SYSTEMATIC REVIEW

blood advances

Immunogenicity of COVID-19 vaccines in patients with hematologic malignancies: a systematic review and meta-analysis

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The objectives of this study were to assess the immunogenicity and safety of COVID-19 vaccines in patients with hematologic malignancies. A systematic review and meta-analysis of clinical studies of immune responses to COVID-19 vaccination stratified by underlying malignancy and published from January 1, 2021, to August 31, 2021, was conducted using MEDLINE, EMBASE, and Cochrane CENTRAL. Primary outcome was the rate of seropositivity after 2 doses of COVID-19 vaccine with rates of seropositivity after 1 dose, rates of positive neutralizing antibodies, cellular responses, and adverse events as secondary outcomes. Rates were pooled from single-arm studies while rates of seropositivity were compared against the rate in healthy controls for comparator studies using a random effects model and expressed as a pooled odds ratios with 95% confidence intervals. Forty-four studies (16 mixed group, 28 disease specific) with 7064 patients were included in the analysis (2331 after first dose, 4733 after second dose). Overall seropositivity rates were 62% to 66% after 2 doses of COVID-19 vaccine and 37% to 51% after 1 dose. The lowest seropositivity rate was 51% in patients with chronic lymphocytic leukemia and was highest in patients with acute leukemia (93%). After 2 doses, neutralizing antibody response rates were 57% to 60%, and cellular response rates were 40% to 75%. Active treatment, ongoing or recent treatment with targeted and CD-20 monoclonal antibody therapies within 12 months were associated with poor immune responses to COVID-19 vaccine. New approaches to prevention are urgently required to reduce COVID-19 infection morbidity and mortality in high-risk patient groups that respond poorly to COVID-19 vaccination.

Introduction

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has resulted in global mortality of more than 3 million deaths. SARS-CoV-2 is likely to remain an endemic viral pathogen, with new variants continuously emerging.[1] There is a significant burden of morbidity and mortality from COVID-19 infection in hematology patients. More than 80% of hematology patients require hospitalization, and up to 50% present with severe disease.[2-5] Approximately 15% require admission to the intensive care unit, and mortality rates are high at 30% to 40%, depending on

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underlying disease.[2-7] Poor control of infection because of immune compromise lead to emergence of new variants which further complicate management.[8]

Vaccination is an effective public health measure for reducing the risk of infection and severe complications from COVID-19.[9] However, patients with hematologic malignancies were excluded from the pivotal trials that preceded regulatory approvals of the currently recommended COVID-19 vaccines.[10-13] Understanding the impact of COVID-19 vaccines on patients with cancer is critical as social distancing restrictions are being eased in countries with relatively high rates of vaccination coverage.[14] Assessing immune response after vaccination is the basis of many vaccination studies in patients with hematologic malignancies and is often used as a surrogate marker of vaccine efficacy.[15-17] These studies are the basis for vaccination recommendations contained within international guidelines.[18,19] Therefore, this study was conducted to systematically review available data on the humoral and cellular immune responses to COVID-19 vaccination in patients with hematologic malignancies to build the evidence base for its utility.

The main objective of this systematic review was to assess the immunogenicity (ie, vaccine-induced immune response) of COVID-19 vaccines in patients with hematologic malignancies, stratified by underlying disease type. The secondary objective was to assess the safety of COVID-19 vaccines in the same patient groups.

Methods

This systematic review was preregistered with PROSPERO (CRD42021276851), and conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20]

Types of studies and participants

Studies eligible for inclusion into the systematic review were those that investigated the vaccine-induced immunity in patients with hematologic malignancies who received at least 1 dose of COVID-19 vaccine. Randomized controlled trials (RCTs), quasi-RCTs, and observational studies were eligible for inclusion. All types of observational studies were included (eg, prospective and retrospective studies and studies with or without a control group). This systematic review evaluated all studies that reported on at least 1 of the following hematology patient groups: all patients with hematologic malignancies; patients with multiple myeloma (MM); patients with chronic lymphocytic leukemia (CLL); patients with lymphoma, Hodgkin lymphoma (HL), or non-Hodgkin lymphoma (NHL); patients with acute myeloid leukemia (AML) or acute lymphocytic leukemia (ALL); patients who are undergoing or have completed hematopoietic stem cell transplantation (HCT) or chimeric antigen receptor (CAR) T-cell therapy; and patients with myeloproliferative neoplasms (MPNs) and chronic myeloid leukemia (CML).

Types of intervention and evaluation

The type of intervention was the use of 1 or 2 doses of COVID-19 vaccine (of any type). Immune response to COVID-19 vaccination included humoral and cellular immune responses. For the purpose of this systematic review, humoral response consists of seropositivity which was defined by the SARS-CoV-2 spike/receptor binding domain–specific immunoglobulin G (IgG) level above the threshold of detection for the assay used in each study. Rate of positive neutralizing antibody (nAb) response was defined by SARS-CoV-2–specific nAb level above the threshold established by the dedicated neutralization assay used in each study. A positive cellular response was defined by the appropriate increase in frequency of SARS-CoV-2–specific $CD4^+/CD8^+$ T cells after vaccination according to assays used. Where available, the immune response for each hematologic malignancy patient group was compared with a control group. If there was no comparator group, the immune response for each hematology patient group was described and summarized.

Outcome measures

The primary outcome was rates of seropositivity after 2 doses of COVID-19 vaccine stratified by disease groups. Secondary outcome measures were the rates of seropositivity after 1 dose of vaccine, rates of positive nAb response after 1 or 2 doses of COVID-19 vaccine, rates of positive cellular response after 1 or 2 doses of COVID-19 vaccine, and rates of systemic and/or local adverse events (AEs; whichever rate was higher) after 2 doses of COVID-19 vaccine.

Search strategy

Literature searches were conducted by an experienced research librarian (S.L.) using the Ovid MEDLINE, EMBASE, and Cochrane CENTRAL databases to identify relevant articles published in English from January 1, 2020, to August 31, 2021. A combination of subjects and keyword terms encompassing hematologic cancers, COVID-19, vaccines, and all their associated terms were used for the search. The terms used in our search included: hematologic neoplasms, leukemia, lymphoma, multiple myeloma, myeloproliferative disorders, myelodysplastic-myeloproliferative diseases, stem cell transplantation, bone marrow transplantation, chimeric antigen receptor therapy, COVID-19, SARS-CoV-2, vaccines, vaccination, immunize, immunization, BNT162b2, ChAdOx1, AZD 1222, mRNA-1273, Ad26, Ad5, and NVX-CoV2373. All word variations were searched, and medical subject headings were exploded. The detailed search strategy is summarized in the supplemental data.

Selection of studies

Studies were excluded from the systematic review if they did not measure or report immunogenicity after COVID-19 vaccination, if insufficient details were reported for the hematology patient groups in mixed-group studies, if there were <10 patients including case reports, if data were exclusive to pediatric patients younger than age 18 years, or if they were animal studies. Studies that were not peer reviewed and/or had not been published (eg, preprints, abstracts, and government reports) were excluded. Review articles and other publications without original data such as expert opinions, editorials, and consensus statements were also excluded.

Study eligibility was assessed by 2 independent reviewers (B.W.T., J.S.K.T.), and Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) was used to screen titles, abstracts, and full texts. Irrelevant reports were discarded, and the full texts of the other reports were accessed. Disagreements between the 2 main reviewers with respect to

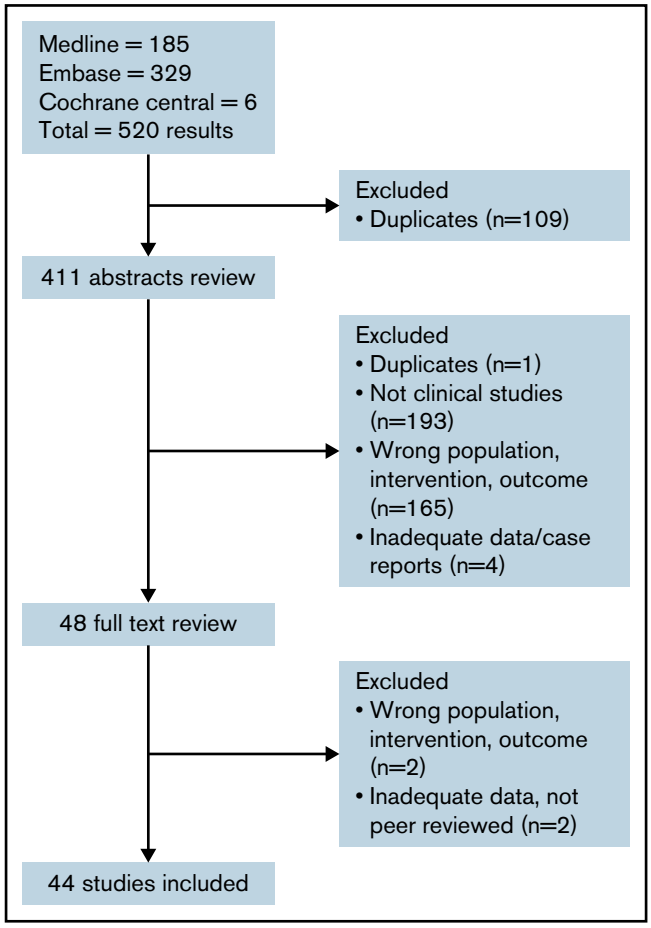

Figure 1. Flow diagram of studies identified, screened, and included.

study eligibility were resolved by discussion or via consultation with a third author.

Data extraction

For studies that fulfilled the inclusion criteria, data were extracted manually and independently by authors (J.S.K.T., J.C., B.W.T.) by using a predefined data extraction form. Extracted data elements included study design (enrollment, follow-up period, randomization/allocation, laboratory analysis, predefined outcomes, adjusted analysis, funding source), participant information (inclusion criteria, number of participants, characteristics, disease, treatment), intervention (vaccine type, dose, schedule, comparator group), and outcomes (definitions, timing, AEs).

Assessment of risk of bias

Two review authors (Z.C.F.N., M.A.S.) independently assessed the risk of bias of each cohort study by using the Newcastle-Ottawa Scale.[21] Each included study was assessed on the basis of 3 domains: (1) the selection of the study groups, (2) the comparability of the study groups, and (3) the ascertainment of outcome of interest. The rating system proposed by Sharmin et al[22] was adopted; a good-quality study scored 3 or 4 stars in the selection domain, 1 or 2 stars in comparability domain, and 2 or 3 stars in the outcome domain. For single-arm studies, a good-quality study scored 3 stars in the selection domain and 2 or 3 stars in the outcome domain.

Measures of treatment effect

For each study, the number of patients who achieved seropositivity and the total number of patients who received vaccination was extracted and expressed as a proportion. For the meta-analysis, rate of response after Ad26 vaccine was analyzed at the same time point and therefore summarized as part of a 2-vaccine dose response. For each hematology disease group, the proportions from each study were pooled using the inverse variance method via the metaprop function in R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and expressed as an overall proportion (response rate) with 95% confidence intervals (CIs).

For each study with a control group, the number of patients with seropositivity in each group and the total number of patients who received vaccination were extracted, expressed as a proportion with 95% CIs, and compared against each other. A meta-analysis was performed if there were 2 or more studies identified with a similar population and sufficient data for the outcomes of interest. The rate of seropositivity as a dichotomous outcome of interest across studies was summarized using a random effects model and expressed as a pooled odds ratios (ORs) with 95% CIs. Comparative analysis was performed using R 4.1.1 software.

Assessment of heterogeneity and missing data

Clinical and methodologic heterogeneity between included studies was assessed by comparing the key patient factors and study factors (vaccine type, type of assay used, threshold for positive response, duration of follow-up). Statistical heterogeneity was assessed by using the I^2 statistic and χ^2 with a P value $\leq .05$ considered significant for the presence of heterogeneity. Reason(s) for missing data were outlined if they were available,. Because of time limitations, further information was not sought from the original or the corresponding author(s).

Subgroup analysis

Preplanned subgroup analysis was performed to evaluate the impact of active treatment (vs no active treatment), anti–CD-20 therapy in the last 12 months, including current CD-20 therapy (vs anti–CD-20 therapy 12 or more months ago), targeted therapy (defined as Bruton tyrosine kinase inhibitor [BTKi], BCL-2 antagonist venetoclax) in the last 12 months (vs no targeted therapy), timing of vaccination in relation to HCT (within 12 months vs longer than 12 months), and response by type of vaccine (BNT162b2 also known as Comirnaty or tozinameran [Pfizer] vs others, including messenger RNA-1273 or mRNA-1273 also known as Spikevax or elasomeran [Moderna], ChAdOx1 also known as Vaxzevria [AstraZeneca], or Ad26 [Janssen]). For subgroup analysis, only studies containing sufficient level of detail for the outcome of interest (eg, therapy <12 months) were included. For analysis by vaccine type, only studies reporting use and immune response of multiple vaccines types were included.

Results

Search results

A search of electronic databases yielded 520 results, and after duplicate results were excluded, 411 abstracts were reviewed. Forty-eight studies were identified for full-text review; subsequently, 44 studies fulfilled the inclusion criteria and underwent data

Table 1. Summary of study characteristics and outcomes for patients with hematologic malignancies by overall cohort and specific underlying disease

Study	Type/location	Study population/ comparator	No. of participants analyzed/ controls	Median age, y (range or IQR)	M/F	Vaccine type	Analysis	Seropositivity	Rate of positive nAb/cellular response	AEs
Mixed-group										
Addeo et al[23]	Multicenter prospective cohort study Europe, North America	Hem Solid tumor	25 106	NR for hem	NR for hem	BNT162b2, mRNA-1273, NR for hem	SARS-CoV-2 spike, IgG Roche (≥0.8 IU/mL = positive)	Hem: 3-4 weeks after first dose, 18 (72%) of 25; 3-4 weeks after second dose, 17 (77%) of 22. Solid tumor: first dose, 80 (83%) of 96; second dose, 99 (98%) of 101	NR	NR
Agha et al[24]	Single-center retrospective cohort study/ United States	Hem	67	71 (IQR, 65-77)	35/32	BNT162b2, mRNA-1273, 51%; 42%; unknown, 7%	SARS-CoV-2 spike, IgG Beckman Coulter (≥1.00 = positive)	21 days after second dose, 36 (54%) of 67	NR	NR
Benda et al[25]	Single-center prospective cohort study/ Austria	Hem Solid tumor	123 34% myeloma, 38% CLL/ lymphoma/WM, 28% AML/ MDS/MPNs 136	NR for hem	NR for hem	BNT162b2	SARS-CoV-2 spike, IgG Roche (≥0.8 IU/mL = positive)	21 days after first dose, 53 (43%) of 123; 28 days after second dose, 85 (71%) of 119	NR	NR for hem
Cohen et al[26]	Single-center retrospective study/Israel	Hem	54	69 (IQR, 61-77)	32/22	BNT162b2	SARS-CoV-2 spike, IgG Roche (≥0.8 IU/mL = positive)	2-3 weeks after second dose, 34 (63%) of 54	NR	NR
Gavriatopoulou et al[27]	Single-center prospective cohort study/ Greece	Hem Control group	58 48% WM, 38% CLL, 14% NHL 213	75 (40-88)	28/30	BNT162b2, 76%; ChAdOx1, 24%	nAb GenScript (≥30% = positive; ≥50% = clinically relevant inhibition)	22 days after first dose, ≥30%, 8 (14%) of 58 patients vs 114 (54%) of 213 controls	22 days after first dose, ≥50%, 3 (5%) of 58 patients vs 50 (24%) of 213 controls	NR
Greenberger et al[28]	Multicenter prospective cohort study/ United States	Hem	1445: 45% CLL, 25% NHL, 5% HL, 15% MM, 4% acute leukemia, 2% CML, 2% MPNs, 2% other	68 (16-110)	574/871	BNT162b2, 55%; mRNA-1273, 45%	SARS-CoV-2 spike, IgG Roche (≥0.8 IU/mL = positive)	>14days after second dose, 1088 (75%) of 1445	NR	NR
Herzog Tzarfati et al[29]	Single-center prospective cohort study/ Israel	Hem Matched healthy controls	315 22% MPNs, 17% myeloma, 16% aggressive NHL, 13% indolent NHL, 11% CLL, 7% CML, 5% HL, 5% acute leukemia, 5% MDS 108	70 (IQR, 61-77)	223/200	BNT162b2	SARS-CoV-2 spike, IgG DiaSorin (≥12 AU/mL = positive)	30-60 days after second dose, 235 (75%) of 315 vs 107 (99%) of 108 controls	NR	NR
Iacano et al[30]	Single-center prospective cohort study/ Italy	Hem ≥80 y; health care worker controls ≥66 y (results NR)	10	NR for hem	NR for hem	BNT162b2	SARS-CoV-2 spike, IgG Abbott (≥50 AU/mL = positive)	28 days after second dose, 4 (40%) of 10	NR	NR
Jurgens et al[31]	Single-center prospective cohort study/ United States	Hem Health care worker controls	67 31% CLL, 63% NHL, 6% HL 35	71 (24-90)	36/31	BNT162b2, 46%; mRNA-1273, 54%	SARS-CoV-2 spike, IgG in-house (OD 450 ≥3 = positive)	21 days after second dose, 41 (61%) of 67 vs 35 (100%) of 35 controls	NR	NR
Maneikis et al[32]	Multicenter prospective cohort study/ Europe	Hem Health care worker controls	857 68	65 (IQR, 54-72)	404/453	BNT162b2	SARS-CoV-2 spike, IgG Abbott (≥50 AU/mL = positive)	7-21days after first dose, 481 (56%) of 857; NR for control group	NR	At least 1 AE; dose 1, 56 (9%) of 575; dose 2, 72 (13%) of 575
Malard et al[33]	Single-center retrospective cohort study/ France	Hem Healthy controls	195 27% myeloma, 23% NHL, 3% HL, 13% CLL, 16% AML, 2% ALL, 9% MPNs, 7% other 30	69 (22-92)	117/78	BNT162b2	SARS-CoV-2 spike, IgG Abbott (≥50 AU/mL = positive; ≥3100 AU/mL = neutralization >30%; SARS-CoV-2 T-cell response, ELI-SPOT ≥10 spot-forming cells per 10^6 PBMCs and ratio 2.5 = positive)	≥3100 AU/mL threshold*; 28 days after first dose, 3 (2%) of 195; 14 days after second dose, 91 (47%) of 196 vs 26 (87%) of 30 controls	Cellular response 14 days after second dose, 36 (53%) of 68	At least 1 AE; dose 1, 88 (57%) of 154; dose 2, 55 (34%) of 163

AEs, adverse events; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BAU, binding antibody unit; CLL, chronic lymphotic leukemia; COV, cut-off value; EC_{50}, median effective concentration; ET, essential thrombocythemia; F, female; GVHD, graft-versus-host disease; hem, hematology; HL, Hodgkin lymphoma; ICA, intracellular cytokine assay; ID_{50}, median infective dose; IFN-γ, interferon-γ; IL-2, interleukin-2; IQR, interquartile range; M, male; MF, myelofibrosis; MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; ND, not determined; NE, not extractable; NHL, non-Hodgkin lymphoma; NR, not reported; OD, optical density; PBMC, peripheral blood mononuclear cell; PV, polycythemia vera; RBD, receptor-binding domain; SMM, smoldering multiple myeloma; WM, Waldenström macroglobulinemia.

*Excluded from meta-analysis.

Table 1. (continued)

Study	Type/location	Study population/ comparator	No. of participants analyzed/ controls	Median age, y (range or IQR)	M/F	Vaccine type	Analysis	Seropositivity	Rate of positive nAb/cellular response	AEs
Monin et al[34]	Multicenter prospective cohort study/ United Kingdom	Hem Health care worker controls	56: 68% B-cell malignancies, 9% T-cell malignancies, 18% myeloid or acute leukemia, 5% other 54	73 (IQR, 65-80)	NE for hem	BNT162b2	SARS-CoV-2 spike, IgG (≥70 EC_{50} = positive); SARS-CoV-2–specific T-cells secreting IFN-γ and/or IL-2 >7 cytokine-secreting cells per 10^6 PBMCs = positive)	21 days after first dose, 8 (18%) of 44 vs 32 (94%) of 34 controls; 35 days after first dose, 4 (11%) of 36 vs 18 (86%) of 21 controls; 35 days after first dose (with second dose), 3 (60%) of 5 vs 12 (100%) of 12 controls	Cellular response 21 days after first dose, 9 (50%) of 18 vs 14 (82%) of 17 controls; 35 days after first dose, 6 (33%) of 18 vs 9 (69%) of 13 controls; 35 days after first dose (with second dose), 3 (75%) of 4 vs 3 (100%) of 3 controls	NE for hem patients
Ollila et al[35]	Single-center retrospective cohort study/ United States	Hem	160: 36% aggressive and 21% indolent lymphoma, 15% plasma cell leukemia, 12% CLL, 9% other lymphoma, 6% myeloid leukemia	72 (65-79)	86/74	BNT162b2, 60%; mRNA-1273, 31%; Ad26, 7%; ND, 1%	SARS-CoV-2 spike, IgG Abbott (signal/cutoff ratio ≥1.4 = positive)	56 days after first dose, 63 (39%) of 160	NR	NR
Pimpinelli et al[36]	Single-center prospective study/ Italy	Hem Older age (>80 y) control group	92 46% myeloma, 54% MPN 36	73 (47-78)/ 70 (28-80)	Myeloma: 23/19; MPN: 26/24	BNT162b2	SARS-CoV-2 spike, IgG DiaSorin (≥15 AU/mL = positive)	21 days after first dose, 9 (21%) of 42; myeloma, 26 (52%) of 50 MPNs vs 19 (53%) of 36 controls; 14 days after second dose, 33 (79%) of 42; myeloma 44 (88%) of 50 MPNs vs 36 (100%) of 36 controls; ≥80 AU/mL threshold*: 14 days after second dose, 23 (55%) of 42; myeloma 42 (84%) of 50 MPNs vs 34 (97%) of 36 controls	NR	Reported with different patient numbers
Re et al[37]	Multicenter retrospective cohort study/ France	Hem	102: 45% lymphoma, 22% myeloma, 13% MDS/ AML, 10% CLL, 10% MPNs	76 (33-93)	67/35	BNT162b2, 93%; mRNA-1273, 7%	SARS-CoV-2 spike, IgG; range of commercial kits using their own threshold	21-28 days after second dose, 64 (62%) of 102	NR	NR
Thakkar et al[38]	Single-center prospective and retrospective cohort study/ United States	Hem Solid tumors Healthy controls	6639% lymphoid malignancies, 27% myeloid malignancies, 33% plasma cell leukemia 134 26	NR for hem	NR for hem	BNT162b2, 58%; mRNA-1273, 31%; Ad26, 10%; mRNA type unknown, 2%	SARS-CoV-2 spike, IgG Abbott (≥50 AU/mL = positive)	>7 days after second dose, 56 (85%) of 66 vs 131 (98%) of 134 solid tumors; rate NR for controls	NR	NR for hem
Myeloma-specific										
Avivi et al[39]	Single-center prospective cohort study/ Israel	Myeloma Healthy volunteers	171 64	70 (38-94)	96/75	BNT162b2	SARS-CoV-2 spike, IgG Roche (≥0.8 IU/mL = positive)	14-21 days after second dose, 133 (78%) of 171 vs 63 (98%) of 64 controls	NR	At least 1 AE; 90 (53%) of 161 vs 29 (55%) of 53 controls
Bird et al[40]	Single-center retrospective cohort study/ United Kingdom	Myeloma	93	67 (47-87)	55/38	BNT162b2, 52%; ChAdOx1, 48%	SARS-CoV-2 spike, IgG Ortho clinical (≥1 signal/cutoff = positive)	≥21 days after first dose, 52 (56%) of 93	NR	NR

AEs, adverse events; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BAU, binding antibody unit; CLL, chronic lymphotic leukemia; COV, cut-off value; EC_{50}, median effective concentration; ET, essential thrombocythemia; F, female; GVHD, graft-versus-host disease; hem, hematology; HL, Hodgkin lymphoma; ICA, intracellular cytokine assay; ID_{50}, median infective dose; IFN-γ, interferon-γ; IL-2, interleukin-2; IQR, interquartile range; M, male; MF, myelofibrosis; MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; ND, not determined; NE, not extractable; NHL, non-Hodgkin lymphoma; NR, not reported; OD, optical density; PBMC, peripheral blood mononuclear cell; PV, polycythemia vera; RBD, receptor-binding domain; SMM, smoldering multiple myeloma; WM, Waldenström macroglobulinemia.

*Excluded from meta-analysis.

Table 1. (continued)

Study	Type/location	Study population/ comparator	No. of participants analyzed/ controls	Median age, y (range or IQR)	M/F	Vaccine type	Analysis	Seropositivity	Rate of positive nAb/cellular response	AEs
Ghandili et al[41]	Single-center prospective cohort study/ Germany	Myeloma	82	68 (40-85)	49/33	BNT162b2, 77%; ChAdOx1, 23%	SARS-CoV-2 spike, IgG DiaSorin (≥34 AU/mL = positive)	21 days after first dose, 17 (23%) of 74	NR	NR
Ramasamy et al[42]	Multicenter web-based prospective cohort study/ United Kingdom	Myeloma	105-28 patients sampled	63	67/42	BNT162b2, 42%; ChAdOx1, 58%	SARS-CoV-2 spike, IgG Abbott (COV ≥50 = positive)	>21 days after first dose, 17 (61%) of 28	NR	NR
Stampfer et al[43]	Single-center prospective cohort study/ United States	Myeloma Healthy controls Pre-COVID-19 controls	103 31 34	68 (35-88)	61/42	BNT162b2, 50%; mRNA-1273, 50%	SARS-CoV-2 spike, IgG in-house (50-250 IU/mL = positive partial response) (>250 IU/mL = clinically relevant response)	14-21 days after first dose, 20 (21%) of 96; 14-21 days after second dose, 64 (67%) of 96 vs 31 (100%) of 31 controls; >250 IU/mL: 14-21 days after first dose, 2 (2%) of 96; 14-21 days after second dose, 45 (46%) of 96 vs 29 (94%) of 31 controls	NR	NR
Terpos et al[44]	Single-center prospective cohort study/ Greece	Myeloma Matched controls	48 102	83 (59-92)	29/19	BNT162b2	SARS-CoV-2 nAb GenScript (≥30% = positive; ≥50% = clinically relevant)	≥30%: 22 days after first dose, 12 (25%) of 48 vs 57 (55%) of 102 controls	≥50%: 22 days after first dose, 4 (8%) of 48 vs 21 (20%) of 102 controls	NR
Terpos et al[45]	Single-center prospective cohort study/ Greece	Myeloma Matched controls	276 77% myeloma, 14% sMM, 9% MGUS 226	74 (62-80)	151/125	BNT162b2, 78%; ChAdOx1, 22%	SARS-CoV-2 nAb GenScript (≥30% = positive; ≥50% = clinically relevant)	≥30%; day 22 after first dose, 117 (42%) of 276 vs 145 (64%) of 226 controls; day 50 after first dose, 196 (71%) of 276 vs 204 (90%) of 226 controls	≥50%; day 22 after first dose, 55 (20%) of 276 vs 73 (32%) of 226 controls; day 50 after first dose, 158 (57%) of 276 vs 183 (81%) of 226 controls	First dose of BNT162b2, 71 (33%) of 215 local reaction; 28 (13%) of 215 systemic reaction; ChAdOx1, 20 (33%) of 61 local reaction. Second dose of BNT162b2, 68 (32%) of 215 local reaction; 45 (21%) of 215 systemic reaction
Van Oekelen et al[46]	Single-center prospective and retrospective cohort study/ United States	Myeloma Matched health care worker controls	320 260 sampled 67	68 (38-93)	185/135	BNT162b2, 69%; mRNA-1273, 27%; unknown, 4%	SARS-CoV-2 spike, IgG in-house (≥5 AU/mL = positive)	51 days after second dose, 219 (84%) of 260 vs 67 (100%) of 67 controls	NR	NR
CLL-specific										
Benjamini et al[47]	Multicenter prospective cohort study/ Israel	CLL patients	373	70 (40-89)	222/151	BNT162b2	SARS-CoV-2 spike, IgG DiaSorin (≥15 AU/mL = positive); Abbott (>50 U/mL = positive); in-house (>1.1 = positive)	14-21 days after second dose, 160 (43%) of 373	nAb 14-21 days after second dose, 27 (60%) of 45	At least 1 AE; 151 (47%) of 331
Del Poeta et al[48]	Single-center prospective cohort study/ Italy	CLL patients	46	NR	29/17	BNT162b2	SARS-CoV-2 spike, IgG MAGLUMI (≥1.1 = positive)	14-21 days after second dose, 25 (54%) of 46	NR	NR
Herishanu et al[49]	Single-center prospective cohort study/ Israel	CLL patients Age- and sex-matched controls	167 52	71 (63-76)	112/55	BNT162b2	SARS-CoV-2 spike, IgG Roche (≥0.8 IU/mL = positive)	14-21 days after second dose, 66 (40%) of 167 patients vs 52 (100%) of 52 controls	NR	First dose, 52 (31%) of 167 local reaction; 21 (13%) of 167 systemic reaction. Second dose, 56 (34%) of 167 local reaction; 21 (23%) of 167 systemic reaction

AEs, adverse events; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BAU, binding antibody unit; CLL, chronic lymphotic leukemia; COV, cut-off value; EC_{50}, median effective concentration; ET, essential thrombocythemia; F, female; GVHD, graft-versus-host disease; hem, hematology; HL, Hodgkin lymphoma; ICA, intracellular cytokine assay; ID_{50}, median infective dose; IFN-γ, interferon-γ; IL-2, interleukin-2; IQR, interquartile range; M, male; MF, myelofibrosis; MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; ND, not determined; NE, not extractable; NHL, non-Hodgkin lymphoma; NR, not reported; OD, optical density; PBMC, peripheral blood mononuclear cell; PV, polycythemia vera; RBD, receptor-binding domain; SMM, smoldering multiple myeloma; WM, Waldenström macroglobulinemia.

*Excluded from meta-analysis.

Table 1. (continued)

Study	Type/location	Study population/ comparator	No. of participants analyzed/ controls	Median age, y (range or IQR)	M/F	Vaccine type	Analysis	Seropositivity	Rate of positive nAb/cellular response	AEs
Parry et al[50]	Single-center prospective cohort study/ United Kingdom	CLL patients Healthy age-matched controls	299 93	69 (IQR, 63-74)	159/140	BNT162b2, 52%; ChAxOd1, 48%	SARS-CoV-2 spike, IgG Roche (≥0.8 IU/mL = positive); dried blood sampling Roche (ratio ≥1.0 = positive)	43 days after first dose, serum 29 (34%) of 86 vs 89 (94%) of 95 controls; dried blood* 63 (24%) of 267 vs 66 (71%) of 93 controls; 18 days after second dose, serum 9 (75%) of 12 vs 59 (100%) of 59 controls; dried blood* 39 (71%) of 55 vs 36 (97%) of 37 controls	NR	NR
Roeker et al[51]	Single-center retrospective cohort study United States	CLL patients	44	71 (37-89)	23/21	BNT162b2, 57%; mRNA-1273, 43%	SARS-CoV-2 spike, IgG DiaSorin (≥15 AU/mL = positive)	21 days after second dose, 23 (52%) of 44	NR	NR
Tadmor et al[52]	Multicenter prospective observation study/ Israel	CLL patients	84	69 (44-87)	53/29	BNT162b2	SARS-CoV-2 spike, IgG Abbott (≥50 U/mL = positive); SARS-CoV-2 RBD IgG (>1.1 = positive)	22 days after second dose, 49 (58%) of 84	NR	NR
Lymphoma-specific										
Ghione et al[53]	Single-center prospective cohort study/ United States	B-cell lymphoma Nursing home controls Health care worker controls	86 47 154	70 (35-91)	45/41	BNT162b2, 47%; mRNA-1273, 52%; Ad26, 1%	SARS-CoV-2 spike, IgG BioRad (≥1.0 = positive)	14-56 days after completion of vaccination, 36 (42%) of 86 patients vs 43 (92%) of 47 nursing home controls, 154 (100%) of 154 health care worker controls	NR	NR
Gurion et al[54]	Multicenter prospective cohort study/ Israel	Lymphoma	162: 88% NHL, 12% HL	65 (52-73)	89/73	BNT162b2	SARS-CoV-2 spike, IgG Abbott (≥50 IU/mL = positive)	28 days after second dose, 83 (51%) of 162	NR	NR
Lim et al[55]	Multicenter prospective cohort study interim analysis/ United Kingdom	Lymphoma Healthy controls	129 recruited, 119 analyzed/ 150: 66% indolent B-cell NHL, 29% aggressive B-cell NHL, 10% HL, 3% other	69 (IQR, 57-74)	81/48	BNT162b2, ChAdOx1	SARS-CoV-2 spike, IgG Meso Scale Discovery (>0.55 BAU/mL = positive); RBD IgG (>0.73 BAU/mL = positive)	14 days after first dose, 32 (54%) of 59 patients vs 65 (100%) of 65 controls; 14-28 days after second dose, 61 (71%) of 86 patients vs 85 (100%) of 85 controls	NR	NR
Perry et al[56]	Single-center prospective cohort study/ Israel	Lymphoma, B-cell NHL Healthy controls	149 53% indolent NHL, 47% aggressive NHL 65	64 (20-92)	88/61	BNT162b2	SARS-CoV-2 spike, IgG Roche (≥0.8 IU/mL = positive)	14-21 days after second dose, 73 (49%) of 149 vs 64 (99%) of 65 controls; 38 (48%) of 80 indolent NHL; 34 (49%) of 69 aggressive NHL	NR	At least 1 AE; 60 (51%) of 118; 44 (37%) of 118 local AE; 23 (20%) of 118 systemic AE
HCT-specific										
Easdale et al[57]	Single-center retrospective cohort study/ United Kingdom	Allo-HCT >3 months	55	50 (18-73)	34/21	BNT162b2, 38%; ChAdOx1, 62%	SARS-CoV-2 spike, IgG Ortho clinical (≥1 signal/cutoff = positive)	42 days after first dose, 21 (38%) of 55	NR	NR
Redjoul et al[58]	Single-center retrospective cohort study/ France	Allo-HCT	88	NR	47/41	BNT162b2	SARS-CoV-2 spike, IgG Abbott (>21 AU/mL = positive; >4160 AU/mL = neutralization)	28 days after second dose, 69 (78%) of 88; >4160 AU/mL 28 days after second dose, 52 (59%) of 88	NR	NR

AEs, adverse events; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BAU, binding antibody unit; CLL, chronic lymphotic leukemia; COV, cut-off value; EC_{50}, median effective concentration; ET, essential thrombocythemia; F, female; GVHD, graft-versus-host disease; hem, hematology; HL, Hodgkin lymphoma; ICA, intracellular cytokine assay; ID_{50}, median infective dose; IFN-γ, interferon-γ; IL-2, interleukin-2; IQR, interquartile range; M, male; MF, myelofibrosis; MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; ND, not determined; NE, not extractable; NHL, non-Hodgkin lymphoma; NR, not reported; OD, optical density; PBMC, peripheral blood mononuclear cell; PV, polycythemia vera; RBD, receptor-binding domain; SMM, smoldering multiple myeloma; WM, Waldenström macroglobulinemia.

*Excluded from meta-analysis.

Table 1. (continued)

Study	Type/location	Study population/ comparator	No. of participants analyzed/ controls	Median age, y (range or IQR)	M/F	Vaccine type	Analysis	Seropositivity	Rate of positive nAb/cellular response	AEs
Ram et al[59]	Single-center prospective cohort study/ Israel	Allo-HCT and CAR T cells >3 months	80: 83% allo-HCT, 17% CAR T cells	65 (23-83)	44/37	BNT162b2	SARS-CoV-2 spike, IgG Roche (≥0.8 U/mL = positive); SARS-CoV-2–specific cells ELISPOT (IFN, IL-2) (4 spots per well = positive)	7-14 days after second dose, 47 (75%) of 63 allo-HCT; 5 (36%) of 14 CAR T cells	Cellular response 7-14 days after second dose, 7 (19%) of 37 allo-HCT; 6 (50%) of 12 CAR T cells	At least 1 AE; first dose, 11 (14%) of 80, 3 (4%) of 80 GVHD; second dose, 18 (24%) of 74, 3 (4%) of 74 GVHD
Dhakal et al[60]	Single-center retrospective cohort study/ United States	Auto-HCT, allo-HCT, CAR T cells	130: 45 auto-HCT, 71 allo-HCT, 14 CAR T cells	Auto-HCT, 65 (45-75); allo-HCT, 64 (25-77); CAR T cells, NR	NR	BNT162b2, 59%; mRNA-1273, 36%; Ad26, 5%	SARS-CoV-2 spike, IgG EUROIMMUN (≥1.1 signal/ cutoff = positive)	14 days after completion of vaccination, 27 (60%) of 45 auto-HCT; 49 (38%) of 71 allo-HCT; 3 (21%) of 14 CAR T cells	NR	NR
MPN- and CML-specific										
Caocci et al[61]	Single-center prospective cohort study/ Italy	MPN	20: 65% MF, 30% ET, 5% PV	66 (48-82)	NR	BNT162b2	SARS-CoV-2 spike, IgG DiaSorin (≥15 AU/mL = positive)	42 days after second dose, 13 (65%) of 20	NR	NR
Chowdhury et al[62]	Single-center retrospective cohort/ United Kingdom	CML and MPN Health care workers age >60 years	59 232	62 (IQR, 52-73)	27/32	BNT162b2, 37%; ChAdOx1, 63%	SARS-CoV-2 spike, IgG Abbott (≥50 AU/mL = positive)	≥2 weeks after first dose, 34 (57%) of 59 vs 224 (97%) of 232 controls	NR	NR
Guglielmelli et al[63]	Single-center prospective cohort study/ Italy	MPN Healthy controls	30 43% MF, 33% PV, 23% ET 14	NR overall	10/20	BNT162b2, 83%; mRNA-1273, 17%	SARS-CoV-2 spike/ RBD IgG (NS)	21 to 28 days after first dose, 18 (60%) of 30 vs 14 (100%) of 14 controls	nAb, 21-28 days after first dose, 13 (43%) of 30 vs 14 (100%) of 14 controls	NR
Harrington et al[64]	Single-center prospective cohort study/ United Kingdom	CML	16	45 (23-74)	12/4	BNT162b2	SARS-CoV-2 spike, IgG in-house (1:25 = positive); SARS-CoV-2 neutralizing in-house (ID_{50} = positive); SARS-CoV-2 T cells ICA (IFN, IL-2) (threefold increase = positive)	21 days after first dose, 14 (88%) of 16	nAb 21 days after first dose, 6 (38%) of 16; cellular response, 14 (80%) of 15	Local AEs, 8 (50%) of 16; systemic AEs, 9 (56%) of 16
Harrington et al[65]	Single-center prospective cohort study/ United Kingdom	MPN	21	58 (36-72)	7/21	BNT162b2	SARS-CoV-2 spike, IgG in-house (1:25 = positive); SARS-CoV-2 neutralizing in-house (ID50 = positive); SARS-CoV-2 T cells ICA (IFN, IL-2) (threefold increase = positive)	21 days after first dose, 16 (76%) of 21	nAb 21 days after first dose, 18 (86%) of 21; cellular response (CD4), 15 (75%) of 20	At least 1 AE; 12 (57%) of 21 local; 10 (48%) of 21 systemic
Pimpinelli et al[66]	Single-center prospective cohort study/ Italy	MPN	42: 40% ET, 36% PV, 24% MF	72 (52-82)	20/22	BNT162b2	SARS-CoV-2 spike, IgG DiaSorin (≥15 AU/mL = positive)	21 days after first dose, 23 (55%) of 42; 14 days after second dose, 36 (86%) of 42	NR	NR

AEs, adverse events; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BAU, binding antibody unit; CLL, chronic lymphotic leukemia; COV, cut-off value; EC_{50}, median effective concentration; ET, essential thrombocythemia; F, female; GVHD, graft-versus-host disease; hem, hematology; HL, Hodgkin lymphoma; ICA, intracellular cytokine assay; ID_{50}, median infective dose; IFN-γ, interferon-γ; IL-2, interleukin-2; IQR, interquartile range; M, male; MF, myelofibrosis; MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma; ND, not determined; NE, not extractable; NHL, non-Hodgkin lymphoma; NR, not reported; OD, optical density; PBMC, peripheral blood mononuclear cell; PV, polycythemia vera; RBD, receptor-binding domain; SMM, smoldering multiple myeloma; WM, Waldenström macroglobulinemia.

*Excluded from meta-analysis.

Table 2. Summary of pooled seropositivity rates for patients with hematologic malignancies by underlying disease type and number of vaccine doses

		Single-arm studies			Malignancy arm of comparator studies			Control arm of comparator studies			Intervention vs control cohort			
	No. of patients	Pooled response rate (95% CI)	I^2 (%)	*P*	Pooled response rate (95% CI)	I^2 (%)	*P*	Pooled response rate (95% CI)	I^2 (%)	*P*	OR (95% CI)	*P*	I^2 (%)	*P*
Overall: Patients with hematologic malignancies														
After second dose	4733	0.62 (0.55-0.70)	92	<.01	0.66 (0.57-0.75)	93	<.01	0.99 (0.97-1.00)	53	0.01	0.04 (0.02-0.08)	<.01	70	<.01
After first dose	2331	0.51 (0.38-0.64)	92	<.01	0.37 (0.23-0.51)	90	<.01	0.78 (0.62-0.95)	98	<.01	0.10 (0.04-0.29)	<.01	86	<.01
Myeloma														
After second dose	1218	0.80 (0.64-0.95)	85	<.01	0.76 (0.70-0.82)	90	<.01	0.98 (0.95-1.00)	71	<.01	0.09 (0.03-0.29)	<.01	49	.08
After first dose	685	0.43 (0.18-0.68)	91	<.01	0.29 (0.09-0.48)	81	<.01	0.64 (0.42-0.87)	76	<.01	0.23 (0.05-0.99)	.05	49	.11
CLL														
After second dose	1446	0.51 (0.37-0.65)	91	<.01	0.51 (0.34-0.68)	56	.06	1.00 (0.99-1.00)	0	.07	0.01 (0.01-0.03)	<.01	0	.9
After first dose	111	Single study			0.18 (0.00-1.00)	89	<.01	0.92 (0.52-1.00)	0	.32	0.03 (0.00-0.80)	.05	0	.60
Lymphoma														
After second dose	1227	0.52 (0.28-0.75)	97	<.01	0.55 (0.35-0.76)	84	<.01	0.99 (0.98-1.00)	0	.72	0.02 (0.01-0.02)	<.01	0	1.0
After first dose	69	No studies available			0.33 (0.00-1.00)	93	<.01	0.95 (0.09-1.00)	71	.06	0.01 (0.0-1.24)	.05	0	.7
HSCT and cellular therapies														
After second dose	401	0.61 (0.42-0.80)	88	.05	Single study			Single study			Single study			
After first dose	21	Single study			No studies available			No studies available			No studies available			
Acute leukemia and MDS														
After second dose	113	0.93 (0.80-1.00)	29	.24	Single study			Single study			Single study			
After first dose	13	Single study			Single study			Single study			Single study			
MPN and CML														
After second dose	281	0.88 (0.72-1.00)	70	.01	0.87 (0.81-0.92)	0	.83	0.99 (0.98-1.00)	0	.90	0.07 (0.0-1.55)	.06	0	.77
After first dose	222	0.71 (0.30-1.00)	76	.01	0.54 (0.37-0.71)	0	.46	0.85 (0.51-1.00)	90	<.01	0.13 (0.01-1.71)	.09	88	<.01

AEs, adverse events; CLL, chronic lymphotic leukemia; CML, chronic myeloid leukemia; HSCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms.

extraction (Figure 1). Overall, there were 44 studies of COVID-19 vaccination in patients with hematologic malignancies. Sixteen studies[23-38] involved mixed group of patients with various underlying hematologic malignancies, and 28 studies focused on specific malignancies and treatments: 8 myeloma studies,[39-46] 6 CLL studies,[47-52] 4 lymphoma studies,[53-56] 4 studies of HCT[57,58] and chimeric antigen receptor (CAR) T-cell therapy,[59,60] and 6 MPN studies.[61-66] A total of 7064 patients were included in the analysis (2331 after first dose and 4733 after second dose). Characteristics of patients and primary and secondary outcomes in the included studies are summarized in Table 1.

Risk of bias and quality assessment

Overall, 23 studies (52%) were evaluated as being of good or fair quality (good, 11; fair, 12) with low risk of bias, whereas the remaining 21 studies were rated as poor quality (high risk of bias) primarily because of lack of details regarding patient selection, demonstration that outcome of interest was not present at the start of study, comparability of cohorts (design or analysis), and duration of follow-up. Risk of bias and quality assessment of studies are summarized in supplemental Table 1.

Seropositivity rates

There were 44 studies measuring humoral immune responses in patients with hematologic malignancies. The majority of studies evaluated the use of BNT162b2 and used SARS-CoV-2 spike-specific IgG levels above the threshold of detection (seropositivity). Twenty-three studies (52%) reported sufficient data on the spike/receptor binding domain IgG antibody levels (median value or geometric mean titer) after 1 dose (6 studies),[27,35,37,41,62,63] 2 doses (13 studies),[24,26,29,30,38,39,46,48,49,55,59-61] and after both 1 and 2 doses (4 studies).[36,43,50,66] Antibody levels achieved were lower compared with those in control cohorts after 1 and 2 doses of COVID-19 vaccine.[27,29,30,39,46,49,62,63] In 3 studies,[36,43,66] the magnitude of increase in antibody levels between doses was 5-fold to 15-fold, whereas the fourth study by Parry et al[50] reported a 132-fold increase between the first and second doses in 12 of 299 patients with CLL.

Several studies attempted to establish potential thresholds for clinical protection with higher antibody levels than the seropositivity threshold used. Malard et al[33] correlated SARS-CoV-2 spike IgG levels with nAb levels, and ≥3100 arbitrary units (AU)/mL on the Abbott assay was predictive of an nAb level ≥30%. Using this threshold, the rate of humoral response was 47% in hematology patients compared with 97% in healthy controls after a second dose of the BNT162b2 vaccine.[33] Pimpinelli et al[36] also evaluated humoral responses using a higher threshold of ≥80 AU/mL (DiaSorin, Saluggia, Italy) and noted response rates of 55% for patients with myeloma and 84% for patients with MPNs compared with 97% for healthy controls. Other studies correlated SARS-CoV-2 IgG levels with plaque reduction neutralization tests or with levels seen in clinical vaccination trials. Stampfer et al[43] defined >250 IU/mL (in-house assay) as a clinically relevant response that was attained by 45% of patients with myeloma after 2 doses of a COVID-19 vaccine. For HCT patients, Redjoul et al[58] used a threshold of 4160 AU/mL (Abbott Laboratories, Wiesbaden, Germany), and 59% of patients achieved this response after 2 doses.

Overall pooled seropositivity rates in patients with hematologic malignancies were 62% in single-arm studies and 66% in comparator studies after 2 doses of COVID-19 vaccination. After a single dose, the pooled seropositivity rates were 51% in single-arm studies and 37% in comparator studies. Compared with healthy or older matched controls, patients with hematologic malignancies were less likely to achieve seropositivity with ORs of 0.04 (95% CI, 0.02-0.08; $P < .01$) after 2 doses (Figure 2A) and 0.10 (95% CI, 0.04-0.29; $P < .01$) after a single dose (Figure 2B) of COVID-19 vaccine. Heterogeneity was 70% and 86%, respectively ($P < .01$). Pooled seropositivity rates by disease type and vaccine doses are summarized in Table 2 and Figure 3. Overall results were graded as having moderate quality due to statistical and clinical heterogeneity and the proportion of studies with a high risk of bias (48%).

Patients with myeloma. There were 8 dedicated studies and 9 other studies that reported immune response rates in patients with myeloma (supplemental Table 2). For the 2 studies by Terpos et al,[44,45] only nAbs at 2 levels were reported; a threshold of ≥30% was used to define seropositivity and a threshold of ≥50% was used to define rate of positive nAbs. There were 1218 patients with myeloma who received 2 doses of vaccine, and seropositivity rates were 76% to 80%. Seropositivity rates were 29% to 43% after 1 dose of COVID-19 vaccine in 685 patients. The OR for achieving seropositivity was 0.09 (95% CI, 0.03-0.29; $P < .01$) in patients with myeloma compared with those in the healthy control group after 2 vaccine doses and 0.23 (95% CI, 0.05-0.99; $P = .05$) after 1 dose (Table 2).

Patients with CLL. A total of 1557 patients with CLL in 12 studies (6 CLL specific, 6 hematology) were included in this review (supplemental Table 3). Pooled seropositivity rates were 51% in 1446 patients with CLL after 2 doses of COVID-19 vaccine. Rate of seropositivity was 18% after 1 dose of COVID-19 vaccine, and it was 37% in a single-arm study by Ollila et al.[35] ORs for seropositivity were 0.01 (95% CI, 0.01-0.03; $P < .01$) for patients with CLL after 2 doses and 0.03 (95% CI, 0.00-0.80; $P = .05$) after 1 dose of vaccine compared with that for healthy controls.

Patients with lymphoma. For 1296 patients with lymphoma across 11 studies (supplemental Table 4), pooled seropositivity rates were 52% to 55% after 2 doses and 33% after 1 dose of COVID-19 vaccine. ORs for achieving seropositivity were 0.01 to 0.02 for patients with lymphoma compared with a healthy cohort (Table 2).

Patients after HCT and CAR T-cell therapy. A total of 6 studies included in this review reported on immune responses after HCT and CAR T-cell therapy (supplemental Table 5). Two studies involved patients who received an allogeneic HCT (allo-HCT)[57,58]: One study included patients who received an allo-HCT and those who received CAR T-cell therapy,[59] and the other included all patients who received HCTs and those who received CAR T-cell therapy.[60] Two studies were larger studies of hematology patients with subsets of patients treated with HCT or CAR T cells.[28,29] There were 422 patients of whom 401 received 2 doses of COVID-19 vaccine and the remainder received 1 dose. Pooled seropositivity rate was 61% after 2 doses of COVID-19 vaccine. The seropositivity rate was 74% after allo-HCT and 31% after treatment with CAR

Table 3. Summary of pooled rates of positive nAb, cellular responses, and AEs

	Positive nAb response		Positive cellular response		Atleast 1 AE rate			
	Pooled response rate	95% CI	Pooled response rate	95% CI	Pooled response rate	95% CI	I^2 (%)	*P*
Overall: Patients with hematologic malignancies								
After second dose	Single arm: 0.60 (single study)		Single arm: 0.40	0.00-1.00	0.36	0.24-0.48	97	<.01
	Malignancy arm of comparator studies: 0.57 (single study)		Malignancy arm of comparator studies: 0.75 (single study)					
After first dose	Single arm: 0.63	0.00-1.00	Single arm: 0.86	0.00-1.00	0.39	0.18-0.60	97	<0.01
	Malignancy arm of comparator studies: 0.18	0.00-0.44	Malignancy arm of comparator studies: 0.33 (single study)					

T cells. In a single study with a healthy control cohort, seropositivity rate was 81% in patients who received an autologous HCT (auto-HCT) compared with 99% in an age-matched group without haematologic malignancy.[29] In the only study of immune response after 1 dose of COVID-19 vaccine, the rate of seropositivity was 38% in patients who received an allo-HCT.[57]

Patients with acute leukemia or myelodysplastic syndrome (MDS). There were no dedicated studies of COVID-19 vaccination in patients with acute leukemia. A subset of 126 patients with acute leukemia or MDS were reported in 6 studies (supplemental Table 6), and the seropositivity rate was 93% after 2 doses of COVID-19 vaccine. In a single study, the seropositivity rate was 80% in patients with acute leukemia and 94% in patients with MDS compared with 99% in the control group.[29] No patients with acute leukemia mounted an immune response after a single vaccine dose compared with 86% of controls.[34]

Patients with MPNs or CML. Of 12 studies (supplemental Table 7) encompassing 503 patients with MPNs or CML (281 after 2 doses, 222 after a single dose), rates of seropositivity were 87% to 88% after 2 doses and 54% to 71% after 1 dose of vaccine. Compared with a healthy patient cohort, the OR was 0.07 (95% CI, 0.0-1.55; $P = .06$) for patients with MPNs or CML achieving seropositivity with 2 doses of COVID-19 vaccine and 0.13 (95% CI, 0.01-1.71; $P = .09$) after a single dose.

Rates of nAb and cellular response and AEs

Only 7 studies (16%) reported nAb responses and 5 studies (11%) reported cellular responses. After 2 doses of COVID-19 vaccine, 57% of patients with myeloma achieved a positive nAb response compared with 81% of the control group, whereas 60% of patients with CLL achieved a positive nAb response in a subpopulation of a single-arm study.[45,47] After 1 dose of COVID-19 vaccine, the overall pooled rate for a positive nAb response was 18% for all patients with hematologic malignancies (Table 3). The pooled rate of 2 single-arm studies of patients with MPNs was 63%. After COVID-19 vaccination, the rate of achieving a positive cellular response was 40% to 75% for all patients after 2 doses and 33% to 86% after a single dose. In a single study, the cellular response rates after 2 doses of COVID-19 vaccine were 19% for patients who received treatment with allo-HCT and 50% for those who received treatment with CAR T cells.[59] In patients with MPNs, this rate was 86% after 1 dose.[64,65]

In 10 studies (22%), at least 1 systemic or local AE was reported. Overall, the pooled rate of at least 1 AE was 36% after 2 doses and 39% after a single dose (Table 3). Overall, local and systemic AEs were mild (grade 1 to 2) except for a single study in which grade 3 systemic AEs rates were ~1% to 2%.[32,33,39,45,47,49,56,64,65] In patients who received an HCT, a 5% rate of exacerbation of graft-versus-host disease (grade 1 to 2) and grade 3 to 4 neutropenia or thrombocytopenia (self-resolved) was noted.[59] Most commonly reported AEs were injection site pain, fatigue, myalgia, headache, and fever.[32,33,39,45,47,49,56,59,64,65]

Subgroup analysis

Study characteristics and outcomes of studies included in subgroup analyses are summarized in supplemental Tables 8-12. Receiving 2 doses of vaccine during active therapy was associated with

Table 4. Summary of subgroup analysis by active treatment, timing of CD20 antibody therapy, HCT, receipt of targeted therapies, and type of COVID-19 vaccine

	Intervention arm			Control arm			Intervention vs control cohort			
	Pooled response rate (95% CI)	I^2(%)	*P*	Pooled response rate (95% CI)	I^2(%)	*P*	OR (95% CI) Heterogeneity	*P*	I^2(%)	*P*
Active therapy vs no active therapy										
After second dose	0.28 (0.08-0.48)	83	<.01	0.62 (0.39-0.86)	94	<.01	0.21 (0.06-0.67)	.02	75	<.01
After first dose	0.42 (0.09-0.75)	49	.08	0.81 (0.66-0.95)	0	.62	0.19 (0.03-1.19)	.06	24	.27
CD-20 antibody therapy within 12 months vs CD-20 therapy 12 or more months										
After second dose	0.19 (0.00-0.50)	88	<.01	0.61 (0.41-0.82)	88	<.01	0.08 (0.01-0.59)	.02	57	.04
After first dose	Single study			Single study			Single study			
Targeted therapy										
After second dose	0.35 (0.19-0.52)	94	<.01	No controls			No analysis			
After first dose	Single study			No controls			No analysis			
HSCT or cellular therapy within 12 months vs after 12 or more months										
After second dose	0.66 (0.43-0.88)	0	.63	0.68 (0.40-0.95)	45	.16	0.96 (0.11-8.74)	.94	36	.21
After first dose	Single study			Single study			Single study			
BNT162b2 vs non-BNT162b2 vaccine type*										
After second dose	0.77 (0.40-1.00)	98	<.01	0.81 (0.56-1.00)	87	<.01	1.08 (0.20-5.92)	.90	64	.04
After first dose	0.51 (0.13-0.90)	86	<.01	0.64 (0.36-0.91)	73	.01	0.59 (0.22-1.60)	.19	7	.36

*Non-BNT162b2 includes mRNA-1273, ChAdOx1, and Ad26 vaccines.

seropositivity rates of 28% compared with a rate of 62% when patients were not receiving active therapy with an OR of 0.21 (95% CI, 0.06-0.67; $P = .02$). Lower seropositivity rates (19% vs 61%) were reported with vaccination during or within 12 months of CD-20 antibody therapy compared with vaccination 12 or more months after completion of therapy. Use of targeted therapy was associated with a pooled seropositivity rate of 35% after 2 doses of COVID-19 vaccine. Seropositivity rates did not differ by timing of vaccination in relation to HCT (66% vs 68%) or vaccine type (BNT162b2 vs others, including mRNA-1273, ChAdOx1, Ad26; [51% vs 64%] [77% vs 81%]) after 1 or 2 doses. Table 4 summarizes the seropositivity rates by each subgroup analyzed.

Sensitivity analysis

Excluding single-arm studies that were assessed as poor quality or as having a high risk of bias did not alter the pooled seropositivity rates, but in comparator studies, OR was 0.17 (95% CI, 0.04-0.75; $P = .03$) after 1 dose instead of 0.10 (supplemental Table 13).

Discussion

In this systematic review and meta-analysis of more than 7000 patients with hematologic malignancies, rate of seropositivity was 62% to 66% after 2 doses and 37% to 51% after 1 dose of COVID-19 vaccine. Compared with age-matched and non–age-matched healthy controls (primarily health care workers), odds of achieving seropositivity were significantly lower by 96% after 2 doses of COVID-19 vaccine and 90% after 1 dose. Statistical heterogeneity was substantial at more than 70%, and studies were also clinically heterogenous because of the variety of underlying hematologic malignancies, lack of standardized laboratory platforms by which to measure immune response to vaccination, and variable follow-up periods. Reassuringly, reported rates of at least 1 AE after vaccination were lower at 36% compared with rates of AEs (51% to 88%) reported in clinical trials of the general population.[10,13]

Among different hematologic malignancies, pooled seropositivity rates after 2 doses were highest at close to 90% in patients with acute leukemia, MDS, or MPNs and the lowest at 51% in patients with CLL. Patients with CLL respond poorly to vaccination, especially to new or novel antigens compared with recall antigens from previous infections or vaccination.[67] Poor response is compounded by use of B-cell–depleting and targeted therapies such as CD-20 monoclonal antibodies (mAb) and BTKi's.[67] Immune response to other vaccines, including the seasonal influenza vaccine, is negatively impacted by these therapies, and the poor response persists for at least 6 to 12 months after cessation of therapy.[68]

A similar negative impact of treatment on COVID-19 vaccine responses was noted in subgroup analysis of published studies. Rates of seropositivity were lower in the setting of active treatment (28%), and the lowest response rates were reported in the setting of current or CD-20 mAb therapy within 12 months (19%), targeted therapies (35%), and after therapy with CAR T cells (31%). Seropositivity rates were 2 to 3 times higher at 62% when patients were vaccinated when they were not receiving active therapy and 61% when vaccinated at 12 or more months after completion of mAb CD-20 therapy.

Unvaccinated patients with CLL have a high burden of morbidity from COVID-19 infection with close to 90% of patients requiring hospital admission, 35% requiring admission to intensive care units, and a mortality rate of 33%.[4] Yet patients with CLL have poor humoral responses to vaccination: 18% after 1 dose and 51% after 2 doses. In patients with CLL, immune suppression from underlying disease and ongoing treatments such as anti-CD20 mAb's and BTKi's continue to pose a risk for SARS-CoV-2 infection and concurrently limit protective responses from vaccination. Although vaccination remains highly recommended, new strategies are required to

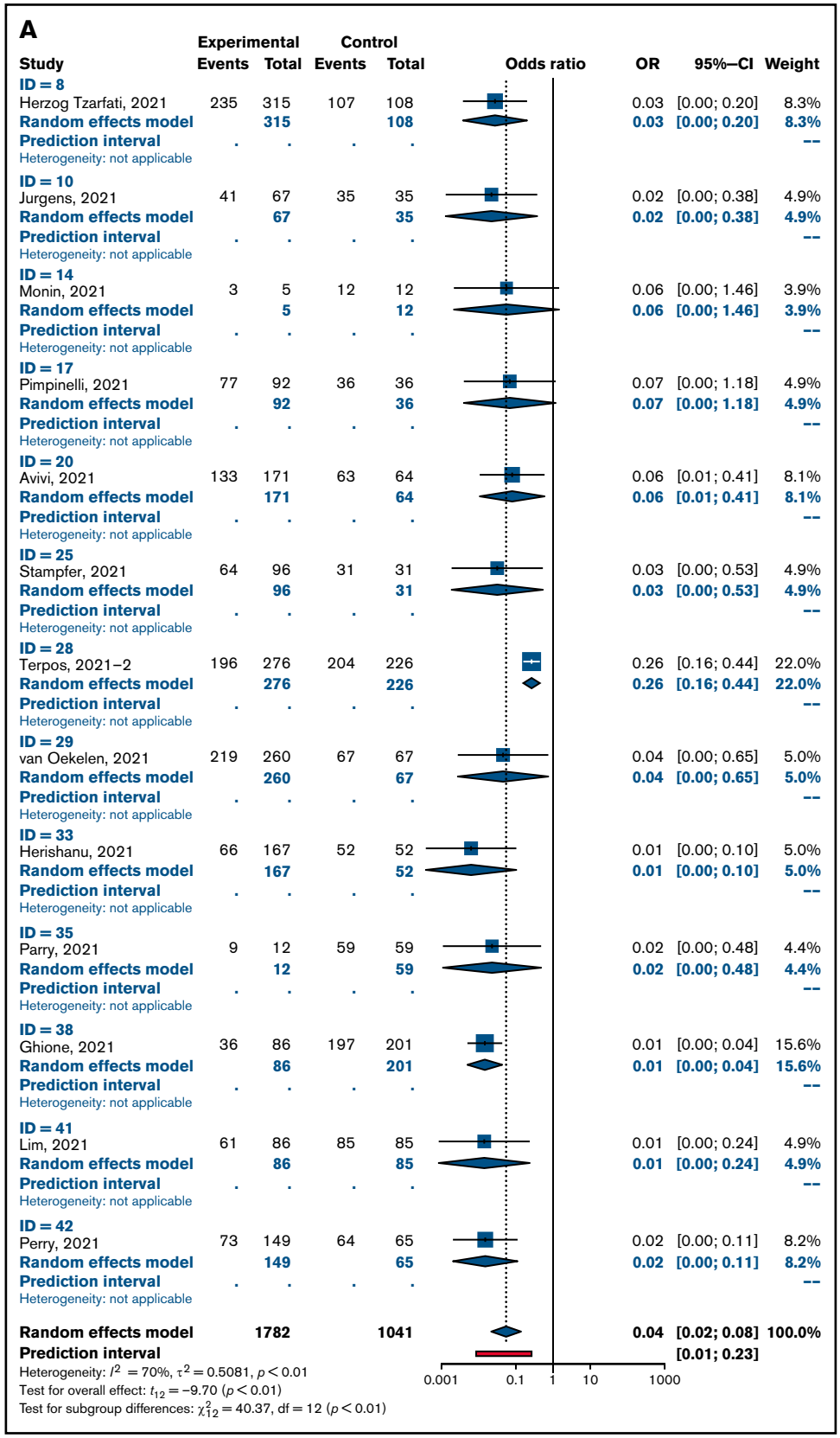

Figure 2. OR for achieving seropositivity in patients with hematologic malignancies vs healthy control group after 2 doses (A) and 1 dose of COVID-19 vaccine (B).

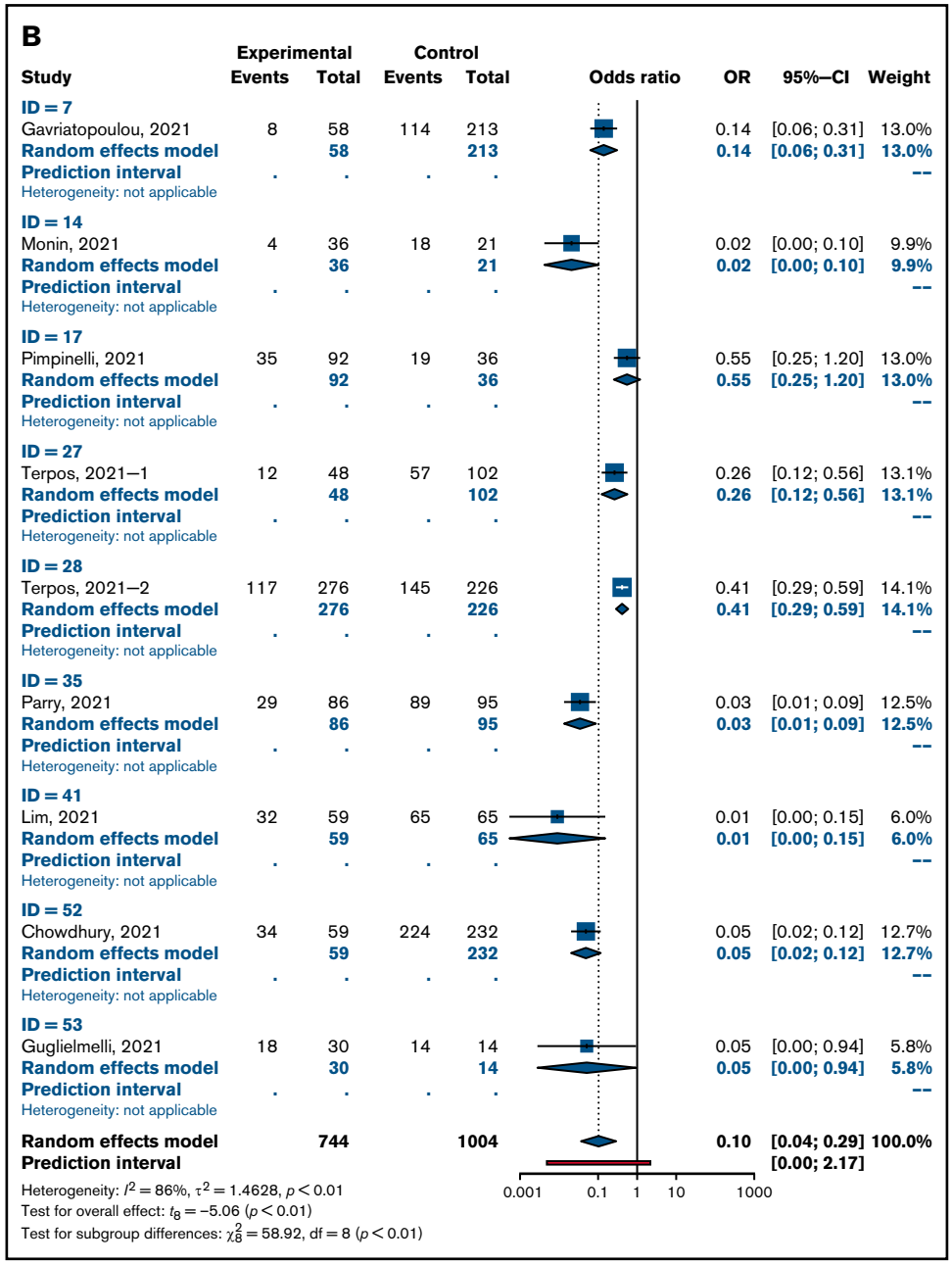

Figure 2. (continued)

further improve immune responses in this high-risk patient population. In other groups of immune compromised patients, the use of an additional dose of COVID-19 vaccine improved serologic response rates by 37%, and the use of heterologous vaccination schedules (mixing vaccine types) appears promising.[69-71] International health groups now recommend a third dose of COVID-19 vaccine for immune compromised patients, including those with hematologic malignancies.[72,73] Heterologous prime boost or use of high-dose vaccine formulations have been used in randomized trials of seasonal influenza vaccination in hematology and in patients who have received an HCT with mixed success.[17,74] In addition, other preventative approaches such as the use of anti–SARS-CoV-2 mAb therapy as pre-exposure (NCT04625725) and post-exposure prophylaxis require further evaluation in vulnerable patient groups who respond poorly to vaccination.[75]

Serologic responses are classically used as surrogate end points for clinical efficacy in clinical trials of vaccination in patients with hematologic malignancies.[15-17] Serologic thresholds for protection (seroprotection) after vaccination have been established for infections such as seasonal influenza.[17] In the majority of studies included in this review, however, the outcome of interest was seropositivity as defined by antibody levels above the detection threshold. This is not equivalent to seroprotection because thresholds

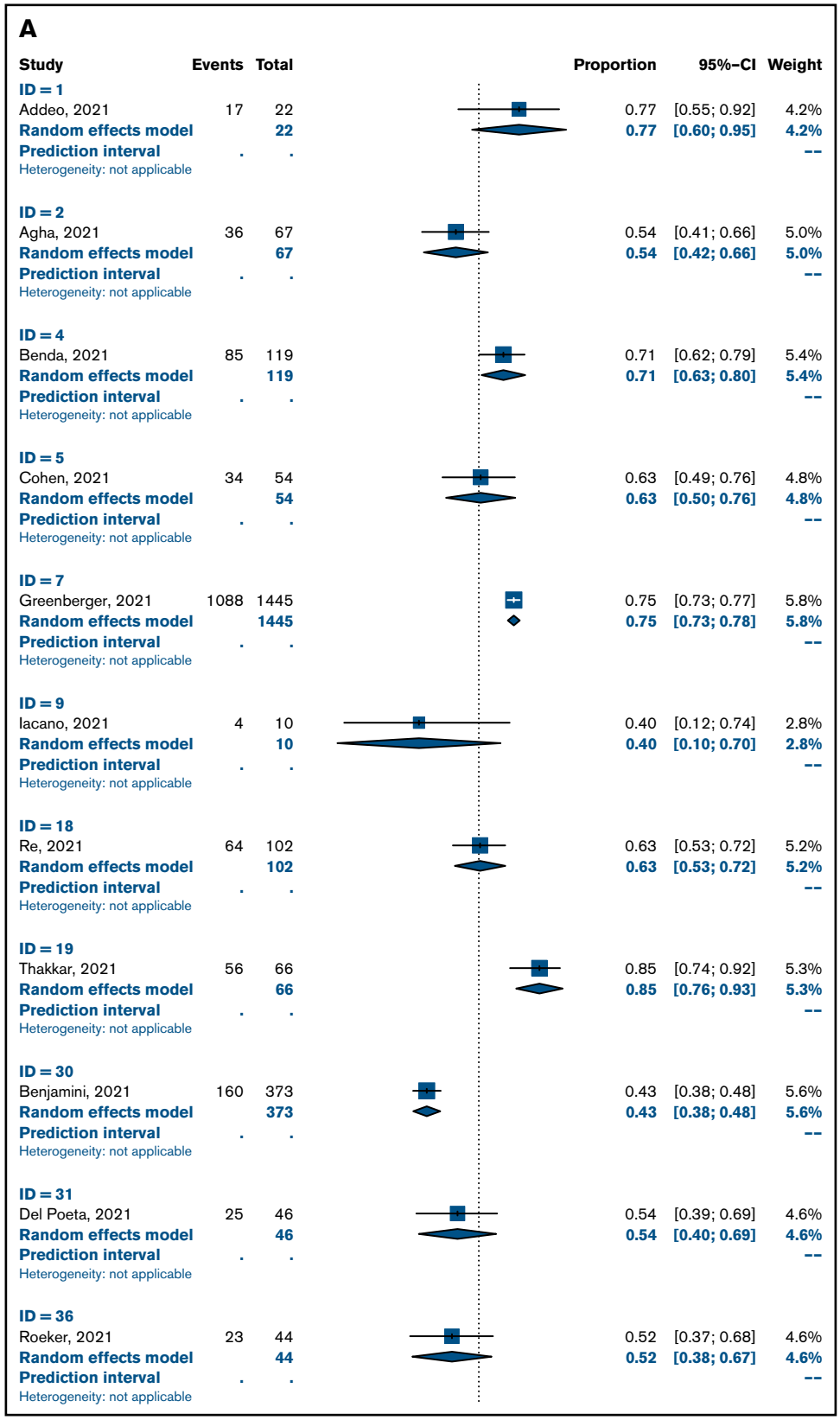

Figure 3. Pooled rates of seropositivity in single-arm studies involving patients with hematologic malignancies after 2 doses (A) and 1 dose of COVID-19 vaccine (B).

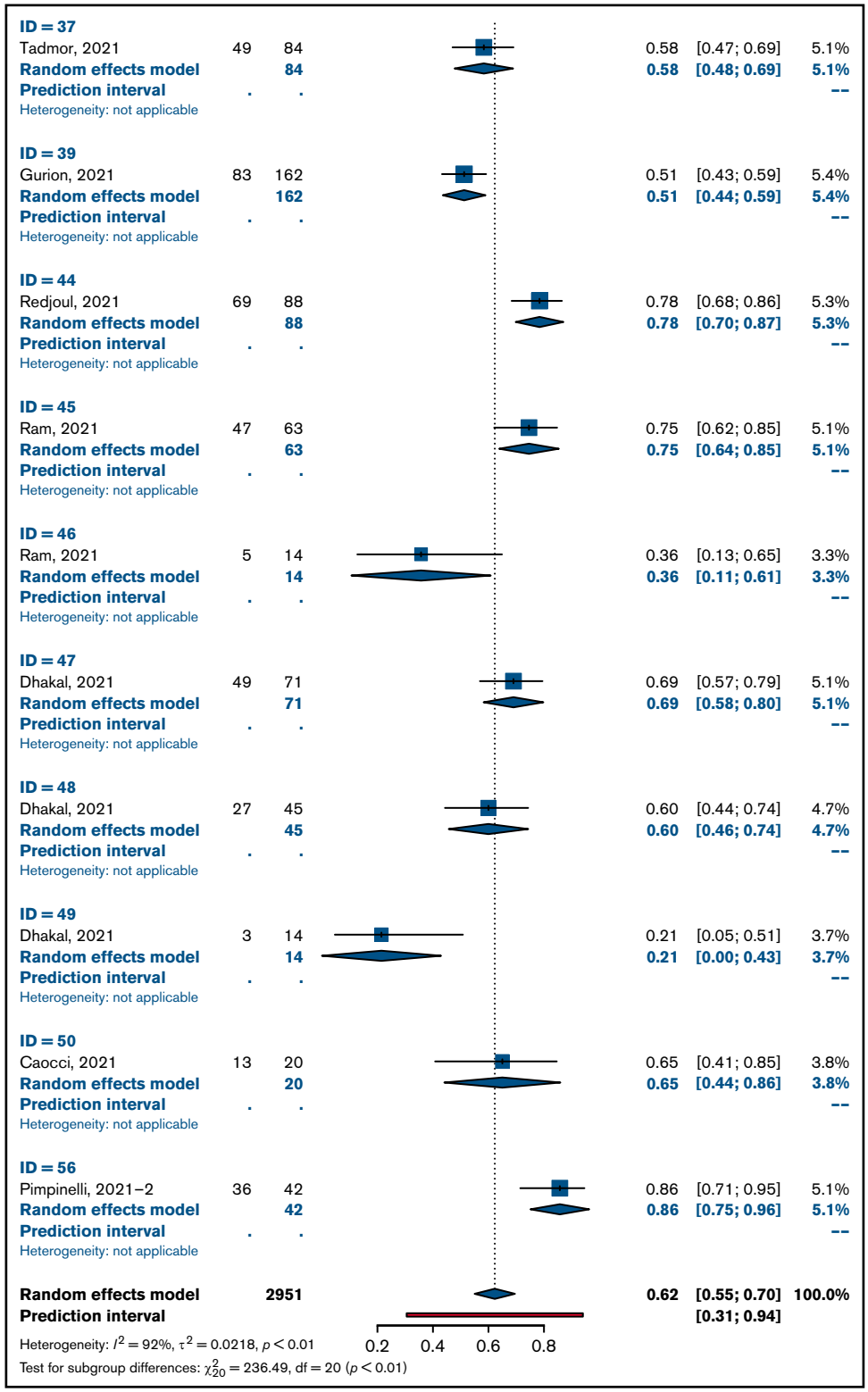

Figure 3. (continued)

have not been standardized nor have they been established across the variety of commercial and research platforms used by these studies. Some authors such as Malard et al,[33] Stampfer et al,[43] and Redjoul et al[58] have attempted to define serologic thresholds that correlate with nAb and clinical protection. Unsurprisingly, a lower proportion of patients (by 20% to 35% compared with pooled

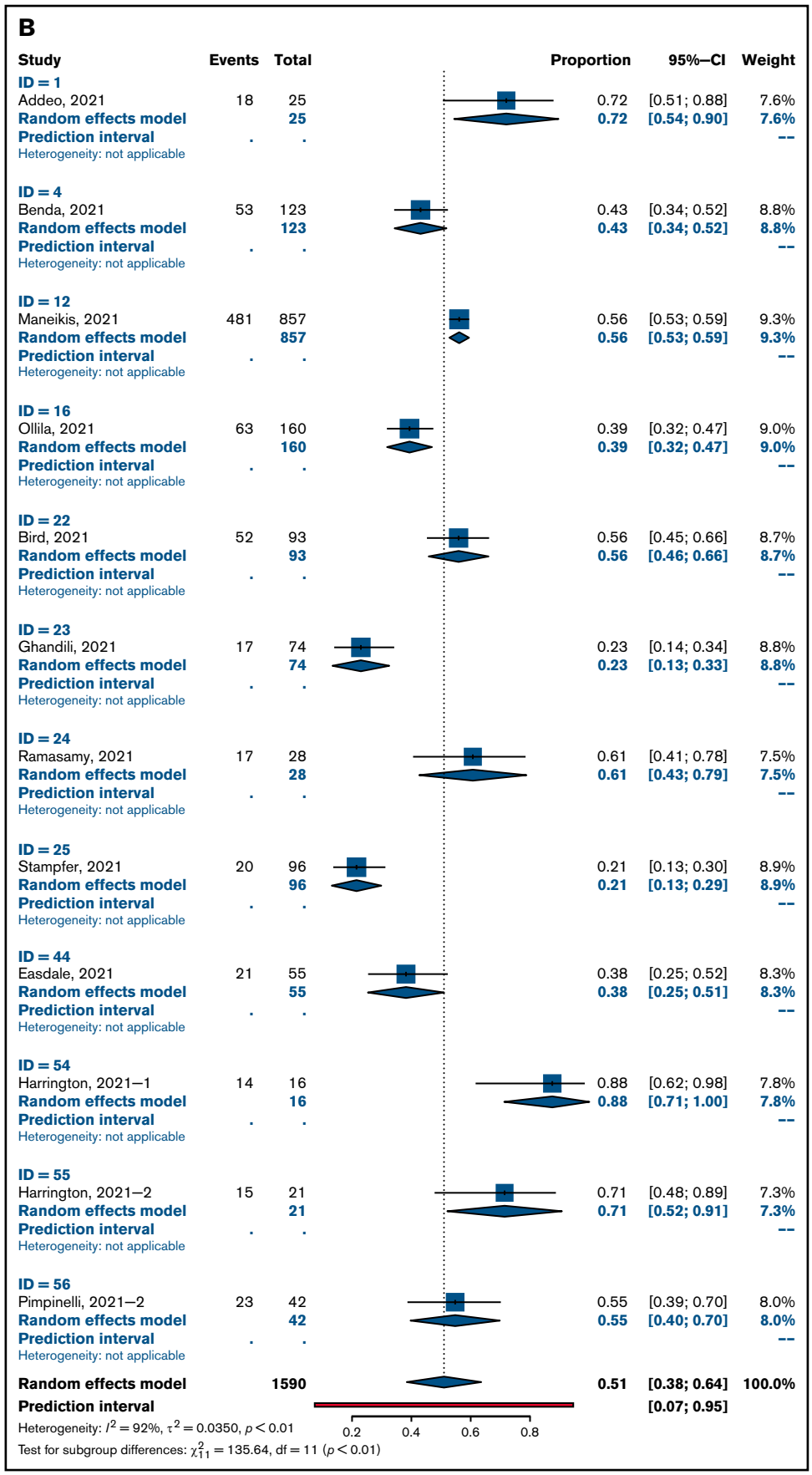

Figure 3. (continued)

rates) achieved these higher antibody thresholds.[33,43,58] For serologic response measurement to guide clinical management of COVID-19 vaccination, further work is required to achieve harmonization across testing platforms and to derive and validate thresholds that correlate with clinical protection.

Measurement of serologic responses offers only a glimpse of the potential breadth of immune responses to COVID-19 vaccination. Both nAb and cellular responses to vaccination play complementary and vital roles in protection against COVID-19 and remain under-reported.[76-78] In 16% of studies, at least 18% of hematology patients achieved a positive nAb response. Positive cellular response rates were at least 15% higher than nAb responses after 1 or 2 doses of vaccine. Although serologic responses have been used as surrogate end points in vaccination studies of immune compromised patients, further large studies are required to identify new immune markers for vaccine response and to determine the efficacy of vaccination.

This review has several limitations. In particular, the findings are of moderate quality because of significant clinical and statistical heterogeneity of included studies and the proportion of studies of poorer quality. In line with other established studies of vaccination in hematology patients, only immune response data were analyzed because clinical efficacy data were limited.

In conclusion, this systematic review and meta-analysis has comprehensively summarized the latest data on response to COVID-19 vaccination in patients with hematologic malignancies. Overall, seropositive rates were reasonable at 66% after 2 doses of vaccine. Higher-risk patient groups were identified, namely patients with CLL and patients receiving active therapy, including targeted and CD-20 mAb therapies. New approaches to treating high-risk patients who are poor responders to vaccination are urgently required.

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Authorship

Contribution: B.W.T coordinated the study, performed abstract and full-text screening and data extraction, and wrote the manuscript; J.S.K.T. performed abstract and full-text screening and data extraction; J.C. developed the study protocol and performed data extraction; S.L. developed the search strategy; T.S. conducted the statistical analysis; Z.C.F.N. and M.A.S. assessed the risk of bias in the studies; and all authors reviewed and revised the manuscript.

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