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RESEARCH ARTICLE

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Immunogenicity of COVID-19 vaccines in patients with diverse health conditions: A comprehensive systematic review

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Abstract

It remains unclear how effective COVID-19 vaccinations will be in patients with weakened immunity due to diseases, transplantation, and dialysis. We conducted a systematic review comparing the efficacy of COVID-19 vaccination in patients with solid tumor, hematologic malignancy, autoimmune disease, inflammatory bowel disease, and patients who received transplantation or dialysis. A literature search was conducted twice using the Medline/PubMed database. As a result, 21 papers were included in the review, and seropositivity rate was summarized by specific type of disease, transplantation, and dialysis. When different papers studied the same type of patient group, a study with a higher number of participants was selected. Most of the solid tumor patients showed a seropositivity rate of more than 80% after the second inoculation, but a low seropositivity was found in certain tumors such as breast cancer. Research in patients with certain types of hematological malignancy and autoimmune diseases has also reported low seropositivity, and this

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may have been affected by the immunosuppressive treatment these patients receive. Research in patients receiving dialysis or transplantation has reported lower seropositivity rates than the general population, while all patients with inflammatory bowel disease have converted to be seropositive. Meta-analysis validating these results will be needed, and studies will also be needed on methods to protect patients with reduced immunity from COVID-19.

KEYWORDS
COVID-19, health status, immunogenicity, seropositivity, vaccine

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been a major threat to global health since December 2019. COVID-19 is caused by the virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Common symptoms of the disease included fever, cough, and myalgia.[2] A pandemic was declared by the World Health Organization (WHO), and according to WHO, the cumulative number of confirmed cases worldwide was 304 million and the death toll was 5.4 million as of January 11, 2022.[3] COVID-19 has also resulted in multiple detrimental social, economic, and environmental outcomes, such as strained medical facilities and job cuts in several industries.[4]

To counter the threat of COVID-19, countries around the world have shifted resources to rapid and intensive COVID-19 vaccine development.[5] As of February 24, 10 vaccines have been granted emergency use listing by WHO.[6] There are two types of RNA-based vaccines that contain RNA that makes viral protein, two types of inactivated vaccines that contain copies of already dead viruses, and the other three types are vaccines made of nonreplicated viral vectors.[7] In addition, although not approved by WHO, there are several vaccines used in each country. As of November 25. 2021, 53.8% of the world's population was inoculated with at least one vaccine dose, and 42.7% were fully vaccinated.[8]

Vaccines currently in use are generally known to be more than 90% effective against COVID-19.[9–11] However, it is unclear how effective these vaccines are in patients with underlying diseases and weakened immunity. Seropositivity rates according to individual diseases and conditions have been studied, but no studies have integrated and summarized the literature on this topic. Therefore, we conducted a systematic review to summarize the seropositivity for each patient's disease and condition, according to the type of vaccine and the number of days after vaccination.

2 | METHODS

2.1 | Search strategy and selection criteria

This comprehensive systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] The PRISMA checklist is presented in Supporting Information: Supplement 1. Two researchers (K. C. and S. P.) searched the PubMed/Medline database and Cochrane Library from inception until September 5, 2021. An additional search was conducted on December 1, 2021. The following search terms were used: (COVID-19 or SARS-CoV-2) and (vaccine) and (seropositivity or seropositive).

Inclusion criteria were (a) studies reporting seropositivity data for patients with underlying diseases or receiving transplantation or dialysis, (b) studies presenting seropositivity for each specific disease such as breast cancer and lung cancer, not simply "cancer," (c) studies with data on type of vaccine, number of vaccinations, vaccination date, and follow-up period, and (d) studies written in English. Exclusion criteria were (a) studies targeting general public or healthcare workers without diseases (however, those who had COVID-19 and recovered now were included), (b) studies presenting summarized seropositivity data on several vaccines without data for individual vaccines.

If there were studies on patients with the same disease or transplantation or dialysis, a study with a larger sample size was selected. However, if the number of days from vaccination to antibody measurement was different, or the type of vaccine was different, data were all adopted even if the disease was the same.

2.2 | Data extraction and analysis

From all the selected studies, two researchers (K. C. and S. P.) independently extracted data. Any discrepancies between the two researchers were resolved through discussion and subsequent agreement. The following data were extracted: the first author's name, publication year, study design, characteristic of participants (types of diseases, transplantation, or dialysis, age, sex [% female], race, country), criteria for judging that the participant is seropositive, sample size, the type of vaccine, the number of received dose, dose interval, antibody test date, and seropositivity rate.

Using the extracted sample size and seropositivity rate, we performed random-effects proportional meta-analyses to estimate the 95% confidence interval (CI) of seropositivity rate of patients in each health status. We evaluated the statistical heterogeneity

between the studies using the I^2 value. R version 4.1 was used for the analysis.

3 | RESULT

3.1 | Search description

As a result of conducting the literature search from inception until September 5, 2021, 173 papers were retrieved, after removing duplicate papers. Of those, 126 papers were excluded from the title and abstract screening process. Of the remaining 51 papers, 35 were excluded, and 16 eligible articles remained in the review.

An additional literature search was conducted on December 5, 2021, 76 papers were retrieved, 46 papers were excluded after title and abstract screening, and 25 papers were excluded after full-text screening. Finally, five papers were additionally included in the study. On February 27, 2022, the second additional search was performed using Cochrane Library. Thirty-three papers were searched, and seven papers satisfied the inclusion criteria. However, two of them were already included papers, and the other five were not included because they targeted at general healthy adults.

As a result, 21 eligible articles were included in the final review. Since all papers targeting patients seropositive in baseline showed 100% seropositivity, only the paper with the largest number of patients were included. In other cases, all papers were included because at least one of the disease type, vaccine type, vaccination interval, and test date was different. A flow-chart of literature search is shown in Figure 1, and specific reasons for exclusion are presented in Supporting Information: Supplement 2.

3.2 | Summary of included studies

The characteristics of included studies are presented in Table 1 and Supporting Information: Supplement 2. Table 1 and Supporting Information: Supplement 2 summarize which participants were included, which controls were included, what criteria determined that the participants are seropositive, which vaccines were used, and intervals for which the participants were vaccinated twice.

Participants could be largely divided into solid tumor patients, hematologic malignancy patients, autoimmune disease patients, inflammatory bowel disease (IBD) patients, transplantation or hemodialysis recipients, and patients who were seropositive for SARS-CoV-2 antibodies at baseline or had COVID-19. There was a total of five types of vaccines, and the most frequently used Pfizer-BioNTech BNT162b2 vaccine was used in 19 studies. CoronaVac, Oxford-AstraZeneca ChAdOx1 nCov-19 (AZD1222), and Moderna mRNA-1273 were used in two studies each, and there was one study using Sputnik V. The interval between vaccination doses 1 and 2 was 21 or 28 days in total, however, some studies did not report data on vaccination interval. Binding antibody detection tests were used in the majority of studies as a criterion for determining whether a patient is seropositive or not, and levels of immunoglobulin G (IgG) against SARS-CoV-2 S-protein or N-protein were mainly measured.

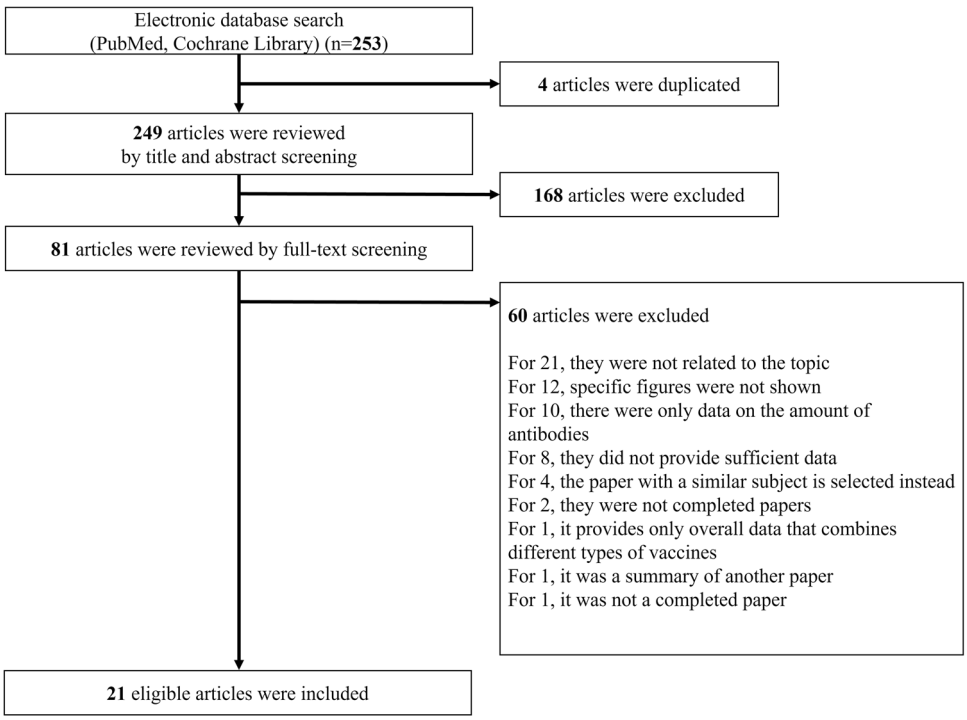

FIGURE 1 PRISMA flow.

TABLE 1 The characteristics of studies included in the comprehensive systematic review.

References	Subjects (population)	Comparison	Criteria for seropositivity	Vaccine	Dose interval
Salvagno et al.[13]	925 subjects who completed the two-dose vaccine cycle. 206 subjects were classified as baseline seropositive	NA	A test was considered positive if anti-SARS-CoV-2 RBD antibodies level was ≥0.8 U/ml	Pfizer	21 days between the first and the second dose
Blain et al.[14]	Nursing home residents without prior COVID-19 and residents with prior COVID-19	Younger healthcare workers	A test was considered positive if a signal to cutoff ratio was ≥0.8	Pfizer	21 days between the first and the second dose
Rozen-Zvi et al.[15]	Adult kidney transplant recipients who were vaccinated with two doses of BNT162b2 vaccine	NA	A test was considered positive if IgG was ≥50 AU/ml	Pfizer	21 days between the first and the second dose
Herzog Tzarfati et al.[16]	Patients with hematologic malignancies treated at Shamir Medical, having received two doses of vaccination	An age-matched group with no hematologic malignancy	Samples were considered positive for antibody titers >12 AU/ml	Pfizer	Not clearly defined
Perry et al.[17]	Patients aged > = 18 years diagnosed with B-NHL	Healthy volunteers who had received 2 COVID-19 vaccine doses	IgG (aimed at the SARS-CoV-2 S protein receptor-binding domain) concentration of >0.80 U/ml considered to be positive	Pfizer	21 days between the first and the second dose
Claro et al.[18]	Individuals who presented for vaccination in a public hospital in Caracas, Venezuela	NA	A titer with an S/P (sample to positive) ratio of at least 40% was considered positive	Sputnik V	21 days between the first and the second dose
Ligumsky et al.[19]	Patients with solid tumors, actively-treated at the day-care center of the oncology division	Vaccinated healthy adults with no history of cancer	Anti-SARS-CoV-2 S IgG (Immunoglobulin G) antibodies (Abs) were measured, using level > 50 AU/ml as cutoff for seropositivity	Pfizer	Not clearly defined
Furer et al.[20]	Patients with autoimmune inflammatory rheumatic diseases	General population, consisting mainly of healthcare personnel	Seropositivity was defined as IgG ≥ 15 BAU/ml	Pfizer	21 days between the first and the second dose
Lacson et al.[21]	Patients receiving maintenance dialysis	NA	A test was considered positive if IgG against the receptor-binding domain of the S1 subunit of SARS-CoV-2 spike-antigen was ≥2 U/L	Pfizer/Moderna	Not clearly defined
Itzhaki et al.[22]	Heart transplant recipients who have received a two-dose SARS-CoV-2 mRNA vaccine	NA	S-IgG value (geometric mean titers) of 50 AU/ml and greater was interpreted as seropositive	Pfizer	21 days between the first and the second dose
Bayram et al.[23]	HCW of both genders, 18 years of age or older	NA	SARS-CoV-2 antispike antibodies greater than or equal to the cutoff value 50.0 AU/ml were reported as positive	CoronaVac	28 days between the first and the second dose
Eyre et al.[24]	HCW from Oxford University Hospitals	NA	A test was considered positive if anti-spike antibody responses were ≥50 AU/ml	Pfizer/ AstraZeneca	Median (IQR) dosing interval: 24 (21–28) days

(Continues)

TABLE 1 (Continued)

References	Subjects (population)	Comparison	Criteria for seropositivity	Vaccine	Dose interval
Goshen-Lago et al.[25]	Patients with solid tumors receiving intravenous treatment	Age-matched healthy HCW	A test was considered positive if S1/S2 IgG antibodies values were ≥ 15 AU/ml	Pfizer	21 days between the first and the second dose
Narasimhan et al.[26]	Lung-transplant recipients	People who are non-transplanted and nonexposed to COVID-19	Two Index values of ≥1.4 (IgGNC), ≥1.0 (IgMSP), and ≥50 AU/ml (IgGSP) were interpreted as positive	Pfizer/Moderna	Not clearly defined
Waldhorn et al.[27]	Patients with solid tumors receiving intravenous treatment	Healthy HCW	A test was considered positive if S1/S2 IgG antibodies values were ≥ 15 AU/ml	Pfizer	21 days between the first and the second dose
Haskin et al.[28]	Kidney transplant recipients	Previous COVID-19 infection that was confirmed by RT-PCR	A test was considered positive if IgG was >50 antibody unit (AU)/ml	Pfizer	21 days between the first and the second dose
Edelman-Klapper et al.[29]	Patients with inflammatory bowel diseases (IBD) aged ≥18 years	Healthcare professionals without known gastrointestinal diseases	SARS-CoV-2 IgG II values ≥ 50 activity units (AU)/ml are consdiered positive	Pfizer	21–28 days between the first and the second dose
Fox et al.[30]	Patients on treatment or treated within the last 24 months for a B-cell malignancy	NA	Positive if antibodies for both the nucleocapsid antigen and the spike protein receptor binding domain were ≥0.8/ml	Pfizer/ AstraZeneca	Not clearly defined
Grupper et al.[31]	People who were vaccinated at least 1 month before kidney transplant and who were vaccinated after transplant	39 vaccinated HCW	A test was considered positive if LIAISON SARS-CoV-2 S1/S2 IgG was >15 AU/ml	Pfizer	21 days between the first and the second dose
Murt et al.[32]	All of the patients were maintenance hemodialysis patients over 18 years old	Healthy HCW vaccinated with CoronaVac	A test was considered positive if IgG antibodies toward spike receptor-binding domain of SARS-CoV-2 was over 50 AU/ml	Pfizer/ CoronaVac	28 days between the first and the second dose
Novak et al.[33]	Adult patients with multiple sclerosis and currently treated with anti-CD20 therapy	NA	A test was considered positive if IgG antibodies against SARS-CoV-2 spike receptor-binding domain were over 254 BAU/ml	Pfizer	Not clearly defined

Abbreviations: BAU, binding antibody units; HCW, healthcare workers; NHL, non-Hodgkin lymphoma.

3.3 | Solid tumor

Seropositivity of COVID-19 among solid tumor patients is reported in Figures 2 and 3 and Supporting Information: Supplement 3. Three studies were included, and Pfizer vaccine was used in all studies.[19,25,27]

After the first vaccination, most solid tumor patients showed low seropositivity. As a result of meta-analysis of all patients, seropositivity was only 27.1% (95% CI: [14.1%, 41.6%], *N* = 86).

Based on the seropositivity after the second inoculation, the seropositivity of sarcoma cancer was the lowest at 50% (95% CI: [1.3%, 98.7%], *N* = 2), followed by esophagus and gastric cancer (60.0%, 95% CI: [14.7%, 94.7%], *N* = 5) and neurologic cancer (66.7%, 95% CI: [9.4%, 99.2%], *N* = 3). Moreover, the seropositivity of breast cancer patients was 76.3% (95% CI: [59.8%, 88.6%], *N* = 38) on 14 days after the second inoculation and 73.1% (95% CI: [52.2%, 84.4%], *N* = 26) after 180 days. When analyzed for all solid tumor patients, the seropositivity was 90.5% (95% CI: [87.3%, 93.4%], *N* = 605)

3.4 | Hematologic malignancy

Seropositivity of COVID-19 among hematologic malignancy patients is reported in Figure 4 and Supporting Information: Supplement 4. Three studies were included.[16,17,30] Most of the data were on the Pfizer vaccine, and there was one data on AstraZeneca vaccine.

For aggressive non-Hodgkin lymphoma (NHL) and indolent NHL, there were seropositivity data 14–21 days after the second inoculation, 49.3% (95% CI: [37.0%, 61.6%], *N* = 69) and 47.5% (95% CI: [36.2%, 59.0%], *N* = 80), respectively. When receiving anti-CD20 antibodies treatment, the seropositivity decreased to 47.0% (95% CI: [34.6%, 59.7%], *N* = 66) and 30.9% (95% CI: [19.1%, 44.8%], *N* = 55), respectively. Based on the seropositivity of 30 days after the second inoculation, the seropositivity of chronic lymphocytic leukemia (CLL) was the lowest at 47.1% (95% CI: [29.8%, 64.9%], *N* = 34), followed by indolent NHL (60%, 95% CI: [43.3%, 75.1%], *N* = 40). CML, Hodgkin lymphoma, and myelodysplastic syndromes reported seropositivity rates of more than 90%. Furthermore, when a patient with hematologic malignancy was vaccinated with AstraZeneca and Pfizer once, seropositivity rates of 35.7% and 36.6%, respectively, were shown 30 days later (Supporting Information: Supplement 3). When analyzed for all hematologic malignancy patients, the seropositivity was 67.0% (95% CI: [55.4%, 77.0%], *N* = 585).

3.5 | Autoimmune disease

Seropositivity of COVID-19 among autoimmune disease patients is reported in Figure 5 and Supporting Information: Supplement 5. Two studies were included, and Pfizer vaccine was used in all studies.[20,33]

For antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and idiopathic inflammatory myositis (IIM), there were seropositivity data 14–42 days after the second inoculation, 30.8% (95% CI: [14.3%, 51.8%], *N* = 26) and 36.8% (95% CI: [16.3%, 61.6%], *N* = 19), respectively. MS patients treated with anti-CD20 antibodies reported the seropositivity rate of 13.5% (95% CI: [4.5%, 28.8%], *N* = 37) on the 7th and 35.1% (95% CI: [20.2%, 52.5%], *N* = 37) between the 14th and 28th after the second inoculation. In all other types of autoimmune disease, there was a seropositivity rate of more than 80%. When analyzed for all autoimmune disease patients, the seropositivity was 70.1% (95% CI: [48.7%, 87.8%], *N* = 737).

3.6 | Dialysis

Seropositivity of COVID-19 among dialysis recipients is reported in Figure 5 and Supporting Information: Supplement 6. Two studies were included, and Pfizer, Moderna, and CoronaVac vaccines were used in the studies.[21,32]

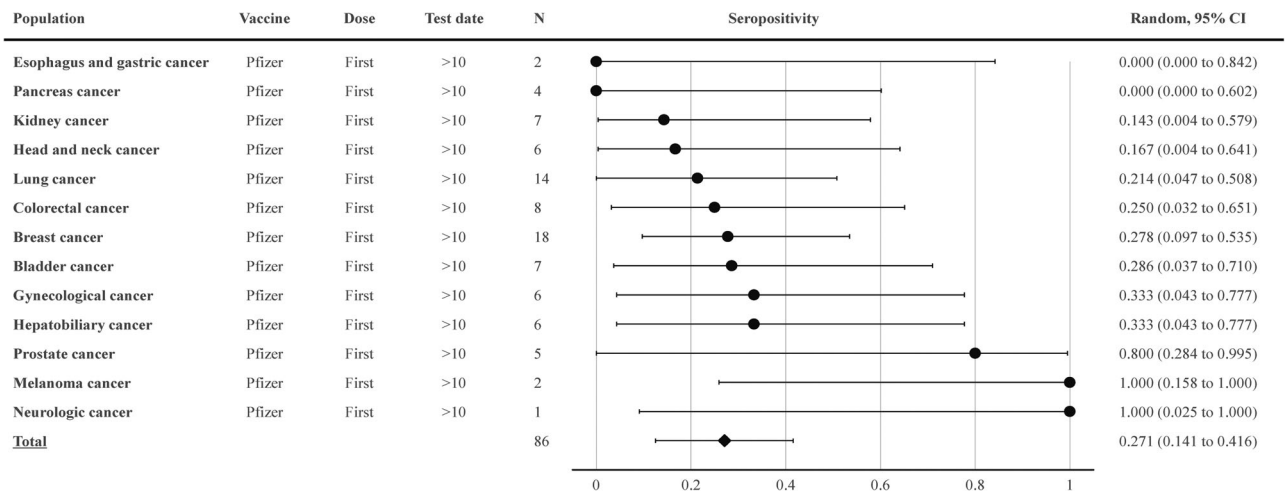

FIGURE 2 Seropositivity of COVID-19 in solid tumor patients after the first vaccination.

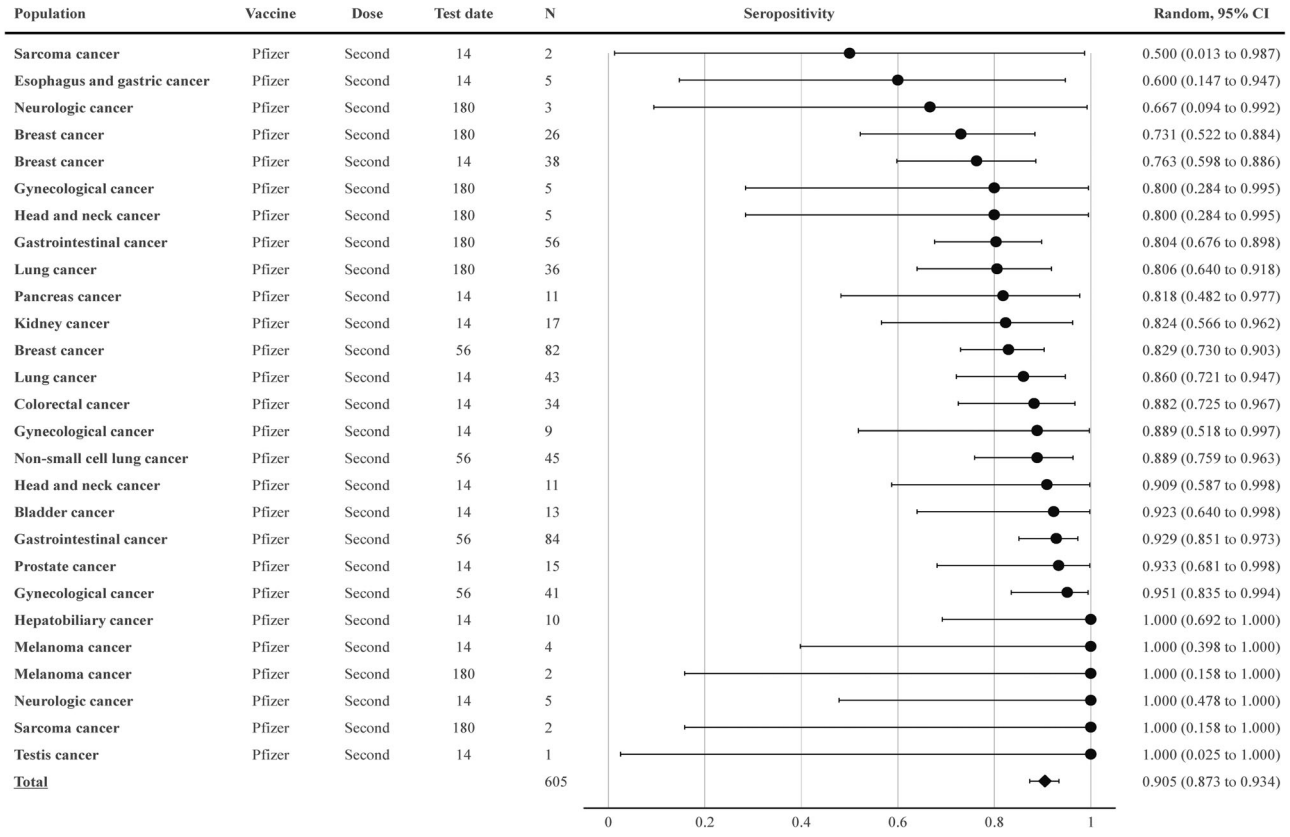

FIGURE 3 Seropositivity of COVID-19 in solid tumor patients after the second vaccination.

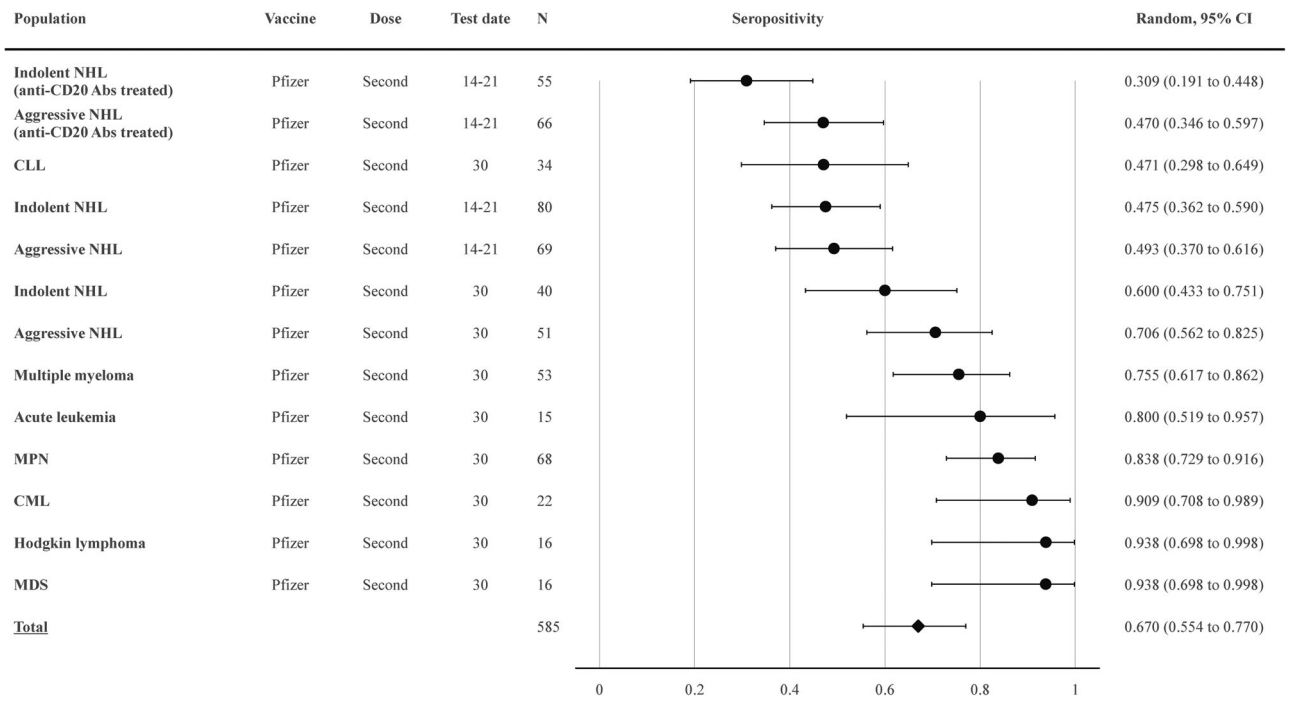

FIGURE 4 Seropositivity of COVID-19 in hematologic malignancy patients. CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms; NHL, non-Hodgkin lymphoma.

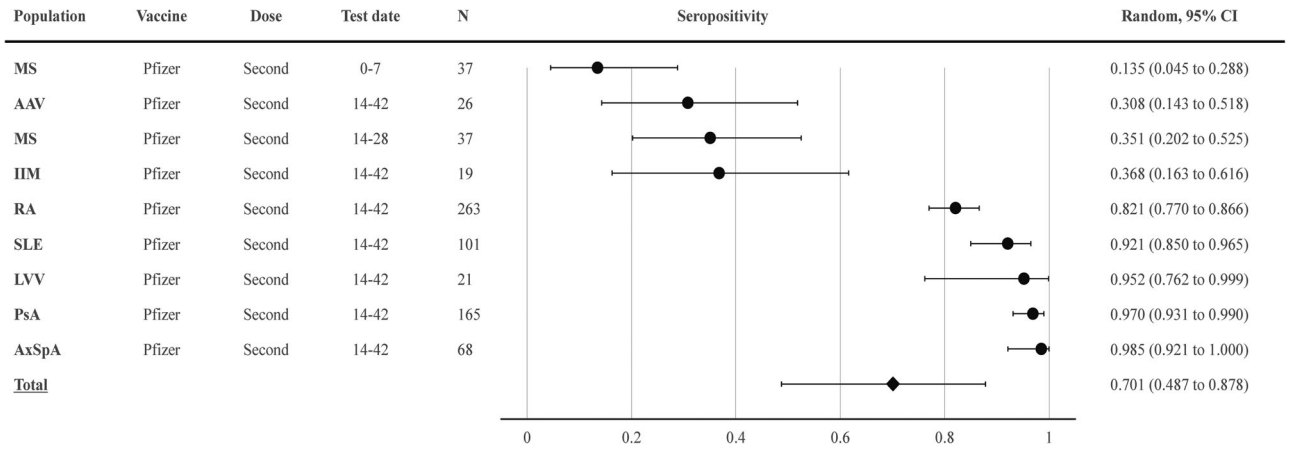

FIGURE 5 Seropositivity of COVID-19 in autoimmune disease patients. AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; AxSpA; axial spondylarthritis; IIM, idiopathic inflammatory myositis; LVV, large vessel vasculitis; MS, multiple sclerosis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

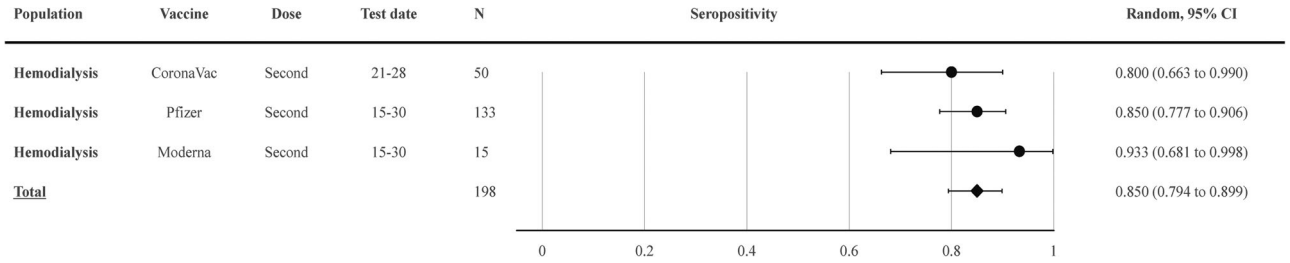

FIGURE 6 Seropositivity of COVID-19 in patients who received hemodialysis.

When CoronaVac, Pfizer, and Moderna vaccine were inoculated in hemodialysis patients, the seropositivity rate was 80.0% (95% CI: [66.3%, 90.0%], *N* = 50), 85.0% (95% CI: [77.7%, 90.6%], *N* = 133), and 93.3% (95% CI: [68.1%, 99.8%], *N* = 15) respectively on 15–30 days after the second inoculation. When analyzed for all hemodialysis patients, the seropositivity was 85.0% (95% CI: [79.4%, 89.9%], *N* = 198).

3.7 | Transplant

Seropositivity of COVID-19 among transplant recipients is reported on Figure 6 and Supporting Information: Supplement 6. Five studies were included, and Pfizer vaccine was used in all studies.[15,22,26,28,31] Moderna vaccine was inoculated in lung transplantation recipients.

Heart transplant recipients reported seropositivity of 48.6% (95% CI: [31.9%, 78.2%], *N* = 38).

On 14–19 days after the second Pfizer vaccination. After two inoculations of Pfizer vaccine, the seropositivity rate of kidney transplant recipient was 36.4% (95% CI: [31.0%, 42.0%], *N* = 308) at the mean age of 57.51, and 63.2% (95% CI: [46.0%, 78.2%], *N* = 38) at the mean age of 16.8. In a study comparing the order of vaccination and kidney transplantation, the seropositivity was higher at 89.9% (95% CI: [82.7%, 94.9%], *N* = 109) in the case of vaccination after transplantation than in the opposite case (44.95%, 95% CI: [24.4%, 71.1%], *N* = 19). When lung transplant recipients were inoculated Pfizer and Moderna vaccine, the seropositivity rate was 18.8% (95% CI: [8.9%, 32.6%], *N* = 48) and 36.0% (95% CI: [18.0%, 57.5%], *N* = 25), respectively, after the second inoculation. When analyzed for all transplant patients, the seropositivity was 44.9% (95% CI: [24.4%, 66.0%], *N* = 623).

3.8 | IBD

Seropositivity of COVID-19 among IBD is reported in Supporting Information: Supplement 7. Only one study was included, and it compared patients who received anti-tumor necrosis factor (TNF)-α with those who did not.[29] After the first inoculation, 91.04% of those who were treated with anti-TNF-α and 93.22% of those who did not receive treatment were seropositive. However, seropositivity converted to 100% after the second inoculation in both cases.

3.9 | Infected/seropositive at baseline

Seropositivity of COVID-19 among participants who were seropositive at baseline, or had COVID-19, or were infected during study

is reported in Supporting Information: Supplement 8. Six studies were included.[13,14,18,23] Up to the second inoculation, in most cases, high seropositivity rate was found close to 100%.

4 | DISCUSSION

Patients with underlying diseases, or patients who received dialysis or transplantation, are at high risk of COVID-19. According to the study of F. Javanmardi, the underlying disease plays an important role in the severity and high mortality of COVID-19.[34] A study from Italy showed that only 0.8% of patients who deceased of COVID-19 have no disease.[35]

Vaccination is underway to protect patients from COVID-19. However, to the best of our knowledge, there is no comprehensive study on how effectively antibodies are produced by vaccines for each disease and condition. Therefore, we incorporated evidence from 21 studies and summarized the seropositivity rate of patients under various conditions in this review.

In most types of solid tumor, patients showed a seropositivity rate of more than 80% after the second inoculation. In the type of solid tumor that reported a seropositivity rate of approximately 60% (e.g., esophagus and gastric cancer, neurologic cancer), the number of patients was small, so further research is likely to be needed. The seropositivity of solid tumor patients was relatively higher than that of hematologic malignancy patients or patients with reduced immunity due to transplantation or dialysis. This reflects that the treatment of solid cancer has a smaller effect of immunosuppression than that of hematologic malignancy treatment, transplantation, and dialysis.[19] Several papers report low seropositivity in patients with hematologic malignancy. Especially in patients with CLL, less than 40% of seropositivity rate has been reported, and if they received treatment with anti-CD20 antibodies or BCL2 inhibitors, the rate is further reduced.[36] In addition, it is known that JAK1/JAK2 inhibitor, which is widely used in the treatment of hematological malignancy patients, is associated with low seropositivity.[16] These treatments exhibit a wide range of anti-inflammatory capabilities. One paper reported that these features help treat severe COVID-19.[37] Therefore, it can be seen that the JAK1/JAK2 inhibitor attenuates the immune response caused by the vaccination.

Among patients with autoimmune diseases, rheumatoid arthritis (RA), AAV, and IIM patients particularly showed a low serologic response. MS patients treated with CD20 inhibitors also reported low seropositivity. It may be a decrease in humoral response depending on the type of disease, but underlying treatment would have had an effect. In RA patients, MTX, a type of immunosuppressive treatment is associated with lower levels of antibodies, but the degree is not that large.[20,38] Therefore, vaccination and MTX treatment can be implemented together. Meanwhile, according to some studies, anti-CD20 therapy negatively affects antibody production after vaccination.[39,40] B-cell depletion due to anti-CD20 is related with a reduced humoral response.[41] If clinically possible, it may be reasonable to pause anti-CD20 therapy for a while before vaccination.[20] Further research will also be needed on whether patients with low serological response can respond to COVID-19 with an immune response through T-cells.

Patients with IBD were found to be seropositive after the second inoculation regardless of receiving anti-TNF-α. However, the serologic response of patients with IBD treated with anti-TNF-α was much lower than patients who were not treated with anti-TNF-α.[29] According to recent studies, it was shown that patients treated with anti-TNF-α are less capable of producing antibodies.[42] This is a point to consider when using anti-TNF-α in other immune related diseases, and it will also be necessary to consider additional vaccinations for patients undergoing anti-TNF-α treatment.[42]

Patients receiving hemodialysis showed slightly lower seropositivity compared to the seropositivity of the public. These patients usually have immune dysfunction, and the drugs they take can affect their immune response.[43] Examples of immune dysfunction include loss function of antigen presenting cells and vulnerability of B-cells to programmed cell death.[44] Meanwhile, the difference in efficacy between mRNA vaccine and inactivated vaccine could also be observed. When comparing the protective ability, mRNA vaccine was better. However, according to one study, when comparing whether there were side effects, inactivated vaccine showed fewer side effects. It may be due to a higher immune response through the mRNA vaccine.[32]

Research in patients receiving transplantation reported low seropositivity. Less than half of the lung transplant patients were seroconverted and only about half of heart transplant patients converted to seropositive. Seropositivity was also below the general level for kidney transplant patients. These results are likely due to the reduced host immunity of immunosuppressive patients required to produce a complete immune response after vaccination.[45] In addition, immunosuppressive treatments mainly taken by transplant recipients to prevent transplant rejection may have lowered the vaccine efficacy.[46] If there is no humoral response, increasing the amount of vaccine dose can be one method, but there is still the risk of rejection with vaccines.

Since there were not many trial and study participants for each disease, it was difficult to perform subgroup analysis, and we think the lack of research on heterogeneity is the limitation of our study. In Supporting Information: Supplement 9C,D, the heterogeneity was shown to be high, because patients who received anti-CD20 antibody treatment were included. This should be noted when understanding the average value for the summary effect. It is also necessary to refer to Figures 5 and 6 as it indicates whether patients received anti-CD20 antibody treatment or not. Similarly, in Supporting Information: Supplement 9F, the heterogeneity was calculated by combining all transplant patients, and it seems necessary to understand individual data based on Figure 7.

Findings from the present study should be interpreted in light of its limitations. First, a small number of papers were included for some disease groups. There is a potential risk of bias because only one paper was included in IBD, and two papers were included in autoimmune disease and dialysis. Meta-analysis may be conducted

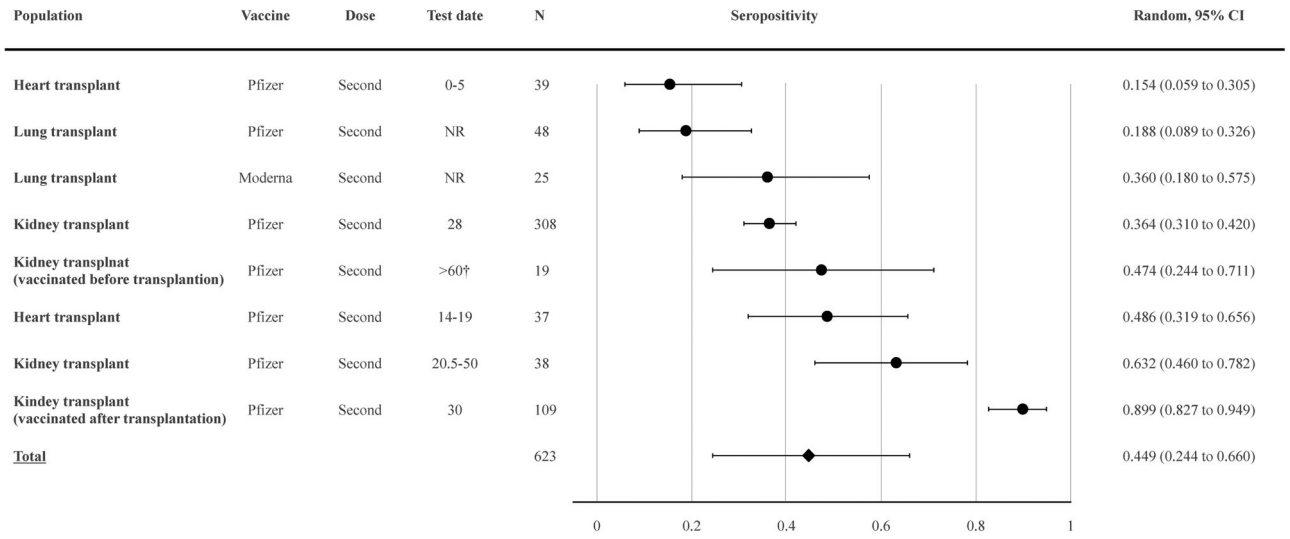

FIGURE 7 Seropositivity of COVID-19 in patients who received transplantation. †Vaccination was performed at least 30 days before transplantation, and seropositivity was measured at least 30 days after transplantation (Figure 2).

if more seropositivity data on various patient groups are accumulated. In addition, some studies have a small number of participants, so it may not be possible to generalize results.

Moreover, it should be noted that the criteria for determining whether the patient is seropositive in each study was different. Although many studies have conducted studies based on antibody level, it is difficult to completely determine the immune effect of the COVID-19 vaccine with antibody level alone without further research on T-cell response.

Despite the above limitations, this study is the first comprehensive analysis to summarize the seropositivity of various patient groups. The COVID-19 vaccine showed low efficacy when immunosuppressive treatment was performed for disease treatment such as hematological malignancy or when the immune function was deteriorated due to dialysis and transplantation. Various methods can be utilized to improve the vaccine efficacy of patients with reduced immunity. For example, patients can get the same vaccine booster dose or mix different types of vaccines.[47,48] More specific studies should be conducted for each patient's disease and treatment, and several methods should be devised to protect patients from COVID-19. Also, there is a paper on how seropositivity rates differ in different groups of immunocompromised patients,[49] but more studies are needed to explain the reasons for this variation.

AUTHOR CONTRIBUTIONS

Kyuyeon Cho and Seoyeon Park had full access to all the data in the study and take responsibility for the data analysis. All authors approved the protocol, drafted, and revised the article for intellectual content, and approved the final version.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated during this study are fully available in published cited literature and included in this article and its supplementary information files. The data are also available from the corresponding author upon request.

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REFERENCES

1. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol*. 2021;19(3):141-154.
2. Huang D, Lian X, Song F, et al. Clinical features of severe patients infected with 2019 novel coronavirus: a systematic review and meta-analysis. *Ann Transl Med*. 2020;8(9):576.
3. World Health Organization. Weekly epidemiological update on COVID-19—11 January 22. COVID-19 Weekly Epidemiological Update. 2021;67(1):1.
4. Ita K. Coronavirus disease (COVID-19): current status and prospects for drug and vaccine development. *Arch Med Res*. 2021;52(1):15-24.
5. Soleimanpour S, Yaghoubi A. COVID-19 vaccine: where are we now and where should we go? *Expert Rev Vaccines*. 2021;20(1):23-44.
6. WHO—COVID19 Vaccine Tracker. 10 Vaccines Granted Emergency Use Listing (EUL) by WHO; 2022. Accessed February 24, 2022. https://covid19.trackvaccines.org/agency/who/
7. WHO—COVID19 Vaccine Tracker. Types of Vaccines; 2021. Accessed December 5, 2021. https://covid19.trackvaccines.org/agency/who/
8. Ritchie H, Mathieu E, Rodes-Guirao L, et al. Coronavirus Pandemic (COVID-19); 2021. Accessed December 5, 2021. https://ourworldindata.org/coronavirus
9. Knoll MD, Wonodi C. Oxford-AstraZeneca COVID-19 vaccine efficacy. *Lancet*. 2021;397(10269):72-74.

10. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615.
11. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403-416.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8(5):336-341.
13. Salvagno GL, Henry BM, di Piazza G, et al. Anti-SARS-CoV-2 receptor-binding domain total antibodies response in seropositive and seronegative healthcare workers undergoing COVID-19 mRNA BNT162b2 vaccination. *Diagnostics (Basel)*. 2021;11(5):832.
14. Blain H, Tuaillon E, Gamon L, et al. Antibody response after one and two jabs of the BNT162b2 vaccine in nursing home residents: the CONsort-19 study. *Allergy*. 2021;77:271-281.
15. Rozen-Zvi B, Yahav D, Agur T, et al. Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. *Clin Microbiol Infect*. 2021;27(8):1173.e1-1173.e4.
16. Herzog Tzarfati K, Gutwein O, Apel A, et al. BNT162b2 COVID-19 vaccine is significantly less effective in patients with hematologic malignancies. *Am J Hematol*. 2021;96:1195-1203.
17. Perry C, Luttwak E, Balaban R, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with B-cell non-Hodgkin lymphoma. *Blood Adv*. 2021;5(16):3053-3061.
18. Claro F, Silva D, Rodriguez M, Rangel R, de Waard JH. IgG antibody response to the Sputnik V vaccine: previous SARS-CoV-2 seropositive individuals might need just one vaccine dose. *Int J Infect Dis*. 2021;111:261-266.
19. Ligumsky H, Safadi E, Etan T, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine among actively treated cancer patients. *J Natl Cancer Inst*. 2021.
20. Furer V, Eviatar T, Zisman D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. *Ann Rheum Dis*. 2021;80:1330-1338.
21. Lacson E, Argyropoulos CP, Manley HJ, et al. Immunogenicity of SARS-CoV-2 vaccine in dialysis. *J Am Soc Nephrol*. 2021;32:2735-2742.
22. Itzhaki Ben Zadok O, Shaul AA, Ben-Avraham B, et al. Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients—a prospective cohort study. *Eur J Heart Fail*. 2021;23:1555-1559.
23. Bayram A, Demirbakan H, Günel Karadeniz P, Erdoğan M, Koçer I. Quantitation of antibodies against SARS-CoV-2 spike protein after two doses of CoronaVac in healthcare workers. *J Med Virol*. 2021;93(9):5560-5567.
24. Eyre DW, Lumley SF, Wei J, et al. Quantitative SARS-CoV-2 anti-spike responses to Pfizer-BioNTech and Oxford-AstraZeneca vaccines by previous infection status. *Clin Microbiol Infect*. 2021;27(10):1516.e7-1516.e14.
25. Goshen-Lago T, Waldhorn I, Holland R, et al. Serologic status and toxic effects of the SARS-CoV-2 BNT162b2 vaccine in patients undergoing treatment for cancer. *JAMA Oncol*. 2021;7:1507-1513.
26. Narasimhan M, Mahimainathan L, Clark AE, et al. Serological response in lung transplant recipients after two doses of SARS-CoV-2 mRNA vaccines. *Vaccines (Basel)*. 2021;9(7):708.
27. Waldhorn I, Holland R, Goshen-Lago T, et al. Six month efficacy and toxicity profile of BNT162b2 vaccine in cancer patients with solid tumors. *Cancer Discov*. 2021;11:2430-2435.
28. Haskin O, Ashkenazi-Hoffnung L, Ziv N, et al. Serological response to the BNT162b2 COVID-19 mRNA vaccine in adolescent and young adult kidney transplant recipients. *Transplantation*. 2021;105:e226-e233.
29. Edelman-Klapper H, Zittan E, Bar-Gil Shitrit A, et al. Lower serologic response to COVID-19 mRNA vaccine in patients with inflammatory bowel diseases treated with anti-TNFα. *Gastroenterology*. 2021;162:454-467.
30. Fox TA, Kirkwood AA, Enfield L, et al. Low seropositivity and suboptimal neutralisation rates in patients fully vaccinated against COVID-19 with B-cell malignancies. *Br J Haematol*. 2021;195(5):706-709.
31. Grupper A, Katchman E, Ben-Yehoyada M, et al. Kidney transplant recipients vaccinated before transplantation maintain superior humoral response to SARS-CoV-2 vaccine. *Clin Transplant*. 2021;35:e14478.
32. Murt A, Altiparmak MR, Yadigar S, et al. Antibody responses to the SARS-CoV-2 vaccines in hemodialysis patients: Is inactivated vaccine effective? *Ther Apher Dial*. 2021. doi:10.1111/1744-9987.13752
33. Novak F, Nilsson AC, Nielsen C, et al. Humoral immune response following SARS-CoV-2 mRNA vaccination concomitant to anti-CD20 therapy in multiple sclerosis. Mult Scler Relat Disord. 2021;56:103251.
34. Javanmardi F, Keshavarzi A, Akbari A, Emami A, Pirbonyeh N. Prevalence of underlying diseases in died cases of COVID-19: a systematic review and meta-analysis. *PLoS One*. 2020;15(10):e0241265.
35. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA*. 2020;323(18):1775-1776.
36. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood*. 2021;137(23):3165-3173.
37. La Rosée F, Bremer HC, Gehrke I, et al. The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. *Leukemia*. 2020;34(7):1805-1815.
38. Kapetanovic MC, Roseman C, Jonsson G, Truedsson L, Saxne T, Geborek P. Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate-treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors. *Arthritis Rheum*. 2011;63(12):3723-3732.
39. Hua C, Barnetche T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor alpha, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2014;66(7):1016-1026.
40. Westra J, van Assen S, Wilting KR, et al. Rituximab impairs immunoglobulin (Ig)M and IgG (subclass) responses after influenza vaccination in rheumatoid arthritis patients. *Clin Exp Immunol*. 2014;178(1):40-47.
41. Spiera R, Jinich S, Jannat-Khah D. Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS- CoV-2 vaccination in patients with rheumatic diseases. *Ann Rheum Dis*. 2021;80(10):1357-1359.
42. Wong SY, Dixon R, Martinez Pazos V, et al. Serologic response to messenger RNA coronavirus disease 2019 vaccines in inflammatory bowel disease patients receiving biologic therapies. *Gastroenterology*. 2021;161(2):715-718.e4.
43. Sharif MR, Chitsazian Z, Moosavian M, et al. Immune disorders in hemodialysis patients. *Iran J Kidney Dis*. 2015;9(2):84-96.
44. Kato S, Chmielewski M, Honda H, et al. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol*. 2008;3(5):1526-1533.
45. Eckerle I, Rosenberger KD, Zwahlen M, Junghanss T. Serologic vaccination response after solid organ transplantation: a systematic review. *PLoS One*. 2013;8(2):e56974.
46. Natori Y, Shiotsuka M, Slomovic J, et al. A double-blind, randomized trial of high-dose vs standard-dose influenza vaccine

in adult solid-organ transplant recipients. *Clin Infect Dis*. 2018;66(11):1698-1704.

47. Pfizer. Pfizer and biontech initiate a study as part of broad development plan to evaluate Covid-19 booster and new vaccine variants; 2021. Accessed December 17, 2021. https://indiaeducationdiary.in/pfizer-and-biontech-initiate-a-study-as-part-of-broad-development-plan-to-evaluate-covid-19-booster-and-new-vaccine-variants/
48. Ledford H. Could mixing COVID vaccines boost immune response? *Nature*. 2021;590(7846):375-376.
49. Galia R. BNT162b2 mRNA COVID-19 vaccination in immuno-compromised patients: a prospective cohort study. *EClinicalMedicine*. 2021;41:101158.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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