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A systematic review and meta-analysis of immune response against first and second doses of SARS-CoV-2 vaccines in adult patients with hematological malignancies

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ARTICLE INFO

Keywords:
COVID-19 vaccines
Hematological malignancy
Lymphoma
Leukemia
Myeloma
Immunogenicity
Systematic review

ABSTRACT

Background: Cancer patients particularly those with hematological malignancies are at higher risk of affecting by severe coronavirus disease 2019 (COVID-19). Due to the immunocompromised nature of the disease and the immunosuppressive treatments, they are more likely to develop less antibody protection; therefore, we aimed to evaluate the immunogenicity of COVID-19 vaccines in patients with hematological malignancies.

Methods: A comprehensive systematic search was conducted in PubMed, Scopus, and Web of Science databases, as well as Google scholar search engine as of December 10, 2021. Our primary outcomes of interest comprised of estimating the antibody seropositive rate following COVID-19 vaccination in patients with hematological malignancies and to compare it with those who were affected by solid tumors or healthy subjects. The secondary outcomes were to assess the vaccine’s immunogenicity based on different treatments, status of the disease, and type of vaccine. After the two-step screening, the data were extracted and the summary measures were calculated using a random-effect model.

Results: A total of 82 articles recording 13,804 patients with a diagnosis of malignancy were included in the present review. The seropositive rates in patients with hematological malignancies after first and second vaccine doses were 30.0% (95% confidence interval (95%CI): 11.9–52.0) and 62.3% (95%CI 56.0–68.5), respectively. These patients were less likely to develop antibody response as compared to cases with solid tumors (RR 0.73, 95%CI 0.67–0.79) and healthy subjects (RR 0.62, 95%CI 0.54–0.71) following complete immunization. Chronic lymphocytic leukemia (CLL) patients had the lowest response rate among all subtypes of hematological malignancies (first dose: 22.0%, 95%CI 13.5–31.8 and second dose: 47.8%, 95%CI 41.2–54.4). Besides, anti-CD20 therapies (5.7%, 95%CI 2.0–10.6) and bruton’s tyrosine kinase inhibitors (26.8%, 95%CI 16.9–37.8) represented the lowest seropositiveness post first and second doses, respectively. Notably, patients who were in active status of disease showed lower antibody detection rate compared to those on remission status (RR 0.87, 95%CI 0.76–0.99). Furthermore, lower rate of seropositivity was found in patients received BNT162.b2 compared to ones who received mRNA-1273 (RR 0.89, 95%CI 0.79–0.99).

Conclusion: Our findings highlight the substantially low rate of seroprotection in patients with hematological malignancies with a wide range of rates among disease subgroups and different treatments; further highlighting the fact that booster doses might be acquired for these patients to improve immunity against SARS-CoV-2.
1. Introduction

The outbreak caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was officially declared as a pandemic on 11 March 2020 [1]. The disease caused by SARS-CoV-2, known to be coronavirus disease 2019 (COVID-19) led to a vast range of presentations from asymptomatic carriers to severe and critical disease with a reported 3.3% case fatality rate [2]. Following an emergency use authorization, the United States Food and Drug Administration (FDA) approved BNT162b2 as the first COVID-19 vaccine [3] and afterward several more vaccines such as mRNA-1273 [4], Ad26.COV2.s [5], AZD1222 [6], and BBIP-CorV [7] have been authorized in a short period of time. Based on the findings of phase III clinical trials, all these vaccines are effective against both mild and moderate to severe diseases in the general population [8].

Hematological malignancies are responsible for approximately 9% of all neoplasms, and the incidence has been increasing in recent years [9–10]. These patients are more prone to severe and critical COVID-19 [11]. This susceptibility is caused by the natural immunosuppressive course of hematological cancers, anti-cancer treatments, other existing comorbidities, more frequent hospital visits, or a combination of these items [12–14]. Consequently, the mortality rate among patients with hematological malignancies is higher and they are in priority of COVID-19 vaccination [12,14].

Since most vaccine clinical trials excluded these patients, data on COVID-19 vaccine efficacy for cases suffering from hematological malignancies is limited [15]. Although multiple studies have investigated seroconversion rate and other vaccine-related effects in these patients, many questions are still unanswered. The severity of immunosuppression and the response to the vaccines varies vastly among different types of malignancies from solid tumors to hematological malignancies and various anti-cancer treatments [16–17]. Taken together, since the data on the immunogenicity of COVID-19 vaccines in patients with hematological malignancies are increasing rapidly, we aimed to summarize the information and establish an overall conclusion from the available researches. Therefore, the current review was conducted to evaluate the response rate of patients with hematological malignancies to different types of COVID-19 vaccines and to compare the immunogenicity of COVID-19 vaccines between patients with solid tumors and healthy subjects. Also, the results were reported by type of treatment option, vaccine, and disease status.

2. Method

Present study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [18].

2.1. Data sources and searches

The systematic literature search was conducted in PubMed, Scopus, and Web of Science databases, as well as Google scholar engine up to December 10, 2021 to identify publications evaluating the immunogenicity of COVID-19 vaccines in patients with hematological malignancies. The language of papers was restricted to English. Grey literature was screened through searching the first 100 pages of Google scholar engine as recommended by Haddaway et al. [19]. The following query terms were employed: (“SARS-CoV-2” OR “COVID-19”) AND (“vaccine”) AND (“hematologic* malignancy” OR “haematologic* malignancy” OR “lymphoma” OR “myeloma” OR “leukemia”). The detailed information on the search strategy is represented in Supplementary Table 1. The reference list of our eligible studies and relevant review articles were also screened for finding any further potential publication.

2.2. Study selection

After importing the yield of the database searches to the EndNote X9 software (Clarivate Analytics) and deduplicating using the same software, two investigators (S.A. and F.A.) reviewed the title and abstracts. The full-texts of the selected articles were assessed independently by the same two authors according to the inclusion and exclusion criteria. In the case of any disagreement, a third researcher was consulted.

2.3. Eligibility criteria

Studies providing data on the immunogenicity of COVID-19 vaccines in adult patients with hematological malignancies (i.e. lymphomas, plasma cell disorders, myeloproliferative neoplasms (MPN), myelodysplastic syndrome (MDS), acute leukemia, and chronic lymphocytic leukemia (CLL)) were included if they had the following criteria: 1) retrospective and prospective observational studies or interventional experiments with >10 participants; 2) adult patients (i.e. ≥18 years old); 3) reported the antibody seropositivity after COVID-19 vaccination with either first or second vaccine doses; and 4) provided the data to calculate the effect sizes (e.g. provided the data of the response rate of patients with haematological malignancies to those with solid tumours). Studies were excluded if: 1) they were case reports, case series, in-vitro studies, review articles, editorials, and conference abstracts; 2) reported not enough data in the case of seropositivity after immunization (e.g. not reporting the dose and name of vaccine or absolute number of total patients and those who seroconverted); 3) assessed the immunogenicity of a third dose; 4) evaluated the immunogenicity of heterologous vaccine types for first and second dose; and 5) provided data for cellular response, solely.

2.4. Data extraction

The data was extracted into a standardized data collection form in Microsoft Office Excel. Following items were extracted from individual studies: 1) basic information of the studies including title, digital object identifier (doi), date of publication, first author name, and study design; 2) patient’s characteristics such as age, sex, history of SARS-CoV-2 infection, type of hematological malignancy, status of disease at the time of vaccination, dose of vaccine received, the vaccine manufacturer, time interval between immunizations, time point of serum collection post vaccination, total number of vaccinated patients with hematological malignancies, solid tumors and healthy subjects, and number of participants who were seropositive after vaccination; 3) laboratory information regarding type of antibody detected, methods and techniques, and the cut-off point for each assay; and 4) treatment status including type of therapies that patients received at the time of vaccination, time interval between the last line of therapy and vaccination, and the number of participants who were seropositive following immunization based on each treatment. The extracted data were double-checked and validated by two researchers.

2.5. Outcome measures

Our primary outcomes were to estimate the seroprotection rate after immunization in adult patients with hematological malignancies and to estimate how much these patients are less likely to become seroprotected as compared to patients with solid tumors or healthy subjects. Our secondary outcomes were to estimate the rate of seroprotection after immunization by the therapies that patients with hematological malignancies received. In addition, where applicable, we compared the immunogenicity of vaccines according to the last time of treatment.

2.6. Quality assessment

Studies were assessed using the Newcastle–Ottawa scale of assessment [20]. The quality assessment was performed independently by two investigators (S.A. and F.A.) and a third researcher was consulted in the case of any disagreement.

2.7. Statistical analysis

The meta-analyses were performed using the Review Manager (RevMan) version 5.4 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) using the fixed-effects model. Heterogeneity was assessed using the Cochrane’s Q test and the I² statistic. A forest plot was created to visualize the results of the studies. The summary odds ratio (OR) was calculated for the primary and secondary outcomes. A p-value of <0.05 was considered significant. The main analysis was adjusted by the type of malignancies, comorbidities, anti-cancer treatments, treatment status, interval between immunizations, time point of serum collection, and dose of vaccine received.
2.6. Risk of bias assessment

The methodological quality of eligible studies was assessed using the Newcastle Ottawa Scale [20]. The tool was validated to assess the quality of non-randomized studies based on eight items which were categorized into three domains, known to be selection (4 points), comparability (2 points), and outcome (3 points). The quality score ranged from 0 to 9 in which 0 to 4, 5 to 6, and 7 to 9 were considered as low, moderate, and high quality, respectively. Appraising the quality of included studies was conducted by two reviewers (S.A. and F.A.), independently and any discrepancies were resolved by discussion or consultation with a third reviewer.

2.7. Statistical analysis

A random-effects, pairwise meta-analysis was conducted in STATA (version 16) using DerSimonian and Laird method. Risk ratios were presented for comparing dichotomous variables, and proportions were calculated for estimating the rate of seropositivity with 95% confidence intervals (95% CIs). The metaprop commend was used for estimating the pooled antibody response rate in STATA [21]. Statistical heterogeneity was analyzed using the I^2 statistic with values interpreted as moderate (30–60%), substantial (50%-90%), and considerable (75–100%) heterogeneity [22]. Moreover, the analyses were sub-grouped based on the dose of vaccination. It should be noted that since Ad26.COV2.s is a single shot vaccine, the data related to this vaccine was accounted in the second dose immunization analysis. Thereafter, the results were displayed on forest plots. Whenever the synthesis of data was not feasible through meta-analysis due to variations in reporting our outcomes of interest, the data were summarized qualitatively.

3. Results

3.1. Study selection

Our systematic search in PubMed, Scopus, and Web of Science resulted in 1,077 records, of which 569 remained after removal of 508 records identified from databases:
- PubMed (262)
- Scopus (631)
- Web of Science (184)

Records screened (n = 1,077)

Duplicate records (n = 508)

Excluded after title and abstract screening (n = 479)

Records excluded, with reasons:
- (n = 8) not related
- (n = 7) provided not enough data
- (n = 4) evaluated the immunogenicity of a booster dose
- (n = 2) conference abstract
- (n = 2) case reports
- (n = 2) reported cellular outcome
- (n = 1) reanalyzed the data of the same included studies
- (n = 1) protocol
- (n = 1) commentary

Studies included in review (n = 82)

Fig. 1. Study selection process.
duplicated publications. Of the remaining 90 publications, 62 studies fulfilled the eligibility criteria and 28 were excluded due to the following reasons: eight studies were not related to our topic [23–30], seven studies provided not enough data in the case of seropositivity after immunization [31–37], four studies evaluated the immunogenicity of a third dose [38–41], two studies were conference abstracts [42–43], two studies were case reports [44–45], two studies reported the cellular outcomes solely [46–47], one study reanalyzed the data of the same included studies [48], one study was a protocol of an original article [49], and one study was commentary [50]. Furthermore, 20 additional articles were retrieved from other sources, resulting in inclusion of 82 potential studies to be included in the final analysis (Fig. 1).

### 3.2. Quality assessment

The average quality score of our included studies was 6.86 ranging from 5 to 9. Forty-six (56%) studies were considered as high quality, 36 (44%) as moderate quality, and no study scored as low quality. The highest scoring items were reporting the ascertainment of exposure, assessment of outcome, follow-up duration, and adequacy of follow-up of cohorts. Furthermore, comparability of cohorts on the basis of the design or analysis achieved the lowest score among selected publications (Supplementary Table 2).

### 3.3. Study characteristics

Of the 82 included studies, 79 were published in peer-review journals [51–129] and three were pre-prints [130–132]. Twenty-one studies were conducted in the USA, 14 in the UK, 13 in Israel, 10 in Italy, 5 in Greece, 4 in Australia, and 15 in other countries. A total of 13,804 patients with hematological malignancies were included in our analysis. The remaining studies included patients regardless of their background cancer patients ranged from 44.5 to 83 years of age. A prior history of COVID-19 infection was negative in all participants of 50 studies, while the remaining studies included patients regardless of their background of SARS-CoV-2 seropositivity at baseline.

There were 33 studies that assessed the immunogenicity of BNT162b2 (Pfizer-BioNTech) vaccine alone, while 24 studies assessed the humoral response to both BNT162b2 and mRNA-1273 (Moderna) vaccines, and 13 studies evaluated the immune response to BNT162b2 together with AZD1222 (Oxford-AstraZeneca) vaccine. Furthermore, three types of vaccines including BNT162b2, mRNA-1273, and AZD1222 were utilized in 6 studies and 5 studies used BNT162b2, mRNA-1273, and Ad26.COV2.s (Johnson & Johnson) vaccines. Meanwhile, a single study examined the immunogenicity of BBIP-CorV (Sinopharm) vaccine in cancer patients.

The immune response was measured after first dose vaccination in 10 studies, post second dose in 48 studies, and following both first and second dose in 24 investigations. The sera were collected and evaluated for antibody response at least 7 days to a maximum of median 134 days post immunization. Moreover, response rate to COVID-19 vaccines was measured through assessment of SARS-CoV-2 spike/RBD IgG antibody levels in 69 studies, neutralizing antibody (nAb) levels in 6 studies, and both IgG and nAb titers in 7 studies. The main study characteristics are represented in Supplementary Table 3.

### 3.4. Immunogenicity of COVID-19 vaccines stratified by the type of hematological malignancy

Overall, the antibody response rate after first dose vaccination was 30.0% (95%CI 11.9–52.0, I² = 97.8%), while it was 62.3% (95%CI 56.0–68.5, I² = 92.3%) following second immunization among 955 and 4004 patients with hematological malignancies, respectively (Table 1 and Fig. 2). Comparing with patients suffering from solid tumors, subjects with hematological malignancies were less likely to develop high antibody levels. The humoral response to both BNT162b2 and mRNA-1273 (Moderna) vaccines was represented in Supplementary Table 3.

### Table 1

Pooled antibody response rate in different types of hematological malignancies and risk ratios of seropositivity in patients with hematological malignancies compared to patients with solid tumors and healthy subjects following either first or second dose of COVID-19 vaccination.

|                                | Pooled antibody response rate | HM compared to solid tumors | HM compared to healthy subjects |
|--------------------------------|-------------------------------|-----------------------------|---------------------------------|
|                                | N Proportion (95% CI) I² (p value) | N RR (95% CI) I² (p value) | N RR (95% CI) I² (p value) |
| All hematological malignancies  |                               |                             |                                |
| First dose                     | 955 Proportion (95% CI) I² (p value) | 535 0.74 (0.62-0.89) 52.4% (0.06) | 523 0.36 (0.21-0.61) 91.5% (0.0) |
| Second dose                    | 4004 Proportion (95% CI) I² (p value) | 1061 0.73 (0.67-0.79) 61.7% (0.0) | 1309 0.62 (0.54-0.71) 87.0% (0.0) |
| Lymphoid malignancies          |                               |                             |                                |
| First dose                     | 1720 Proportion (95% CI) I² (p value) | 36 0.52 (0.25-1.09) N/A | 1196 0.39 (0.31-0.48) 83.1% (0.0) |
| Second dose                    | 6595 Proportion (95% CI) I² (p value) | 1049 0.76 (0.68-0.84) 66.2% (0.01) | 3286 0.66 (0.62-0.71) 87.7% (0.0) |
| Myeloid malignancies           |                               |                             |                                |
| First dose                     | 225 Proportion (95% CI) I² (p value) | 6 0.44 (0.07-2.75) N/A | 146 0.67 (0.50-0.89) 54.4% (0.09) |
| Second dose                    | 692 Proportion (95% CI) I² (p value) | 133 0.97 (0.70-1.35) 92.6% (0.0) | 241 0.81 (0.72-0.91) 68.8% (0.02) |
| Plasma cell disorders          |                               |                             |                                |
| First dose                     | 931 Proportion (95% CI) I² (p value) | 10 0.80 (0.29-2.19) N/A | 673 0.49 (0.39-0.62) 70.8% (0.0) |
| Second dose                    | 2522 Proportion (95% CI) I² (p value) | 385 0.91 (0.84-0.98) 38.3% (0.17) | 1543 0.79 (0.75-0.85) 60.4% (0.0) |
| Hodgkin lymphoma               |                               |                             |                                |
| First dose                     | 56 Proportion (95% CI) I² (p value) | 1 0.66 (0.06-0.74) N/A | 23 0.43 (0.24-0.79) 0.0% (0.69) |
| Second dose                    | 164 Proportion (95% CI) I² (p value) | 51.6% (0.05) N/A | 42 0.96 (0.89-1.03) 0.0% (0.89) |
| Non-Hodgkin lymphoma           |                               |                             |                                |
| First dose                     | 358 Proportion (95% CI) I² (p value) | 17 0.47 (0.16-1.39) N/A | 180 0.32 (0.17-0.62) 74.8% (0.02) |
| Second dose                    | 1312 Proportion (95% CI) I² (p value) | 145 0.72 (0.63-0.82) 0.0% (0.97) | 413 0.54 (0.43-0.67) 82.1% (0.00) |
| Chronic lymphocytic leukemia (CLL) |                               |                             |                                |
| First dose                     | 270 Proportion (95% CI) I² (p value) | 6 0.44 (0.07-2.75) N/A | 270 0.26 (0.18-0.37) 49.8% (0.11) |
| Second dose                    | 1957 Proportion (95% CI) I² (p value) | 186 0.54 (0.42-0.71) 33.5% (0.22) | 526 0.51 (0.42-0.62) 76.6% (0.00) |
| Myeloproliferative neoplasm (MPN) |                               |                             |                                |
| First dose                     | 207 Proportion (95% CI) I² (p value) | 1 0.66 (0.06-0.74) N/A | 128 0.69 (0.55-0.87) 32.1% (0.22) |
| Second dose                    | 405 Proportion (95% CI) I² (p value) | 64.8% (0.0) N/A | 160 0.85 (0.79-0.91) 0.0% (0.39) |
| Myelodysplastic neoplasm (MDS) |                               |                             |                                |
| First dose                     | 13 Proportion (95% CI) I² (p value) | N/A | 13 0.48 (0.27-0.86) N/A |
| Second dose                    | 90 Proportion (95% CI) I² (p value) | 75.6% (0.01) N/A | 59 0.77 (0.50-1.18) 89.8% (0.0) |
| Acute leukemia                 |                               |                             |                                |
| First dose                     | N/A Proportion (95% CI) I² (p value) | N/A | N/A |
| Second dose                    | 74 Proportion (95% CI) I² (p value) | 90.6% (82.0-97.0) 0.0% (0.49) | N/A |

HM: Hematologic malignancies; N: Number of patients with hematologic malignancies; RR: Risk ratio; CI: Confidence interval; N/A: Not available.
detectable antibody titers following COVID-19 vaccination with a RR of 0.74 (95% CI 0.62–0.89, I² = 52.4%) post two-dose immunization. Likewise, SARS-CoV-2 vaccination were less seroprotective in patients with hematological malignancies as compared to healthy controls after both first (RR 0.36, 95%CI 0.21–0.61, I² = 91.5%) and second dose (RR 0.62, 95%CI 0.54–0.71, I² = 87.0%) vaccination (Table 1 and Fig. 3). An obvious publication bias was detected, revealing an asymmetry in funnel plot (Supplementary Fig. 1A, Egger’s test p = 0.01).

Focusing on the two major subtypes of hematological malignancies, the pooled seropositivity rate was lower in lymphoid than myeloid cancers, both after partial (35.7%, 95% CI 28.5–43.3, I² = 89.7%) and complete vaccination (62.3%, 95% CI 57.7–66.9, I² = 92.5%) vs. 83.6%, 95% CI 76.3–89.9, I² = 80.7%, respectively (Supplementary Figs. 2 and 3). When comparing with healthy subjects, those with lymphoid malignancies achieved lower antibody response after either single shot with a RR of 0.39 (95%CI 0.31–0.48, I² = 83.1%) or double shot with a RR of 0.66 (95%CI 0.62–0.71, I² = 87.7%). Similarly, myeloid malignancy was associated with lower immune response after both first dose (RR 0.67, 95%CI 0.50–0.89, I² = 54.4%) and second dose (RR 0.81, 95%CI 0.72–0.91, I² = 68.8%) when we compared the immune response of these patients with healthy controls (Table 1 and Supplementary Figs. 4 and 5). In addition, while an evidence of publication bias was noted in lymphoid malignancy analysis (Supplementary Fig. 1B, Egger’s test p = 0.02), it was not detectable for myeloid malignancies (Supplementary Fig. 1C, Egger’s test p = 0.946).

When we categorized the hematological malignancies more specifically, the lowest seropositivity rate was evident in patients with CLL (22.0%, 95% CI 13.5–31.8, I² = 58.0% and 47.9%, 95%CI 41.2–54.4, I² = 83.7%), followed by those suffering from non-Hodgkin lymphoma (NHL) (28.4%, 95% CI 19.0–38.8, I² = 70.8% and 52.1%, 95%CI 41.6–62.5, I² = 92.6%) after first and second dose immunization, respectively. In addition, the highest seropositive rate post one dose of COVID-19 vaccines was observed in patients with MPN (64.1%, 95%CI 52.9–74.8, I² = 46.3%), then in those with MDS (46.1%, 95%CI 0.62–0.71, I² = 87.7%).
Considering the immune response following second dose vaccination, the highest seropositive rate was demonstrated in Hodgkin lymphoma (HL) (94.1%, 95% CI 85.3–99.5, $I^2 = 51.6\%$) and acute leukemia (90.6%, 95% CI 82.0–97.0, $I^2 = 0.0\%$), respectively. Besides, RRs for lower antibody response to COVID-19 vaccines in patients with hematological malignancies compared to healthy cohort were statistically significant in CLL (RR 0.26, 95% CI 0.18–0.37, $I^2 = 49.8\%$ and RR 0.51, 95% CI 0.42–0.62, $I^2 = 76.6\%$), NHL (RR 0.32, 95% CI 0.17–0.62, $I^2 = 74.8\%$ and RR 0.54, 95% CI 0.43–0.67, $I^2 = 82.1\%$), plasma cell disorder (RR 0.49, 95% CI 0.39–0.62, $I^2 = 70.8\%$ and RR

![Fig. 3. Risk ratios of seropositivity in patients with all hematological malignancies compared to patients with solid tumors and healthy subjects following either first or second dose of COVID-19 vaccination.](image)
0.79, 95%CI 0.75–0.83, \( I^2 = 60.4\% \), and MPN (RR 0.69, 95%CI 0.55–0.87, \( I^2 = 32.1\% \) and RR 0.85, 95%CI 0.79–0.91, \( I^2 = 0.0\% \)) patients following both first and second immunizations, respectively. However, a considerable lower rate of seropositivity was only evident for the first dose vaccination of MDS (RR 0.48, 95%CI 0.27–0.86, \( I^2 = N/A \)) and HL (RR 0.43, 95%CI 0.24–0.79, \( I^2 = 0.0\% \)) patients (Table 1 and Supplementary Figs. 6–18).

3.5. Immunogenicity of COVID-19 vaccines stratified by the type of therapies

We then stratified the pooled antibody response in patients with hematological malignancies based on the treatment that they received. The lowest seroprotection rate following partial immunization was observed in anti-CD20 therapy, such that out of 167 patients, only a small proportion of 5.7% (95%CI 2.0–10.6, \( I^2 = 0.0\% \)) achieved detectable antibody titers. Beside anti-CD20 therapy, the lowest seropositivity rate after one dose vaccination was evident for those who received anti-CD38 treatments (42.3%, 95%CI 3.2–87.2, \( I^2 = 88.4\% \)). Conversely, the highest proportion of antibody response after first dose was estimated for patients who were administered autologous SCT (75.4%, 95%CI 62.9–84.8, \( I^2 = N/A \)) and chemotherapy (47.2%, 95%CI 32.0–63.0, \( I^2 = N/A \)). Following complete immunization, the lowest rate of achieving antibody response was observed for patients with hematological malignancies who were on bruton’s tyrosine kinase inhibitors (BTK inhibitors) (26.8%, 95%CI 16.9–37.8, \( I^2 = 76.1\% \)) and chimeric antigen receptor (CAR) T-cell therapy (28.4%, 95%CI 12.4–47.0, \( I^2 = 62.7\% \)), while the highest rate achieved for those who were on autologous SCT (81.7%, 95%CI 75.8–87.0, \( I^2 = 75.7\% \)) and proteasome inhibitors (PIs) (80.0%, 95%CI 71.7–87.3, \( I^2 = 69.8\% \)) respectively (Table 2 and Supplementary Figs. 19–29).

At the time of vaccination, patients who were on active treatment (i.e. receiving treatment at the time of vaccination) were less likely to mount detectable antibody titers as compared to those who were not on active therapy with a RR of 0.58 (95%CI 0.47–0.73, \( I^2 = 74.0\% \)) (Supplementary Fig. 30). According to anti-CD20 therapy status of patients with hematological malignancies, cases who were on these medications at the time of vaccination represented lower antibody response than cases who were not (RR 0.47, 95%CI 0.40–0.54, \( I^2 = 0.0\% \)). Similarly, receiving anti-CD20 therapy within 6 months before vaccination compared to at least six-month interval between the completion of anti-CD20 therapy was associated with lower immune response (RR 0.20, 95%CI 0.11–0.37, \( I^2 = 57.7\% \)). A same relationship was also observed for a time point of 12 months, where anti-CD20 therapy was associated with lower immune response (RR 0.58, 95%CI 0.47–0.73, \( I^2 = 74.0\% \)) (Supplementary Fig. 31). Furthermore, no difference was identified in antibody response following COVID-19 vaccination for those who were on anti-CD38 (RR 0.89, 95%CI 0.76–1.05, \( I^2 = 36.5\% \)), IMIDs (RR 0.97, 95%CI 0.87–1.08, \( I^2 = 0.0\% \)), and PIs (RR 1.05, 95%CI 0.95–1.14, \( I^2 = 0.0\% \)) during vaccination program as compared to subjects who did not receive these therapies. In contrast, patients with a history of HSCT showed substantially higher (RR 1.15, 95%CI 1.05–1.26, \( I^2 = 11.9\% \)) and those who received ruxolitinib represented a significant lower rate of antibody detection (RR 0.73, 95%CI 0.57–0.94, \( I^2 = 25.3\% \)) (Supplementary Figs. 32–36). Moreover, type of HSCT (allogenic vs. autologous SCT: RR 0.97, 95%CI 0.86–1.09, \( I^2 = 36.6\% \)) was associated not with seropositivity. Finally, lower that 24 month time period from HSCT to COVID-19 vaccination relative to above 24 month time period resulted in lower seropositivity rate (RR 0.75, 95%CI 0.61–0.93, \( I^2 = 74.4\% \)) (Table 3 and Supplementary Fig. 32).

3.6. Immunogenicity of COVID-19 vaccines stratified by disease status and type of vaccine

Comparing antibody response in patients with hematological malignancies who were in active status of the disease compared to remission status showed a significant inverse association (RR 0.87, 95% CI 0.76–0.99, \( I^2 = 65.0\% \)) (Supplementary Fig. 37). Also, type of the vaccine was related to lower rate of seropositivity in patients received BNT162.b2 compared to ones who received mRNA-1273 (RR 0.89, 95% CI 0.79–0.99, \( I^2 = 64.7\% \), but no relationship was found for BNT162.b2 vs. AZD1222 (RR 0.95, 95%CI 0.86–1.05, \( I^2 = 0.0\% \)) and BNT162.b2 vs. Ad26.COV2.s (RR 1.30, 95%CI 0.36–4.45, \( I^2 = 53.1\% \)) (Supplementary Fig. 38).

### Table 2

**Pooled antibody response rate across different treatment options for patients with hematological malignancies following either first or second dose of COVID-19 vaccination.**

| Treatment | First dose | Second dose |
|-----------|------------|-------------|
| N          | Proportion (95% CI) | \( I^2 \) (p value) |
| Anti-CD20 | 167 | 5.7% (2.0–10.6) | 0.0% (0.71) |
|           | 1250 | 31.2% (24.7–38.1) | 79.7% (0.0) |
| Anti-CD38 | 70 | 42.3% (3.2–87.2) | 88.4% (0.0) |
|           | 385 | 69.7% (58.3–80.1) | 71.6% (0.0) |
| BTK inhibitors | First dose | N/A | N/A |
|           | Second dose | N/A | N/A |
| IMIDs     | First dose | 585 | 26.8% (16.9–37.8) | 76.1% (0.0) |
|           | Second dose | 589 | 79.1% (71.3–86.1) | 75.8% (0.0) |
| PIs       | First dose | 52 | 43.3% (29.7–57.3) | N/A |
|           | Second dose | 418 | 80.0% (71.7–87.3) | 69.8% (0.0) |
| Ruxolitinib | First dose | 26 | 45.9% (26.3–66.2) | N/A |
|           | Second dose | 56 | 66.3% (52.8–78.7) | N/A |
| Allogenic SCT | First dose | 315 | 45.9% (34.3–57.7) | 70.7% (0.0) |
|           | Second dose | 1364 | 79.2% (75.2–83.0) | 56.1% (0.0) |
| Autologous SCT | First dose | 57 | 75.4% (62.9–84.8) | N/A |
|           | Second dose | 885 | 81.7% (75.8–87.0) | 75.7% (0.0) |
| BCL2 inhibitors | First dose | N/A | N/A |
|           | Second dose | 125 | 33.3% (19.9–47.9) | 41.2% (0.12) |
| Chemotherapy | First dose | 36 | 47.2% (32.0–63.0) | N/A |
|           | Second dose | 594 | 58.2% (42.0–73.7) | 89.7% (0.0) |
| CAR T-cell therapy | First dose | N/A | N/A |
|           | Second dose | 89 | 28.4% (12.4–47.0) | 62.7% (0.0) |

BTK inhibitors: Bruton’s tyrosine kinase inhibitors; IMIDs: Immunomodulatory imide drugs; PIs: Proteasome inhibitors; HSCT: Hematopoietic stem cell transplantation; BCL2 inhibitors: B-cell lymphoma 2 inhibitors; CAR T-cell therapy: Chimeric antigen receptor T-cell therapy; N: Number of patients with hematological malignancies; CI: Confidence interval; N/A: Not available.

Due to the immunocompromised nature of the disease coupled with the immunosuppressive treatments, cancer patients particularly those with hematological malignancies are more likely to develop less antibody protection. The results of the present study which aimed to evaluate the immune response to SARS-CoV-2 vaccines in hematological malignancies showed that these patients had a significantly reduced rate of seroprotection following the first and second doses of vaccines compared with healthy controls (RR 0.36 and 0.62, respectively). We found that the antibody response rate after the first dose of immunization was 30%, notifying 26% and 64% less detectable antibody titers compared with those with solid tumors and healthy controls, respectively. Accordingly, a previous study represented a seropositivity rate of 37–51% following the first COVID-19 vaccines dose in patients with...
lymphoid malignancies among about 20 colleagues revealed a lower seroconversion rate for patients with following the first and second vaccine doses, respectively [134]. In accordance, our study showed 62.3% (56.0–67.8%) and 74.0% (67% after the second dose. It has been reported that boosting the vaccinations with a third dose can somewhat improve the immune response; however, a great proportion of patients with NHL still continued to represent lower antibody level than the healthy participants [142]. Furthermore, Susol and colleagues evaluated the immunogenicity of COVID-19 vaccines in patients with hematological malignancies who did not achieve the antibody seroconversion rate. They showed that 23% of patients with initial failure seroconverted after a third dose. Nevertheless, none of the CLL patients responded to the third dose [143]. Likewise, Mair et al. reported that 66.7% of hematologic malignant patients with ongoing anti-B-cell treatments did not develop antibodies after the third dose, whereas it was the case in 7.5% of patients without anti-B-cell therapy [144]. Consequently, timely measurement of antibody levels for planning the dose and schedule of subsequent COVID-19 vaccine might be necessary in these patients particularly who are on active therapies.

| Treatment | On active therapy vs. not on active therapy |
|-----------|---------------------------------------------|
| N         | RR (95% CI) | I² (p value) |
| Treatment | On active therapy vs. not on active therapy |
| Anti-CD20 | Any vs. non 944 | 0.47 (0.40–0.54) | 0.0% |
| < 6 m vs. > 6 m between treatment and vaccination 411 | 0.20 (0.11–0.37) | 0.04 |
| < 12 m vs. > 12 m between treatment and vaccination 561 | 0.21 (0.09–0.50) | 0.0 |
| HSCT | Any vs. non 764 | 1.15 (1.05–1.26) | 0.34 |
| Allogeneic SCT vs. Autologous SCT 820 | 0.97 (0.86–1.09) | 0.18 |
| < 12 m vs. > 12 m between transplantation and vaccination 1007 | 0.78 (0.60–1.01) | 0.0 |
| < 24 m vs. > 24 m between transplantation and vaccination 487 | 0.75 (0.61–0.93) | 0.01 |
| Anti-CD38 | Any vs. non 494 | 0.89 (0.76–1.05) | 0.18 |
| IMIDs | Any vs. non 408 | 0.97 (0.87–1.08) | 0.49 |
| Pts | Any vs. non 399 | 1.05 (0.95–1.14) | 0.0 |
| Ruoxolitinib | Any vs. non 154 | 0.73 (0.57–0.94) | 0.26 |

IMIDs: Immuno-modulatory intracellular drugs; Pts: Proteasome inhibitors; HSCT: Hematopoietic stem cell transplantation; N: Number of patients with hematological malignancies; RR: Risk ratio; CI: Confidence interval.

hematological malignancies which increased to 61–67% after the second dose [133]. In accordance, our study showed 62.3% (56.0–68.5%) seroconversion following the second dose of COVID-19 vaccines. The findings were consistent with the results of another meta-analysis of 27 studies which showed a seroconversion rate of 37.3% and 78.3% following the first and second vaccine doses, respectively [134].

Following complete vaccination, lymphoid malignancies had less seropositivity than myeloid neoplasms. Inline, the article by Guven and colleagues revealed a lower seroconversion rate for patients with following the first and second vaccine doses, respectively [134]. In accordance, our study showed 62.3% (56.0–67.8%) and 74.0% (67% after the second dose. It has been reported that boosting the vaccinations with a third dose can somewhat improve the immune response; however, a great proportion of patients with NHL still continued to represent lower antibody level than the healthy participants [142]. Furthermore, Susol and colleagues evaluated the immunogenicity of COVID-19 vaccines in patients with hematological malignancies who did not achieve the antibody seroconversion rate. They showed that 23% of patients with initial failure seroconverted after a third dose. Nevertheless, none of the CLL patients responded to the third dose [143]. Likewise, Mair et al. reported that 66.7% of hematologic malignant patients with ongoing anti-B-cell treatments did not develop antibodies after the third dose, whereas it was the case in 7.5% of patients without anti-B-cell therapy [144]. Consequently, timely measurement of antibody levels for planning the dose and schedule of subsequent COVID-19 vaccine might be necessary in these patients particularly who are on active therapies.

Our study is the most up-to-date study which evaluated different aspects of the immune response to COVID-19 vaccines in patients with malignancies. While a previous study has also reported the pooled response rate in these patients, the risk ratios for comparing with solid tumors and healthy subjects were not reported [145]. In addition, with including 82 eligible publications, we still believe that our review is the most comprehensive to date. Nevertheless, we acknowledge that the present study has several limitations: 1) including results of preprint studies which has not yet been peer-reviewed might lead to bias in the study findings; 2) due to the effects of prior history of SARS-CoV-2 infection on the antibody response rates of individuals [146], inclusion of studies which did not report the status of prior COVID-19 can affect the interpretation of the analyses; 3) the antibody titers and seropositivity were assessed in a wide range of follow-up from 7 to 124 days, so the duration might not be enough for antibody production in some studies and might affect the results of pooling the results; 4) because most of the included articles assessed the immune response due to BNT162b2 and mRNA-1273 vaccines, therefore, the generalizability of the findings to other vaccine types and platforms is limited; 5) included patients of different studies were on treatments with different types of medications and various doses which might cause differences in response to COVID-19 vaccines; 6) the included studies only evaluated the effects of first and second doses and COVID-19 vaccines, whereas the

| Risk ratio (95% CI) | N | RR (95% CI) |
|-------------------|---|------------|
| Treatment on active therapy vs. not on active therapy | 1072 | 0.58 (0.47–0.73) |
| Anti-CD20 Any vs. non | 944 | 0.47 (0.40–0.54) |
| < 6 m vs. > 6 m between treatment and vaccination | 411 | 0.20 (0.11–0.37) |
| < 12 m vs. > 12 m between treatment and vaccination | 561 | 0.21 (0.09–0.50) |
| HSCT Any vs. non | 764 | 1.15 (1.05–1.26) |
| Allogeneic SCT vs. Autologous SCT | 820 | 0.97 (0.86–1.09) |
| < 12 m vs. > 12 m between transplantation and vaccination | 1007 | 0.78 (0.60–1.01) |
| < 24 m vs. > 24 m between transplantation and vaccination | 487 | 0.75 (0.61–0.93) |
| Anti-CD38 Any vs. non | 494 | 0.89 (0.76–1.05) |
| IMIDs Any vs. non | 408 | 0.97 (0.87–1.08) |
| Pts Any vs. non | 399 | 1.05 (0.95–1.14) |
| Ruoxolitinib Any vs. non | 154 | 0.73 (0.57–0.94) |

M. Noori et al. International Immunopharmacology 110 (2022) 109046

Table 3 Risk ratios of seropositivity in patients with hematological malignancies based on treatment status.
immune response to booster vaccine doses was not assessed in the current study; 7) the studies were carried out in different time ranges when a specific SARS-CoV-2 variant was dominant, so the results could not be applicable to newly emerging variants like Omicron; 8) since we only included adult patients with hematological malignancies, the findings are not applicable to children and adolescents with malignancies; finally, the effects of demographic characteristics of included participants like age, sex, and race on antibody response to vaccines were not evaluated in the present study.

5. Conclusions

The present study shows that patients with hematological malignancies have lower antibody titers than those with solid tumors or healthy individuals. As a result, patients with lymphoid tumors, especially CLL and those who are on anti-CD20 therapies should more strictly comply with COVID-19 prevention protocols or even be prioritized for booster vaccine dose. According to the meta-analysis results, those on active status of the disease and receiving treatment at time of vaccination had less detectable antibodies. Further studies are recommended to evaluate T-cell responses after immunization, the effects of other newly developed COVID-19 vaccines on antibody response of patients with malignancies and to evaluate the effects of booster doses of SARS-CoV-2 in order to develop guidelines for COVID-19 vaccination in patients with hematological or solid cancers.

Availability of data, code and other materials

The data that support the findings of this study are available upon reasonable request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

The authors would like to express their gratitude to Shahid Beheshti University of Medical Sciences (Tehran, Iran) and Iran University of Medical Sciences (Tehran, Iran) for supporting this study.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2022.109046.

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