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The efficacy of COVID-19 vaccination in cystic fibrosis patients: a systematic review

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Abstract

This systematic review evaluates the efficacy and safety of COVID-19 vaccines in individuals with cystic fibrosis (CF). A systematic search of major databases conducted between December 2019 and January 2024 identified eight cohort studies comprising 1,361 CF patients. Studies without subgroup analyses specific to CF patients were excluded, which may have limited the generalizability of findings, particularly for CF lung transplant recipients. COVID-19 vaccines generally induced robust serological responses following the second and third doses, although reduced antibody levels were observed in lung transplant recipients. Factors influencing humoral response included prior SARS-CoV-2 infection, age, inhaled corticosteroid use, and immunosuppressive therapy. Vaccination-related adverse events were predominantly mild. Although breakthrough infections were reported, severe COVID-19 outcomes were infrequent among vaccinated CF patients. The evidence supports the immunogenicity and safety of COVID-19 vaccines in the CF patients. However, individualized vaccination strategies may be necessary for CF lung transplant recipients and those on immunosuppressive therapies. Further research is essential to optimize vaccination strategies and to identify risk factors associated with breakthrough infections in this high-risk population.

Keywords Cystic fibrosis, Covid-19, Vaccination, Efficacy, Safety

Introduction

Since its identification in December 2019 in Wuhan, China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has initiated a global pandemic, resulting in significant morbidity and mortality worldwide [1]. To date, SARS-CoV-2 has claimed over 6.8 million lives, positioning it among the most lethal viruses in human history [2]. The primary mode of transmission for SARS-CoV-2 is via respiratory droplets. Infected individuals may present with a spectrum of symptoms, ranging from mild respiratory discomfort to severe complications, including pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and death [3]. Certain populations, such as the elderly and those

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with pre-existing health conditions, are at a higher risk of developing severe illness [4].

Cystic fibrosis (CF) is an autosomal recessive genetic disorder caused by pathogenic mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, leading to the production of thick, viscous mucus that predominantly affects the lungs and digestive system [5, 6]. This condition leads to chronic respiratory infections and diminished lung function, placing CF patients at heightened risk for severe respiratory infections, including COVID-19. The compromised pulmonary status and recurrent exacerbations in CF patients exacerbate the potential severity of COVID-19, highlighting the critical importance of effective vaccination in this population [7].

The development and deployment of COVID-19 vaccines have been pivotal in controlling the spread of the virus and reducing disease severity. Multiple vaccine platforms have been developed and assessed across various clinical phases, including protein subunits, inactivated viruses, virus-like particles, viral vectors (both non-replicating [VVnr] and replicating [VVr]), live attenuated viruses, RNA, DNA, and viral vectors combined with antigen-presenting cells [8].

Vaccines such as those developed by Pfizer-BioNTech, Moderna, and AstraZeneca have shown high efficacy in the general population [9]. These vaccines function primarily by inducing an immune response that can neutralize the virus, thereby preventing infection and mitigating severe disease outcomes. However, the unique physiological and immunological challenges faced by CF patients, such as chronic inflammation, recurrent respiratory infections, and immune dysregulation, necessitate a specific evaluation of how well these vaccines perform in this vulnerable subgroup [10]. Evidence from studies on other vaccines, such as influenza and pneumococcal vaccines, suggests that CF patients may exhibit differing immune responses compared to the general population [11].

Furthermore, lung transplant recipients, who comprise a significant subgroup of the CF patients, face additional challenges due to immunosuppressive therapy, which can significantly attenuate vaccine-induced immunity. These differences underscore the importance of studying COVID-19 vaccine efficacy and safety specifically in CF patients, both with and without lung transplantation [12].

This systematic review aims to critically assess and synthesize existing research on the efficacy of COVID-19 vaccines in CF patients. It includes CF patients with a history of lung or other organ transplantation, as they represent a clinically significant subgroup within the CF patients. While it is well-established that immunosuppressive therapy reduces vaccine responses, understanding COVID-19 vaccine efficacy and safety in this subgroup is essential for tailoring vaccination strategies.

Method

Search strategy

This analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature search was performed across four major databases: PubMed, Scopus, Web of Science, and Embase. The search query involved medical subject headings (MeSH) terms related to cystic fibrosis, Covid-19, and vaccination. Details of the complete search strategy are provided in Supplementary File 1. The search was conducted from December 2019 until January 2024, and only publications written in English were considered.

Study selection

Two independent reviewers (AS and NZ) were involved in the study selection. Discrepancies were resolved by consultation with a third reviewer (MR). All unrelated publications were removed, and the full texts of the remaining articles were reviewed.

Studies involving lung transplant recipients were included only if they provided subgroup analyses specific to CF patients, as our review focused on the efficacy and safety of COVID-19 vaccines in this population. Studies that did not disaggregate data for CF patients from the broader lung transplant population were excluded due to the inability to extract CF-specific information.

Eligibility criteria

Studies were included in this systematic review if they met the following criteria:

- **Population**: CF patients who received at least one dose of a COVID-19 vaccine.
- **Age**: Participants aged 12 years and older.
- **Study Design**: Cross-sectional studies, case-control studies, cohort studies, or phase I/II/III randomized or non-randomized clinical trials of COVID-19 vaccines.
- **Outcomes**: Data on vaccine efficacy (e.g., seroconversion rates, breakthrough infections) or safety (e.g., adverse events, hospitalizations, or deaths) in CF patients.
- **Language**: Published in English.

The following types of studies were excluded:

- Preclinical or animal studies.
- Meta-analyses, editorials, review articles, or news reports.
- Studies lacking extractable data relevant to vaccine efficacy or safety.

Children aged 12 years and older were included in the review, as this age group qualified for COVID-19 vaccination during the study period. For studies that enrolled mixed populations (e.g., CF transplant recipients and non-transplanted patients), subgroup analyses were considered if data were reported separately.

Data extraction

Four reviewers extracted data from the selected studies. The data items extracted encompassed publication details (year, first author, country), study characteristics (aim/s, timing, design, serological response measurement technique), population characteristics (study population, sample size, gender distribution, confounding factors, exposed/ case group, subgroups, non-exposed/ control group), intervention details (vaccine type, commercial name, minimum and total doses), and outcomes. The outcomes of interest included efficacy outcomes (breakthrough infection, positive serological response after each dose), safety outcomes (COVID-related death and hospitalization following vaccination, vaccination-attributed side effects), and the timing of antibody response measurement after each dose.

Quality assessment

The quality of the included cohort studies was evaluated using the Newcastle-Ottawa Scale (NOS), which assesses three domains: selection of study groups, comparability of cohorts, and ascertainment of exposure or outcomes. Each study is scored based on these criteria, with a maximum of nine points indicating the highest quality. The NOS scores were used to provide an overall assessment of the risk of bias in the included cohort studies and to inform the interpretation of the findings.

Results

The selection process and inclusion of articles in the systematic review are illustrated in Fig. 1, which presents the PRISMA flow diagram. The initial search yielded a total of 453 articles. After removing duplicates ($n=51$), the remaining articles ($n=402$) were screened for keywords and relevance based on their titles and abstracts. In cases of uncertainty, the full-text versions of the publications were reviewed. Only those that fulfilled the inclusion criteria were assessed for eligibility. The full texts of these studies were thoroughly examined. Ultimately, a total of eight articles published between 2022 and 2023 were included in the systematic review.

Study characteristics

This systematic review included eight studies, with Italy contributing the highest number ($n=4$) [13–16], followed by the United States [17], France [18], Austria [19], Greece [20], each contributing to one study. The sample sizes ranged from 13 [19] to 424 [14], and the studies included both prospective and retrospective cohort designs (Table 1). Also the key findings of the study is summarized in Fig. 2.

A total of 1,361 CF patients, representing a comprehensive demographic, were enrolled across all studies. This included 405 patients with a history of lung transplantation, 5 with a history of liver transplantation, and 951 without any transplantation history. Additionally, 92 non-CF healthy individuals were enrolled in two studies as control groups [13, 20]. Regarding gender distribution, the total number of male CF patients reported was 312 (51.1%), and the number of female CF patients was 298 (48.9%). However, two studies did not report gender distribution among the CF subgroup [14, 18] (Table 2).

Quality of evidence

The overall quality of the included studies varied, with three studies classified as good [13, 16, 20], one as fair [17], and four as poor [14, 15, 18, 19], according to the AHQR classification. The strengths of the included studies were that most had a representative exposed cohort and adequately ascertained exposure. Three studies demonstrated that the outcome of interest was not present at the start of the study and had good comparability of cohorts based on the design or analysis controlled for confounders [13, 16, 20]. Most studies also had an adequate assessment of outcomes. However, some weaknesses were identified, such as the lack of a non-exposed cohort or poor selection of the non-exposed cohort in some studies. Several studies did not demonstrate that the outcome of interest was absent at the start of the study, and some lacked comparability of cohorts based on the design or analysis controlled for confounders. A few studies had inadequate follow-up duration or did not report on the adequacy of follow-up of cohorts. The lack of non-exposed cohorts in most studies limits the ability to make direct comparisons and draw conclusions about the specific effects of COVID-19 vaccination in CF patients compared to the general population.

Vaccine platforms and categorization

The vaccine platforms used in these studies included mRNA and adenovirus vector vaccines. The mRNA vaccines comprised Pfizer/BioNTech (BNT162b2), used in almost all studies, and Moderna (mRNA-1273), used in four studies [14, 17–19]. Adenovirus vector vaccines included AstraZeneca (ChAdOx1), used in one study [18], and Janssen (Ad26.COV2.S), used in two studies [17, 18]. Detailed information regarding vaccination details, measurement techniques, and related data are presented in Table 3.

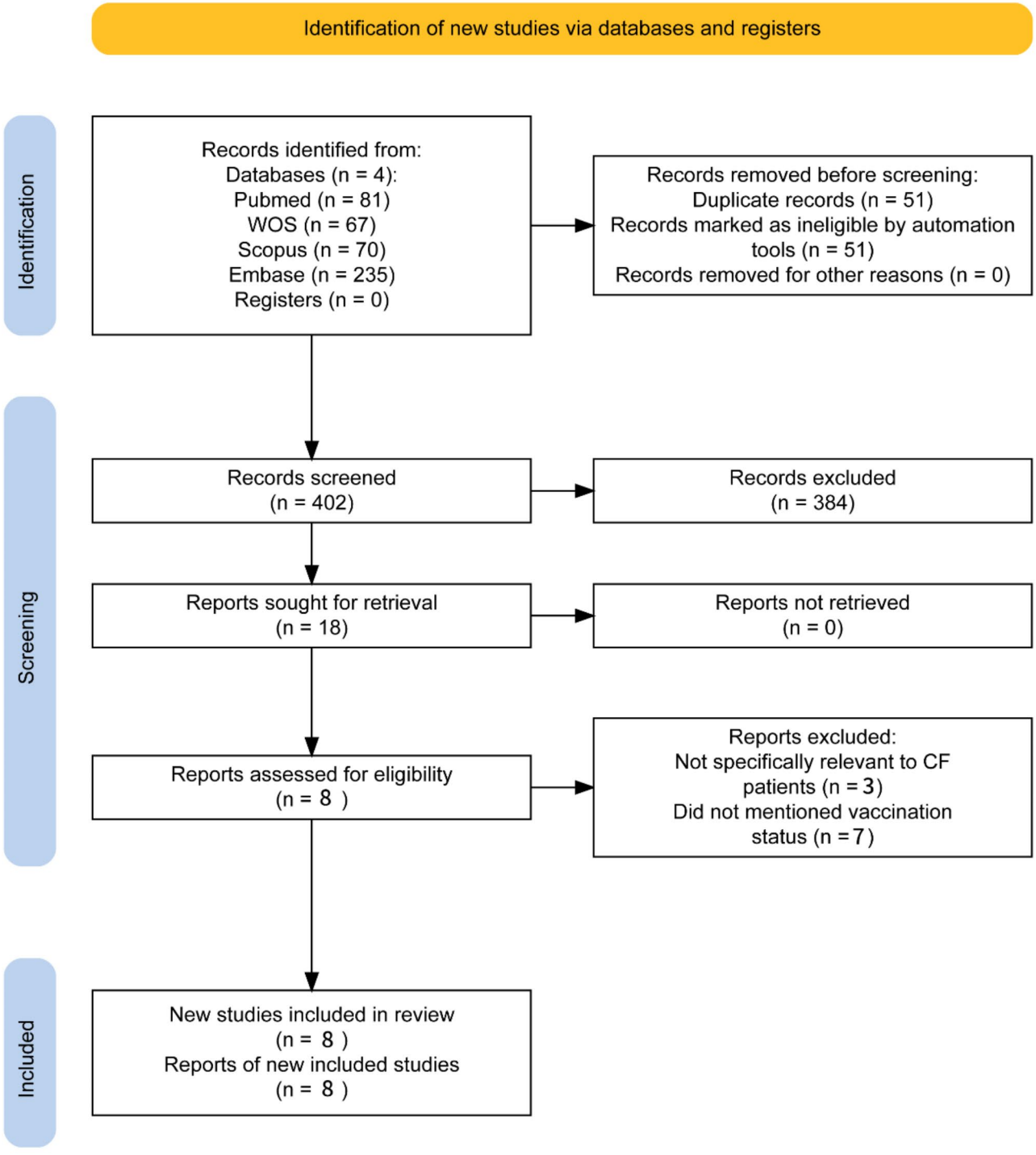

Fig. 1 PRISMA flow diagram of study selection

Methods of measurement of post-vaccine immunity

Seven studies used immunoassays to detect IgG antibodies targeted at the spike protein's receptor-binding domain (RBD) [13, 15–20], except for one study by G. Alicandro et al. [14], which did not mention the measurement method. In addition to anti-SARS-CoV-2 IgG assays, A. Michos et al. [20] reported neutralizing antibodies (NAbs) that block the interaction between RBD and ACE2, while F. Lucca et al. [16] reported anti-SARS-CoV-2 IgA assays. G. Alicandro et al. [13] provided data on cellular immunity, measuring SARS-CoV-2 specific cellular response by interferon-γ (IFNγ) production assay (Table 3).

Table 1 Characteristics of included studies

Title	Year	First Author	Country	Aim/s	Design
Is There a Difference in Immune Response to SARS-CoV-2 Vaccination between Liver and Lung Transplant Patients with Cystic Fibrosis?	2023	T. Fuchs	Austria	Efficacy + Safety	Prospective cohort
Humoral and cell-mediated immune responses to BNT162b2 vaccine against SARS-CoV-2 in people with cystic fibrosis	2023	G. Alicandro	Italy	Efficacy	Prospective cohort
Safety of mRNA-based vaccines against SARS-CoV-2 in people with cystic fibrosis aged 12 years and over	2022	G. Alicandro	Italy	Safety	Prospective cohort
Immunogenicity of BNT162b2 mRNA-Based Vaccine against SARS-CoV-2 in People with Cystic Fibrosis According to Disease Characteristics and Maintenance Therapies	2022	G. Alicandro	Italy	Efficacy + Safety	Prospective cohort
Immunogenicity and Safety of the BNT162b2 COVID-19 Vaccine in Patients with Cystic Fibrosis with or without Lung Transplantation	2023	F. Lucca	Italy	Efficacy + Safety	Prospective cohort
Immunogenicity of the COVID-19 BNT162b2 vaccine in adolescents and young adults with cystic fibrosis	2022	A. Michos	Greece	Efficacy + Safety	Prospective cohort
Seroprevalence and Clinical Characteristics of SARS-CoV-2 Infection in Children with Cystic Fibrosis	2023	G. Hergenroeder	USA	Efficacy + Safety	Prospective cohort
Efficacy of three COVID-19 vaccine doses in lung transplant recipients: a multicentre cohort study	2023	G. Dauriat	France	Efficacy + Safety	Retrospective cohort

Seroconversion rates

Seroconversion in non-transplanted patients

Two of the eight studies reported the efficacy and seroconversion rates after the first vaccination dose. The studies by A Michos et al. [20] and F. Lucca et al. [16] found that 100% and 93.5% of participants with no transplant history achieved seroconversion, respectively. The mean measurement time was specified as 20 days post-vaccination in the A. Michos et al. study, and 21 days post-vaccination in F. Lucca et al. study. Both studies utilized the BNT162b2 mRNA vaccine. F. Lucca et al. also reported an IgA seroconversion rate of 91.5% after the first dose. The remaining studies did not report seroconversion rates after the first dose.

After the second dose, five of the eight studies reported seroconversion rates in non-transplanted CF patients. Four studies, including G. Alicandro et al. [13, 15], A Michos et al. [20], and G. Hergenroeder et al. [17], observed a 100% seroconversion rate, while F. Lucca et al. [16] reported a rate of approximately 81.1%. The measurement times varied across the studies, with A. Michos et al. [20] specifying 51 days post-vaccination, G. Alicandro et al. [13] reported a range of 180–250 days post-vaccination, and F. Lucca et al. [16] reported a range of 168–196 days post-vaccination. G. Alicandro et al. [15] also determined measurement times to be 0, 84, and 168 days post-vaccination. Hergenroeder et al. did not mention the measurement time.

The type of administrated vaccines in G. Alicandro et al., A. Michos et al., and F. Lucca et al. studies was the BNT162b2 mRNA vaccine. The T. Fuchs et al. and Hergenroeder et al. studies utilized one of the following vaccines: BNT162b2 [17, 19], mRNA-1273 [17, 19], or Janssen Ad26.COV2.S [17]. In addition to humoral immunity, G. Alicandro et al. [13] evaluated the rate of vaccine-induced cellular immunity, which was 50% after the second dose, with a measurement range of 180–250. Furthermore, F. Lucca et al. reported the IgA seroconversion rate to be 85%.

Only G. Alicandro et al. [13] reported the seroconversion rate after the third dose in non-transplant patients, which was 100%, measured in a range of 60–119 days, 120–179 days, and 180–250 days post-vaccination. In addition to humoral immunity, this study also evaluated the rate of vaccine-induced cellular immunity after the third dose. The rates were 82.1% with a measurement range of 60–119 days, 84.2% with a measurement range of 120–179 days, and 91.7% with a measurement range of 180–250 days. The types of vaccines used in this study included BNT162b2 (Table 4).

Seroconversion in transplanted patients

Regarding organ-transplanted CF patients, F. Lucca et al. [16] reported a seroconversion rate of 0.1% after the first

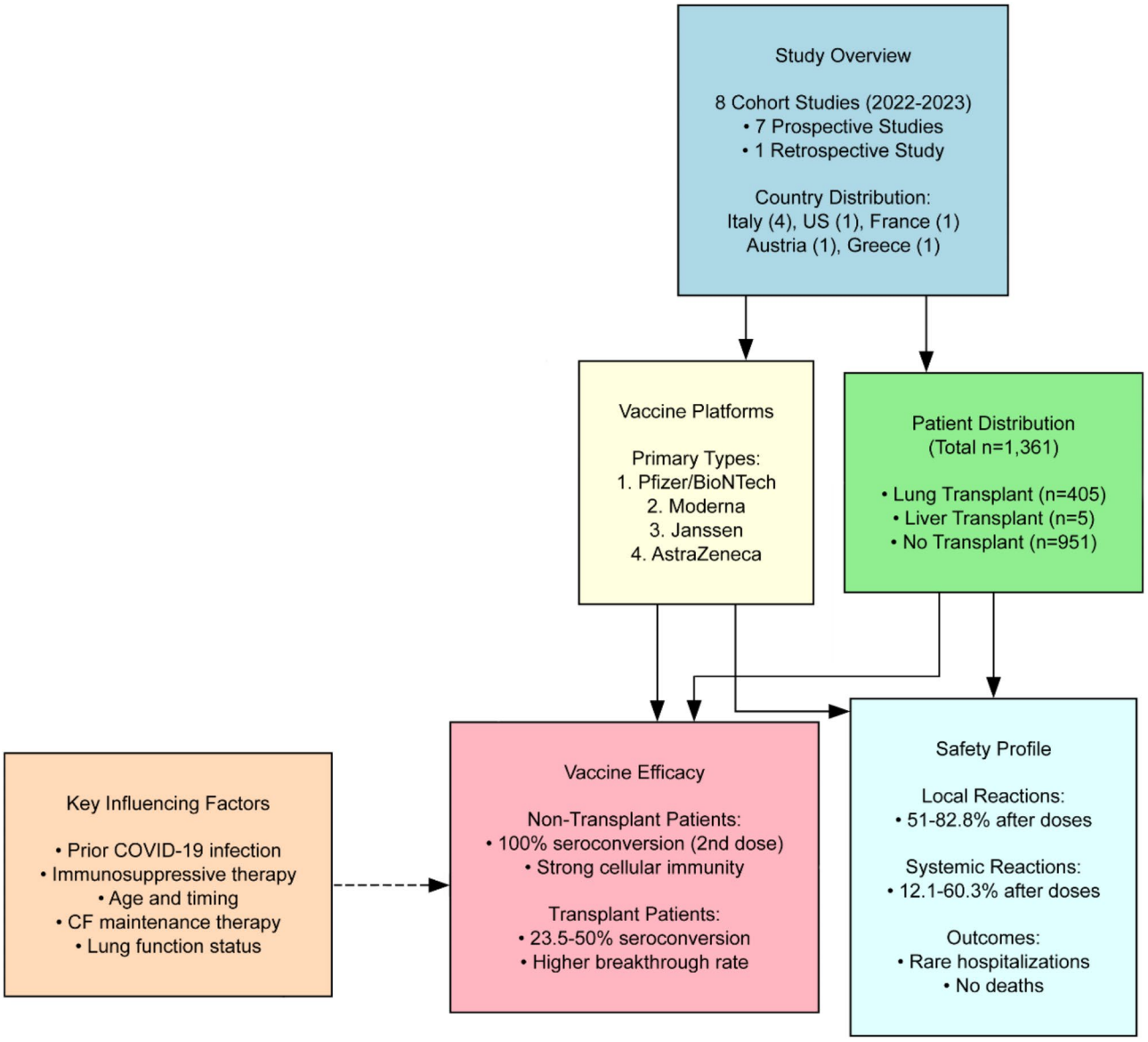

Fig. 2 Key findings of the study on the efficacy and safety of COVID-19 vaccines in CF patients

dose in lung-transplanted patients, measuring 21 days. The IgA seroconversion rate was 17.6% in this study. Furthermore, F. Lucca et al. [16] and T. Fuchs et al. [19] examined the seroconversion rates after the second dose in lung-transplanted patients, reporting rates of 23.5% and 50%, respectively, with a mean measurement time of 47 days for the T. Fuchs et al. study And a range of 168–196 days for the F. Lucca et al. study. The IgA seroconversion rate was 52.9% in the Lucca et al. study. Only T. Fuchs et al. [19] reported a seroconversion rate in liver-transplanted patients after the second dose, which was 100%, with a mean measurement time of 47 days.

G. Dauriat et al. [18] and T. Fuchs et al. [19] reported the seroconversion rate in lung-transplanted patients after the third dose, with values of 26.6% and 71%, respectively. T. Fuchs et al. indicated a mean measurement time of 63 days. Meanwhile, G. Dauriat et al. reported the measurement as 21 days and 168 days post-vaccination. For liver-transplanted CF patients, the seroconversion rate after the third dose was 100%, with a measurement timing of 63 days post-vaccination [19] (Table 4).

Severity of breakthrough COVID-19 in vaccinated CF patients

According to the results from four studies, the rate of breakthrough COVID-19 infections in fully vaccinated CF patients ranged from 0.8 to 37.5% [14, 15, 17, 19]. This rate was higher in CF patients with a history of transplantation. T. Fuchs et al. [19] reported 3 COVID-19

Table 2 Demographic characteristics of study participants and potential confounding factors

First Author	Population	Sample Size (*N*)	Gender (M: F)	Confounders	Subgroups	Exposed Group	Non-Exposed Group
T. Fuchs	adults	13	8:5	Prior infection, age, sex, BMI, time interval since performance of transplantation, lung function, immunosuppressive therapy regimen, CF maintenance therapy (antibiotics/corticosteroids/CFTR modulators)	8 Lung Tx / 5 Liver Tx	CF + Tx	-
G. Alicandro	Pediatrics + adults	144	78:66	Prior infection, age, sex, CFTR genotyping (F508del), lung function,	118 CF patients (no lung Tx)	CF	26 non-CF
G. Alicandro	Pediatrics + adults	424	not specifically mentioned	-	424 CF patients (52 lung Tx)	CF	-
G. Alicandro	Pediatrics + adults (86%)	143	75:68	Prior infection, age, sex, disease severity, CF maintenance therapy (antibiotics/corticosteroids/CFTR modulators), BMI, lung function	143 CF patients (no lung Tx)	CF	-
F. Lucca	Pediatrics + adults	178	92:86	Prior infection, age, sex, transplant status, time since transplant, immunosuppressive therapy regimen	18 Lung Tx	CF	160 non-Lung Tx CF
A. Michos	adults	99	30:69	Transplant status, age, sex, prior infection, blood type, CFTR genotyping, CF maintenance therapy (antibiotics/corticosteroids/CFTR modulators)	33 CF patients (no lung Tx)	CF	66 Healthy
G. Hergenroeder	pediatrics	125	63:62	Prior infection, age, sex, CF maintenance therapy (antibiotics/corticosteroids/CFTR modulators), BMI, lung function, race, CFTR genotyping	111 SARS-CoV-2 seronegative, 14 SARS-CoV-2 seropositive (no lung Tx)	CF	-
G. Dauriat	adults	327	not specifically mentioned	Transplant status, age, sex, prior infection, CF maintenance therapy (antibiotics/corticosteroids/CFTR modulators), immunosuppressive therapy regimen	327 CF patients	1071 Lung Tx	-

breakthrough infections among 8 CF patients with liver or lung transplantation history. At the same time, G. Hergenroeder et al. [17] described COVID-19 breakthrough infections in one patient among 125 fully vaccinated CF patients without transplantation history. Five studies examined the occurrence of COVID-related deaths and hospitalizations after vaccination. No fatalities were reported in any of these studies. However, G. Alicandro et al. [15] documented a single instance of hospitalization due to the COVID-19 infections post-vaccination (Table 4).

Adverse events of COVID-19 vaccines in CF patients

Adverse events of COVID-19 vaccines were reported in half of the studies and were mostly self-limiting. The most frequently reported local adverse events were injection-site reactions, while systemic effects included fever, fatigue, headache, myalgia, and arthralgia. Two studies reported the percentage of local and systemic adverse effects after the first dose of the COVID-19 vaccine [14, 20]. Three studies provided data on adverse effects following the second dose [14, 16, 20]. G. Alicandro et al. reported the adverse effects after the first or second dose [15]. The local reaction after the first dose ranged from 75.8 to 82.8%, while it ranged from 51 to 75.9% for the second dose. The systemic reaction after the first dose ranged from 12.1 to 41.3%, and after the second, it ranged from 27.3 to 60.3%. Detailed values for these adverse effects are presented in Table 4.

Possible confounding factors in the studies

Several possible confounding factors may affect the efficacy and safety of COVID-19 vaccines in CF patients. These factors include prior SARS-CoV-2 infection, age, sex, CF maintenance therapy (antibiotics, corticosteroids, CFTR modulators), BMI, lung function, race, CFTR genotyping (e.g., F508del), disease severity, transplant status, time interval since transplantation, immunosuppressive therapy regimen, and blood type.

Among these factors, prior SARS-CoV-2 infection, age, and sex were the most common, as mentioned in all studies except G. Alicandro et al. study [14]. In five studies, CF maintenance therapy (antibiotics, corticosteroids, CFTR modulators) was identified as potential confounders, while lung function was identified in four studies. Transplant status, BMI, immunosuppressive therapy regimen, and CFTR genotyping were identified in three studies. Disease severity, time interval since transplantation, blood type, and race were each identified as possible confounding factors in one study. Detailed information for these confounding factors is presented in Table 2.

Discussion

The reviewed studies demonstrate that COVID-19 vaccines generally induce a strong serological response in CF patients following the second and third doses. However, lung transplant recipients exhibit notably lower antibody levels compared to non-transplanted CF patients. Factors such as prior SARS-CoV-2 infection, age, use of inhaled corticosteroids, and immunosuppressive therapy may influence the humoral response in CF patients. Among these, immunosuppression in lung transplant recipients, which is necessary to prevent organ rejection, emerges as the most critical factor due to its profound impact on immune function.

The immune response to COVID-19 vaccines in non-transplanted CF patients appears to be robust and comparable to that observed in the general population. Several studies in this review reported high seroconversion rates in non-transplanted CF patients following the second and third doses of COVID-19 vaccines. For instance, Alicandro et al. and Michos et al. observed 100% seroconversion rates in non-transplanted CF patients, indicating strong humoral immunity [13, 15, 20]. These findings indicate that CF patients, in the absence of immunosuppressive therapy, are capable of mounting an adequate immune response to COVID-19 vaccines.

While the overall serological response in non-transplanted CF patients is comparable to non-CF individuals, certain factors unique to CF may influence vaccine efficacy. Chronic inflammation and recurrent respiratory infections, hallmark features of CF, could potentially modulate immune responses. Furthermore, CF-specific therapies, including inhaled corticosteroids and CFTR modulators, may exert immunomodulatory effects. However, none of the studies included in this review directly compared non-transplanted CF patients with non-CF individuals, limiting the ability to draw definitive conclusions regarding differences in immune responses.

Evidence from studies on other vaccines, including influenza and pneumococcal vaccines, supports the idea that CF patients generally mount adequate immune responses, though variability may depend on disease severity and treatment regimens. This aligns with the findings of this review, which indicate that non-transplanted CF patients respond well to COVID-19 vaccines [11].

While local and systemic reactions were common following vaccination, they were generally mild and did not significantly interfere with daily activities in CF patients. Breakthrough infections were documented in some studies; however, severe COVID-19 outcomes, such as hospitalizations and deaths, were rare among vaccinated CF patients. Overall, the evidence supports the immunogenicity and safety of COVID-19 vaccines in CF patients.

Table 3 Vaccination details and measurement techniques used in the included studies

First Author	Response Measurement	Vaccine Type	Commercial Name	Min Doses (*N*)	Total Doses (*N*)	Time to 1st Dose (day)	Time to 2nd Dose (day)	Time to 3rd Dose (day)
T. Fuchs	chemiluminescent microparticle immunoassay (S1RBD)	mRNA	30 µg Comirnaty and/or 50 µg Spikevax Moderna	2	3	-	47 (mean)	63 (mean)
G. Alicandro	enzyme immunoassay (S1RDB) spike-induced interferon-gamma (INF-y) release	mRNA	Comirnaty Pfizer–BioNTech	2	3	-	180–250 (range)	60–119, 120–179 and 180–250 (ranges)
G. Alicandro	-	mRNA	Comirnaty Pfizer–BioNTech Spikevax Moderna	1	2	-	-	-
G. Alicandro	electrochemiluminescence immunoassay (S1RBD)	mRNA	Comirnaty Pfizer–BioNTech	2	3	-	day 0 day 84 day 168	-
F. Lucca	anti-S1RBD IgG, and IgA ELISA	mRNA	Comirnaty Pfizer–BioNTech	2	2	-	T1: day 21 T2: 168–196 (range)	-
A. Michos	enzyme immunoassay (S1RDB)	mRNA	Comirnaty Pfizer–BioNTech	1	2	day 20	day 51	-
G. Hergenroeder	Abbott SARS-CoV-2 nucleocapsid protein IgG Enzyme immunoassay (S1RDB)	mRNA Adenoviral vector	Comirnaty Pfizer–BioNTech Spikevax Moderna Ad26. COV2.S Janssen	2	2	-		-
G. Dauriat	enzyme immunoassay (S1RDB)	mRNA Adenoviral vector	Comirnaty Pfizer–BioNTech Spikevax Moderna Ad26. COV2.S Janssen AstraZeneca ChAdOx1 nCoV-19	3	3	-	-	day 21 day 168

However, further research is required to optimize vaccination strategies, particularly for CF lung transplant recipients and individuals receiving immunosuppressive therapies.

In CF patients, COVID-19 typically manifests with symptoms similar to those observed in the general population, including fever, cough, and fatigue [21, 22]. However, the incidence of COVID-19 among CF patients is generally lower than that observed in the general population. This reduced incidence is likely attributable to the stringent infection prevention measures often practiced by CF patients, such as social distancing and frequent hand hygiene [23]. Additionally, CF patients are typically well-informed about infection prevention and frequently practice social distancing to minimize exposure to infections, including SARS-CoV-2, which has likely contributed to their lower infection rates [23]. Hospitalization rates for CF patients with COVID-19 vary but are often higher than those observed in the general population. Specific subgroups, such as post-transplant patients and those with lower baseline lung function (FEV1 < 70%), are more likely to require hospitalization and intensive care [21, 22]. For instance, McClenaghan et al. reported higher hospitalization rates in post-transplant patients (74%) compared to non-transplant patients (46%) [22]. Similarly, Corvol et al. found that 92% of post-transplant patients were hospitalized, and 75% of ICU admissions were among this subgroup [24].

The increased risk of severe COVID-19 in CF patients due to their underlying respiratory condition underscores the importance of understanding vaccine efficacy in this population. While this risk is particularly heightened in CF patients who have undergone lung transplantation due to immunosuppressive therapy, non-transplanted CF patients also face significant risks. Chronic lung infections, persistent inflammation, and diminished lung function in non-transplanted CF patients may predispose them to severe respiratory complications if infected with SARS-CoV-2. Understanding vaccine efficacy in both subgroups is therefore critical to tailoring protective strategies for the entire CF patients.

Our review highlights the reduced seroconversion rates and higher breakthrough infection rates observed in CF transplant recipients compared to non-transplanted CF patients. These findings underscore the need for individualized vaccination strategies, such as additional vaccine doses or alternative immunization approaches, to enhance protection in this high-risk group. However, CF patients, particularly those who have undergone lung transplantation, may exhibit altered immune responses as a result of their condition and the immunosuppressive therapies they receive, highlighting the need for specific studies on vaccine efficacy in this subgroup [25].

The findings of this review strongly support the immunogenicity and safety of COVID-19 vaccines in CF patients. Despite differences in immune responses between non-transplanted and transplanted CF patients, vaccination remains a critical preventive measure for all individuals in this high-risk group. Given the underlying respiratory vulnerabilities in CF patients, vaccination should remain a cornerstone of COVID-19 prevention strategies for all CF patients, irrespective of transplant status. Tailored approaches, such as additional booster doses and enhanced post-vaccination monitoring, may be necessary to optimize protection, particularly in transplant recipients.

Furthermore, understanding the safety and side effect profiles of COVID-19 vaccines in CF patients is crucial, as this population may have unique concerns and challenges related to vaccination that require special consideration in clinical decision-making and patient education.

Future research should focus on addressing the identified weaknesses by including a representative non-exposed cohort for better comparison, ensuring that the outcome of interest is not present at the start of the study, and adequately controlling for confounding factors. Researchers should also prioritize adequate follow-up duration and reporting on the adequacy of follow-up of cohorts to enhance the quality of evidence in future studies.

Conclusion

This systematic review supports the immunogenicity and safety of COVID-19 vaccines in the CF patients, with strong serological responses observed in non-transplanted CF patients following vaccination. However, CF transplant recipients, particularly lung transplant patients on immunosuppressive therapy, exhibit reduced serological responses and higher rates of breakthrough infections compared to non-transplanted CF patients. These findings underscore the need for individualized vaccination strategies, including additional vaccine doses or alternative immunization approaches, to enhance protection in transplant recipients. Vaccination-related adverse events were generally mild and self-limiting in CF patients. Prioritizing vaccination and refining strategies based on patient characteristics, including transplant status and immunosuppressive therapy, will be essential to protect CF patients from severe COVID-19 outcomes and to improve their overall health and well-being.

Table 4 Seroconversion rates, breakthrough infections, and adverse events following COVID-19 vaccination in CF patients

First Author	Breakthrough Infection (*N*)	COVID Deaths (*N*)	COVID Hospitalizations (*N*)	Response after 1st Dose (%)	Response after 2nd Dose (%)	Response after 3rd Dose (%)	Side Effects (%)
T. Fuchs	3	0	0	-	69	83	0
G. Alicandro	not specifically mentioned	0	0	-	100% humoral response, 50% cell-mediated response	100% humoral response, cell mediated response after 60–119 days: 82.1% 120–179 days: 84.2% 180–250 days: 91.7%	not specifically mentioned
G. Alicandro	13	0	0	-	-	-	Local reactions: after 1st dose (82.8%) after 2nd dose (75.9%) Systemic reactions: after 1st dose (41.3%) after 2nd dose (60.3%)
G. Alicandro	9	0	1	-	100	-	Local reactions after 1st or 2nd dose (89.5%) Systemic reactions after 1st or 2nd dose (72%)
F. Lucca	not specifically mentioned	not specifically mentioned	not specifically mentioned	-	T1: Lung Tx IgG 0.1%, non-Lung Tx IgG 93.5%, Lung Tx IgA 17.6%, Non-Lung Tx IgA 91.5% T2: Lung Tx IgG 23.5%, Non-Lung Tx IgG 81.1%, Lung Tx IgA 52.9%, Non-Lung Tx IgA 85%	-	Local reaction after 2nd dose: 133 (51%) Systemic reaction after 2nd dose: 140 (55.6%)
A. Michos	not specifically mentioned	not specifically mentioned	not specifically mentioned	100	100	-	Local reactions: after 1st dose (75.8%) after 2nd dose (72.7%) Systemic reactions: after 1st dose (12.1%) after 2nd dose (27.3%)
G. Hergenroeder	1	0	0	-	100	-	not specifically mentioned
G. Dauriat	not specifically mentioned	not specifically mentioned	not specifically mentioned	-	-	26.6	not specifically mentioned

Author contributions
Aazam Gholami Shahrebabak: Contributed to the conceptualization and design of the study. Involved in drafting the initial manuscript and revising it critically for important intellectual content.Masoud Rezaei: Participated in the methodology design and data validation process. Conducted quality assessment of the included studies and assisted in interpreting the results. Amirhossein Shahpar: Involved in the formal analysis and data extraction process. Contributed to the creation of the PRISMA flow diagram and tables summarizing study characteristics.Nazanin Zeinali Nezhad: Conducted the literature search and was responsible for the initial screening of articles. Assisted in resolving discrepancies in study selection with the third reviewer. Mohammad Sharifi Sarasyabi: Assisted in data extraction and synthesis. Contributed to writing sections of the results and discussion, focusing on vaccine platforms and seroconversion rates. Mohsen Nakhaie: Provided expertise in clinical implications and contributed to the discussion on the safety and side effect profile of vaccines in CF patients.Maryam Gholami Shahrebabak: Served as the corresponding author, overseeing the entire project. Contributed to the conceptual framework and final approval of the manuscript version to be published.Razman Arabzadeh Bahri: Assisted in the critical review and editing of the manuscript. Provided additional insights into potential confounding factors and implications for future research.

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Data availability
The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request. This includes the full search strategy, data extraction forms, and quality assessment tools used in the systematic review process. All primary studies included in this review are published and publicly available through their respective journals. Any additional data that support the findings of this study are available from the corresponding author upon justified request, subject to data protection regulations and ethical considerations.

Declarations

Ethics approval and consent to participate
This study is a systematic review of previously published literature and does not involve direct contact with human subjects or animals. We are utilizing data extracted from previously published articles. Therefore, there are no specific ethical challenges associated with our research methodology. Consequently, we did not include a reference to a specific norm or standard such as the Declaration of Helsinki. However, we assure that our research adheres to the highest standards of scientific integrity and ethical conduct in reviewing and analyzing published literature. The systematic review process was conducted in accordance with established guidelines for evidence synthesis and reporting.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no conflicts of interest concerning the publication of this article. Each author listed assumes responsibility for the overall integrity of the work and has provided consent for the publication of this version.

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