SARS-CoV-2 Vaccine-Induced Immune Responses among Hematopoietic Stem Cell Transplant Recipients

SARS-COV-2 VACCINE-INDUCED IMMUNE RESPONSES AMONG HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

by

Afoke Kokogho, M.D, MPH

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Project Advisor: Dr. Stephen Walsh & Dr. Amy Sherman

I have reviewed this thesis. It represents work done by the author under my guidance/supervision.

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OVERVIEW OF THE THESIS PAPERS

Paper 1 Overview

This paper presents the results of a retrospective chart review conducted among SARS-CoV-2 vaccinated hematopoietic stem cell transplantation (HSCT) recipients in Boston, Massachusetts. The study aimed to investigate the humoral response to vaccination among HSCT patients and to identify any variables that may impact the response. The study included 152 HSCT recipients who received at least one dose of Pfizer, Moderna, or J&J vaccine. Anti-Spike IgG titer levels were measured using the Roche assay, and responders (≥0.8 U/mL) and non-responders (<0.8 U/mL) were categorized and analyzed. The study found that 92.8% of HSCT recipients were responders, and higher quantitative titers were associated with receipt of more vaccine doses, being female, being younger (<65 years), and not being on anti-CD20 therapy. On the other hand, being male and on anti-CD20 therapy were associated with being a non-responder. We concluded that HSCT recipients had high SARS-CoV-2 responsiveness in this population, and anti-S IgG monitoring may be useful for identifying vaccine failures. The study provides valuable information on the humoral response to SARS-CoV-2 vaccination among HSCT patients, which can inform clinical decision-making and vaccine administration strategies.

Paper 2 Overview

This paper presents a systematic review and meta-analysis that aimed to estimate the prevalence and predictors of attenuated SARS-CoV-2 Vaccine-induced immune response among hematopoietic stem cell transplant (HSCT) recipients. The authors searched several databases for randomized controlled trials and observational studies reporting the serologic response to COVID-19 vaccines in HSCT recipients. The results showed that the prevalence of COVID-19 vaccine failure among HSCT recipients was 16%, and the predictors of vaccine failure included underlying diseases, post-transplantation vaccination, treatment regimen for graft versus host disease (GVHD), and concurrent anti-CD20 therapy. The authors suggest that understanding the prevalence and predictors of vaccine treatment failure could help to understand the magnitude and peculiar risk of HSCT recipients and the need to optimize the benefits of vaccination among this key sub-group of patients.

Paper 1

SARS-CoV-2 Vaccine-Induced Immune Responses among Hematopoietic Stem Cell Transplant Recipients

Afoke Kokogho[1,3]; *Trevor A. Crowell[4,5]; Muneerah Aleissa[1,2]; Ana-Mihaela Lupan[6.], Sonya Davey[1,2.], Jun Bai Park Chang[1,2]; Lindsey R. Baden[1,2,3]; *Stephen R. Walsh[1,2,3]; *Amy C. Sherman[1,2,3]

(1)Division of Infectious Diseases Brigham and Women's Hospital, Boston, MA, (2) Dana-Farber Cancer Institute, Boston, MA, (3) Harvard Medical School, Boston, MA, (4)Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, Maryland, USA (5) U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, Maryland, USA (6) Department of Cell Biology, Harvard Medical School, Boston, MA, USA.

ABSTRACT

Background

Although SARS-CoV-2 vaccination reduces the risk and severity of coronavirus disease 2019 (COVID-19), several variables may impact the humoral response among patients undergoing hematopoietic stem cell transplantation (HSCT).

Methods

A retrospective chart review was conducted among SARS-CoV-2 vaccinated HSCT recipients between 2020 and 2022 at a single center in Boston, Massachusetts. Patients ≥18 years who received dose(s) of Pfizer, Moderna, or J&J vaccine were included. Anti-Spike (S) IgG titer levels were measured using the Roche assay. Responders (≥0.8 U/mL) and non-responders (<0.8 U/mL) were categorized and analyzed. Multivariable linear and logistic regression were used to estimate the correlation coefficient and odds ratio of response magnitude and status.

Results

Of 152 HSCT recipients, 141 (92.8%) were responders with a median anti-S IgG titer of 2500 U/mL (IQR: 107.9, 2500) at a median of 80.5 days (IQR: 36, 153.5) from last dose regardless of the number of doses received. Higher quantitative titers were associated with receipt of more vaccine doses (Coeff=205.79; 95% CI 30.10, 381.47; p= 0.022), being female (coeff= -343.5; 95% CI -682.6, -4.4; p=0.047), being younger (<65 years) (coeff= -365.2; 95% CI -711.3, 19.1; p=0.039) and not being on anti-CD20 therapy (coeff=

-1163.7; 95% CI -1717.7, -609.7; p=0.001). Being male (OR=0.11; CI 0.01, 0.93; p=0.04) and on anti-CD20 therapy (OR=0.16; CI 0.03, 0.70; p=0.016,) were associated with Non-responders.

Conclusion

Overall, most HSCT recipients had high SARS-CoV-2 antibody responses. More vaccine doses improved the magnitude of immune responses. Anti-S IgG monitoring may be useful for identifying vaccine failures.

Keywords COVID-19 vaccine · Anti-spike protein · Allogeneic HSCT · Autologous HSCT .Transplant

INTRODUCTION:

Background

SARS-CoV-2 vaccination reduces the risk and severity of coronavirus disease 2019 (COVID-19) (1–3), but immunogenicity may be reduced in patients undergoing hematopoietic stem cell transplantation (HSCT)(4). HSCT recipients undergo various degrees of disease-related and therapeutic immunosuppression that may compromise their ability to produce an effective immune response. The variables that may impact the humoral response, such as age, gender, pre-transplant diagnosis, transplant type, prior treatments, and vaccine type and number have not been comprehensively described.

Prior to the FDA-authorized use of SARS-CoV-2 vaccines, transplant patients had a significantly higher mortality rate compared to healthy adults after infection with SARS-CoV-2 (5). The pivotal clinical trials that led to the accelerated authorization of the SARS-CoV-2 vaccines were conducted among healthy participants (1,2). Immunocompromised patients, including HSCT recipients, were excluded from the phase 3 COVID-19 vaccine trials despite their uniquely higher risks of severe infection and death (6–9).

Several studies have demonstrated relatively poor SARS-CoV-2 vaccine immune responses among HSCT recipients following vaccination as compared to healthy adults. Sherman et al and Mamez separately reported suboptimal antibody titers with a seropositivity prevalence of about 80% among HSCT recipients when compared to healthy adults (10–13). Before the recommendation for booster dose vaccinations, certain

factors had been linked to poor sero-responsiveness including time post-transplant, presence or absence of graft versus host disease (GVHD), and use of anti-CD20 therapies (14,15). Medications such as methotrexate, sirolimus, high-dose steroids, and mycophenolate mofetil commonly used in the management of GVHD among HSCT recipients have been implicated in poor SARS-CoV-2 vaccine immunogenicity among solid organ transplant recipients (2,5,6,8). In other vaccine studies (e.g. with the influenza vaccine), the appropriate timing of vaccination affected immunogenicity among HSCT recipients (17).

Given the heightened risk of death and severe disease following infection with SARS-CoV-2, knowledge of SARS-CoV-2 vaccine responsiveness remains pertinent in addressing the unique needs of HSCT recipients. The goal of our study was to determine the prevalence of seropositivity and magnitude of anti-spike (S) IgG after SARS-CoV-2 vaccination in HSCT recipients and determine factors associated with seropositivity in this population. Insights gained from this study may aid in the development of improved vaccination strategies against SARS-CoV-2.

METHODS:

Study Population

A single-center, retrospective review of electronic medical record (EMR) data was conducted among HSCT recipients who received SARS-CoV-2 vaccinations between 01 JAN 2020 – AUG 2022 at Brigham and Women's Hospital and Dana-Farber Cancer Insititute in Boston, Massachusetts. Patients were included if they were aged ≥18 years

and had received at least one dose of BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), or Ad26.COV2.S (Janssen) vaccine and had been tested at least once for anti-S IgG. The anti-S IgG response observation period spanned between 28 January 2021 and 25 August 2022. Patients were censored as of the date of monoclonal antibody (mAb) therapy or positive test for SARS-CoV-2 infection. Those who had anti-S IgG assays only prior to transplant or who relapsed and received an alternate treatment were excluded. This study was reviewed by the Mass General Brigham Institutional Review Board.

Study Design

Anti-S IgG titers were quantitatively measured at the provider's discretion during routine care using the Roche Elecsys Anti-SARS-CoV-2 spike immunoassay. The assay has a cut-off defined by the manufacturer as ≥0.8 U/mL. Values below this were imputed to 0.4 U/mL; values above this were considered reactive while values below are considered non-reactive (18). Earlier anti-S IgG assays had a maximum reported titer of 2500 U/mL, while later assays had a higher maximum titer of 12500 U/mL. For the later assays with titers above 2500 U/mL, a different dilutional method was used in the lab. To ensure uniformity in reporting and facilitate appropriate comparisons, all anti-S IgG titers were adjusted to a maximum of 2500 U/mL prior to our analysis. Baseline demographic data, blood cell counts (CD4, WBC), and IgG levels were extracted from the EMR (starting three months before the first vaccination). The pre-transplant conditioning regimen, type of transplant, GVHD prophylaxis, acute and chronic GVHD treatment, SARS-CoV-2 PCR result, COVID-19 treatment status, and type of vaccine received were extracted from the EMR. The retrospective clinical charts were initially screened for eligibility by a pharmacist

(MA). Subsequently, the clinical data were extracted by a physician (AK), a pharmacist (MA), and a research assistant (JC). The study timeline for each eligible participant spanned between three months before the first dose of SARS-CoV-2 vaccination and the date of their last anti-S IgG antibody assay. To determine the time from the last vaccine dose after transplant, we used the results of the anti-S IgG assay that were collected after the last dose for all patient groups. In our retrospective chart review study, missing data made up less than 20% of the total collected data. Some patients had incomplete vaccination records due to not receiving the maximum of five vaccine doses, while others had missing CD4 and IgG counts in their medical records. We considered the missingness to be completely at random, and opted for direct data analysis without imputations. This approach allowed us to analyze the available data without filling in missing values. We conducted sensitivity analyses to assess the robustness of our findings. Overall, our approach to handling missing data was transparent and appropriate for our study.

Statistical Analysis

We categorised patients based on the number of doses of the vaccine(s) received before their last assayed anti-S IgG titer. We analyzed these data using descriptive statistics to assess the quantitative difference in anti-S IgG titer and a Kruskal-Wallis or Mann-Whitney U test to assess for statistical significance between groups. Univariable and multivariable models were used to assess the relationship between key patient demographics, vaccine and treatment characteristics, and their association with the responder status of HSCT recipients. A logistic regression model was used to calculate

odds ratios (ORs) and 95% confidence intervals (CIs) for factors potentially associated with a dichotomous response status to SARS-CoV-2 vaccination (responders vs non-responders). P-values ≤ 0.05 were considered statistically significant. We excluded variables with p-values >0.25 after a univariable analysis. Only variables with p-values ≤0.25 and certain clinically relevant variables regardless of statistical significance, were included in the multivariable analysis. Factors evaluated included age, sex, neutrophil count, lymphocyte count, platelet counts, IgG level, prophylaxis, and treatment for GVHD (e.g mycophenolate mofetil, sirolimus, systemic corticosteroids (≥20mg), tacrolimus, and cyclophosphamide), receipt of anti-CD20 therapy (e.g., rituximab, ocrelizumab, veltuzumab, obinutuzumab), type of transplant, type of conditioning regimen, time from transplant to the first vaccination, time from first vaccination to first anti-S IgG titer assay, time from last dose to last antibody titer, number of vaccine dose (S) received. Stata version 17.0 and GraphPad Prism 9 software were used to analyze the study data and render figures.

RESULTS

Sociodemographic characteristics and magnitude of anti-spike response

A total of 254 HSCT recipients were screened and 152 patient records met the study inclusion criteria. Of these, 82 (54%) were male and the median age was 62 years (IQR 50 - 68.0). Recipients were predominantly white (n=139, 91.5%) and non-Hispanic (n=136, 93.2%). Regarding the type of transplant, 28 (18.4%) had autologous transplant and 124 (81.6%) had allogeneic transplant. Patients had a variable number of doses of

COVID vaccines ranging from one to five doses, with most patients receiving three or more vaccines (98/152, 64.5%). Other characteristics such as underlying disease, preparation intensity, transplant type, and medications used in the prophylaxis and treatment of acute and chronic GVHD, are shown in Table 1.

Descriptive analysis comparing Anti-S IgG levels in various categories:

The results comparing anti-S IgG titers between HSCT recipients who received different numbers of vaccines are shown in Figure 1. Furthermore, the median anti-S IgG titers between recipients based on concurrent receipt of high dose steroid, tacrolimus, anti-CD-20 therapy, and the type of transplant, are shown in Figure 2. The Mann-Whitney U test was used to compare the median anti-S IgG titer between each group in Figure 2. More descriptive analysis comparing the median anti-S IgG titers of other sub-groups can be found in the supplementary tables. Some HSCT recipients (non-responders) failed to seroconvert irrespective of the number of doses received post-HSCT.

Autologous and allogeneic transplant recipients

Autologous transplant patients had a median titer of 2303.5 U/mL (IQR 25.3 - 2500), and a median time of 132 days (IQR 83 -181) from the last vaccine dose. Allogeneic transplant patients had a median titer of 2500 U/mL (IQR 193 - 2500), and a median time of 63 days (36 - 145) from the last vaccine dose.

Patients who had concurrent treatments for acute GVHD with tacrolimus had a median titer of 156.7 U/mL (IQR 3.53 - 1556), and a median time of 107 days (IQR 50 - 148) from the last vaccine dose. Those who did not have tacrolimus treatment had a higher median titer of 2500 U/mL (153.5 - 2500) at a median time of 80.5 days (36 - 154) from the last vaccine dose.

HSCT recipients below vs above 65 years

Patients aged 65 years and older had a lower median titer of 1786 U/mL (IQR 62 - 2500) at a median time of 84 days (IQR 49 -148) from the last vaccine dose. Patients below 65 years had a higher median titer of 2500 U/mL (IQR 249.8 - 2500) at a median time of 63 days (IQR 34 -154) from the last vaccine dose.

Correlates of seropositivity (multi-variable analysis)

The results of the multivariable linear regression analysis indicated a positive correlation between the number of vaccine doses received and the quantitative anti-S IgG titer (Table 2). Specifically, as the number of doses increased, the anti-S IgG titer also increased correspondingly (coeff.=205, 95% CI 30.1,381.5; p=0.022). Being female (coeff.=-343.5, 95% CI=-682.6,-4.4; p=0.047) was also associated with having a higher anti-S IgG titer compared to males. Younger patients had a positive correlation with the quantitative anti-S IgG titer when compared to older patients (coeff= -365.2; 95% CI=-711.3,-19.1; p=0.039). Patients on concurrent anti-CD20 therapy had a statistically significant negative correlation with the quantitative anti-S IgG titer when compared to those who were not receiving the therapy (coeff= -1163.7; 95% CI= -1717.7, -609.7; p=0.001) (Table 2). The

results of the regression analysis indicated that being on treatment for acute GVHD with steroids, and tacrolimus, and having chronic GVHD did not have a significant effect on the quantitative anti-S IgG titer (Table 2).

We then conducted a multivariable logistic regression analysis to identify factors associated with being a non-responder (Table 2). The results showed that concurrent use of anti-CD20 (OR=0.16; 95% CI=0.03,0.70; p=0.016), and being male (OR=0.11; 95% CI=0.01, 0.93; p=0.04) were associated with being a non-responder. Other factors, such as the number of doses, age, and treatment of acute GVHD (aGVHD) using systemic steroids, tacrolimus, or the presence of chronic GVHD (cGVHD), were not found to be statistically significant (Table 2).

DISCUSSION

Our results showed that overall HSCT recipients had high seropositivity rates defined as having detectable antibody titers, but the quantitative antibody titers were lower than reported among participants in the phase 3 COVID vaccine studies (19,20). In these studies, healthy adults had almost a 100% seropositivity rate and higher quantitative titers after the first dose of SARS-CoV-2 vaccines (10,21). While antibody levels are a clear correlate of protection against SARS-CoV-2 infection, there are likely other mechanisms of protection (1,22–28). Therefore, the results of the quantitative anti-S IgG titer and seropositivity in particular must be interpreted with caution and should not be taken as the sole indicator of immune-protectiveness among HSCT recipients.

Our results showed that anti-CD20 therapy was associated with being a non-responder and having significantly lower anti-S IgG titers. This supports previous findings in the literature that anti-CD20 therapies inhibit B-cell antibody production and deplete peripheral B-cells, leading to a decrease in vaccine-elicited IgG titers (21–23). To ensure that HSCT recipients benefit optimally from SARS-CoV-2 vaccination, it may be important to consider the timing of vaccine administration in regards to anti-CD20 therapy if feasible. Furthermore, clinicians should be aware that these patients remain at risk despite vaccination and counsel on continued masking and other social mitigation strategies to protect against COVID-19.

This study found no significant difference in the response to SARS-CoV-2 vaccines between HSCT recipients receiving concurrent GVHD treatment (tacrolimus, steroids) and those who did not, after adjusting for confounding factors. However, another study showed that ongoing GVHD and treatment negatively impact the anti-S IgG response in HSCT recipients compared to healthy adults (29,30). One study among Japanese patients showed that allogeneic transplant patients, some of whom had treatment for GVHD, showed a better overall anti-S IgG response compared to autologous transplant patients in the cohort (31). Further research is needed to fully understand the complex relationship between GVHD, immunosuppressive medications, and vaccine efficacy in HSCT patients.

Patients who had a higher number of doses of the SARS-COV-2 vaccine showed a significantly higher quantitative anti-S IgG response. This result is in keeping with results from studies among healthy individuals and HSCT recipients (13,32). These data, therefore, support the recommendation for booster doses, particularly for transplant

patients who have lower antibody levels and are more vulnerable to severe illness (11). However, the optimal timing of booster doses should be further explored in future studies.

Our results show that women had a significantly higher anti-S antibody level compared to men, consistent with other reports in healthy individuals (29,33). Ongoing research suggests that hormones such as estrogen may have an immunomodulatory function (34). Environmental and genetic factors may also play a role (35). Further studies are needed to understand the underlying mechanisms.

Younger patients under 65 years of age demonstrated a stronger quantitative antibody response compared to older patients 65 and above. This is similar to what was observed in other studies among allogeneic HSCT recipients and healthy participants who had the COVID vaccines (2,36,37). While an age-related decline in immune responses, known as immunosenescence, has been observed in older individuals compared to their younger counterparts (38–40), the mechanisms underlying this phenomenon are an area of active research(41–43).

Limitations

Our study has several limitations that should be taken into account when interpreting the findings. The study was conducted retrospectively, meaning that a causal relationship cannot be established from the results. Additionally, the clinical significance of the findings remains unknown, as correlates of protection may vary between immunocompromised hosts and healthy clinical trial participants. In addition, circulating viral variants complicate the correlates analyses. The study's population was predominantly white, limiting the generalizability of the findings to other racial or ethnic

groups. Furthermore, only a small proportion of the sampled population had the complete vaccine series and serial anti-S IgG titer measurements, which prevented us from assessing vaccination responses longitudinally. Moreover, while the use of different vaccines or the heterologous mix of vaccine types may have influenced the results, most patients received mRNA vaccines. The study also did not consider the duration of prophylaxis or treatment against GVHD, only whether recipients had prophylaxis or not. We acknowledge the possibility of a potential for selection bias with our sampled population. Lastly, the results of this study may be challenging to compare with other studies that used different antibody assay techniques, as the reference range and assay limits may vary. These limitations indicate the need for further research to confirm the results and gain a better understanding of the optimal vaccination strategy for HSCT patients.

CONCLUSION

The study concludes that the FDA-authorized SARS-CoV-2 vaccine series produced an immunogenic response among the majority of HSCT patients, but the response was suboptimal for certain subsets of the cohort, such as older patients and those who had received anti-CD20 therapy. The number of vaccine doses administered correlated with the magnitude of the anti-S IgG response, and quantitative anti-S IgG assays could therefore be conducted for early identification of patients who fail to respond to vaccination. The findings support the current recommendations for HSCT patients to receive a three-dose primary series followed by serial booster COVID vaccines to optimize protection against SARS-CoV-2 infection. Future directions could include the

development of new vaccination strategies or therapies to improve vaccine responses among HSCT patients, as well as continued monitoring of vaccine effectiveness and safety in this population.

TABLES AND FIGURES

Table 1: Demographic, treatment, and SARS-CoV-2 vaccination characteristics of hematopoietic stem cell transplant recipients.

Table 2: Predictors of response status using linear and logistic regression analyses.

Figure 1: Anti-SARS-CoV-2 Spike antibody titers among hematopoietic stem cell transplant (HSCT) recipients. The result of the multivariate analysis shows an association between the number of vaccine doses received and the magnitude of anti-S IgG response. Panel A: anti-spike IgG responses on the y-axis and the number of vaccine doses received on the x-axis. Panel B: shows the corresponding median time between the anti-S IgG assay and the last dose received. A Mann-Whitney U test showed no significant difference in the last dose to assay time between the various dose categories.

Figure 2: Anti-S IgG responses among various categories of HSCT recipients. Titers were compared between patients who were on concurrent immunosuppression therapy versus those who were not. Panel A: high-dose (≥20 mg prednisone equivalent per day) steroid treatment. Panel B: tacrolimus treatment. Panel C: anti-CD20 monoclonal antibody treatment. Panel D: Compares females to males. All panels show a Mann-Whitney U test unadjusted analysis between the groups.

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Consort diagram

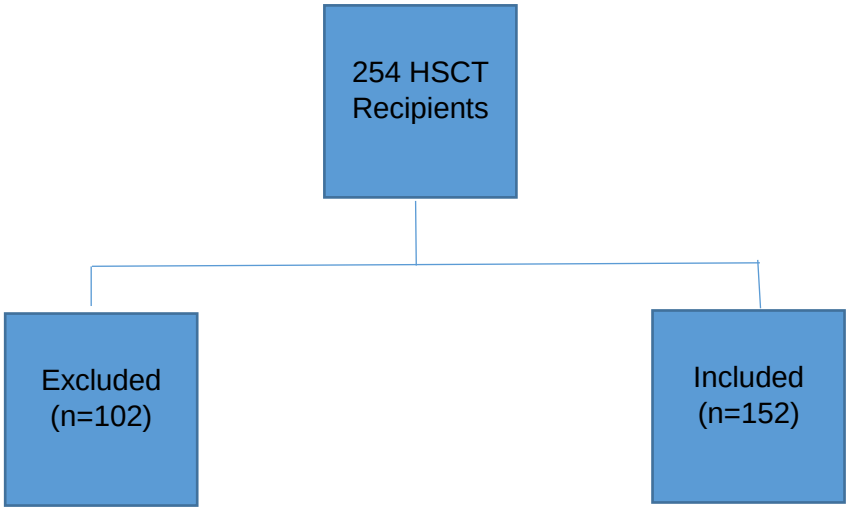


Table 1. Demographic, treatment, and SARS-CoV-2 vaccination characteristics of hematopoietic stem cell transplant recipients

	Total (N=152)	**Responders** (N=141) *Anti-S IgG antibody ≥ 0.8 U/mL*	**Non-Responders** (N=11) *Anti-S IgG antibody < 0.8 U/mL*	**p-value**
Demographic characteristics				
Age, years, median (IQR)	62 (50-68)	62 (50-68)	65 (36-68)	0.57
Sex, n (%)				**0.011**
Female	70 (46.1)	69 (48.9)	1 (9.1)	
Male	30 (53.9)	72 (51.1)	10 (90.9)	
Race, n (%)				0.24
Non-white	13 (8.6)	11 (7.8)	2 (18.2)	
White	139 (91.5)	130 (92.2)	9 (81.8)	
Clinical characteristics				
Disease type, n (%)				0.32
AML/Other Acute Leukemias	41 (27)	38 (27.0)	3 (27.3)	
CML/Other Chronic Leukemias	9 (5.9)	8 (5.7)	1 (9.1)	
ALL	15 (9.9)	14 (9.9)	1 (9.1)	
Lymphomas (HL/NHL)	26 (17.1)	23 (16.3)	3 (27.3)	
Anemias/Hemoglobinopathies	8 (5.3)	6 (4.3)	2 (18.2)	
Myelodysplastic Syndrome/Myelofibrosis	41 (27)	40 (28.4)	1 (9.1)	
Multiple myelomas	12 (7.9)	12 (8.5)	0 (0.0)	
Baseline WBC count, cells x 10^9/L, median (IQR)	4.6 (3.5-6.0)	4.7 (3.5-6.0)	4.6 (3.2-6.2)	0.72
Baseline Lymphocyte count, cells x 10^9/L, median (IQR	1 (0.6-1.5)	1 (0.6-1.5)	1 (0.8-1.1)	0.34
Baseline CD_4 lymphocyte count, cells x 10^6/L, median (	281.5 (183-405)	305.5 (183-420)	225 (171-324)	0.45
Baseline IgG level, mg/dL, median (IQR)	652 (498.5-1020.5)	652 (507-1023)	436 (367-756)	0.18
Preparation intensity, n (%)				0.74
Myeloablative	63 (41.5)	59 (41.8)	4 (36.4)	
Non-myeloablative	7 (4.6)	6 (4.3)	1 (9.1)	
Reduced intensity conditioning	82 (54)	76 (53.9)	6 (54.5)	
Transplant type, n (%)				0.43
Autologous	28 (18.4)	25 (17.7)	3 (27.3)	
Allogeneic	124 (81.6)	116 (82.3)	8 (72.7)	
Acute GVHD, n (%)				0.62
Yes	22 (15.5)	21 (15.9)	1 (10)	
No	120 (84.5)	111 (84.1)	9 (90)	
Chronic GVHD, n (%)				0.57
Yes	57 (37.5)	52 (36.9)	5 (45.5)	
No	95 (62.5)	89 (63.1)	6 (54.5)	
Pharmacotherapy around the time of vaccination				
GVHD prophylaxis (Tacrolimus), n (%)				**< 0.001**
Yes	77 (50.7)	77 (54.6)	0 (0)	
No	75 (49.3)	64 (45.4)	11 (100)	
Acute GVHD treatment (Tacrolimus), n (%)				0.73
Yes	10 (6.6)	9 (6.4)	1 (9.1)	
No	142 (93.4)	132 (93.6)	10 (90.9)	
Chronic GVHD treatment (Tacrolimus), n (%)				0.66
Yes	36 (23.7)	34 (24.1)	2 (18.2)	
No	116 (76.3)	107 (75.9)	9 (81.8)	
Systemic corticosteroids, n (%)				0.85
Yes	65 (42.8)	60 (42.6)	5 (45.5)	
No	87 (57.2)	81 (57.4)	6 (54.5)	
Anti-CD_{20} therapy, n (%)				**0.004**
Yes	16 (10.5)	12 (8.5)	4 (36.4)	
No	136 (89.5)	129 (91.5)	7 (63.6)	
Vaccination characteristics				
Transplant to vaccine time, days, median (IQR)*	140.5 (-48-254)	136 (-56-253)	217 (174-330)	0.096
Number of vaccine doses, n (%)				0.28
1 dose	11 (7.8)	11 (0)	0 (0)	
2 doses	66 (44.0)	62 (31.9)	4 (27.3)	
3 doses	55 (34.0)	48 (44.7)	7 (72.7)	
4 doses	10 (7.1)	10 (7.8)	0 (0)	
5 doses	10 (7.1)	10 (11.3)	0(0)	

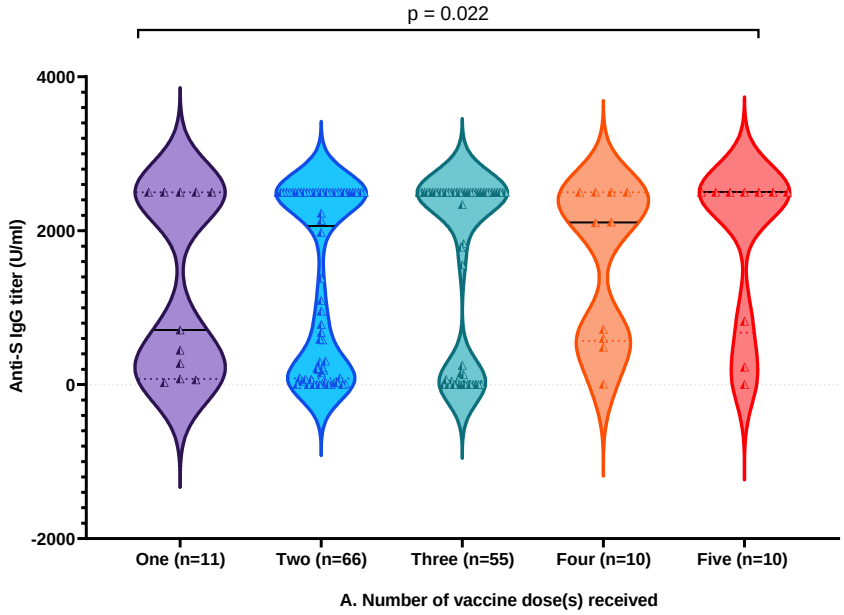
** Negative time means patient had first vaccine dose before transplant.*

***AML** = Acute myelogenous leukemia; **CML** = Chronic myelogenous leukemia; **ALL** = Acute lymphoblastic leukemia; **HL** = Hodgkin lymphoma; **NHL** = Non-Hodgkin lymphoma; **WBC** = White blood cells; **GVHD** = Graft versus host disease; **IQR** = interquartile range.*

Table 2. Predictors of Response Status using Linear and Logistic Regression Analyses

	Univariable analysis Coefficient (95% CI)	p-value	Multivariable analysis Coefficient (95% CI)	p-value
Dose(s) of vaccine received	154.20 (-35.36 - 343.77)	0.110	205.79 (30.10 - 381.47)	**0.022**
Age ≥ 65 Years Old < 65 Years Old (ref.)	-293.60 (-664.22 - 77.03)	0.120	-365.20 (-711.32 - -19.09)	**0.039**
Sex Male Female (ref.)	-451.00 (-808.98 - -92.99)	**0.014**	-343.51 (-682.58 - -4.45)	**0.047**
Anti-CD_{20} therapy Yes No (ref.)	-1256.10 (-1813.74 - -698.45)	**0.000**	-1163.67 (-1717.69 - -609.66)	**0.000**
Systemic corticosteroids Yes No (ref.)	-157.58 (-524.75 - 209.59)	0.398	-28.21 (-399.54 - 343.13)	0.881
Acute GVHD treatment (Tacrolimus) Yes No (ref.)	-769.09 (-1493.01 - -45.17)	**0.037**	-531.75 (-1212.76 - 149.26)	0.125
Chronic GVHD Yes No (ref.)	200.31 (-174.42 - 575.03)	0.293	242.66 (-128.21 - 613.53)	0.198
	Univariable analysis Odds ratio (95% CI)	**p-value**	**Multivariable analysis Odds ratio (95% CI)**	**p-value**
Doses Before Last Titer	0.98 (0.52 - 1.86)	0.948	1.16 (0.59 - 2.31)	0.664
Age ≥ 65 Years Old < 65 Years Old (ref.)	0.74 (0.22 - 2.56)	0.640	0.58 (0.15 - 2.26)	0.436
Sex Male Female (ref.)	0.10 (0.01 - 0.84)	**0.033**	0.11 (0.01 - 0.93)	**0.042**
Anti-CD_{20} therapy Yes No (ref.)	0.16 (0.04 - 0.64)	**0.009**	0.16 (0.03 - 0.70)	**0.016**
Systemic corticosteroids Yes No (ref.)	0.89 (0.26 - 3.05)	0.851	1.75 (0.38 - 8.01)	0.472
Acute GVHD treatment (Tacrolimus) Yes No (ref.)	0.68 (0.08 - 5.93)	0.729	1.20 (0.12 - 11.69)	0.878
Chronic GVHD Yes No (ref.)	0.70 (0.20 - 2.41)	0.573	0.45 (0.10 - 2.09)	0.311

Figure 1A: Anti-Spike IgG responses among hematopoietic transplant recipients by number of doses received. B. Median anti-Spike IgG assay time (days) after the last dose.



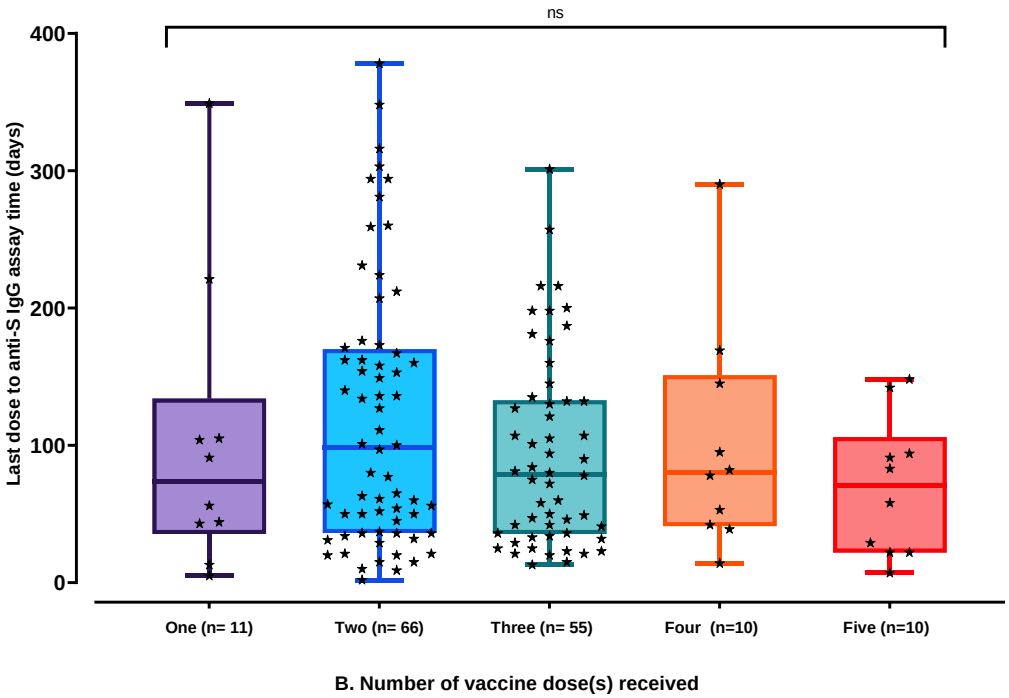
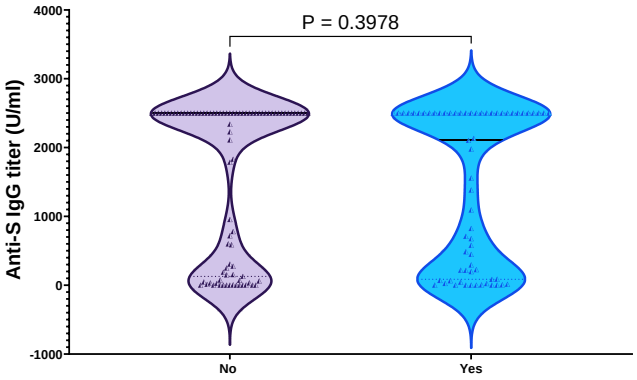
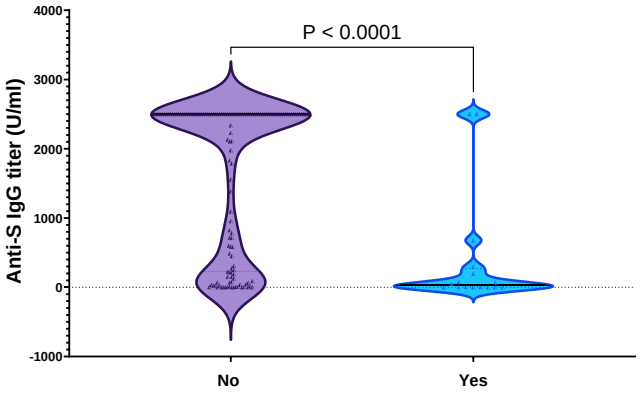


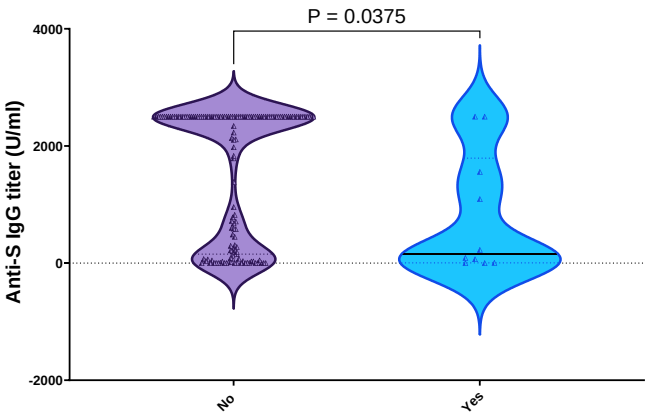
Figure 2: Anti-S IgG responses among different categories of HSCT recipients



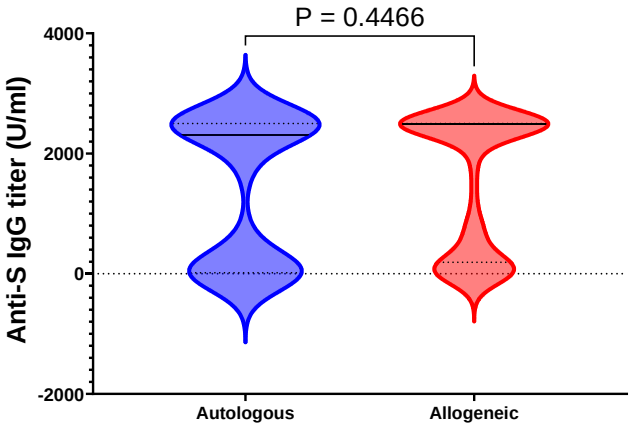
A. High dose steroid treatment (≥20 mg prednisone equivalent per day)



C. Anti-CD20 Therapy



B. Tacrolimus treatment (aGVHD)



Transplant type

Supplementary tables

Anti-S IgG levels stratified by number of vaccine doses			
Vaccine Dose	**Number of Patients**	**Median Titer**	**Median Time from Last Dose**
One Dose	11	710.2 U/mL (IQR 74.1 - 2500)	73.5 days (IQR 43 - 105)
Two Dose	66	2055.5 U/mL (IQR 85.4 - 2500)	98.5 days (IQR 36.5 - 169)
Three Dose	55	2500 U/mL (IQR 46.8 - 2500)	79 days (IQR 36 - 132)
Four Doses	10	2107.5 U/mL (IQR 599.2 - 2500)	80 days (IQR 42 - 145)
Five Doses	10	2500 U/mL (IQR 823.8 - 2500)	70.5 days (IQR 22 - 194)

Anti-S IgG Levels in Primary vs Booster Vaccine Recipients		
Type of Vaccination	**Median Titer**	**Median Time from Last Dose**
Primary Series or Non-Boosted (Up to 3 doses)	2500 U/mL (IQR 71.9 - 2500)	80.5 days (IQR 36 - 160)
Boosted (More than 3 doses)	2500 U/mL (IQR 659 - 2500)	80 days (IQR 34 – 118.5)
Non-responders	0.4 U/mL (IQR 0.4 – 0.4)	61 days (IQR 21 - 107)

Anti-S IgG Levels Between Recipients and Non-Recipients of Immunosuppressive Therapy		
Type of Therapy	**Median Titer**	**Median Time from Last Dose**
Anti-CD20 Therapy	26.3 U/mL (IQR 0.6 – 245.9)	100 days (IQR 75 - 160)
No Concurrent Anti-CD20 Therapy	2500 U/mL (IQR 237.9 - 2500)	78 days (IQR 36 - 153)
Steroids	2104 U/mL (IQR 87.6 - 2500)	81 days (IQR 37 - 160)
No Steroids	2500 U/mL (IQR 128.2 - 2500)	80 days (IQR 36 - 149)

Study Comparing Anti-S IgG Levels Between Males and Females		
Gender	**Median Titer**	**Median Time from Last Dose**
Female	2500 U/mL (IQR 588.3 - 2500)	84 days (36 -160)
Male	1255.25 U/mL (IQR 33.9 - 2500)	78 days (IQR 36 - 145)

Group	**Median Titer (U/mL)**	**Median Time from Last Dose (days)**
Autologous Transplant	2303.5 (IQR 25.3 - 2500)	132 (IQR 83 - 181)
Allogeneic Transplant	2500 (IQR 193 - 2500)	63 (36 - 145)

Group	**Median Titer (U/mL)**	**Median Time from Last Dose (days)**
Tacrolimus Treatment	156.7 (IQR 3.53 - 1556)	107 (IQR 50 - 148)
No Tacrolimus Treatment	2500 (IQR 153.5 - 2500)	80.5 (36 - 154)

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Paper 2

Blunted SARS-CoV-2 Vaccine-induced Immune Response among Hematopoietic Stem Cell Transplant Patients: A Systematic Review and Meta-analysis

Afoke Kokogho[1,3]; Trevor A. Crowell[4,5]; Paul A. Bain[3], Sudaba Popal[1,], Muneerah Aleissa[1,2]; Jun Bai Park Chang[1,2]; Deema Aleissa, Agho Osamade[,6], Lewis Novack[1,2,4], August Heithoff[1,2,]; Lindsey R. Baden[1,2,3] ; Amy C. Sherman[1,2,3] ; Stephen R. Walsh,[1,2,3]

(1) Division of Infectious Diseases Brigham and Women's Hospital, Boston, MA, (2) Dana-Farber Cancer Institute, Boston, MA, (3) Harvard Medical School, Boston, MA, (4) Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD (5) U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, Maryland, USA (6) Internal medicine Solutions (7) Tufts University School of Dental Medicine, Boston, MA (8) Lumen Foundation

Abstract

Background: Hematopoietic stem cell transplant (HSCT) recipients may fail to sero-convert following SARS-CoV-2 vaccination. Existing studies have been mostly observational and limited by sample size. We described the prevalence and identified predictors of this failure.

Methods: After PROSPERO registration (ID 388154), a comprehensive search of electronic databases, including MEDLINE (Ovid), Embase (Elsevier), Web of Science Core Collection (Clarivate), the Cochrane Central Register of Controlled Trials (Wiley), and the Cochrane COVID-19 Study Register was conducted on January 20, 2023. We defined a blunted response as not achieving a seroconversion (positive anti-S IgG titer)

after receiving at least two vaccine doses, indicated by an assay cut-off value. With 95% confidence intervals (CI) across all studies, a random-effects model was used to combine the pooled effect sizes. Quality and risk of bias assessment were determined using the Newcastle-Ottawa Scale and Robins-1 scale respectively.

Results: Out of 903 identified and 439 screened, 45 studies were included in this analysis including 4568 participants (Figure 1). Pooled absent sero-conversion was 20% (95% CI: 17% - 24%) with significant heterogeneity (95.10%) among included studies (1 clinical trial, 1 cross-sectional study, 1 case-control study, and 42 observational cohort studies) (Figure 2A). Subgroup analysis showed no difference between autologous [0.21 (CI 0.12 – 0.31)] and allogeneic [0.20 (CI 0.17 – 0.24)] transplant recipients (Figure 2b and 2C). Identified Predictors included; time interval between transplantation and vaccination, concurrent anti-CD20 therapy, and specific treatments for graft versus host disease (Appendix 3). No publication bias was observed but the Galbraith's plot asymmetry showed evidence of small-study effects (Figure 3).

Conclusion: Our findings emphasize the significant prevalence of blunted responses to SARS-CoV-2 vaccination in HSCT recipients and underscore need for close monitoring and aggressive risk factor management in this immunocompromised population.

Keywords: COVID-19, vaccine, HSCT, predictors, systematic review, meta-analysis, response, sero-conversion, immunogenicity, transplant, antibody

INTRODUCTION

Patients with hematological malignancies may undergo hematopoietic stem cell transplantation (HSCT) if they are unable to achieve remission through immunotherapy, chemotherapy, or radiotherapy (1–3). As a result of their disease or treatment, these patients frequently become immunosuppressed which increases the risk of severe infection with SARS-CoV-2 (4). The availability of Coronavirus disease 2019 (COVID-19) vaccines has reduced mortality and disease severity among HSCT recipients (5), however, HSCT patients have shown variable seroconversion rates and responses following vaccination. Vaccine responsiveness, in terms of neutralizing antibody responses after COVID vaccination, has been shown to correlate with protection in healthy participants (6–10), but immunocompromised individuals were excluded from the large efficacy studies (11). Existing studies among HSCT recipients have been mostly observational and limited by sample size, but many of these studies have noted that transplant recipients can remain unresponsive despite multiple doses of the vaccine (12–15). This meta-analysis aims to evaluate the pooled prevalence of this attenuated response to the COVID-19 vaccine among HSCT recipients. We also aim to describe the risk factors associated with the lack of immunogenicity to the COVID-19 vaccines.

METHODS:

This study was prospectively registered with PROSPERO (https://www.crd.york.ac.uk/prospero), registration (ID 388154). This report was completed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (16).

Study selection:

To identify studies reporting on the attenuated vaccine response in HSCT patients, we searched the electronic databases MEDLINE (Ovid), Embase (Elsevier), Web of Science Core Collection (Clarivate), the Cochrane Central Register of Controlled Trials (Wiley), and the Cochrane COVID-19 Study Register (https://covid-19.cochrane.org). Searches were designed and carried out by a medical librarian (PAB) and included terms for human stem cell transplants and vaccines against SARS-Cov-2 (Appendix 2). Controlled vocabulary terms were included when available. Searches were carried out on January 20, 2023; no date or language limits were applied to the search. In addition, the reference lists of relevant articles and reviews were manually searched to identify additional studies.

Inclusion and Exclusion Criteria:

Studies were included if they were observational or interventional studies (randomized controlled trials), assessed antibody (anti-S IgG) response to COVID vaccines, among adults (≥18 years old) HSCT recipients. Non-responsiveness or an attenuated response was defined as not achieving the pre-specified assay cut-off for positivity. Studies that reported transplant patients other than HSCT recipients or exclusively reported T-cell response to the COVID vaccines were excluded.

Screening and Data Abstraction:

A pair of reviewers (AK, MA, JP, and LN) independently screened the titles and abstracts of all identified studies for eligibility. Full-text articles were then reviewed for inclusion. Any discrepancies were resolved through discussion (between AK, SRW, and ACS) and consensus. Data were abstracted (by AK, SP, JP, MA, LN, DA, and AH) on a spreadsheet (MS Excel) into five (5) broad categories; study design, patient characteristics, vaccination status, the prevalence of vaccination failure, and predictors of attenuated or blunted vaccinate response (Figure 2). Specific data abstracted included: name of the primary author, year of publication, study title, total sample size, duration of the study, type of study, risk of bias, funding source, conflicts of interest, the median age of study participants, number of males versus females, vaccine type, assay cut-off value of positivity, median anti-S IgG titer, number of autologous transplant and

allogeneic transplant recipient, number of HSCT recipients who produced a positive anti-S IgG response, number of HSCT recipients who did not respond positively, number of positive allogeneic HSCT responders and non-responders, number of positive autologous HSCT responders and non-responders, identified risk factors and author contacts (Appendix1).

Quality Assessment:

The quality of the included studies was assessed using the Newcastle-Ottawa Scale for non-randomized studies. Three categories were evaluated: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. Each category was rated using specific criteria and a score was given for each study. Studies were considered to be of high quality if they scored 7 or higher on the Newcastle-Ottawa Scale (17). A pair of reviewers (AK/SP, MA/DA, LA/AK, JP/AH) independently assessed the quality of each study.

Risk of bias assessment:

The Robins-1 bias tool is ideal for assessing the risk of bias in observational studies(18). Using this tool, we assessed this risk in different bias domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Each domain was rated as low, moderate, or serious and an overall risk of bias rating

was assigned to each study based on the ratings of individual domains. A pair of reviewers (AK/SP, MA/DA, LA/AK, JP/AH) independently assessed the risk of bias in each included study using the Robins-1 tool. Disagreements were resolved through discussion and consensus.

Data Analysis:

A meta-analysis was performed using a random-effects model using StataCorp. (2021). Stata statistical software: Release 17. College Station, TX: StataCorp LLC., to estimate the overall prevalence of an attenuated response to SARS-CoV-2 vaccination among HSCT recipients. A funnel plot and regression-based Egger tests were used to investigate publication bias. To quantify the magnitude of small-study effects, regression-based Egger tests were conducted using a random-effects model and residual maximum likelihood (REML) method. The null hypothesis (H0) for both tests was that there is no small-study effect (i.e., beta1 = 0), and the alternative hypothesis (Ha) was that there is a small-study effect (beta1 ≠ 0).

RESULTS:

Electronic data searching returned 439 unique records (Figure 1). Ninety-six reports were selected for full-text examination; 45 reports, representing 45 independent studies, were included in the analysis. The overall prevalence of non-responsiveness to the SARS-CoV-2 vaccine among HSCT recipients was 20% (95% CI: 17% - 24%), with significant heterogeneity among included studies (Figure 2). The random-effects model was used with the REML method, which took into account both within-study and between-study variations in effect size. This heterogeneity was statistically significant, as indicated by a Q-value of 463.51 and a p-value of <0.0001 in the test of homogeneity. and the $ı^2$ statistic (95.10%). This suggests that the variation among the study results is not due to chance and there is substantial heterogeneity in the true effects across studies. Finally, the test of ES=0 indicated that the proportion is significantly different from zero, with a z-value of 10.86 and a p-value of less than 0.05.

The result of a sub-group analysis showed that the pooled proportion of autologous and allogeneic transplant recipients participants with a blunted immune response to SARS-CoV-2 vaccination were 0.21 (CI 0.12 – 0.31) and 0.20 (CI 0.17 – 0.24), respectively (Supplementary table). Figure 3 shows the funnel plot for the meta-analysis. The plot includes 45 studies and displays the standard error (SE) of the effect size estimate on the horizontal axis and the effect size estimate on the vertical axis. The plot demonstrates a roughly symmetric distribution of studies around the overall effect size estimate, suggesting little evidence of publication bias or other small-study effects. We further explored the presence of publications bias and other small–study effects using the Eggers asymmetry test. The results showed evidence of small-study effects in the

meta-analysis. The estimated intercept was 3.94 with a standard error of 0.892. The z-score for the intercept was 4.42 (p=0.001), indicating that the intercept was significantly different from zero (Supplementary figure).

Assessment of Quality and Bias:

The study quality was assessed as mostly either good or fair and studies were mostly prospective or retrospective observational studies. The sample sizes ranged from 22 to 687, with a median of 76 (IQR 56 - 133). The observation periods ranged from one month to 22 months, with the majority of studies having a duration of two to six months (Appendix 1).

overall, our meta-analysis showed a low to moderate risk of bias of selection bias, performance bias, detection bias, and attrition bias using the Robbins-1 tool. However, there was a risk of publication bias identified in our analysis. (Appendix 3).

Predictors of attenuated and blunted SARS-CoV-2 Vaccine response:

The meta-analysis revealed several risk factors associated with attenuated or blunted response to COVID-19 vaccination among patients who had undergone hematopoietic stem cell transplantation (Appendix 3).

In both allogeneic-HSCT and auto-HSCT patients, insufficient protective levels of antibody production were associated with low CD19 + lymphocyte counts and serum IgG levels. Additionally, post-transplant period, use of immunosuppressive drugs, presence of graft-versus-host disease (GVHD), peripheral lymphocyte counts, and CD4 + , CD8 + , and CD 56 + lymphocyte counts were associated with allogeneic-HSCT patients only.

Univariate analysis showed that patients vaccinated within 4.5 years of transplantation, those still receiving immunosuppression, and patients with acute or moderate to severe chronic GVHD were more likely to remain seronegative. Moreover, the time elapsed since HSCT (transplant within one year), recent (<1 year) HSCT, lymphopenia (<1000 cells/μL), and receipt of immunosuppressive treatment or chemotherapy at the time of vaccination were all associated with poor response.

Anti-CD20 monoclonal antibodies, prednisone use, and rituximab administration within one year before vaccination were predictive of poor humoral response. Inconsistent findings were observed for chronic GVHD and ongoing immunosuppressive therapy, with some studies showing a significant association and others showing no significant difference in serological responses.

Other factors associated with a suboptimal antibody response after the third dose of vaccine included chronic kidney disease, haploidentical donor status, and a lower median lymphocyte count at the third dose. Furthermore, vaccine type (Pfizer) was associated with a higher response compared to AstraZeneca among HSCT patients, but the sample size was too small to draw definitive conclusions.

In summary, this meta-analysis identified several risk factors associated with attenuated or blunted responses to COVID-19 vaccination among HSCT patients. These findings can inform clinical decision-making and guide the development of interventions to improve vaccine efficacy in this vulnerable population.

DISCUSSION:

Our meta-analysis aimed to investigate the prevalence of non-responsiveness to the SARS-CoV-2 vaccine among hematopoietic stem cell transplant (HSCT) recipients. In this study, we found a pooled prevalence of non-responsiveness of 20% (95% CI: 17% - 24%) based on the analysis of 45 studies.

Compared to healthy adults (100% positive response rates), HSCT recipients and Other immunocompromised groups may have a sub-optimal or blunted response to COVID-19 vaccines(19–23). Studies among solid organ transplant recipients and patients with immune-mediated inflammatory diseases were comparable to findings in HSCT recipients (23,24). However, the extent of this response may differ between the two groups due to differences in the nature and intensity of their immunosuppression. Solid organ transplant recipients are typically on long-term immunosuppressive therapy to prevent graft rejection, which may lead to a weaker immune response to vaccines(25). A study by Holden et al. reported 65% non-responsiveness in a group of solid organ transplant (SOT) recipients 6 weeks after the second dose vaccination(26). While Kamar et al. reported 32% non-responsiveness after third dose vaccination among SOT recipients (25). Similarly, Boyarsky reported and Werbel et al., in two separate studies, showed 46% and 67% of SOTs failed to respond to the vaccines after second dose vaccinations respectively(27,28).

A study by Hall et al. (2021) reported that only 54% of solid organ transplant recipients developed detectable antibodies after two doses of the Moderna vaccine. However, a third dose of the mRNA vaccine was found to significantly increase the proportion of solid organ transplant recipients who developed detectable antibodies (Boyarsky et al., 2021; Hall et al., 2021). In a large meta-analysis comparable to ours, Sakuraba et al. showed 6158 SOT recipients had a poorer response (36% non-responsiveness) compared to HSCT recipients(24). Another meta-analysis by Sakuraba et l., showed an overall prevalence rate (16.6% non-responsiveness) after two doses, in patients with immune-mediated disease compared to what we observed in HSCT recipients. Therefore, a significant proportion of transplant patients and some immunocompromised groups remain at high risk of infection from SARS-CoV-2 infection as well as its complications.

We observed a high (>75%) heterogeneity among the included studies, as indicated by a Q-value of 463.51 and a p-value of <0.0001 in the test of homogeneity, and the ı2 statistic (95.10%). This suggests that the variation among the study results is not due to chance, and there is substantial heterogeneity in the true effects across studies. This high heterogeneity in our study may be explained by several factors including the differences in study designs, number of doses of vaccines received, assay type, assay time, use of immune-suppressive agents, and type of transplant. A similarly high (88.9%) aloverall heterogeneity was observed in a meta-analysis by Sakuraba et al., for similar reasons(24). With heterogeneity as high as 93.12% on a subgroup analysis among heart and lung transplant recipients and 86% among renal transplant recipients.

Our results of subgroup analysis revealed that the proportion of autologous and allogeneic transplant recipients participants with blunted immune response to SARS-

CoV-2 vaccination were 0.21 (CI 0.12 – 0.31) and 0.20 (CI 0.17 – 0.24), respectively. This finding emphasizes the need for further research and development of vaccination strategies tailored to HSCT recipients to improve vaccine efficacy.

On visual inspection, our funnel plot analysis demonstrated a roughly symmetric distribution of studies around the overall effect size estimate, indicating little evidence of publication bias or other small-study effects. However, Egger's asymmetry test showed evidence of small-study effects in the meta-analysis, suggesting that caution should be exercised in interpreting the results. To reduce the potential impact of publication bias, future research should include both published and unpublished studies.

The meta-analysis identified multiple risk factors associated with attenuated or blunted responses to COVID-19 vaccination among hematopoietic stem cell transplantation (HSCT) patients. Both allogeneic HSCT and auto-HSCT patients had insufficient antibody production when their CD19 + lymphocyte counts and serum IgG levels were low. Post-transplant period, use of immunosuppressive drugs, presence of graft-versus-host disease (GVHD), peripheral lymphocyte counts, and specific lymphocyte counts were associated with allogeneic HSCT patients only. The time elapsed since HSCT, recent HSCT, lymphopenia, receipt of immunosuppressive treatment or chemotherapy at the time of vaccination, and some specific medications were associated with poor response. Additionally, chronic kidney disease, haploidentical donor status, and vaccine type (AstraZeneca) were identified as factors associated with a suboptimal antibody response after the third dose of the vaccine. These findings can guide the development of interventions to improve vaccine efficacy and inform clinical decision-making for this vulnerable population.

Our study adds to the growing body of literature on the prevalence of SARS-CoV-2 vaccine failure in immunocompromised individuals. The frequent occurrence of blunted immune responses to SARS-CoV-2 vaccines in HSCT recipients emphasizes the necessity of further research for effective prophylaxis in this group. Utilizing highly potent neutralizing monoclonal antibodies (mAbs) against SARS-CoV-2 (29) has proven to be a suitable method for immunocompromised individuals such as HSCT recipients unable to mount a vaccine-induced antibody response (30). Although mAb administration has been effective, the emergence of immunoevasive variants of concern, including the omicron variant (30) has limited their deployment. Further studies are needed to identify potential predictors of blunted or attenuated vaccine response to the COVID vaccines and to develop strategies to improve vaccine efficacy in immunocompromised HSCT recipients who do not respond to the COVID-19 vaccines.

In summary, our meta-analysis provides evidence of a high prevalence of non-responsiveness to the SARS-CoV-2 vaccine among HSCT recipients. A lot still needs to be done to improve the vaccination strategy, approach, and efficacy of the COVID vaccines, to optimize the benefits for immunocompromised patients and specifically for HSCT recipients which we understudied.

CONCLUSION:

Overall, the SARS-CoV-2 vaccine did not induce an immune response in about 20% of vaccinated HSCT recipients. This study highlights the most up-to-date estimate of the magnitude of the attenuated SARS-CoV-2 vaccine-induced responses among HSCT recipients. Most significantly, B-cell ablative therapies, time from transplant to the first vaccination, and concurrent specific immunosuppressive therapies have shown strong

associations with SARS-CoV-2 vaccine failure among HSCT recipients. These findings underscore the importance of continuous monitoring of anti-S IgG titers, and the need to develop alternate protective strategies among unresponsive HSCT recipients.

LIMITATIONS:

Our meta-analysis has several limitations that may impact the interpretation of the results. A broad range of COVID-19 vaccines have been approved worldwide, however, our analysis included mostly studies involving the use of mRNA-1273 or BNT162b2, with very few studies using AD26.COV2.S or AZD-1222/ChAdOx1 nCoV-19 which may have impacted our result.

Our primary outcome was focused on the humoural response (antibody) to the vaccines without assessing T-cell responses. It is worth noting that immune protectiveness to the vaccines also depends on the patient's T-cell responses. Although levels of antibody responses are predictive of the risks of SARS-CoV-2 susceptibility(19,20,31–34).

Due to limited data on median antibody titer and uniformity in assay type, timing, and threshold for positivity, we could not conduct more subgroup analysis. However, studies showing median titer responses and levels of neutralizing titers of the COVID vaccines should be encouraged despite the challenges with continually evolving strains of SARS-CoV-2.

One important limitation is the high heterogeneity observed between the included studies. As a result, the findings of this meta-analysis should be interpreted with caution. This could have been due to differences in underlying disease, transplant type, transplant

conditioning, study size and methods, assay types, the threshold for positivity, and so on. It is worth noting also that the predominant antibody analysis for most study used antibody tests marketed by Abbott, Diasorin, and Roche.

Another potential limitation is the reliance on published literature, which may have introduced publication bias into our analysis. In addition, some of the studies included in the meta-analysis were limited by small sample sizes, lack of serological response comparison with healthy individuals, and absence of pre-vaccination status data in some cases.

Lastly, It is important to note that the results of this meta-analysis may be limited to hematopoietic stem cell transplant patients, and may not be generalizable to other populations.

Despite these limitations, our meta-analysis provides important insights into the efficacy of COVID-19 vaccines in hematopoietic stem cell transplant patients.

FUNDING:

This study was not funded by any external source.

ETHICAL COMPLIANCE:

As this study is a systematic review and meta-analysis of published literature, ethical approval was not required. However, all included studies obtained ethical approval and obtained informed consent from their participants.

DATA SHARING:

The data used in this study are publicly available and can be obtained from the original studies.

DECLARATION OF COMPETING INTERESTS:

SRW has received institutional funding from the National Institute of Allergy and Infectious Diseases/National Institutes of Health; and institutional grants or contracts from Sanofi Pasteur, Janssen Vaccines/Johnson & Johnson, Moderna Tx, Pfizer, Vir Biotechnology, and Worcester HIV Vaccine; has participated on data safety monitoring or advisory boards for Janssen Vaccines/Johnson & Johnson; and his spouse holds stock/stock options in Regeneron Pharmaceuticals. ACS is involved in human immunodeficiency virus (HIV), coronavirus (COVID), and other vaccine clinical trials conducted in collaboration with the NIH, HIV Vaccine Trials Network, COVID Vaccine Prevention Network, International AIDS Vaccine Initiative, Crucell/Janssen, and Moderna. The other authors have declared no competing interests.

Figure 1: Selection of studies

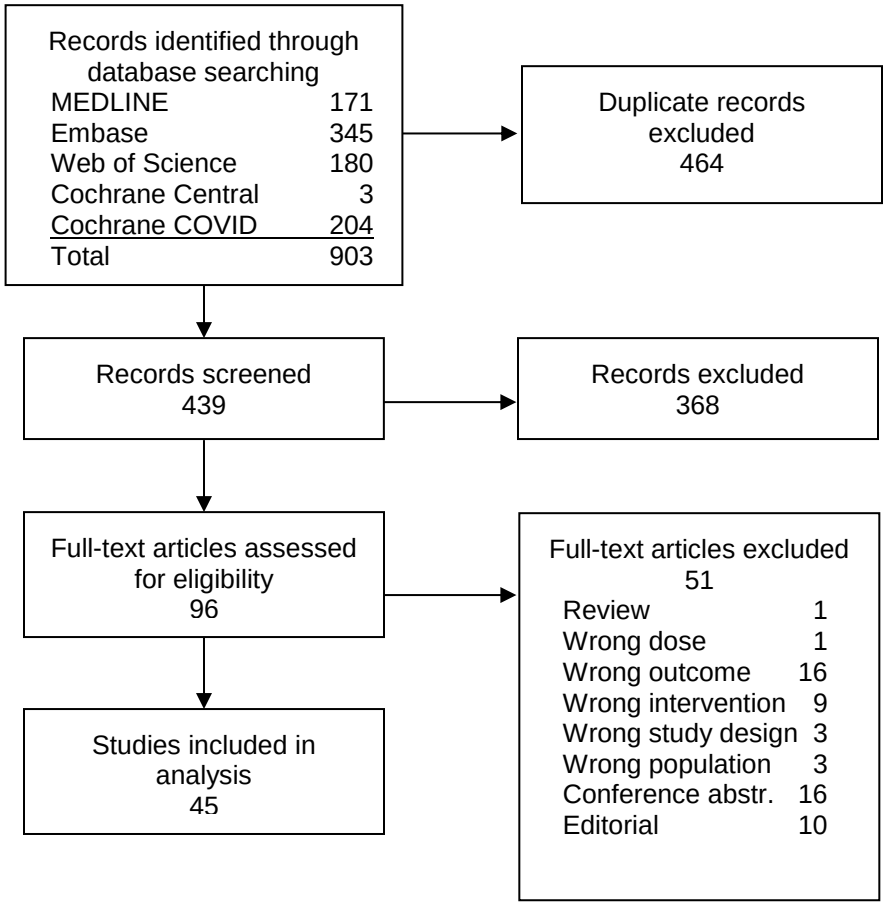


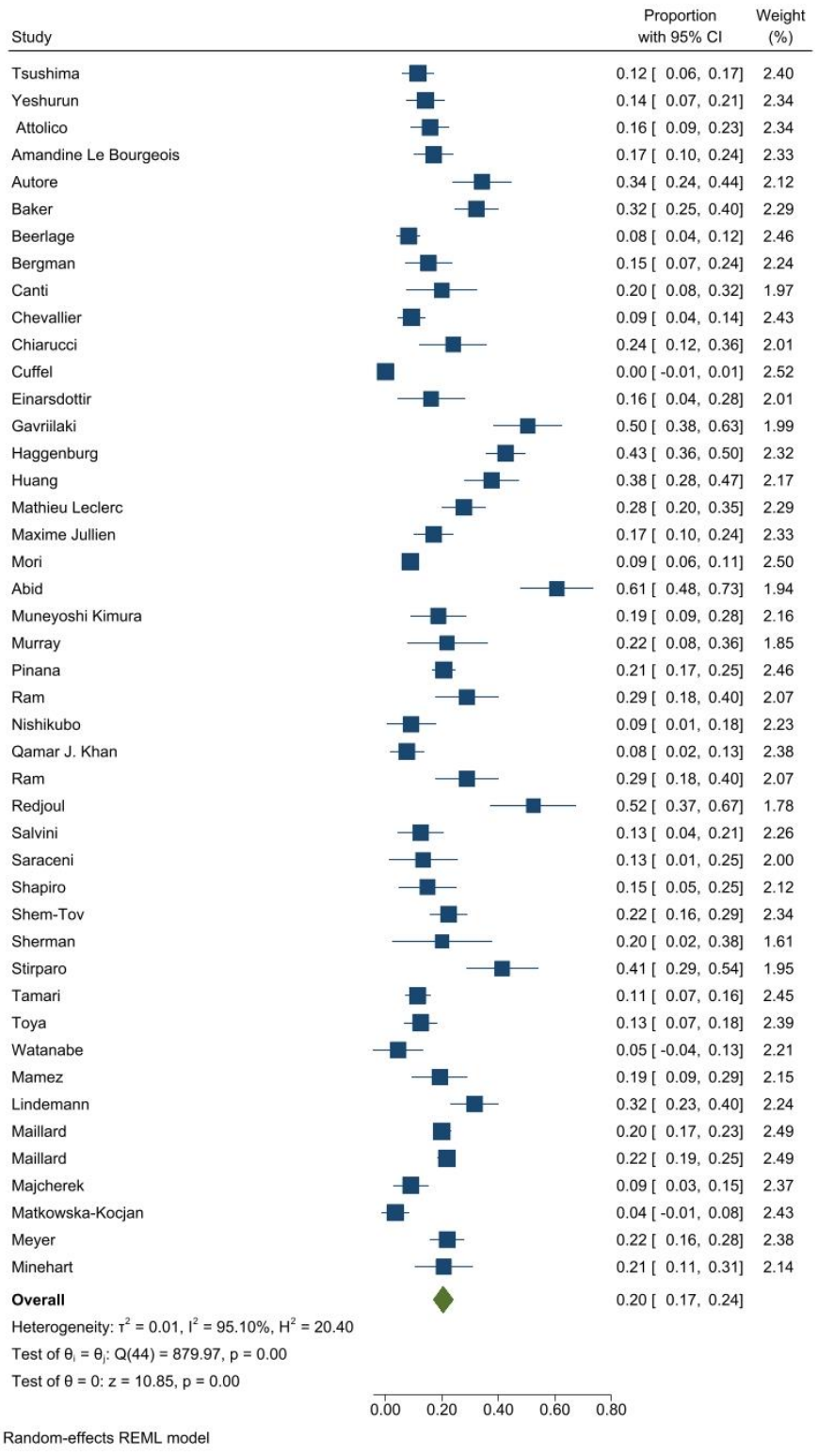
Table 1. Data Abstraction Sheet (Attached as an appendix)

Study ID	Primary Author, year	Year	Study Title	Total Sample Size + Control	Approximate Study Duration (Months)	Study Type
33	Tsushima 2022	2022	Antibody response to COVID-19 vaccine in 130 recipients of hematopoietic stem cell transplantation	270	2	prospective observational study
206	Yeshurun 2022	2022	Humoral serological response to the BNT162b2 vaccine after allogeneic haematopoietic cell transplantation	106	2	prospective cohort study
382	Attolico 2022	2022	Serological response following BNT162b2 anti-SARS-CoV-2 mRNA vaccination in haematopoietic stem cell transplantation patients	221	6	Retrospective Cohort
342	Amandine Le Bourgeois, 2021	2021	Safety and Antibody Response After 1 and 2 Doses of BNT162b2 mRNA Vaccine in Recipients of Allogeneic Hematopoietic Stem Cell Transplant	117	3	Prospective Cohort Study
220	Autore 2022	2022	Immunogenicity of SARS-CoV-2 vaccination in patients undergoing autologous stem cell transplantation. A multicentric experience	82	22	Retrospective Cohort
53	Baker 2021	2021	Assessment of Serology after Sars-Cov-2 Vaccine in Allogeneic HCT Recipients	149	5	Retrospective Cohort
34	Beerlage 2022	2022	Antibody response to mRNA SARS-CoV-2 vaccination in 182 patients after allogeneic hematopoietic cell	182	2	Retrospective Cohort Study

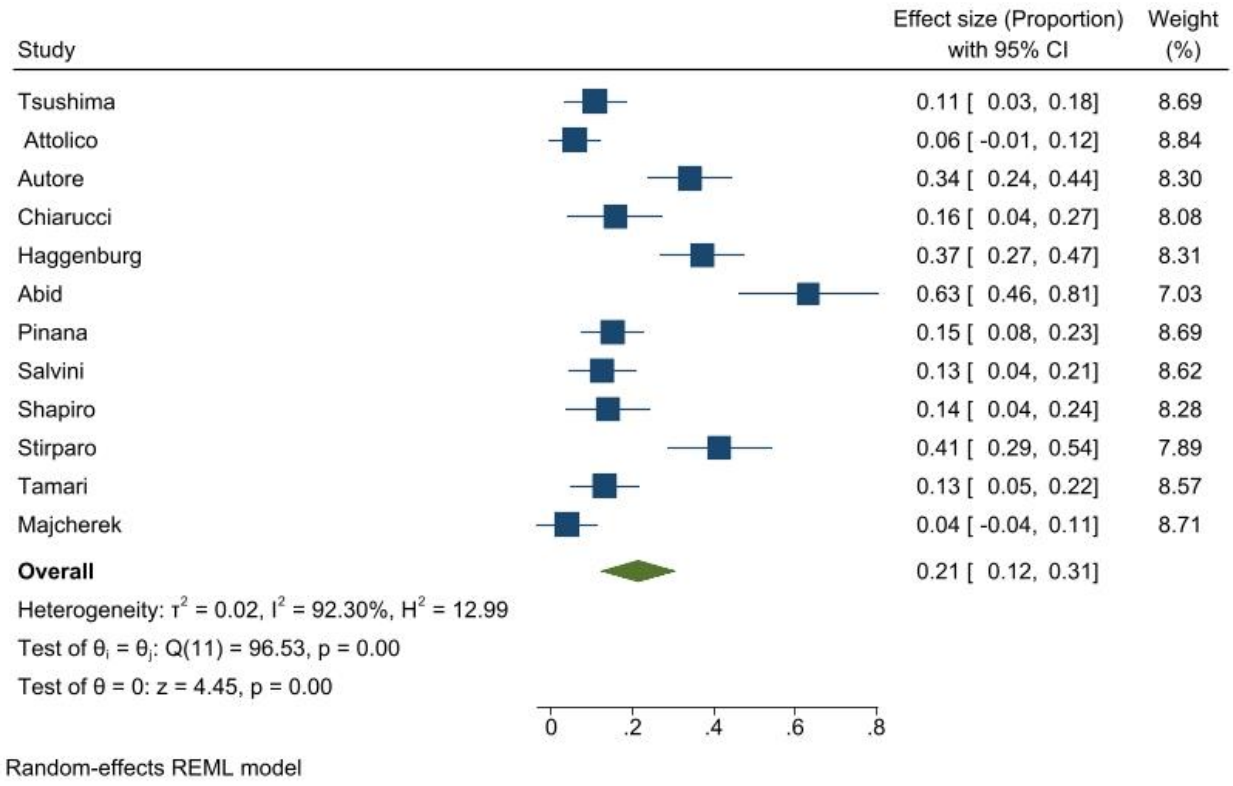
Table 2. The Robbins-1 tool and the Newcastle-Ottawa scale were used for the assessment of quality and bias respectively. (Attached as an appendix)

The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analysis
Selection
Representativeness of the exposed cohort
Truly representative (one star)
Somewhat representative (one star)
Selected group
No description of the derivation of the cohort
Selection of the non-exposed cohort
Drawn from the same community as the exposed cohort (one star)
Drawn from a different source
No description of the derivation of the non exposed cohort
Ascertainment of exposure
Secure record
Structured interview
Written self report
No description
Other
Demonstration that outcome of interest was not present at start of study
Yes (one star
No
Comparability
Comparability of cohorts on the basis of the design or analysis controlled for confounders
The study controls for age, sex and marital status (one star)
Study controls for other factors (list)(one star)
Cohorts are not comparable on the basis of the design or analysis controlled for confounders
Outcome
Assessment of outcome
Independent blind assessment (one star)
Record linkage (one star)
Self report
No description
Other
Was follow-up long enough for outcomes to occur
Yes (one star)
No
Indicate the median duration of follow-up and a brief rationale for the assessment above:_
Adequacy of follow-up of cohorts
Complete follow up- all subject accounted for (one star)
Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% (one star)
Follow up rate less than 80% and no description of those lost
No statement

Figure 2a: Pooled effect size (proportion) of hematopoietic stem cell transplant recipients with blunted vaccine response.



2b. Pooled proportion of autologous hematopoietic stem cell transplant recipients with blunted vaccine response.



2c. Pooled proportion of allogeneic hematopoietic stem cell transplant recipients with bluntedvaccine responses.

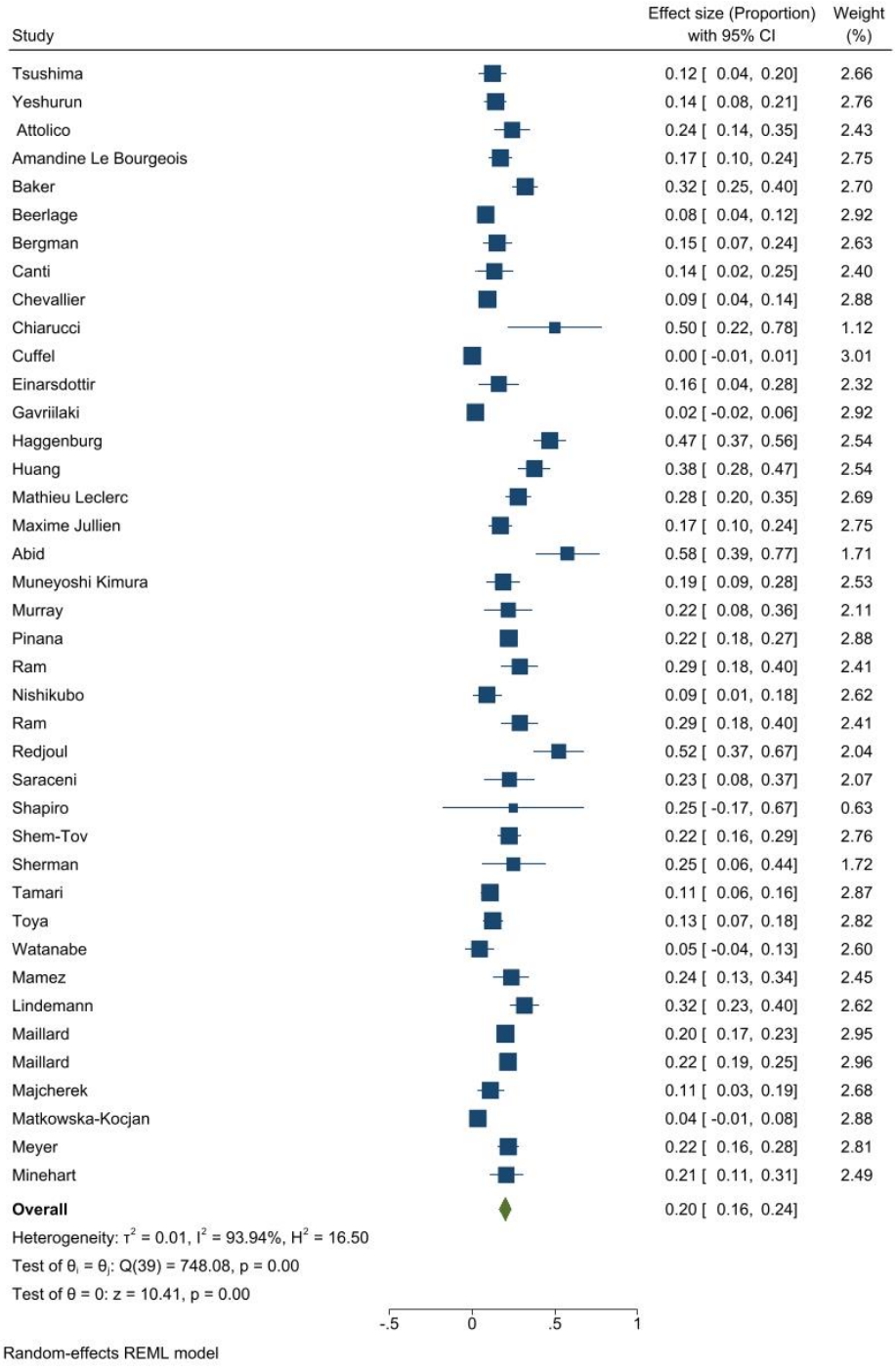
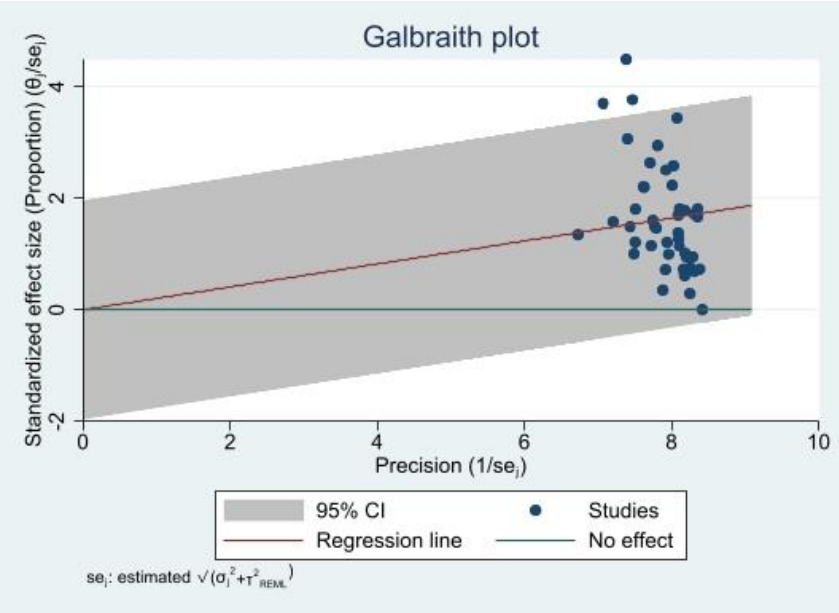
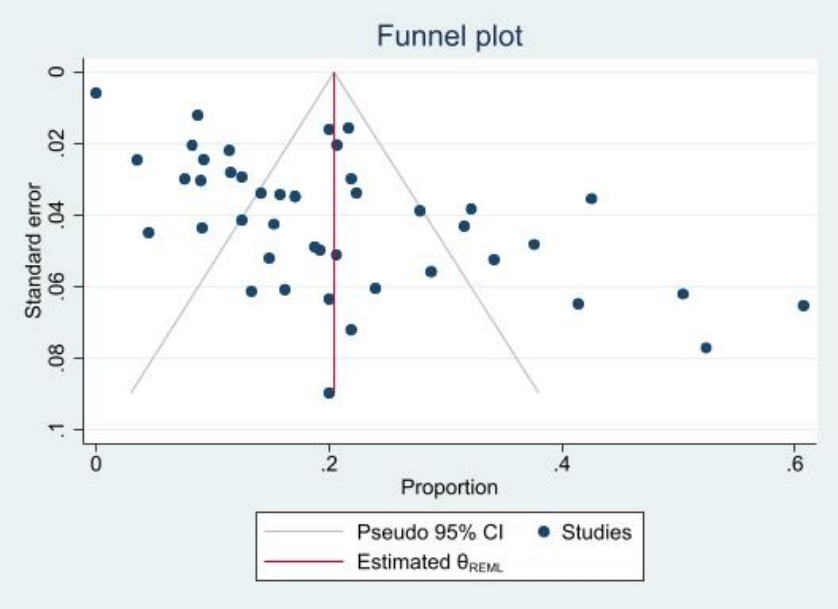


Figure 3: Test of publication bias (Funnel plot) and Galbraith plot of heterogeneity





Appendix 2: electronic database searches

MEDLINE (Ovid)
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to January 19, 2023>
Jan. 20, 2023
171 Records

1. exp stem cell transplantation/ or (exp hematopoietic stem cells/ and exp transplantation/) or (hsct or ((h?ematopoietic or hsc) adj6 transplant*) or (stem cell* adj6 transplant*)).ab,kf,kw,ti. 128377

2. exp covid-19 vaccines/ or (((covid or covid19 or sars-cov-2 or sarscov2 or sars-cov2 or sarscov-2 or n-cov or ncov or coronavirus*) adj6 vaccin*) or mrna-1273* or elasomeran or m-1273 or m1273 or cx-024414 or cx024414 or tak-919 or tak919 or Ad26COVS1 or JNJ-78436735 or JNJ78436735 or bnt-162* or bnt162* or abdavomeran or tozinameran or comirnaty or ChAdOx1 or axd1222 or AZD-1222 or vaxzevria or covishield).ab,kf,kw,ti. 37398

3. 1 and 2 171

Embase (Elsevier, 1974-, Preprints)
Jan. 20, 2023
176 Records

1. 'hematopoietic stem cell transplantation'/exp/mj OR (hsct OR ((hematopoietic OR haematopoietic OR hsc) NEAR/6 transplant*) OR ('stem cell*' NEAR/6 transplant*)):ab,ti,kw 163353

2. 'SARS-CoV-2 vaccine'/exp/mj OR (((covid OR covid19 OR 'sars-cov-2' OR sarscov2 OR 'sars-cov2' OR 'sarscov-2' OR 'n-cov' OR ncov OR coronavirus*) NEAR/6 vaccin*) OR 'mrna-1273*' OR elasomeran OR 'm-1273' OR m1273 OR 'cx-024414' OR cx024414 OR 'tak-919' OR tak919 OR Ad26COVS1 OR 'JNJ-78436735' OR JNJ78436735 OR 'bnt-162*' OR bnt162* OR abdavomeran OR tozinameran OR comirnaty OR ChAdOx1 OR axd1222 OR 'AZD-1222' OR vaxzevria OR covishield):ab,ti,kw 3963

3. #1 AND #2 176

Web of Science Core Collection (Clarivate)

A&HCI , BKCI-SSH , BKCI-S , CCR-EXPANDED , ESCI , IC , CPCI-SSH , CPCI-S , SCI-EXPANDED , SSCI
Jan. 20, 2023
180 Records

1. TS=(hsct OR ((hematopoietic OR haematopoietic OR hsc) NEAR/6 transplant*) OR ("stem cell*" NEAR/6 transplant*)) 126723

2. TS=(((covid OR covid19 OR "sars-cov-2" OR sarscov2 OR "sars-cov2" OR "sarscov-2" OR "n-cov" OR ncov OR coronavirus*) NEAR/6 vaccin*) OR "mrna-1273*" OR elasomeran OR "m-1273" OR m1273 OR "cx-024414" OR cx024414 OR "tak-919" OR tak919 OR Ad26COVS1 OR "JNJ-78436735" OR JNJ78436735 OR "bnt-162*" OR bnt162* OR abdavomeran OR tozinameran OR comirnaty OR ChAdOx1 OR axd1222 OR "AZD-1222" OR vaxzevria OR covishield) 35026

3. #1 AND #2 180

Cochrane Central Register of Controlled Trials (Wiley)
Jan. 20, 2023
3 Records

Title, Abstract, Keyword

(hsct OR ((hematopoietic OR haematopoietic OR hsc) NEAR/6 transplant*) OR (("stem cell" OR "stem cells") NEAR/6 transplant*))
AND
(((covid OR covid19 OR "sars-cov-2" OR sarscov2 OR "sars-cov2" OR "sarscov-2" OR "n-cov" OR ncov OR coronavirus*) NEAR/6 vaccin*) OR "mrna-1273*" OR elasomeran OR "m-1273" OR m1273 OR "cx-024414" OR cx024414 OR "tak-919" OR tak919 OR Ad26COVS1 OR "JNJ-78436735" OR JNJ78436735 OR "bnt-162*" OR bnt162* OR abdavomeran OR tozinameran OR comirnaty OR ChAdOx1 OR axd1222 OR "AZD-1222" OR vaxzevria OR covishield)

Cochrane COVID-19 Study Register
Jan. 20, 2023
204 Records (The search engine reported 174, but 204 records were downloaded and imported into EndNote)

(hsct OR "hematopoietic stem" OR "haematopoietic stem" OR "hematopoietic cell" OR "haematopoietic cell")
AND
(vaccin* OR "mrna-1273" OR elasomeran OR "m-1273" OR m1273 OR "cx-024414" OR cx024414 OR "tak-919" OR tak919 OR Ad26COVS1 OR "JNJ-78436735" OR

JNJ78436735 OR "bnt-162" OR bnt162* OR abdavomeran OR tozinameran OR comirnaty OR ChAdOx1 OR axd1222 OR "AZD-1222" OR vaxzevria OR covishield)
AND
transplant*

Appendix 3: Identified predictors of blunted immune response

Primary author	Predictors of blunted vaccine response	Univariable analysis		Multivariable analysis	
		OR (95%CI)	p-value	OR (95%CI)	p-value
Attolico, 2022	Time elapsed from HSCT (Within 1 year)				
Abid, 2022	Corticosteroid use		0.04		
Amandine, 2021	Haplotransplant		0.03		
	Recent (<1 year) HSCT		<0.001		
	Lymphopenia (<1000 cells/µL)		<0.001		
	Receipt of immunosuppressive treatment at the time of vaccination		<0.001		
	Receipt of hemotherapy at the time of vaccination		<0.001		
Autore, 2022	Rituximab use	0.26 (0.08 - 0.8)	0.022		
	Time elapsed from HSCT			1.21 (1.03 - 1.46)	0.028
	Plasma cell neoplasms			5.34 (1.56 - 21.3)	0.011
Baker, 2021	Prolonged use of prednisone (>8 weeks) - chronic GVHD treatment	0.221(0.106 - 0.456)	<0.001		
	Receipt of rituximab in the preceding 12 months	0.408 (0.197 - 0.844)	0.016	0.026 (0.007-0.099)	<0.001
	Active use of prednisone			0.07 (0.016 - 0.304)	<0.001
Beerlage, 2022	Ongoing immunosuppressive therapy				
	Anti-CD20 antibody therapy				
Bergman, 2021	Severe chronic GvHD	8 (1.43 - 49.82)	0.02		
	Less than 6 months after HSCT	0.98 (0.97 - 0.99)	<0.01		
	Lymphocyte count at baseline	14.07 (2.63 - 260.63)	0.01	14.34 (2.68-265.76)	0.01
Canti, 2021	Moderate or severe chronic GVHD	0.014 (<0.001 - 0.33)	0.008	0.014 (<0.001-0.49)	0.018
Chevallier, 2022	*Highlighted factors associated with low response*				
Chiarucci, 2021	*Highlighted factors associated with low response*				
Cuffel, 2022	*All HCT were responders*				
Einarsdottir 2022	Days between dose 2 and 3		0.01		
Gavriilaki, 2021	Metabolic syndrome				
Haggenburg, 2021	Use of hypomethylating agents				
	Rituximab use				
	Less than 6 months after HSCT (Allo-HSCT)				
Huang, 2022	*Highlighted factors associated with low response*				
Lindemann, 2021	*No associations observed*				
Maillard, 2021	Time-interval from HSCT < 12 months			2.8 (1.6 - 4.8)	
	Absolute lymphocyte count <1g/L			3.0 (1.7 - 5.0)	
	Systemic immunosuppressive treatments within 3 months of vaccination			4.5 (2.7 - 7.5)	
	Use of rituximab within 6 months			15.1 (4.3 - 52.7)	
Majcherek, 2022	Time since HCT to the vaccination in months	1.27 (1.01 - 1.59)	0.042		
	Acute graft-versus-host disease (GVHD) treatment at vaccination	0.25 (0.11 - 0.39)	0.0004		
	Transplant conditioning (intermediate/high)	16.29 (1.80 - 147.55)	0.013		
	Calcineurin inhibitor at vaccination	0.01 (0.00 - 0.13)	0.0003	0.03 (0.00 - 0.79)	0.03
Mamez, 2021	Age			*-1.72 (-3.43 - -0.28)	0.0276
	Time since transplantation			1.97 (0.46 - 3.7)	0.0145
	Anti-thymocyte globulin (ATG) use			*-2.66 (-5.8 - -0.65)	0.0292
Mathieu, 2022	*Highlighted factors associated with low response*				
Matkowska-Kocjan, 2021	*No associations observed*				
Maxime, 2022	B-cell aplasia			0.01 (0.00 - 0.10)	<0.001
Meyer, 2022	No ongoing ISP			0.36 (0.16 - 0.78)	0.011
	Anti-thymocyte globulin (ATG) use			2.41 (1.08 - 5.79)	0.039
	Age at allo-HCT			1.04 (1.01 - 1.08)	0.008
Minehart, 2021	CD4 count greater than 200 cells/mm3			2.14 (0.7 - 3.8)	0.005
Mori, 2022	Age ≥ 60y	1.99 (1.32 - 2.99)	0.001	2.18 (1.27 - 3.74)	0.004
	Donor HLA mismatch	1.42 (0.92 - 2.19)	0.12	1.96 (1.10 - 3.45)	0.02
	Chronic GVHD	3.24 (2.14 - 4.88)	<0.001	1.69 (0.95 - 3.03)	0.07
	Systemic steroid use	5.5 (3.58 - 8.44)	<0.001	2.03 (1.13 - 3.65)	0.02
	Absolute lymphocyte count (<1000/µL)	5.97 (3.28 - 10.85)	<0.001	2.87 (1.37 - 6.01)	0.005
	Number of CD4+ T cells (<300/µL vs. ≥300/µL)	3.52 (2.00 - 6.19)	<0.001		
	Serum IgG level (<500/µL vs. ≥500/µL)	9.76 (4.25 - 22.43)	<0.001	6.34 (2.37 - 17.02)	<0.001
	Number of B cells (<100/µL vs. ≥100/µL)	5.07 (3.31 - 7.75)	<0.001	2.61 (1.54 - 4.45)	<0.001
Muneyoshi, 2022	*Highlighted factors associated with low response*				
Murray, 2022	*Highlighted factors associated with low response*				
Nishikubo, 2022	B cell fraction (≤3%)		0.001		
	Immunosuppressive agent intake at vaccination		0.012		
	Time interval between transplantation and vaccination (≤6 months)		0.006		
	IgG (≤700 mg/dL)		0.003		
	IgM (≤40 mg/dL)		0.004		
Pinana, 2022	Age (years)		0.005		
	Lymphocyte count < 0.5×10^9/ml		0.037		
	Donor type		0.039		
Qamar, 2022	*Highlighted factors associated with low response*				
Ram, 2021	Months from infusion of cells		0.012	*0.032 (1.01 - 1.38)	0.032
	Sex (female vs. male)		0.041	*2.26 (1.6 - 3.06)	0.028
	CD19+ cells		0.012	*1.88 (1.0 - 2.12)	0.047
Redjoul, 2021	B-cell count of more than 0.25 g/L	9.5 (2.1 - 43)	0.0035	7.1 (1.5 - 34.1)	0.0016
Salvini, 2021	Not having aHSCT as last treatment vs aHSCT	9.33 (1.08 - 81.0)	0.04		
	Being on treatment (post-aHSCT)	12.60 (1.45 - 109.82)	0.02	49.45 (2.88 - 849.62)	0.007
Saraceni, 2021	*Highlighted risk after first dose (No associations found after second dose)*				
Shapiro, 2022	Non-Hodgkin lymphoma		0.004		
	Cytotoxic chemotherapy		0.01		
	CAR-T cell therapy		0.00002		
Shem-Tov, 2022	Chronic GVHD		0.002		
	Immunosuppressive therapy (mycophenolate and cyclosporin)		0.0001		
Sherman, 2022	*No associations observed (small sample size)*				
Stirparo, 2022	Rituximab use (aHSCT)		0.01		
Tamari, 2021	Time from cellular therapy to vaccination				
Toya, 2022	Interval from SCT <1 year			0.0840 (0.00709 - 1.00)	0.05
	History of csCMVi			0.114 (0.0143 - 0.908)	0.04
	Steroid use (prednisolone >5 mg/day)			0.0567 (0.00502 - 0.640)	0.02
Tsushima, 2022	Not explored				
Watanabe, 2022	*No associations observed (small sample size)*				
Yeshurun, 2022	Acute graft-versus-host disease (GVHD)	3.3 (0.97 - 11.1)	0.06		
	Moderate to severe chronic GVHD	5.9 (1.2 - 29)	0.03		
	Vaccinated within 4.5 years of transplantation	13.7 (1.8 - 108.5)	0.013		
	Still receiving immunosuppression	9.8 (2.1 - 44.7)	0.004		
	Prednisone treatment	3.8 (1.1 - 12.9)	0.03		

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Summary of Paper 1 and Paper 2 Conclusion

Paper 1 presents the results of a retrospective chart review of SARS-CoV-2 vaccinated hematopoietic stem cell transplantation (HSCT) recipients in Boston. The study found that HSCT recipients had high responsiveness to the vaccine, with 92.8% of patients being responders, and identified variables such as vaccine dosage, age, gender, and use of anti-CD20 therapy that impacted the response. The study recommends monitoring anti-S IgG titers to identify vaccine failures.

Paper 2 is a systematic review and meta-analysis that aimed to estimate the prevalence and predictors of attenuated SARS-CoV-2 vaccine-induced response among HSCT recipients. The study found that the prevalence of vaccine failure was 20%, and identified

underlying diseases, post-transplantation vaccination, GVHD treatment regimen, and concurrent anti-CD20 therapy as predictors of vaccine failure. The authors suggest that identifying the patient-specific needs of HSCT recipients could optimize the benefits of vaccination among this key sub-group of patients.

STRENGTHS, LIMITATIONS, AND FUTURE DIRECTIONS

The strengths of paper 1 are its large sample size and focus on a specific population of HSCT recipients, measuring quantitative antibody titers to assess vaccine response and identifying variables associated with response. However, its retrospective design, the potential for selection bias, and lack of investigation into T-cell responses and breakthrough infections limit the study. Future research could involve prospective studies, or large multi-center clinical trials investigating the efficacy and duration of the immunity conferred by sub-optimal anti-S IgG titers. Furthermore, future studies could investigate specific biomarkers for immune protectiveness against SARS-CoV-2 infections in HSCT

recipients, as well as optimal post-transplant vaccine administration timing. It would also be valuable to investigate the effectiveness of booster doses among HSCT recipients who may have a higher risk of waning immunity. This could inform vaccine administration strategies and help optimize the benefits of vaccination in this key sub-group of patients.

The strengths of paper 2 are its systematic review and meta-analysis design, identifying predictors of attenuated immune response to the SARS-CoV-2 vaccine and potentially informing clinical decision-making. However, the heterogeneity of the included studies and lack of investigation into vaccine efficacy against emerging variants and specific vaccination regimens limit the study. Future research could investigate immunologic mechanisms underlying vaccine failure, such as genetic factors or T-cell responses, and the effectiveness of booster doses. Genetic studies could provide insights into personalized vaccination strategies for HSCT recipients.

DISCUSSION AND PERSPECTIVES

Paper 1 and Paper 2 both provide important insights into the responsiveness of hematopoietic stem cell transplantation (HSCT) recipients to the SARS-CoV-2 vaccine. While Paper 1 provides a retrospective chart review of HSCT recipients in Boston and identifies factors associated with vaccine response, Paper 2 is a systematic review and meta-analysis that estimates the prevalence and predictors of attenuated vaccine response among HSCT recipients.

One important finding from Paper 1 is that HSCT recipients had high responsiveness to the vaccine, with the majority of patients being responders. However, the study also identified various factors that impacted vaccine response, such as vaccine dosage, age,

gender, and use of anti-CD20 therapy. The study suggests that monitoring anti-S IgG titers can help identify vaccine failures, and future research could investigate the effectiveness of booster doses among HSCT recipients.

In Paper 2, the authors estimated the prevalence of vaccine failure among HSCT recipients to be 20%, and identified underlying diseases, post-transplantation vaccination, GVHD treatment regimen, and concurrent anti-CD20 therapy as predictors of vaccine failure. The study recommends identifying patient-specific needs of HSCT recipients to optimize the benefits of vaccination.

Moving forward, future research could investigate specific biomarkers for immune protectiveness against SARS-CoV-2 infections in HSCT recipients, as well as optimal post-transplant vaccine administration timing and the effectiveness of booster doses. Additionally, investigating immunologic mechanisms underlying vaccine failure, such as genetic factors or T-cell responses, could provide insights into personalized vaccination strategies for HSCT recipients.

Finally, the COVID-19 pandemic has highlighted the importance of rapid response to emerging infectious diseases, and the development of vaccines and passive antibody protection are critical tools in this fight. With the emergence of new technologies, the vaccine development process has become more efficient and rapid, with some vaccines developed and ready for clinical trials in under a year. However, there are still challenges facing vaccinologists, including predicting the next pandemic, developing vaccines for rapidly evolving pathogens such as SARS-CoV-2, HIV and multidrug-resistant bacteria, and ensuring access to affordable and effective vaccines for all. To overcome these challenges, future research could focus on developing new vaccine technologies and

strategies, improving global vaccine distribution and access, and investigating new approaches to passive antibody protection. Additionally, the research could focus on identifying biomarkers for immune protectiveness against emerging infections and optimizing vaccine administration timing and strategies for vulnerable populations, such as hematopoietic stem cell transplantation recipients who are the most at risk for severe disease.