

Immunogenicity of COVID-19 Vaccines in Patients with Diverse Health Conditions: a Comprehensive Systematic Review

Kyuyeon Cho^{1†}, Seoyeon Park^{1†}, Eun-Young Kim PhD^{2†}, Ai Koyanagi, M.D.^{3 4}, Louis Jacob, M.D.^{4 5}, Dong Keon Yon, M.D.⁶, Seung Won Lee, M.D.⁷, Min Seo Kim, M.D.⁸, Joaquim Radua^{9 10 11 12}, Elena, Dragioti¹³, Jae Il Shin, M.D.^{14*} and Lee Smith, PhD.¹⁵

1. Yonsei University College of Medicine, Seoul, Republic of Korea
2. Evidence-Based and Clinical Research Laboratory, Department of Health, Social and Clinical Pharmacy, College of Pharmacy, Chung-Ang University, Seoul 06974, Korea
3. ICREA, Pg. Lluís Companys 23, 08010, Barcelona, Spain.
4. Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, 08830, Barcelona, Spain.
5. Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, 78180 Montigny-le-Bretonneux, France
6. Department of Pediatrics, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea
7. Department of Data Science, Sejong University College of Software Convergence, Seoul, Republic of Korea
8. Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, Samsung Medical Center, Seoul, Republic of Korea
9. Early Psychosis: Interventions and Clinical-detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London SE5 8AB, UK.

10. Mental Health Networking Biomedical Research Centre (CIBERSAM), 08036 Barcelona, Spain.
11. Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institute, 11330 Stockholm, Sweden.
12. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), 08036 Barcelona, Spain.
13. Pain and Rehabilitation Centre, and Department of Health, Medicine and Caring Sciences, Linköping University, SE-581 85 Linköping, Sweden.
14. Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea
15. Centre for Health, Performance and Wellbeing, Anglia Ruskin University, Cambridge, UK

† Kyuyeon Cho and Seoyeon Park contributed equally to this article as co-first authors.

Corresponding Author

Prof. Jae Il Shin, MD, PhD.

Address: 50-1 Yonsei-ro, Seodaemun-gu, C.P.O. Box 8044, Department of Pediatrics, Yonsei University College of Medicine, Seoul 03722, Korea

Tel.: +82-2-2228-2050; Fax: +82-2-393-9118; E-mail: shinji@yuhs.ac

Shortened title

Immunogenicity of COVID-19 Vaccines

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 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, vaccine, seropositivity, immunogenicity, health status

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 myalgia². 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 11 January 2022³. 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.

In order to counter the threat of COVID-19, countries around the world have shifted resources to rapid and intensive COVID-19 vaccine development⁵. As of February 24, ten vaccines have been granted emergency use listing by WHO⁶. 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 non-replicated viral vectors⁷. In addition, although not approved by WHO, there are several vaccines used in each country. As of 25 November 2021, 53.8% of the world's population was inoculated with at least one vaccine dose, and 42.7% were fully vaccinated⁸.

Vaccines currently in use are generally known to be more than 90% effective against COVID-19⁹⁻¹¹. 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.

Methods

Search strategy and selection criteria

This comprehensive systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines¹². The PRISMA checklist is presented in Supplement 1. Two researchers (K.C. and S.P.) searched the PubMed/Medline database and Cochrane Library from inception until 5 September 2021. An additional search was conducted on 1 December 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.

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 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.

Result

Search description

As a result of conducting the literature search from inception until 5 September 2021, one hundred seventy-three papers were retrieved, after removing duplicate papers. Of those, one hundred twenty-six papers were excluded from the title and abstract screening process. Of the remaining fifty-one papers, thirty-five were excluded, and sixteen eligible articles remained in the review.

An additional literature search was conducted on December 5 2021, seventy-six papers were retrieved, forty-six papers were excluded after title and abstract screening, and twenty-five 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, twenty-one 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 Supplement 2.

Summary of included studies

The characteristics of included studies are presented in Table 1 and Supplement 2. Table 1 and 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 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 nineteen 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.

Solid tumor

Seropositivity of COVID-19 among solid tumor patients is reported in Figures 2 and 3 and Supplement 3. Three studies were included, and Pfizer vaccine was used in all studies¹³⁻¹⁵.

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)

Hematologic malignancy

Seropositivity of COVID-19 among hematologic malignancy patients is reported in Figure 4 and Supplement 4. Three studies were included¹⁶⁻¹⁸. Most of the data were on the Pfizer vaccine, and there was one data on AstraZeneca vaccine.

For aggressive NHL and indolent NHL, there were seropositivity data 14 to 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 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 MDS 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. (Supplement 3). When analyzed for all hematologic malignancy patients, the seropositivity was 67.0% (95% CI: [55.4%, 77.0%], N=585)

Autoimmune disease

Seropositivity of COVID-19 among autoimmune disease patients is reported in Figure 5 and Supplement 5. Two studies were included, and Pfizer vaccine was used in all studies¹⁹⁻²⁰.

For AAV and IIM, there were seropositivity data 14 to 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)

Dialysis

Seropositivity of COVID-19 among dialysis recipients is reported in Figure 5 and Supplement 6. Two studies were included, and Pfizer, Moderna, and CoronaVac vaccines were used in the studies^{21,22}.

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)

Transplant

Seropositivity of COVID-19 among transplant recipients is reported on Figure 6 and Supplement 6. Five studies were included, and Pfizer vaccine was used in all studies²³⁻²⁷. 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)

Inflammatory bowel disease

Seropositivity of COVID-19 among inflammatory bowel disease (IBD) is reported in Supplement 7. Only one study was included, and it compared patients who received anti-TNF α with those who did not²⁸. 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.

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 Supplement 8. Six studies were included²⁹⁻³³. Up to the second inoculation, in most cases, high seropositivity rate was found close to 100%.

Discussion

Patients with underlying diseases, or patients who receive/d 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-19³⁴. A study from Italy showed that only 0.8% of patients who deceased of COVID-19 have no disease³⁵.

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 twenty-one 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 dialysis¹⁴. 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 reduced³⁶. In addition, it is known that JAK1/JAK2 inhibitor, which is widely used in the treatment of hematological malignancy patients, is associated with low seropositivity¹⁶. These treatments exhibit a wide range of anti-inflammatory capabilities. One paper reported that these features help treat severe COVID-19³⁷. Therefore, it can be seen

that the JAK1/JAK2 inhibitor attenuates the immune response caused by the vaccination.

Among patients with autoimmune diseases, 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^{19, 38}. Therefore, vaccination and MTX treatment can be implemented together. Meanwhile, according to some studies, anti-CD20 therapy negatively affects antibody production after vaccination³⁹⁻⁴⁰. B-cell depletion due to anti-CD20 is related with a reduced humoral response⁴¹. If clinically possible, it may be reasonable to pause anti-CD20 therapy for a while prior to vaccination¹⁹. 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 ²⁸. According to recent studies, it was shown that patients treated with anti-TNF α are less capable of producing antibodies⁴². 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 treatment⁴².

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 response⁴³. Examples of immune dysfunction include loss function of antigen presenting cells and vulnerability of B-cells to programmed cell death⁴⁴. 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 vaccine²².

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 vaccination⁴⁵. In addition, immunosuppressive treatments mainly taken by transplant recipients to prevent transplant rejection may have lowered the vaccine efficacy⁴⁶. 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 Supplement 9C and 9D, 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 Figure 5 and 6 as it indicates whether patients received anti-CD20 antibody treatment or not. Similarly, in 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 inflammatory bowel disease, and two papers were

included in autoimmune disease and dialysis. Meta-analysis may be conducted 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 vaccines⁴⁷⁻⁴⁸. 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 patients⁴⁹, but more studies are needed to explain the reasons for this variation.

Conflict of interest statement

All authors state that they have no actual or potential conflict of interest including any financial, personal, or other relationships with other people or organization.

Author contribution statement

KC and SP 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.

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.

Funding statement

None provided financial support for the conduct of the research and/or preparation of the article.

References

- [1] Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol.* 2021;19(3):141-54.
- [2] Huang D, Lian X, Song F, Ma H, Lian Z, Liang Y, 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 [Internet]. c2021. 10 Vaccines Granted Emergency Use Listing (EUL) by WHO; 2022 Feb 24 [cited 2022 Feb 24]. Available from: <https://covid19.trackvaccines.org/agency/who/>
- [7] WHO – COVID19 Vaccine Tracker [Internet]. c2021. Types of Vaccines; 2021 Aug 1 [cited 2021 Dec 5]. Available from: <https://covid19.trackvaccines.org/agency/who/>
- [8] Ritchie H, Mathieu E, Rodes-Guirao L, et al. Coronavirus Pandemic (COVID-19); [cited 2021 Dec 5]. Available from: <https://ourworldindata.org/coronavirus>
- [9] Knoll MD, Wonodi C. Oxford-AstraZeneca COVID-19 vaccine efficacy. *Lancet.* 2021;397(10269):72-4.
- [10] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med.* 2020;383(27):2603-15.
- [11] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med.* 2021;384(5):403-16.

- [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):336-41.
- [13] Goshen-Lago T, Waldhorn I, Holland R, Szwarcwort-Cohen M, Reiner-Benaim A, Shachor-Meyouhas Y, et al. Serologic Status and Toxic Effects of the SARS-CoV-2 BNT162b2 Vaccine in Patients Undergoing Treatment for Cancer. *JAMA Oncol.* 2021.
- [14] Ligumsky H, Safadi E, Etan T, Vaknin N, Waller M, Croll A, et al. Immunogenicity and Safety of the BNT162b2 mRNA COVID-19 Vaccine Among Actively Treated Cancer Patients. *J Natl Cancer Inst.* 2021.
- [15] Waldhorn I, Holland R, Goshen-Lago T, Shirman Y, Szwarcwort-Cohen M, Reiner-Benaim A, et al. Six Month Efficacy and Toxicity Profile of BNT162b2 Vaccine in Cancer Patients with Solid Tumors. *Cancer Discov.* 2021.
- [16] Herzog Tzarfati K, Gutwein O, Apel A, Rahimi-Levene N, Sadovnik M, Harel L, et al. BNT162b2 COVID-19 vaccine is significantly less effective in patients with hematologic malignancies. *Am J Hematol.* 2021.
- [17] Perry C, Luttwak E, Balaban R, Shefer G, Morales MM, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with B-cell non-Hodgkin lymphoma. *Blood Adv.* 2021;5(16):3053-61.
- [18] Fox TA, Kirkwood AA, Enfield L, O'Reilly M, Arulogun S, D'Sa S, 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):706-9.
- [19] Furer V, Eviatar T, Zisman D, Peleg H, Paran D, Levartovsky 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.

- [20] Novak F, Nilsson AC, Nielsen C, Holm DK, Østergaard K, Bystrup A, 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.
- [21] Lacson E, Argyropoulos C, Manley H, Aweh G, Chin A, Salman L, et al. Immunogenicity of SARS-CoV-2 Vaccine in Dialysis. *J Am Soc Nephrol*. 2021.
- [22] Murt A, Altiparmak MR, Yadigar S, Yalin SF, Ozbey D, Yildiz Z, et al. Antibody responses to the SARS-CoV-2 vaccines in hemodialysis patients: Is inactivated vaccine effective? *Ther Apher Dial*. 2021.
- [23] Grupper A, Katchman E, Ben-Yehoyada M, Rabinowich L, Schwartz D, Schwartz IF, et al. Kidney transplant recipients vaccinated before transplantation maintain superior humoral response to SARS-CoV-2 vaccine. *Clin Transplant*. 2021:e14478.
- [24] Haskin O, Ashkenazi-Hoffnung L, Ziv N, Borovitz Y, Dagan A, Levi S, et al. Serological Response to the BNT162b2 COVID-19 mRNA Vaccine in Adolescent and Young Adult Kidney Transplant Recipients. *Transplantation*. 2021.
- [25] Itzhaki Ben Zadok O, Shaul AA, Ben-Avraham B, Yaari V, Ben Zvi H, Shostak Y, et al. Immunogenicity of the BNT162b2 mRNA vaccine in heart transplant recipients - a prospective cohort study. *Eur J Heart Fail*. 2021.
- [26] Narasimhan M, Mahimainathan L, Clark AE, Usmani A, Cao J, Araj E, et al. Serological Response in Lung Transplant Recipients after Two Doses of SARS-CoV-2 mRNA Vaccines. *Vaccines (Basel)*. 2021;9(7).
- [27] Rozen-Zvi B, Yahav D, Agur T, Zingerman B, Ben-Zvi H, Atamna A, 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-e4.
- [28] Edelman-Klapper H, Zittan E, Bar-Gil Shitrit A, Rabinowitz KM, Goren I, Avni-Biron I, et al. Lower Serologic Response to COVID-19 mRNA Vaccine in Patients With

Inflammatory Bowel Diseases Treated with Anti-TNF α . *Gastroenterology*. 2021.

[29] 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):5560-7.

[30] Blain H, Tuaillon E, Gamon L, Pisoni A, Miot S, Rolland Y, et al. Antibody response after one and two jabs of the BNT162b2 vaccine in nursing home residents: The CONsort-19 study. *Allergy*. 2021.

[31] 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.

[32] Eyre DW, Lumley SF, Wei J, Cox S, James T, Justice A, 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-.e14.

[33] Salvagno GL, Henry BM, di Piazza G, Pighi L, De Nitto S, Bragantini D, 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).

[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):1775-6.

[36] Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood*. 2021;137(23):3165-73.

- [37] La Rosee F, Bremer HC, Gehrke I, Kehr A, Hochhaus A, Birndt S, et al. The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. *Leukemia*. 2020;34(7):1805-15.
- [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):3723-32.
- [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):1016-26.
- [40] Westra J, van Assen S, Wilting KR, Land J, Horst G, de Haan A, et al. Rituximab impairs immunoglobulin (Ig)M and IgG (subclass) responses after influenza vaccination in rheumatoid arthritis patients. *Clin Exp Immunol*. 2014;178(1):40-7.
- [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):1357-9.
- [42] Wong SY, Dixon R, Martinez Pazos V, Gnjjatic S, Colombel JF, Cadwell K, et al. Serologic Response to Messenger RNA Coronavirus Disease 2019 Vaccines in Inflammatory Bowel Disease Patients Receiving Biologic Therapies. *Gastroenterology*. 2021;161(2):715-8 e4.
- [43] Sharif MR, Chitsazian Z, Moosavian M, Raygan F, Nikoueinejad H, Sharif AR, et al. Immune disorders in hemodialysis patients. *Iran J Kidney Dis*. 2015;9(2):84-96.
- [44] Kato S, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, et al. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol*. 2008;3(5):1526-

33.

[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, Hoschler K, Ferreira V, Ashton P, 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):1698-704.

[47] Pfizer. Pfizer and biontech initiate a study as part of broad development plan to evaluate Covid-19 booster and new vaccine variants. 2021 [Internet]. [cited 2021 Dec 17]. Available from: <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-initiate-study-part-broad-development>.

[48] Ledford H. Could mixing COVID vaccines boost immune response? *Nature*. 2021;590(7846):375-6.

[49] Galia R. BNT162b2 mRNA COVID-19 vaccination in immunocompromised patients: A prospective cohort study. *EClinicalMedicine*. 2021;41:101158

Tables and Figures

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

Author, year	Subjects (Population)	Comparison	Criteria for seropositivity	Vaccine	Dose interval
G. L. Salvagano, 2021	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
H. Blain, 2021	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
B. Rozen-Zvi, 2021	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
K. Herzog Tzarfati, 2021	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
C. Perry, 2021	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
F. Claro, 2021	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
H. Ligumsky, 2021	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
V. Furer, 2021	Patients with autoimmune inflammatory rheumatic diseases	General population, consisting mainly of healthcare personnel	Seropositivity was defined as IgG ≥ 15 binding antibody units (BAU)/mL	Pfizer	21 days between the first and the second dose
E. Lacson, 2021	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
O. Itzhaki, 2021	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
A. Bayram, 2021	Healthcare workers (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
D. W. Eyre, 2021	Healthcare workers 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

Figure 1. PRISMA flow

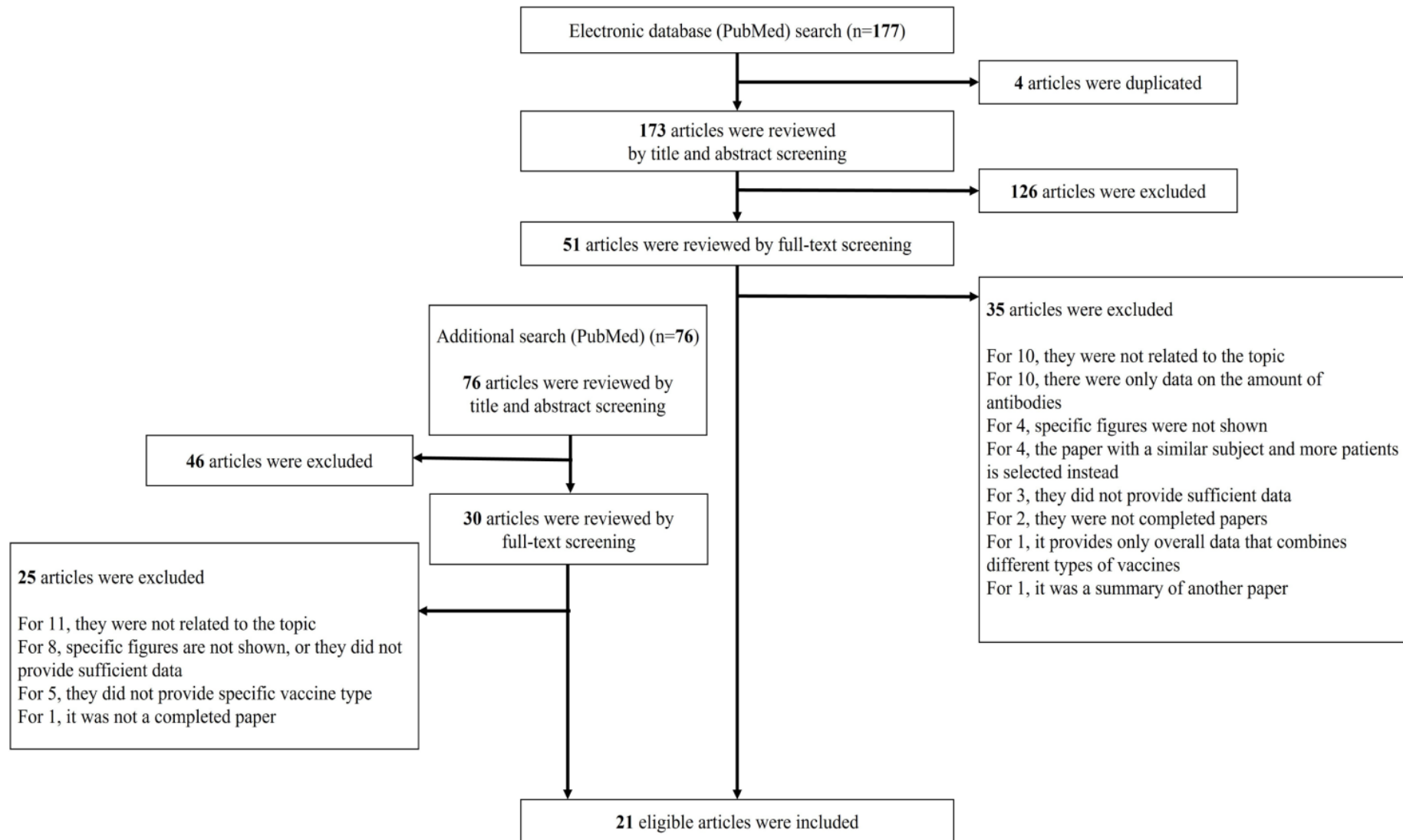


Figure 2. Seropositivity of COVID-19 in solid tumor patients after the first vaccination

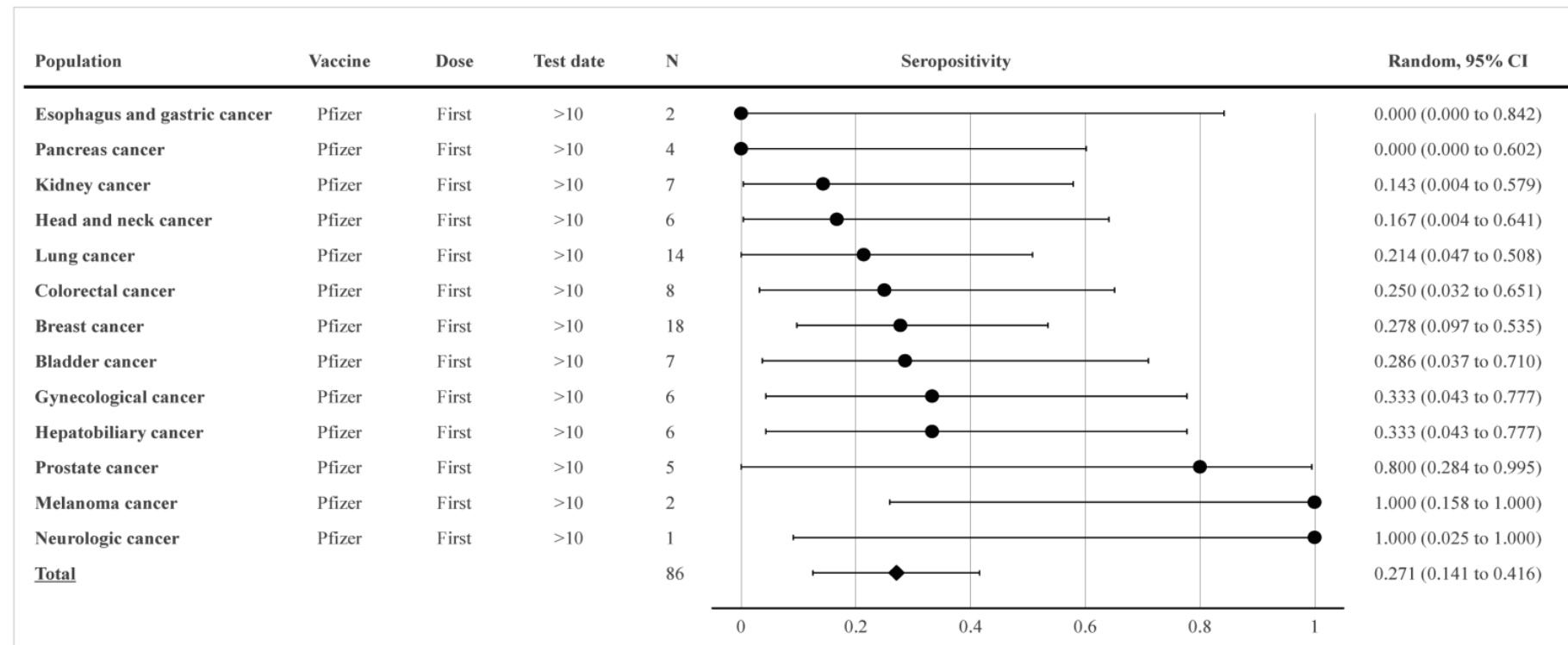


Figure 3. Seropositivity of COVID-19 in solid tumor patients after the second vaccination

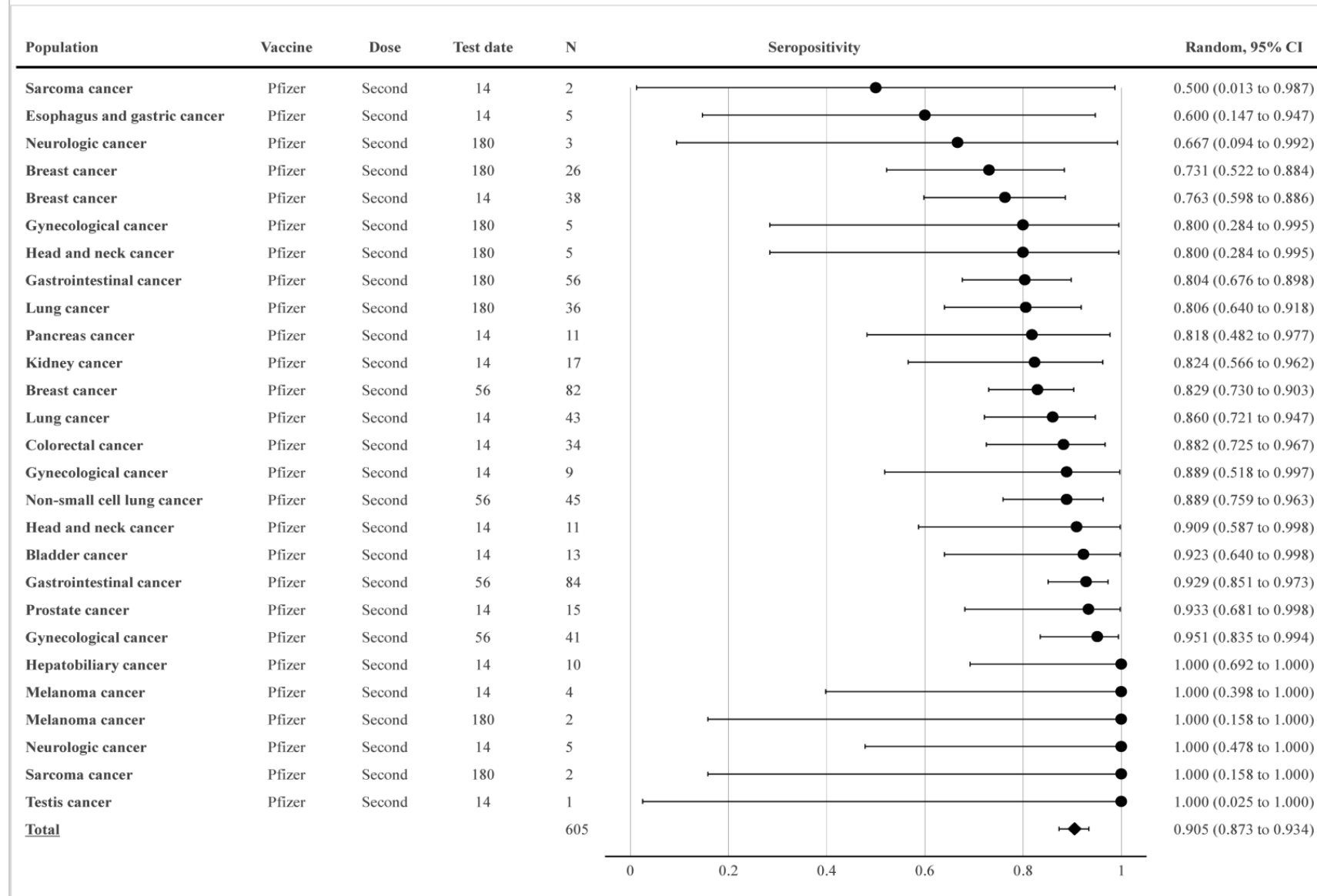


Figure 4. Seropositivity of COVID-19 in hematologic malignancy patients (NHL, Non-Hodgkin lymphoma; CLL, Chronic lymphocytic leukemia; MPN, myeloproliferative neoplasms; CML, chronic myeloid leukemia; MDS, myelodysplastic syndromes)

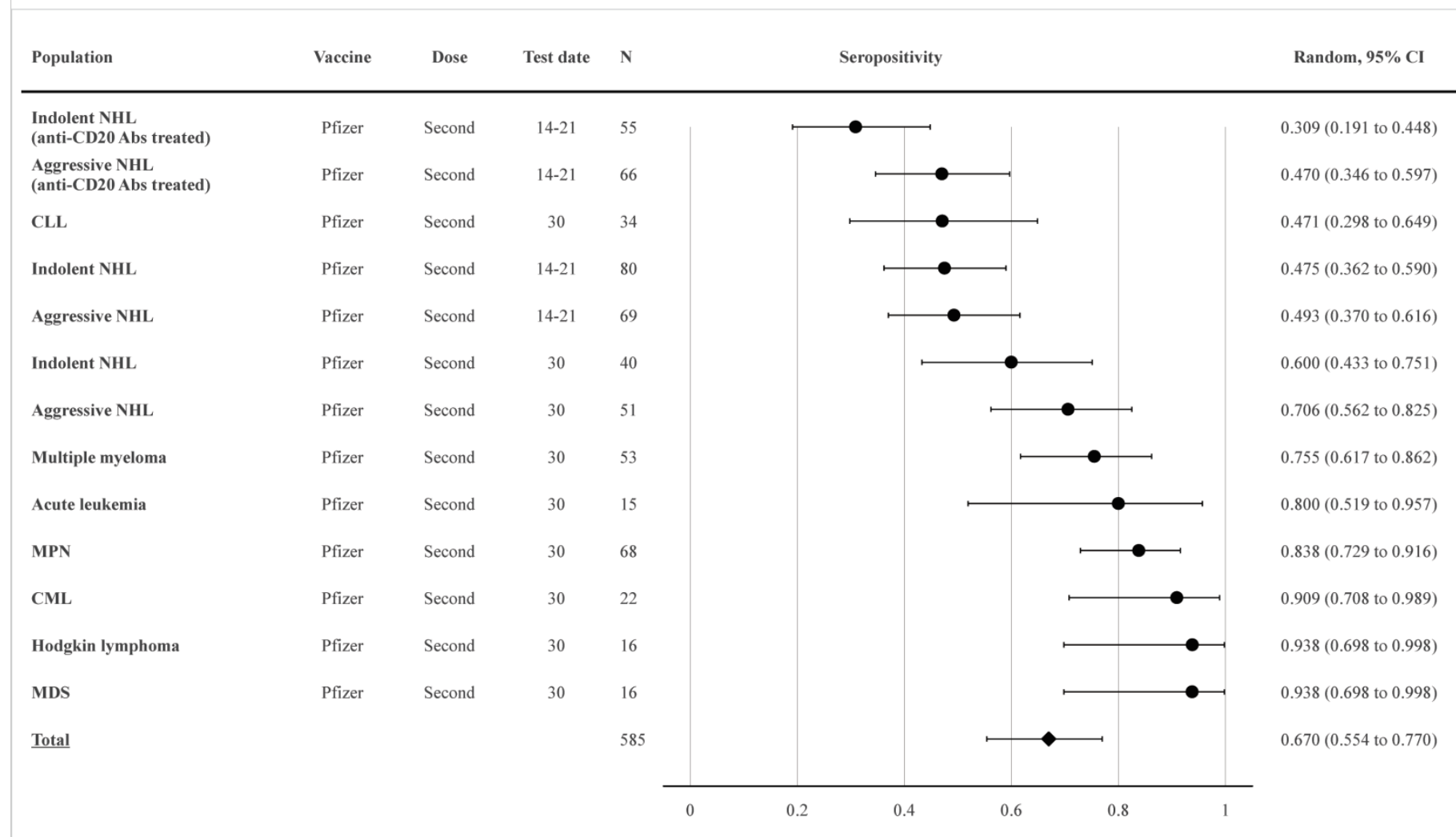


Figure 5. Seropositivity of COVID-19 in autoimmune disease patients (MS, multiple sclerosis; AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; IIM, idiopathic inflammatory myositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; LVV, large vessel vasculitis; PsA, psoriatic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

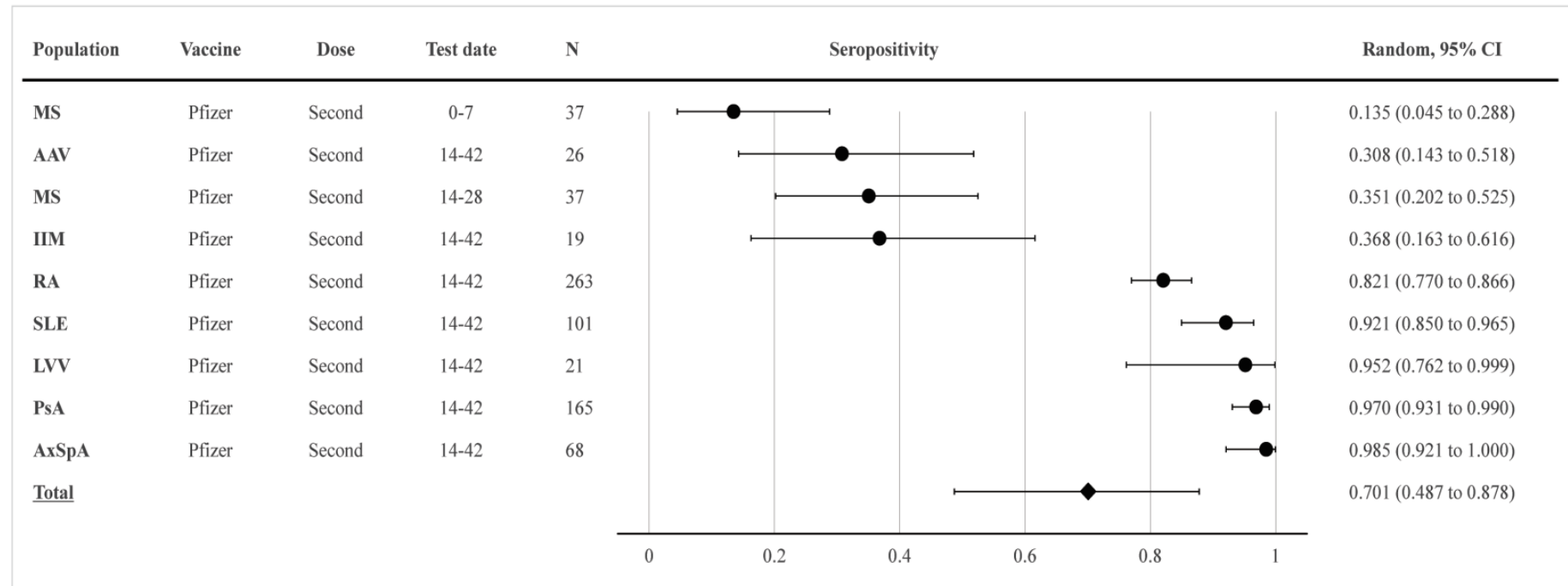


Figure 6. Seropositivity of COVID-19 in patients who received hemodialysis

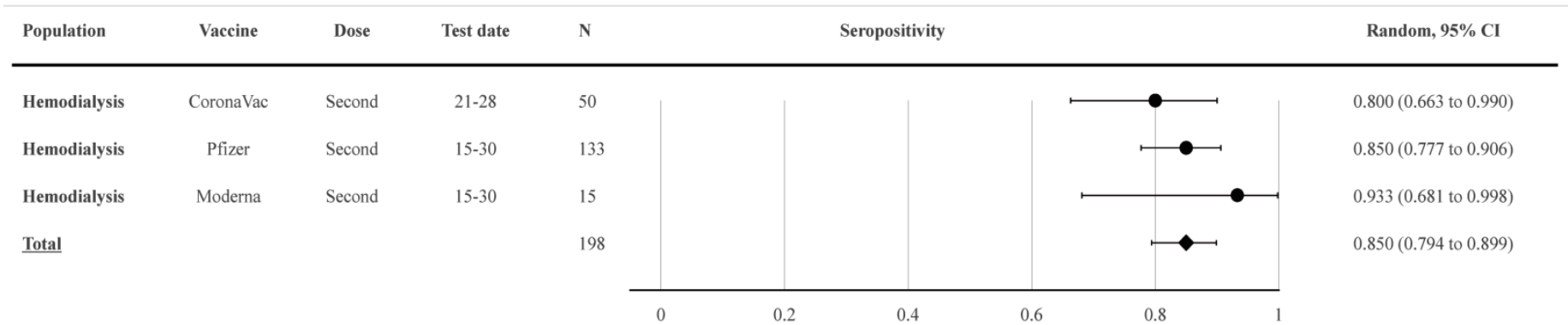
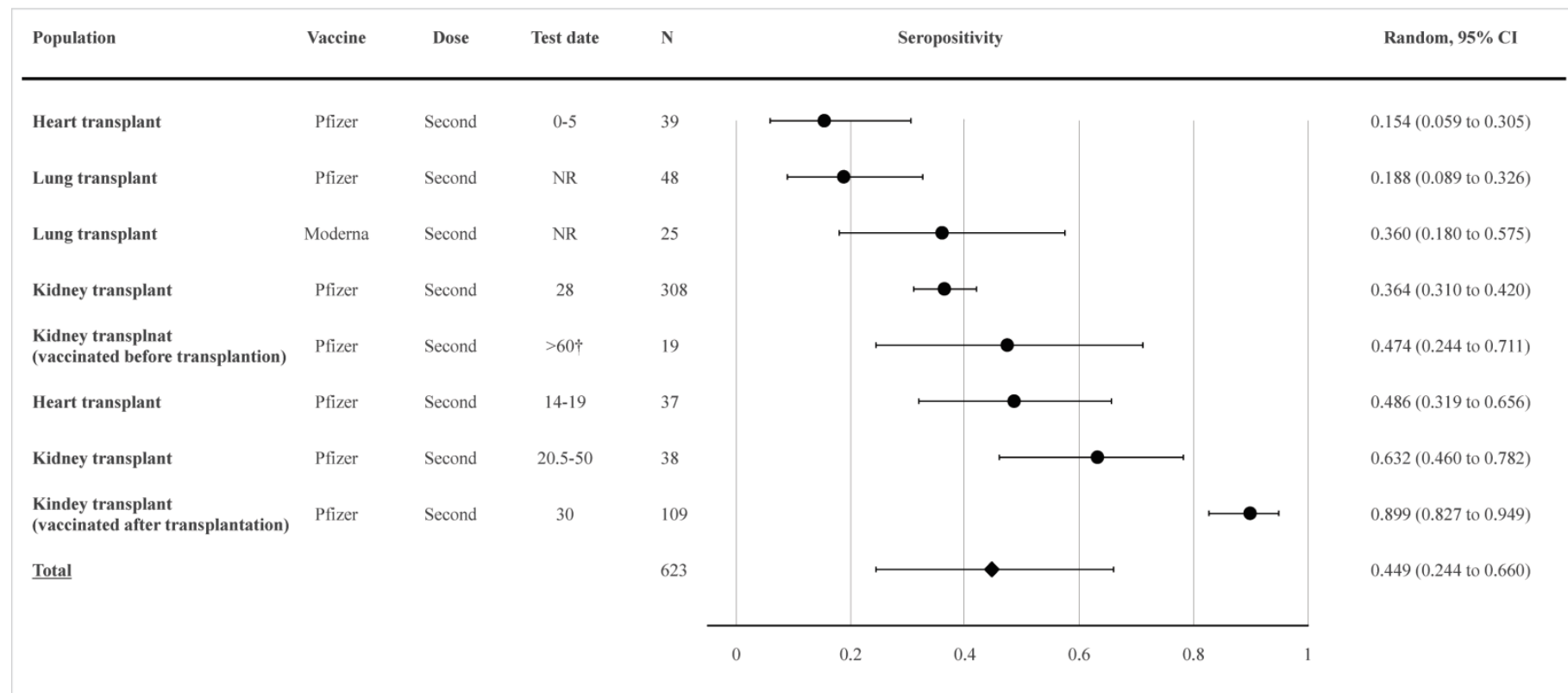


Figure 7. Seropositivity of COVID-19 in patients who received transplantation

† Vaccination was performed at least 30 days before transplantation, and seropositivity was measured at least 30 days after transplantation.



Supplement 1. PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention	

Section and Topic	Item #	Checklist item	Location where item is reported
methods		characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured Supplements or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	

Section and Topic	Item #	Checklist item	Location where item is reported
biases			
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Supplement 2. The characteristics of studies included in the systematic review.

Author, year	Subjects (Population)	Comparison	Criteria for seropositivity	Vaccine	Dose interval
G. L. Salvagano, 2021	1) The initial study population consisted of 1003 employees of the Pederzoli Hospital of Peschiera del Garda, who voluntarily agreed to undergo vaccination with Pfizer COVID 19 mRNA Vaccine Comirnaty. The final study population consisted of 925 subjects (mean age, 44 ± 13 years; 457 (49.4%) women) who completed the two-dose vaccine cycle and had serum samples drawn at all the three time points. 2) Two hundred and six (22.3%) subjects had measurable total anti-SARS-CoV-2 RBD antibodies level (i.e., ≥ 0.8 U/mL) before vaccination, and were hence classified as baseline seropositive.	NA	Humoral response was assessed with Roche Elecsys Anti-SARS-CoV-2 S total antibodies, on Roche Cobas 6000 (Roche Diagnostics). Quantitative assessment of total anti-SARS-CoV-2 RBD antibodies in human serum and plasma specimens was conducted. Test results < 0.8 U/mL are classified as non-reactive, while those ≥ 0.8 U/mL are classified as reactive.	Pfizer	Exactly 21 days between the first and the second dose
H. Blain, 2021	Nursing home residents without prior COVID-19 (with repeated negative RT-PCR and negative N-protein IgG measured 3 weeks after the jab) vs. residents with prior COVID-19 (confirmed either by a positive RT-PCR or by detectable N-protein IgG)	Used a control group of younger healthcare workers to assess the differences with NH residents who had never had a positive RT-PCR and who had undetectable N-protein IgG levels after vaccination	S-RDB-protein IgG against the SARS-CoV-2 receptor-binding domain (RBD) of the S1 subunit was detected using the SARS-CoV-2 IgG II Quant assay (Abbott Diagnostics). Results were expressed as arbitrary units per ml (AU/ml; positive threshold: 50 AU/ml; upper limit: 40,000 AU/ml; a level $\geq 1,050$ AU/ml was considered as a significant response ²¹ and a level ≥ 4160 AU/ml indicated a high neutralising effect according to the manufacturer). N-protein IgG was detected using the SARS-CoV-2 IgG assay (Abbott Diagnostics). Results were expressed as a signal to cutoff ratio (S/CO; Abbott Alinity; positive threshold: 0.8 S/CO).	Pfizer	Three weeks between the first and the second dose

B. Rozen-Zvi, 2021	Adult kidney transplant recipients who were vaccinated with two doses of BNT162b2 vaccine, 21 days apart, and followed at the Rabin Medical Center (RMC) kidney transplantation follow-up clinic between 8th and 28th February 2021	NA	A test was considered positive if IgG was ≥ 50 AU/mL	Pfizer	Not clearly defined
K. Herzog Tzarfati, 2021	Patients with hematologic malignancies treated at Shamir Medical Center in Israel, having received two doses of vaccination - Participants with solid cancer or immune diseases were not excluded. - Patients with prior COVID-19 infection were excluded from the study	An age-matched group of subjects with no hematologic malignancy	Serologic testing for SARS-CoV2 IgG was performed using the Liaison SARS-CoV-2 S1/S2 IgG test (DiaSorin, Saluggia, Italy), a chemiluminescence immunoassay for the quantitative determination of anti-S1- and anti-S2-specific IgG antibodies to SARS-CoV-2 in human serum or plasma samples. Samples were considered positive for antibody titers >12 AU/mL.	Pfizer	Not clearly defined
C. Perry, 2021	patients aged ≥ 18 years diagnosed with B-NHL, including diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma and follicular lymphoma and marginal zone lymphoma (1) Treatment-naïve patients (patients with indolent lymphoma under 'watch-and-wait' management) (2) Actively treated patients who were receiving treatment with anti-CD-20 Ab (3) Patients who had completed chemoimmunotherapy / immune monotherapy / maintenance > 6 months before vaccination	Age compatible, healthy volunteers, aged >18 years, who had received 2 consecutive COVID-19 vaccine doses	Serum samples were analyzed by using the Elecsys Anti-SARS-CoV-2S assay, performed on the Cobas e601 (Roche Diagnostics) enzyme-linked immunosorbent assay reader for quantitative detection of antibodies, predominantly IgG, aimed at the SARS-CoV-2 S protein receptor binding domain. A concentration of <0.80 U/mL considered to be a negative result and >0.80 U/mL considered to be positive	Pfizer	21 days between the first and the second dose

F. Claro, 2021	Individuals who presented for vaccination in a public hospital in Caracas, Venezuela - Only vaccine recipients who provided a baseline (pre-vaccine) sample, a sample at the moment of the application of dose 2 and a sample 6 weeks after dose 2 were included in this study	NA	A positive antibody response or seroconversion, was defined as a titer with an S/P (sample to positive) ratio of at least 40%. S/P ratios of < 40% were considered negative	Sputanik V	Three weeks between the first and the second dose
H. Ligumsky, 2021	Patients with solid tumors, actively-treated at the day-care center of the oncology division. Active treatment was defined as any IV anti-cancer medication, administered during a period starting at two weeks before the 1st vaccine dose, and ending two weeks after the 2nd vaccine dose	Fully vaccinated healthy adults with no personal history of cancer or active immune suppressive medications, who were either health care workers at the oncology division of TASMC offered to be tested for anti-SARS-CoV-2S IgG antibodies or individuals opted to test immunogenicity at the Integrated Cancer Prevention Center at TASMC	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

V. Furer, 2021	<ul style="list-style-type: none"> - Adult patients (aged ≥ 18 years) - Patients with autoimmune inflammatory rheumatic diseases (rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, systemic lupus erythematosus, systemic vasculitis, antineutrophil cytoplasmic antibody-associated vasculitis, central nervous system vasculitis, idiopathic inflammatory myositis) - Exclusion : pregnancy, history of past vaccination allergy, and previous COVID-19 infection 	<p>The control group included a sample of the general population, consisting mainly of healthcare personnel</p> <ul style="list-style-type: none"> - Exclusion : history of AIIRD and immunosuppressive treatment, pregnancy, history of past vaccination allergy, and previous COVID-19 infection 	Seropositivity was defined as IgG ≥ 15 binding antibody units (BAU)/mL	Pfizer	3 weeks apart
E. Lacson, 2021	Patients receiving maintenance dialysis	NA	<p>Response was based on levels of immunoglobulin-G against the receptor binding domain of the S1 subunit of SARS-CoV-2</p> <p>spike-antigen (seropositive ≥ 2 U/L) using an FDA-approved semi-quantitative chemiluminescent assay (ADVIA Centaur® XP/XPT COV2G)</p>	Pfizer / Moderna	Not clearly defined
O. Itzhaki, 2021	<p>Heart transplant recipients who have received a two-dose SARS-CoV-2 mRNA vaccine</p> <ul style="list-style-type: none"> - Major exclusion criteria were HTx within the previous 30 days, patient's refusal to get a full two-dose vaccine schedule or to participate in the study and a known prior SARS-CoV-2 infection 	NA	S-IgG value (geometric mean titres) of 50 AU/mL and greater was interpreted as seropositive.	Pfizer	21 days between the first and the second dose

A. Bayram, 2021	Healthcare workers (HCW) of both genders, 18 years of age or older, who agreed to participate in the prospective study - HCWs who had COVID-19 in less than 90 days, and who were pregnant were not vaccinated and were not included in the study	NA	Detection and quantitation of SARS-CoV-2 antispikes antibodies were performed by the chemiluminescent microparticle immunoassay (SARS-CoV-2 IgG II Quant; Abbott). Results 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
D. W. Eyre, 2021	Healthcare workers from Oxford University Hospitals	NA	Quantitative post-vaccination anti-spike antibody responses were measured using the Abbott SARS-CoV-2 IgG II Quant assay (detection threshold: 50 AU/mL).	Pfizer / AstraZeneca	Median (IQR) dosing interval : 24 (21-28) days
T. Goshen-Lago, 2021	Patients with solid tumors receiving intravenous treatment administered at the infusional ambulatory unit of the oncology center or inpatient service within the Rambam Health Care Campus (RHCC), Haifa, Israel - Hematologic malignant neoplasms are treated in a separated institution and hence were not included in the study population	Age-matched healthy health care workers who underwent serologic testing before the second vaccination dose	Serum samples were analyzed at all measurement times for the detection of anti-SARS-CoV2 antibodies. For IgG expression, we used SARS-CoV-2 anti-spike (S) S1/S2 IgG assay (Liaison; DiaSorin) to detect S1/S2 IgG antibodies. Cutoff values for positive serologic findings were 15 arbitrary units per milliliter	Pfizer	21 days between the first and the second dose

M. Narasimhan, 2021	Lung-transplant recipients	People who are non-transplanted and non-exposed to COVID-19	Antibody responses were semi-quantitatively assessed using serum samples analyzed on the Alinity i platform (Abbott Laboratories, Abbott Park, IL, USA) using the FDA-approved SARS-CoV-2 anti-nucleocapsid protein IgG assay (IgGNC), the SARS-CoV-2 anti-spike protein IgM assay (IgMSP), or the SARS-CoV-2 anti-spike protein IgG II assay (IgGSP), as previously described. Two Index values of ≥ 1.4 (IgGNC), ≥ 1.0 (IgMSP), and ≥ 50 AU/mL (IgGSP) were interpreted as positive	Pfizer / Moderna	Not clearly defined
I. Waldhorn, 2021	Patients with solid tumors receiving intravenous treatment administered at the infusional ambulatory unit of the oncology center within the Rambam Health Care Campus, Haifa, Israel. (follow-up report of 'T. Goshen-Lago, 2021')	Healthy healthcare workers who were tested for serology at the same time points	For IgG expression, we used SARS-CoV-2 anti-spike (S) S1/S2 IgG assay (Liaison; DiaSorin) to detect S1/S2 IgG antibodies. Cutoff values for positive serologic findings were 15 arbitrary units per milliliter	Pfizer	21 days between the first and the second dose
O. Haskin, 2021	Kidney transplant recipients were recruited at Schneider Children's Medical Center, a tertiary-care pediatric hospital that houses a nephrology institute. The inclusion criterion for the study group was completion of the 2-dose regimen of the Pfizer-BioNTech COVID-19 vaccine according to the manufacturer's recommended dose and time schedule.	The inclusion criterion for the control group was a previous COVID-19 infection that was confirmed by nasopharyngeal swab real-time quantitative reverse transcription–polymerase chain reaction.	The SARS-CoV-2 IgG II Quant assay (Abbott, Abbott Park, IL) was used for quantitative measurement of IgG antibodies against the spike protein of SARS-CoV-2. A test was considered positive if IgG was >50 antibody unit (AU)/mL.	Pfizer	Three weeks between the first and the second dose

H. Edelman-Klapper, 2021	Patients with inflammatory bowel diseases (IBD) aged ≥ 18 years. IBD diagnosis was defined by accepted criteria. Patients were stratified at baseline into those treated with anti-TNF α , or those not treated with anti-TNF α but other IBD treatments. Patients with past COVID-19 infection proved by SARS-CoV-2 polymerase chain reaction test and pregnant women were excluded.	Healthcare professionals and their relatives without known gastrointestinal diseases	SARS-CoV-2 IgG II quantitative testing was performed using the Abbott architect i2000sr platform in accordance with manufacturer's instructions. Values ≥ 50 activity units (AU)/mL are considered positive.	Pfizer	21-28 days between the first and the second dose
T. A. Fox, 2021	Patients on treatment or treated within the last 24 months for a B-cell malignancy and receiving either the BNT162b2 (Pfizer-BioNTech) or ChAdOx1 nCov-19 (Oxford-AstraZeneca) vaccines were recruited.	NA	Serum samples were screened for anti-severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) antibodies using quantitative double-antigen sandwich immunoassays for both the nucleocapsid (N) antigen and the spike (S) protein receptor binding domain (RBD) (both Roche, Basel, Switzerland) Values ≥ 0.8 U/mL are considered as reactive.	Pfizer / AstraZeneca	Not clearly defined
A. Grupper, 2021	(1) Pre-transplant vaccination group (Pre-Tx Vac group), composed of 19 consecutive adult kidney transplant recipients, who received full vaccination (two doses 21 days apart) at least 1 month prior to kidney transplantation, (2) Post-transplant vaccination group (Post-Tx Vac group), composed of 116 kidney recipients who were vaccinated after transplantation. The subjects were included if they had negative history of COVID-19 and were never found to have positive polymerase chain reaction (PCR) to SARS-CoV-2.	39 vaccinated healthcare workers	LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescent assay (DiaSorin S.p.A., Saluggia, Italy) was used according to the manufacture instructions, to detect IgG antibodies directed against a recombinant S protein (S1/S2). Samples displaying <12.0 AU/ml were considered negative, those ranging between 12.0 and 15.0 AU/ml are equivocal, and those > 15 AU/ml were considered as positive.	Pfizer	21 days between the first and the second dose

A. Murt, 2021	All of the patients were maintenance hemodialysis patients over 18 years old. Patients who had previous or active infection with SARS-CoV-2, who have active malignancy or who received any kind of immunosuppressive treatments in the previous 12 months were excluded from the study.	Healthy healthcare workers who were vaccinated with CoronaVac in a similar protocol with the study subjects.	The analysis was carried out by Abbott SARS-CoV-2 IgG II Quant (Chicago, USA) via Abbott ARCHITECT i1000 (Chicago, USA) equipment that measures IgG antibodies toward spike receptor-binding domain (RBD) of SARS-CoV-2. 50 AU/ml was accepted as the cut-off value for positivity.	Pfizer / CoronaVac	28 days between the first and the second dose
F. Novak, 2021	Adult patients (age ≥ 18 years) with multiple sclerosis (2010 McDonald Criteria) and currently treated with anti-CD20 therapy (ocrelizumab). The patients did not receive any other immunosuppressive therapy during this study and were negative to IgG Abs against SARS-CoV-2 prior to inclusion.	NA	IgG antibodies against SARS-CoV-2 spike receptor-binding domain (RBD) were determined in plasma samples, using the SARS-CoV-2 IgG II Quant assay (Abbott Laboratories). Antibody-Levels above 254 BAU/ml was defined as sufficient levels. Values between <254 BAU/ml and >54 BAU/ml were considered intermediate and below <54 BAU/ml as low.	Pfizer	Not clearly defined

Supplement 3. SARS-CoV-2 seropositivity among solid tumor patients

[illegible]

Gynecological cancer	T. Goshen-Lago, 2021	6	Israel	NR	NR	Pfizer	>10	First	33.33
	T. Goshen-Lago, 2021	9	Israel	NR	NR	Pfizer	14	Second	88.89
	H. Ligumsky, 2021	41	Israel	NR	NR	Pfizer	56	Second	95.12
	I. Waldhorn, 2021	5	Israel	NR	NR	Pfizer	180	Second	80
Head and neck cancer	T. Goshen-Lago, 2021	6	Israel	NR	NR	Pfizer	>10	First	16.67
	T. Goshen-Lago, 2021	11	Israel	NR	NR	Pfizer	14	Second	90.91
	I. Waldhorn, 2021	5	Israel	NR	NR	Pfizer	180	Second	80
Hepatobiliary cancer	T. Goshen-Lago, 2021	6	Israel	NR	NR	Pfizer	>10	First	33.33
	T. Goshen-Lago, 2021	10	Israel	NR	NR	Pfizer	14	Second	100
Kidney cancer	T. Goshen-Lago, 2021	7	Israel	NR	NR	Pfizer	>10	First	14.29
	T. Goshen-Lago, 2021	17	Israel	NR	NR	Pfizer	14	Second	82.35
Lung cancer	T. Goshen-Lago, 2021	14	Israel	NR	NR	Pfizer	>10	First	21.43
	T. Goshen-Lago, 2021	43	Israel	NR	NR	Pfizer	14	Second	86.05
	I. Waldhorn, 2021	36	Israel	NR	NR	Pfizer	180	Second	80.56
Non-small cell lung cancer	H. Ligumsky, 2021	45	Israel	NR	NR	Pfizer	56	Second	88.89

[illegible]

[illegible]

Supplement 4. SARS-CoV-2 seropositivity among hematological malignancy patients (NHL, Non-Hodgkin lymphoma; B-NHL, B-cell Non-Hodgkin lymphoma)

Population	Author, year	n	Country	Age	Sex (female %)	Vaccine	Test Date (day)	Dose	Seropositivity (%)
Aggressive NHL	C.Perry, 2021	69	Israel	NR	NR	Pfizer	14-21	Second	49.3
	K. Herzog Tzarfati, 2021	51	Israel	NR	NR	Pfizer	30	Second	71
anti-CD20 Abs treated	C.Perry, 2021	66	Israel	NR	NR	Pfizer	14-21	Second	47
Indolent NHL	C.Perry, 2021	80	Israel	NR	NR	Pfizer	14-21	Second	48.1
	K. Herzog Tzarfati, 2021	40	Israel	NR	NR	Pfizer	30	Second	60
anti-CD20 Abs treated	C.Perry, 2021	55	Israel	NR	NR	Pfizer	14-21	Second	30.9
Hodgkin lymphoma	K. Herzog Tzarfati, 2021	16	Israel	NR	NR	Pfizer	30	Second	94
Multiple myeloma	K. Herzog Tzarfati, 2021	53	Israel	NR	NR	Pfizer	30	Second	76
CLL	K. Herzog Tzarfati, 2021	34	Israel	NR	NR	Pfizer	30	Second	47
Acute leukemia	K. Herzog Tzarfati, 2021	15	Israel	NR	NR	Pfizer	30	Second	80
MDS	K. Herzog Tzarfati, 2021	16	Israel	NR	NR	Pfizer	30	Second	94

MPN	K. Herzog Tzarfati, 2021	68	Israel	NR	NR	Pfizer	30	Second	84
CML	K. Herzog Tzarfati, 2021	22	Israel	NR	NR	Pfizer	30	Second	91
Total	T. A. Fox, 2021	41	UK	NR	NR	Pfizer	30	First	36.58
	T. A. Fox, 2021	14	UK	NR	NR	Astrazeneca	30	First	35.71
	K. Herzog Tzarfati, 2021	315	Israel	Median (IQR) 71 (61-78)	NR	Pfizer	30	Second	74.60

Supplement 5. SARS-CoV-2 seropositivity among autoimmune disease patients (RA, rheumatoid arthritis; PsA, psoriatic arthritis; AxSpA, axial spondylarthritis; SLE, systemic lupus erythematosus; IIM, idiopathic inflammatory myositis; LVV, large vessel vasculitis; AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; MS, multiple sclerosis; Abs, antibodies)

Population	Author, year	n	Country	Age	Sex (female %)	Vaccine	Test Date (day)	Dose	Seropositivity (%)
RA	V. Furer, 2021	263	Israel	Median (Range) 64 (20-88)	81.75	Pfizer	14-42	Second	82.1
PsA	V. Furer, 2021	165	Israel	Median (Range) 55 (20-86)	47.56	Pfizer	14-42	Second	96.9
AxSpA	V. Furer, 2021	68	Israel	Median (Range) 49.5 (21-83)	52.94	Pfizer	14-42	Second	98.5
SLE	V. Furer, 2021	101	Israel	Median (Range) 46 (22-80)	88.12	Pfizer	14-42	Second	92.1
IIM	V. Furer, 2021	19	Israel	Median (Range) 64 (34-76)	73.68	Pfizer	14-42	Second	36.8
LVV	V. Furer, 2021	21	Israel	Median (Range) 70 (26-85)	80.95	Pfizer	14-42	Second	95.2
AAV	V. Furer, 2021	26	Israel	Median (Range) 60.5 (26-85)	53.85	Pfizer	14-42	Second	30.8
MS anti-CD20 Abs treated	F. Novak, 2021	37	Denmark	Median (Range) 47 (24-62)	78.4	Pfizer	0-7	Second	13.51
	F. Novak, 2021	37	Denmark	Median (Range) 47 (24-62)	78.4	Pfizer	14-28	Second	35.14
Other	V. Furer, 2021	23	Israel	Median (Range) 56 (19-77)	52.17	Pfizer	14-42	Second	86.6

Supplement 6. SARS-CoV-2 seropositivity among dialysis or transplant patients

† Vaccination was performed at least 30 days before transplantation, and seropositivity was measured at least 30 days after transplantation.)

Population	Author, year	n	Country	Age	Sex (female %)	Vaccine	Test Date (day)	Dose	Seropositivity (%)
Hemodialysis	E. Lacson, 2021	133	US	Mean (SD) 71.2 (10.6)	45.8	Pfizer	15-30	Second	84.96
	E. Lacson, 2021	15	US	Mean (SD) 67.9 (12.2)	61.1	Moderna	15-30	Second	93.33
	A. Murt, 2021	50	Turkey	Mean (SD) 61.3 (15.1)	42	CoronaVac	21-28	Second	80
Heart transplant	O. Itzhaki, 2021	39	Israel	Median (IQR) 61 (64-69)	17	Pfizer	0-5	Second	15
	O. Itzhaki, 2021	37	Israel	Median (IQR) 61 (64-69)	17	Pfizer	14-19	Second	49
Kidney transplant	B. Rozen-Zvi, 2021	308	Israel	Mean (SD) 57.51 (13.84)	36	Pfizer	28	Second	36.36
	O. Haskin, 2021	38	Israel	Mean (SD) 16.8 (2.8)	34	Pfizer	20.5-50	Second	63.2
vaccinated before transplantation	A. Grupper, 2021	19	Turkey	Mean (SD) 54 (3.6)	42	Pfizer	>60†	Second	44.95
vaccinated after transplantation	A. Grupper, 2021	109	Turkey	Mean (SD) 57 (12.9)	37	Pfizer	30	Second	89.47
Lung transplant	M. Narasimhan, 2021	48	US	NR	17.5 (median)	Pfizer	NR	Second	18.75
	M. Narasimhan, 2021	25	US	NR	19 (median)	Moderna	NR	Second	36

Supplement 7. SARS-CoV-2 seropositivity among inflammatory bowel disease patients who received anti-TNF- α treatment

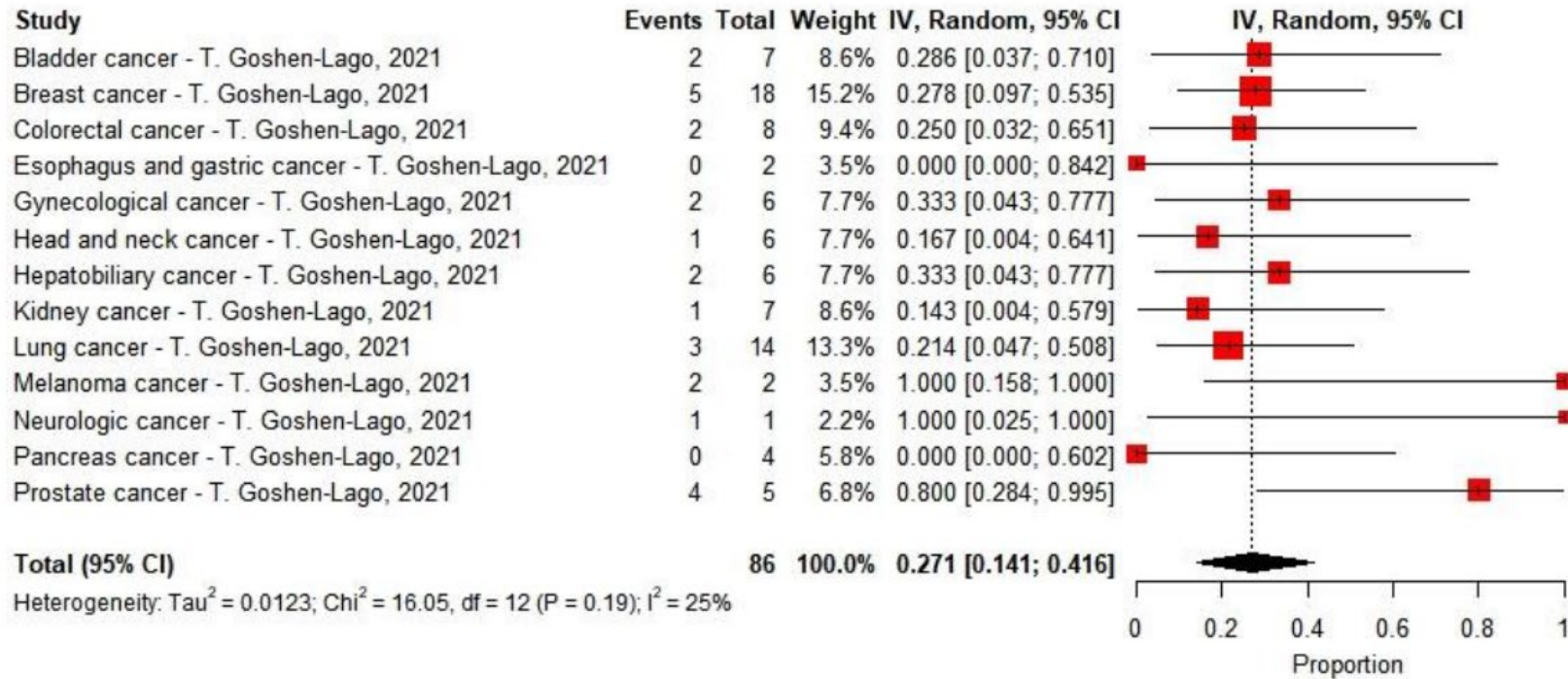
Population	Author, year	n	Country	Age	Sex (female %)	Vaccine	Test Date (day)	Dose	Seropositivity (%)
Inflammatory Bowel Disease									
anti TNF- α treated	H. Edelman-Klapper, 2021	67	Israel	Mean (SD) 37.8 (14.3)	35.8	Pfizer	14-21	First	91.04
anti TNF- α not treated	H. Edelman-Klapper, 2021	118	Israel	Mean (SD) 38.2 (14.3)	41.5	Pfizer	14-21	First	93.22
anti TNF- α treated	H. Edelman-Klapper, 2021	67	Israel	Mean (SD) 37.8 (14.3)	35.8	Pfizer	21-35	Second	100
anti TNF- α not treated	H. Edelman-Klapper, 2021	118	Israel	Mean (SD) 38.2 (14.3)	41.5	Pfizer	21-35	Second	100

Supplement 8. SARS-CoV-2 seropositivity among participants who were seropositive at baseline, or had COVID-19, or were infected during study

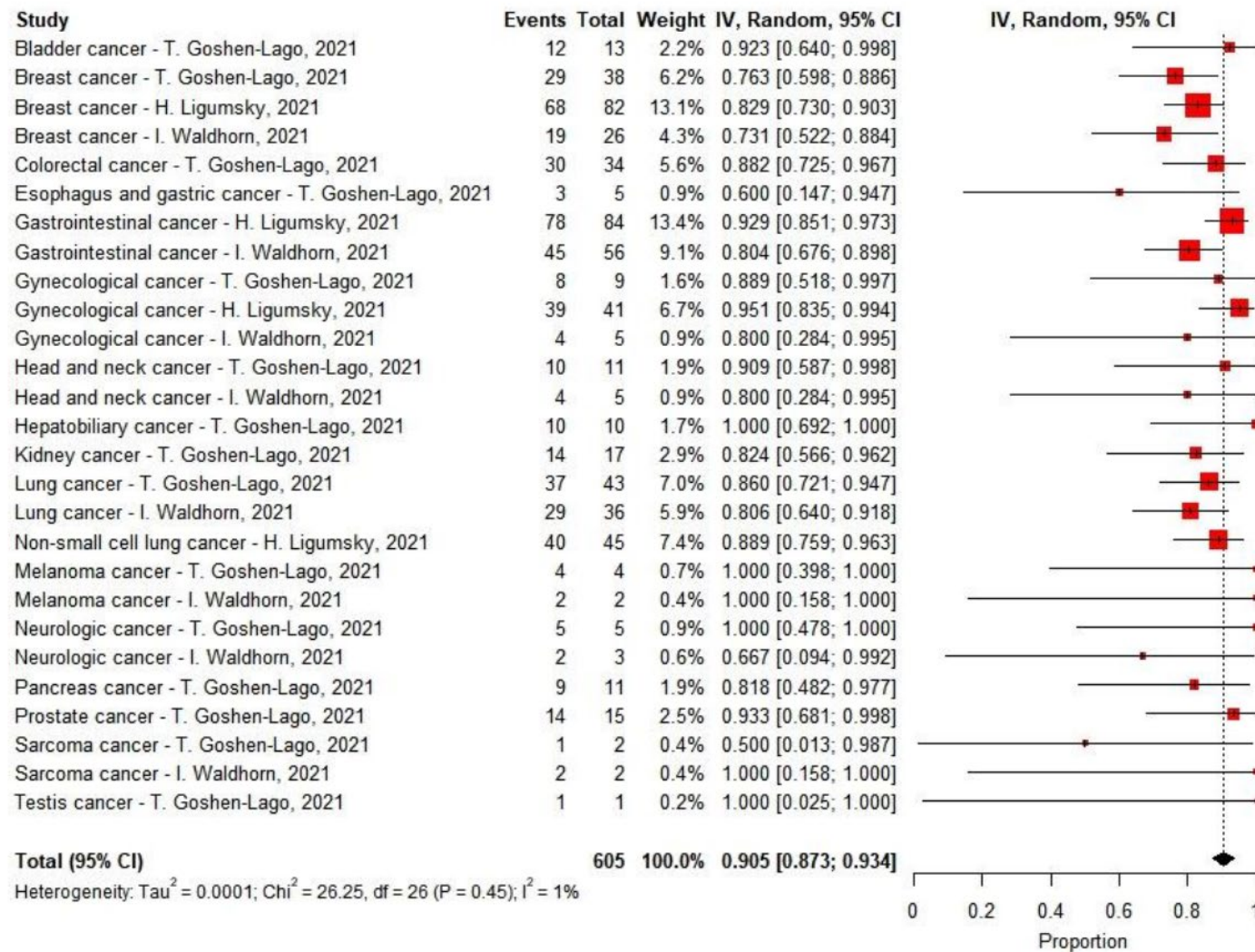
Population	Author, year	n	Country	Age	Sex (female %)	Vaccine	Test Date (day)	Dose	Seropositivity (%)
Seropositive at baseline	G. L. Salvagano, 2021	206	Italy	Mean (SD) 43 (13)	70	Pfizer	-	Before	100
	G. L. Salvagano, 2021	206	Italy	Mean (SD) 43 (13)	70	Pfizer	21	Second	100
	G. L. Salvagano, 2021	206	Italy	Mean (SD) 43 (13)	70	Pfizer	50	Second	100
	F. Claro, 2021	27	Venezuela	NR	NR	Sputnik V	0	Before	70
	F. Claro, 2021	27	Venezuela	NR	NR	Sputnik V	21	First	100
	F. Claro, 2021	27	Venezuela	NR	NR	Sputnik V	21	Second	100
Had COVID-19									
RT-PCR positive 3-7 months ago	H. Blain, 2021	94	France	Mean (Range) 86.6 (54-100)	70.2	Pfizer	21	First	95.4
	H. Blain, 2021	72	France	Mean (Range) 86.6 (54-100)	72.2	Pfizer	42	Second	100
RT-PCR positive 9-12 months ago	H. Blain, 2021	176	France	Mean (Range) 87.8 (54-100)	78	Pfizer	21	First	97.9
	H. Blain, 2021	150	France	Mean (Range) 87.8 (54-100)	80.7	Pfizer	42	Second	99.3
RT-PCR date not reported	A. Bayram, 2021	50	Turkey	Range 18-34	Male	Sinovac	28	First	100
	A. Bayram, 2021	46	Turkey	Range 18-34	Male	Sinovac	21	Second	100
	A. Bayram, 2021	107	Turkey	Range 18-34	Female	Sinovac	28	First	99.1
	A. Bayram, 2021	97	Turkey	Range 18-34	Female	Sinovac	21	Second	100
	A. Bayram, 2021	73	Turkey	Range 35-59	Male	Sinovac	28	First	97.2
	A. Bayram, 2021	69	Turkey	Range 35-59	Male	Sinovac	21	Second	100

	A. Bayram, 2021	40	Turkey	Range 35-59	Female	Sinovac	28	First	97.5
	A. Bayram, 2021	40	Turkey	Range 35-59	Female	Sinovac	21	Second	100
	A. Bayram, 2021	5	Turkey	Range ≥ 60	Male	Sinovac	28	First	100
	A. Bayram, 2021	5	Turkey	Range ≥ 60	Male	Sinovac	21	Second	100
	A. Bayram, 2021	2	Turkey	Range ≥ 60	Female	Sinovac	28	First	100
	A. Bayram, 2021	2	Turkey	Range ≥ 60	Female	Sinovac	21	Second	100
	D.W. Eyre, 2021	37	UK	NR	NR	Astrazeneca	0	Before	84
	D.W. Eyre, 2021	21	UK	NR	NR	Astrazeneca	1-7	First	100
	D.W. Eyre, 2021	16	UK	NR	NR	Astrazeneca	8-14	First	88
	D.W. Eyre, 2021	26	UK	NR	NR	Astrazeneca	15-21	First	100
	D.W. Eyre, 2021	59	UK	NR	NR	Astrazeneca	1-7	Second	98
	D.W. Eyre, 2021	53	UK	NR	NR	Astrazeneca	8-14	Second	100
	D.W. Eyre, 2021	14	UK	NR	NR	Astrazeneca	15-21	Second	100
	D.W. Eyre, 2021	20	UK	NR	NR	Astrazeneca	>21	Second	100
Infected during study	F. Claro, 2021	4	Venezuela	NR	NR	Sputanik V	-	Before	0
	F. Claro, 2021	4	Venezuela	NR	NR	Sputanik V	21	First	0
	F. Claro, 2021	4	Venezuela	NR	NR	Sputanik V	21	Second	100

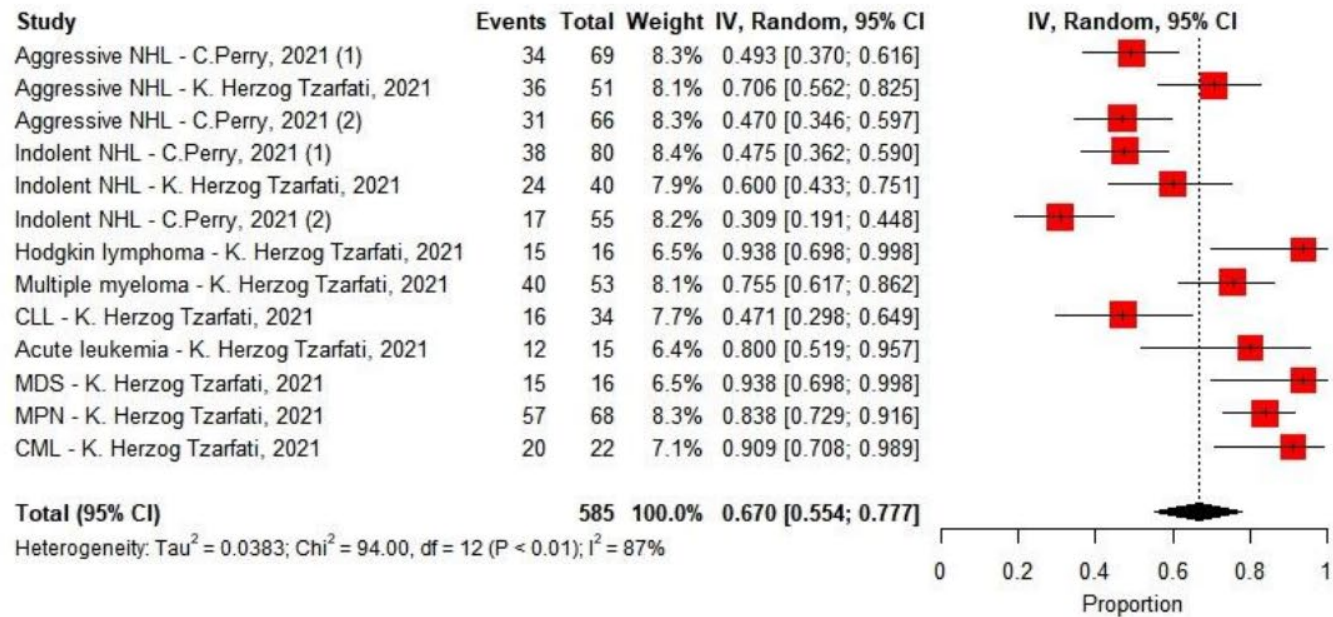
Supplement 9 (A) Random-effects of meta-analysis of COVID-19 seropositivity in solid tumor patients after first inoculation



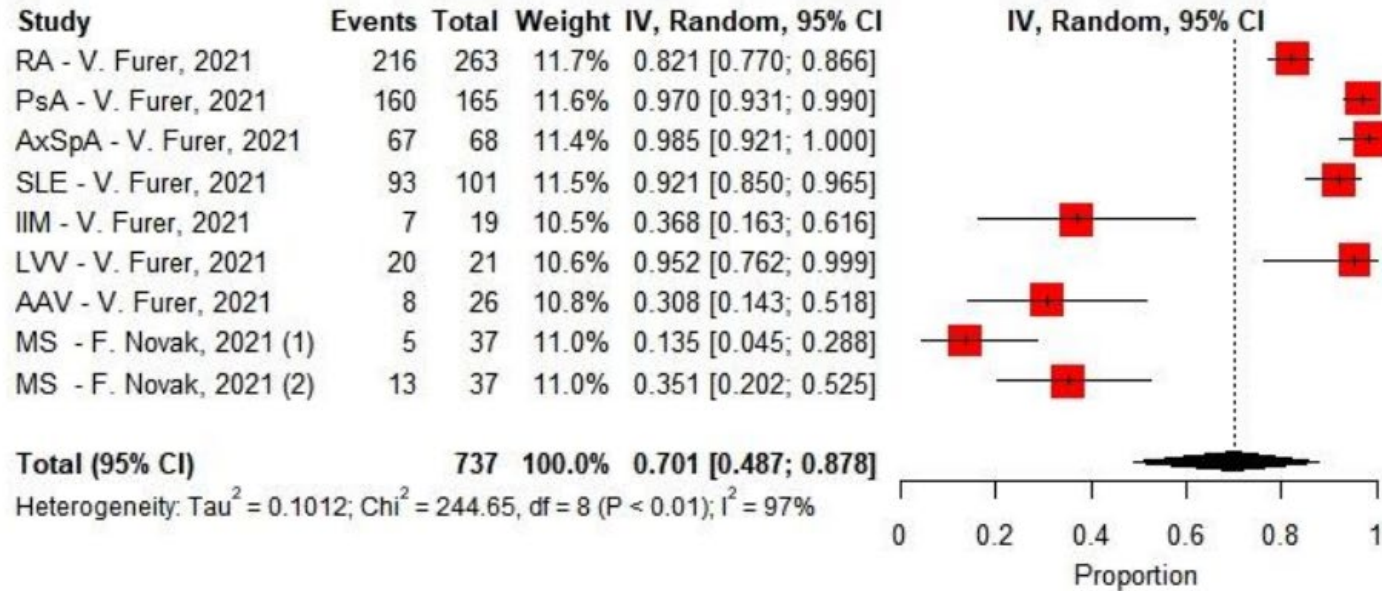
Supplement 9 (B) Random-effects of meta-analysis of COVID-19 seropositivity in solid tumor patients after second inoculation



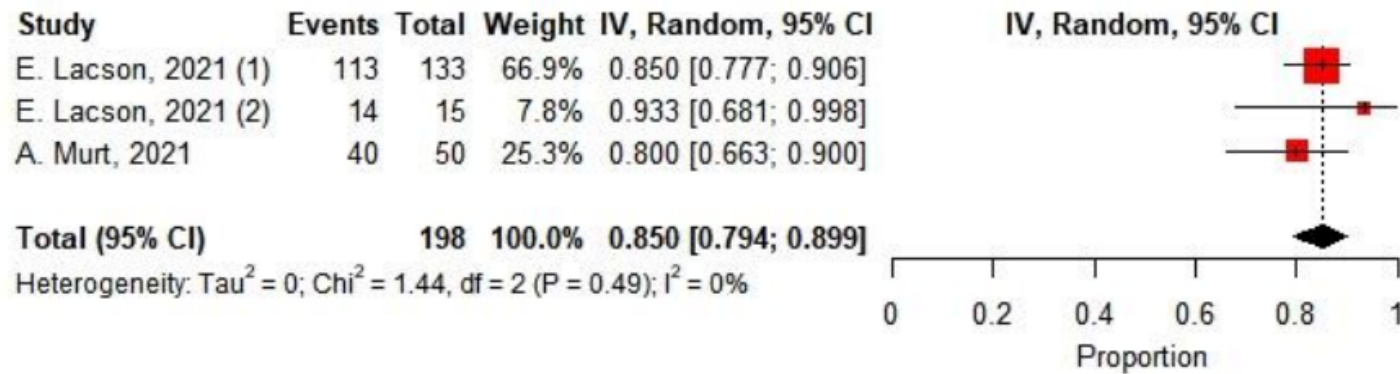
Supplement 9 (C) Random-effects of meta-analysis of COVID-19 seropositivity in hematologic malignancy patients after second inoculation



Supplement 9 (D) Random-effects of meta-analysis of COVID-19 seropositivity in autoimmune disease patients



Supplement 9 (E) Random-effects of meta-analysis of COVID-19 seropositivity in hemodialysis recipients



Supplement 9 (F) Random-effects of meta-analysis of COVID-19 seropositivity in transplant recipients

