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Review

Short-term effectiveness of COVID-19 vaccines in immunocompromised patients: A systematic literature review and meta-analysis



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ARTICLE INFO

Article history:

Accepted 27 December 2021

Available online 1 January 2022

Keywords:

COVID-19 vaccine

Effectiveness

Immunocompromised patients

Meta-analysis

SUMMARY

Objectives: We aimed to assess the short-term effectiveness of COVID-19 vaccines among immunocompromised patients to prevent laboratory-confirmed symptomatic COVID-19 infection.

Methods: Systematic review and meta-analysis. We calculated the pooled diagnostic odds ratio [DOR] (95% CI) for COVID-19 infection between immunocompromised patients and healthy people or those with stable chronic medical conditions. VE was estimated as 100% x (1-DOR). We also investigated the rates of developing anti-SARS-CoV-2 spike protein IgG between the 2 groups.

Results: Twenty studies evaluating COVID-19 vaccine response, and four studies evaluating VE were included in the meta-analysis. The pooled DOR for symptomatic COVID-19 infection in immunocompromised patients was 0.296 (95% CI: 0.108–0.811) with an estimated VE of 70.4% (95% CI: 18.9%–89.2%). When stratified by diagnosis, IgG antibody levels were much higher in the control group compared to immunocompromised patients with solid organ transplant (pOR 232.3; 95% CI: 66.98–806.03), malignant diseases (pOR 42.0, 95% CI: 11.68–151.03), and inflammatory rheumatic diseases (pOR 19.06; 95% CI: 5.00–72.62).

Conclusions: We found COVID-19 mRNA vaccines were effective against symptomatic COVID-19 among the immunocompromised patients but had lower VE compared to the controls. Further research is needed to understand the discordance between antibody production and protection against symptomatic COVID-19 infection.

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Background

The first coronavirus disease 19 (COVID-19) vaccine was authorized by the U.S. Food and Drug Administration (FDA) on December 11, 2020 for prevention of severe illness or death. That mRNA vaccine demonstrated an efficacy of 95%¹ and humoral and cellular responses were triggered within 1 week after the second dose.² Sub-

sequently, eight more vaccines have been authorized after phase III trials.³

Previous studies evaluated vaccine effectiveness (VE) among individuals who were healthy or had stable chronic medical conditions¹. Since immunocompromised patients were excluded from trials conducted early in this pandemic, there is less data on immunocompromised patients compared with other patient populations. Due to growing concern over a poor response to vaccination among immunocompromised patients who are particularly at risk for severe disease, and some evidence for the benefit of booster doses⁴ the U.S. FDA gave emergency use authorization for an additional dose of COVID-19 vaccines for immunocompromised people on August 12, 2021.⁵

Recently, some studies provided real-world data on VE in people with immunocompromising conditions.^{6,7} Other studies evaluated the humoral immune response among these patients.⁸ Studies suggested that immunocompromised patients who received COVID-19 vaccines might not develop high neutralizing antibody titers or be as protected against severe COVID-19 outcomes as are immunocompetent patients.^{9,10} Vaccine responsiveness in patients who were receiving an immunosuppressor drug therapy exhibited impaired serological immune responses.^{9,11} Though there is growing evidence that VE and immune response among immunocompromised patients seem lower than in healthy people, limited data are available.^{4,6,8} Given higher complication and mortality rates from COVID-19,¹² it is important to quantify vaccine effectiveness and assess whether this group is capable of producing neutralizing antibodies.

We aimed to review the literature on the impact of COVID-19 vaccination on neutralizing antibodies and the short-term effectiveness of COVID-19 vaccines among immunocompromised patients to prevent laboratory-confirmed symptomatic COVID-19 infection.

Methods

Systematic literature review and inclusion and exclusion criteria

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement¹³ and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.¹⁴ This study was registered on Prospero (<https://www.crd.york.ac.uk/PROSPERO/>) on 6/17/2021 (registration number CRD42021261306). Institutional Review Board approval was not required. Immunocompromised patients were defined as those treated with immunosuppressive medication (e.g., corticosteroids, chemotherapy, or other immunosuppressive medications), solid organ transplant, hematopoietic stem cell transplant, HIV, thalassemia, or active cancer (current cancer, in treatment, or received diagnosis within last 12 months).¹⁵

Inclusion criteria for studies in this systematic literature review were as follows: original research manuscripts; published in peer-reviewed, scientific journals; involved vaccinated immunocompromised patients and vaccinated healthy control group or other vaccinated control group with similar clinical conditions; conducted in acute care settings or nursing homes that evaluated the effectiveness of COVID-19 vaccine in immunocompromised people after phase III COVID-19 vaccine clinical trials in immunocompetent participants; and observational study design. The literature search was limited to December 1, 2019 to August 10, 2021. Randomized clinical trials (phase III), commentaries, studies with overlapping patients, studies in pediatric populations, and studies from non-peer reviewed studies (e.g., MedRxiv) were excluded. Studies in which there was no comparison between vaccinated immunocompromised patients and vaccinated control groups, evaluating just

one dose of COVID-19 vaccine, and those in which no VE data were published were also excluded.

Search strategy

We performed literature searches in PubMed, Cumulative Index to Nursing and Allied Health (CINAHL), Embase (Elsevier Platform), Cochrane Central Register of Controlled Trials, Scopus, and Web of Science. The entire search strategy is described in Supplementary Appendix 1. We reviewed the reference lists of retrieved articles to identify studies that were not identified from the preliminary literature searches. After applying exclusion criteria, we reviewed 71 papers, 33 of which met the inclusion criteria and were included in the systematic literature review [Fig. 1].

Data abstraction and quality assessment

Titles and abstracts of all articles were screened to assess whether they met inclusion criteria. The reviewers (ARM, TK, HS, MAA, BMT, LMB, and MAA) abstracted data for each article. Reviewers resolved disagreements by consensus.

The reviewers abstracted data on study design, population and setting, study period (weeks or months), number of patients (immunocompromised vs. the control group), the total number of participants who produced neutralizing antibodies after one or two doses between immunocompromised vs. the control group, the mean or the median antibody levels after one or two doses among immunocompromised and the control groups, humoral and cellular immunity studies, and the immunosuppressive drugs used in each study. The FDA recommends defining the COVID-19 endpoint as virologically confirmed SARS-CoV-2 infection accompanied by symptoms.¹⁶ For that reason, we have defined the primary outcome as symptomatic COVID-19 infection.

Risk of bias was assessed using the Downs and Black scale.¹⁷ Reviewers followed all questions from this scale as written except for question #27 (a single item on the Power subscale, scored 0 to 5), which was changed to a yes or no. For the analysis, we classified the studies as good (19–23 of 28 possible points), or fair (14–18 points of 28 possible points) quality. Two authors performed component quality analysis independently, reviewed all inconsistent assessments, and resolved disagreements by consensus.¹⁸

Statistical analysis

To meta-analyze the extracted data, COVID-19 vaccine response was assessed using a random-effects model to estimate pooled odds ratios and 95% confidence intervals with weights as described by DerSimonian and Laird.¹⁹ We performed stratified analyses of the associations between anti-SARS-CoV-2 spike protein IgG production after two doses of COVID-19 vaccine between immunocompromised patients and the control group. We also performed stratified analyses among studies in patients with solid organ transplants, with malignancy or with inflammatory rheumatic diseases, respectively, in studies that evaluated neutralizing antibodies after COVID-19 vaccine, and in studies classified as good vs. fair per the Downs and Black score. In our stratified analyses we did not include studies that did not report the absolute number of patients that produced anti-SARS-CoV-2 spike protein IgG after the second vaccine dose. We did not include in our meta-analysis studies where only mean or the median antibody levels were reported. Heterogeneity between studies was evaluated with I^2 estimation and the Cochran Q statistic test. We used the Cochrane Review Manager version 5.3.

We also calculated the pooled diagnostic odds ratio [DOR] (95% confidence interval) for symptomatic COVID-19 between vaccinated

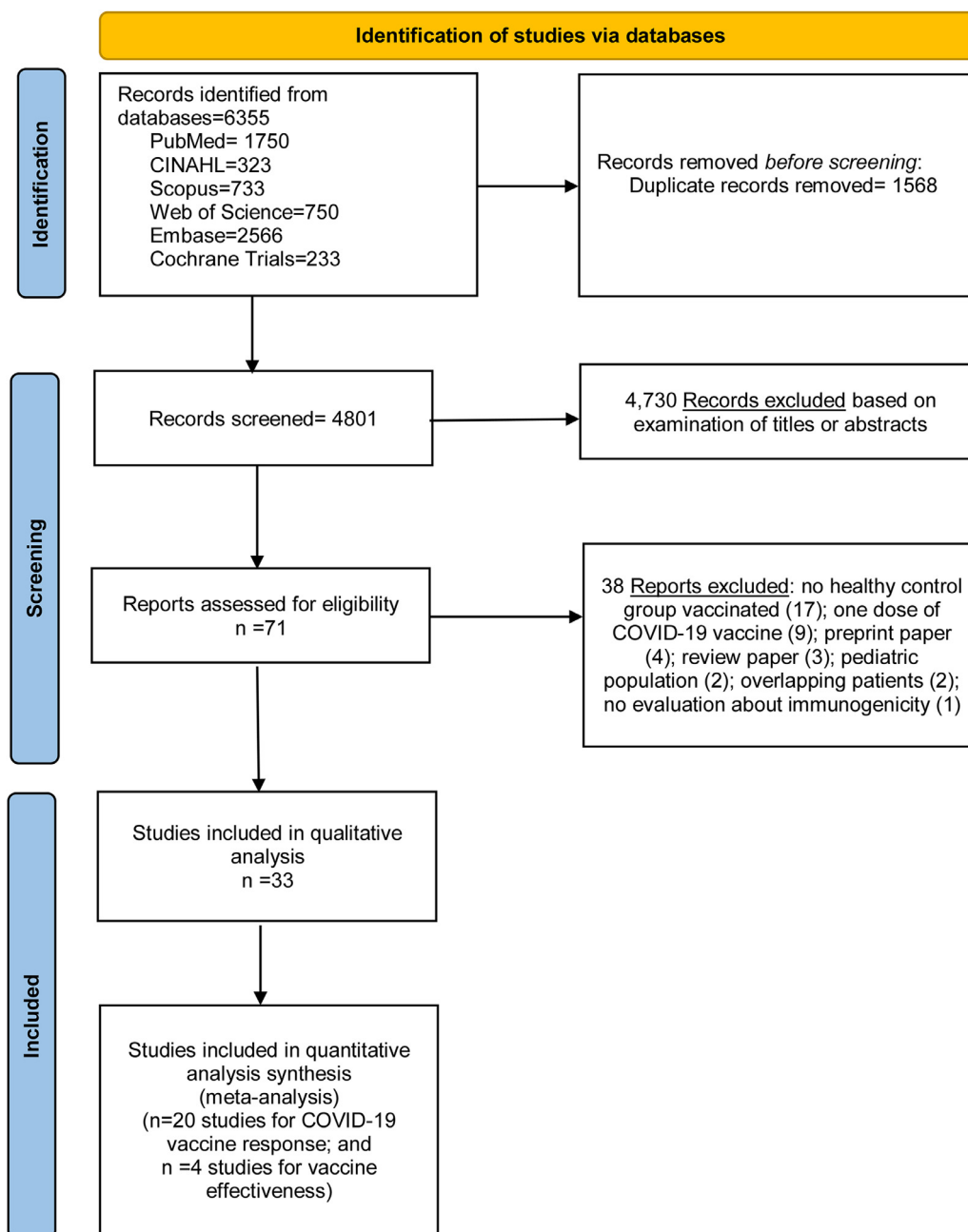


Fig. 1. Literature search for articles on COVID-19 vaccine effectiveness among immunocompromised patients.

immunocompromised patients and vaccinated healthy controls or other vaccinated controls with similar clinical conditions. VE was estimated as $100\% \times (1 - \text{DOR})$. We performed statistical analysis using R version 4.1.0 with mada package version 0.5.4.²⁰ Analogous to the meta-analysis of the odds ratio methods for the DOR, an estimator of random effects model following the approach of DerSimonian and Laird is provided by mada package.²⁰ For the meta-analysis of estimates of COVID-19 VE, we used a bivariate random effects model, adopting a similar concept of calculating diagnostic accuracy, which enables simultaneous pooling of sensitivity and specificity with mixed-effect linear modeling while allowing for the trade-off between them.^{21,22} Heterogeneity between studies was also evaluated with I^2 estimation and the Cochran Q statistic test. Publication bias was assessed using funnel plots.

Results

Characteristics of included studies

Thirty-three studies met the inclusion criteria^{23–55} and were included in the final review (Fig. 1). All of these studies were non-randomized, of which, twenty-seven were prospective cohort studies,^{24,25,27,28,30–37,39,41–54} and six were retrospective cohort studies.^{23,26,29,38,40,55} The majority of them (32 studies) evaluated the Pfizer/BioNTech mRNA COVID-19 vaccine.^{23–51,53–55} Six of these studies also analyzed the Moderna mRNA COVID-19 vaccine^{28,32,33,40,53,55} and another also analyzed the AstraZeneca COVID-19 vaccine⁴². Just one study evaluated the Coronavac COVID-19 vaccine.⁵² None of the studies evaluated the VE for the Johnson & Johnson/Janssen vaccine.

The majority of the studies included in our review were conducted in Israel (nine studies),^{23,27,29,31,34,37,38,47,48} following by the United States (six studies),^{33,35,40,53–55} Germany (five studies),^{32,41,49–51} France (four studies),^{25,26,30,43} Italy (two studies),^{39,45} the United Kingdom (two studies),^{42,46} and Czech Republic,³⁶ Denmark,²⁴ Lithuania,⁴⁴ Spain,²⁸ and Turkey⁵² with one study each. All studies were performed between December 2020 and May 2021^{23–55}. Eleven studies evaluated solid organ transplant recipients^{26,30,34,36,41,45,47–51}, being two studies of them evaluated hemodialysis patients.^{26,30} Eight studies evaluated patients with malignant diseases,^{25,33,37–39,42,44,46} six studies evaluated patients with inflammatory rheumatic diseases,^{24,27,31,32,35,52} two studies evaluated patients with inflammatory bowel diseases,^{40,55} two studies evaluated patients with chronic kidney failure on hemodialysis,^{28,43} one study evaluated patients with multiple sclerosis,²³ and one study evaluated HIV patients.⁵⁴ The definition of immunocompromised condition was not reported in two studies.^{29,53}

Studies varied on their reporting of characteristics of the serological tests, including when they were performed, cutoff levels for antibody positivity, and the type of serological test analysis performed (Supplementary Appendix 2). Eight studies did not report the cut-off level for their specific assay.^{29,32,36,40,46,47,49,53} Three studies did not use serological tests to determine vaccine effectiveness.^{29,40,53} The cellular immunity investigation was performed in 10 studies with different approaches^{26,28,35,36,45,46,49–51,54} (Supplementary Appendix 2). Twenty-three studies did not report any cellular immune investigation.^{23–25,27,29–34,37–44,47,48,52,53,55}

Four studies evaluated the variants of concerns (VOC) in some of patients' samples.^{44,46,53,54} One study found that HIV patients and the healthy control group had similar levels of neutralizing antibodies to the vaccine strain spike protein and spike proteins from VOC including, alpha (B.1.1.7), beta (B.1.351), and gamma (P.1) strains.⁵⁴ One study detected neutralization assays of VOC alpha lineage.⁴⁶ Another one studied seven patients with hematological malignancies with breakthrough infection detecting mutations of the alpha (B.1.1.7 strain) variant⁴⁴. Only one study performed genomic surveillance detecting the SARS-CoV-2 (alpha), beta, and gamma variants, where alpha variant was the most common lineage.⁵³ The majority of the included studies did not perform genomic surveillance.^{23–43,45,47–52,55}

Regarding the quality assessment scores of the 33 included studies, more than half of the studies (22 studies) were considered good (19–23 of 28 possible points) per the Downs and Black quality tool.^{24,27–29,31–38,40, 41,43,44,46,48,51–53,55} Eleven studies were considered fair (14–18 points),^{23,25,26,30,39,42,45,47,49,50,54} and no study was considered poor quality (<14 points).

Outcomes measures – antibody response and vaccine effectiveness

Antibody response (anti-SARS-CoV-2 spike protein IgG)

Among 33 studies identified for the systematic literature review, 30 studies evaluated the COVID-19 vaccine response with anti-SARS-CoV-2 spike protein IgG after the second dose.^{23–28,30–35,37–39,41–55} Of them, 10 studies reported only mean or median of anti-SARS-CoV-2 spike protein IgG, but they did not report positive rates^{24,26–28,32,36,39,44,50,54}. Twenty studies reported positive rates of anti-SARS-CoV-2 spike protein IgG with a total of 2219 immunocompromised patients, and were included in the meta-analysis.^{23,25,30,31,33–35,37,38,41–43,45–49,51,52,55} The positive rate ranged from 0% to 100%. Among 2219 immunocompromised patients, 63.0% developed anti-SARS-CoV-2 spike protein IgG compared to 99.1% (1400/1413) in the healthy control group. The control group had significantly higher odds of developing anti-SARS-CoV-2 spike protein IgG compared to immunocompromised patients (pooled odds ratio 58.18; 95% confidence interval [95% CI]:

21.61–156.61) [Fig. 2]. After performing a stratified analysis, the pooled odds ratio for developing neutralizing antibodies among the control group was 181.9 (95% CI: 22.76–1453.93) compared to immunocompromised patients. [Supplementary Appendix 3, Fig. 3]. With regards to the stratified analysis by immunocompromising conditions, the proportion of patients who developed anti-SARS-CoV-2 spike protein IgG changed to 25.2% in patients with solid organ transplant, 68.0% with malignancy, and 86% with inflammatory rheumatic diseases. The pooled odds ratio (pOR) for developing the anti-SARS-CoV-2 spike protein IgG production was higher in the control group compared to those immunocompromised patients with solid organ transplant at (pOR 232.3; 95% CI: 66.98–806.03), those with malignant diseases (pOR 42.0; 95% CI: 11.68–151.03), and to those with inflammatory rheumatic diseases (pOR19.06; 95% CI: 5.00–72.62) [Table 2, Supplementary Appendix 3, Figs. 4–6].

After stratifying by the risk of bias (Downs and Black score) there was still a difference in antibody response for the control group. The pooled odds ratio for developing anti-SARS-CoV-2 spike protein IgG among the control group was 36.5 (95% CI: 10.59–124.77) compared to the immunocompromised group in studies with good Downs and Black score (19–23 of 28 points) and was 136.80 (95% CI: 31.97–585.29) in studies with fair Downs and Black score (14–18 of 28 points) [Table 2, Supplementary Appendix 3, Fig. 7].

Vaccine effectiveness

Four studies with a total of 42,821 patients evaluated VE against symptomatic COVID-19 infection among immunocompromised patients vaccinated with 2 doses.^{29,36,40,53} VE ranged from 62.9% to 80.4% and all four studies were included for the meta-analysis. The pooled DOR for symptomatic COVID-19 infection was 0.296 (95% CI: 0.108–0.811) with an estimated VE of 70.4% (95% CI: 18.9%– 89.2%). The result of this meta-analysis was homogeneous for symptomatic COVID-19 (heterogeneity $I^2=0\%$) [Table 3].

Publication bias

We assessed publication bias by creating funnel plots of studies evaluating COVID-19 vaccine response with anti-SARS-CoV-2 spike protein IgG (Supplementary Appendix 3, Fig. 8). Aside from studies with extreme ORs (<1 or >10), studies were reasonably balanced around the pooled OR, and studies with null results were included. Thus, there was little evidence of publication bias.

Discussion

Based on studies evaluating short-term VE between December 2020 and May 2021, this systematic literature review and meta-analysis showed that COVID-19 vaccines (primarily the mRNA COVID-19 vaccines) decrease symptomatic COVID-19 infection with a VE of 70.4% in immunocompromised patients. This number was lower compared to VE in the general population reported in the randomized trials^{1,56} in a noncontrolled setting,⁵⁷ and also in a recent meta-analysis among healthcare workers (HCWs).⁵⁸ We also found that a wide range of anti-SARS-CoV-2 spike protein IgG development has been reported after two doses of COVID-19 vaccines among those immunocompromised and the rate of response was significantly lower compared to the control group in these studies.

There is no test to quantify the level of immunosuppression in an immunocompromised patient. However in our meta-analysis we were able to identify that immunocompromised patients with a variety of underlying conditions, produced lower levels of anti-SARS-CoV-2 spike protein IgG after two doses of COVID-19 vaccine in comparison to a non-immunocompromised control group.^{23,25,30,31,33–35,37,38,41–43,45–49,51,52,55} The pooled OR for developing the antibody is significantly higher among people

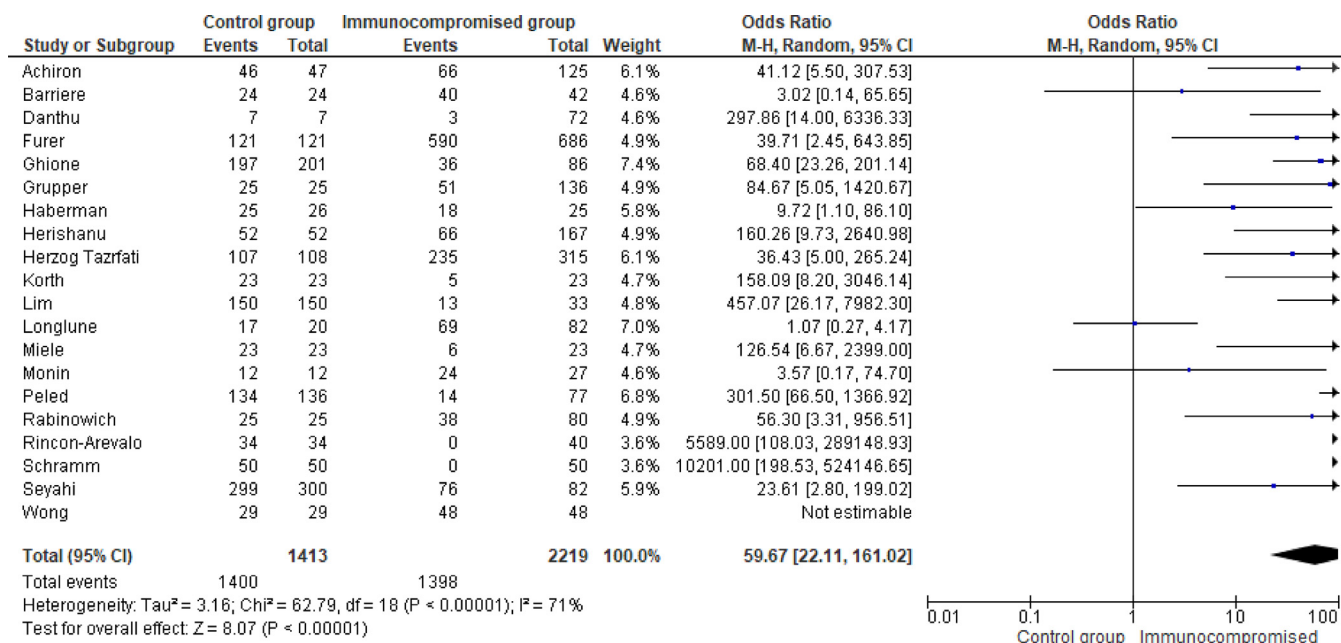


Fig. 2. Forest plot of COVID-19 vaccine response (anti-SARS-CoV-2 spike protein IgG) after two doses of COVID-19 vaccine [n = 20 studies] with control group and immunocompromised condition group. Odds ratios (OR) were determined with the Mantel-Haenszel random-effects method. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

in the healthy or stable condition group (i.e., control group) compared to those with solid organ transplant (pOR=232.3), malignant diseases (pOR=42.0), and inflammatory rheumatic diseases (pOR=19.1). This might represent the severity of the immunosuppression for each different diagnosis category.

Immunocompromised patients have a higher incidence of persistent SARS-CoV-2 infection, possibly representing an important reservoir for the emergence of novel viral variants.^{59,60} SARS-CoV-2 has been recovered in viral culture from immunocompromised patients several months after their primary infection^{61,62} signifying that certain individuals may be able to transmit the virus beyond the period of their acute illness.⁶² Real-world observational studies demonstrated that vaccination of the most vulnerable immunosuppressed population is not fully protective and therefore suggests the need for a third COVID-19 vaccine in immunocompromised patients as well as other protective measures (facial masks and social distancing) until more data on short- and long-term vaccine effectiveness is obtained.^{57,58} Prior studies demonstrated chronic kidney disease patients undergoing hemodialysis have more IgG antibody levels after receiving COVID-19 vaccines than kidney transplant recipients.^{26,30} Also, a recent European cohort study of patients with hemato-oncological diseases and a control group of HCWs suggested that patients with cancer developed lower antibody, and those receiving chemotherapy and B cell-targeting agents showed a particularly impaired serological response.⁹ This could suggest that the immunosuppressant therapy may be a critical factor implicated in this lack of humoral response.

For the humoral response, the most utilized and reported method was IgG antibody titers. These could be total antibody levels or levels against specific structural proteins, such as spike (S) or membrane proteins of SARS-CoV-2. The antibody response can be reported as positive or negative based on the manufacturer's criteria, actual titers, or relative titers as ratio to an internal control.⁶³ Measurement of neutralizing capability against live viruses or pseudo-viruses is more reflective of the robustness of humoral response because it directly measures the capability to suppress viral growth.⁶⁴ However, the U.S. FDA does not recommend antibody testing for SARS-CoV-2 to determine immunity or protection from

COVID-19, especially among those who are vaccinated.⁶⁵ In fact, our study showed extremely variable level of antibody response ranging from 0 to 100% among immunocompromised patients, yet the VE was moderately high at 70%. Further research is needed to understand the discordance between antibody production and protection against symptomatic COVID-19 infection.

Our study had several limitations. First, we only included observational studies for the meta-analysis, which are subject to multiple biases.⁶⁶ However, this is the most common type of study in the infection prevention literature.⁶⁶ Second, since we estimated the VE based on only short-term durations, we could not evaluate the long term VE or need for a third vaccine dose. One recent study published after our systematic search ended evaluated the long term VE among those immunocompromised and reported the effectiveness of mRNA vaccination against COVID-19 hospitalization was lower (77%) among immunocompromised individuals than among immunocompetent individuals (90%) over nine months.¹⁰ There is a need for longer-term observational studies to assess sustained immune response and VE. Third, each study adopted different serological tests to quantify antibody response to SARS-CoV-2 after COVID-19 vaccine among immunocompromised patients.^{23–55} Fourth, we do not have any data to evaluate how good enough were cellular immunity to prevent severe disease or mortality among immunocompromised populations. This could represent that many of the studies reviewed were challenging due to lack of information regarding the intensity of immunosuppression or capture of the incidence of COVID-19 outside the hospital. Fifth, our systematic review has not included studies that detected the delta variant, which contributed to the majority of recent breakthrough infections around the world.^{67,68} We need more studies on the SARS-CoV-2 variants of concerns (VOC) that have multiple spike protein mutations and appear to be more infectious or cause more disease than other circulating SARS-CoV-2 variants.⁶⁹ One recent study performed genomic surveillance detecting the new SARS-CoV-2 delta variant, alpha variant, and other variants.⁷⁰ It was not included in our systematic review because there is an overlapping of patients in this study with another study,⁵³ and we were unable to extract data for the meta-analysis to cal-

Table 1
Summary of characteristics of studies included in the systematic literature review.

First author, year, location	COVID-19 vaccine	Study design/D&B score (max score 28)	Study duration [dates]	Number of patients [immunocompromised vs. healthy controls]	Total or% participants with neutralizing antibodies [immunocompromised vs. healthy controls]		Mean (SD) or median [IQR] antibody titers [immunocompromised vs. healthy control]		Immunocompromised patients: Symptomatic COVID-19 (N) /No symptomatic COVID-19 (N) [vaccinated vs. unvaccinated]		Immunosuppressive therapy
					After 1st dose	After 2nd dose	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose	
Achiron, 2021, Israel	Pfizer/BioNTech	Retrospective cohort 18	NR	93 on treatment for MS Vs. 32 with untreated MS Vs. 47 healthy controls	NR	34 (32.3%) treatment for MS Vs. 32 (100%) with untreated MS Vs. 46 (97.9%) healthy controls	NR	7 (6.5–8.1) on cladribine, 0.27 (0.12–0.45) on Fingolimod and 0.29 (0.006–0.89) on Ocrelizum Vs. 8.1 (7.5–8.4) for untreated MS Vs. 7.4 (6.4–8.1) for healthy controls	NR	NR	Claribine, Fingolimod, Ocrelizumab
Ammitzbøll, 2021, Aarhus, Denmark	Pfizer/BioNTech	Prospective cohort 21	4 months [Dec, 2020 Apr, 2021]	61 patients with SLE Vs. 73 patients with RA	NR	SLE patents: 89% (54/61) Vs. RA patients: 67% (49/73)	NR	NR	NR	NR	Prednisone, Hydroxychloroquine, MMF, Azathioprine Rituximab NR
Barriere 2021, Nice, France	Pfizer/BioNTech	Prospective cohort 18	2 months [Jan 18, 2021 – Mar 15, 2021]	122 immunocompromised patients (solid tumors) Vs. 29 healthy controls	58/122 Vs. 13/13	40/42 Vs. 24/24	0.52 UI/mL Vs. 21.6 UI/mL	245.2 UI/mL Vs. 2517 UI/mL	NR	NR	
Bertrand, 2021, France	Pfizer/BioNTech	Retrospective cohort 17	2 months [Jan 2021 – Mar 2021]	45 kidney transplant recipients Vs. 10 hemodialysis patients	NR	NR	311 AU/mL for kidney transplant recipients Vs. 178.9 AU/mL for HD patients	671 AU/mL (IQR: 172–1523) for kidney transplant recipients Vs. 1052 AU/mL (IQR: 515–2689) for HD patients	NR	NR	Tacrolimus, Belatacept
Braun-Moscovici, 2021, Israel	Pfizer/BioNTech	Prospective Cohort 22	NR	NR	NR	227 (86%) immunocompromised [rheumatic inflammatory disease] who took the vaccine Vs. 24 (92.3%) - COVID19 recovered immunocompromised	NR	6764.27 AU/mL (9291.61) immunocompromised who took the vaccine Vs. 2044.8 AU/mL (4944.8) - COVID19 recovered immunocompromised	NR	NR	conventional DMARDs, colchicine, nintedanib, biological/targeted DMARDs, and corticosteroids
Broseta, 2021, Spain	Pfizer/BioNTech and Moderna	Prospective cohort 21	11 weeks [Feb 3, 2021 – Apr 2021]	10 HD patients on immunosuppression Vs. 165 HD patients without immunosuppression	NR	6 (60%) for patients on immunosuppression Vs. 161 (97.6%) for patients without immunosuppression	NR	NR	NR	NR	Tacrolimus, eclizumab
Chodick, 2021, Israel	Pfizer/BioNTech	Retrospective Cohort 21	2 months [Dec 19, 2020 – Feb 20, 2021]	25,459 immunocompromised patients with 2 doses Vs. 27,822 immunocompromised patients with 1 dose	NR	NR	NR	NR	NR	56/25,403 [vaccinated] Vs. 79/27,743 [unvaccinated]	NR

(continued on next page)

Table 1 (continued)

First author, year, location	COVID-19 vaccine	Study design/D&B score (max score 28)	Study duration [dates]	Number of patients [immunocompromised vs. healthy controls]	Total or% participants with neutralizing antibodies [immunocompromised vs. healthy controls]		Mean (SD) or median [IQR] antibody titers [immunocompromised vs. healthy control]		Immunocompromised patients: Symptomatic COVID-19 (N) /No symptomatic COVID-19 (N) [vaccinated vs. unvaccinated]		Immunosuppressive therapy
					After 1st dose	After 2nd dose	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose	
Danthu, 2021, France	Pfizer/ BioNTech	Prospective cohort 17	14 weeks [vaccine time: Feb 2, 2021 – Mar, 15, 2021; and 58 days of follow-up]	74 kidney transplant patients Vs. 78 patients on HD Vs. 7 healthy controls	NR	3 (4.1%) for patients after kidney transplant, 59 (85.5%) for patients on HD, and 7 (100%) for healthy control	NR	6.6 AU/mL (2.1–19) for patients on HD, 1082 AU/mL (735–1662) for healthy control. Titer not shown for transplant patients (only 3 were positive)	NR	NR	Antimetabolite, Steroid
Furer, 2021, Tel Aviv, Israel	Pfizer/ BioNTech	Prospective cohort 22	3 months [Dec 2020 – Mar 2021]	686 patients with AIIRD Vs. 121 healthy controls	NR	Immunocompromised: 86% (590/686) Vs. Healthy control: 100% (121/121)	NR	Immunocompromised: S1/S2 IgG: 132.9 (+/- 91.7) BAU/mL Vs. Healthy controls S1/S2 IgG: 218.6 (+/- 82.06) BAU/mL	NR	NR	Anti-CD20, Methotrexate, MMF, Interleukin 6 inhibitor, Janus kinase inhibitor, Glucocorticoids, Abatacept
Geisen, 2021, Kiel, Germany.	Pfizer/ BioNTech and Moderna	Prospective cohort 19	6 weeks [NR]	26 immunocompromised (patients with chronic inflammatory conditions, and immunosuppressive therapy) Vs. 42 healthy controls	NR	Immunocompromised: 26(100%)) Vs. Healthy controls 42 (100%)	NR	Immunocompromised: Anti-SARS-COV-2 IgG: 2053 BAU/mL (+/- 1218); Neutralizing antibodies: 87.42% (+/-17.94); IgA: 24.52 U/mL (+/- 30.48) Vs. Healthy controls: Anti-SARS-COV-2 IgG: 2685 BAU/mL (+/-1102); Neutralizing antibodies: 96.04% (+/-1551); IgA: 47.65 U/mL (+/-45.12)	NR	NR	Biological DMARD; Conventional DMARD; Steroids (prednisolone)
Ghione, 2021, Buffalo, NY, United States	Pfizer/ BioNTech and Moderna	Prospective cohort 20	2 months [NR]	65 lymphoma patients with treatment Vs. 21 Lymphoma patients without treatment Vs. 194 healthy controls 136 kidney transplant patients Vs. 25 healthy controls	NR	36/86 Vs. 197/201	NR	0.13 in patients with recent treatment 20.7 in patients with prior treatment	NR	NR	Anti-CD20, Bruton tyrosine kinase, inhibitors based therapies, chimeric antigen receptor (CAR) T cell therapy
Grupper, 2021, Israel	Pfizer/ BioNTech	Prospective cohort 23	NR	136 kidney transplant patients Vs. 25 healthy controls	NR	NR	NR	5.9 (3.8–4.2) for kidney transplants Vs. 189 (141.1–248) for healthy controls	NR	NR	Methylprednisolone + Basiliximab for induction; Calcineurin inhibitors + Mycophenolate mofetil + Prednisone for maintenance

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Table 1 (continued)

First author, year, location	COVID-19 vaccine	Study design/D&B score (max score 28)	Study duration [dates]	Number of patients [immunocompromised vs. healthy controls]	Total or% participants with neutralizing antibodies [immunocompromised vs. healthy controls]		Mean (SD) or median [IQR] antibody titers [immunocompromised vs. healthy control]		Immunocompromised patients: Symptomatic COVID-19 (N) /No symptomatic COVID-19 (N) [vaccinated vs. unvaccinated]		Immunosuppressive therapy
					After 1st dose	After 2nd dose	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose	
Haberman, 2021, United States	Pfizer/ BioNTech	Prospective cohort 19	4 months [Dec 23, 2020 – Mar 31, 2021]	101 with immunemediated inflammatory diseases Vs. 26 healthy controls	NR	NR	NR	46,901 ²⁵ –694,528 ²⁸ units for Methotrexate group. 113,608 ²⁵ –737,310 ³¹⁰ units for the immunosuppressed without methotrexate and 104,354 units (141–601,185) for healthy controls	NR	NR	disease-modifying antirheumatic drugs (TNF inhibitor) with or without Methotrexate
Havlin, 2021, Prague Czech Republic	Pfizer/ BioNTech	Prospective cohort 19	NR	48 LTR patients Vs. 33 LTR patients post-COVID-19 infection Vs. 10 healthy controls	NR	LTR patients: 0% (0/48) Vs. LTR patients post-COVID-19: 85% (28/33) Vs. Healthy control: 100% (10/10)	NR	NR	NR	3/43 [vaccinated] Vs. 1/1 [unvaccinated]	NR
Herishanu 2021 Tel-Aviv, Israel	Pfizer/ BioNTech	Prospective cohort 22	3 months [Dec 2020 – Feb 2021]	167 immunocompromised (chronic lymphocytic leukemia) Vs. 52 healthy controls	NR	Immunocompromised: 39.5% (66/167) patients with CLL Vs. Healthy controls: 52 (100%)	NR	Immunocompromised: Median: 0.824 U/ml (IQR: 0.4–167.3) Vs. Healthy controls: Median: 1084 U/mL (IQR: 128.9–1879)	NR	NR	Anti-CD20 (rituximab or obinutuzumab), Venetoclax
Herzog Tzarfati, 2021, Israel	Pfizer/ BioNTech	Retrospective cohort 21	NR	315 immunocompromised (hematologic CA) Vs. 108 healthy controls	NR	74.6% for hematologic CA Vs. CIT (29%); single agent anti CD20 Ab (0%); BCL2i (25%); BTKi (40%), JAK2i (42%) Vs. 99.1% for controls	85 (10.7–172) AU/mL - median	157 (130–221) AU/mL - median	NR	NR	Chemotherapy, chemo-immunotherapy (CIT), single agent anti CD20, proteasome inhibitors, IMiDs, BCR-ABL TKI, BCL2 inhibitors, JAK2 inhibitors, BTK inhibitors
Iacono, 2021, Italy	Pfizer/ BioNTech	Prospective Cohort 16	NR	36 hematologic CA Vs. 72 healthy controls	NR	NR	NR	2369.1 (0–3276.3) AU/mL in the immunosuppressed Vs. 8737.49 (398.9–967,280) AU/mL for healthy controls	NR	NR	Rituximab, Paclitaxel + Transtuzumab, Corticosteroids
Khan, 2021, VA across the United States	Pfizer/ BioNTech and Moderna	Retrospective cohort 21	4 months [Dec 18, 2020 – April 20, 2021]	7376 immunocompromised patients [IBD] with vaccines Vs. 7211 immunocompromised patients without vaccine	NR	NR	NR	NR	NR	14/7098 [vaccinated] Vs. 197/14,500 [unvaccinated]	Mesalamine Thiopurine Anti TNF Vedolizumab Ustekinumab Tofacitinib Methotrexate steroid

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Table 1 (continued)

First author, year, location	COVID-19 vaccine	Study design/D&B score (max score 28)	Study duration [dates]	Number of patients [immunocompromised vs. healthy controls]	Total or% participants with neutralizing antibodies [immunocompromised vs. healthy controls]		Mean (SD) or median [IQR] antibody titers [immunocompromised vs. healthy control]		Immunocompromised patients: Symptomatic COVID-19 (N) /No symptomatic COVID-19 (N) [vaccinated vs. unvaccinated]		Immunosuppressive therapy
					After 1st dose	After 2nd dose	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose	
Korth 2021 Kronach Germany	Pfizer/ BioNTech	Prospective cohort 19	2 months [Jan 2021 – Feb 2021]	23 Immunocompromised: (KTR) Vs. 23 healthy controls	NR	Immunocompromised: 22% (5/23) Vs. Healthy controls: 100% (23/23)	NR	Immunocompromised: IgG: 50.9 (+/- 138.7) AU/mL Vs. Healthy controls IgG: 727.7 (+/- 151.3) AU/mL	NR	NR	Tacrolimus, MMF, corticosteroids
Lim, 2021, UK	Pfizer/ BioNTech; AstraZeneca	Prospective Cohort 18	NR	119 immunocompromised patients: 44% (52/119) with lymphoma on treatment Vs. 150 healthy controls	Immuno compromised: 9/31 (28%) Vs. healthy control: -	Immuno compromised: 13/33 (39%) Vs. not on treatment: Hodgkin lymphoma (100%); aggressive B-cell non-Hodgkin lymphoma (81%); indolent B-cell non-Hodgkin lymphoma (89%)	Immuno compromised: Vs. healthy control: Pfizer/ BioNTech: 172 BAU/mL (95% CI 109–272) AstraZeneca: 67 BAU/mL ^{40–111}	Immunocompromised: on treatment: 2.5 BAU/mL (95% CI 1.1–5.8) Vs. not on treatment: 141.8 BAU/mL (75.6–266.0); Hodgkin lymphoma: 652.2 BAU/mL (95% CI 604.7–703.4); aggressive B-cell non-Hodgkin lymphoma: 244.6 BAU/mL (31.12–1923); Vs. healthy control: Pfizer/ BioNTech: 2339 BAU/mL ^{1,923–2,844} AstraZeneca: 199 BAU/mL (140–282)	NR	NR	Anti-lymphoma therapy
Longlune, 2021, France	Pfizer/ BioNTech	Prospective cohort 21	NR	20 HD patients on immunosuppression, Vs. 92 HD patients without immunosuppression	5 (4.5%) in total	10 (58.8%) for patients on immunosuppression Vs. 76 (95.0%) for patients without immunosuppression	NR	NR	NR	NR	mTOR inhibitor, Mycophenolic acid, steroid
Maneikis, 2021, Lithuania	Pfizer/ BioNTech	Prospective cohort 21	3.5 months [Jan 8, 2021 – April 21, 2021]	857 patients with hematologic CA Vs. 68 healthy controls	NR	NR	NR	6961 AU/mL (IQR: 1292–20,672) for hematologic CA Vs. 21,395 AU/mL (IQR: 14,831–33,553) for healthy controls Mean: 87.32 AU/mL for SOT patients Vs. Mean: 233 AU/mL for healthy controls	NR	NR	Anti-CD20, Tyrosine kinase inhibitors, Nivolumab, Ruxolitinib, Venetoclax, Aregrelide or interferon
Miele, 2021, Palermo, Italy	Pfizer/ BioNTech	Prospective cohort 18	4 months [Dec 2020 – Mar 2021]	16 SOT patients Vs. 23 healthy controls	NR	NR	NR	Immunocompromised: 37% (6/16) Vs. Healthy control: 100% (23/23)	NR	NR	Tacrolimus, Everolimus, MMF, Corticosteroids

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Table 1 (continued)

First author, year, location	COVID-19 vaccine	Study design/D&B score (max score 28)	Study duration [dates]	Number of patients [immunocompromised vs. healthy controls]	Total or% participants with neutralizing antibodies [immunocompromised vs. healthy controls]		Mean (SD) or median [IQR] antibody titers [immunocompromised vs. healthy control]		Immunocompromised patients: Symptomatic COVID-19 (N) /No symptomatic COVID-19 (N) [vaccinated vs. unvaccinated]		Immunosuppressive therapy
					After 1st dose	After 2nd dose	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose	
Monin 2021 London, UK	Pfizer/ BioNTech	Prospective cohort 21	2 months [Dec 8, 2020 – Feb 18, 2021]	151 immunocompromised (solid and hematologic CA) Vs. 54 healthy controls	Solid CA: Week 3: 21; 28% ²⁶⁻⁵¹ ; Week 5: 10; 30% ¹⁷⁻⁴⁷ Vs. Hematologic CA: Week 3: 8; 18% ¹⁰⁻³² Week 5: 4; 11% ⁴⁻²⁵ Vs. Healthy controls: Week 3: 32; 94% (81–98); Week 5: 18; 86% ⁶⁵⁻⁹⁵	Solid CA: 18; 95% (75–99) Vs. Hematological CA:; 60% ²³⁻⁸⁸ Vs. Healthy controls: 12; 100% (76–100)	NR	NR	NR	NR	NR
Peled, 2021, Israel	Pfizer/ BioNTech	Prospective cohort 16	NR	77 patients after heart transplant Vs. 136 healthy controls	NR	8 (10.4%) for heart transplant patients Vs. 127 (93.4%) for healthy controls (47.5%) 38/80 in immunocompromised patients Vs. (100%) 25/25 in healthy controls	NR	NR	NR	NR	Calcineurin inhibitor, prednisone
Rabinowich, 2021, Tel Aviv-Yafo, Israel	Pfizer/ BioNTech	Prospective cohort 20	6 weeks [Dec 2020 – Jan 2021]	80 in immunocompromised patients (liver transplant recipients) Vs. 25 healthy controls	NR	95.4 AU/ml (+– 92.4) Vs. 200.5 AU/ml (+–65.1) in healthy controls	NR	Immunocompromised: 95.4 AU/ml (+– 92.4) Vs. 200.5 AU/ml (+–65.1) in healthy controls	NR	NR	Prednisone, Tacrolimus/cyclosporin, Everolimus, Azathioprine, MMF
Rincon-Arevalo, 2021, Berlin, Germany	Pfizer/ BioNTech	Prospective cohort 18	7 weeks [NR]	44 on dialysis Vs. 40 in kidney transplant patients Vs. 34 healthy controls	NR	30/44 in dialysis group Vs. 0/10 in transplant group	NR	NR	NR	NR	MMF, Steroid, Calcineurin inhibitor
Sattler, 2021, Germany	Pfizer/ BioNTech	Prospective Cohort 17	NR	39 immunocompromised (KTR) Vs. 26 patients with kidney failure on HD Vs. 39 healthy controls	NR	Immunocompromised:IgG: 1 (2.6%); IgA: 4 (10.26%); Neutralizing antibodies: 0 Vs. Patients with kidney failure on hemodialysis: IgG: 22 (84.62%); IgA: 22 (84.62%); Neutralizing antibodies: 20 (76.92%) Vs. Healthy patients: IgG: 39 (100%); IgA: 38 (97.44%); Neutralizing antibodies: 39 (100%)	NR	NR	NR	NR	Cyclosporin, Tacrolimus MMF, corticosteroids

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Table 1 (continued)

First author, year, location	COVID-19 vaccine	Study design/D&B score (max score 28)	Study duration [dates]	Number of patients [immunocompromised vs. healthy controls]	Total or% participants with neutralizing antibodies [immunocompromised vs. healthy controls]		Mean (SD) or median [IQR] antibody titers [immunocompromised vs. healthy control]		Immunocompromised patients: Symptomatic COVID-19 (N) /No symptomatic COVID-19 (N) [vaccinated vs. unvaccinated]		Immunosuppressive therapy
					After 1st dose	After 2nd dose	After 1st dose	After 2nd dose	After 1st dose	After 2nd dose	
Schramm, 2021, Germany	Pfizer/BioNTech	Prospective Cohort 19	NR	50 cardiothoracic transplant recipients Vs. 50 healthy controls	NR	NR	96% below the cut off in the immunosuppressed group Vs. Abbott: 82 ⁴¹⁻¹⁴⁹ ; Roche: 33 ¹²⁻⁷⁵ ; Euroimmun: 62 ²⁷⁻¹⁰⁰ in healthy controls	90% below the cut off in the immunosuppressed group Vs. Abbott 1417 (732-2,589); Roche: >250; Euroimmun: >100 in healthy controls	NR	NR	Calcineurin inhibitor, MMF
Seyahi, 2021, Instabul, Turkey	Coronavac	Prospective cohort 22	15 weeks [Jan 14, 2021 – May 2, 2021]	Elderly immunocompromised [inflammatory rheumatic disease]: 22 elderly healthy control: 47 Vs. immunocompromised [inflammatory rheumatic disease]: hospital workers: 82 Vs. healthy controls (health care workers): 300	NR	1 (14.3%) for RTX Vs. 22 (88%) for non-RTX biological agents Vs. 25 (92.6%) for conventional DMARDs-Vs. 16 (100%) for colchicine Vs. 29 (100%) for no treatment	NR	NR	NR	NR	RTX, non-RTX biological agents-based regimen, conventional DMARDs-based regimen, colchicine
Tenforde, 2021, United States	Pfizer/BioNTech and Moderna	Prospective cohort 19	4 months [Mar 11, 2021 – May 5, 2021]	254 in immunocompromised patients Vs. 958 healthy controls	NR	NR	NR	NR	NR	20/59 [vaccinated] Vs. 62/60 [unvaccinated]	NR but definition for immunocompromised active solid organ CA (treated or newly diagnosed in the past 6 months), active hematologic CA (e.g., leukemia, lymphoma, myeloma), HIV infection without AIDS, AIDS, congenital immunodeficiency syndrome, previous splenectomy, SOT, immunosuppressive medication, SLE, RA, psoriasis, scleroderma, or IBD Antiretroviral therapy*
Woldemeskel, 2021, United States	Pfizer/BioNTech	Prospective cohort 14	NR	12 patients with HIV Vs. 17 healthy controls	NR	NR	NR	median 8.84 for HIV patients Vs. median 9.49 for healthy controls	NR	NR	NR
Wong, 2021, NY, United States	Pfizer/BioNTech and Moderna	Retrospective cohort 22	2 months [Dec 14, 2020 –Feb 12, 2021]	48 patients with IBD receiving biologic therapies Vs. 14 HCWs and 29 healthy volunteers	NR	NR	NR	NR	NR	NR	TNF antagonist monotherapy, vedolizumab monotherapy, ustekinumab

AIIRD=Autoimmune inflammatory rheumatic diseases; Anti-RBD=Anti receptor-binding domain; AU=Arbitrary units; BAU=Binding antibody units; BCL2 inhibitors= B-cell lymphoma 2; BCR-ABL TKI; BTK inhibitors= Bruton tyrosine kinase; CA=cancer; 95% CI=95% Confidence Interval; DMARDs=Disease modifying anti-rheumatic drugs; HD=Hemodialysis; IBD=Inflammatory Bowel Disease; IMIDs= Immune modulatory drugs; IQR=Interquartile range; JAK2= Janus kinase 2; KTR= Kidney transplant recipient; LTR=Lung transplant recipient; MDS=Myelodysplastic syndrome; MMF=Mycophenolate mofetil; MS=Multiple Sclerosis; mTOR= mammalian target of rapamycin; N=number reported; NR=Not reported; RA=Rheumatoid Arthritis; RTX=Rituximab; S=Spike; SCT=Stem Cell Transplantation; SD=Standard Deviation; SLE=Systemic Lupus Erythematosus; SOT=Solid organ transplant; TKI= Tyrosine kinase inhibitor; TNF=tumor necrosis factor; UI= Units; VE=Vaccine Effectiveness.

* All HIV patients were on antiretroviral therapy and had a median CD4+ T cell count on 913 cells/uL (range of 649 to 1678 cells/uL).

Table 2

Subset analyses evaluating the association between COVID-19 vaccine response (anti-SARS-CoV-2 spike protein IgG) after two doses of COVID-19 vaccine with control group and immunocompromised condition (20 studies)*.

Subset	Number of Studies Included	Pooled Odds Ratio, M-H, Random, comparing Control Group with Immunocompromised Group (95% CI)	I ² test for heterogeneity
Anti-SARS-CoV-2 Spike protein IgG	20	58.18 (21.61, 156.61)	71%
Neutralizing antibodies	3	181.92 (22.76, 1453.93)	55%
Anti-SARS-CoV-2 Spike protein IgG in control group compared with solid organ transplant patients	8	232.35 (66.98, 806.03)	35%
Anti-SARS-CoV-2 Spike protein IgG in control group compared with patients with malignant diseases	6	42.00 (11.68, 151.03)	47%
Anti-SARS-CoV-2 Spike protein IgG in control group compared with patients with inflammatory rheumatic diseases	3	19.06 (5.00, 72.62)	0%
Studies with 19–23 of 28 points (D&B, Good)	13	36.35 (10.59, 124.77)	73%
Studies with 14–18 of 28 points (D&B, Good)	7	136.80 (31.97, 585.29)	54%

CI=Confidence Interval; D&B=Downs & Black score; M-H=Mantel-Haenszel; Random=Random-effects method.

*Reasons for not including the other 13 studies in the meta-analysis: there are no raw numbers to perform the COVID-19 vaccine response (produced anti-SARS-CoV-2 spike protein IgG) after two doses of COVID-19 vaccine for immunocompromised patients.

Table 3

Meta-analyses evaluating the COVID-19 Vaccine Effectiveness among immunocompromised patients (4 studies*).

	Studies Included (n)	Immunocompromised patients (n)	Pooled Diagnostic Odds Ratio [DOR] (95% CI)	I ² test for heterogeneity	Vaccine Effectiveness* (95%CI)
All studies evaluating vaccinated immunocompromised patients (two doses) and symptomatic COVID-19	4	42,821	0.296 (0.108, 0.811)	0%	70.4% (18.9%, 89.2%)

CI=Confidence Interval.

*Vaccine Effectiveness was estimated as 100% x (1-DOR).

[Chodick 2021; Havlin 2021; Khan 2021; Tenforde 2021*]

*We have opted to include in our meta-analysis Tenforde 2021 CID [50] because in Tenforde 2021 MMWR study [67] there are no raw numbers to perform the vaccine effectiveness for immunocompromised patients.

culate VE for symptomatic COVID-19 infection. Sixth, different definitions were used in different studies for immunocompromising conditions. There may also be diagnostic overlap since immunocompromised patients can have multiple comorbidities. Finally, the results of our meta-analysis should be interpreted with caution, particularly since only four studies were included to calculate the COVID-19 VE among immunocompromised patients. Additionally, there was considerable heterogeneity in the identified studies, and there was not enough data to run additional stratified analysis for asymptomatic COVID-19, or COVID-19 breakthrough infections.

We found that the COVID-19 mRNA vaccines were moderately effective against symptomatic COVID-19 among immunocompromised patients. More studies are needed to evaluate VE of other COVID-19 vaccines, COVID-19 breakthrough post-vaccination, VE against new variants, and to better understand the clinical significance of anti-SARS-CoV-2 spike protein IgG antibody levels in immunosuppressed populations (Table 1).

Funding

This study was not funded.

Conflict of Interest

All authors report no conflict of interest relevant to this article.

Acknowledgements

We thank Jennifer Deberg, MLS, from the Hardin Library for the Health Sciences, University of Iowa Libraries, for assistance with the search methods.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jinf.2021.12.035](https://doi.org/10.1016/j.jinf.2021.12.035).

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