The impact of COVID-19 on cancer patients

Demi Wekking [a], Thilini H. Senevirathne [b], Josie L. Pearce [c], Marco Aiello [d], Mario Scartozzi [e], Matteo Lambertini [f,g], Pushpamali De Silva [h,i,*,1,2], Cinzia Solinas [j,**,1,2]

[a] *Amsterdam UMC, Location Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands*
[b] *Faculty of Science, Katholieke Universiteit Leuven, Kasteelpark Arenberg, Leuven, Belgium*
[c] *Wellman Center for Photomedicine, Massachusetts General Hospital and Harvard Premedical Program, Cambridge, MA, USA*
[d] *Medical Oncology Unit A.O.U. Policlinico – Vittorio Emanuele di Catania, Italy*
[e] *Department of Medical Oncology, University of Cagliari, Cagliari, Italy*
[f] *Department of Medical Oncology, U.O.C. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, 16132, Genoa, Italy*
[g] *Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genoa, Genoa, Italy*
[h] *Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA*
[i] *Broad Institute of MIT and Harvard, Cambridge, MA, USA*
[j] *Medical Oncology, AOU Cagliari, P.O. Duilio Casula, Monserrato, CA, Italy*

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ABSTRACT

The COVID-19 pandemic poses a significant challenge for individuals with compromised immune systems, such as patients with cancer, as they face a heightened susceptibility to severe infections compared to the general population. Such severe infections substantially increase the risk of morbidity and mortality among these patients. Notable risk factors for mortality include advanced age (> 70 years), current or past smoking history, advanced disease stage, the use of cytotoxic chemotherapy, and an Eastern Cooperative Oncology Group (ECOG) score of 2 or higher. Multiple types of vaccines have been developed and implemented, demonstrating remarkable efficacy in preventing infections. However, there have been observable reductions in their ability to elicit an immune response, particularly among individuals with hematological malignancies. The situation becomes more challenging due to the emergence of viral variants of concern (VOCs). Despite the increase in neutralizing antibody levels after vaccination, they remain lower in response to these evolving variants. The need for booster vaccinations has become apparent, particularly for this vulnerable population, due to the suboptimal immune response and waning of immunity post-vaccination. Examining and comprehending how the immune system reacts to various vaccination regimens for SARS-CoV-2 and its VOCs in cancer patients is crucial for designing clinical and public health strategies. This review aims to provide an updated overview of the effectiveness of COVID-19 vaccines in cancer patients, including those undergoing treatments such as hematopoietic stem cell transplantation (HCT) or chimeric antigen receptor (CAR) T cell therapy, by exploring the extent of both humoral and cellular immune responses to COVID-19 vaccination. Furthermore, it outlines risk factors and potential biomarkers that are associated with severe SARS-CoV-2 infection and vaccine responses, and offers suggestions for improving SARS-CoV-2 protection in cancer patients.

1. Introduction

In December 2019, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel coronavirus causing Coronavirus disease 2019 (COVID-19), emerged in Wuhan, China, and has since infected more than 750 million people around the globe [1,2]. Severe SARS-CoV-2 infections are associated with immune dysregulation involving reduced production of type I and type III interferons and hypersecretion of pro-inflammatory cytokines such as IL-6, IFN- γ, and TNFα [3–5]. Consequently, these elevated levels of cytokines have a detrimental

* Corresponding author at: Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA.
** Corresponding author.
E-mail addresses: pushpamali_desilva@dfci.harvard.edu (P. De Silva), c.solinas@aoucagliari.it (C. Solinas).
[1] PDS and CS equally contributed as co-senior authors.
[2] Present address: Brigham and Women's Hospital, Boston, MA, USA

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effect on T cell survival and proliferation [6]. Activated macrophages, neutrophils, and monocytes release additional pro-inflammatory cytokines in response to the depletion of lymphocytes, amplifying the production of a cytokine storm. This contributes to the rapid progression of patients to severe conditions such as acute respiratory distress syndrome and multiple organ dysfunction.

The pandemic poses a significant challenge for patients with an immunocompromised status due to their higher risk of developing severe infections than the general population. Cancer patients are particularly vulnerable as they are susceptible to disease-associated and therapy-induced dysregulation of the immune system, and severe infection places these patients at an elevated risk of morbidity and mortality. The upregulation of cytokines such as IL-1β, IL-6, TNF, IL-8, and IL-17 is associated with advanced stages of malignancy [7]. Moreover, overexpression of vascular endothelial growth factor in patients with solid tumors impairs the development and function of immune cells in the microenvironment [8]. When these cytokines are upregulated in the context of severe SARS-CoV-2 infection, it may contribute to the poorer outcomes observed in some cancer patients. Beyond the direct health effects, the pandemic has increased cancer-specific mortality as medical procedures have been modified, delayed, or canceled [9].

Four years after the pandemic outbreak, remarkable efforts have been dedicated to understating the challenges posed by the SARS-CoV-2 virus and its variants of concern (VOC) in patients with cancer [10]. Multiple vaccine types have been developed and implemented, mainly using the viral spike (S) protein, demonstrating remarkable effectiveness in preventing infection and symptomatic illness [11,12]. One unique feature of these vaccines is their ability to stimulate both humoral and cellular immunity, crucial in providing enduring protection against the virus. However, while COVID-19 vaccines have provided some protection against infection and severe illness in individuals with cancer, there have been noticeable reductions in their ability to trigger an immune response and their effectiveness in real-world scenarios [2,13,14]. The suboptimal immunogenicity and the decline in immunity after vaccination have highlighted the necessity for booster vaccinations, particularly among this susceptible group. Analyzing and comprehending how the immune system responds to different vaccination regimens for SARS-CoV-2 and VOCs among cancer patients is crucial for shaping clinical and public health strategies.

In this review, we provide an updated overview of the efficacy of COVID-19 vaccines in cancer patients, as well as those undergoing hematopoietic stem cell transplantation (HCT) or chimeric antigen receptor (CAR) T cell therapy, by exploring the extent of the humoral and cellular immune response to COVID-19 vaccination. Furthermore, we describe risk factors and potential biomarkers for severe SARS-CoV-2 infection and vaccine responses and offer suggestions to increase SARS-CoV-2 protection in cancer patients.

2. The impact of SARS-CoV-2 infection and vaccines on cancer patients

2.1. Epidemiology and burden of COVID-19: the real-world data

The increased risk of contracting COVID-19 in cancer patients was evaluated in several studies [15–18]. An Italian study observed that, while the prevalence of cancer was not associated with an increased risk of infection (odds ratio [OR] = 0.97; 95% confidence interval [CI] 0.89 – 1.06), cancer patients had a higher rate of hospitalization (56.6% versus 34.4% among other people) and mortality (14.7% versus 4.5%) compared to those without cancers [18]. The risk of adverse outcomes of a COVID-19 infection was significantly higher, particularly for males and older people [18]. In contrast to the Italian-based study, Liang et al. found a higher incidence of COVID-19 in cancer patients (1% of screened patients had a history of tumors) compared to the general population in China (0.29% according to the 2015 cancer epidemiology statistic [19]), with lung cancer being the most common cancer type among infected patients [15]. These COVID-19-positive cancer patients were older (mean age 63.1 vs. 48.7 years), with a smoking history (22% vs. 7%), and more severe baseline CT scan findings (94% vs. 71%) compared to non-oncological cases. No significant differences in sex, initial symptoms, and other comorbidities were observed. Finally, Liang et al. found that patients with cancer presented a higher risk of severe events compared to patients without cancer (39% vs. 8%; OR = 5.39; 95% CI 1.80–16.17, p = 0.0003).

In addition to this Chinese study, Yu et al. performed a retrospective analysis of cancer patients and estimated a 0.79% (12 of 1524 patients; 95% CI, 0.3–1.2%) SARS-CoV-2 infection rate among cancer patients admitted to their institution, which was higher than the cumulative incidence of all diagnosed COVID-19 cases reported in Wuhan in the same period (0.37%; 41,152 of 1181,000 cases) [16]. They also found a higher incidence of COVID-19 in patients aged 60 or older with Non-Small Cell Lung Cancer (NSCLC) than those younger than 60 (4.3% vs. 1.8%). They concluded that cancer patients were at higher risk of being infected by COVID-19 (OR = 2.31; 95% CI, 1.89–3.02) compared to the general population, possibly due to their compromised immune systems [16]. Variations in findings between the Italian and Chinese studies regarding cancer patients' vulnerability to COVID-19 may stem from differences in study endpoints, smaller sample sizes in Chinese studies, and a higher proportion of elderly patients in the Veneto region study.

Another important study in this setting is the France-based study from Gustave Roussy Cancer Center [17]. Albiges et al. identified several risk factors for death, including age over 70, current or former smoking habits, advanced disease, cytotoxic chemotherapy, and an Eastern Cooperative Oncology Group (ECOG) score of $\geqslant$ 2. However, in the multivariate analysis, the ECOG score remained the only predictor of death. Conversely, immunotherapy, hormone therapy, and targeted therapy did not seem to increase clinical deterioration or risk of death.

2.2. Risk factors associated with the severity of COVID-19 infection in cancer patients

Cancer is considered one of the most critical risk factors for developing severe COVID-19 symptoms in the general population, alongside conditions such as diabetes, hyperlipidemia, hypertension, and coronary artery disease [20]. Patients with cancer, especially those with lung cancer, experience an elevated risk of severe outcomes and mortality when infected with SARS-CoV-2 [15–18,21]. A study from the U.S. reported that 62% of lung cancer patients with COVID-19 required hospitalization, with a 25% mortality rate [22]. Factors like smoking and chronic obstructive pulmonary disease (COPD) were closely related to the COVID-19 severity in these patients [22]. A univariate analysis by Garassino et al. involving thoracic malignancies found that older age (>65), smoking, comorbidities, and chemotherapy were related to higher mortality risk [23]. In contrast, only current or former smokers were associated with an increased risk of death in the multivariate analysis [23]. Advanced age, also one of the main factors associated with the onset of cancer, alongside conditions such as smoking, pulmonary abnormalities, and cancer-related metabolic disorders, such as systemic immunosuppression, cardiovascular stress, pulmonary fibrosis, and enhanced cellular senescence, may also contribute to this elevated risk [24,25]. A recent study by Russell et al. highlighted the increased risk of COVID-19 mortality among cancer patients of male sex, Asian ethnicity, hematological malignancies, or a cancer diagnosis > 2 years [26]. Thus, tumor type and patient demographics are essential considerations in clinical decision-making.

Anti-cancer therapies such as radiotherapy, chemotherapy, and immunotherapy may further impact the severity of COVID-19 in cancer patients [17,22,27,28]. Specific anti-cancer therapies, e.g., R-CHOP, platinum combined with etoposide, and DNA methyltransferase inhibitors were associated with high 30-day all-cause mortality [29]. Immunotherapy, specifically immune checkpoint inhibitors

administered within the month before COVID-19 symptom onset, has been related to increased severity and death in cancer patients [27,28]. However, conflicting findings suggested that the severity of COVID-19 was comparable among those who received programmed cell death 1 (PD-1) inhibitors and those who did not, as observed in a single-center observational study of outpatients with lung cancer with confirmed COVID-19 [30,31]. It remains unclear whether cancer is an independent risk factor for severe COVID-19 symptoms or if cancer patient demographic and comorbidities are primarily responsible for the risk of developing severe complications from SARS-CoV-2 infection.

2.3. Risk factors associated with vaccine effectiveness in patients with cancer

mRNA vaccines elicit immune responses more effectively than adenovirus-vectored vaccines in cancer patients, particularly the mRNA-1273 vaccine [32]. Risk factors for reduced seroconversion in patients with solid tumors partially overlap with those observed in the general population. These factors include older age, male sex, and the type of vaccine administered. Following vaccination, factors linked to a diminished humoral immune response in patients with hematological malignancy include advanced age, active malignancy, and lymphoproliferative disorders. In a multivariate analysis conducted among patients actively undergoing treatment, independent predictors for seroconversion were identified, including receiving anti-CD20 treatment ($P < 0.001$), having a diagnosis of aggressive B-cell lymphoma ($P = 0.002$), and having low immunoglobulin M levels (<40 mg/dl, $P = 0.030$) [33].

Several cancer treatments, e.g., CAR-T cell therapy, JAK inhibitors, CD38-targeted therapies, BCMA-targeted therapies, BTK or BCL inhibitors, and monoclonal antibodies inducing B-cell depletion, are known to impair the immune responses induced by vaccination [32]. Recent chemotherapy received within 28 days to 6 months before vaccination impairs seroconversion and neutralizing responses, consistent with reports of decreased vaccine effectiveness in this population. Furthermore, chemotherapy or steroid treatment within 15 days of vaccination has been linked to diminished T cell responses to vaccination [32]. However, T cell responses have been detected in patients undergoing chemotherapy or immune checkpoint inhibitor therapy, even without antibody responses. T cell responses to spike peptide pools specific to VOCs have also been observed in these individuals. One unique scenario where a reduced T cell response can occur despite sufficient virus-specific antibody levels is in patients undergoing graft-versus-host disease prophylaxis after allogeneic stem cell transplantation.

2.4. Biomarkers for COVID-19 illness and vaccine response in cancer patients

Studies delved into the implications of biomarkers in predicting COVID-19 severity and vaccine effectiveness. High C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels were significantly associated with an increased risk of clinical worsening. In addition, CRP and D-dimer levels were related to an increased risk of death [17]. Elevated concentrations of several other potential biomarkers, including ferritin, IL-2R, IL-6, and PCT, exhibit a positive association with the severity of COVID-19 [34]. Furthermore, heightened levels of CRP, ferritin, and LDH in cancer patients undergoing immunotherapy indicate an unfavorable prognosis. The COVID-19 antiviral response in a pan-tumor immune monitoring (CAPTURE) study has demonstrated that the concentrations of several cytokines and chemokines, including IFN-γ, IL-18, IL-6, IL-8, IL-9, IP-10, and macrophage inflammatory protein (MIP)1-β, correlate with the severity of disease [35]. During the acute infection phase, the concentrations of IFN-γ and IL-18 in the serum were significantly higher in patients with hematological malignancies compared to those with solid cancer. These findings highlight the potential differences in immune responses and cytokine profiles based on the type and stage of cancer, as well as the severity of SARS-CoV-2 infection.

Multivariable analyses revealed that systemic inflammation could be a prognostic factor in patients with cancer infected by SARS-CoV-2 [36]. Lymphocytopenia and hypoalbuminemia, as quantified by the OnCovid inflammatory score, independently predict severe COVID-19, supporting their utility in risk stratification survival (Hazard Ratio [HR] of 2.48 in the validation set, 95% CI: 1.47–4.20, $p = 0.001$; adjusted concordance index score of 0.611). Another study revealed angiotensin-converting enzyme 2 (ACE2) as a potential biomarker for susceptibility and fatality in patients with lung cancer [37]. Elevated ACE2 expression facilitates viral entry and cytokine storm, and likely contributes to lung cancer progression, suggesting that heightened ACE2 expression might render lung cancer patients more susceptible to COVID-19.

Age-associated B cells (ABCs) are found in cancer patients undergoing immune checkpoint blockade therapy and may impact the long-term effectiveness of COVID-19 vaccination [38]. Individuals with higher baseline ABC frequencies tend to have fewer receptor binding domain (RBD)-specific memory B cells and a reduced ability to neutralize SARS-CoV-2. Furthermore, ABCs express elevated levels of the inhibitory FcγRIIB receptor, enhancing the clearance of immune complexes. Consequently, the expansion of ABCs could serve as a useful biomarker for identifying individuals at risk of suboptimal responses to vaccination.

Pinder et al. found a significant association between the frequency of $CD19^{+}$ cells and serological output [39]. This association was observed at various time points after vaccination, affecting both the strength of the antibody response and its neutralization capability. Additionally, a negative correlation between total $CD3^{+}$ T cells and neutralization titers after the fourth dose was observed. Conversely, a positive association post-fourth dose between neutralization titers and the frequency of NK cells was found. NK cells can play a role in influencing the development of neutralizing antibodies and the response to vaccination. However, further research into the potential of NK cell frequency as a predictor of vaccine response is warranted, especially for immunocompromised patients who consistently exhibit poor responses to vaccine boosting.

Lastly, six immune biomarkers were identified that independently predict a diminished immunogenic response following COVID-19 vaccine efficacy in hematological cancer patients and were unaffected by patient demographics and clinical characteristics [40]. Specifically, the levels of neutrophils, classical monocytes, CD4 and CD8 effector memory $CD127^{low}$ T cells, as well as naive $CD21^{+}$ and $IgM^{+}D^{+}$ memory B cells, are predictive of weak immunogenicity.

2.5. COVID-19 vaccination strategies and efficacy in cancer patients

Patients diagnosed with cancer can receive COVID-19 vaccines so long as they do not have any contraindications to the vaccine or ingredients in the vaccine [41]. Researchers at Stanford found that mRNA vaccines effectively prevented COVID-19 infections in most cancer patients. The patients who experienced the best protection had completed their cancer treatment more than six months before receiving the COVID-19 vaccine. The mRNA vaccines were ~85% effective in patients whose last cancer treatment was at least six months before their first dose, whereas the vaccines were only 54% effective among patients whose cancer treatments concluded within three months of the first dose [42,43]. Systemic cancer treatments are likely to weaken the immune response one has to an mRNA vaccine [43,44]. In alignment with findings observed in the general population, VOCs' vaccine effectiveness has gradually declined in cancer patients, especially among individuals with hematologic malignancies [32].

Because cancer patients are at high risk for COVID-19 infection, vaccination should be prioritized for this population, even though vaccination may be less effective than in the general population [13,14]. Additional booster injections after the initial two-dose series of mRNA vaccines have proven especially helpful among patients with blood

cancers [45]. Boosting vaccinations is linked to an enhanced capacity to neutralize VOCs; more patients exhibit detectable neutralizing responses to VOCs post-booster [32].

A study by Lee et al. assessed the efficacy of third dose COVID-19 boosters and demonstrated effectiveness against breakthrough infections (59.1%), symptomatic infections (62.8%), coronavirus-related hospitalizations (80.5%), and mortality (94.5%) in cancer patients [46]. Specifically, individuals with lymphoma showed limited protection against symptomatic disease. Despite the administration of third-dose boosters, it was found that cancer patients, after multivariable adjustment, continued to face an elevated risk of coronavirus-related hospitalization and mortality compared to the general population (OR of 3.38 and 3.01, respectively; $p < 0.001$).

However, when comparing the incidence rate ratios (IRRs) for COVID-19 hospitalization and disease severity between the three-dose and four-dose groups and the two-dose group (used as a reference) during the delta and the omicron waves in both cancer and control populations, significantly lower IRRs were observed [47]. During the delta wave, the IRRs for severe disease in actively treated patients, cancer survivors, and controls were 0.14, 0.13, and 0.07, respectively in the three-dose group. These IRRs were 0.29, 0.19, and 0.21 during the omicron wave. Notably, the IRRs for severe disease in the four-dose group during the omicron wave were even lower, at 0.13, 0.10, and 0.10, respectively. Each COVID-19 vaccine booster dose was associated with significant clinical protection in patients with cancer, which was sustained for at least five months in actively treated patients and cancer survivors. This underscores the importance and clinical benefit of each booster dose in this population.

In addition, heterologous booster vaccination strategies offer the potential to leverage the distinctive strengths of different vaccines. For instance, BNT162b2 vaccination can effectively stimulate B-cell immunity and generate high levels of neutralizing antibodies, while the AZD1222 vaccine is known to elicit robust T cell responses [48]. This combined approach is particularly relevant for patients diagnosed with cancer. Moreover, the neutralization efficacy of an additional heterologous vaccine surpassed that of a homologous vaccine, supporting the sequential administration of heterologous vaccines as a superior approach for booster doses [49–51]. Notably, this strategy demonstrated enhanced immunity against the Omicron variant as well. These findings have immediate implications for regions using the CoronaVac regimen for their vaccination campaigns, and these areas should consider the utilization of mRNA vaccine boosters in response to the spread of the Omicron variant.

3. Immunogenicity of COVID-19 vaccines in cancer patients

Numerous studies have primarily focused on antibody responses to the RBD or spike protein of SARS-CoV-2 as a measure of protection against infection, although neutralizing assays are conducted in some studies. In addition, cellular responses can also serve as indicators associated with disease severity. After vaccination, differences in antibody levels and neutralizing antibodies against VOCs were observed among cancer patients [52]. Moreover, different neutralizing abilities and duration of these responses against VOCs were observed, with some vaccines eliciting stronger and longer-lasting immune responses than others. Understanding the underlying factors contributing to the suboptimal response of patients diagnosed with cancer toward the COVID-19 mRNA vaccines is imperative. Moreover, examining the vaccine efficacy in generating antibodies against SARS-CoV-2 wild-type, VOCs, and subvariants is needed to get insights into protecting this vulnerable patient population against the different SARS-CoV-2 strains.

3.1. Humoral immune response

As previously described, patients with hematological malignancies have an increased risk of COVID-19 mortality. In these patients, the seroconversion rates varied between 38.1% and 99.1% across studies after SARS-CoV-2 vaccination (BNT162b2, mRNA-1273, AZD1222, Janssen, rAd5, BBIBP-CorV, CoronaVac), with myeloproliferative diseases showing the highest response rate and patients with chronic lymphocytic leukemia having the lowest [53]. B-cell-depleting treatment reduces seroconversion rates compared to other targeted treatments or chemotherapy, with consistently lower rates in hematological malignancy than in healthy individuals. Lower seroconversion rates were also observed in mature T/NK-cell neoplasms [54]. Kobayashi et al. found that patients with mature T/NK-cell neoplasms exhibited lower seroconversion rates and antibody titers after the second vaccination (BNT162b2 or mRNA-1273) compared to healthy controls. Seroconversion reached 100% with a booster dose, although median antibody titers remained lower than the healthy controls. The antibody titers could be influenced by CHOP therapy and other chemotherapy treatments, as well as the inherent immunodeficiency in malignant lymphoma. Interestingly, elderly patients with weaker initial responses demonstrated significant antibody level increases post-booster, suggesting a potential benefit from more than three vaccine doses, especially for mature T/NK cell neoplasms. Piechotta et al. also revealed that B-cell-depleting treatments, particularly within 12 months of vaccine administration (BNT162b2, mRNA-1273, AZD1222, Janssen, rAd5, BBIBP-CorV, CoronaVac), negatively influence the humoral vaccine response [53]. Interestingly, initiating B-cell depleting treatment shortly after vaccination did not significantly impair the humoral vaccine response. Notably, patients receiving anti-CD20 treatment demonstrated a favorable T cell response, highlighting vaccination's protective potential even in those with treatment-related B cell depletions. Nevertheless, no conclusions were made regarding protecting these patients against VOCs.

The CAPTURE study (NCT03226886) examined seroconversion rates and neutralizing antibody titers against wild-type and VOCs (Alpha, Beta, Delta) for hematological and solid malignancies [55]. Patients with hematological malignancies exhibited lower seroconversion rates (59%) compared to those with solid malignancies (85%) after the second dose (AZD1222 or BNT162b2). Only 54% of infection-naive patients with cancer had functionally relevant neutralizing antibodies against the Delta variant (62% for solid malignancy and 31% for hematological malignancy). After the first dose, 90% of patients receiving AZD1222 and 95% receiving BNT162b2 had undetectable neutralizing antibodies against the Delta variant. AZD1222 had a higher neutralizing antibody titer against the wild-type strain than BNT162b2. Following the second dose, neutralizing antibody titers increased; however, they were still lower against VOC compared to the WT strain. This difference was more pronounced with AZD1222 (50% detectable neutralizing antibody against Delta) than BNT162b2 (68% detectable neutralizing antibody against Delta) among infection-naive patients. In patients with solid cancers who had not been previously infected with SARS-CoV-2, 92% developed NAb against the WT virus, 70% against the Alpha variant, 61% against the Beta variant, and 62% against the Delta variant after receiving the second dose. In contrast, in infection-naive patients with hematological malignancies, the proportions were notably lower both after the first dose (25% had NAb against WT, 7% against Alpha, 5% against Beta, and 1% against Delta) and after the second dose (56% had NAb against WT, 35% against Alpha, 28% against Beta, and 31% against Delta). This impaired generation of immune response in patients with hematological malignancies was observed in the SARS-CoV-2 for cancer Patients (SOAP) study as well [56]. Herein, the third vaccine (BNT162b2) dose restored immunity in most individuals, except for many patients with hematologic malignancies. The frequency of individuals with anti-Spike IgG titers above the background level varied across different groups: healthy controls increased from 50% to 100%, solid cancer patients rose from 32% to 100%, myelodysplastic syndrome patients reached 92%, while other hematologic malignancy patients only reached 50%. Higher Spike-specific IgG levels were associated with greater efficacy in neutralizing wild-type SARS-CoV-2 as well as the

VOCs Delta and Omicron (BA.1). The nonresponse to the third dose was associated with the type of cancer and the treatment schedule. Consistent with previous reports, Azeem et al. demonstrated that the majority of patients with multiple myeloma remained susceptible to SARS-CoV-2 Omicron subvariants (BA.1, BA.2, and BA.5) despite receiving mRNA booster vaccination [57]. In many patients, BNT162b2 and mRNA-1273 did not generate detectable variant-specific neutralizing antibodies or an increase in $CD8^+$ T cells. Like in patients with hematological malignancies, there was a reduction in neutralizing activity against the Omicron variant in patients with solid tumors. In addition, there was a significantly reduced rate of responder subjects compared to the wild-type strain (77.5% versus 95%; P = 0.0022) and the Delta variant (77.5% versus 93.7%; P = 0.0053) [58]. Nevertheless, this study demonstrates a significant humoral and cellular immune response against VOCs in patients with solid tumors six months after receiving the third dose of the BNT162b2 vaccine.

In NSCLC patients, neutralizing antibody titers against the Delta, Beta, and Omicron (B.1.1.529) variants were also notably lower compared to the wild-type strain (P < .0001) [59]. Subsequent mRNA booster vaccination substantially increased the neutralizing antibody titers against the wild-type strain and the Omicron variant (P = .0001). However, two to four months post-booster, a five- to seven-fold decline in titers against wild-type and Omicron viruses was observed. Importantly, PD-1 monotherapy, chemotherapy, or a combination did not significantly impact antibody responses to BNT162b2 and mRNA-1273 vaccinations. The Vaccination Against COVID-19 in Cancer (VOICE) trial (NCT04715438) supports these findings, with most patients with solid tumors receiving immunotherapy and/or chemotherapy responding well to the mRNA-1273 vaccine [60]. Between 28 and 6 months post-second mRNA-1273 vaccination, SARS-CoV-2-binding antibody levels and neutralizing titers were reduced in all cohorts [61]. Observed adequate responses decreased from 93.1% to 32% in patients receiving immunotherapy, 83.8–42% in patients receiving chemotherapy, and 88.8–25% in patients receiving chemo-immunotherapy. An adequate response declined from 99.6% to 51% among the control subjects. In addition, 6 months post-second vaccination did not promote neutralizing antibodies against Omicron (B.1.1.529) in most patients. 96% of patients with an inadequate initial response experienced increased antibody levels post-third vaccination, suggesting that a third mRNA-1273 vaccination may still elicit an adequate response in those who did not reach the 300 virus-binding antibody threshold post-second vaccination. The 18-month data indicate that patients undergoing chemotherapy, immunotherapy, or chemo-immunotherapy for solid tumors during their initial vaccination maintain consistently high SARS-CoV-2-binding antibody levels, which are comparable to the control group. The longitudinal antibody response over time is primarily influenced by additional vaccinations and prior infections rather than ongoing cancer treatment [62]. However, in 82% of CAR-T cell recipients who received BNT162b2 or mRNA-1273 vaccinations, no detectable levels of specific IgG antibodies were observed, and neither experiencing a COVID-19 infection nor receiving an additional booster dose had a discernible impact on enhancing IgG antibody production [63]. Moreover, among allogeneic HCT, autologous HCT, CAR-T, and bispecific T cell engager (BiTE), seroconversion remained low after administration of a booster, 58%, 63%, 40%, and 67%, respectively [64].

3.2. Cellular immune response

T cells, known for recognizing a wide range of epitopes, play a crucial role in the immune response to viral infections [32]. Unlike neutralizing antibodies, T cell responses tend to retain their activity against VOCs. This is attributed to T cell targeting multiple epitopes across various viral proteins, not just the spike protein.

In the CAPTURE study (NCT03226886), SARS-CoV-2 vaccination (AZD1222 or BNT162b2) led to a substantial enhancement in T cell responses in previously unexposed patients [65]. Post-second dose, 79% of the patients exhibited a detectable T cell response to the wild-type S peptide pools. SFU levels significantly increased both after the first vaccine dose (median 3.3-fold increase) and after the second dose (13-fold increase). In patients with hematological malignancies, the T cell responses to the wild-type spike peptide pools were slightly different from that of patients with solid cancer (post-second dose, 83% vs 78%, respectively). In addition, no notable differences in SFU numbers between different cancer subtypes were observed. However, patients with hematologic malignancies exhibited lower T cell responses than solid tumor patients and healthcare workers post-third mRNA vaccination [66]. Notably, the third dose significantly boosted T cell responses (P < 0.0001), leading to a substantial decrease in the percentage of "double-negatives." Unlike the humoral response, T cell responses were similar in all groups post-mRNA vaccines regardless of treatments such as anti-CD20 monoclonal antibody, CAR-T cell, allogeneic HCT, and chemotherapy. The SOAP study by McKenzie et al. also observed resilience to waning between vaccine doses, which assessed functional T cell responses after the third vaccine (BNT162b2) [56]. Among participants, 86% of healthy controls, 77% of solid cancer patients, and 42% of hematological malignancy patients exhibited SARS-CoV-2-specific IFN-γ or IL-2 T cell responses to the spike 2 peptides or RBD following third vaccination with BNT162b2. More than 6 months post-second mRNA--vaccine, T cell responses in 79%, 79%, and 39% were detected, respectively. In addition, a gradual plateauing of T cell responses was also demonstrated in a study by Pinder et al. Authors analysed spike-specific T cell responses over time, which increased from 29.2% to 75.5% post-second dose (BNT162b2 or AZD1222), sustained for up to six months before the third dose, with a slight decrease in patients above the threshold (63.9%) [39]. The third vaccine dose (BNT162b2) notably boosted spike-specific T cell responses, increasing the median response from 15 to 39 spot-forming units (SFU), with 83.3% having a positive response. A similar pattern was observed after administering the fourth dose (BNT162b2), with a further increase in median response (65 SFU) and a higher percentage of patients with a positive response (90.3%). Additionally, T cell responses against the Omicron variant (BA.1/B1.1.529.1) were investigated. Although T cell responses against Omicron-specific epitopes were smaller in magnitude compared to responses against wild-type spike, an anti-Omicron T cell response prior to the third dose was observed, which increased after the third vaccine dose from 28.6% to 46.7%. This response increased further after the fourth vaccine dose, with 54.8% of patients developing a T cell response against the Omicron variant.

Souan et al. investigated the kinetics of the immune responses to BNT162b2 and BBIBP-CorV in patients with cancer [67]. The results indicated that individuals who received the BNT162b2 vaccine exhibited notably higher IFN-γ levels in response to $CD4^+$ $CD8^+$ T cell epitopes from the S1 and S2 subunits of the S protein (Ag2) compared to BBIBP-CorV vaccine recipients (p = 0.028). Notably, there was a significant disparity in the T cell response to Ag2 between T0 and 2–3 weeks after the second BNT162b2 vaccination (p-value = 0.036). Conversely, in those who received the BBIBP-CorV vaccine, a significant difference in T cell response for $CD4^+$ T cell epitopes derived from the S1-RBD subunit (Ag1) between the time points T0 and T2 was observed (p-value = 0.010). Another prospective study assessed the serological and T cell responses following complete mRNA vaccination in lymphoid malignancies (chronic lymphocytic leukemia, B- and T cell lymphomas, and multiple myeloma) [33]. T cell immune responses were detectable in 98% of seropositive patients and 74% of seronegative patients. 86% of patients with lymphoid malignancies had T cell-mediated immune responses against the spike protein of SARS-CoV-2, with IFN-γ levels exceeding 12 pg/ml. However, compared to the control group, their IFN-γ and TNF-α levels were lower (P < 0.0001), although they had higher IL-2 levels. There were positive correlations observed between IFN-γ levels and IL-2 levels (R = 0.5723, P < 0.0001) as well as between IFN-γ levels and TNF-α levels (R = 0.4813, P < 0.0001). Additionally, a

positive correlation was confirmed between IL-2 and TNF-α levels ($R = 0.4813$, $P < 0.0001$). However, Th1-associated cytokine levels did not significantly correlate with serological responses, whether assessing IFN-γ levels ($R = 0.071$, $P > 0.05$) or IL-2 levels ($R = 0.048$, $P > 0.05$).

Among patients who received chemotherapy with or without anti-CD20 antibody within the last month, the IFN-γ levels were lower (75%) compared to those who had received this treatment more than two months before vaccination (90%). Additionally, cytokine release was higher in patients on active treatment with immunomodulatory drugs (94%) or novel oral agents like ibrutinib or venetoclax (91%). 13% of patients were "double negative," exhibiting no T cell or humoral immune responses after vaccination completion. Among these non-responders, 11 had received chemotherapy with or without an anti-CD20 antibody in the last month, one was treated with lenalidomide, and one with ibrutinib. This subgroup represents individuals potentially at high risk for COVID-19 infection. These findings raise concerns about the level of protection that patients with lymphoid malignancies, especially those receiving anti-CD20 antibodies, may derive from vaccination. Also, for CAR-T cell recipients, concerns are rising; a notable reduction of specific T cell responses (57.6%) was observed, irrespective of the number of booster doses received [63]. Patients with low T cell levels experienced the most severe cases of COVID-19 and had the highest mortality rates, even for those generating antibodies against SARS-CoV-2 [3]. Patients receiving anti-CD20 antibodies and CAR-T should adhere strictly to all protective measures, as their response to vaccination may be compromised.

4. Concluding remarks and future directions

The advent of anti-COVID-19 vaccines has revolutionized the battle against SARS-CoV-2 infection [68,69]. While their impact on the general population is well-documented, this paper emphasized the need to address the unique challenges faced by patients with cancer in their fight against the virus [70]. The findings presented here, along with research conducted by Pinato et al., underscore the significant clinical benefit of vaccination in patients with cancer. Through a retrospective analysis, it was demonstrated that complete vaccination reduced the probability of severe disease and mortality in cancer patients who tested positive for SARS-CoV-2, further solidifying the importance of vaccines as a therapeutic strategy in this population [71]. It is important to remember that vaccination immunity differs between cancer patients and declines in those with hematological malignancies [14].

The complexity of immune responses to SARS-CoV-2 vaccination in cancer patients arises from various factors, including different treatment regimens such as anti-CD20 monoclonal antibodies and timing of B-cell depletion, which can influence humoral vaccine responses. Adding to the complexity are the emerging viral VOCs, which pose additional challenges. Despite an increase in neutralizing antibody titers following vaccination, they remain lower against these evolving variants. This highlights the significance of booster vaccinations to boost protection, particularly given these evolving variants.

Furthermore, our review highlights the crucial role of T cell responses in combatting SARS-CoV-2. T cells demonstrated remarkable adaptability and stability across various treatment regimens. A significant percentage of seronegative patients exhibited T cell responses, highlighting the importance of T cell-mediated immunity in these individuals. Unlike patients with hematologic malignancies, solid tumors showed immune responses more similar to healthy individuals. This suggests a partial compensation by certain T cell responses, particularly $CD8^+$ T cell, and non-spike-specific T cell, in the absence of robust humoral responses.

In light of these findings, advocating for repeated vaccinations and targeted campaigns to encourage at-risk individuals, particularly those with B-cell malignancies, to receive COVID-19 vaccination is paramount. The vulnerability of these patients to severe COVID-19 highlights the potential utility of antiviral agents in managing acute infections within this specific patient group. Plasma therapy may be useful in patients with limited ability to mount a humoral immune response to positively impact the outcomes of severe COVID-19 [72]. In addition, CoVac-1, a peptide-based T cell activator of specific SARS-CoV-2 epitopes, may enhance T cell responses after vaccination, particularly in individuals who cannot generate antibody responses [73]. The global objective of SARS-CoV-2 vaccination and the increasing availability of new treatments against COVID-19 such as monoclonal antibodies and specific antiviral agents, should remain the key to managing patients with cancer, extending beyond the COVID-19 pandemic. However, these efforts must be underpinned by studies tailored to the cancer populations. These studies will not only enhance our knowledge of vaccination responses, but also shed light on the interplay between systemic cancer treatments and the long-term effects of SARS-CoV-2 infection, while considering the existing adverse effects of cancer therapies.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Matteo Lambertini reports advisory role for Roche, Lilly, Novartis, Astrazeneca, Pfizer, Seagen, Gilead, MSD and Exact Sciences and speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Knight and Takeda, Travel Grants from Gilead and Daiichi Sankyo, and research support (to the Institution) from Gilead outside the submitted work. Cinzia Solinas reports on travel grants from Ipsen and Eli Lilly. All other authors have no conflict of interest to declare related to the present topic.

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