Immunogenicity of COVID-19 mRNA Vaccines in Immunocompromised Patients: A Systematic Review and Meta-Analysis

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Abstract

Background

Immunocompromised (IC) patients are at higher risk of severe SARS-CoV-2 infection, morbidity, and mortality compared to general population. They should be prioritized for primary prevention through vaccination. In this study, we aimed to evaluate the efficacy of COVID-19 mRNA vaccines in IC patients through a systematic review and meta-analysis approach.

Method

PubMed-MEDLINE, Scopus, and Web of Science were searched for original articles reporting the immunogenicity of two doses of mRNA COVID-19 vaccines in adult patients with IC condition between June 1, 2020 and September 1, 2021. Meta-analysis was performed using either random or fixed effect according to the heterogeneity of the studies. Subgroup analysis was performed to identify potential sources of heterogeneity.

Results

A total of 26 studies on 3207 IC patients and 1726 healthy individuals were included. The risk of seroconversion in IC patients was 48% lower than those in controls (RR= 0.52 [0.42, 0.65]). IC patients with autoimmune condition were 54% and patients with malignancy were 42% more likely to have positive seroconversion compared to those with transplant (P<0.01). Subgroup meta-analysis based on type of malignancy, revealed significantly higher proportion of positive seroconversion in solid organ compared to hematologic malignancies (RR= 0.88 [0.85, 0.92] vs. 0.61 [0.44, 0.86], P= 0.03). Subgroup meta-analysis based on type of transplantation (kidney vs. others), showed no statically significant between group difference of seroconversion (P= 0.55).

Conclusions

IC patients, especially transplant patients, developed lower immunogenicity with two-dose of COVID-19 mRNA vaccines. Among patients with IC, those with autoimmune condition and solid organ malignancies are mostly benefited from COVID-19 vaccination. Findings from this meta-analysis, could aid health care policy makers upon making decision regarding the importance of the booster dose or more strict personal protections in the IC patients.

Introduction

Immunocompromised (IC) conditions are estimated to affect approximately 2.7% of United States adults (1). Such patients are at higher risk of severe SARS-CoV-2 infection, extended hospitalization, intensive care admission, and mortality compared to general population (2-6). Besides, prolonged viral shedding and potential sources of novel SARS-CoV-2 variants in this population are also of particular importance (7-9). Thus, IC patients should be prioritized for primary prevention through Coronavrus infectious disease 2019 (COVID-19) vaccination.

Global efforts have been taken to develop SARS-CoV-2 vaccines since the initiation of the current COVID-19 pandemic. The mRNA vaccines (i.e., mRNA-1273 and BNT162b2) are the most commonly approved vaccines worldwide which are utilized in different clinical trials in global scale (10). The overall efficacy and safety of COVID-19 vaccines in phase III trials were promising (11), sparking global hope toward ending the current outbreak. However, the application of COVID-19 vaccines in patients with impaired immune system remains as an ongoing subject of debate as they were excluded from the original trials (12, 13). IC patients due to either the primary disease or the immunosuppressive treatments are more likely to show weak or suboptimal immune response to COVID-19 vaccines given previous studies on influenza vaccines (14). Hence, the real-world statistics regarding the efficacy of COVID-19 vaccines are required to provide physicians a better insight towards decision-making in this group of high-risk patients.

In this study, we aimed to systematically review the literature and analyze the pooled effectiveness of COVID-19 vaccination in IC patients compared to healthy controls using meta-analysis. We also assessed the efficacy of mRNA vaccines in IC patients based on their etiological factor including malignancy, transplantation, and autoimmune diseases.

Methods And Materials

Protocol and Literature search

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

PubMed-MEDLINE, Scopus, and Web of Science were searched for original articles reporting the efficacy in adult patients with IC condition between June 1, 2020 and September 1, 2021. The search terms were as follows: ((COVID-19) OR (SARS-CoV-2) OR (novel coronavirus)) AND ((vaccine) OR (vaccination)) OR (vaccinated)) AND ((immunocompromised) OR (immunosuppressed) OR (corticosteroid) OR (chemotherapy) OR (cancer) OR (malignancy) OR (rheumatologic disease) OR (immunodeficiency) OR (autoimmune) OR (AIDS) OR (HIV) OR (transplant)).

The references of the selected articles were further screened to search for potentially relevant articles. Two reviewers independently performed the literature search, and any disagreement regarding study inclusion was resolved by consensus. The authors were not blinded to the authors, institutions, or journals while selecting studies or extracting data. EndNote version X9 was used for literature management.

Eligibility criteria

Studies investigating the immunogenicity of COVID-19 mRNA vaccination in IC patients were eligible for inclusion. The included studies met the following criteria: (1) *Population*: studies on IC patients with a sample size ≥ 30 participants and control group of healthy individuals. IC patients included patients with solid organ or hematologic malignancies who receive chemotherapy, patients with inherited or acquired immunodeficiency diseases, patients with autoimmune or rheumatologic diseases, patients with other conditions (i.e., asthma) receiving long-term corticosteroid, and transplant recipients. (2) *Intervention*: mRNA COVID-19 vaccination (3) *Study design*: all retrospective and prospective studies as well as clinical trials with healthy control group were included. (4) *Outcomes*: main outcome of this study was seroconversion in IC patients using anti-SARS-CoV-2 spike IgG ≥ 14 days after the second dose of COVID-19 mRNA vaccines. The subgroup analysis was performed to determine the efficacy of COVID-19 mRNA vaccines in different groups of patients based on etiology of IC condition.

The exclusion criteria were as follows: (1) reviews and editorials; (2) case reports or case series <30 patients; (3) partially overlapping patient cohorts; (4) articles not written in English; (5) single-arm studies or with non-healthy control group; and (6) non-human studies. Two reviewers independently reviewed the literature in consensus.

Data Collection

Eligible studies were evaluated by two experts independently and the following data was extracted from each included publication: author, date of publications, country of origin, study design, study sample size, definition of IC conditions, inclusion and exclusion criteria, the number of IC patients, variables matched, the proportion of male, mean age, duration of disease, type and etiology of the immunodeficiency and its proportion to the total population, type of vaccination, and efficacy of the vaccination.

Any conflicts in data extraction were discussed or consulted by a third expert and resolved.

Quality assessment

National Institutes of Health (NIH) quality assessment tool (15) to evaluate the included studies. The scores of 11–14, 6–10, and 0–5 were considered as good, fair, and poor quality, respectively. Moreover, the studies were evaluated in terms of methodology by two experts, independently; any conflict of opinion was discussed or referred to third expert and resolved.

Statistical analyses

STATA version 16 for Windows (Stata Corp, College Station, Texas) was utilized for the meta-analysis. At least three studies in each group were required to synthesize the data on outcomes. The heterogeneity of studies was measured using I^2 or Q test. A fixed model was employed, if the heterogeneity of studies was below 40% and a random effect model in case of heterogeneity above 40%. Effect measures were calculated. Also, based on the heterogeneity of studies, either meta-regression analysis or subgroup analysis was performed for potential moderators. Moreover, funnel plot asymmetry and the Eggers test were used to assess publication bias. In case of significant publication bias, the adjustment was performed for the effect size using the trim and fill method. A *P*-value less than 0.05 was considered statistically significant.

Results

Study selection

The study selection flowchart is presented in Figure 1. The literature search, after removing duplicates, resulted in 2093 studies, of which 1992 were considered irrelevant following title and abstract screening. Of the remaining 101, a further 75 were removed according to the exclusion criteria. Therefore, in total, 26 studies (16-41) were eligible for the meta-analysis of seroconversion after the second dose of the vaccine.

Characteristics of included studies

Characteristics of the included studies are provided in Table 1. All 26 included studies on 3207 IC patients and 1726 healthy controls showed that 65.8 % IC patients and 99.2 % healthy controls had seropositive IgG test following second dose of COVID-19 mRNA vaccines. All of the studies were conducted in 2021. Sample sizes, from which relevant data were available for extraction, varied from 40 to 807. Participants' mean age ranged from 42 to 71.4 years. The majority of the studies (18, 20, 23-25, 27, 29-34, 36-41) had a prospective cohort design (n = 18). Five studies (17, 19, 21, 22, 28) had a retrospective cohort design and three (16, 26, 35) were cross-sectional.

Table 1
Details of the data presented by the included studies.

Study (First Author)	Country	Study design	Total sample size	Case			Control			Etiology of IC condition	Type of vaccine
				No of cases	Male% of cases	Age	No of Non-cases (if applicable)	Male% of Non-cases	Age		
Sattler A	Germany	Prospective Cohort	78	39	71.8	57.3	39	51.2	53.0	Transplant	BNT162b2 (Pfizer/BionTech)
Rincon-Arevalo H	Germany	Prospective Cohort	75	40	70	62.4 [51.2-69.5]*	35	57.1	51 [34-80]*	Transplant	BNT162b2 (Pfizer/BionTech)
Korth J	Germany	Prospective Cohort	46	23	48	57.7	23	39	44.4	Transplant	BNT162b2 (Pfizer/BionTech)
Rabinowich L	Israel	Cross-sectional	105	80	70	60.1	25	32	52.7	Transplant	BNT162b2 (Pfizer/BionTech)
Schramm R	Germany	Prospective Cohort	100	50	64	55	50	34	47	Transplant	BNT162b2 (Pfizer/BionTech)
Cao J	USA	Retrospective Cohort	47	37	72.9	64 [50-69]*	10	20	66 [57-75]*	Transplant	mRNA-1273 (Moderna) or BNT162b2 (Pfizer/BionTech)
Grupper A	Israel	Retrospective Cohort	151	136	81.7	58.6	25	32	52.7	Transplant	BNT162b2 (Pfizer/BionTech)
Marinaki S	Greece	Prospective Cohort	150	34	79.4	60 [49.1-68.4]*	116	-	-	Transplant	BNT162b2 (Pfizer/BionTech)
Rashidi-Alavijeh J	Germany	Prospective Cohort	63	43	60.5	57 [49–64]*	20	45	43.5 [38-53.5]*	Transplant	BNT162b2 (Pfizer/BionTech)
Hod T	Israel	Prospective Cohort	322	120	80	59.7	141	30.2	57.04	Transplant	BNT162b2 (Pfizer/BionTech)
Stumpf J	Germany	Prospective Cohort	512	368	65.5	57.3	144	23.6	48	Transplant	(a) mRNA-1273 (Moderna) (n=143); (b) BNT162b2 (Pfizer/BionTech) (n=369)
Firket L	USA	Retrospective Cohort	40	20	45	51.2	20	65	48.3	Transplant	BNT162b2 (Pfizer/BionTech)
Peled Y	Israel	Prospective Cohort	213	77	64	62 [49-68]*	136	37	63	Transplant	BNT162b2 (Pfizer/BionTech)
Monin L	UK	Prospective Cohort	205	151	52	73 [64.5-79.5]*	54	52	40.5 [31.3-50]*	Malignancy	BNT162b2 (Pfizer/BionTech)
Pimpinelli F	Italy	Prospective Cohort	128	92	53/2	70*	36	0	81	Malignancy	BNT162b2 (Pfizer/BionTech)
Massarweh A	Israel	Prospective Cohort	180	102	57	66 [56-72]*	78	32	62 [49-70]*	Malignancy	BNT162b2 (Pfizer/BionTech)
Agbarya A	Israel	Cross-sectional	355	140	54	65.3	215	37.2	62.5	Malignancy	BNT162b2 (Pfizer/BionTech)
Herishanu Y	Israel	Prospective Cohort	219	167	67.1	71 [63-76]*	52	-	69 [63-73.7]*	Malignancy	BNT162b2 (Pfizer/BionTech)
Iacono D	Italy	Cross-sectional	108	36	41.6	82*	72	-	≥66	Malignancy	BNT162b2 (Pfizer/BionTech)
Malard F	France	Retrospective Cohort	225	195	60	68.9*	30	-	-	Malignancy	BNT162b2 (Pfizer/BionTech)
Eliakim-Raz N	Israel	Prospective Cohort	161	95	58	65 [56-72]*	66	32	62 [50-70]*	Malignancy	BNT162b2 (Pfizer/BionTech)

Study (First Author)	Country	Study design	Total sample size	Case			Control			Etiology of IC condition	Type of vaccine
				No of cases	Male% of cases	Age	No of Non-cases (if applicable)	Male% of Non-cases	Age		
Herzog Tzarfati K	Israel	Prospective Cohort	423	315	56	71 [61-78]*	108	44	69 [58-74]*	Malignancy	BNT162b2 (Pfizer/BionTech)
Reuken P	Germany	Prospective Cohort	55	28	46.4	42 [36–59]*	27	-	-	Autoimmune	BNT162b2 (Pfizer/BionTech)
Geisen UM	Germany	Retrospective Cohort	68	42	35.7	50.5	26	30.8	37.5	Autoimmune	mRNA-1273 (Moderna) or BNT162b2 (Pfizer/BionTech)
Furer V	Israel	Prospective Cohort	807	686	30.7	59 [19-88]*	121	35	50*	Autoimmune	BNT162b2 (Pfizer/BionTech)
Prendecki M	UK	Prospective Cohort	155	85	52.1	52 [39.9-63.9]*	70	-	41.4*	Autoimmune	BNT162b2 (Pfizer/BionTech)

*: Median [IQR] is reported; otherwise the mean is reported.

Quality assessment of included studies

Quality assessment of the included studies is presented in **Supplementary Table S1**. The majority of the studies (n = 18) (16-18, 21-23, 25, 27, 28, 30, 31, 33, 34, 37-41) were of good quality and 8 (19, 20, 24, 26, 29, 32, 35, 36) had fair quality.

Seroconversion in immunocompromised patients vs. controls

Meta-analysis of 26 studies revealed that the risk of positive seroconversion in IC patients were 48% lower than healthy controls. (RR= 0.52; 95% CI: 0.42, 0.65; $P < 0.01$). Subgroup meta-analysis based on type of IC (i.e. autoimmune, transplant, and malignancy), revealed a statistically significant between-group difference ($P < 0.01$) (Figure 2). When comparing each two subtypes of immunodeficiency, the results showed that IC patients due to transplant were less likely to develop positive seroconversion than IC patients due to autoimmune disorder ($P < 0.01$) as well as IC patients due to malignancy ($P < 0.01$). There was no statistically significant difference in seroconversion between IC patients with autoimmune disorder and those with malignancy ($P = 0.19$).

Seroconversion in patients with autoimmune disease vs. controls

Four (20, 21, 34, 37) of the included studies were conducted on IC patients with autoimmune immunodeficiency. Although the proportion of positive seroconversion in these patients was lower than the controls, the pooled analysis showed no statistically significant difference in relative risk of seroconversion between two groups. (RR= 0.87; 95% CI: 0.75, 1.01; $P = 0.07$) (Figure 2).

Seroconversion in patients with malignancy vs. controls

Meta-analysis of 9 studies (16, 18, 23, 24, 26, 28, 30, 31, 33) revealed IC patients with malignancy were 0.75 times as likely to seroconvert than healthy controls (RR = 0.75; 95% CI: 0.63, 0.89; $P < 0.01$). Subgroup meta-analysis was conducted based on type of malignancy (hematologic vs. solid organ). Four (23, 24, 28, 33) of the studies were on patients with hematologic malignancy and three (16, 18, 30) were on patients with solid organ malignancy. The relative risk of seroconversion among IC patients with solid organ was significantly higher than those with hematologic malignancies (RR= 0.88; 95% CI: 0.85, 0.92 vs. RR= 0.61; 95% CI: 0.44, 0.86; $P = 0.0.03$) (Figure 3).

Seroconversion in transplant patients vs. controls

Of the included studies, 13 (17, 19, 22, 25, 27, 29, 32, 35, 36, 38-41) were on IC patients with transplant. The meta-analysis showed transplant patients were 67% less likely to develop seroconversion than controls (RR= 0.33; 95% CI: 0.24, 0.47; $P < 0.01$). Seven (19, 22, 25, 27, 38, 39, 41) of the included studies were on patients with kidney transplant and the remaining (17, 29, 32, 35, 36, 40) were on patients with different transplants; none of which with more than three studies to be separated in the subgroup analysis. Hence, subgroup meta-analysis was conducted based on type of transplantation (kidney vs. others). The analysis did not reveal any statistically significant difference in relative risk of seroconversion in patients with kidney transplant compared to other types of transplants (RR = 0.30; 95% CI: 0.20, 0.47) vs. RR = 0.38; 95% CI: 0.21, 0.66; $P = 0.55$) (Figure 4).

Publication bias

Funnel plot for seroconversion was asymmetrical and Egger test showed statistically significant evidence of publication bias ($P < 0.01$, z = -9.09). Trim and fill method was used to adjust the effect size (Pooled estimate = 0.87; 95% CI: 0.85, 0.88; number of studies = 84) (Figure 5).

Discussion

Immunodeficiency comprises a wide range of disorders from primary (e.g., congenital) to numerous secondary conditions acquired consequently to a disease process or its treatment (e.g., human immunodeficiency virus (HIV) infection, radiation therapy, and immunosuppressive medications) (42). Although inconclusive, it has been shown that IC patients might be at a higher risk of severe COVID-19 (43, 44). On the other hand, limited number of studies revealed reduced vaccine efficacy of vaccines in IC patients (45). Nevertheless, data are limited on the efficacy of COVID-19 vaccines in this critical group of patients.

In this meta-analysis on the immunogenicity of COVID-19 mRNA vaccines in IC patients, we found lower risk of positive seroconversion in this group of patients compared to healthy controls. In addition, subgroup analysis revealed significantly lower risk of positive seroconversion in transplant patients in comparison with autoimmune disorder and patients with malignancy. Intriguingly, COVID-19 mRNA vaccines seem to achieve lower efficacy in patients with hematologic malignancies compared to solid organ.

We found significantly lower risk of positive seroconversion after the second dose of the vaccine in IC patients than controls. The controls were all healthy individuals, and this finding might not be surprising as observed with the administration of previous vaccines (e.g., Influenza vaccine) (46). However, it does not undermine the importance of vaccine in IC patients, as evidence highlights that the immune response after vaccines is more robust than that of natural SARS-CoV-2 infection (47, 48). It can also imply the importance of booster dose administration in this group of patients. As per recent Center for Disease Control and Prevention (CDC) guidelines, patients with moderately to severely compromised immune systems are recommended to receive an additional dose of COVID-19 mRNA vaccine (49). Furthermore, studies have shown the promotion of immune response in transplant patients receiving the third dose of mRNA vaccines, namely mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech) (50, 51). However, a dichotomous view toward the booster dose seems to be insufficient since the degree and etiology of immunosuppression tend to be two important factors regarding immune response and the need for an additional dose (52). Whether a booster dose is necessarily associated with an enhanced immune response is also a matter of debate. There is evidence that initial post-vaccine antibody titer was predictive of response to booster, and some IC patients will never mount an antibody response (53) and a more restricted personal protection is highly recommended even after vaccination (54).

Interestingly, our analysis revealed significantly lower relative risk of positive seroconversion in patients with transplant compared to patients with autoimmune disorder and patients with malignancy. A study by Evison *et al*., on the efficacy of Influenza vaccine showed that vaccine response rate was higher among patients with HIV and patients who received dialysis compared to renal transplant recipients and patients with rheumatologic disease (55). This can be justified by the fact that treatment regimen may be an important contributing factor. Mycophenolate mofetil has been shown to accompany less immune response compared to a regimen consisting of prednisone, cyclosporine, and azathioprine (56-58). These drugs which are used to prevent allograft rejection interfere with T and B cell activation and proliferation leading to impediment of antibody generation (59). Although we did find any significant difference between kidney transplant and other organ transplant recipients, transplant recipients seem to be more vulnerable to vaccine failures in general, and special attention should be directed toward this group of patients. Studies proposed some approach to increase immunogenicity of vaccine in transplant recipients such as modulation of immunosuppression, adjuvants, intradermal injection, high antigen doses, and booster administration (59).

Hematologic diseases are believed to have the highest level of immunosuppression amongst malignancies (60). This group of patients also 3-4-fold higher rates of severe/critical COVID-19 disease and mortality (61, 62). Hematologic malignancies are associated with immune dysfunction with alterations in both innate and adaptive immunity (63). Cytopenia, B/plasma cells reduction, hypogammaglobulinemia, anti-cancer therapy are amongst the underlying cause of immunodeficiency in these patients (64); thus, lower vaccine efficacy might be observed consequently, which is consistent with our findings about the lower immunogenicity of mRNA vaccines in patients with hematologic malignancies.

It is also worth mentioning that there are numerous approaches to the assessment of immune response after vaccine administration which are related to anti-SARS-COV-2 recombinant spike, receptor binding domain or neutralizing IgG or total antibodies (52). We included articles with the main outcome of anti-SARS-CoV-2 spike IgG level; however, seropositivity may not necessarily show protection against SARS-CoV-2 (53), and routine assessment COVID-19 vaccine responses is not recommended (53).

We confined this meta-analysis to mRNA vaccines due to limited studies on other COVID-19 vaccine types and to reduce heterogeneity. However, a study by Boekel *et al*., on the development of antibody in patients with autoimmune disease did not show any significant different between immunogenicity induced by an mRNA vaccine (BNT162b2) and a viral vector type (ChAdOx1 nCoV-19) (65). It has also been shown that inactivated COVID-19 vaccine (CoronaVac) can induce immune response in patients with immune-mediated disease; still, the titer of antibody is associated with age and type of immunosuppressive therapy (66).

This study indeed has some limitations. There was a lack data regarding HIV and other primary immunodeficiency disorders, and they are not included in this meta-analysis. Furthermore, we included studies with both retrospective and prospective design, which may reduce the level of evidence.

Conclusion

The risk of positive seroconversion in IC patients was almost half of those in healthy individuals. However, IC conditions due to autoimmune disorders did not lower the risk of positive seroconversion. Among IC conditions, transplantation induced lowest immunogenicity with 67% lower risk of seroconversion than healthy individuals. Besides, we found that vaccination among IC patients with hematological malignancy induced lower risk of seroconversion than those among IC patients with solid organ malignancy. Findings from this meta-analysis, could aid health care policy makers upon making decision regarding the importance of the booster dose or more strict personal protections in the IC patients.

Abbreviations

IC: Immunocompromised; COVID-19: Coronavrus infectious disease 2019; HIV: human immunodeficiency virus.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The authors stated that all information provided in this article could be shared.

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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Authors' contributions

The conception and design of the study: MM, HD, SS, NR; acquisition of data: MM, AH, AA, MS, MT; drafting the article: MM, FM, MT; revising it critically for important intellectual content: SS, MM, NR, HD; final approval of the version to be submitted: NR, SS. All authors read and approved the final manuscript.

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Figures

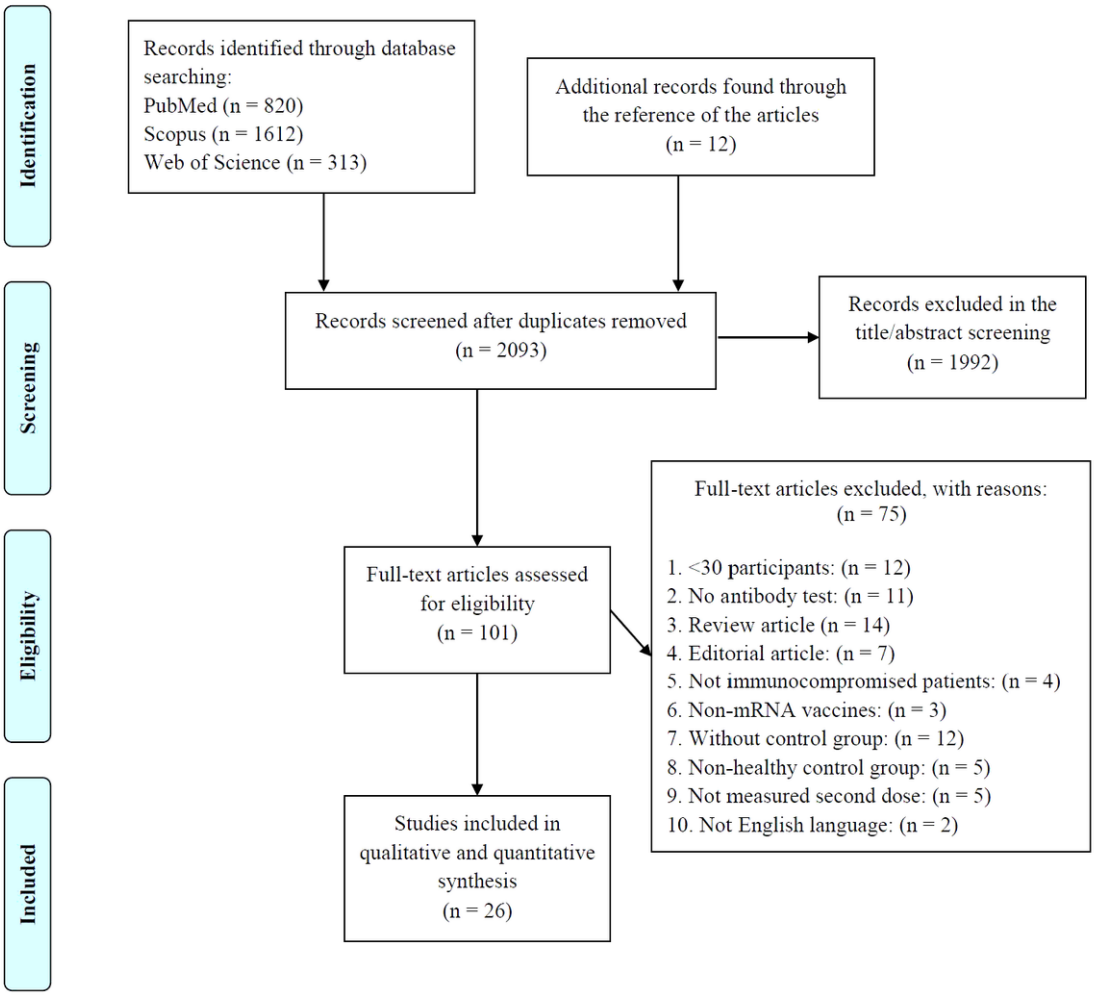

Figure 1

The PRISMA 2009 flow diagram of the study.

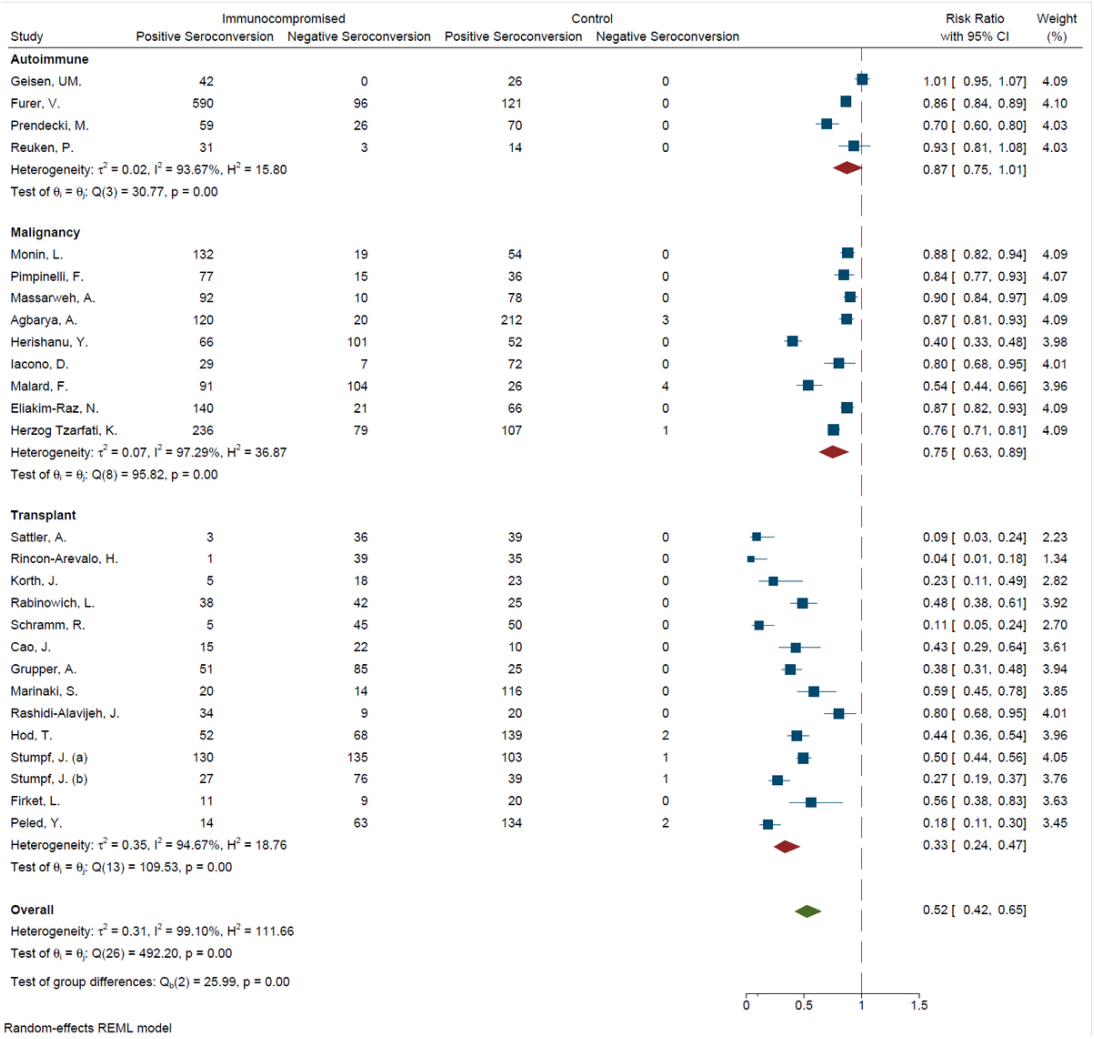

Figure 2

Meta-analysis of seroconversion in immunocompromised patients vs controls, based on type of immunodefeciency

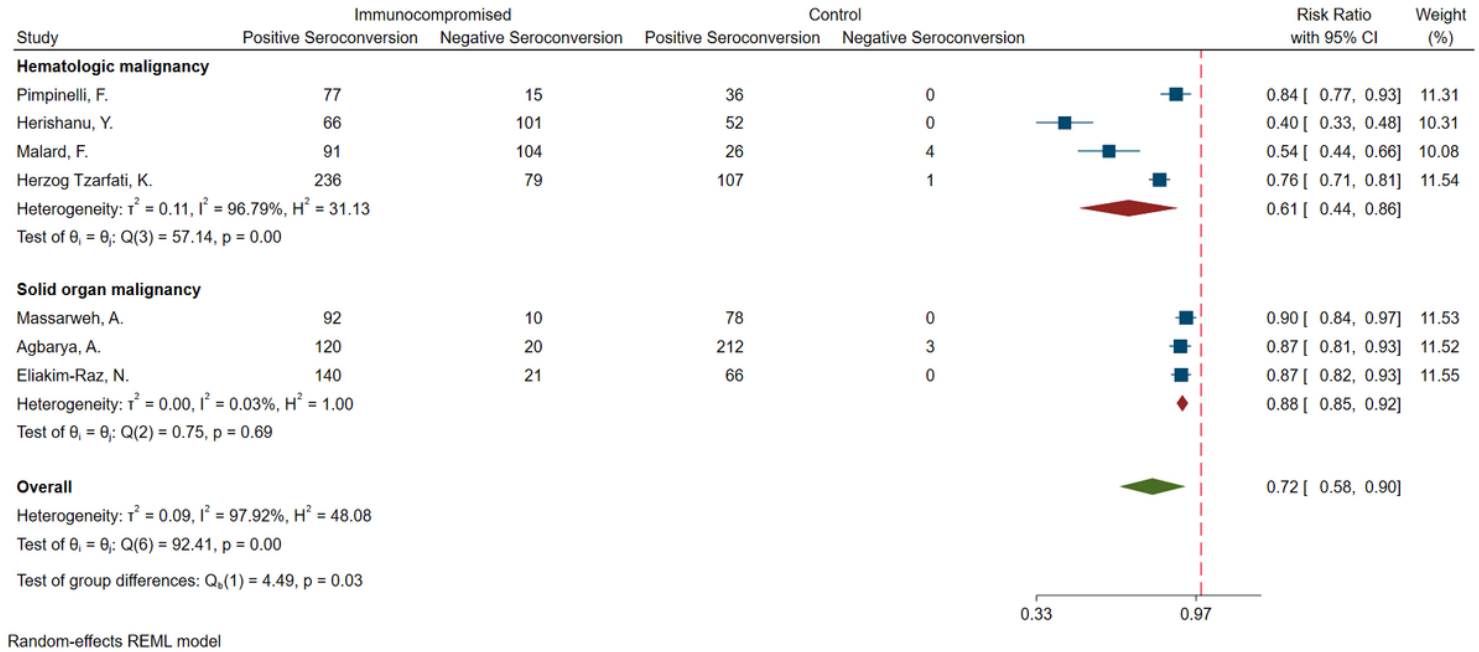

Figure 3

Meta-analysis of seroconversion in immunocompromised patients with malignancy vs controls, based on type of maliganacy

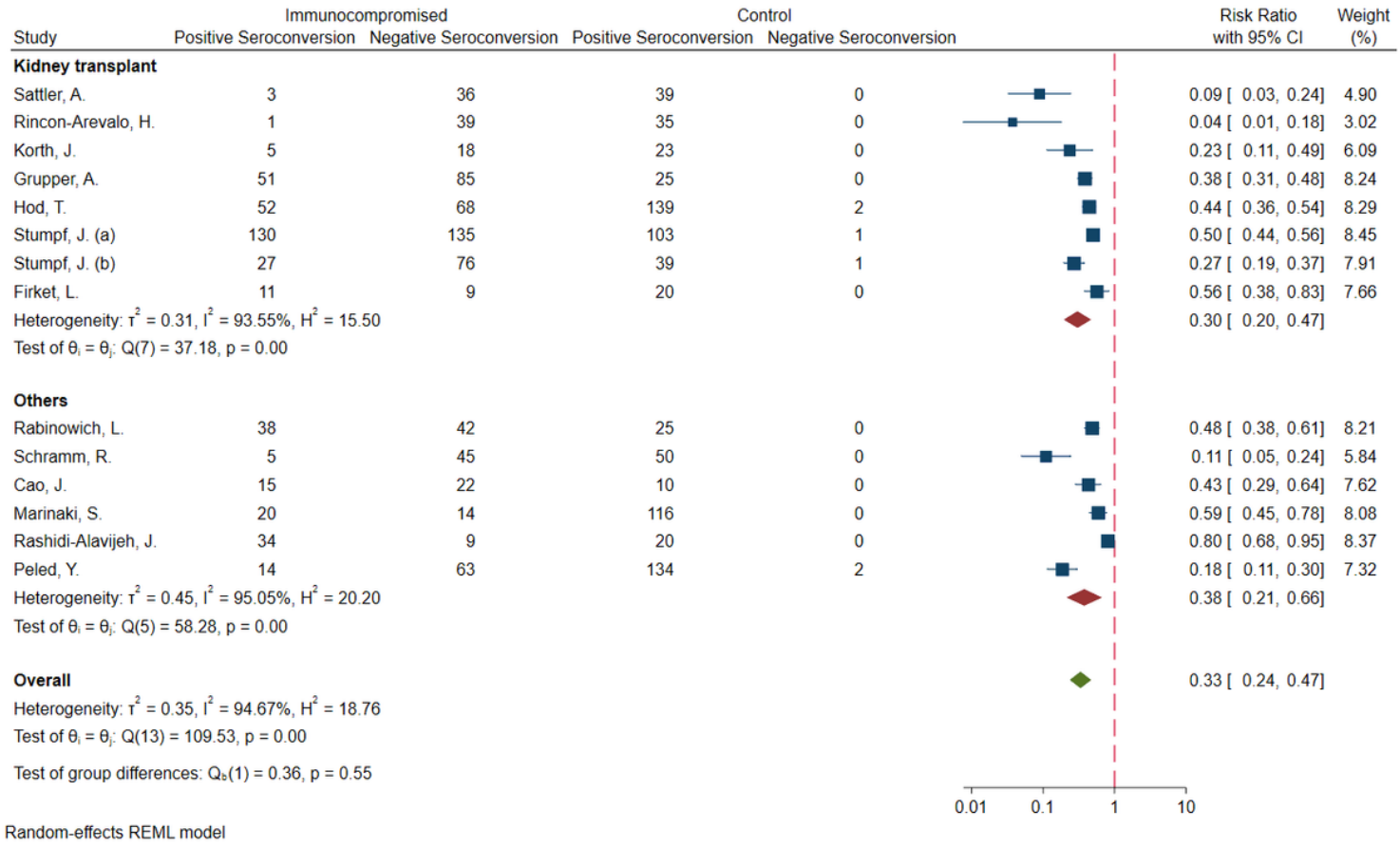

Figure 4

Meta-analysis of seroconversion in transplant patients vs controls, based on type of transplant

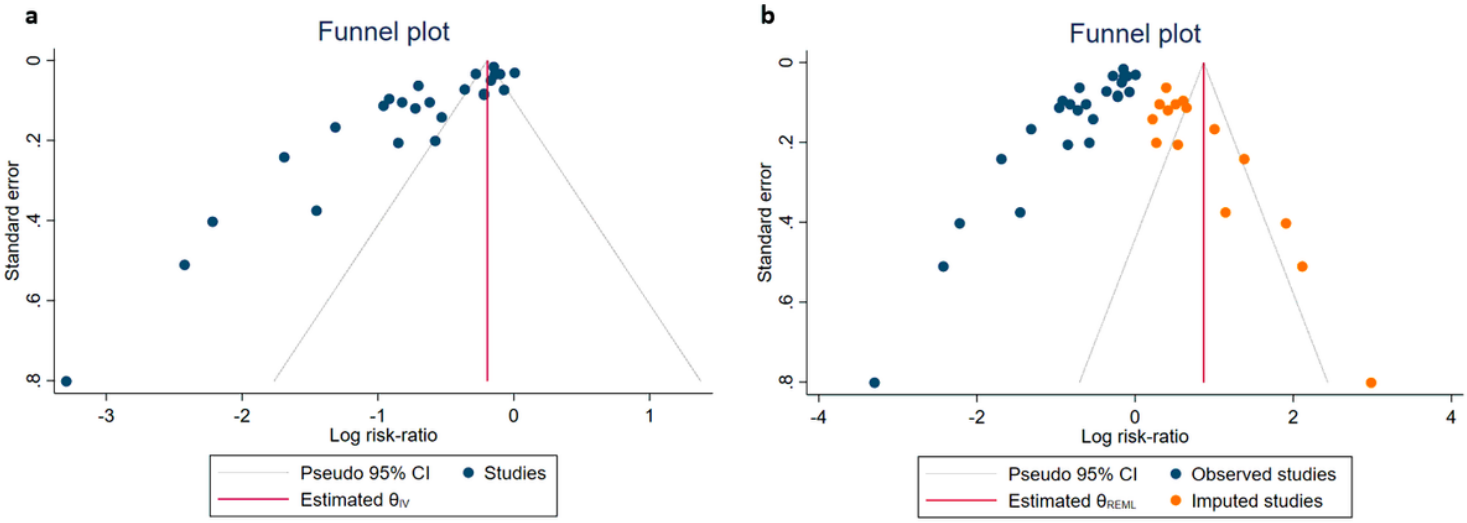

Figure 5

Funnel plot (a) and trim and fill funnel plot (b) for meta-analysis of seroconversion in patients with immunodeficiency

Supplementary Files

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