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COVID-19 mRNA Vaccine in Patients With Lymphoid Malignancy or Anti-CD20 Antibody Therapy: A Systematic Review and Meta-Analysis

Yusuke Ito, 1 Akira Honda, 1 Mineo Kurokawa 1,2

Abstract

Messenger RNA (mRNA) vaccines have been widely used for the prevention of coronavirus disease 2019 (COVID-19). This meta-analysis of 52 articles demonstrated that lymphoid malignancies and anti-CD20 antibody therapy impaired humoral response.

Background: The humoral response to vaccination in individuals with lymphoid malignancies or those undergoing anti-CD20 antibody therapy is impaired, but details of the response to mRNA vaccines to protect against COVID-19 remain unclear. This systematic review and meta-analysis aimed to characterize the response to COVID-19 mRNA vaccines in patients with lymphoid malignancies or those undergoing anti-CD20 antibody therapy. Materials and Methods: A literature search retrieved 52 relevant articles, and random-effect models were used to analyze humoral and cellular responses. Results: Lymphoid malignancies and anti-CD20 antibody therapy for non-malignancies were significantly associated with lower seropositivity rates (risk ratio 0.60 [95% CI 0.53-0.69]; risk ratio 0.45 [95% CI 0.39-0.52], respectively). Some subtypes (chronic lymphocytic leukemia, treatment-naïve chronic lymphocytic leukemia, myeloma, and non-Hodgkin's lymphoma) exhibited impaired humoral response. Anti-CD20 antibody therapy within 6 months of vaccination decreased humoral response; moreover, therapy > 12 months before vaccination still impaired the humoral response. However, anti-CD20 antibody therapy in non-malignant patients did not attenuate T cell responses. Conclusion: These data suggest that patients with lymphoid malignancies or those undergoing anti-CD20 antibody therapy experience an impaired humoral response, but cellular response can be detected independent of anti-CD20 antibody therapy. Studies with long-term follow-up of vaccine effectiveness are warranted (PROSPERO registration number: CRD42021265780).

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Keywords: Cellular response, Humoral response, Seropositivity, CLL, B-cell target therapy

Introduction

Individuals with hematological malignancies are highly susceptible to severe coronavirus disease 2019 (COVID-19). 1,2 The risk for death predominately among the hospitalized adult population has been reported to be as high as 34%. 3 Patients with chronic lymphocytic leukemia (CLL), 4,5 myeloma, 6,7 or lymphoma 8 are likely to develop serious symptoms due to immunological abnormalities caused by the disease itself and the corresponding immunosuppressive therapies. 7,10 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to angiotensin-converting enzyme 2 receptors expressed on oral mucosa epithelial cells and lung alveolar type II cells through the receptor binding domain in its spike protein. 11-13 Messenger RNA (mRNA) vaccines targeting the spike protein have been rapidly developed, 14,15 and two, BNT162b2 16 and mRNA-1273, 17 conferred approximately 95% protection against COVID-19 in clinical trials. However, immunocompromised subjects were excluded from these trials; thus, the efficacy of mRNA vaccines in those with hematological malignancies remains under investigation. Lymphoid malignancies and B cell depletion agents, such as anti-CD20 antibody, have been shown to attenuate conventional vaccine effectiveness. 18,19 Anti-CD20 antibody therapy is efficacious against lymphoma, as well as multiple sclerosis and rheumatic diseases, and some guidelines for rheumatic diseases recommend delaying the administration of vaccines for 5 to 6 months after anti-CD20 therapy to maximize humoral response 20,21; nevertheless, evidence for mRNA vaccines remains insufficient in this regard.

Neutralizing antibodies generated by the humoral response exert immune protection, 22 while the SARS-CoV-2-specific cellular response is also essential for viral elimination and prevention of disease aggravation. 23-25 It remains controversial whether...
A Systematic Review and Meta-Analysis

Figure 1 PRISMA flow diagram of study selection. After the screening of titles and abstracts of 493 articles, 80 articles were considered to be relevant. Among them, 28 articles were excluded due to several reasons, and 52 articles were included for the analysis.

lymphoid malignancies or B cell depletion therapies attenuate cellular responses to the vaccine, and the interaction between T cells and B cells is indispensable for infection control.26-29 Two mRNA vaccines have been approved for use against COVID-19, and real-world data regarding the response to these vaccines in various patient types have accumulated rapidly. The present systematic review and meta-analysis investigated humoral and cellular immune responses to COVID-19 mRNA vaccines in patients with lymphoid malignancies and those who underwent treatment with anti-CD20 antibody.

Materials and Methods

Literature Search Strategy

This study was registered with PROSPERO (CRD42021265780) and performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.30 The PubMed and World Health Organization (WHO) COVID-19 database were searched for articles published up to October 2, 2021, without language restriction using the following terms: (“lymphoid malignancy” OR “lymphoid neoplasm” OR lymphoma OR myeloma OR MM OR MGUS OR CLL OR anti-CD20 OR CD20 OR rituximab OR obinutuzumab OR ofatumumab OR ocrelizumab OR veltuzumab OR ocraratumumab OR ublituximab OR tositumomab OR ibritumomab) AND vaccin* AND (COVID-19 OR SARS-CoV-2).

Study Selection and Quality Assessment

Two authors (YI and AH) independently assessed the titles and abstracts of all articles retrieved in the electronic literature search. Subsequently, the full texts of potentially eligible articles were screened. Studies that lacked sufficient information needed to evaluate outcomes, those that analyzed data only after the first dose of mRNA vaccines, duplicate publications using overlapping patient cohorts, and case series or cohorts with < 10 patients were excluded. Any discrepancies between the authors were resolved through discussion until consensus was reached. A flow diagram of
Table 1  Characteristics of Studies Included in the Meta-Analysis

| Author        | Ref | Location | Disease                                | Total | Pos | Age | Control | Total | Pos | Age | Vaccine | Interval | Antibody | Measurement assay | Cut-off | NOS |
|---------------|-----|----------|----------------------------------------|-------|-----|-----|---------|-------|-----|-----|---------|----------|----------|-------------------|---------|-----|
| Chiarucci M   | 36  | Italy    | Lymphoma, Myeloma after auto-HSCT      | 38    | 32  | 60  | healthy | 45    | NR  | NR  | BNT162b2 | 30 d     | Spike    | LIAISON SARS-CoV-2 Trimeric S IgG assay (CLIA) | 15 AU/mL | 6   |
| Gavriatopoulou M | 37  | Greece   | WM                                     | 74    | 31  | 73  | healthy | 212   | 181 | 66  | BNT162b2, AZD1222 | 4 wk     | NAb      | cPASS SARS-CoV-2 Nabs Detection Kit (ELISA) | 50%     | 9   |
| Shapiro LC    | 48  | US       | Lymphoid malignancy                    | 86    | 71  | 70.5| -       |       |     |     | BNT162b2, mRNA-1273, Ad26.COV2.S | > 2 wk   | RBD      | AdviseDx SARS-CoV-2 IgG II assay (CLIA) | 50 AU/mL | 6   |
| Peeters M     | 59  | Belgium  | Lymphoid malignancy with RTX           | 29    | 2   | 63  | healthy | 40    | 40  | 48  | BNT162b2 | 28 d     | RBD      | Wantai SARS-CoV-2 IgG (ELISA) | 200 IU/mL | 8   |
| Bergman P     | 60  | Sweden   | CLL                                    | 79    | 50  | NR  | healthy | 78    | 78  | NR  | BNT162b2 | 14 d     | RBD      | Elecsys Anti-SARS-CoV-2 S | 0.80 U/mL | 8   |
| Terpos E      | 61  | Greece   | Lymphoid malignancy                    | 132   | 58  | 64.6| healthy | 214   | 204 | 69.8| BNT162b2 | 4 wk     | NAb      | cPASS SARS-CoV-2 Nabs Detection Kit (ELISA) | 50%     | 9   |
| Lim SH        | 62  | UK       | Lymphoma                              | 55    | 39  | 69  | healthy | 65    | 65  | 45  | BNT162b2 | 2-4 wk   | Spike    | Meso Scale Discovery (ECLIA) | 0.55 BAU/mL | 8   |
| Perry C       | 63  | Israel   | B-NHL                                 | 149   | 73  | 64  | healthy | 65    | 64  | 66  | BNT162b2 | 2-3 wk   | RBD      | Elecsys Anti-SARS-CoV-2 S | 0.80 U/mL | 9   |
| Jurgens EM    | 64  | US       | Lymphoma, CLL                         | 67    | 41  | 71  | healthy | 35    | 35  | NR  | BNT162b2, mRNA-1273 | 24.5 d   | spike    | ELISA | 10,000 | 8   |
| Thakkar A     | 65  | US       | Lymphoma with anti-CD20 Ab            | 23    | 16  | 67  | healthy | 26    | 26  | 64  | BNT162b2, mRNA-1273, Ad26.COV2.S | > 7 d   | RBD      | AdviseDx SARS-CoV-2 IgG II assay (CLIA) | 50 AU/mL | 9   |
| Benda M       | 38  | Austria  | Lymphoid malignancy                   | 89    | 57  | 65.1| -       |       |     |     | BNT162b2 | 4-5 wk   | RBD      | Elecsys Anti-SARS-CoV-2 S | 0.82 BAU/mL | 6   |
| Henriquez S   | 39  | France   | Myeloma                               | 60    | 51  | 69.86| healthy | 20    | 20  | NR  | BNT162b2 | 1-2 mo   | spike    | S-flow SARS-CoV-2 IgG | 40%     | 8   |

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### Table 1 (continued)

| Author       | Ref | Location | Disease                  | Total | Pos  | Age  | Control | Total | Pos  | Age  | Vaccine          | Interval | Antibody            | Measurement assay                     | Cut-off | NOS |
|--------------|-----|----------|--------------------------|-------|------|------|---------|-------|------|------|-------------------|----------|---------------------|----------------------------------------|---------|-----|
| Terpos E     | 40  | Greece   | Myeloma                  | 276   | 158  | 74   | healthy | 226   | 183  | NR   | BNT162b2, AZD1222 | 4 wk     | NAb                 | cPASS SARS-CoV-2 Nabs Detection Kit (ELISA) | 50%     | 9   |
| Maneikis K   | 41  | Lithuania| Lymphoid malignancy      | 163   | 97   | 65   | healthy | 67    | 67   | 40   | BNT162b2           | 7-21 d   | spike (S1)          | Abbott Architect SARS-CoV-2 IgG Quant II (CMIA) | 50 AU/mL | 8   |
| Parry H      | 42  | UK       | CLL                      | 55    | 39   | 69   | healthy | 37    | 36   | NR   | BNT162b2, ChAdOx1 | 18 d     | spike               | Dried blood spot ELISA                 | ratio 1  | 9   |
| Stampfer SD  | 43  | US       | Myeloma                  | 103   | 50   | 68   | healthy | 31    | 29   | 61   | BNT162b2, mRNA-1273 | 14-21 d  | spike              | ELISA                                  | 250 IU/mL | 9   |
| Gurion R     | 44  | Israel   | Lymphoma                 | 162   | 83   | 65   | -       | BNT162b2 | 2-6 wk | spike | Abbott Architect SARS-CoV-2 IgG Quant II (CMIA) | 50 AU/mL | 6   |
| Benjamini O  | 45  | Israel   | CLL                      | 373   | 160  | 70   | -       | BNT162b2 | 2-3 wk | spike | Liaison SARS-CoV-2 S1/S2 IgG or Architect AdstebDx SARS-CoV-2 IgG II or RBD-IgG ELISA | 15 U/mL or 50 U/mL or 1.1 | 6   |
| Avivi I      | 46  | Israel   | Myeloma                  | 171   | 133  | 70   | healthy | 64    | 63   | 67   | BNT162b2           | 14-21 d  | RBD                 | Elecsys Anti-SARS-CoV-2 S                 | 0.80 U/mL | 9   |
| Ghione P     | 47  | US       | Lymphoma, Myeloma        | 86    | 36   | 70   | healthy | 201   | 197  | NR   | BNT162b2, mRNA-1273, Ad26.COV2.S | 2-8 wk   | spike (S1)          | KSL chemiluminescence immunoassay (CLIA) | 1.0 COI  | 8   |
| Tzarfati KH  | 49  | Israel   | Lymphoid malignancy      | 194   | 131  | 71   | healthy | 108   | 107  | 69   | BNT162b2           | 32 d     | spike               | Liaison SARS-CoV-2 S1/S2 IgG (CLIA)        | 12 AU/mL | 9   |
| Oekelen OV   | 50  | US       | Myeloma                  | 260   | 219  | 68   | healthy | 67    | 67   | NR   | BNT162b2, mRNA-1273 | > 10 d   | spike              | Kantrao COVID-SeroKlir IgG Ab kit (ELISA)   | 5 AU/mL  | 8   |
| Dietenbach C | 51  | US       | Lymphoma, CLL            | 18    | 4    | 63   | healthy | 3     | 3    | NR   | BNT162b2, mRNA-1273 | 4-8 wk   | RBD                 | multiplex bead-binding assay             | mean +3 x s.d. | 8   |
| Pimpinelli F | 52  | Italy    | Myeloma                  | 42    | 33   | 73   | healthy | 36    | 36   | 81   | BNT162b2           | 2 wk     | spike              | Liaison SARS-CoV-2 S1/S2 IgG (CLIA)        | 15 AU/mL | 9   |

(continued on next page)
| Author          | Ref | Location | Disease                          | Total | Pos | Age | Control | Total | Pos | Age | Vaccine                        | Interval | Antibody                     | Measurement assay            | Cut-off | NOS |
|-----------------|-----|----------|----------------------------------|-------|-----|-----|---------|-------|-----|-----|--------------------------------|----------|-------------------------------|-----------------------------|---------|-----|
| Yusuke Ito et al |     |          |                                   |       |     |     |         |       |     |     |                                |          |                               |                             |         |     |
| Table 1 (continued) | | | | | | | | | | | | | | |
| Roeker LE       | 53  | US       | CLL                              | 44    | 23  | 71  | -       |       |     |     | BNT162b2, mRNA-1273            | 21 d     | spike                        | Liaison SARS-CoV-2 S1/S2 IgG (CLIA) | 15 AU/mL | 6   |
| Herishanu Y     | 54  | Israel   | CLL                              | 167   | 66  | 71  | healthy | 52    | 52  | 68  | BNT162b2                      | 2-3 wk   | RBD                          | Elecsys Anti-SARS-CoV-2 S    | 0.80 U/mL | 9   |
| Agha M          | 55  | US       | Lymphoid malignancy              | 63    | 33  | 71  | -       |       |     |     | BNT162b2, mRNA-1273            | 23 d     | RBD                          | semi-quantitative Beckman Coulter SARS-CoV-2 platform | 1.0 S/CO | 6   |
| Dhakal B        | 56  | US       | Lymphoma, Myeloma after auto-HSCT| 45    | 27  | 65  | -       |       |     |     | BNT162b2, mRNA-1273, Ad26.COV2.S | >2 wk    | spike (S1)                    | EUOIMMUN (ELISA)             | NR      | 6   |
| Greenberger LM  | 57  | US       | Lymphoid malignancy              | 1311  | 969 | 66  | -       |       |     |     | BNT162b2, mRNA-1273            | 14 d     | RBD                          | Elecsys Anti-SARS-CoV-2 S    | 0.8 U/mL | 6   |
| Re D            | 58  | France   | Lymphoid malignancy              | 79    | 45  | 75.5| -       |       |     |     | BNT162b2, mRNA-1273            | 3-5 wk   | spike                        | anti-spike IgG                | -       | 6   |
| - Non-malignant diseases treated with anti-CD20 Ab - | | | | | | | | | | | | | | |
| Sormani MP      | 66  | Italy    | MS                               | 179   | 83  | 45.8| untreated MS | 87    | 87  | 45.8| BNT162b2, mRNA-1273            | 4 wk     | RBD                          | Elecsys Anti-SARS-CoV-2 S    | 0.80 U/mL | 8   |
| Disanto G       | 67  | Switzerland | MS                             | 56    | 29  | 56  | untreated MS | 13    | 13  | 51.8| BNT162b2, mRNA-1273            | 26 d     | RBD                          | Abbott Architect SARS-CoV-2 IgG Quant II (CMIA) | 50 AU/mL | 9   |
| Brill L         | 78  | Israel   | MS                               | 49    | 20  | 47.9| healthy | 35    | 35  | 45.3| BNT162b2                      | 2-4 wk   | RBD                          | Abbott Architect SARS-CoV-2 IgG Quant II (CMIA) | 50 AU/mL | 9   |
| Apostolidis SA  | 81  | US       | MS                               | 20    | 10  | 40  | healthy | 10    | 10  | 35  | BNT162b2, mRNA-1273            | 25-30 d  | RBD                          | ELISA                      | NR      | 9   |
| Sabatino JJ     | 82  | US       | MS                               | 35    | 9   | 46  | healthy | 13    | 13  | 35  | BNT162b2, mRNA-1273            | 2 wk     | RBD                          | Luminex assay                | MFI 5.0 | 8   |
| Novak F         | 83  | Denmark, US | MS                            | 60    | 22  | 47  | -       |       |     |     | BNT162b2                      | 2-4 wk   | RBD                          | Abbott Architect SARS-CoV-2 IgG Quant II (CMIA) | 7.1 BAU/mL | 6   |

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| Author      | Ref | Location | Disease                  | Total | Pos | Age | Control | Total | Pos | Age | Vaccine                          | Interval | Antibody                        | Measurement assay | Cut-off | NOS |
|------------|-----|----------|--------------------------|-------|-----|-----|---------|-------|-----|-----|----------------------------------|----------|---------------------------------|-------------------|---------|-----|
| Moor MB    | 84  | Switzerland | Autoimmunity/Cancer/Transplantation | 96    | 47  | 67  | healthy | 29    | 29  | 54  | BNT162b2, mRNA-1273             | 1.8 mo    | spike (S1)                       | EUROIMMUN (ELISA) | 1.1 index | 8   |
| Mrak D     | 85  | Austria   | Immune-mediated inflammatory disease | 74    | 29  | 61.7 | healthy | 10    | 10  | NR   | BNT162b2, mRNA-1273             | 21.9 d    | RBD                            | Elecsys Anti-SARS-CoV-2 S | NR    | 8   |
| Ali A      | 86  | US        | MS, NMO                  | 22    | 8   | 43.5 | healthy | 7     | 7   | 41.6 | BNT162b2, mRNA-1273             | 3 wk      | RBD                            | Siemens SARS-CoV-2 spike RBD total antibody assay (CLIA) | index value | 9   |
| Benucci M  | 87  | Italy     | RA                       | 14    | 10  | 58  | -       |       |     |     | BNT162b2                        | 3 wk      | RBD                            | ThermoFisher (FEIA) | NR    | 6   |
| Gadani SP  | 68  | US        | MS                       | 39    | 22  | 47.78 | untreated MS | 14   | 14  | 57.42 | BNT162b2, mRNA-1273, Ad26.COV2.S | 4-8 wk    | spike (S1)                       | EUROIMMUN (ELISA) | 1.24  | 9   |
| Prendecki M| 69  | UK        | Autoimmune disease       | 75    | 40  | 53.7 | healthy | 70   | 70  | 41.4 | BNT162b2, ChAdOx1               | 21 d      | spike                          | Abbott Architect SARS-CoV-2 IgG Quant II (CMI) | 7.1 BAU/mL | 8   |
| Connolly CM| 70  | US        | AAV                      | 44    | 17  | 69  | -       |       |     |     | BNT162b2, mRNA-1273, Ad26.COV2.S | NR       | spike                          | Elecsys or Liaison or EUROIMMUN | NR        | 6   |
| Tallantyre EC | 71 | UK        | MS                       | 134   | 33  | 50.2 | MS without DMT | 92   | 85  | 50.2 | BNT162b2, ChAdOx1               | 4.6 wk    | RBD                            | Dried blood spot ELISA | 0.56  | 8   |
| Madelon N  | 72  | Switzerland | MS, RD              | 37    | 24  | 45.6 | -       |       |     |     |                                 |           |                                |                   |         |     |

(continued on next page)
| Author          | Ref | Location  | Disease   | Total | Pos | Age  | Control   | Total | Pos | Age  | Vaccine                      | Interval | Antibody             | Measurement assay         | Cut-off | NOS |
|-----------------|-----|-----------|-----------|-------|-----|------|-----------|-------|-----|------|----------------------------|----------|------------------------|---------------------------|---------|-----|
| 58.0            | healthy | 22      | 22        | 54.5  | 30  | RBD  | 0.8 IU/mL | 9     |     |     | BNT162b2, mRNA-1273         | 3-4 wk   | EUROIMMUN (ELISA)      |                           | NR      | 9   |
| Stefanski AL    | 73  | Germany   | RA, AAV   | 19    | 13  | 58   | healthy   | 30    | 30  | 57   | BNT162b2, mRNA-1273, ChAdOx1 | 1 wk     | VITROS SARS-CoV-2 total antibody (CLIA) | 1 S/CO         | 6       |     |
| Ammitzbøll C   | 74  | Denmark   | SLE, RA   | 17    | 4   | 70   | healthy   | 5     |     |     | BNT162b2                     | > 2 wk   | Abbott/Elecsys          |                           | NR      | 6   |
| Guerrieri S    | 75  | Italy     | MS        | 16    | 6   | 43.3 | -         | 53.5  | 2   | 2    | BNT162b2, mRNA-1273         | 18 d     | Elecsys/Siemens healthineers |                           | NR      |     |
| Bigaut K       | 76  | France    | MS        | 11    | 3   | 53.5 | MS without DMT | 2    |     | 2    | BNT162b2, mRNA-1273         | 2 wk     | Elecsys/Euroimmun (ELISA) |                           | index value | 9   |
| Spiera R       | 77  | US        | RD        | 30    | 10  | 61.3 | healthy   | 47    | 46  | 54.3 | BNT162b2                    | 1 mo     | ELISA                  |                           | NR      |     |
| Achiron A      | 79  | Israel    | MS        | 44    | 10  | 53.2 | healthy   | 53    | 52  | 43.4 | BNT162b2, mRNA-1273         | 1-2 wk   | ELISA                  |                           | NR      |     |
| Deepak P       | 80  | US        | chronic inflammatory disease | 10    | 5   | 45.5 | healthy   | 53    | 52  | 43.4 | BNT162b2, mRNA-1273         | 1 mo     | Elecsys/Euroimmun (ELISA) |                           | index value | 9   |

Abbreviations: AAV = ANCA-associated vasculitis; Anti-CD20 Ab = anti-CD20 antibody; auto-HSCT = autologous hematopoietic stem cell transplantation; B-NHL = B-cell non-Hodgkin Lymphoma; CLIA = chemiluminescence immunoassay; CLL = chronic lymphocytic leukemia; CMIA = chemiluminescent microparticle immunoassay; DMT = disease modifying therapy; ECLIA = electrochemiluminescence immunoassay; ELISA = enzyme-linked immunosorbent assay; FEIA = fluorimetric enzyme-linked immunoassay; Interval = interval from second vaccination to antibody test; MS = multiple sclerosis; Nab = neutralizing antibody; NM = neuromyelitis optica; NOS = Newcastle-Ottawa scale; NR = not reported; Pos = positive number; RA = rheumatoid arthritis; RBD = receptor binding domain; RD = rheumatic disease; RTX = rituximab; SLE = systemic lupus erythematosus; Total = total number; UK = United Kingdom; US = United States; WM = Waldenström macroglobulinemia.
the data extraction process is presented in Figure 1. The Newcastle-Ottawa scale was used to assess the quality of non-randomized trials.

Endpoints
The primary outcome in the present review was the risk ratio (RR) of the seropositivity rates of SARS-CoV-2-specific antibody after the second dose of mRNA vaccine. The secondary outcome was the RR of SARS-CoV-2-specific T cell-positive rates after vaccination. Regarding the interval from anti-CD20 antibody therapy to the first vaccine dose, data were extracted from figures whenever possible. The focus was on mRNA vaccines (BNT162b2 and mRNA-1273); however, some articles included adenoviral vaccines: AZD1222 (ChAdOx1 nCoV-19) and Ad26.Cov2.S.32

Statistical Analysis
Data were analyzed using EZR (Easy R) statistical software.33 For each trial, the vaccine response in patients and controls was calculated using RRs. Data were entered into the EZR software for statistical analysis. An RR < 1 indicated an impaired response in the patient group. The random effect model was used in accordance with the method described by Der Simonian-Laird.34 Trial results were assessed using the chi-square test of heterogeneity and the I² measure of inconsistency. Heterogeneity was considered to be statistically significant at P < .10 or an I² statistic > 50%. Publication bias was examined using funnel plots coupled with the Egger’s test. Pooled estimates were calculated using the MetaXL add-in for Excel (Microsoft Corporation, Redmond, WA).35

Results
Study Selection
The literature search of the PubMed and WHO COVID-19 database retrieved 493 articles after removal of duplicates, of which 80 were considered to be relevant through evaluation of titles and abstracts. Among them, 52 studies fulfilled the criteria for the present meta-analysis: 30 investigated lymphoid malignancies42-65; and 22 investigated anti-CD20 antibody therapy for non-malignant diseases, such as multiple sclerosis and rheumatic diseases.66-87 28 articles were excluded with the following reasons: (1) insufficient data of outcomes,88-96 (2) duplicate publications from an overlapping cohort,97-106 and (3) case series or cohorts with < 10 patients.107-115 A flow diagram of the article selection process is shown in Figure 1, and the characteristics of each study are summarized in Table 1.

Humoral Response in Lymphoid Malignancies
Data regarding humoral response in lymphoid malignancies compared with healthy controls were reported in 20 articles37,39,43,46,47,49,52,54,59-65 that included 2203 patients with CLL, myeloma, non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL). Patients with lymphoid malignancies exhibited significantly lower seropositivity rates than healthy controls (RR 0.60 [95% confidence interval (CI) 0.53-0.69]), with high heterogeneity (I² = 94%, P < .01) (Figure 2A). The funnel plot suggested a publication bias (P < .05, Figure 2B).

Humoral Response in Individual Subtypes of Lymphoid Malignancies
Individual subtypes of lymphoid malignancies were analyzed. First, for CLL, a positive humoral response was observed in 52% (95% CI 43%-62%)42,45,49,53-55,57,60,64 (Figure 3A). Data for 356 patients in five articles were eligible for the analysis of RR.42,49,54,60,64 Patients with CLL exhibited significantly lower seropositive rates than healthy controls (RR 0.55 [95% CI 0.43-0.71]) (Figure 3B). Second, for myeloma, a positive humoral response was observed in 78% (95% CI 69%-86%)43,48-50,52,55-58 (Figure 3C). Data regarding
1041 patients from 8 cohorts were eligible for the analysis of RR, and myeloma significantly reduced seropositive rates (RR 0.76 [95% CI 0.69-0.83]) (Figure 3D). Third, for NHL, a positive humoral response was observed in 61% [95% CI 50%-71%] (Figure 3E). Data for 282 patients from 3 articles were eligible for the analysis of RR, which revealed a low seropositivity rate in patients with NHL (RR 0.58 [95% CI 0.48-0.71]) (Figure 3F). When NHL was subdivided into aggressive and indolent NHL, both subgroups exhibited lower seropositivity rates than control (aggressive NHL, RR 0.60 [95% CI 0.42-0.86]; indolent NHL, RR 0.54 [95% CI 0.43-0.67]) (Figures 3G and H). With regard to T-cell NHL, one article reported
that the seropositivity rate was 84.6% (11 out of 13 patients).\(^{37}\)

Fourth, for HL, a positive humoral response was observed in 95% (95% CI 89%-99%)\(^{36,44,48,49,57,64}\) (Figure 3C). Data that could be compared with healthy controls were available from only 2 articles (20 patients),\(^{39,63}\) which revealed no significant difference from control (RR 0.95 [95% CI 0.85-1.07]) (Figure 3J). 

**Humoral Response in Treatment-Naïve Patients**

Low-risk patients with CLL, smoldering multiple myeloma (SMM), and indolent NHL are often offered “watchful waiting” until disease progression, and data regarding treatment-naïve patients can be used to estimate the extent to which lymphoid malignancy itself impairs immune function. First, for CLL, positive humoral response was observed in 77% (95% CI 63%-88%) of treatment-naïve patients,\(^{42,45,53,56,60,64}\) which was significantly lower than control (RR 0.79 [95% CI 0.63-1.00]), \(P = .047\)\(^{42,54,60,64}\) (Figure 4A and 4B). On the other hand, SMM and treatment-naïve indolent NHL did not exhibit a significant difference from healthy controls, although patient numbers were relatively small (SMM, seropositivity rate, 94% [95% CI 76%-100%]\(^{40,43,46,50,57}\); treatment-naïve indolent NHL, seropositivity rate, 84% [95% CI 75%-92%]\(^{34,63,64}\); RR 0.90 [95% CI 0.81-1.01]\(^{65,64}\)) (Figure 4C-4F).

**Humoral Response in Lymphoid Malignancies With B-Cell Target Therapy**

Next, the impact of B-cell target therapy on humoral response was analyzed, first focusing on anti-CD20 antibody. Patients treated with anti-CD20 antibody exhibited a lower seropositivity rate than healthy controls (RR 0.37 [95% CI 0.24-0.57])\(^{41,47,49,54,59,61,63,65}\) (Figure 5A). When divided according to the interval from the last infusion with anti-CD20 antibody to the first vaccine dose, treatment within the past 6 months was significantly associated with decreased rates of seropositivity compared to treatment > 6 months before vaccination (RR 0.21 [95% CI 0.09-0.46])\(^{41,44,48,63,64}\) (Figure 5B). Treatment within the past 12 months also decreased the rates of seropositivity (RR 0.23 [95% CI 0.10-0.57])\(^{46,47,49,54,58,59,61,63,65}\) (Figure 5C). Moreover, treatment > 12 months before vaccination resulted in a lower seropositivity rate than healthy controls (RR 0.61 [95% CI 0.51-0.73])\(^{41,54,64,65}\) (Figure 5D). With regard to other B-cell target therapies, myeloma patients undergoing anti-CD38 therapy exhibited decreased seropositivity rates compared to patients without anti-CD38 therapy (RR 0.86 [95% CI 0.76-
Humoral response in lymphoid malignancies with B-cell target therapy. (A) Risk ratios (RRs) for seropositivity rates of patients treated with anti-CD20 antibody compared with healthy controls. (B-D) RRs for seropositivity rates of patients with (B) < 6 months from therapy vs. > 6 months from therapy, and (C) < 12 months from therapy vs. > 12 months from therapy, and (D) > 12 months from therapy vs. healthy controls. (E and F) RRs for seropositivity rates of patients (E) with anti-CD38 therapy vs. without anti-CD38 therapy, and (F) with BTK inhibitor vs. without BTK inhibitor. BTK = Bruton’s tyrosine kinase.

Humoral Response in Non-Malignant Diseases With Anti-CD20 Antibody

The impact of anti-CD20 antibody on immune response, including cellular immunity, was further analyzed by focusing on nonmalignant patients treated with anti-CD20 antibody. First, the relationship between humoral response and anti-CD20 antibody was investigated. Data from 16 articles (900 patients) revealed that anti-CD20 antibody treatment significantly decreased seropositivity rates compared with the control group (RR 0.45 [95% CI 0.39-0.52]) (Figure 6A).66-69,71-73,75,78,81,84-86 The funnel plot did not reveal any publication bias (P = .12, Figure 6B). Treatments within the past 6 months,67-70,74-76,83,84,86 9 months,67,68,74,78,87 and 12 months68,77,84,85,86 were all associated with significantly decreased seropositivity rates compared with treatment > 6, 9, and 12 months before vaccination, respectively (within 6 months, RR 0.45 [95% CI 0.35-0.57]; within 9 months, RR 0.54 [95% CI 0.34-0.84]; within 12 months, RR 0.49 [95% CI 0.33-0.73]) (Figure 6C-6E). Patients treated > 12 months before vaccination still had decreased seropositivity rates compared with the control group (RR 0.70 [95% CI 0.55-0.88])65,84,85 (Figure 6F).

Cellular Response Among Individuals Undergoing Anti-CD20 Antibody Treatment

The influence of anti-CD20 antibody therapy on cellular response was investigated. Six studies examined SARS-CoV-2-specific T cell responses using the interferon gamma (IFN-γ) assay,65,69,78,84,85,87 and revealed that 78% of patients treated with anti-CD20 antibody elicited a positive cellular response (95% CI 45%-99%) (Figure 7A) that was comparable with the control group (RR 0.77 [95% CI 0.55-1.08])65,69,78,84,85 (Figure 7B). In addition, four studies examined cellular responses using an activation-induced marker (AIM) assay, two of which revealed no significant difference without available quantitative data.81,82 The meta-analysis of other two articles exhibited no difference between patients treated with anti-CD20 antibody and controls (AIM-positive CD4 cell, RR 0.98 [95% CI 0.82-1.18]; AIM-positive CD8 cell, RR 0.93 [95% CI 0.43-2.04])72,73 (Figure 7C and 7D).

Discussion

Lymphoid malignancies attenuated the humoral response to COVID-19 mRNA vaccines. Moreover, subgroup analysis further
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Figure 6 Humoral response in non-malignant diseases with anti-CD20 antibody. (A) Risk ratios (RRs) for seropositivity rates of patients treated with anti-CD20 antibody compared with controls, and (B) funnel plot. (C-F) RRs for seropositivity rates of patients with (C) < 6 months from therapy vs. > 6 months from therapy, (D) < 9 months from therapy vs. > 9 months from therapy, (E) < 12 months from therapy vs. > 12 months from therapy, and (F) > 12 months from therapy vs. controls.

revealed that CLL, NHL, and myeloma patients exhibited decreased seropositivity rates. Patients with lymphoid malignancies are immunocompromised due to the disease itself. In particular, treatment-naïve CLL patients exhibited lower seropositivity rates than healthy controls. In CLL patients, the humoral response was also impaired after contracting COVID-19, and the effectiveness of other conventional vaccines was attenuated. These data reflect the substantial immune abnormalities associated with CLL itself. On the other hand, patients with HL and treatment-naïve SMM exhibited high seropositivity rates that were equivalent to healthy controls, suggesting a difference in the influence of disease subtype on the immune system.

With regard to the influence of treatment on humoral response, anti-CD20 antibody, anti-CD38 therapy, and BTK inhibitor significantly decreased seropositivity rates. These agents target B cell function, and many studies have demonstrated a correlation between B cell counts in peripheral blood and seropositivity rates. These agents have also been reported to decrease the effectiveness of several other conventional vaccines. Regarding anti-CD20 antibody therapy, we analyzed vaccine immunogenicity divided by the interval from the last infusion to the first vaccine dose. An interval of < 6 months and 12 months significantly attenuated seropositivity rates. These results were confirmed in a meta-analysis of non-malignant patients treated with anti-CD20 antibody. B cell reconstitution occurs > 6 months after anti-CD20 antibody therapy, and some guidelines for rheumatic diseases recommend delaying administration of the vaccine for 5 to 6 months after anti-CD20 therapy. A recent meta-analysis...
of influenza vaccine also demonstrated that anti-CD20 antibody treatment within at least the past 6 months abrogated the humoral response,\textsuperscript{19} which is consistent with the results of our meta-analysis. Moreover, some articles reported that recovery of the memory B-cell pool after anti-CD20 antibody therapy in the lymphoma population is delayed compared with normal B-cell ontogeny and remains impaired after 12 months.\textsuperscript{47,124} Our meta-analysis revealed that anti-CD20 antibody therapy >12 months before vaccination still attenuated the humoral response compared with healthy controls, which suggests a prolonged immunosuppressive state caused by B cell depletion.

Humoral and cellular responses work closely together against viral infection and vaccines\textsuperscript{125}; however, it is controversial whether B cell activity is essential for T cell priming, activation, and expansion.\textsuperscript{26-29} We analyzed T cell responses against mRNA vaccines under conditions of B-cell depletion caused by anti-CD20 antibody therapy, which demonstrated that mRNA vaccines elicited SARS-CoV-2-specific T cell response without adequate B cell function, and there was no correlation between antibody formation capacity and T cell response. A previous study about influenza vaccine was consistent with our data,\textsuperscript{127} suggesting that patients treated with anti-CD20 antibody should not avoid vaccination. On the other hand, several large-scale studies have reported that anti-CD20 therapy increases the exacerbation risk from COVID-19 in patients with multiple sclerosis and rheumatic diseases\textsuperscript{28-132}, thus, highlighting the importance of B cell response during infection. Our analysis of T cell response was only from studies performed in vitro; thus, whether immune memory by cellular response can prevent infection and disease aggravation in the absence of immune protection by humoral response\textsuperscript{15} should be further evaluated in clinical long-term follow-up studies. However, CD8-positive T cells can positively influence recovery;\textsuperscript{13,134} thus, activation of cellular immunity without humoral response can provide a level of efficacy.

This meta-analysis had several limitations. First, we evaluated antibody formation several weeks after vaccination. In addition to immunogenicity, long-term vaccine effectiveness is an important parameter in evaluating vaccine function. Several studies have shown that antibody titers tend to be lower than in healthy controls, even in seropositive patients with lymphoid malignancies; thus, long-term follow-up is further warranted. Second, the heterogeneity in disease status and treatment history in each study will affect the seroresponse to vaccines. For example, MM patients with a complete response (CR) achieved higher antibody levels than non-CR patients,\textsuperscript{43} and exposure to >3 novel anti-myeloma drugs were associated with lower response rates.\textsuperscript{46} Therefore, humoral response in each status should be further analyzed individually. Also, anti-CD20 antibody is often used with cytotoxic agents or other immunosuppressive agents as combination therapy, and these agents will affect the humoral response to vaccines. Third, the measurement method for SARS-CoV-2 antibodies and cutoff values of seropositivity differed among the selected studies as summarized in Table 1. Most studies evaluated antibodies against the receptor binding domain or total spike protein instead of neutralizing antibody using different assays, such as chemiluminescent immunoassay, enzyme-linked immunosorbent assay, and flow-cytometry analysis. The receptor binding domain is poorly conserved among SARS coronaviruses and relatively specific to SARS-CoV-2, whereas the antibody against the entire spike protein can be elevated after other coronavirus infections.\textsuperscript{135,136} However, the results from most of the assays were correlated with one another,\textsuperscript{137} and also with neutralizing antibodies.\textsuperscript{81,138} Fourth, regarding the measurement method for the SARS-CoV-2-specific T cell response, several studies evaluated the response using SARS-CoV-2 spike peptides through IFN-γ production or AIM assay.\textsuperscript{139} Whether these in vitro data can predict clinical outcomes of COVID-19 remains unknown, and some argue that these available evidences remain insufficient for clear guidance.\textsuperscript{140} Additionally, all
data used for our meta-analysis were from non-malignant patients, and there is only one study that evaluated the T cell response against patients with lymphoid malignancies to date. 39 This article revealed that T cell response was attenuated in myeloma patients compared with healthy controls, and also showed the discrepancy between T cell response and antibody formation capacity. In comparison with multiple sclerosis, 141 lymphoid malignancies cause a high disorder of lymphoid systems, 9,18; thus, cellular response in these groups should be further analyzed.

Conclusion
This meta-analysis demonstrated that lymphoid malignancies, as well as some subtypes, including CLL, NHL, and myeloma, attenuated humoral response. Treatment-naive CLL and B-cell target therapy including anti-CD20 antibody, anti-CD38 therapy, and BTK inhibitor also demonstrated decreased humoral response. Regarding the interval from last anti-CD20 antibody therapy to the first vaccine dose, an interval < 6 months significantly attenuated seropositivity rates, and anti-CD20 antibody therapy > 12 months before vaccination still impaired humoral response. Cellular response was detected independent of anti-CD20 antibody therapy or antibody formation capacity. Further studies focusing on long-term follow-up and T cell responses in lymphoid malignancies are warranted.

Clinical Practice Points
Patients with hematological malignancies are highly susceptible to severe COVID-19. mRNA vaccines have been widely used against COVID-19.

Patients with lymphoid malignancies or those undergoing anti-CD20 antibody therapy experience an impaired humoral response. Cellular response can be detected independent of anti-CD20 antibody therapy in non-malignant patients.

Authorship Statement
Y.I. conceptualized and designed the research, performed literature search, analyzed data, and wrote the manuscript. A.H. performed literature search and analyzed data. M.K. supervised the research.

Disclosure
Y.I. declares no competing financial interests. A.H. reports honoraria from Janssen Pharmaceutical. M.K. reports honoraria from AstraZeneca, Chugai Pharmaceutical, Janssen Pharmaceutical, Sanofi, and Pfizer, and research funding from Chugai Pharmaceutical and Pfizer.

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