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REGULAR ARTICLE

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Impact of SARS-CoV-2 vaccination and monoclonal antibodies on outcome post–CD19-directed CAR T-cell therapy: an EPICOVIDEHA survey

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Data are available on request from the corresponding authors, Jaap A. van Doesum (j.a.van.doesum@umcg.nl) and Jon Salmanton-García (jon.salmanton-garcia@uk-koeln.de).

The full-text version of this article contains a data supplement.

Key Points

- Vaccination did not improve COVID-19 attributed mortality; still progression is milder with shorter hospitalization and ICU admission.
- Use of monoclonal antibodies was effective in reducing attributable mortality.

Patients with previous CD19-directed chimeric antigen receptor (CAR) T-cell therapy have a prolonged vulnerability to viral infections. Coronavirus disease 2019 (COVID-19) has a great impact and has previously been shown to cause high mortality in this population. Until now, real-world data on the impact of vaccination and treatment on patients with COVID-19 after CD19-directed CAR T-cell therapy are lacking. Therefore, this multicenter, retrospective study was conducted with data from the EPICOVIDEHA survey. Sixty-four patients were identified. The overall mortality caused by COVID-19 was 31%. Patients infected with the Omicron variant had a significantly lower risk of death due to COVID-19 compared with patients infected with previous variants (7% vs 58% [P = .012]). Twenty-six patients were vaccinated at the time of the COVID-19 diagnosis. Two vaccinations showed a marked but unsignificant reduction in the risk of COVID-19–caused mortality (33.3% vs 14.2% [P = .379]). In addition, the course of the disease appears milder with less frequent intensive care unit admissions (39% vs 14% [P = .054]) and a shorter duration of hospitalization (7 vs 27.5 days [P = .022]). Of the available treatment options, only monoclonal antibodies seemed to be effective at reducing mortality from 32% to 0% (P = .036). We conclude that survival rates of CAR T-cell recipients with COVID-19 improved over time and that the combination of prior vaccination and monoclonal antibody treatment significantly reduces their risk of death. This trial was registered at www.clinicaltrials.gov as #NCT04733729.

Introduction

The introduction of CD19-directed chimeric antigen receptor T-cell (CAR T-cell) therapy for patients with relapsed or refractory large B-cell lymphoma meant an incredible leap forward in the survival of these patients.[1,2] Indications for CAR T-cell therapy keep expanding in commercial and clinical trial settings. The major long-term adverse effect of CD19-directed CAR T cells is prolonged B-cell aplasia and subsequent (viral) infections.[3,4]

Early reports of patients with coronavirus disease 2019 (COVID-19) after CD19-directed CAR T-cell therapy showed a dismal outcome of just 50% overall survival (OS).[5,6] Updates on the outcome during the following years and subsequent severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) variants are lacking. In addition, the impact of vaccination and treatment with monoclonal antibodies (MoAbs) or convalescent plasma on outcomes is not known.

Several studies assessed the impact of vaccination on the humoral immune response.[7-9] However, only a small subset of patients obtain a serological conversion after vaccination. This is in line with larger vaccination studies in hematological patients that underpin the need for B cells for mounting a humoral response to vaccination.[7,10] Although little data have been published about cellular response in this specific patient category,[11,12] in the general population, T-cell response is considered an important factor in successful SARS-CoV-2 vaccination.[13] Nevertheless, T-cell function could be impaired because of the CAR T-cell conditioning therapy with fludarabine/cyclophosphamide or bendamustine, especially in the first few months.

We hypothesize that vaccination and treatment with MoAbs will yield protection against adverse outcome. Therefore, we conducted this study to assess the impact of vaccination and treatment with MoAbs on the outcome of patients with COVID-19 after CD19-directed CAR T-cell therapy.

Methods

In this retrospective observational multicenter study, data were collected of all adult patients who were diagnosed with COVID-19 and for whom the last line of treatment immediately before the infection for their hematological malignancy was CD19-directed CAR T-cell therapy. The data were collected within the EPICOVIDEHA survey,[14] an initiative of the European Hematology Association infectious diseases working group. EPICOVIDEHA was approved by the local ethics committee of 276 the Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Università Cattolica del Sacro 277 Cuore of Rome, Italy (study ID: 3226). The study was conducted in accordance with the Declaration of Helsinki, and the trial was registered at www.clinicaltrials.gov as #NCT04733729. Deidentified data on demographics, comorbidities, outcome, underlying hematological malignancy, and treatment were collected at the survey on www.clinicalsurveys.net. The data cutoff date was 1 July 2022.

The aim of this study is to assess the impact of COVID-19 on survival. The hematological prognosis of patients with relapsed disease after CAR T-cell therapy is very poor. To avoid this competing risk, we chose not to present the data as OS, but as event-free survival (EFS), whereby an event was defined as death caused by COVID-19. Patients were censored at day of death because of a cause other than COVID-19. Deaths caused by COVID-19 were patients who either died solely because of COVID-19 or COVID-19 in combination with other diseases (eg, progression lymphoma). Death due to progression was limited to only those cases where it was clear that there was no relation to

COVID-19. Data are presented up to day 90 after COVID-19 infection, when 75% of the patients had an event or were censored. Patients were considered vaccinated when they had at least the minimum number of vaccinations that were recommended by the manufacturer in the general population (eg, 2 vaccinations with Comirnaty, Spikevax and 1 if Jcovden) and the time between the last vaccination and COVID-19 must be at least 7 days.

For statistical analyses, SPSS v25.0 (IBM Corp, Chicago, IL) was used. Categorical variables are presented using frequency and percentage; continuous variables are shown by median and interquartile range (IQR). EFS was estimated with the Kaplan-Meier method. Risk factors were evaluated using a Cox proportional hazard model. Because of the limited number of events, we applied a limited multivariate analysis in the form of pairwise Cox regression. For half of the patients, the viral variant was not known, so the year of the COVID-19 was used in the multivariate analysis, assuming that in 2020 and 2021, most of the patients had an infection with a non-Omicron variant, and in 2022, all patients were infected with an Omicron variant.

Results

In total, 64 patients with COVID-19 and CD19-directed CAR T-cell therapy as their most recent treatment were identified in 34 centers across 15 countries (supplemental Figure 1). The median follow-up was 50.5 days (IQR, 25-90), the median age at COVID-19 diagnosis was 56 years (IQR, 47-65), and 38 (54.3%) were male. At the time of COVID-19 diagnosis, 42 patients (60%) had complete remission of their hematological malignancy, 3 (4.3%) had stable disease, and 17 (24.3%) had active disease; for 2 patients, the disease status was missing. The median number of previous treatment lines was 3 (IQR, 3-4). Sixteen patients (25.0%) had been treated previously with autologous hematopoietic stem cell transplantation (auto HSCT). The median time since transplantation and COVID-19 diagnosis was 602 days (IQR, 276-1108). The most often used CAR T-cell constructs were axicabtagene ciloleucel (50.0%) and tisagenlecleucel (42.2%). The median time since CAR T-cell infusion until COVID-19 diagnosis was 202.5 days (IQR, 85-450). In 50.0% of all cases, the SARS-CoV-2 variant was not determined. Of the patients for whom variants were tested, most were infected with an Omicron variant (28.1%). Twenty-six patients (40.6%) had received at least 1 vaccination before COVID-19. Comorbidities (hypertension, cardiovascular disease, pulmonary dysfunction, diabetes, renal impairment, liver disease, or smoking history) were present in 39 patients. Twenty-two patients (34.4%) had 1 comorbidity, 10 (15.6%) had 2 comorbidities, and 7 (10.9%) had 3 or more comorbidities. Full demographic and clinical characteristics are summarized in Table 1.

Outcome

In total, 50 patients (78.1%) were hospitalized because of COVID-19, and 18 patients (28.1%) were admitted to intensive care units (ICU), underscoring the severe impact of COVID-19 in this patient population. The median duration of hospitalization was 25.0 days. COVID-19 treatment consisted of corticosteroids in 30 patients (46.9%), viral replication inhibitors in 18 patients (28.1%), convalescent plasma in 16 patients (25.0%), MoAbs in 14 patients (21.9%), and tocilizumab in 6 patients (9.4%). At last follow-up, 38

Table 1. Overall patient and treatment characteristics

	All patients (N = 64) N (%)
Sex	
Male	38 (59.4)
Female	26 (40.6)
Age, median (IQR)	56 (47-66)
Diagnosis	
Diffuse large B-cell lymphoma	49 (76.6)
High-grade B-cell lymphoma with MYC and BCL2/BCL6	2 (3.1)
Primary mediastinal B-cell lymphoma	4 (6.3)
Transformed follicular lymphoma	2 (3.1)
Mantle cell lymphoma	2 (3.1)
Follicular lymphoma	3 (4.7)
B-ALL	2 (3.1)
Number of previous lines of therapy, median (IQR)	3 (3-4)
Previous auto HSCT	16 (25.0)
Time since auto HSCT, days median (IQR)	602 (276-1108)
CAR T-cell product	
Axicabtagene ciloleucel	32 (50.0)
Lisocabtagene maraleucel	1 (1.6)
Tisagenlecleucel	27 (42.2)
Other	2 (3.1)
Unknown	2 (3.1)
CAR T-cell therapy conditioning	
Fludarabine/cyclophosphamide	61 (95.3)
Bendamustine	1 (1.6)
Other	1 (1.6)
Unknown	1 (1.6)
Time since CAR T-cell infusion, days median (IQR)	183 (81-461)
Variant of SARS-CoV-2 infection	
Wild-type	7 (10.9)
Alpha mutation	3 (4.7)
Delta mutation	4 (6.3)
Omicron mutation	18 (28.1)
Unknown	32 (50.0)
≥1 vaccinations before COVID-19	26 (40.6)
Comorbidities*	
Not present	25 (39.1)
1 comorbidity	22 (34.4)
2 comorbidities	10 (15.6)
≥3 comorbidities	7 (10.9)
Leukocyte count (cells per mm^3) at COVID-19 diagnosis, median (IQR)	2515 (1770-3915)
Neutrophil count (cells per mm^3) at COVID-19 diagnosis, median (IQR)	1450 (620-2300)
Lymphocyte count (cells per mm^3) at COVID-19 diagnosis, median (IQR)	485 (260-899)

ALL, acute lymphoid leukemia; auto HSCT, autologous HSCT.
*One or more comorbidities present (chronic cardiomyopathy, chronic pulmonary disease, diabetes, liver disease, obesity, renal impairment, smoker).

Table 1 (continued)

	All patients (N = 64) N (%)
Severity of infection	
At home	14 (21.9)
Admitted to the hospital	50 (78.1)
Duration of hospitalization, days median (IQR)	20 (7-38)
Admitted to the ICU	18 (28.1)
Duration of ICU admittance, days median (IQR)	11.5 (4.75-30.5)
Treatment with MoAbs	14 (21.9)
Treatment with convalescent plasma	16 (25.0)
Treatment with viral replication inhibitor	18 (28.1)
Treatment with steroids	30 (46.9)
Treatment with tocilizumab	6 (9.4)
Outcome	
Survived	38 (59.4)
Deceased	26 (40.6)
Attribution of death	
COVID-19, or contributed by COVID-19	20 (31.2)
Hematological malignancy	6 (9.3)

ALL, acute lymphoid leukemia; auto HSCT, autologous HSCT.
*One or more comorbidities present (chronic cardiomyopathy, chronic pulmonary disease, diabetes, liver disease, obesity, renal impairment, smoker).

(59.4%) patients were alive (Figure 1). In 26 deceased patients, death was caused by the underlying hematological malignancy in 6 (23.1%) and due to COVID-19 in 20 (76.9%). EFS at day 90 was 68.8% (Figure 2A).

Development over time

The number of patients diagnosed with COVID-19 each year was equally distributed over the years. In 2020, there were 23 patients diagnosed with COVID-19, in 2021, 18 patients and in 2022, 23 patients (until 1 July 2022). For full patient details, refer to supplemental Table 1. There was no difference in hospital admission rate between the years, and the duration of hospitalization in 2022 was significantly shorter (18 vs 34 days; $P = .039$). In 2022, the frequency of ICU admittance was significantly lower compared with 2020: 8.7% vs 47.8% ($P = .004$). When comparing patients infected with the Omicron variant and those with other variants, there was no difference in hospitalization rate ($P = .568$) or duration ($P = .648$), but patients infected with Omicron were less frequently admitted to the ICU ($P = .020$). We found a decrease in COVID-19–caused mortality with each passing year; refer to Figure 2B. Among patients with virus variant determined (N = 32, 14 patients with wild-type/alpha/delta variants, 18 patients with the Omicron variant), there was a significantly better EFS with the Omicron variant as compared with the wild-type and alpha and delta variants ($P = .012$; supplemental Figure 3).

Vaccination

In total, 26 patients had received at least 1 vaccination before their COVID-19 diagnosis. All but 2 were solely vaccinated with a mRNA-based vaccine. One patient received a vector-based vaccine, and 1 patient received a mRNA-based vaccine followed by a vector-based vaccine. Ten patients received the first vaccination

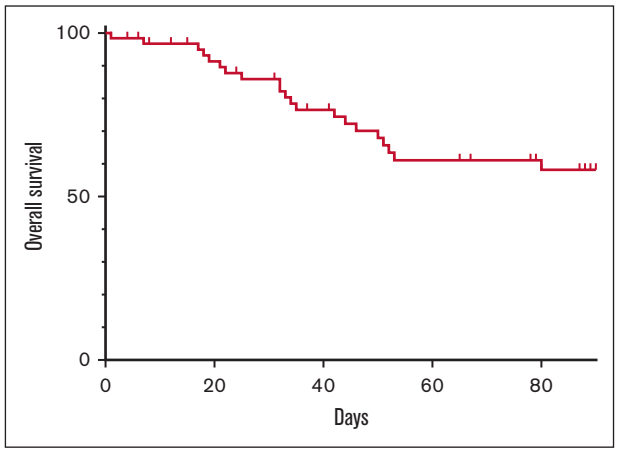

Figure 1. OS.

before CAR T-cell therapy, and 16 patients received the first vaccination after CAR T-cell therapy. The antibody response was tested by local standards in 6 of the 26 vaccinated patients. Three patients had antibodies above the cutoff value of the test that was used. There were no significant differences between the vaccinated and unvaccinated groups in age, sex, hematological malignancy, number of previous therapies, CAR T-cell constructs, or cell counts at the time of COVID-19 diagnosis. The vaccinated group had a significantly longer interval between vaccination and CAR T-cell infusion, median 159 vs 386 days ($P \leq .001$). In the vaccinated group, the Omicron variant was more common (10.5% vs 53.8%; $P \leq .001$). There were no significant differences in treatment of COVID-19 except that MoAbs were more often used in the vaccinated group (7.9% vs 42.3%; $P < .001$). The median follow-up of the unvaccinated group was longer than in the vaccinated group (50.5 vs 36 days; $P = .025$). For full vaccination and patient details, refer to Table 2.

No difference was observed in frequency of hospitalization ($P = .847$) or ICU admission ($P = .054$), but the duration of hospitalization was significantly shorter in the vaccinated patients: 7 vs 27.5 days ($P = .022$). Vaccination showed a marked reduction in the risk of COVID-19–caused mortality (33.3% vs 14.2% [$P = .379$]), refer to Figure 2C. Furthermore, there is no significant difference in EFS between the patients vaccinated before CAR T-cell therapy and those vaccinated after ($P = .519$; supplemental Figure 4).

MoAbs

Fourteen patients were treated with MoAbs. Sex, age, status of hematological malignancy, and the CAR T-cell construct did not differ from those without MoAbs. In patients treated with MoAbs, the median time since CAR T-cell infusion was longer than in the non-MoAb group (162 vs 358 days; $P = .028$). They were more often infected with an Omicron variant (22.0% vs 50.0%; $P = .046$) and were significantly more often vaccinated (85.7% vs 32.0% [<.001]). See Table 3 for full details. There is a significant reduction in the risk of death due to COVID-19 between those treated with MoAbs and those without ($P = .036$; Figure 2D). There were no significant differences in hospitalization rate or duration, nor in ICU admission rates.

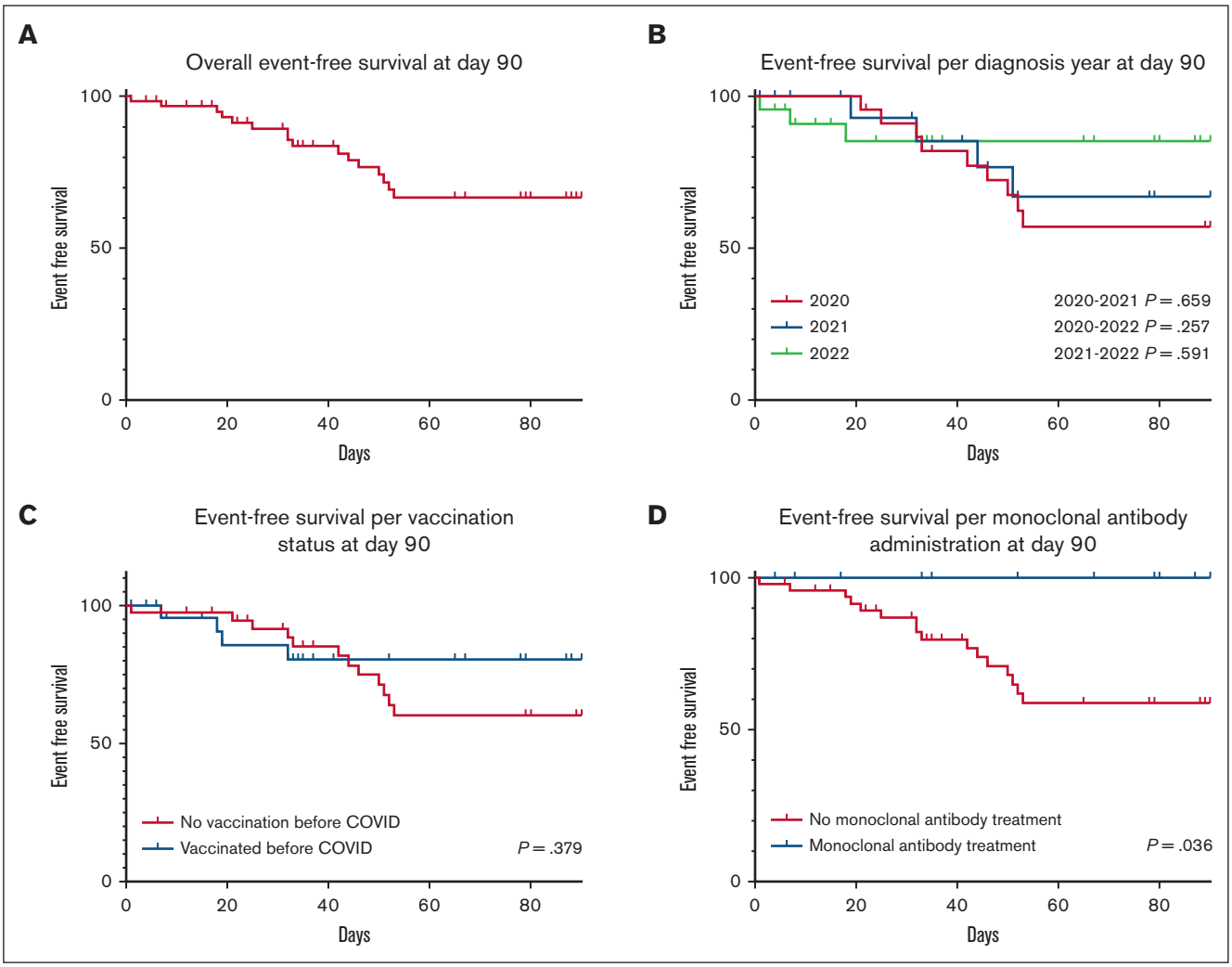

Figure 2. EFS analyses at day 90. (A) Overall EFS at day 90. (B) EFS per diagnosis year at day 90. (C) EFS per vaccination status at day 90. (D) EFS per MoAb administration at day 90.

Predictors for EFS

In univariate analysis, factors associated with death attributed to COVID-19 were age ($P = .020$; hazard ratio, 1.055; 95% confidence interval, 1.009-1.104) and infection with other variants than Omicron. The risk of death due to Omicron was lower than with other variants ($P = .040$; hazard ratio, 0.110; 95% confidence interval, 0.014-0.900). For all regression results, refer to supplemental Tables 2 and 3.

To elucidate a possible interaction between interventions and characteristics (age and year of COVID-19 infection), a pairwise Cox regression was conducted. In this limited number of events, only age was still a significant factor. In addition, there is a trend for reduction in the risk of dying due to COVID-19 when treated with MoAbs. Surprisingly, the year of COVID-19 (and thereby the SARS-CoV-2 variant) seemed to have less impact on the patient's outcome.

Discussion

We report on the impact of vaccination and treatment in patients with COVID-19 after previous CD19-directed CAR T-cell therapy. The main findings were a 40% overall mortality and a 31% mortality rate due to COVID-19, and thus a better prognosis than the previously reported 50% overall mortality.[5,6] Although still poor compared with the general population[15,16] and patients with other hematological malignancies, in which the mortality was 9% after vaccination.[17] Our results indicate that a large proportion (23%) of mortality is because of the progression of lymphoma, and taking this into account, the OS of 60% after 90 days is comparable to earlier studies.

Although not significant, there is a trend for better survival over the years, as shown by a reduction in COVID-19–caused mortality from 43.5% to 13.0%. The chance to be hospitalized or to be admitted to the ICU also reduced over time, and the duration of hospitalization is significantly shorter. There are several interacting factors that could cause a better outcome. In the early days of COVID-19, only patients who were admitted to the hospital were tested and diagnosed. Later on, testing became available for the outpatient clinic, resulting in a selection bias. With an improved understanding of COVID-19, new treatment options and interventions became available.

Table 2. Treatment characteristics of nonvaccinated and vaccinated patients

	Nonvaccinated (N = 38) N (%)	Vaccinated (N = 26) N (%)	*P* value
Sex			
Male	21 (55.3)	17 (65.4)	.418
Female	17 (44.7)	9 (34.6)	
Age, median (IQR)	55.5 (34.75-65.50)	59 (47.0-66.75)	.124
Diagnosis			
Diffuse large B-cell lymphoma	30 (78.9)	19 (73.1)	.792
High-grade B-cell lymphoma with MYC and BCL2/BCL6	1 (2.6)	1 (3.8)	
Primary mediastinal B-cell lymphoma	3 (7.9)	1 (3.8)	
Transformed follicular lymphoma	1 (2.6)	1 (3.8)	
Mantle cell lymphoma	0 (0)	2 (7.6)	
Follicular lymphoma	1 (2.6)	2 (7.6)	
B-ALL	2 (5.2)	0 (0)	
Number of previous lines of therapy, median (IQR)	3 (3-4)	3.5 (3-5)	.083
Previous auto HSCT	9 (23.7)	7 (25.0)	.769
Time since auto HSCT, days median (IQR)	603 (477-1266)	1051 (846-2046)	
CAR T-cell product			.784
Axicabtagene ciloleucel	19 (50.0)	13 (50.0)	
Lisocabtagene maraleucel	1 (2.6)	0 (0)	
Tisagenlecleucel	17 (44.7)	10 (38.5)	
Other	0 (0)	2 (7.7)	
Unknown	1 (2.8)	1 (3.8)	
CAR T-cell therapy conditioning			.404
Fludarabine/cyclophosphamide	35 (92.1)	26 (100)	
Bendamustine	1 (2.6)	0 (0)	
Other	1 (2.6)	0 (0)	
Unknown	1 (2.6)	0 (0)	
Time since CAR T-cell infusion, days median (IQR)	159 (37-305)	386 (124-747)	<.001
Variant of SARS-CoV-2 infection			<.001
Wild-type	7 (18.4)	0 (0)	
Alpha mutation	1 (2.6)	2 (7.7)	
Delta mutation	1 (2.6)	3 (11.5)	
Omicron mutation	4 (10.5)	14 (53.8)	
Unknown	25 (65.8)	7 (25.0)	
Number of vaccinations			<.001
0	38 (100)	0 (0)	
1	0 (0)	1 (3.8)	
2	0 (0)	18 (69.2)	
3	0 (0)	3 (11.5)	
4	0 (0)	4 (15.4)	
Timing of vaccination			<.001
Before CAR T-cell infusion	0 (0)	10 (38.5)	
After CAR T-cell infusion	0 (0)	16 (61.5)	
Comorbidities*			.404
Not present	16 (42.1)	14 (53.8)	
1 comorbidity	11 (28.9)	10 (38.5)	

ALL, acute lymphoid leukemia; auto HSCT, autologous HSCT.
*One or more comorbidities present (chronic cardiomyopathy, chronic pulmonary disease, diabetes, liver disease, obesity, renal impairment, smoker).

Table 2 (continued)

	Nonvaccinated (N = 38) N (%)	Vaccinated (N = 26) N (%)	*P* value
2 comorbidities	6 (15.8)	1 (3.8)	
≥3 comorbidities	5 (13.1)	1 (3.8)	
Leukocyte count (cells per mm^3) at COVID-19 diagnosis, median (IQR)	2465 (1282-3947)	2550 (1900-3922)	.590
Lymphocyte count (cells per mm^3) at COVID-19 diagnosis, median (IQR)	420 (215-1070)	500 (300-697)	.985
Neutrophil count (cells per mm^3) at COVID-19 diagnosis, median (IQR)	1300 (555-2450)	1480 (690-2515)	.677
Severity of infection			
At home	8 (21.2)	7 (23.1)	.847
Admitted to the hospital	30 (78.9)	19 (73.1)	
Duration of hospitalization, days median (IQR)	27.5 (15-43.8)	7 (6-16)	.022
Admitted to the ICU	14 (36.8)	4 (15.4)	.054
Duration of ICU admittance, days median (IQR)	9 (4.50-29.25)	23 (6.50-51.50)	.481
Treatment with MoAbs	3 (7.9)	11 (42.3)	<.001
Treatment with convalescent plasma	11 (28.9)	5 (19.2)	.378
Treatment with viral replication inhibitor	12 (31.6)	6 (23.1)	.457
Treatment with steroids	17 (44.7)	13 (50.0)	.679
Treatment with tocilizumab	2 (5.3)	4 (15.4)	.172
Outcome			
Alive	21 (68.4)	20 (76.9)	
Dead	15 (39.5)	6 (23.1)	.209
Cause of death			
COVID-19 or contributed by COVID-19	12 (31.6)	4 (15.4)	.142
Hematological malignancy	3 (7.9)	2 (7.7)	.589

ALL, acute lymphoid leukemia; auto HSCT, autologous HSCT.
*One or more comorbidities present (chronic cardiomyopathy, chronic pulmonary disease, diabetes, liver disease, obesity, renal impairment, smoker).

After observing the clinical course of vaccinated patients, this seems to be milder, with a significantly shorter duration of hospital stay and a trend showing the chance to be admitted to the ICU. This is concordant with other studies in patients with hematological malignancies.[18] There was no difference in EFS between the patients receiving the first vaccination before CAR T-cell therapy compared with those receiving the first vaccination after CAR T-cell therapy. One can presume that all patients were already B-cell depleted because of previous anti–B-cell therapy, as the median number of previous therapies was 3, possibly resulting in an impaired vaccination response. Information about serological response to vaccination is unfortunately limited in this survey. Presumably, serologic responses to vaccination were not different among patients in vaccination studies, with only one-third showing seroconversion.[19] Although half of the vaccinated patients were infected with the Omicron variant, the trend is still present when we focus only on the vaccinated non-Omicron group (data not shown). In addition, we found that patients who received CAR T-cell therapy benefit from the milder clinical course of the Omicron variant with less frequent ICU admittance ($P = .019$), although the duration of hospitalization is not different compared with the non-Omicron–infected patients (22.8 vs 26.7 days [$P = .648$]). The mortality is significantly lower in the Omicron group, with 8% vs 68% in the non-Omicron group at day 90 ($P = .012$). This is in line with previous studies in patients with hematological malignancies infected with Omicron, where the mortality was 8.4%.[20]

Treatment with steroids, viral replication inhibitors, IL-6 inhibition, and convalescent plasma showed no improvement in survival or chance to be hospitalized (data not shown). Treatment with MoAbs showed the largest impact on EFS, with none of the patients dying because of COVID-19. Taking into account that all but 2 patients were also vaccinated at the time of infection, we can conclude that the combination of vaccination and treatment with MoAbs seems to give significant protection against COVID-19 mortality.

The study population represents the real-world population treated with CD19-directed CAR T-cell therapy by distribution of sex, age, previous lines of therapy (including auto HSCT), and CAR T-cell constructs used.[21-23] The outcome data may be applicable to the general CD19-directed CAR T-cell–treated population.

Like in the general population and in previous studies of patients with hematological malignancies, advanced age and non-Omicron variant SARS-COV-2 infection are risk factors for death due to COVID-19.[15,17,24] Although the general population showed an improvement in survival over the past 3 years,[16] we found that the CAR T-cell population does have limited benefit from improved treatment and vaccination options. A possible explanation could be

Table 3. Treatment characteristics of patients treated with and without MoAbs

	Non-MoAb (N = 50) N (%)	MoAb (N = 14) N (%)	*P* value
Sex			
Male	28 (56.0)	10 (71.4)	.299
Female	22 (44.0)	4 (28.6)	
Age, median (IQR)	57 (50-67)	54 (47-67)	.409
Diagnosis			
Diffuse large B-cell lymphoma	39 (78.0)	10 (71.4)	
High-grade B-cell lymphoma with MYC and BCL2/BCL6	1 (2.0)	1 (7.1)	
Primary mediastinal B-cell lymphoma	3 (6.0)	1 (7.1)	
Transformed follicular lymphoma	1 (2.0)	1 (7.1)	.516
Mantle cell lymphoma	1 (2.0)	1 (7.1)	
Follicular lymphoma	3 (6.0)	0 (0)	
B-ALL	2 (4.0)	0 (0)	
Number of previous lines of therapy, median (IQR)	3 (3-4)	3 (3-4)	.719
Previous auto HSCT	14 (28.0)	2 (14.3)	.487
Time since auto HSCT, days median (IQR)	428 (255-892)	1221 (734-1707)	.267
CAR T-cell product			.472
Axicabtagene ciloleucel	23 (46.0)	9 (64.3)	
Lisocabtagene maraleucel	1 (2.0)	0 (0)	
Tisagenlecleucel	23 (46.0)	4 (28.6)	
Other	2 (4.0)	0 (0)	
Unknown	1 (2.0)	1 (7.1)	
CAR T-cell therapy conditioning			
Fludarabine/cyclophosphamide	47 (94.0)	14 (100.0)	1.000
Bendamustine	1 (2.0)	0 (0)	
Other	1 (2.0)	0 (0)	
Unknown	1 (2.0)	0 (0)	
Time since CAR T-cell infusion, days median (IQR)	162 (65-420)	358 (126-730)	.028
Variant of SARS-CoV-2 infection			
Wild-type	7 (14.0)	0 (0.0)	
Alpha mutation	2 (4.0)	1 (7.1)	.046
Delta mutation	2 (4.0)	2 (14.3)	
Omicron mutation	11 (22.0)	7 (50.0)	
Unknown	28 (56.0)	4 (28.6)	
Number of vaccinations			
0	34 (68.0)	2 (14.3)	<.001
1	2 (4.0)	1 (7.1)	
2	11 (22.0)	7 (50.0)	
3	0 (0.0)	3 (21.4)	
4	3 (6.0)	1 (7.1)	
Comorbidities*			
Not present	19 (38.0)	6 (42.9)	1.000
1 comorbidity	17 (34.0)	5 (35.7)	
2 comorbidities	8 (16.0)	2 (14.3)	
≥ 3 comorbidities	6 (12.0)	1 (7.1)	
Leukocyte count (cells per mm^3) at COVID-19 diagnosis, median (IQR)	2670 (1720-4200)	2350 (2150-2950)	.786

ALL, acute lymphoid leukemia; auto HSCT, autologous HSCT.
*One or more comorbidities present (chronic cardiomyopathy, chronic pulmonary disease, diabetes, liver disease, obesity, renal impairment, smoker).

Table 3 (continued)

	Non-MoAb (N = 50) N (%)	MoAb (N = 14) N (%)	*P* value
Lymphocyte count (cells per mm^3) at COVID-19 diagnosis, median (IQR)	500 (230-1000)	400 (270-700)	.931
Neutrophil count (cells per mm^3) at COVID-19 diagnosis, median (IQR)	1250 (570-2620)	1740 (1245-2045)	.470
Severity of infection			
At home	10 (20.0)	4 (28.6)	.493
Admitted to the hospital	40 (80.0)	10 (71.4)	.493
Admitted to the ICU	15 (30.0)	3 (21.4)	.659
Treatment with MoAb**s**	0 (0.0)	14 (100.0)	<.001
Type of MoAb			
Bamlanivimab/etesevimab	0 (0.0)	1 (7.1)	
Casirivimab/imdevimab	0 (0.0)	3 (21.4)	<.001
Sotrovimab	0 (0.0)	10 (71.4)	
Treatment with convalescent plasma	13 (26.0)	3 (21.4)	.725
Treatment with viral replication inhibitor	14 (28.0)	4 (28.6)	.966
Treatment with steroids	24 (48.0)	6 (42.9)	.733
Treatment with tocilizumab	5 (10.0)	1 (7.1)	.746
Outcome			
Alive	31 (62.0)	12 (85.7)	.095
Dead	19 (38.0)	2 (14.3)	
Cause of death			
COVID-19 or contributed by COVID-19	16 (32.0)	0 (0.0)	.015
Hematological malignancy	3 (6.0)	2 (14.0)	.476

ALL, acute lymphoid leukemia; auto HSCT, autologous HSCT.
*One or more comorbidities present (chronic cardiomyopathy, chronic pulmonary disease, diabetes, liver disease, obesity, renal impairment, smoker).

that most vaccinated patients included in this study were vaccinated twice. As shown in previous publications, patients with hematological malignancies need to be vaccinated 3 times for an optimal response.[19] The importance of a fourth vaccination and its protective effect were also shown in a previous EPICOVIDEHA study.[18] Here, 6 patients received a third or even fourth vaccination, and none of these patients died because of COVID-19 (data not shown).

Recent studies show promising T-cell responses after vaccination in the CAR T-cell–treated patient category.[11,12] Unfortunately, this is not reflected in our data on survival or hospitalization rates. Probably this highlights the important role of humoral immunity in response to SARS-COV-2. After CD19-directed CAR T-cell therapy, there is a deep and long-lasting B-cell depletion.[3,4] Presumably this is the main reason for the poor serological response to vaccination.[7,10] By treatment with MoAbs, the patients seem to overcome the lack of B cells, and the combination with improved T-cell responses owing to vaccination reduces the mortality risk. A major limitation of MoAb treatment is the constant need to adjust the antibody if there is a new viral mutation, limiting its use in daily practice. But showing the high efficacy in this patient category underpins the need for the continuous development of new antibodies and should encourage investors to invest in this life-saving type of therapy.

A limitation of this study is the small sample size, its retrospective nature, the varying treatment protocols over time and country, and the fact that in half the patients, the viral variant is unknown. In addition, data for in-depth analyses of B-cell and T-cell recovery and the timing of interventions are missing. We need to be cautious with definitive conclusions and larger studies are therefore needed. Moreover, because of the restricted therapeutic interventions at relapse after CAR T-cell therapy, the mortality of COVID-19 could be overestimated. In 14% of the cases, it was reported that the malignancy contributed to death. Possibly, it was decided to give patients with active disease only part of the full COVID-19 treatment, including intensive care. Another bias could be the underreporting of outpatients in the survey, resulting in a higher relative mortality attributed to COVID-19.

In conclusion, we find that the survival of CAR T-cell recipients with COVID-19 is better than previously reported, that vaccination significantly reduces the duration of hospitalization, and that the combination of vaccination and MoAbs significantly reduces the risk of death due to COVID-19 in these patients. However, because of the retrospective nature of this study and the ongoing improvement in both COVID-19 treatment and viral variants, a causal relationship cannot be established.

As such, we strongly advise patients who received CAR T-cell therapy to get vaccinated and for clinicians to consider therapy with MoAbs if available. Thereby also highlighting the need to for further development of new MoAbs against SARS-Cov-2 and other viral infections.

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Authorship

Contribution: J.A.v.D. and J.S.-G. performed statistical analysis, interpreted the data, and wrote the manuscript; J.S.-G., F.M., L.P., and O.A.C. are in charge of the management of EPICOVIDEHA registry; and all authors recruited participants, collected and interpreted data, contributed to manuscript writing and review of the manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*. 2017;377(26):2531-2544.
2. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380(1):45-56.
3. Strati P, Varma A, Adkins S, et al. Hematopoietic recovery and immune reconstitution after axicabtagene ciloleucel in patients with large B-cell lymphoma. *Haematologica*. 2021;106(10):2667-2672.
4. Jacobson C, Locke FL, Ghobadi A, et al. Long-term survival and gradual recovery of B cells in patients with refractory large B cell lymphoma treated with axicabtagene ciloleucel (Axi-Cel). *Blood*. 2020;136(suppl 1):40-42.
5. Busca A, Salmanton-Garcia J, Corradini P, et al. COVID-19 and CAR-T cells: current challenges and future directions-a report from the EPICOVIDEHA survey by EHA-IDWP. *Blood Adv*. 2022;6(7):2427-2433.
6. Spanjaart AM, Ljungman P, de La Camara R, et al. Poor outcome of patients with COVID-19 after CAR T-cell therapy for B-cell malignancies: results of a multicenter study on behalf of the European Society for Blood and Marrow Transplantation (EBMT) Infectious Diseases Working Party and the European Hematology Association (EHA) Lymphoma Group. *Leukemia*. 2021;35(12):3585-3588.
7. Haggenburg S, Lissenberg-Witte BI, van Binnendijk RS, et al. Quantitative analysis of mRNA-1273 COVID-19 vaccination response in immunocompromised adult hematology patients. *Blood Adv*. 2022;6(5):1537-1546.
8. Dhakal B, Abedin S, Fenske T, et al. Response to SARS-CoV-2 vaccination in patients after hematopoietic cell transplantation and CAR T-cell therapy. *Blood*. 2021;138(14):1278-1281.
9. Gastinne T, Le Bourgeois A, Coste-Burel M, et al. Safety and antibody response after one and/or two doses of BNT162b2 Anti-SARS-CoV-2 mRNA vaccine in patients treated by CAR T cells therapy. *Br J Haematol*. 2022;196(2):360-362.
10. Okamoto A, Fujigaki H, Iriyama C, et al. CD19-positive lymphocyte count is critical for acquisition of anti-SARS-CoV-2 IgG after vaccination in B-cell lymphoma. *Blood Adv*. 2022;6(11):3230-3233.
11. Marasco V, Carniti C, Guidetti A, et al. T-cell immune response after mRNA SARS-CoV-2 vaccines is frequently detected also in the absence of seroconversion in patients with lymphoid malignancies. *Br J Haematol*. 2022;196(3):548-558.
12. Atanackovic D, Kreitman RJ, Cohen J, et al. T cell responses against SARS-CoV-2 and its Omicron variant in a patient with B cell lymphoma after multiple doses of a COVID-19 mRNA vaccine. *J Immunother Cancer*. 2022;10(7):e004953.
13. Moss P. The T cell immune response against SARS-CoV-2. *Nat Immunol*. 2022;23(2):186-193.
14. Salmanton-Garcia J, Busca A, Cornely OA, et al. EPICOVIDEHA: a ready to use platform for epidemiological studies in hematological patients with COVID-19. *Hemasphere*. 2021;5(7):e612.

15. Ward IL, Bermingham C, Ayoubkhani D, et al. Risk of COVID-19 related deaths for SARS-CoV-2 Omicron (B.1.1.529) compared with delta (B.1.617.2): retrospective cohort study. *BMJ*. 2022;378:e070695.

16. Bechman K, Yates M, Mann K, et al. Inpatient COVID-19 mortality has reduced over time: results from an observational cohort. *PLoS One*. 2022;17(1): e0261142.

17. Pagano L, Salmanton-Garcia J, Marchesi F, et al. Breakthrough COVID-19 in vaccinated patients with hematologic malignancies: results from EPICOVIDEHA survey. *Blood*. 2022;140(26):2773-2787.

18. Salmanton-Garcia J, Marchesi F, Glenthoj A, et al. Improved clinical outcome of COVID-19 in hematologic malignancy patients receiving a fourth dose of anti-SARS-CoV-2 vaccine: an EPICOVIDEHA report. *Hemasphere*. 2022;6(11):e789.

19. Haggenburg S, Hofsink Q, Lissenberg-Witte BI, et al; COBRA KAI Study Team. Antibody response in immunocompromised patients with hematologic cancers who received a 3-dose mRNA-1273 vaccination schedule for COVID-19. *JAMA Oncol*. 2022;8(10):1477-1483.

20. Blennow O, Salmanton-Garcia J, Nowak P, et al. Outcome of infection with omicron SARS-CoV-2 variant in patients with hematological malignancies: an EPICOVIDEHA survey report. *Am J Hematol*. 2022;97(8):E312-E317.

21. Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. *Nat Med*. 2022;28(10):2145-2154.

22. Kuhnl A, Roddie C, Kirkwood AA, et al. A national service for delivering CD19 CAR-Tin large B-cell lymphoma - the UK real-world experience. *Br J Haematol*. 2022;198(3):492-502.

23. Bethge WA, Martus P, Schmitt M, et al. GLA/DRST real-world outcome analysis of CAR T-cell therapies for large B-cell lymphoma in Germany. *Blood*. 2022;140(4):349-358.

24. Bhaskaran K, Bacon S, Evans SJ, et al. Factors associated with deaths due to COVID-19 versus other causes: population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. *Lancet Reg Health Eur*. 2021;6:100109.