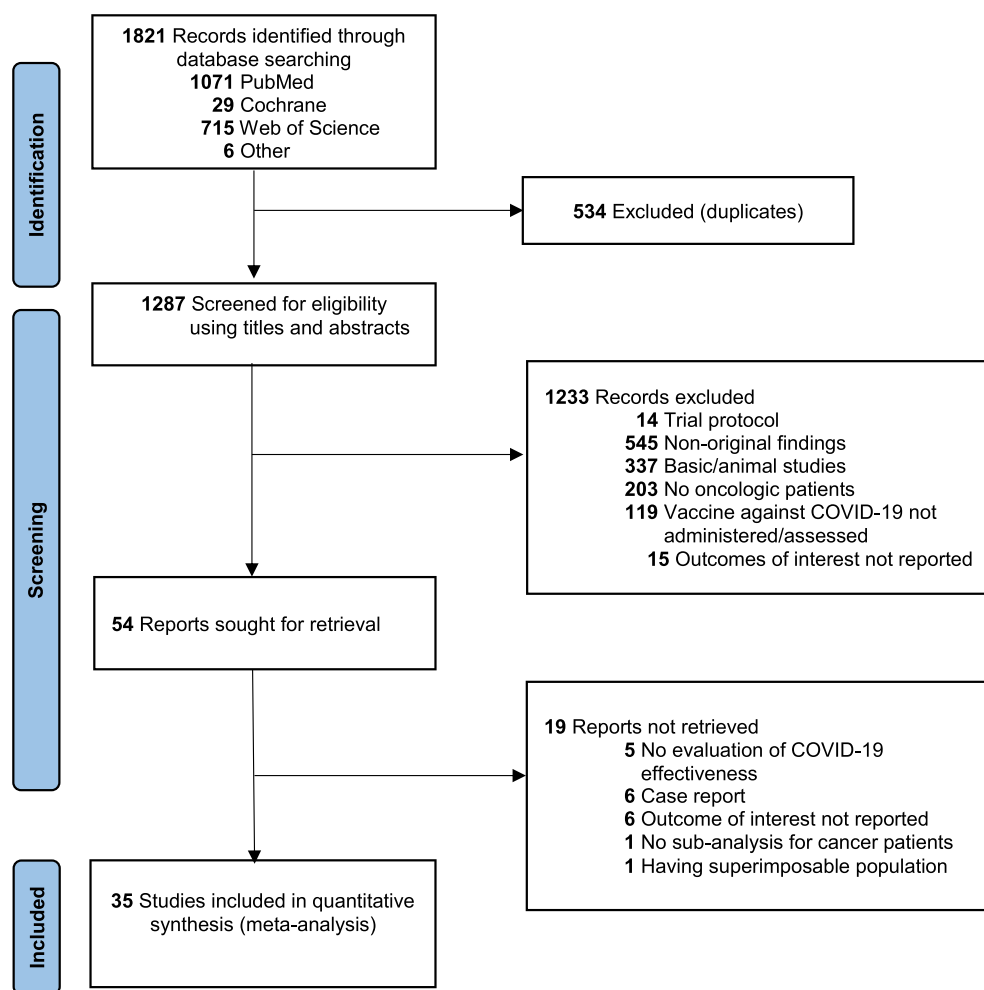
Fig. 1. **The PRISMA flowchart summarising the process for the identification of eligible studies.** Abbreviations: COVID-19, Coronavirus Disease 2019; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Overall, 23 studies evaluated patients with haematological malignancies, five with solid tumours, and seven included both cancer types. Twenty-six studies assessed the effectiveness of mRNA, eight mRNA and viral vector and one inactivated COVID-19 vaccines. Regarding the COVID-19 immunisation regimen, nine studies evaluated patients with incomplete vaccination schemes, 15 assessed fully vaccinated patients, and 11 included both regimens. Only 18 studies had a control group (non-cancer patients). Table 1 summarises the characteristics of the studies included in the meta-analysis. Most studies had a moderate risk of bias (Supplemental eTable 1).

3.2. Anti-S Severe Acute Respiratory Syndrome Coronavirus 2 immunoglobin G seroconversion rates

Of the included 35 studies, 20 reported the seroconversion rate in patients with cancer after partial COVID-19 immunisation (2574 patients) [17,20,24—31,37,42—44,47—52] and 24 after complete vaccination schemes (4708 patients) [17—20,27,30—42, 45,46,48,49,53,54]. A lower seroconversion rate was achieved by those with incomplete vaccination regimens (51%; 95% CI 41—62) compared with those with patients who were fully immunised (73%; 95% CI 64—81) ($P = 0.0009$) (Fig. 2).

A total of 17 studies that compared seroconversion rates among oncological patients and non-cancer controls (nine with incomplete and 13 with complete immunisation schemes) were analysed. Compared with controls, patients with cancer with an incomplete vaccination scheme had a 55% reduced likelihood of achieving anti-S IgG titres above the threshold level (RR 0.45; 95% CI 0.35—0.58), whereas a 31% reduced likelihood of seroconversion was documented among those with a complete vaccination scheme (RR 0.69, 95% CI 0.56—0.84) (test for subgroup differences $P = 0.0026$) (Fig. 3). After adjusting for small-study effects, the overall RR was 0.72 (95% CI 0.70—0.75) for seroconversion in oncological patients receiving at least one COVID-19 vaccine compared with controls (Supplemental eFig. 1). Sensitivity analysis of 14 studies evaluating mRNA vaccines (seven with

Table 1
Characteristics of included studies and patient population.

Author	Country	Design	No. of cancer patients	No. of controls	Patients' age (years)	Type of cancer	Vaccine type	Vaccine scheme	Reported outcomes
Addeo et al. [17]	Switzerland/USA	Multicentre, prospective, cohort	244	NA	63 (IQR 55−69)	Haematological malignancy and solid tumour	mRNA (BNT162b2/mRNA1273)	Incomplete and complete	Anti-S IgG Ab, adverse effects, SARS-CoV-2 infection
Agha et al. [41]	USA	Single-centre, prospective, cohort	67	NA	71 (IQR 65−77)	Haematological malignancy	mRNA (BNT162b2/mRNA1273)	Complete	Anti-S IgG Ab
Barrière et al. [42]	France	Single-centre, prospective, cohort	122	29	69.5 (range 44−90)	Solid tumour	mRNA (BNT162b2)	Incomplete and complete	Anti-S IgG Ab, adverse effects
Benda et al. [37]	Austria	Single-centre, prospective, cohort	259	NA	65.1 (SD 12.2)	Haematological malignancy and solid tumour	mRNA (BNT162b2)	Incomplete and complete	Anti-S IgG Ab, adverse effects, SARS-CoV-2 infection
Benjamini et al. [53]	Israel	Multicentre, prospective, cohort	373	NA	70 (range 40−89)	Haematological malignancy	mRNA (BNT162b2)	Complete	Anti-S IgG Ab, anti-N IgG Ab, adverse effects
Bird et al. [43]	UK	Single-centre, retrospective, cohort	93	NA	67 (IQR 59−73)	Haematological malignancy	mRNA (BNT162b2) and viral vector (AZD1222)	Incomplete	Anti-S IgG Ab
Chowdhury et al. [44]	UK	Multi-centre, prospective, cohort	59	232	62 (IQR 52−73)	Haematological malignancy	mRNA (BNT162b2) and viral vector (AZD1222)	Incomplete	Anti-S IgG Ab, anti-N IgG Ab
Cohen et al. [45]	Israel	Single-centre, prospective, cohort	54	NA	68.8 (IQR 61.2−76.8)	Haematological malignancy	mRNA (BNT162b2)	Complete	Anti-S IgG Ab, adverse effects
Ehmsen et al. [54]	Denmark	Single-centre, prospective	524	NA	70 (IQR 63−75)	Haematological malignancy and solid tumour	mRNA	Complete	Anti-S IgG Ab, T-cell response
Ghandili et al. [47]	Germany	Single-centre, prospective, cohort	74	NA	67.5 (range 40−85)	Haematological malignancy	mRNA and viral vector	Incomplete	Anti-S IgG Ab, SARS-CoV-2 infection
Ghione et al. [46]	USA	Multicentre, prospective, cohort	86	201	NA	Haematological malignancy	mRNA (BNT162b2/mRNA1273) and viral vector (AD26.COV2.S)	Complete	Anti-S IgG Ab
Goshen-Lago et al. [24]	Israel	Single-centre, prospective, cohort	86	261	66 (SD 12.09)	Solid tumour	mRNA (BNT162b2)	Incomplete	Anti-S IgG Ab, adverse effects, SARS-CoV-2 infection
Greenberger et al. [36]	USA	Prospective, cohort	1445	NA	68 (range 16−110)	Haematological malignancy	mRNA (BNT162b2/mRNA1273)	Complete	Anti-S IgG Ab
Guglielmelli et al. [51]	Italy	Single-centre, retrospective, cohort	30	14	60.8 (range 36.9−80.3)	Haematological malignancy	mRNA (BNT162b2/mRNA1273)	Incomplete	Anti-S IgG Ab
Harrington, Lavallade et al. [25]	UK	Single-centre, prospective, cohort	21	NA	55 (SD 10.71)	Haematological malignancy	mRNA (BNT162b2)	Incomplete	Anti-S IgG Ab, anti-N IgG Ab, NAb, T-cell response, adverse effects
Harrington, Doores et al. [26]	UK	Multicentre, prospective, cohort	16	NA	45.6 (SD 14.8)	Haematological malignancy	mRNA (BNT162b2)	Incomplete	Anti-S IgG Ab, anti-N IgG Ab, NAb, T-cell response, adverse effects

(continued on next page)

Table 1 (*continued*)

Author	Country	Design	No. of cancer patients	No. of controls	Patients' age (years)	Type of cancer	Vaccine type	Vaccine scheme	Reported outcomes
Herishanuet al [19]	Israel	Multicentre, prospective, cohort	167	52	71 (IQR 63–76)	Haematological malignancy	mRNA (BNT162b2)	Complete	Anti-S IgG Ab, anti-N IgG Ab, adverse effects
Heudel et al. [52]	France	Prospective, cohort	1503	NA	NA	Haematological malignancy and solid tumour	mRNA (BNT162b2/ mRNA1273) and viral vector (ChAdOx1)	Incomplete and complete	Anti-S IgG Ab, SARS-CoV-2 infection
Karacin et al. [35]	Turkey	Multicentre, prospective, cohort	47	NA	73 (range 64–80)	Solid tumour	Inactivated (CoronaVac)	Complete	Anti-S IgG Ab
Lim et al. [27]	UK	Multicentre, prospective, cohort	129	150	69 (IQR 57–74)	Haematological malignancy	mRNA (BNT162b2) and viral vector (ChAdOx1)	Incomplete and complete	Anti-S IgG Ab, anti-N IgG Ab
Malard et al. [40]	France	Single-centre, retrospective, cohort	195	30	68.8 (range 21.5 –91.7)	Haematological malignancy	mRNA (BNT162b2)	Complete	Anti-S IgG Ab, T-cell response
Maneikis et al. [28]	Lithuania	Single-centre, prospective, cohort	857	68	65 (IQR 54–72)	Haematological malignancy	mRNA (BNT162b2)	Incomplete and complete	Anti-S IgG Ab, adverse effects, SARS-CoV-2 infection
Massarweh et al. [18]	Israel	Single-centre, prospective, cohort	102	78	66 (IQR 56–72)	Solid tumour	mRNA (BNT162b2)	Complete	Anti-S IgG Ab
Monin et al. [20]	UK	Multicentre, prospective, cohort	151	54	73 (IQR 64.5–79.5)	Haematological malignancy and solid tumour	mRNA (BNT162b2)	Incomplete and complete	Anti-S IgG Ab, T-cell response, adverse effects, SARS-CoV-2 infection
Palich et al. [29]	France	Single-centre, prospective, cohort	110	25	66 (IQR 54–74)	Solid tumour	mRNA (BNT162b2)	Incomplete	Anti-S IgG Ab, anti-N IgG Ab
Parry et al. [48]	UK	Single-centre, prospective, cohort	286	93	69 (IQR 63–74)	Haematological malignancy	mRNA (BNT162b2) and viral vector (ChAdOx1)	Incomplete and complete	Anti-S IgG Ab
Pimpinelli et al. [30]	Italy	Single-centre, prospective, cohort	92	36	74 (range 47–78)	Haematological malignancy	mRNA (BNT162b2)	Incomplete and complete	Anti-S IgG Ab, adverse effects, SARS-CoV-2 infection
Pimpinelli, Marchesi et al. [50]	Italy	Single-centre, prospective	42	NA	72 (range 52–82)	Haematological malignancy	mRNA (BNT162b2)	Incomplete	Anti-S IgG Ab
Re et al. [39]	France	Prospective, cohort	45	NA	77 (range 37–92)	Haematological malignancy	mRNA (BNT162b2)	Complete	Anti-S IgG Ab, anti-N IgG Ab, T-cell response
Revon-Riviere et al. [31]	France	Single-centre, retrospective, cohort	13	NA	17 (IQR 16–18)	Haematological malignancy and solid tumour	mRNA (BNT162b2)	Incomplete and complete	Anti-S IgG Ab, adverse effects, SARS-CoV-2 infection
Re, Barrière et al. [38]	France	Single-centre, retrospective, cohort	102	NA	75.5 (range 33–93)	Haematological malignancy	mRNA (BNT162b2/ mRNA1273)	Complete	Anti-S IgG Ab
Stampfer et al. [49]	USA	Single-centre, prospective, cohort	103	31	68 (range 35–88)	Haematological malignancy	mRNA (BNT162b2/ mRNA1273)	Incomplete and complete	Anti-S IgG Ab, SARS-CoV-2 infection

Thakkar et al. [32]	USA	Multicentre, retrospective, cohort	67 (range 27–90)	200	26	Haematologic malignancy and solid tumour	mRNA (BNT162b2/mRNA1273) and viral vector (AD26.COV2.S)	Complete	Anti-S IgG Ab, adverse effects
Tzarfati et al. [33]	Israel	Single-centre, prospective, cohort	71 (IQR 61–78)	315	108	Haematological malignancy	mRNA (BNT162b2)	Complete	Anti-S IgG Ab, SARS-CoV-2 infection
Van Oekelen et al. [34]	USA	Single-centre, retrospective, cohort	68 (range 38–93)	320	67	Haematological malignancy	mRNA (BNT162b2/mRNA1273)	Complete	Anti-S IgG Ab, SARS-CoV-2 infection

Data are expressed as no. (%) unless otherwise noted.
Abbreviations: USA, United States of America; UK, United Kingdom; NA, not available; IQR, interquartile range; SD, standard deviation; Anti-S Ab, anti-spike antibody; Anti-N Ab, anti-nucleocapsid antibody; NAb, neutralising antibody; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

incomplete and 10 with complete schemes) (Supplemental eFig. 2) and studies with low-to-moderate risk of bias showed similar results (Supplemental eFig. 3).

Meta-regression analyses revealed that incomplete immunisation scheme was a risk factor for lower seroconversion among patients with cancer (RR 0.65, 95% CI 0.50–0.86; $P = 0.003$). No significant association was found for vaccine type and time from the last vaccine dose to the serologic test (Supplemental eTable 2).

A subgroup analysis was performed including six studies that assessed seroconversion rates among patients with solid malignancies compared with non-cancer controls. Four studies assessed patients with incomplete vaccination schemes [20,24,29,42], with a total of 359 oncological patients and 333 controls. Compared with non-cancer controls, patients with solid cancer had a 55% reduced likelihood of achieving threshold humoural response after the first dose of a COVID-19 vaccine (RR 0.45; 95% CI 0.37–0.55). Moreover, in studies evaluating 297 patients with cancer who had completed their vaccination regimen [18,20,32,42], a lower seroconversion rate was documented when compared with 140 controls (RR 0.95; 95% CI 0.92–0.99) (Fig. 4).

In a subgroup analysis of 13 records evaluating humoural seroconversion rates in patients with haematological malignancies compared with non-cancer controls, six included patients with a partial immunisation regimen [20,27,30,44,48,51], seven with a complete scheme [19,32–34,40,46,49] and four with both partial and complete vaccination [20,27,30,48]. In the incomplete immunisation scheme analysis, of the 997 included participants (523 oncological patients and 474 controls), patients with cancer had a 57% reduced likelihood of achieving an adequate humoural response compared with non-cancer controls (RR 0.43; 95% CI 0.29–0.63). Similarly, in the fully vaccinated analysis, patients with haematological malignancies had lower seroconversion rates than non-cancer controls (RR 0.63; 95% CI 0.52–0.75) (Fig. 5).

When comparing serological response between types of malignancies after partial immunisation, patients with haematological cancer achieved a numerically lower response (49%; 95% CI 35–63) than those with solid tumours (53%; 95% CI 33–72) ($P = 0.183$) (Fig. 6). When analysing serological response after complete immunisation regimens, patients with haematologic malignancies had a significantly reduced humoural response (65%; 95% CI 57–72) than those with solid cancer (94%; 95% CI 86–97) ($P < 0.001$) (Fig. 7).

3.3. Severe Acute Respiratory Syndrome Coronavirus 2 infection after vaccination

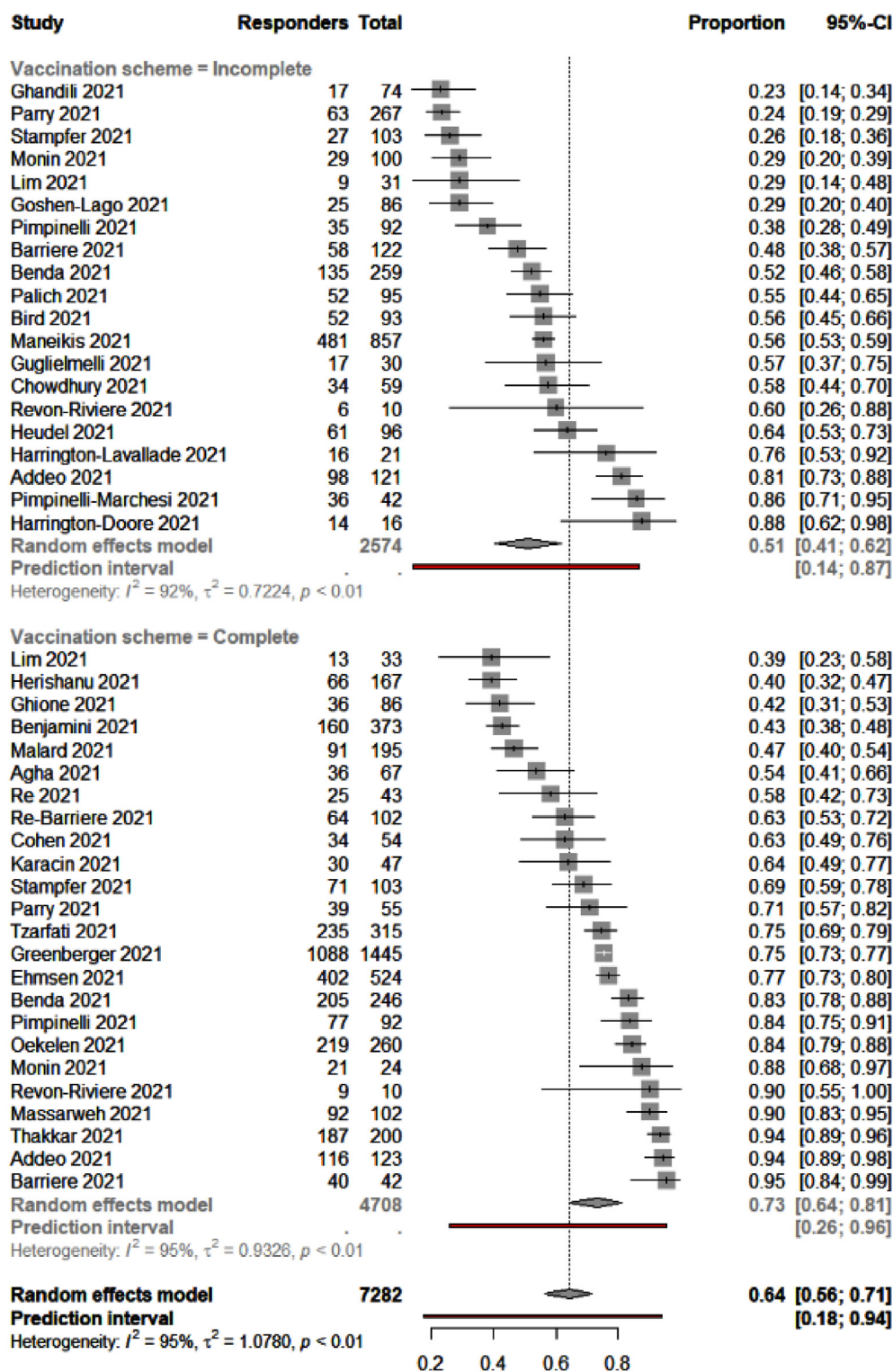In a pooled analysis of 14 studies including patients with haematological or solid malignancies

Fig. 2. **Rates of seroconversion in patients with cancer as per the vaccination regimen.** Squares represent indirect effect size (Risk ratio [RR]). Horizontal lines indicate 95% Confidence Interval (CI). Diamonds indicate the meta-analytic pooled RR, calculated separately by vaccination scheme (i.e., partial or complete), and the overall pooled RR (95%CI) in patients with cancer.

[17,20,24,28−31,33,34,37,42,47,49,52], a subsequent SARS-CoV-2 infection was documented in 0.78% (95% CI 0.18−3.26; I^2 = 33%) of the 1444 patients with a partial COVID-19 vaccination regimen and in 0.41% (95% CI 0.09−1.89; I^2 = 51.5%) of the 3000 patients with a complete vaccination regimen (*P* = 0.4976). Overall, patients with cancer had a 0.55% (95% CI 0.20−1.5; I^2 = 59.5%) likelihood of
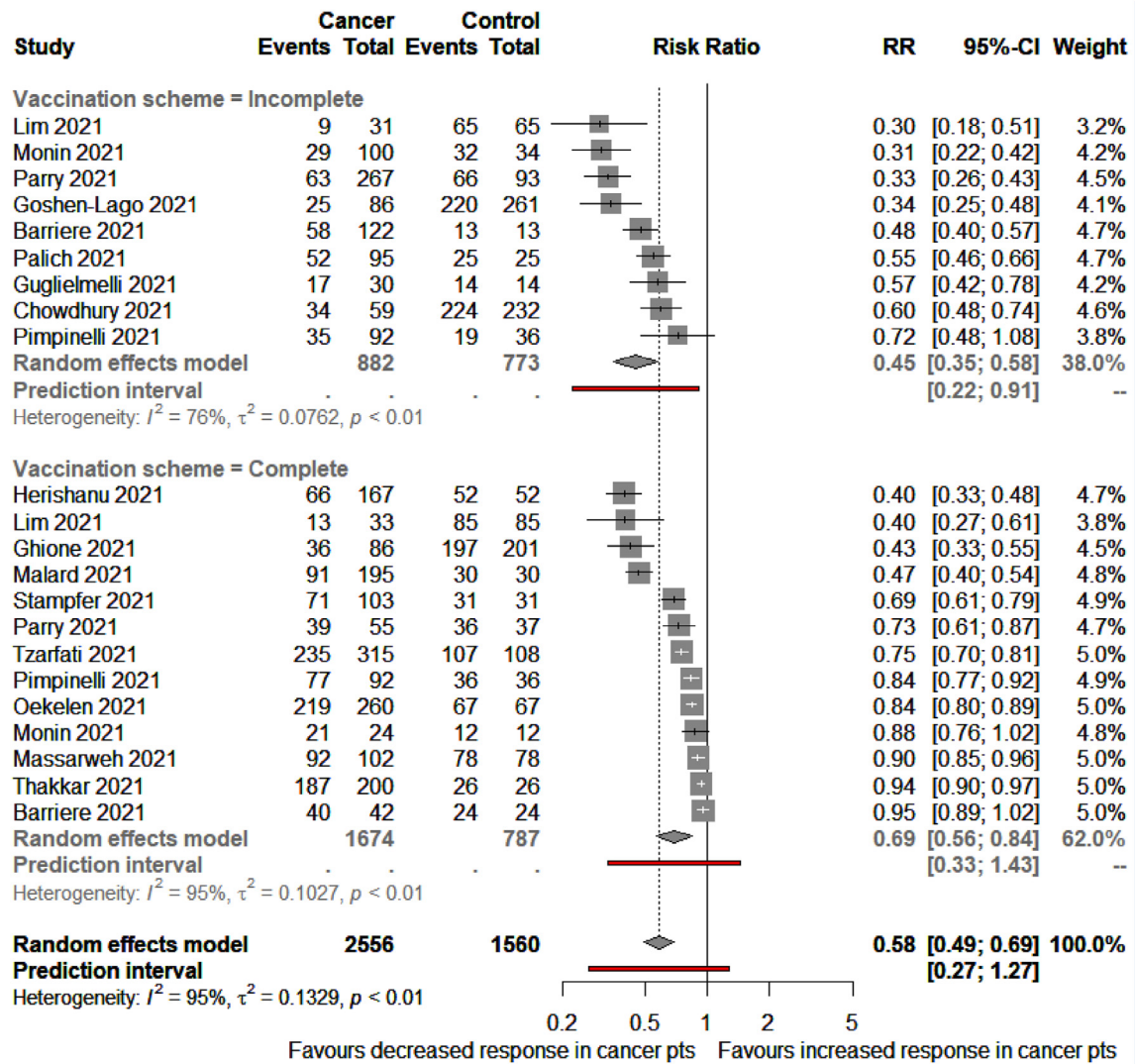
Fig. 3. **Rates of seroconversion in oncological patients versus non-cancer controls as per vaccination scheme.** Squares represent indirect effect size (Risk ratio [RR]). Horizontal lines indicate 95% Confidence Interval (CI). Diamonds indicate the meta-analytic pooled RR, calculated separately by vaccination scheme (i.e., partial or complete), and the overall pooled RR (95%CI) in patients with cancer.

SARS-CoV-2 infection after being immunised with at least one dose of COVID-19 vaccines. Moreover, when compared with non-cancer controls, oncological patients had a tendency towards increased documented SARS-CoV-2 infection after partial (RR 3.21; 95% CI 0.35−29.04) and complete COVID-19 immunisation (RR 2.04; 95% CI 0.38−11.10) (Fig. 8).

3.4. Anti-S Severe Acute Respiratory Syndrome Coronavirus 2 immunoglobin G antibody titres

No meta-analysis was conducted regarding anti-S IgG titres owing to the wide heterogenicity in serological immunoassays used in the eight studies reporting data on this outcome for both patients and controls (Supplemental eTable 3) [18,19,28,29,33,34,42,44]. Overall, lower anti-S IgG titres were documented

in patients with cancer after partial and complete immunisation among individual studies.

3.5. T-cell response among oncological patients

A pooled analysis of six studies [20,25,26,39,40,54] including 84 patients with incomplete and 634 with complete vaccination regimens showed that 78% (95% CI 30−97) and 60% (95% CI 30−84) developed an adequate T-cell response, respectively (Supplemental eFig. 4).

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis assessing the immunogenicity of COVID-19 vaccines in the oncological population. Results of this meta-analysis demonstrate that patients
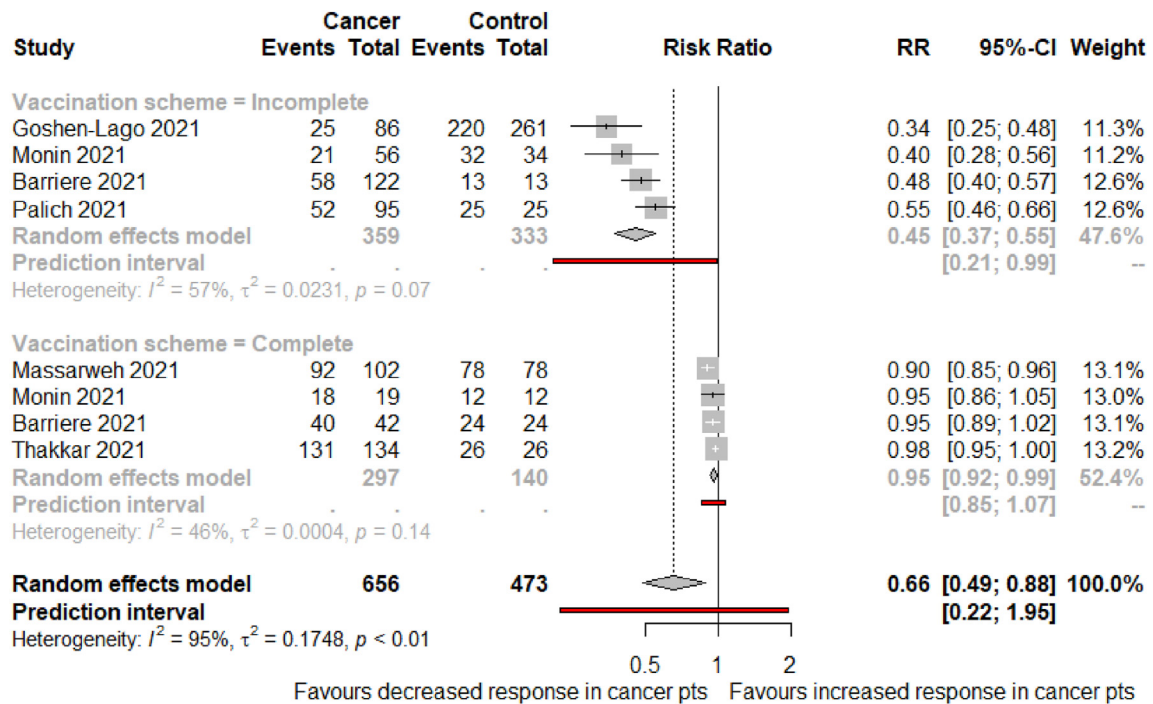
Fig. 4. **Rates of seroconversion in patients with solid malignancies versus non-cancer controls as per vaccination scheme.** Squares represent indirect effect size (Risk ratio [RR]). Horizontal lines indicate 95% Confidence Interval (CI). Diamonds indicate the meta-analytic pooled RR, calculated separately by vaccination scheme (i.e., partial or complete), and the overall pooled RR (95%CI) in patients with cancer.

with cancer have a lower likelihood of attaining acceptable immune response after COVID-19 immunisation when compared with non-cancer patients. However, despite the suboptimal seroconversion rates observed in this group, a notable increase in humoral response was documented among patients with cancer who completed a COVID-19 vaccination regimen.

The low humoral immune response mounted by oncological patients after being vaccinated against SARS-CoV-2 is of utmost importance owing to their higher risk of developing severe disease with consequent poor prognosis if infected [4,11,55,56]. Immunisation against COVID-19 has been widely recommended among patients with cancer, regardless of the site of disease, setting and type of treatment, as its benefits outweigh the potential risks [55,57]. Oncological patients should be encouraged to adhere to COVID-19 prevention guidelines and complete their vaccination schemes after the recommended intervals between doses (i.e. three or four weeks for mRNA vaccines). As shown by this meta-analysis, a substantial proportion of patients with cancer do not mount an appropriate immunological response after partial vaccination and could be at a relatively high risk of infection and severe COVID-19 when delaying the second dose.

Furthermore, despite patients with cancer having a higher risk of SARS-CoV-2 infection after vaccination compared with controls, only 0.55% of patients developed COVID-19 after being immunised. These findings are encouraging as they highlight that even though this

population has a lower likelihood of mounting an adequate immune response after vaccination, their risk of infection may drop significantly after being vaccinated. However, conclusions should be cautiously drawn as the low rate of infection documented in each study may be influenced by the epidemic burden of COVID-19 across countries and specific time points, as well as the underestimation of SARS-CoV-2 cases owing to the lack of testing in asymptomatic participants, which could be as high as 20% [58], and to an inadequate follow-up.

Growing evidence suggests that among patients with cancer, those with haematological malignancies are less likely to develop robust anti-S IgG after SARS-CoV-2 vaccination owing to immunosuppression induced by disease-related lineage defects and its treatments [3,17,35,36]. Consistently, when stratifying by type of cancer, we observed that patients with haematological malignancies had the highest risk of being non-responders after complete COVID-19 vaccination. Furthermore, oncologic regimens based on monoclonal antibodies (anti-CD20, anti-CD38), Bruton tyrosine kinase inhibitor, Bcl-2 inhibitor, Janus Kinase 1/2 inhibitors and chimeric antigen receptor T-cell therapy have been associated with lower seroconversion rates [17,19,27–29,33,34,38–40,42,44–48,51,53,54]. Of note, monoclonal antibodies (i.e. anti-CD20) might not only blunt B-cell response by decreasing the neutralising antibodies titres but may also affect patients' T-cell immunity [3,17,36,58]. Thus, a markedly reduced response to COVID-19 immunisation could be expected in
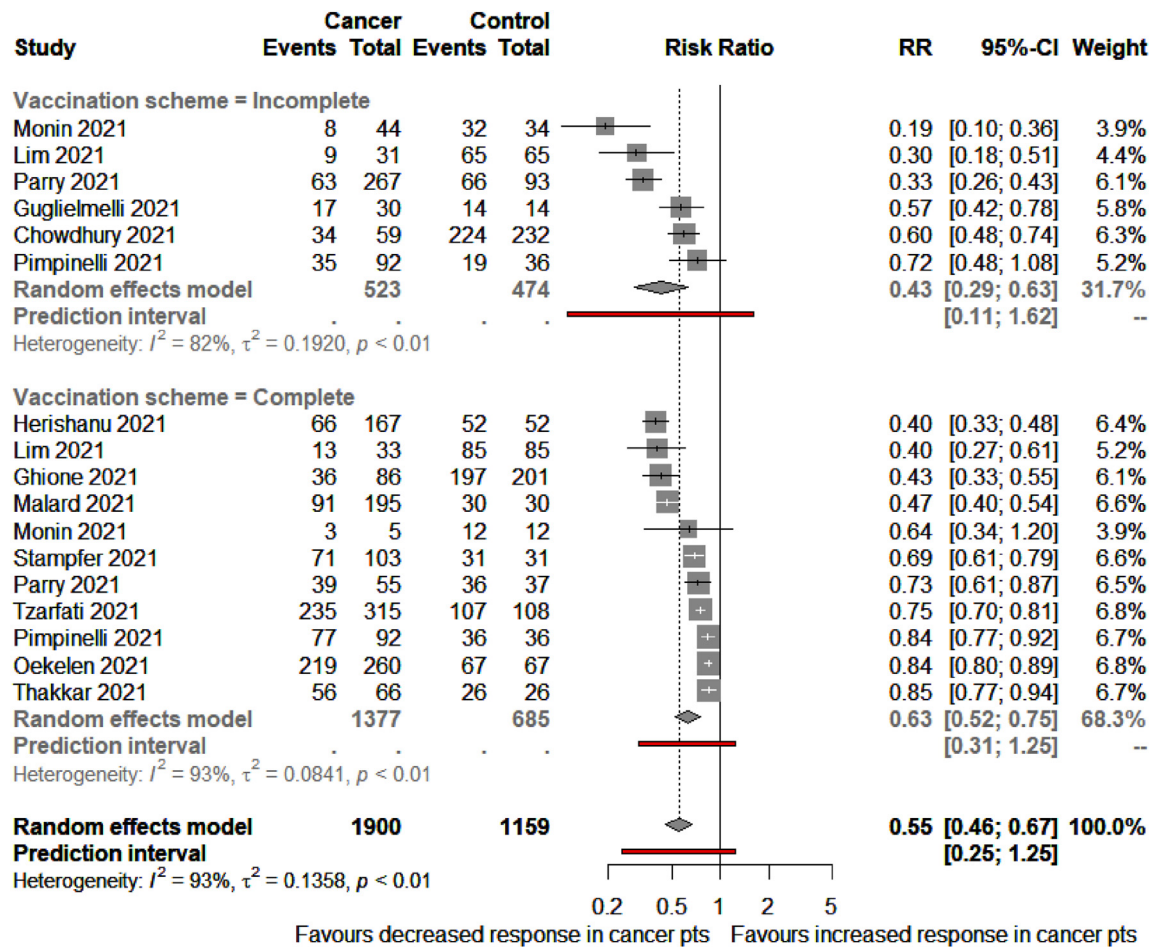
Fig. 5. **Rates of seroconversion in patients with haematological malignancies versus non-cancer controls as per vaccination scheme.** Squares represent indirect effect size (Risk ratio [RR]). Horizontal lines indicate 95% Confidence Interval (CI). Diamonds indicate the meta-analytic pooled RR, calculated separately by vaccination scheme (i.e., partial or complete), and the overall pooled RR (95%CI) in patients with cancer.

patients receiving therapeutic agents that interfere with humoural and cellular response.

Recent data suggest that among patients with suboptimal humoural immunogenicity to COVID-19 vaccines a substantial proportion developed T-cell response, most likely owing to cross-reactivity to other human coronaviruses [58]. Although new evidence from the Vaccination Against COVID in Cancer (VOICE) and Coronavirus Disease 2019 Antiviral Response in a Pan-tumor Immune Monitoring (CAPTURE) trials have shown that chemotherapy was not a significant predictor for suboptimal immunogenicity in patients with solid tumours [58,59], numerous studies have documented the potential detrimental impact that chemotherapy could have in seroconversion rates after COVID-19 immunisation in patients with cancer [17,18,20,25,30,33,35,38,41,46,54]. Further studies with sufficient statistical power to evaluate the influence of different oncological treatments on COVID-19 vaccine immunogenicity among patients with solid and haematological malignancies are warranted.

The optimal approach for administering COVID-19 vaccines among patients with higher risk of non-responsiveness remains unclear. As per NCCN guidelines, only patients with stem cell transplant and those receiving cellular therapy should wait for at least three months after finishing the therapy to get vaccinated against COVID-19, otherwise, patients with cancer should get vaccinated as soon as they can [57]. However, the administration of anti-CD20 monoclonal antibodies within 12 months and chemotherapy within four weeks before vaccination could diminish patients' immune response [17,19,27,28,38–40,58,59]. Thus, oncologists should warn patients, particularly those with haematological malignancies such as leukaemia, lymphoma, multiple myeloma and those who received COVID-19 vaccines while being under these treatments that they might not have an appropriate protection against SARS-CoV-2 wild-variant and variants of concern [58].

Several studies have already demonstrated the benefits of a booster COVID-19 vaccine dose after completion of the standard immunisation scheme among
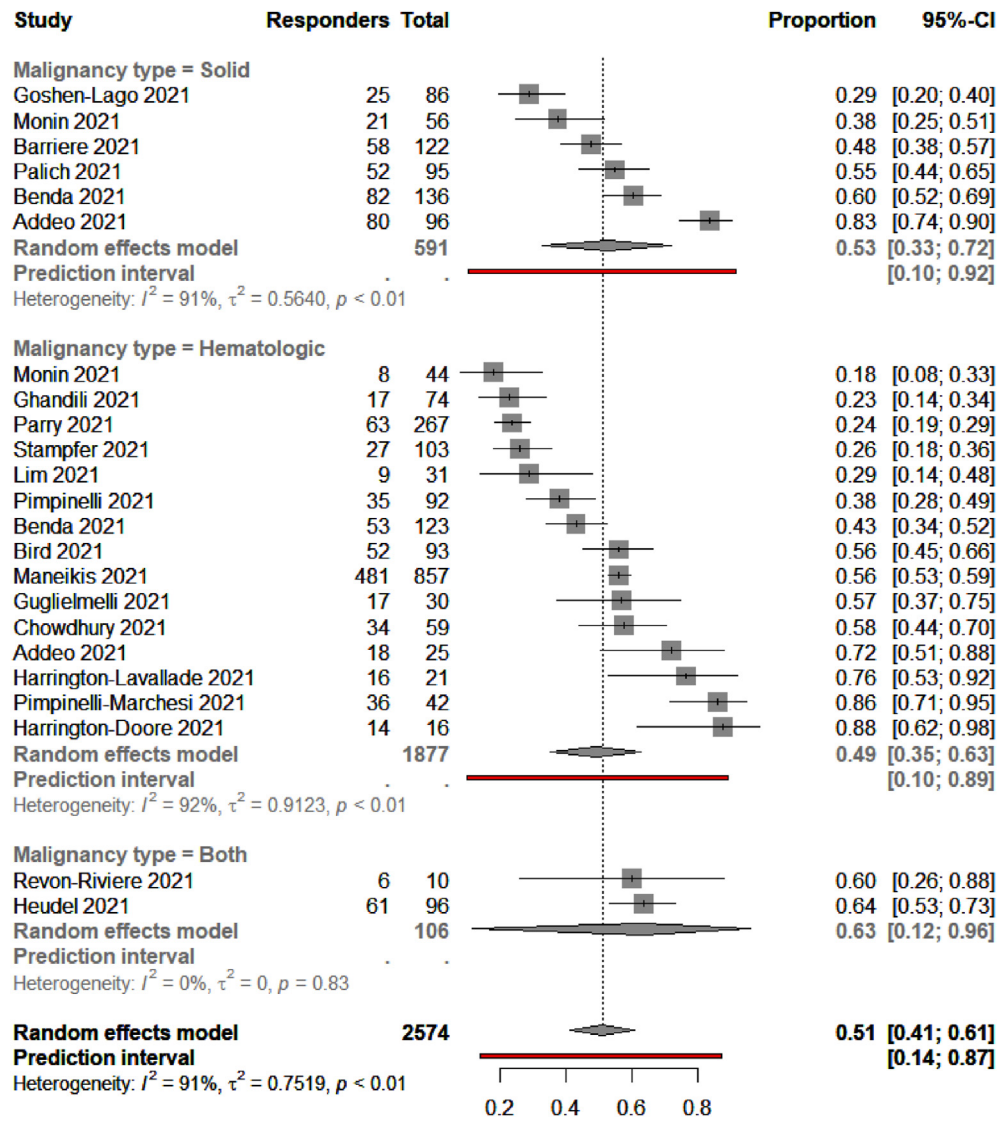
Fig. 6. **Rates of seroconversion in patients with haematological versus solid malignancies and incomplete COVID-19 vaccination regimen.** Squares represent indirect effect size (Risk ratio [RR]). Horizontal lines indicate 95% Confidence Interval (CI). Diamonds indicate the meta-analytic pooled RR, calculated separately by vaccination scheme (i.e., partial or complete), and the overall pooled RR (95%CI) in patients with cancer. COVID-19, Coronavirus Disease 2019.

immunocompromised and patients with cancer [39,60–64]. Therefore, health authorities in France, Israel, Germany and the United Kingdom have issued statements advocating for a booster vaccine dose in immunocompromised patients [17]. In addition, the Food and Drug Administration and the Centers for Disease Control and Prevention have recently authorised the administration of a homologous booster dose for solid organ transplant recipients and those with an equivalent level of immunosuppression [65,66]. The implementation of this strategy has demonstrated a significant increase in patients' humoural response [39,61,62,64]. Nonetheless, a substantial proportion of the evaluated patients did not attain seroconversion even after receiving a third dose, which could limit the

benefits of homologous booster vaccination for immunocompromised patients [39,60–62,64].

Another promising strategy that has gained interest for enhancing patients' immune response after COVID-19 vaccination is the use of heterologous vaccine regimens. Recent studies assessing this approach among the general population have yielded encouraging results, reporting higher anti-S IgG titres and neutralising antibodies against certain SARS-CoV-2 variants of concern, as well as an increased CD4 T-cell response compared with homologous COVID-19 vaccine regimens [67–70]. Clinical investigators, industry and regulatory stakeholders should encourage the development of clinical and observational studies such as the COVID-19 Vaccine Cohort in Specific Populations
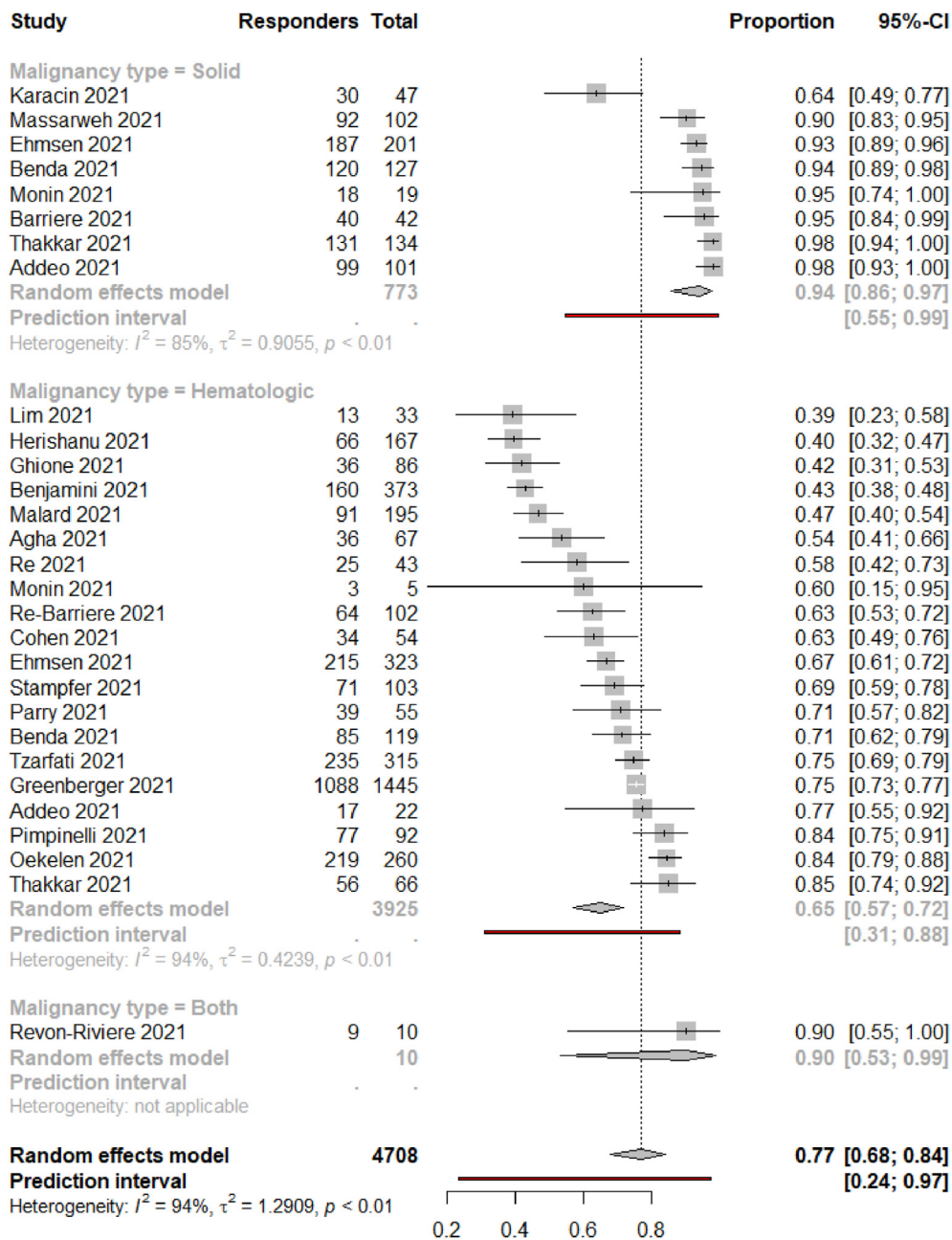
Fig. 7. **Rates of seroconversion in patients with haematologic versus solid malignancies and complete COVID-19 vaccination regimen.** Squares represent indirect effect size (Risk ratio [RR]). Horizontal lines indicate 95% Confidence Interval (CI). Diamonds indicate the meta-analytic pooled RR, calculated separately by vaccination scheme (i.e., partial or complete), and the overall pooled RR (95%CI) in patients with cancer. COVID-19, Coronavirus Disease 2019.

(COV-POPART) study [71] that aims to evaluate different immunisation approaches in the oncological population, including the use of booster doses and heterologous vaccination schemes.

As the most effective strategy for tackling the burden imposed by the COVID-19 pandemic, immunisation should be particularly encouraged among the oncological population. Efforts should also be focused on increasing the available information regarding the effectiveness, safety profile and benefits of COVID-19

vaccination among patients with cancer. Moreover, the promotion of vaccine literacy and the active participation of oncologists and other health-care workers should be emphasised, as these remain key to increase patients' acceptance and adherence to the recommended vaccination schemes [72–75]. Despite several countries having removed restrictions such as the use of face masks and social distancing for those that have completed their COVID-19 vaccination scheme, these measures should be taken cautiously and should not be extended
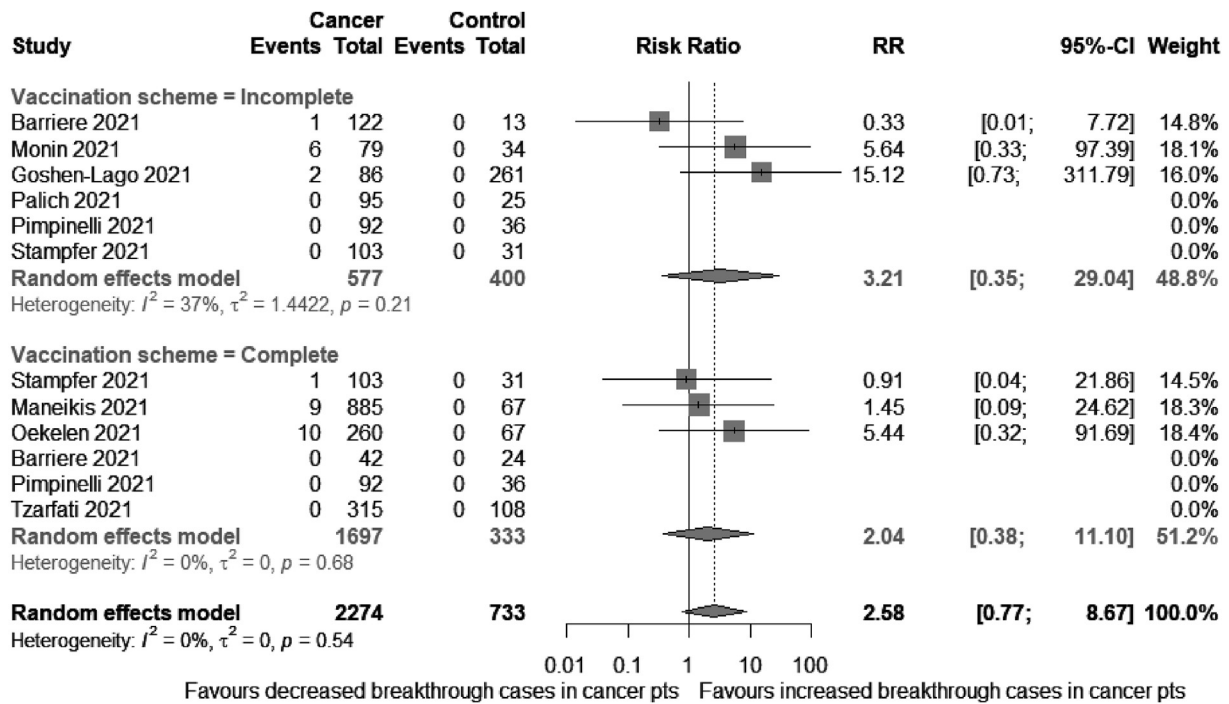
Fig. 8. **Rates of SARS-CoV-2 infection in oncological patients after vaccination compared with controls.** Squares represent indirect effect size (Risk ratio [RR]). Horizontal lines indicate 95% Confidence Interval (CI). Diamonds indicate the meta-analytic pooled RR, calculated separately by vaccination scheme (i.e., partial or complete), and the overall pooled RR (95%CI) in patients with cancer. SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

automatically to all patients with cancer in whom vaccine effectiveness is not comparable to that of the general population.

5. Limitations

Among the limitations of this meta-analysis, it should be considered that the number of included studies, as well as the heterogeneity across them regarding patient and control characteristics, patients' type of malignancy and treatment, immunogenicity assessment and type of vaccine, may limit the generalisation of the results. It is particularly important to highlight that the included studies are observational and subject to potential sources of bias, such as selection bias or confounding, that cannot be adjusted through meta-analytical techniques. All included studies evaluated anti-S IgG as a surrogate for COVID-19 immunogenicity, and just a few assessed cellular response or SARS-CoV-2 infection after vaccination. However, owing to the high sensitivity and specificity of most immunoassays and the minimal likelihood of infection in immunised patients, it is reasonable to expect that anti-S IgG levels correlate with neutralising antibodies against SARS-CoV-2 [17], thus allowing for an adequate COVID-19 effectiveness evaluation. Owing to the substantial heterogeneity in immunoassays and threshold values for anti-S IgG measurements, differences in mean titres between patients with cancer and controls could not be

compared. The present results have limited generalisability to COVID-19 vaccines different from mRNA Pfizer-BioNTech (BNT162b2), as only a few studies included patients who received other types of vaccines. Although the type of treatment administered in parallel with a COVID-19 vaccine could play an important role in the degree of humoural and cellular responses attained by oncological patients, the lack of sufficient data did not allow to perform subgroup analyses in this regard. Finally, an important amount of funnel plot asymmetry was detected, particularly towards the null hypothesis. However, the difference in seroconversion rates between patients with cancer and controls remained significant after adjusting the pooled effect by limit meta-analysis. As the number of studies in oncological patients increases, robust methodologies to explore the sources of heterogeneity should be implemented, such as meta-regression, which could help refine our current estimates.

6. Conclusion

This systematic review and meta-analysis suggest that oncological patients attain a lower immunological response when compared with non-cancer controls. Even after completing the immunisation scheme, patients with haematological and solid malignancies showed inferior seroconversion rates than those without cancer. Despite this suboptimal immunologic response,

SARS-CoV-2 infection was documented only in a small percentage of immunised cancer patients. Studies focussing on strategies to enhance the immune response among oncological patients are urgently warranted, as well as those evaluating the effectiveness, feasibility and optimal timing for this population to receive a booster dose after completing the COVID-19 immunisation regimen.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Cynthia Villarreal-Garza declares grants from AstraZeneca and Roche; speaking honoraria from Roche, Myriad Genetics, Novartis, Pfizer and Eli Lilly; travel fees from Roche, MSD Oncology and Pfizer; and advisory roles at Roche, Novartis, Pfizer and Eli Lilly. Matteo Lambertini declares advisory role for Roche, Lilly, Novartis, Exact Sciences and AstraZeneca; speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz and Takeda outside the submitted work. Marco Tagliamento declares travel grants from Roche, Bristol-Myers Squibb, AstraZeneca and Takeda: honoraria as medical writer from Novartis and Amgen outside the submitted work. No other disclosures to report.

Author contributions

Andrea Becerril-Gaitan, Bryan F. Vaca-Cartagena, Ana S. Ferrigno and Fernanda Mesa-Chavez contributed to the study conceptualisation and methodology. Cynthia Villarreal-Garza should be recognised for the project administration and supervision. Andrea Becerril-Gaitan, Bryan F. Vaca-Cartagena, Ana S. Ferrigno and Fernanda Mesa-Chavez performed the data collection. Ana S. Ferrigno and Tonatiuh Barrientos-Gutiérrez conducted the formal data analyses. Andrea Becerril-Gaitan and Bryan F. Vaca-Cartagena performed the writing of the original draft and visualisation. Andrea Becerril-Gaitan, Bryan F. Vaca-Cartagena, Ana S. Ferrigno, Fernanda Mesa-Chavez, Tonatiuh Barrientos-Gutiérrez, Matteo Lambertini, Marco Tagliamento and Cynthia Villarreal-Garza reviewed and edited the article. All authors read and approved the final article.

Funding

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.10.014.

References

[1] Johns Hopkins Coronavirus Resource Center. COVID-19 map - johns hopkins coronavirus resource center. https://coronavirus.jhu.edu/map.html. [Accessed 21 August 2021].

[2] Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21:335. https://doi.org/10.1016/S1470-2045(20)30096-6.

[3] Griffiths EA, Segal BH. Immune responses to COVID-19 vaccines in patients with cancer: promising results and a note of caution. Cancer Cell 2021;39:1045–7. https://doi.org/10.1016/J.CCELL.2021.07.001.

[4] Tagliamento M, Agostinetto E, Bruzzone M, Ceppi M, Saini KS, de Azambuja E, et al. Mortality in adult patients with solid or hematological malignancies and SARS-CoV-2 infection with a specific focus on lung and breast cancers: a systematic review and meta-analysis. Crit Rev Oncol Hematol 2021:163. https://doi.org/10.1016/j.critrevonc.2021.103365.

[5] WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 - 3 March 2020. 2021. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—3-march-2020. [Accessed 13 July 2021].

[6] Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med 2021. https://doi.org/10.1016/S2213-2600(21)00331-3. In press.

[7] RECOVERY Collaborative Group. Randomised evaluation of COVID-19 therapy. 2021. https://www.recoverytrial.net/results. [Accessed 21 September 2021].

[8] RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with covid-19. N Engl J Med 2021;384:693–704. https://doi.org/10.1056/NEJMoa2021436.

[9] RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021;397:1637–45. https://doi.org/10.1016/S0140-6736(21)00676-0.

[10] Mallapaty S. Can COVID vaccines stop transmission? Scientists race to find answers. Nature 2021. https://doi.org/10.1038/D41586-021-00450-Z. https://www.nature.com/articles/d41586-021-00450-z; 2021. [Accessed 13 July 2021].

[11] de Azambuja E, Brandão M, Wildiers H, Laenen A, Aspeslagh S, Fontaine C, et al. Impact of solid cancer on in-hospital mortality overall and among different subgroups of patients with COVID-19: a nationwide, population-based analysis. ESMO Open 2020;5. https://doi.org/10.1136/esmoopen-2020-000947.

[12] Ribas A, Sengupta R, Locke T, Zaidi S, Campbell K, Carethers J, et al. Priority COVID-19 vaccination for patients with cancer while vaccine supply is limited. Cancer Discov 2021;11:233–6. https://doi.org/10.1158/2159-8290.CD-20-1817.

[13] Ong MBH. Cancer groups urge CDC to prioritize cancer patients for COVID-19 vaccination - the Cancer Letter. 2021. https://cancerletter.com/covid-19-cancer/20210108_2/. [Accessed 13 July 2021].

[14] MC G, JG W, LC H, A T, V T, F A, et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. Lancet Oncol 2020;21: 914—22. https://doi.org/10.1016/S1470-2045(20)30314-4.

[15] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N Engl J Med 2020;383:2603—15. https://doi.org/10.1056/nejmoa2034577.

[16] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403—16. https://doi.org/10.1056/nejmoa2035389.

[17] Addeo A, Shah PK, Bordry N, Hudson RD, Albracht B, Marco M Di, et al. Immunogenicity of SARS-CoV-2 messenger RNA vaccines in patients with cancer. Cancer Cell 2021;39: 1091—1098.e2. https://doi.org/10.1016/J.CCELL.2021.06.009.

[18] Massarweh A, Eliakim-Raz N, Stemmer A, Levy-Barda A, Yust-Katz S, Zer A, et al. Evaluation of seropositivity following BNT162b2 messenger RNA vaccination for SARS-CoV-2 in patients undergoing treatment for cancer. JAMA Oncol 2021;7(8): 1133—40. https://doi.org/10.1001/JAMAONCOL.2021.2155.

[19] Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood 2021;137: 3165—73. https://doi.org/10.1182/BLOOD.2021011568.

[20] Monin L, Laing AG, Muñoz-Ruiz M, McKenzie DR, del M del Barrio I, Alaguthurai T, et al. Safety and immunogenicity of one versus two doses of the COVID-19 vaccine BNT162b2 for patients with cancer: interim analysis of a prospective observational study. Lancet Oncol 2021;22:765—78. https://doi.org/10.1016/S1470-2045(21)00213-8.

[21] Desai A, Gainor JF, Hegde A, Schram AM, Curigliano G, Pal S, et al. COVID-19 vaccine guidance for patients with cancer participating in oncology clinical trials. Nat Rev Clin Oncol 2021; 18:313—9. https://doi.org/10.1038/s41571-021-00487-z. 185 2021.

[22] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:332—6. https://doi.org/10.1136/BMJ.B2535.

[23] Villarreal-Garza C, Becerril-Gaitan A, Vaca-Cartagena B, Ferrigno A, Mesa-Chavez F. Immunogenicity of COVID-19 vaccines among patients with cancer: a systematic review and meta-analysis protocol. Natl Inst Heal Res 2021. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=261974. [Accessed 13 July 2021].

[24] Goshen-Lago T, Waldhorn I, Holland R, Szwarcwort-Cohen M, Reiner-Benaim A, Shachor-Meyouhas Y, et al. Serologic status and toxic effects of the SARS-CoV-2 BNT162b2 vaccine in patients undergoing treatment for cancer. JAMA Oncol 2021;7(10): 1507—13. https://doi.org/10.1001/JAMAONCOL.2021.2675.

[25] Harrington P, de Lavallade H, Doores KJ, O'Reilly A, Seow J, Graham C, et al. Single dose of BNT162b2 mRNA vaccine against SARS-CoV-2 induces high frequency of neutralising antibody and polyfunctional T-cell responses in patients with myeloproliferative neoplasms. Leuk 2021;2021:1—5. https://doi.org/10.1038/s41375-021-01300-7.

[26] Harrington P, Doores KJ, Radia D, O'Reilly A, Lam HPJ, Seow J, et al. Single dose of BNT162b2 mRNA vaccine against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) induces neutralising antibody and polyfunctional T-cell responses in patients with chronic myeloid leukaemia. Br J Haematol 2021; 194(6):999—1006. https://doi.org/10.1111/BJH.17568.

[27] Lim SH, Campbell N, Johnson M, Joseph-Pietras D, Collins GP, Fox CP, et al. Antibody responses after SARS-CoV-2 vaccination in patients with lymphoma. Lancet Haematol 2021;8:e542—4. https://doi.org/10.1016/S2352-3026(21)00199-X.

[28] Maneikis K, Šablauskas K, Ringelevičiūtė U, Vaitekėnaitė V, Čekauskienė R, Kryžauskaitė L, et al. Immunogenicity of the BNT162b2 COVID-19 mRNA vaccine and early clinical outcomes in patients with haematological malignancies in Lithuania: a national prospective cohort study. Lancet Haematol 2021;8: e583—92. https://doi.org/10.1016/S2352-3026(21)00169-1.

[29] Palich R, Veyri M, Marot S, Vozy A, Gligorov J, Maingon P, et al. Weak immunogenicity after a single dose of SARS-CoV-2 mRNA vaccine in treated cancer patients. Ann Oncol 2021;32: 1051—3. https://doi.org/10.1016/J.ANNONC.2021.04.020.

[30] Pimpinelli F, Marchesi F, Piaggio G, Giannarelli D, Papa E, Falcucci P, et al. Fifth-week immunogenicity and safety of anti-SARS-CoV-2 BNT162b2 vaccine in patients with multiple myeloma and myeloproliferative malignancies on active treatment: preliminary data from a single institution. J Hematol Oncol 2021;14:1—12. https://doi.org/10.1186/S13045-021-01090-6. 141 2021.

[31] Revon-Riviere G, Ninove L, Min V, Rome A, Coze C, Verschuur A, et al. The BNT162b2 mRNA COVID-19 vaccine in adolescents and young adults with cancer: a monocentric experience. Eur J Cancer 2021;154:30—4. https://doi.org/10.1016/J.EJCA.2021.06.002.

[32] Thakkar A, Gonzalez-Lugo JD, Goradia N, Gali R, Shapiro LC, Pradhan K, et al. Seroconversion rates following COVID-19 vaccination among patients with cancer. Cancer Cell 2021;39(8): 1081—1090.e2. https://doi.org/10.1016/J.CCELL.2021.06.002.

[33] Herzog Tzarfati K, Gutwein O, Apel A, Rahimi-Levene N, Sadovnik M, Harel L, et al. BNT162b2 COVID-19 vaccine is significantly less effective in patients with hematologic malignancies. Am J Hematol 2021;96(10):1195—203. https://doi.org/10.1002/AJH.26284.

[34] Oekelen O Van, Gleason CR, Agte S, Srivastava K, Beach KF, Aleman A, et al. Highly variable SARS-CoV-2 spike antibody responses to two doses of COVID-19 RNA vaccination in patients with multiple myeloma. Cancer Cell 2021;39. https://doi.org/10.1016/J.CCELL.2021.06.014.

[35] Karacin C, Eren T, Zeynelgil E, Imamoglu GI, Altinbas M, Karadag I, et al. Immunogenicity and safety of the CoronaVac vaccine in patients with cancer receiving active systemic therapy. Future Oncol 2021;17(33):4447—56. https://doi.org/10.2217/fon-2021-0597.

[36] Greenberger LM, Saltzman LA, Senefeld JW, Johnson PW, DeGennaro LJ, Nichols GL. Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies. Cancer Cell 2021;39:1031—3. https://doi.org/10.1016/J.CCELL.2021.07.012.

[37] Benda M, Mutschlechner B, Ulmer H, Grabher C, Severgnini L, Volgger A, et al. Serological SARS-CoV-2 antibody response, potential predictive markers and safety of BNT162b2 mRNA COVID-19 vaccine in haematological and oncological patients. Br J Haematol 2021. https://doi.org/10.1111/bjh.17743. bjh.17743. In Press.

[38] Re D, Barrière J, Chamorey E, Delforge M, Gastaud L, Petit E, et al. Low rate of seroconversion after mRNA anti-SARS-CoV-2 vaccination in patients with hematological malignancies. Leuk Lymphoma 2021;26:1—3. https://doi.org/10.1080/10428194.2021.1957877.

[39] Re D, Seitz-Polski B, Carles M, Brglez V, Graça D, Benzaken S, et al. Humoral and cellular responses after a third dose of BNT162b2 vaccine in patients treated for lymphoid malignancies. MedRxiv 2021. https://doi.org/10.1101/2021.07.18.21260669.

[40] Malard F, Gaugler B, Gozlan J, Bouquet L, Fofana D, Siblany L, et al. Weak immunogenicity of SARS-CoV-2 vaccine in patients with hematologic malignancies. Blood Cancer J 2021;11:142. https://doi.org/10.1038/s41408-021-00534-z.

[41] Agha M, Blake M, Chilleo C, Wells A, Haidar G. Suboptimal response to COVID-19 mRNA vaccines in hematologic

malignancies patients. MedRxiv Prepr Serv Heal Sci 2021. https://doi.org/10.1101/2021.04.06.21254949.

[42] Barrière J, Chamorey E, Adjtoutah Z, Castelnau O, Mahamat A, Marco S, et al. Impaired immunogenicity of BNT162b2 anti-SARS-CoV-2 vaccine in patients treated for solid tumors. Ann Oncol 2021;32:1053–5. https://doi.org/10.1016/J.ANNONC.2021.04.019.

[43] Bird S, Panopoulou A, Shea RL, Tsui M, Saso R, Sud A, et al. Response to first vaccination against SARS-CoV-2 in patients with multiple myeloma. Lancet Haematol 2021;8:e389–92. https://doi.org/10.1016/S2352-3026(21)00110-1.

[44] Chowdhury O, Bruguier H, Mallett G, Sousos N, Crozier K, Allman C, et al. Impaired antibody response to COVID-19 vaccination in patients with chronic myeloid neoplasms. Br J Haematol 2021;194(6):1010–5. https://doi.org/10.1111/bjh.17644.

[45] Cohen D, Hazut Krauthammer S, Cohen YC, Perry C, Avivi I, Herishanu Y, et al. Correlation between BNT162b2 mRNA Covid-19 vaccine-associated hypermetabolic lymphadenopathy and humoral immunity in patients with hematologic malignancy. Eur J Nucl Med Mol Imag 2021;2021:1–10. https://doi.org/10.1007/S00259-021-05389-X.

[46] Ghione P, Gu J, Attwood K, Torka P, Goel S, Sundaram S, et al. Impaired humoral responses to COVID-19 vaccination in patients with lymphoma receiving B-cell directed therapies. Blood 2021;138(9):811–4. https://doi.org/10.1182/BLOOD.2021012443.

[47] Ghandili S, Schönlein M, Lütgehetmann M, Schulze zur Wiesch J, Becher H, Bokemeyer C, et al. Post-vaccination anti-SARS-CoV-2-antibody response in patients with multiple myeloma correlates with low CD19+ B-lymphocyte count and anti-CD38 treatment. Cancers (Basel) 2021;13:3800. https://doi.org/10.3390/cancers13153800.

[48] Parry H, McIlroy G, Bruton R, Ali M, Stephens C, Damery S, et al. Antibody responses after first and second Covid-19 vaccination in patients with chronic lymphocytic leukaemia. Blood Cancer J 2021;11(7):136. https://doi.org/10.1038/s41408-021-00528-x.

[49] Stampfer SD, Goldwater M-S, Jew S, Bujarski S, Regidor B, Daniely D, et al. Response to mRNA vaccination for COVID-19 among patients with multiple myeloma. Leukemia 2021. https://doi.org/10.1038/s41375-021-01354-7. In press.

[50] Pimpinelli F, Marchesi F, Piaggio G, Giannarelli D, Papa E, Falcucci P, et al. Lower response to BNT162b2 vaccine in patients with myelofibrosis compared to polycythemia vera and essential thrombocythemia. J Hematol Oncol 2021;14. https://doi.org/10.1186/s13045-021-01130-1.

[51] Guglielmelli P, Mazzoni A, Maggi L, Kiros ST, Zammarchi L, Pilerci S, et al. Impaired response to first SARS-CoV-2 dose vaccination in myeloproliferative neoplasm patients receiving ruxolitinib. Am J Hematol 2021;96(11):E408–10. https://doi.org/10.1002/ajh.26305. ajh.26305.

[52] Heudel P, Favier B, Assaad S, Zrounba P, Blay J-Y. Reduced SARS-CoV-2 infection and death after two doses of COVID-19 vaccines in a series of 1503 cancer patients. Ann Oncol 2021;32(11):1443–4. https://doi.org/10.1016/j.annonc.2021.07.012.

[53] Benjamini O, Rokach L, Itchaki G, Braester A, Shvidel L, Goldschmidt N, et al. Safety and efficacy of BNT162b mRNA Covid19 Vaccine in patients with chronic lymphocytic leukemia. Haematologica 2021. https://doi.org/10.3324/haematol.2021.279196. In press.

[54] Ehmsen S, Asmussen A, Jeppesen SS, Nilsson AC, Østerlev S, Vestergaard H, et al. Antibody and T cell immune responses following mRNA COVID-19 vaccination in patients with cancer. Cancer Cell 2021;39:1034–6. https://doi.org/10.1016/j.ccell.2021.07.016.

[55] Saini KS, Martins-Branco D, Tagliamento M, Vidal L, Singh N, Punie K, et al. Emerging issues related to COVID-19 vaccination in patients with cancer. Oncol Ther 2021. https://doi.org/10.1007/s40487-021-00157-1. In press.

[56] Giannakoulis VG, Papoutsi E, Siempos II. Effect of cancer on clinical outcomes of patients with COVID-19: a meta-analysis of patient data. 2020. p. 799–808. https://doi.org/10.1200/GO.20.00225.

[57] NCCN. COVID-19 vaccination guide for people with cancer 2021. https://www.nccn.org/docs/default-source/covid-19/covid-vaccine-and-cancer-05.pdf?sfvrsn=45cc3047_2. [Accessed 8 August 2021].

[58] Fendler A, Shepherd S, Au L, Wilkinson K, Wu M, Byrne F, et al. Adaptive immunity and neutralizing antibodies against SARS-CoV-2 variants of concern following vaccination in patients with cancer: the CAPTURE study. Nat Cancer 2021. https://doi.org/10.1038/s43018-021-00274-w. In press.

[59] Oosting S, van der Veldt A, GeurtsvanKessel C, Fehrmann R, van Binnendijk R, Dingemans AM, et al. mRNA-1273 COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or chemoimmunotherapy for solid tumours: a prospective, multicentre, non-inferiority trial. Lancet Oncol 2021. https://doi.org/10.1016/S1470-2045(21)00574-X. In press.

[60] Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA covid-19 vaccine in solid-organ transplant recipients. N Engl J Med 2021;385(7):661–2. https://doi.org/10.1056/nejmc2108861.

[61] Werbel WA, Boyarsky BJ, Ou MT, Massie AB, Tobian AAR, Garonzik-Wang JM, et al. Safety and immunogenicity of a third dose of SARS-CoV-2 vaccine in solid organ transplant recipients: a case series. Ann Intern Med 2021;174(9):1330–2. L21-0282 https://10.7326/L21-0282.

[62] Benotmane I, Gautier G, Perrin P, Olagne J, Cognard N, Fafi-Kremer S, et al. Antibody response after a third dose of the mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients with minimal serologic response to 2 doses. JAMA 2021;326(11):1063–5. https://doi.org/10.1001/JAMA.2021.12339.

[63] Hill JA, Ujjani CS, Greninger AL, Shadman M, Gopal AK. Immunogenicity of a heterologous COVID-19 vaccine after failed vaccination in a lymphoma patient. Cancer Cell 2021;39:1037–8. https://doi.org/10.1016/j.ccell.2021.06.015.

[64] Hall VG, Ferreira VH, Ku T, Ierullo M, Majchrzak-Kita B, Chaparro C, et al. Randomized trial of a third dose of mRNA-1273 vaccine in transplant recipients. N Engl J Med 2021;385(13):1244–6. https://doi.org/10.1056/NEJMc2111462.

[65] FDA. Coronavirus (COVID-19) update: FDA authorizes additional vaccine dose for certain immunocompromised individuals. 2021. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-vaccine-dose-certain-immunocompromised. [Accessed 15 August 2021].

[66] CDC. Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States. 2021. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. [Accessed 15 August 2021].

[67] Barros-Martins J, Hammerschmidt SI, Cossmann A, Odak I, Stankov MV, Morillas Ramos G, et al. Immune responses against SARS-CoV-2 variants after heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. Nat Med 2021;27(9):1525–9. https://doi.org/10.1038/s41591-021-01449-9.

[68] Normark J, Vikström L, Gwon Y-D, Persson I-L, Edin A, Björsell T, et al. Heterologous ChAdOx1 nCoV-19 and mRNA-1273 vaccination. N Engl J Med 2021;385(11):1049–51. https://doi.org/10.1056/nejmc2110716.

[69] Schmidt T, Klemis V, Schub D, Mihm J, Hielscher F, Marx S, et al. Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination. Nat Med 2021;27(9):1530–5. https://doi.org/10.1038/s41591-021-01464-w.

[70] Liu X, Shaw RH, Stuart ASV, Greenland M, Aley PK, Andrews NJ, et al. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial. Lancet 2021;398(10303):856–69. https://doi.org/10.1016/S0140-6736(21)01694-9.

[71] Loubet P, Wittkop L, Tartour E, Parfait B, Barrou B, Blay J, et al. A French cohort for assessing COVID-19 vaccine responses in specific populations. Nat Med 2021;27. https://doi.org/10.1038/S41591-021-01435-1.

[72] Villarreal-Garza C, Vaca-Cartagena BF, Becerril-Gaitan A, Ferrigno AS, Mesa-Chavez F, Platas A, et al. Attitudes and factors associated with COVID-19 vaccine hesitancy among patients with breast cancer. JAMA Oncol 2021;7(8):1242–4. https://doi.org/10.1001/jamaoncol.2021.1962.

[73] Barrière J, Gal J, Hoch B, Cassuto O, Leysalle A, Chamorey E, et al. Acceptance of SARS-CoV-2 vaccination among French patients with cancer: a cross-sectional survey. Ann Oncol 2021;32: 673–4. https://doi.org/10.1016/j.annonc.2021.01.066.

[74] Noronha V, Abraham G, Kumar Bondili S, Rajpurohit A, Menon RP, Gattani S, et al. COVID-19 vaccine uptake and vaccine hesitancy in Indian patients with cancer: a questionnaire-based survey. Cancer Res Stat Treat 2021;4:211–8. https://doi.org/10.4103/crst.crst_138_21.

[75] Villarreal-Garza C, Vaca-Cartagena B, Becerril-Gaitan A, Ferrigno A. Strategies aimed at overcoming COVID-19 vaccine hesitancy among oncologic patients. Cancer Res Stat Treat 2021; 4(3):561–2. https://doi.org/10.4103/crst.crst_173_21.