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

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Review

Booster doses of COVID-19 vaccines for patients with haematological and solid cancer: a systematic review and individual patient data meta-analysis

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KEYWORDS
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Abstract ***Importance:*** Patients with cancer have an increased risk of severe disease and mortality from COVID-19, as the disease and antineoplastic therapy cause reduced vaccine immunogenicity. Booster doses have been proposed to enhance protection, and efficacy data are emerging from several studies.
Objective: To evaluate the proportion of COVID-19 primary vaccination non-responders with cancer who seroconvert after a booster dose.
Methods: PubMed, EMBASE, CENTRAL and medRxiv were searched from 1st January 2021 to 10th March 2022. Quality was assessed using the Joanna Briggs Institute Critical Appraisal checklist.
Results: After the eligibility assessment, 22 studies were included in this systematic review and 17 for meta-analysis of seroconversion in non-responders, pooling a total of 849 patients with haematological cancer and 82 patients with solid cancer. Haematological cancer non-responders exhibited lower seroconversion at 44% (95% CI 36–53%) than solid cancer at 80% (95% CI 69–87%). Individual patient data meta-analysis found the odds of having a meaningful rise in antibody titres to be significantly associated with increased duration between the second and third dose (OR 1.02, 95% CI 1.00–1.03, $P \leq 0.05$), age of patient (OR 0.960, 95% CI 0.934–0.987, $P \leq 0.05$) and cancer type. With patients with haematological cancer as a reference, patients with lung cancer had 16.8 times the odds of achieving a meaningful increase in antibody titres (OR 16.8, 95% CI 2.95–318, $P \leq 0.05$) and gastrointestinal cancer patients had 25.4 times the odds of achieving a meaningful increase in antibody titres (OR 25.4, 95% CI 5.26–492.21, $P \leq 0.05$).
Conclusions: administration of a COVID-19 vaccine booster dose is effective in improving seroconversion and antibody levels. Patients with haematological cancer consistently demonstrate poorer response to booster vaccines than patients with solid cancer.

1. Introduction

Over the course of the pandemic, it has been well-established that COVID-19 poses a serious threat to the health of patients with cancer. With a reduced ability of host immunity to mount a protective response to COVID-19 [1], patients with cancer have a higher risk of hospitalisation [2], severe illness [3] and mortality [4–6]. Several antineoplastic therapies also compromise a patient's ability to mount an immune response, including chemotherapy, immunotherapy and radiotherapy [7,8,60]. Impairments in the immune system have been purported to last as long as 12 months after stopping antineoplastic treatment [9].

COVID-19 vaccines have proven highly efficacious in preventing severe infection and complications in healthy individuals [10,11], as well as to be cost effective at the population level [12]. Evidence has also shown favourable benefits and safety profiles in patients with cancer [13,14]. However, it has been determined that patients with cancer have a significantly blunted immune response even to complete regimens of vaccination [15]. By contrast, most healthy individuals become seropositive after the standard regimen of vaccination, with seroconversion rates approaching 100% [16].

While there have been several real-world studies conducted to date to study the efficacy and immunogenicity of booster doses, there is yet to be conclusive evidence about its utility in patients with cancer as defined by the proportion of seroconversion in previously non-seroconverted patients and the change in serological titres. Furthermore, the methods of serological measurement are heterogeneous and lead to difficulties in comparing studies.

We evaluated the efficacy of booster vaccination against COVID-19 in seroconverting patients with cancer, and elucidated disease- and therapy-related factors that increase the risk of non-seroconversion. We found the booster vaccination to be effective in protecting patients with cancer against COVID-19, with patients with solid cancer mounting better responses compared to those with haematological cancer.

2. Methods

2.1. Protocol and guidance

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. This review is registered with the National Institute for Health Research international prospective register of systematic reviews (PROSPERO) at CRD42022301256.

2.2. Search strategy

Searches of databases MEDLINE via PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and the preprint database medRxiv were searched in January 2022 for articles published

from 1st January 2021 to 10th March 2022. Searches of databases were conducted using a combination of terms including 'COVID', 'cancer' and 'vaccines' (Supplementary Table 1).

2.3. Selection of articles

We included studies that met the following inclusion criteria: (1) studies that involved human participants with solid or haematological cancers who received a booster dose of any approved COVID-19 vaccine after having completed an initial regimen of vaccination; (2) were prospective or retrospective observational studies, interventional studies or case series. Single case reports were not considered; (3) included and reported data related to the following primary and secondary outcome, with the primary outcome being seroconversion status of participants who were seronegative after the initial regimen and who received a booster dose, and secondary outcome being mean or median degree of rise in serological titre of participants who received a booster dose.

2.4. Data extraction

Data were extracted according to a pre-determined proforma in Microsoft Excel Version 16.45 by two researchers. All key extracted data were reviewed and quality-checked at the end of the data-extraction phase.

Study characteristics comprised setting, primary and secondary outcomes, study design, sample size, dropout and non-response rates and inclusion and exclusion criteria. Participant data collected comprised age, sex and comprehensive cancer and treatment history, including antineoplastic regimen. Intervention-related data included vaccine type and brand, dosing schedule and number of subjects receiving each type and brand of vaccine and median or mean interval between doses. Outcome-related data comprised assay, antibody measured, method of measurement and definition of seroconversion. We also approached the corresponding authors of included articles for individual patient data for further analysis.

2.5. Data analysis

All analyses were run using R Version 4.1.0. We used the generalised linear mixed effects model to pool the logit transformed proportions of patients with cancer who achieved seroconversion after a booster dose of COVID-19 vaccine. We assessed for and considered between-study heterogeneity as significant if the p-value of the Q-test was <0.10, or if the I statistic was $\geq 50\%$. Sensitivity analyses was performed by comparing the results to other meta-analysis models including fixed effect models and excluding trials with a high risk of bias.

Subgroup analyses were planned according to key categorical variables including (1) treatment received, (2) haematological or solid cancer, (3) if heterologous or homologous booster vaccines were administered and (4) type and/or brand of booster vaccine.

As COVID-19 antibody titre levels are measured heterogeneously with variation across studies in the specific antibody measured, type and brand of serology kit and whether index values were available, we assessed serological titres before and after the booster dose with systematic review, instead of meta-analysis.

For the individual patient data meta-analysis, we defined patients with 'a meaningful rise in antibody titres' as those who were seropositive after the booster dose and had a two-fold or more increase in antibody titres. We conducted a multivariate logistic regression to determine the association of cancer type, age, sex and the days between the last dose of the normal vaccine regimen and the booster dose, with the odds of achieving a meaningful rise in antibody titres. The beta-coefficient is exponentiated to produce an odds ratio (OR) with its corresponding 95% CI.

2.6. Risk of bias assessment

Quality of all included studies was assessed using the Joanna Briggs Institute Critical appraisal checklist by two reviewers independently. All discrepancies were resolved by the consultation of a third reviewer.

3. Results

3.1. Summary of included studies

A total of 22 studies were included following the eligibility assessment (Fig. 1) [18–39], with 17 analysed in the quantitative synthesis of seroconversion rates post-booster dose [18,20–23,25,27–29,31,32,34–39]. Of these, 14 studies included patients with haematological cancers [18,22,23,25,27–29,31,34–39], while three involved those with solid tumours [20,21,32]. Thirteen studies included patients receiving either the Pfizer-BioNTech, Moderna or Janssen vaccines [18–22,24–26,31,33,35,36,38]; seven included solely those receiving Pfizer-BioNTech [23,27,28,30,32,34,37]; one study included only patients receiving Janssen [29] and one study included only patients receiving Moderna [39]. Konishi *et al.* [24] and Shroff *et al.* [32] further included healthy subjects as control; Marlet *et al.* [25] compared patients with chronic lymphocytic leukaemia to kidney transplant recipients; Zeng *et al.* [33] compared patients in receipt of the booster dose with those only receiving the standard two-dose regimen; the remaining included studies did not include a control group. Further details of these studies can be found in Table 1. On assessment with the Joanna Briggs Institute Critical appraisal checklist, studies were not found to be at significant risk of bias (Supplementary Table 2).

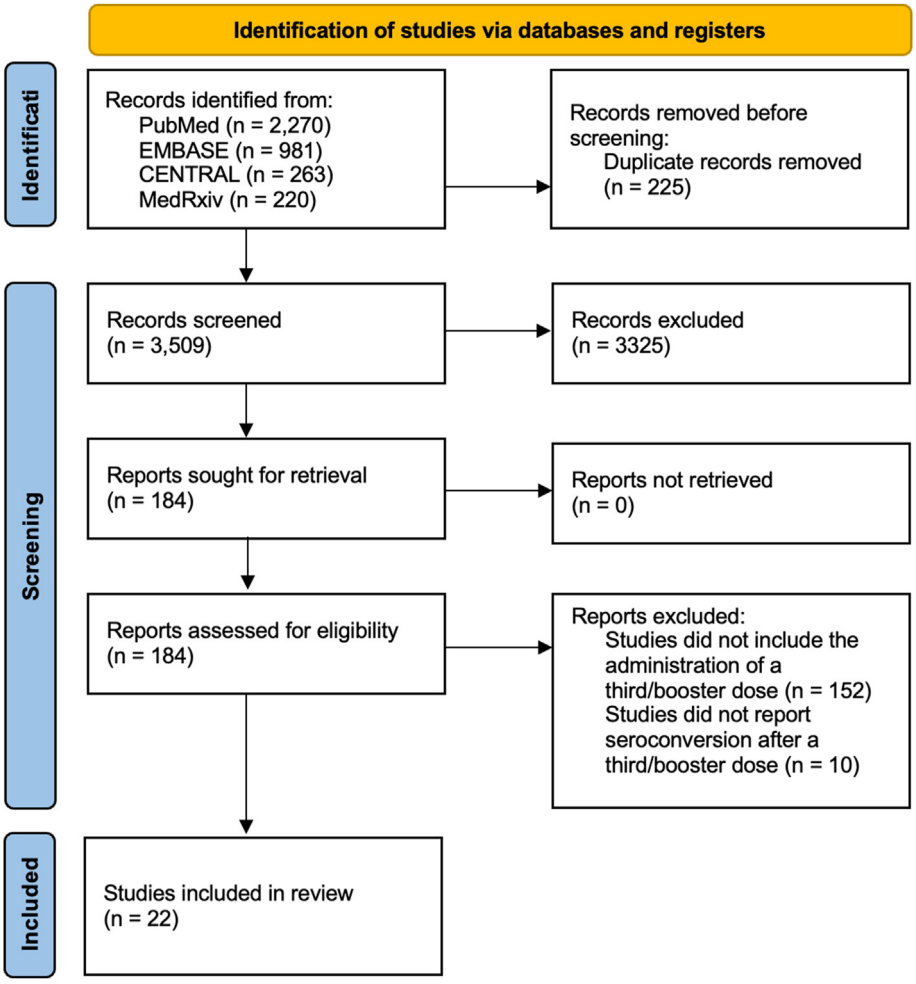

Fig. 1. PRISMA flowchart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

3.2. Seroconversion rates following booster shot

In our meta-analysis (Fig. 2), we found that the overall seroconversion rate after the administration of a booster dose was 50% (95% CI 41–60) with the random-effects model, with significant heterogeneity (I^2 = 84%). We undertook further subgroup analyses by considering only patients with haematological malignancies or solid tumours (Fig. 1). There was a significant difference between the two subgroups ($P < 0.01$), with the prevalence of seroconversion in patients with haematological cancer markedly lower at 44% (95% CI 36–53) compared to patients with solid tumours at 80% (95% CI 69–87).

By visual inspection of the funnel plot, minimal asymmetry was observed (Supplementary Fig. 1). This was further reinforced with Egger's linear regression test (Supplementary Fig. 2) in which funnel plot asymmetry was not detected ($p = 0.1277$).

3.3. Elevation in antibody titre post-booster dose

Amongst patients who were seropositive after the standard COVID-19 vaccination regimen in the study by Re *et al.* [27], the anti-spike protein antibody titre increased from a median of 87.1 U/mL (range 1.2–693) post-second dose to a median of 3386 U/mL (range 6.6–20312). Greenberger *et al.* [22] similarly reported a substantial increase with a median of 2128 AU/mL (IQR 563.5-14,585) amongst patients who were already seropositive. Marlet *et al.* [25], in addition, reported an increase in the anti-spike IgG titre from a median of 0.63 BAU/mL to 10.7 BAU/mL ($P = 0.0002$), while Redjoul *et al.* [28] found a rise from a mean of 737 ± 1009 AU/mL to 11,099 ± 18,607 AU/mL. Lastly, Shroff *et al.* [32] reported a three-fold increase in the median virus-neutralising antibody titres, from 60 to 180 ($P = 0.01$).

3.4. Individual patient meta-analysis

We included individual patient data from four studies, pooling 316 patients: 88 patients from Shapiro *et al.*, 36 patients from Rottenberg *et al.*, 20 patients from Shroff *et al.* and 172 patients from Herishanu *et al.* (Table 2) [23,30–32]. The median number of days between the 2nd and 3rd doses was 181 days (range: 94 days–216 days). Our multivariate analysis of the factors associated

Table 1
Summary of included articles.

Study	N	Vaccine	Malignancy	Control	Assay	Median age, years	Median end-point, days	Median time between 2nd and 3rd dose, days
Bagacean *et al.* [18]	530	Pfizer-BioNTech, Moderna	Various haematological malignancies	None	Abbott SARS-CoV-2 IgG II Quant assay	71	28	42–56
Fendler *et al.* [19]	353	Pfizer-BioNTech, Oxford-AstraZeneca	Various haematological malignancies and solid tumours haematological - 82, solid - 271	None	–	–	23	176
Fenioux *et al.* [20]	163	Pfizer-BioNTech, Moderna	Various solid tumours	None	Abbott Architect	66	28	–
Gounant *et al.* [21]	26	Pfizer-BioNTech, Moderna, Oxford-AstraZeneca	Various solid tumours	None	Abbott Architect	67	–	–
Greenberger *et al.* [22]	49	Pfizer-BioNTech, Moderna, Janssen	CLL, NHL, WM and MM	None	Elecsys	66	28	–
Herishanu *et al.* [23]	172	Pfizer-BioNTech	CLL, SLL	None	Architect AdviseDx	72.1	21	179
Konishi *et al.* [24]	25	Pfizer-BioNTech, Moderna, Janssen	MM, WM, SMM, SWM and MGUS	Healthy	Quest diagnostics	–	33	–
Marlet *et al.* [25]	20	Pfizer-BioNTech, Moderna	CLL	None	Abbott Architect	–	42	63
Naranbhai *et al.* [26]	13	Pfizer-BioNTech, Moderna, Janssen	Various haematological malignancies and solid tumours	None	Roche Elecsys	68	–	81
Re *et al.* [27]	43	Pfizer-BioNTech	CLL, B cell NHL and MM	None	Elecsys	77	27	–
Redjoul *et al.* [28]	42	Pfizer-BioNTech	Patients with HSCT	None	Abbott Architect	59	26 (mean)	51 (mean)
Reimann *et al.* [29]	29	Janssen	Various haematological malignancies and solid tumours	None	Elecsys	73	28	–
Rottenberg *et al.* [30]	37	Pfizer-BioNTech	Various solid tumours	None	Liaison	67	86	214
Shapiro *et al.* [31]	32	Pfizer-BioNTech, Moderna, Janssen	Various haematological malignancies and solid tumours	None	–	69	28	177
Shroff *et al.* [32]	20	Pfizer-BioNTech	Various solid tumours	Healthy	–	64	–	–
Zeng *et al.* [33]	50	Pfizer-BioNTech, Moderna	Various haematological malignancies and solid tumours	Patients who received 2 doses	Pseudotyped-lentivirus neutralisation assay	–	47	95
Einarsdottir *et al.* [36]	37	Pfizer-BioNTech, Moderna	Patients with HSCT	None	Abbott SARS-CoV-2 IgG II Quant assay	Responders: 60 non-responders: 63	24	127
Susol *et al.* [39]	80	Moderna	HL, NHL, CLL, MM, MDS and MPN	None	Euroimmun	–	–	–
Canti *et al.* [37]	38	Pfizer-BioNTech	Patients with HSCT	None	Abbott SARS-CoV-2 IgG II Quant assay	60	28	–
Saiag *et al.* [34]	124	Pfizer-BioNTech	Various haematological malignancies	None	Abbott SARS-CoV-2 IgG II Quant assay	72	23	–
Ehmsen *et al.* [35]	115	Pfizer-BioNTech, Moderna	CLL/SLL, MM, DLBCL, FL, MCL and MZL	None	Abbott SARS-CoV-2 IgG II Quant assay	72	180	39 (mean)

(*continued on next page*)

Table 1 (*continued*)

Study	N	Vaccine	Malignancy	Control	Assay	Median age, years	Median end-point, days	Median time between 2nd and 3rd dose, days
Abid *et al.* [38]	75	Pfizer-BioNTech, Moderna	Patients with HSCT	None	Abbott Architect	Responders: 70, non-responders: 66	Responders: 58, non-responders: 47	Responders: median 172, non-responders: median 165

Abbreviations: CLL, chronic lymphocytic leukaemia; NHL, non-Hodgkin lymphoma; WM, Waldenstrom's macroglobulinemia; MM, multiple myeloma; SLL, small lymphocytic leukaemia; SMM, smouldering multiple myeloma; SWM, smouldering Waldenstrom's macroglobulinemia; MGUS, monoclonal gammopathy of undetermined significance; HSCT, haematopoietic stem cell transplant; HL, Hodgkin's lymphoma; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.

with a meaningful increase in antibody titres showed that the odds of a meaningful increase in titres increased by 1.02 times (or 2%) for every added day between the second and third dose (OR 1.02, 95% CI 1.00−1.03, $P \leq 0.05$). The odds of a meaningful rise in titres reduced by 0.96 (or 4%) for every year increase in the cancer patient's age (OR 0.960, 95% CI 0.934−0.987, $P \leq 0.05$). With patients with haematological cancer as a reference, we found patients with lung cancer had 16.8 times the odds of achieving a meaningful increase in antibody titres (OR 16.8, 95% CI 2.95−318, $P \leq 0.05$) and patients with gastrointestinal cancer had 25.4 times the odds of achieving a meaningful increase in antibody titres (OR 25.4, 95% CI 5.26−492.21, $P \leq 0.05$).

3.5. Safety and tolerability

Majority of the studies included did not report any severe adverse events (AEs). Herishanu *et al.* [23] reported mild AEs as frequently as in 26.8% of the patients, with the most frequent symptoms being fatigue, weakness, myalgia and fever. Reimann *et al.* [29], however, reported 2 events of severe AEs (defined as grade III or IV), with the 2 patients suffering from fever and fatigue, respectively. In addition, another patient was hospitalised for hypertensive crisis, albeit likely unrelated to the COVID-19 booster dose.

4. Discussion

This meta-analysis sought to assess the efficacy of booster vaccination against COVID-19 in patients with cancer, especially those who remained seronegative after the standard vaccination regimen. We found that the provision of a booster dose resulted in substantial seroconversion, with a pooled 50% of patients having seroconverted after the booster dose. Significantly, our subgroup analysis also revealed that rates of seroconversion in patients with haematological cancers were almost half that of patients with solid cancer tumours. The proportion of seroconversion among patients with haematological cancer was pooled at 44%, compared to 80% in the solid cancer group.

Despite the relatively lower efficacy, vaccination and the subsequently conferred protection against COVID-19 in patients with cancer remains critical. Notably, patients with active cancer are especially vulnerable to acquiring a COVID-19 infection and suffer from a greater mortality risk [40,41]. Previous studies have also shown that COVID-19 infection is associated with poorer prognosis in cancer survivors [42]. The results of our study are thus promising and clinically important, providing impetus for patients with cancer who were previously not seroconverted to receive a booster dose.

A key determinant of vaccine efficacy in patients with cancer is the type of malignancy [40]; haematological malignancies, as shown in this paper, have a greater

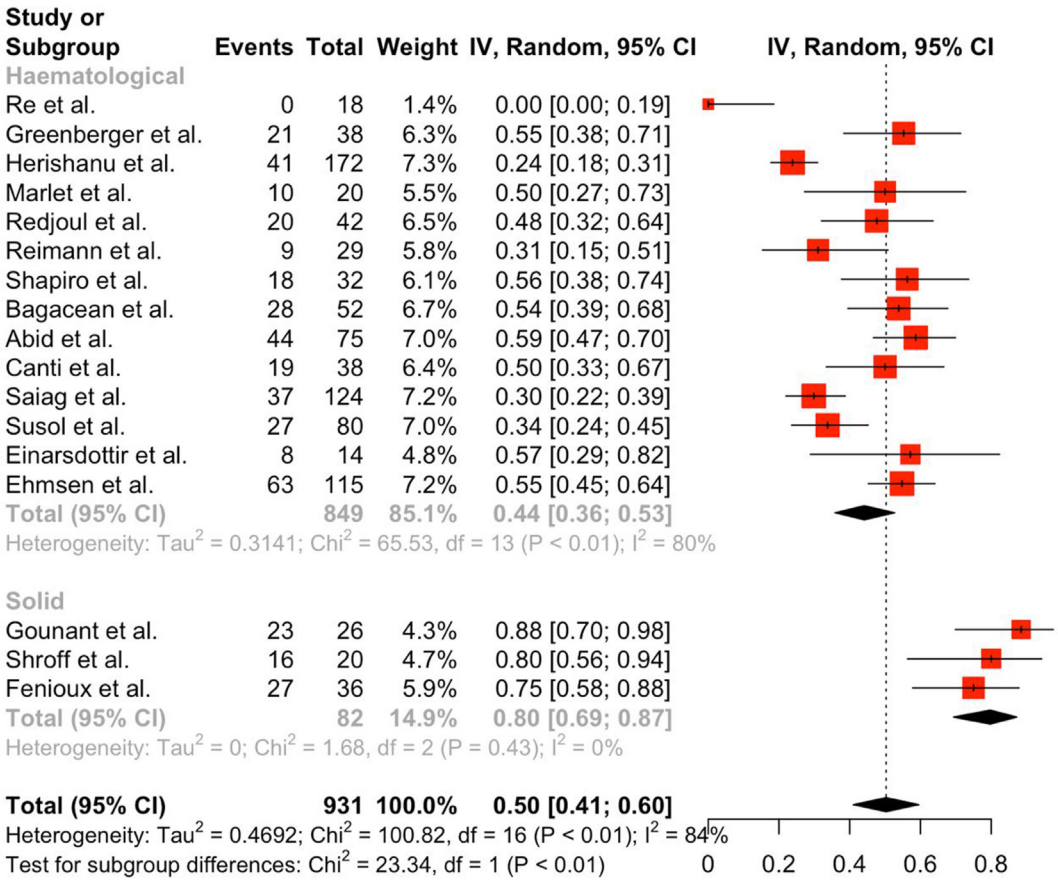

Fig. 2. Meta-analysis of seroconversion rate after a booster dose amongst non-responders to initial COVID-19 vaccination regimen.

adverse impact on seroconversion rates compared with solid tumours. The findings in a recent review conducted by our group corroborate this, revealing that haematological malignancies resulted in a much poorer seroconversion after the standard two doses COVID-19 regimen [6]. In addition, Tzarfati *et al.* [43] similarly demonstrated the greatly reduced efficacy of the BNT162b2 COVID-19 vaccine in patients with haematological cancers when compared with patients with non-haematological cancers.

Table 2
Results of a multivariate logistic regression of factors associated with the odds of achieving a meaningful rise in antibody titres after provision of a booster dose.

	OR	2.50%	97.50%	Pr(>|z|)
Age	0.960	0.934	0.987	≤0.05
Days between the second and third dose	1.02	1.00	1.03	≤0.05
GI cancer (relative to haematological cancer)	25.4	5.00	464	≤0.05
Lung cancer (relative to haematological cancer)	16.8	2.95	318	≤0.05
Other solid cancers (relative to haematological cancer)	6.38	2.60	18.1	≤0.05
(Intercept)	0.49	0.0280	8.39	≤0.05

Abbreviations: OR, odds ratio.

An additional factor of much importance is the therapy administered to patients with cancer, and this can greatly suppress the vaccine-induced immune response. Fortunately, most therapeutic modalities still allow patients to mount protective responses with COVID-19 vaccination [44]. Seroconversion and immunity against COVID-19 can similarly be expected in patients receiving targeted therapies and radiotherapy [44]. However, seroconversion could still be impaired in these patients compared with healthy subjects [45], and physicians should be more vigilant in monitoring this population.

Lymphodepleting or plasma cell-depleting therapies, however, is an exception; patients undergoing such treatments are extremely unlikely to generate an adequate immune response to COVID-19 vaccination. Anti-CD20 therapy, of note, deplete peripheral B cells for at least 4 months [46,47]. Since these treatments will likely render COVID-19 vaccination futile, general recommendations suggest the administration of vaccines after at least 6 months of stopping therapy [48,49]. Considering the special risk of patients on anti-B cell therapy contracting severe COVID-19 [50] and the demonstrable safety profile of the COVID-19 vaccine [44], COVID-19 vaccination must be considered in these vulnerable patients.

Hormone deprivation therapy, such as in breast and prostate cancer, may be associated with poor seroconversion as well. Sex steroids were demonstrated to influence the immune response to COVID-19 infection [51], and hormone deprivation, therefore, could result in a weakened immune system in this subgroup of patients [52]. Fortunately, studies have demonstrated that the majority of patients on such treatments still experience seroconversion [45,53]. Further, boosters against COVID-19 should therefore be used in these patients as well.

Yet another factor for consideration is the timing of COVID-19 vaccination in patients in receipt of active cancer therapy. While estimates of the optimal day of administration vary across studies, timing relative to the last day of the therapeutic cycle may be important as shown by studies examining the lung and breast cancer cohorts [54–56]. While our study was unable to examine the time of booster vaccination from the last therapeutic cycle, we found the median time between the third and second doses to be about 6 months (188 days, IQR 162–203). General considerations for timing the vaccination chiefly revolve around the return to activities of daily life and restoration of normal blood counts [57]. Overall, similar to other immunocompromised groups receiving immunosuppressive therapy, such as patients with immune-mediated inflammatory diseases and solid organ transplant recipients, booster doses are crucial to afford protection against COVID-19 [58,59].

Despite its important findings, this article has several limitations. First, we were unable to conduct quantitative subgroup analyses according to the treatments administered due to insufficient data, which is a key point for consideration when vaccinating patients with cancer. Second, we were only able to qualitatively describe the studies examining the emerging COVID-19 variants and vaccine efficacy, and further data would be needed before a quantitative synthesis can be attempted. Lastly, the granularity of the data analysed in this article were limited to study-level data, and methodological as well as demographic differences between the studies might have led to the levels of heterogeneity observed in the article.

5. Conclusion

The present study has demonstrated that booster doses of COVID-19 vaccines are effective in improving seroconversion and antibody levels, with patients with haematological cancer consistently demonstrating poorer response than patients with solid cancer. Nevertheless, our results show that vaccinating these patients with a booster dose is effective in inducing seroconversion thus affording greater protection in these vulnerable immunocompromised populations. Further research is needed to determine additional booster doses would be desired especially in patients with haematological cancer.

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The funder was not involved in any decision making that may influence the study.

Author contributions

Conceptualisation: ARYBL, YYS, RS and MXL; Data curation: ASM, ARYBL, RYKT, LS, AT, BH, AG, YH, OB, TT, RTS, BJL and DB; Formal analysis: ASM, ARYBL and RYKT; Funding acquisition: Not applicable; Investigation: ASM, ARYBL and RYKT; Methodology: ARYBL, YYS, RS and MXL; Project administration: ARYBL and RS; Resources: Not applicable; Software: ASM, ARYBL, RYKT and JT; Supervision: PS, SCL, LYAC, YYS, RS and MXL; Validation: LS, AT, BH, AG, YH, OB, TT, RTS, BJL, DB, SP, JT, YYS, RS and MXL; Visualisation: ASM, ARYBL and RYKT; Writing – original draft: ASM, ARYBL and RYKT; Writing – review & editing: LS, AT, BH, AG, YH, OB, TT, RTS, BJL, DB, SP, JT, SCL, LYAC, YYS, RS and MXL. ASM, ARYBL and RYKT contributed equally to this paper and are joint first authors. All authors approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Disclaimers

All authors have no disclaimers.

Prior presentations

The submitted work has not been presented in any form.

Data availability statement

No additional data is available.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: YYS—honoraria (AstraZeneca); RS—honoraria (MSD, Eli Lilly, BMS, Roche, Taiho, Astra Zeneca, DKSH), consulting or advisory role (Bristol Myers Squibb, Merck, Eisai, Bayer, Taiho, Novartis, MSD, GSK), research funding (Paxman Coolers, MSD), travel (Roche, Astra Zeneca, Taiho, Eisai, DKSH). DB—Sana Biotechnology has licensed

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.05.029.

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