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2021 L Street NW, Suite 900,
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Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

COVID-19 and CAR-T cells: current challenges and future directions-a report from the EPICOVIDEHA survey by EHA-IDWP

Tracking no: ADV-2021-005616R1

Alessandro Busca (A.O.U. Città della Salute e della Scienza, Italy) Jon Salmanton-García (3) University of Cologne, Faculty of Medicine and University Hospital Cologne, Chair Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne,, Germany) Paolo Corradini (University of Milan & Fondazione IRCCS Istituto Nazionale dei Tumori, Italy) Francesco Marchesi (IRCCS Regina Elena National Cancer Institute, Italy) Alba Cabirta (7) Departament de Medicina, Universitat Autònoma de Barcelona,, Spain) Roberta Di Blasi (Hopital Saint Louis, France) Remy Dulery (Saint-Antoine Hospital, Assitance Publique - Hôpitaux de Paris . Sorbonne Université . INSERM UMRs 938, France) Sylvain Lamure (Montpellier University Hospital, France) Francesca Farina (San Raffaele Scientific Institute, Italy) Barbora Weinbergerová (Masaryk University and University Hospital Brno, Czech Republic) Josip BATINIĆ (14) Croatian Cooperative Group for Hematological Diseases (CROHEM), Croatia, Croatia, Republic of) Anna NORDLANDER (Department of Infectious Diseases, Karolinska University Hospital,, Sweden) Alberto Lopez-Garcia (Fundacion Jimenez Diaz University Hospital, Health Research Institute IIS-FJD, Spain) Lubos Drgona (Oncohematology Clinic, Faculty of Medicine, Comenius University and National Cancer Institute, Slovak Republic) Ildefonso Espigado (Hospital Univesitario Virgen del Rocío, Seville,, Spain) Iker Falces-Romero (La Paz University Hospital, Spain) Ramon Garcia-Sanz (University Hospital of Salamanca, Spain) Carolina Garcia-Vidal (Hospital Clinic of Barcelona, Spain) Anna Guidetti (Fondazione IRCCS Istituto Nazionale Tumori, Italy) Nina Khanna (University Hospital and University of Basel, Switzerland) Austin Kulesekararaj (Kings College Hospital, United Kingdom) Johan Maertens (KU Leuven, Belgium) Martin HOENIGL (, United States) nikolai KLIMKO (Department of Clinical Mycology, Allergy and Immunology, North Western State Medical University, Russian Federation) Philipp Koehler (University Hospital Cologne, Germany) Antonio Pagliuca (King's College Hospital, United Kingdom) Francesco Passamonti (University of Insubria, Italy) Oliver Cornely (, Germany) Livio Pagano (, Italy)

Abstract:
Patients receiving chimeric antigen receptor T cells (CAR-T cells) therapy may be particularly susceptible to coronavirus disease 2019 (COVID-19) because of several factors including the immunosuppression associated to the underlying disease and delayed cytopenias. Regrettably, data on outcomes of CAR-T recipients with COVID-19 are extremely scarce. The aim of this study was to investigate the characteristics and outcomes of COVID-19 in patients treated with CAR-T therapy. The European Hematology Association - Scientific Working Group Infection in Hematology endorsed a survey to collect and analyze data from patients developing COVID-19 after CAR-T therapy. Overall, 459 patients treated with CAR-T cells were reported from 18 European centers. The prevalence of COVID-19 cases was 4.8%. Median time from CAR-T therapy and COVID-19 diagnosis was 169 days. Severe infection occurred in 66.7% of patients and 43.3% of the subjects required admission to ICU. The COVID-19 mortality was 33%. In multivariable analysis, the disease status at the time of COVID-19 trended marginally towards adverse outcome (P=0.075). In conclusion, we documented a high fatality rate for CAR-T patients with COVID-19, supporting the need to design successful interventions to mitigate the risk of infection in this vulnerable group of patients.

Conflict of interest: COI declared - see note

COI notes: AB has received lecture honoraria from Gilead Sciences, Merck, Pfizer Pharmaceuticals, Basilea, Biotest and Jazz Pharmaceuticals; he was Board member of Gilead Science and Takeda. SL received supports from Janssen, Gilead, Roche, Abbvie, Sanofi, Novartis, Actelion, Pfizer; Research grant from Janssen LD has received lecture honoraria from Abbvie, Amgen, Celgene, Egis, Gilead, Kyowa Kirin, MSD, Pfizer, Roche, Sandoz, Servier, Takeda, Teva; he was Board member of Abbvie, Gilead, Novartis, Pfizer and Takeda. MH reports research funding from Gilead, Astellas, Pfizer and MSD, outside the submitted work. NK reports research funding and honoraria from Gilead, Astellas, Pfizer and MSD, outside the submitted work. PK is supported by the German Federal Ministry of Research and Education and the State of North Rhine-Westphalia, Germany and has received non-financial scientific grants from Miltenyi Biotec GmbH, Bergisch Gladbach, Germany, and the Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Cologne, Germany, and received lecture honoraria from and/or is advisor to Akademie für Infektionsmedizin e.V., Ambu GmbH, Astellas Pharma, European Confederation of Medical Mycology, Gilead Sciences, GPR Academy Ruesselsheim, MSD Sharp & Dohme GmbH, Noxxon N.V., Pfizer Pharma GmbH and University Hospital, LMU Munich outside the submitted work. OAC is

supported by the German Federal Ministry of Research and Education, is funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy - CECAD, EXC 2030 - 390661388 and has received research grants from, is an advisor to, or received lecture honoraria from Actelion, Allecra Therapeutics, Al-Jazeera Pharmaceuticals, Amplyx, Astellas, Basilea, Biosys, Cidara, Da Volterra, Entasis, F2G, Gilead, Grupo Biotoscana, Immunic, IQVIA, Janssen, Matinas, Medicines Company, MedPace, Melinta Therapeutics, Menarini, Merck/MSD, Mylan, Nabriva, Noxxon, Octapharma, Paratek, Pfizer, PSI, Roche Diagnostics, Scynexis, and Shionogi. All the remaining authors declare nothing to disclose.

Preprint server: No;

Author contributions and disclosures: A.B., J.S-A, P.C. and L.P. conceived of and codesigned the database; A.B, J.S-A. and L.P. contributed to data analysis; A.B. wrote the manuscript; and all authors critically reviewed and revised the manuscript and provided final approval.

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: email to the corresponding Author

Clinical trial registration information (if any):

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Alessandro **BUSCA**, MD [1*], Jon **SALMANTON-GARCÍA**, PhD [2,3*], Paolo **CORRADINI**, MD [4], Francesco **MARCHESI**, MD [5], Alba **CABIRTA**, MD [6,7], Roberta **DI BLASI**, MD [8], Remy **DULERY**, MD [9], Sylvain **LAMURE** [10]**,** Francesca **FARINA**, MD [11], Barbora **WEINBERGEROVÁ**, MD [12], Josip **BATINIĆ**, MD [13,14,15], Anna **NORDLANDER,** MD [16], Alberto **LÓPEZ-GARCÍA**, MD [17], Ľuboš **DRGOŇA**, MD [18], Ildefonso **ESPIGADO-TOCINO**, MD [19], Iker **FALCES-ROMERO**, PharmD [20], Ramón **GARCÍA-SANZ**, MD [21], Carolina **GARCÍA-VIDAL**, MD, PhD [22], Anna **GUIDETTI**, MD [23] Nina **KHANNA**, MD [24], Austin **KULASEKARARAJ**, MD [25], Johan **MAERTENS**, MD [26], Martin **HOENIGL**, MD [27,28,29], Nikolai **KLIMKO**, MD [30], Philipp **KOEHLER**, MD [2,3], Antonio **PAGLIUCA**, MD [31], Francesco **PASSAMONTI**, MD [32], Oliver A. **CORNELY**, MD [2,33,34,35], Livio **PAGANO**, MD [36,37]

*These authors have contributed equally to this work

Affiliations

1) Stem Cell Transplant Center, AOU Citta' della Salute e della Scienza, Turin, Italy
2) University of Cologne, Faculty of Medicine and University Hospital Cologne, Department I of Internal Medicine, Excellence Center for Medical Mycology (ECMM), Cologne, Germany
3) University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany
4) University of Milan & Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
5) Hematology and Stem Cell Transplant Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy
6) Department of Hematology, Vall d'Hebron Hospital Universitari, Experimental Hematology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain
7) Departament de Medicina, Universitat Autònoma de Barcelona, Bellaterra, Spain
8) Hôpital Saint Louis, AP-HP, Paris, France
9) Service d'Hématologie Clinique et de Thérapie Cellulaire, Hôpital Saint Antoine, Assistance Publique-Hôpitaux de Paris, Sorbonne Université, Inserm UMRs 938, Paris, France
10) Department of Clinical Hematology, Montpellier University Hospital, IGMM UMR1535 CNRS, University of Montpellier, Montpellier, France

11) IRCCS Ospedale San Raffaele, Milan, Italy
12) Masaryk University Hospital Brno - Department of Internal Medicine - Hematology and Oncology, Brno, Czech Republic
13) University Hospital Centre Zagreb, Zagreb, Croatia
14) Croatian Cooperative Group for Hematological Diseases (CROHEM), Croatia
15) Faculty of Medicine University of Zagreb, Zagreb, Croatia
16) Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden
17) Fundacion Jimenez-Díaz, Madrid, Spain
18) Comenius University and National Cancer Institute, Bratislava, Slovakia
19) Hospital Univesitario Virgen del Rocío, Seville, Spain
20) La Paz University Hospital, Madrid, Spain
21) Hospital Universitario de Salamanca, Salamanca, Spain
22) Hospital Clinic, Barcelona, Spain
23) Division of Hematology and Bone Marrow Transplantation, Fondazione IRCCS Istituto Nazionale dei Tumori, University of Milano, Milan, Italy
24) Division of Infectious Diseases and Hospital Epidemiology, and Department of Clinical Research, University and University Hospital of Basel, Basel, Switzerland
25) King's College Hospital, London, United Kingdom
26) KU Leuven, Leuven, Belgium
27) Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California San Diego, San Diego, CA, United States
28) Clinical and Translational Fungal-Working Group, University of California San Diego, La Jolla, CA, United States
29) Division of Infectious Diseases, Department of Internal Medicine, Medical University of Graz, Graz, Austria
30) Department of Clinical Mycology, Allergy and Immunology, North Western State Medical University, St Petersburg, Russia
31) Department of Hematological Medicine, Kings College Hospital NHS Foundation Trust, London, United Kingdom
32) Department of Medicine and Surgery, University of Insubria and ASST Sette Laghi, Ospedale di Circolo of Varese, Varese, Italy
33) University of Cologne, Faculty of Medicine and University Hospital Cologne, Clinical Trials Centre Cologne (ZKS Köln), Cologne, Germany
34) German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany

35) University of Cologne, Faculty of Medicine and University Hospital Cologne, Chair Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany
36) Hematology, Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Rome, Italy
37) Hematology, Università Cattolica del Sacro Cuore, Rome, Italy

ORCID numbers of authors

Alessandro **BUSCA** abusca@cittadellasalute.to.it	https://orcid.org/0000-0001-5361-5613
Jon **SALMANTON-GARCÍA** jon.salmanton-garcia@uk-koeln.de	https://orcid.org/0000-0002-6766-8297
Paolo **CORRADINI** paolo.corradini@unimi.it	https://orcid.org/0000-0002-9186-1353
Francesco **MARCHESI** francesco.marchesi@ifo.gov.it	https://orcid.org/0000-0001-6353-2272
Alba **CABIRTA** alba.cabirta.touzon@gmail.com	https://orcid.org/0000-0001-7198-8894
Roberta **DI BLASI** roberta.diblasi@aphp.fr	https://orcid.org/0000-0001-9001-573X
Rémy **DULÉRY** remy.dulery@aphp.fr	https://orcid.org/0000-0002-5024-1713
Sylvain **LAMURE** s-lamure@chu-montpellier.fr	https://orcid.org/0000-0001-5980-305X
Francesca **FARINA** farina.francesca@hsr.it	https://orcid.org/0000-0002-4350-3105
Barbora **WEINBERGEROVÁ** Weinbergerova.Barbora@fnbrno.cz	https://orcid.org/0000-0001-6460-2471
Josip **BATINIĆ** batinic.josip@gmail.com	https://orcid.org/0000-0001-5595-9911
Alberto **LÓPEZ-GARCÍA** alberto.lgarcia@quironsalud.es	https://orcid.org/ 0000-0002-5354-5261
Ľuboš **DRGOŇA** lubos.drgona@nou.sk	https://orcid.org/0000-0002-5089-3201
Ildefonso **ESPIGADO-TOCINO**	https://orcid.org/0000-0002-4043-6613

Ildefonso.espigado.sspa@juntadeandalucia.es	
Iker **FALCES-ROMERO** falces88@gmail.com	https://orcid.org/0000-0001-5888-7706
Ramón **GARCÍA-SANZ** rgarcias@usal.es	https://orcid.org/0000-0003-4120-2787
Carolina **GARCÍA-VIDAL** carolgv75@hotmail.com	https://orcid.org/0000-0002-8915-0683
Anna **GUIDETTI** Anna.Guidetti@istitutotumori.mi.it	https://orcid.org/0000-0002-9186-1353
Nina **KHANNA** nina.khanna@usb.ch	https://orcid.org/0000-0002-2642-419X
Austin **KULASEKARARAJ** austin.kulasekararaj@nhs.net	https://orcid.org/0000-0003-3180-3570
Johan **MAERTENS** johan.maertens@uzleuven.be	https://orcid.org/0000-0003-4257-5980
Martin **HOENIGL** hoeniglmartin@gmail.com	https://orcid.org/0000-0002-1653-2824
Nikolai **KLIMKO** n_klimko@mail.ru	https://orcid.org/0000-0001-6095-7531
Philipp **KOEHLER** philipp.koehler@uk-koeln.de	https://orcid.org/0000-0002-7386-7495
Antonio **PAGLIUCA** antonio.pagliuca@kcl.ac.uk	https://orcid.org/0000-0003-2519-0333
Francesco **PASSAMONTI** francesco.passamonti@asst-settelaghi.it	https://orcid.org/0000-0001-8068-5289
Oliver A. **CORNELY** oliver.cornely@uk-koeln.de	https://orcid.org/0000-0001-9599-3137
Livio **PAGANO** Livio.Pagano@unicatt.it	https://orcid.org/0000-0001-8287-928X

Running Title: COVID-19 in CAR-T cells therapy recipients

Keywords: COVID-19, hematology, CAR-T cells, registry

Word count (Abstract): 202

Word count (Main manuscript): 1745

Correspondence: Alessandro Busca MD

Stem Cell Transplant Unit, AOU Cittadella Salute e della Scienza, Turin – ITALY. Corso Bramante 88, 10126 Turin

Email: abusca@cittadellasalute.to.it

Alternative correspondence: Jon Salmanton-García PhD

University Hospital Cologne

Internal Medicine I, Infectious Diseases 2

Herderstrasse 52-54

50931 Cologne (Germany)

Email: jon.salmanton-garcia@uk-koeln.de

Abstract

Patients receiving chimeric antigen receptor T cells (CAR-T cells) therapy may be particularly susceptible to coronavirus disease 2019 (COVID-19) because of several factors including the immunosuppression associated to the underlying disease and delayed cytopenias. Regrettably, data on outcomes of CAR-T recipients with COVID-19 are extremely scarce. The aim of this study was to investigate the characteristics and outcomes of COVID-19 in patients treated with CAR-T therapy. The European Hematology Association – Scientific Working Group Infection in Hematology endorsed a survey to collect and analyze data from patients developing COVID-19 after CAR-T therapy. Overall, 459 patients treated with CAR-T cells were reported from 18 European centers. The prevalence of COVID-19 cases was 4.8%. Median time from CAR-T therapy and COVID-19 diagnosis was 169 days. Severe infection occurred in 66.7% of patients and 43.3% of the subjects required admission to ICU. The COVID-19 mortality was 33%. In multivariable analysis, the disease status at the time of COVID-19 trended marginally towards adverse outcome (*P*=0.075). In conclusion, we documented a high fatality rate for CAR-T patients with COVID-19, supporting the need to design successful interventions to mitigate the risk of infection in this vulnerable group of patients.

Key Points

- The EHA-IDWP developed an observational registry collecting data on COVID-19 infection in patients who received CAR-T therapy
- The prevalence of COVID-19 was 4.8%, and overall mortality was 50%, highlighting the need for prevention of infection in these patients.

Introduction

Since the initial report in China, coronavirus disease 2019 (COVID-19) had spread rapidly across the world and the number of cases increased exponentially **(1)**. Initial reports suggest that patients with cancer have an estimated two-fold increased risk of contracting severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) than the general population **(2)**. More importantly, it would be expected that COVID-19 be particularly life-threatening in patients with hematological malignancies due to their immune dysfunction. Recent studies have reported an overall COVID-19 related mortality of 29-42% **(3-8**) in hematological patients depending on the type of malignancy, in contrast to the 2-7% observed in the general population. Regrettably, there remains a lack of studies about COVID-19 in patients receiving cellular therapies including chimeric antigen receptor T cells (CAR-T cells) (**9,10**). CAR-T cells are genetically modified autologous T cells showing great promise in the treatment of advanced malignant hematologic disorders including non-Hodgkin lymphoma, acute lymphoblastic leukemia (ALL), and multiple myeloma **(11).** CAR-T cell recipients have significant B-cell aplasia requiring IgG replacement therapy, and may also develop delayed cytopenias, making these patients unable to mount any humoral response to viral infections **(12)**. Shah et al demonstrated that the seroconversion rate in a small cohort of patients receiving hemopoietic stem cell transplantation (HSCT) and CAR-T therapy did not exceed 66% **(10).**

According to these observations, the outcome of COVID-19 in patients treated with CAR-T cells remains unanswered. The aim of this study was to describe the clinical outcome of patients developing COVID-19 after treatment with CAR-T cells.

Methods

In this retrospective observational, multicenter study, we collected data on all consecutive adult patients who received CAR T-cell therapy with symptomatic COVID-19 between January 2020 and February 2021 across 18 European centers (Spain [n=6], France [n=3], Italy [n=2], and Belgium, Croatia, Czechia, Slovakia, Sweden, Switzerland, and the United Kingdom [n=1, each]), who participated in the survey promoted by the European Hematology Association (EHA) – Scientific Working Group Infection in Hematology (EPICOVIDEHA survey) **(13)**. the European Hematology Association – Infectious Diseases Working Party **(**EHA-IDWP; EPICOVIDEHA survey). Confirmed cases of COVID-19 were defined by a positive RT-PCR assay of a specimen collected on a nasopharyngeal swab. Each institutional review board independently approved the study. The study was conduct in accordance with the Declaration of Helsinki. Researchers at each center collected data using an online questionnaire hosted at www.clinicalsurveys.net , EPICOVIDEHA is registered at http://www.clinicaltrials.gov, with the identifier (NCT number): NCT 04733729. Only de-identified data have been entered and analyzed. We obtained demographic

data, comorbidities, and underlying hematological disease including clinically significant outcomes (hospital admission and intensive care unit [ICU] admission, vital status) and management strategies of COVID-19. The severity of COVID-19 at admission was graded according to the China Centers for Disease Control and Prevention definitions: mild (non-pneumonia and mild pneumonia), severe (dyspnea, respiratory frequency ≥30 breaths per min, SpO2 ≤93%, PaO2/FiO2 50%), and critical (respiratory failure, septic shock, or multiple organ dysfunction or failure).

Statistical analysis

SPSSv25.0 was employed for statistical analyses (SPSS, IBM Corp., Chicago, IL, United States). Categorical variables were presented using frequencies and percentages, while continuous variables by median, interquartile range (IQR) and absolute range. Additionally, overall mortality was evaluated by employing a Cox proportional hazard model. Univariable Cox regression model was performed with variables suspected to play a role in the mortality of CAR-T + COVID-19 patients. Variables with a p value ≤0.1 were considered for a multivariable analysis. Multivariable Cox regression model was calculated with the Wald backward method, and only statistically significant variables were reported. A p value ≤0.05 was considered statistically significant.

Results

Overall, 459 patients received CAR-T cell therapy, of whom 30 met the criteria for diagnosis of COVID-19. The median age at COVID-19 diagnosis was 57 years (IQR: 51 - 64, range 18 - 74), 13 patients (43,3%) were female and 17 patients (56.7%) were male. Demographic and clinical characteristics of CAR-T cell recipients with COVID-19 are summarized in **table 1.** Patients received CAR-T cells for the treatment of large B-cell lymphoma (n=28) (LBCL), multiple myeloma (n=1) and ALL (n=1). The majority of patients received CAR-T therapy in 2020 (n=17), 3 in 2018, 9 in 2019 and 1 in 2021. CAR-T cells were tisagenlecleucel (Kymriah) in 16 cases and axicabtagene (Yescarta) in 13 cases, while one patient with multiple myeloma was treated with CAR T- B-cell maturation antigen (BCMA) cells. The majority of patients received bridging therapy (n=21/30) and fludarabine-cyclophosphamide as lymphodepletion conditioning (n=29/30). Severe (grade ≥3) cytokine release syndrome (CRS) after CAR-T cells was observed in one patient only. No patient received COVID-19 vaccine. Seventeen patients (56,7%) developed COVID-19 within 6 months from CAR-T infusion, while 13 (43,3%) patients beyond 6 months.

Prevalence of COVID-19 in our subjects was 4.8%, based on the total number of CAR-T patients reported by participating Centers in 2020 (17/353).

The median time from CAR-T cell treatment and COVID-19 diagnosis was 169 days (IQR: 37 - 313, range: 1 - 635). Cellular and humoral immune reconstitution after CAR-T cells showed that 90 days after the infusion, absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) were 1700/mm³ (IQR: 1090 - 2700, range: 300 - 11260) and 435/mm³ (IQR: 200 - 775, range: 80 - 3500) respectively, while at the time of COVID-19 diagnosis, the median number of ANC and ALC was 925/mm³ (IQR: 495 - 2450, range: 18 - 11510) and 370/mm³ (IQR: 200 - 1250, range: 6-1750), respectively. Overall, 10% (n=3), 20% (n=6) and 66.7% (n=20) of patients had asymptomatic, mild or severe COVID-19. Comorbidities preceding the diagnosis of COVID-19 were detected in 19 patients (76.7%), including chronic cardiopathy (n=8, 23.3%), chronic pulmonary diseases (n=7, 23.3%), smoking history (n=6, 20.0%) or obesity (n=5, 16.7%). In total, 13 patients (43,3%) required admission to ICU after COVID-19, and 9 of them (66.7%) required mechanical ventilation.

Patients received treatments for COVID-19 according to the local policy: 15 patients were treated with convalescent plasma alone (n=3) or combined with remdesivir ± steroids (n=8), remdesivir-lopinavir/ritonavir and steroids (n=1) and tocilizumab + steroids (n=3); five patients were treated with steroids alone (n=4) or combined with remdesivir and tocilizumab (n=1), one patient was treated with azithromycin and one patient with remdesivir alone. In total 5 patients did not require any specific treatment, in 2 cases due to the poor general conditions; in 3 cases the treatment was unknown.

The median follow-up was of 71 days (IQR: 44 - 142, range: 21 - 379) after CAR-T infusion, and at the last follow-up, 15 patients (50,0%) were alive and 15 patients (50,0%) died. Ten patients (33%) died of COVID-19 infection (associated to pulmonary embolism plus heart failure in 1 case and possible fungal infection in 1 case), while 5 patients died of recurrent underlying disease (associated to COVID-19 infection in 3 patients). Seven of the 11 patients (63,6%) with relapsed/refractory (R/R) diseases died, while 7 of the 17 patients (41,1%) with complete remission (CR)/stable disease (SD), died of COVID-19. In two patients the baseline malignancy status was unknown, one patient died and one survived.

Severe (grade ≥3) cytokine release syndrome (CRS) after CAR-T cells was observed in one patient only" and "In total 8/15 patients (53,3%) who developed CRS after CAR-T infusion required treatment with tocilizumab ± steroids. None of the parameters analyzed in the univariate analysis had a significant impact on the outcome of the patients. Only the disease status at the time of COVID-19 was marginally significant for adverse outcome (p=0.075), adjusted by sex (male vs female p=0.0092) **(table 2).**

Discussion

In the present multicenter international study, we sought to evaluate the outcome of COVID-19 in a cohort of 459 consecutive patients who received CAR-T cell therapy. Several studies have addressed the clinical course and outcome of COVID-19 in hematologic patients as well as the presence of risk factors for a more aggressive life-threatening disease **(4,7,14-16).** Patients with hematological malignancies may be considered more vulnerable than the general population, however the exact prevalence of SARS-CoV-2 infection in this setting is still unclear. We documented a 4.8% prevalence of COVID-19 in our study group, remarkably higher than 0.1% reported in the general population, and the median onset of COVID-19 was 169 days after CAR-T therapy. Several factors could explain the high rate of COVID-19 in CAR-T patients. Our study included a homogeneous group of severely pretreated patients with LBCL who received at least two lines of treatment before CAR-T cells and a lymphodepletion therapy. Delayed cytopenias and impaired immune reconstitution leading to a significant risk of infectious complications have been well documented after CAR-T cell therapy **(12)**. Consistent with findings seen in prior studies, we observed a low lymphocyte count 90 days after CAR-T (median ALC 435/mm^3) and at the time of COVID-19 diagnosis (median ALC 370/mm^3 with 23% of the patients having <200 lymphocytes/mm3), although the presence of both neutropenia and lymphocytopenia at COVID-19 diagnosis did not result statistically significant in univariate analysis. In addition, it should be emphasized that the presence of R/R disease in one third of patients at the time of COVID-19 should be taken into account as a potential confounding factor. Regrettably, we were unable to investigate in detail humoral and cellular immune reconstitution and whether worsening of lymphopenia during infection had an impact on survival. Notably, our results showed that half of the patients developed COVID-19 beyond the first 6 months post-CAR-T, underscoring that prolonged delayed immune recovery may persist for a long period of time after cellular therapy (**17**). Currently there are few clinical trials evaluating the potential role of COVID-19 treatments in patients with cancer (**18**) and also observational studies are extremely limited. In our study patients received a great array of treatments making difficult to draw any firm conclusion. Based on the presence of an impaired humoral and cellular immune reconstitution after CAR-T cell therapy in a consistent number of patients, it would be expected a suboptimal response to the current treatments utilized in patients with COVID-19, although specific studies are eagerly needed to address this issue.

The mortality rate in cellular therapy patients has been reported in few studies. Altuntas et al evaluated 32 recipients of autologous and allogeneic grafts and found 33% case fatality rate among patients still receiving immunosuppressive agents at the time of COVID-19 diagnosis **(9)**. Similar results have been reported by the EBMT group with a mortality rate reaching 25%: older age, need for ICU and moderate/high immunodeficiency index increased the risk for mortality **(19)**. The CIBMTR reported the results of 318 HSCT patients (n=184 allogeneic; n= 134 autologous)

with COVID-19. The overall mortality was 22% among allogeneic HSCT recipients: age over 50, male sex and time from HSCT to COVID-19 diagnosis < 6 months were factors significantly associated with mortality **(20)** Shah et al, evaluated 77 patients with COVID-19 who received HSCT (n=72) and CAR-T therapy (n=5): the overall death rate was 41%, roughly similar to what reported in our study and was largely driven by patients with advance disease **(10).** The 50% mortality rate was remarkably high in our patients also considering that 10 out of 15 deaths were due to COVID-19 or COVID-19 related events. In this respect, it is worthwhile recalling that two thirds of the patients had a severe infection and 30% of the patients required mechanical ventilation. In addition, the advanced disease status at the time of COVID-19 diagnosis should be considered as a potential factor limiting the favorable outcome of the patients, as underpinned by the univariate analysis. Several factors might explain the higher mortality rate observed in our study as compared to that reported in HSCT recipients. Patients with relevant comorbidities are usually excluded from a HSCT program, while CAR-T cells treatment is not precluded to these vulnerable patients. The time interval from HSCT to COVID-19 emerged as a factor associated with mortality in many studies, spanning from 13.7 up to 18.9 months (CIBMTR, Varma Ljiungman, Coll), significantly longer than the median time from CAR-T to COVID-19 reported in our series (median time 169 days).

Preliminary data in HSCT recipients showed that COVID-19 is associated with low lymphocyte counts, particularly in T cell compartment, however lymphopenia does not appear to impair immune reconstitution in recovery from COVID-19. Regrettably, we do not have data on the lymphocyte subsets after COVID-19 in our cohort of patients, however protracted and profound lymphopenia after CAR-T cells have been reported in several studies. In addition, whether differences in CAR-T cell products may affect the kinetics of immunodeficiency recovery, remain to be determined.

If prospective large studies will corroborate our preliminary results, it seems wise to define strategies able to mitigate the adverse events occurring in CAR-T patients who develop COVID-19. Prioritization of COVID-19 vaccination in hematologic patients is of paramount importance, however based on existing knowledge of the reduced immunogenicity in the immunocompromised host, CAR-T cell recipients are not expected to generate robust responses to COVID-19 vaccine. In this respect, additional preventive measures should be explored. It has been shown that cellular therapies may be safely administered throughout the COVID-19 pandemic when appropriate interventions are instituted including antimicrobial stewardship programs, screening of donors and recipients, safe delivery of cellular products. Appealing alternatives to vaccination are monoclonal antibodies or prophylaxis with oral agents (fluvoxamine, molnupiravir), although clinical trials in hematologic patients are eagerly needed.

Our study is limited by being a retrospective study that includes a small number of patients. Nevertheless, our results highlight a significant mortality rate in COVID-19 patients who have received CAR-T therapy. Therapeutic strategies will need to be developed to ensure that CART therapy can be delivered safely and successfully whilst COVID-19 remains endemic. Furthermore, data on vaccinations in this cohort are eagerly awaited to help formulate the safe delivery.

Acknowledgements

The authors thank all contributors for their utmost contributions and support to the project during a pandemic situation and to Susann Blossfeld and Corinna Kramer for their administrative and technical assistance.

Data sharing statement: For data sharing, contact the corresponding author: abusca@cittadellasalute.to.it.

Authorship

A.B., J.S.G., P.C. and L.P. conceived of and codesigned the database; A.B, J.S.G. and L.P. contributed to data analysis; A.B. wrote the manuscript; and all authors critically reviewed and revised the manuscript and provided final approval.

AB has received lecture honoraria from Gilead Sciences, Merck, Pfizer Pharmaceuticals, Basilea, Biotest and Jazz Pharmaceuticals; he was Board member of Gilead Science and Takeda. **SL** received supports from Janssen, Gilead, Roche, Abbvie, Sanofi, Novartis, Actelion, Pfizer; Research grant from Janssen **LD** has received lecture honoraria from Abbvie, Amgen, Celgene, Egis, Gilead, Kyowa Kirin, MSD, Pfizer, Roche, Sandoz, Servier, Takeda, Teva; he was Board member of Abbvie, Gilead, Novartis, Pfizer and Takeda. **MH** reports research funding from Gilead, Astellas, Pfizer and MSD, outside the submitted work. **NK** reports research funding and honoraria from Gilead, Astellas, Pfizer and MSD, outside the submitted work. **PK** is supported by the German Federal Ministry of Research and Education and the State of North Rhine-Westphalia, Germany and has received non-financial scientific grants from Miltenyi Biotech GmbH, Bergisch Gladbach, Germany, and the Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Cologne, Germany, and received lecture honoraria from and/or is advisor to Akademie für Infektionsmedizin e.V., Ambu GmbH, Astellas Pharma, European Confederation of Medical Mycology, Gilead Sciences, GPR Academy Ruesselsheim, MSD Sharp & Dohme GmbH, Noxxon N.V., Pfizer Pharma GmbH and University Hospital, LMU Munich outside the submitted work. **OAC** reports grants or contracts from Amplyx, Basilea, BMBF, Cidara, DZIF, EU-DG RTD (101037867), F2G, Gilead, Matinas, MedPace, MSD, Mundipharma, Octapharma, Pfizer, Scynexis; Consulting fees from Amplyx, Biocon, Biosys, Cidara, Da Volterra, Gilead, Matinas, MedPace, Menarini, Molecular Partners, MSG-ERC, Noxxon, Octapharma, PSI, Scynexis, Seres; Honoraria for lectures from Abbott, Al-Jazeera Pharmaceuticals, Astellas, Grupo Biotoscana/United Medical/Knight, Hikma, MedScape, MedUpdate, Merck/MSD, Mylan, Pfizer; Payment for expert testimony from Cidara; Participation on a Data Safety Monitoring Board or Advisory Board from Actelion, Allecra, Cidara, Entasis, IQVIA, Jannsen, MedPace, Paratek, PSI, Shionogi; A pending patent currently reviewed at the German Patent and Trade Mark Office; Other interests from DGHO, DGI, ECMM, ISHAM, MSG-ERC, Wiley. All the remaining authors declare nothing to disclose.

EPICOVIDEHA has received funds from Optics COMMITTM (COVID-19 Unmet Medical Needs and Associated Research Extension) COVID-19 RFP program by GILEAD Science, United States (Project 2020-8223).

A complete list of the members of the EPICOVIDEHA Study Group appears in “Appendix.”

Alessandro Busca MD

Stem Cell Transplant Unit, AOU Cittadella Salute e della Scienza, Turin – ITALY. Corso Bramante 88, 10126 Turin

Email: abusca@cittadellasalute.to.it

Alternative correspondence: Jon Salmanton-García PhD

University Hospital Cologne

Internal Medicine I, Infectious Diseases 2

Herderstrasse 52-54

50931 Cologne (Germany)

Email: jon.salmanton-garcia@uk-koeln.de

Appendix: All investigators are part of the EPICOVIDEHA Study Group, with two different statuses: 1) authors and 2) collaborators.

Authors are:

Alessandro Busca, Jon Salmanton-García, Paolo Corradini, Francesco Marchesi, Alba Cabirta, Roberta Di Blasi, Remy Dulery, Sylvain Lamure, Francesca Farina, Barbora Weinbergerová, Josip Batinić, Anna Nordlander, Alberto López-García, Ľuboš Drgoňa, Ildefonso Espigado-Tocino, Iker Falces-Romero, Ramón García-Sanz, Carolina García Vidal, Anna Guidetti, Nina Khanna, Austin Kulasekararaj, Johan Maertens, Martin Hoenigl, Nikolai Klimko, Philipp Koehler, Antonio Pagliuca, Francesco Passamonti, Oliver A. Cornely, Livio Pagano

Collaborators are:

Jiří Mayer, Cristina de Ramón-Sánchez, Jenna Essame, Nicole García-Poutón, Raúl Córdoba, Marina Machado, Juan-Alberto Martín-González, Ola Blennow, Elisa Roldán, Jakob Passweg

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Table 1. Characteristics of the 30 patients receiving CAR-T cells therapy and COVID-19

Patient	Baseline haematological malignancy	Disease status at COVID-19 diagnosis	Days from CAR-T to COVID-19	CAR-T cell construct	Bridging therapy	Lympho-depletion	CRS/ICANS Treatment				Reason for death (days after COVID-19 diagnosis)
							CRS (at CAR-T)	ICANS	Tocilizumab	Steroids	
1	NHL - LBCL	Refractory/Resistant	37	Axi-cel	x	Flu-Cyc	1	1			Malignancy (35d)
2	NHL - LBCL	Complete remission	221	Axi-cel	x	Flu-Cyc	1	NA			NA
3	NHL - LBCL	Complete remission	240	Axi-cel		Flu-Cyc	2	NA	x	x	COVID-19 + Other (52d)
4	NHL - LBCL	Refractory/Resistant	1	Tisa-cel	x	Flu-Cyc	2	NA	x	x	COVID-19 (25d)
5	NHL - LBCL	Complete remission	85	Axi-cel		Flu-Cyc	1	2		x	NA
6	NHL - LBCL	Stable disease	14	Tisa-cel	x	Benda	2	1	x	x	COVID-19 + Other (170d)
7	MM	Refractory/Resistant	90	BCMA ARI-0002	x	Flu-Cyc	NA	NA			NA
8	NHL - LBCL	Refractory/Resistant	42	Tisa-cel	x	Flu-Cyc	2	NA	x	x	Malignancy + COVID-19 (33d)
9	NHL - LBCL	Refractory/Resistant	397	Tisa-cel	x	Flu-Cyc	2	NA	x		NA
10	NHL - LBCL	Complete remission	313	Axi-cel	x	Flu-Cyc	1	NA	x		NA
11	ALL	Unknown	9	Tisa-cel		Flu-Cyc	NA	NA			NA
12	NHL - LBCL	Refractory/Resistant	302	Axi-cel	x	Flu-Cyc	1	NA	x		COVID-19 (42d)
13	NHL - LBCL	Complete remission	95	Tisa-cel	x	Flu-Cyc	NA	NA			NA
14	NHL - LBCL	Complete remission	457	Axi-cel	x	Flu-Cyc	1	NA			NA
15	NHL - LBCL	Refractory/Resistant	158	Axi-cel	x	Flu-Cyc	1	NA	x	x	Malignancy (22d)
16	NHL - LBCL	Refractory/Resistant	65	Tisa-cel	x	Flu-Cyc	1	3	x	x	Malignancy + COVID-19 (21d)
17	NHL - LBCL	Complete remission	270	Axi-cel	x	Flu-Cyc	3	NA	x	x	NA
18	NHL - LBCL	Unknown	19	Tisa-cel		Flu-Cyc	2	NA	x		COVID-19 (50d)
19	NHL - LBCL	Refractory/Resistant	180	Tisa-cel		Flu-Cyc	1	NA	x	x	NA
20	NHL - LBCL	Complete remission	186	Tisa-cel		Flu-Cyc	1	NA			COVID-19 (51d)
21	NHL - LBCL	Complete remission	348	Axi-cel		Flu-Cyc	2	2	x	x	NA

22	NHL - LBCL	Complete remission	19	Tisa-cel	x	Flu-Cyc	1	NA			NA
23	NHL - LBCL	Complete remission	605	Tisa-cel	x	Flu-Cyc	NA	NA			COVID-19 (46d)
24	NHL - NOS	Complete remission	635	Axi-cel		Flu-Cyc	1	NA			COVID-19 (44d)
25	NHL - LBCL	Refractory/Resistant	180	Tisa-cel	x	Flu-Cyc	1	NA			Malignancy + COVID-19 (32d)
26	NHL - LBCL	Complete remission	485	Axi-cel	x	Flu-Cyc	1	NA			COVID-19 (53d)
27	NHL - LBCL	Complete remission	510	Axi-cel		Flu-Cyc	1	NA			COVID-19 (124d)
28	NHL - LBCL	Complete remission	66	Tisa-cel	x	Flu-Cyc	1	NA	x		NA
29	NHL - LBCL	Refractory/Resistant	12	Tisa-cel	x	Flu-Cyc	1	1			NA
30	NHL - LBCL	Complete remission	35	Tisa-cel	x	Flu-Cyc	NA	NA			NA

Other reasons for death: Patient #3, possible IFI; patient #6, pulmonary embolism and heart failure).

Table 2. Univariate and multivariate analysis of factors associated with the mortality of CAR-T patients with COVID-19

	All patients								CAR-T ≤ 6 months before COVID-19				CAR-T > 6 months before COVID-19			
	Univariable				Multivariable				Univariable				Univariable			
	p value	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
Sex																
Female	-	-	-	-	-	-	-	-								
Male	0.093	2.682	0.849	8.474	0.092	2.742	0.848	8.861	-	-	-	-	-	-	-	-
Age									0.141	4.897	0.591	40.604	0.401	1.928	0.417	8.902
< 50 years old	-	-	-	-	-	-	-	-								
≥ 50 years old	0.115	5.119	0.673	38.955	-	-	-	-	-	-	-	-	-	-	-	-
Number of comorbidities									0.580	1.809	0.222	14.742	0.254	42.159	0.068	26050.639
No comorbidities	-	-	-	-	-	-	-	-								
1 comorbidity	0.111	3.093	0.772	12.393	-	-	-	-	-	-	-	-	-	-	-	-
2 comorbidities	0.229	3.021	0.498	18.328	-	-	-	-	0.111	3.093	0.772	12.393	0.218	3.438	0.482	24.537
3 or more comorbidities	0.414	1.880	0.413	8.562	-	-	-	-	0.229	3.021	0.498	18.328	0.558	2.055	0.185	22.871
Malignancy status at COVID-19 diagnosis									0.414	1.880	0.413	8.562	0.077	6.111	0.820	45.529
Controlled disease	-	-	-	-	-	-	-	-								

	All patients								CAR-T ≤ 6 months before COVID-19				CAR-T > 6 months before COVID-19			
	Univariable				Multivariable				Univariable				Univariable			
	p value	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
Active disease	0.067	2.707	0.931	7.870	0.075	2.652	0.907	7.754	-	-	-	-	-	-	-	-
Unknown	0.674	1.579	0.188	13.238	0.958	1.059	0.123	9.132	0.944	2.707	0.931	7.870	0.916	1.121	0.133	9.449
CAR-T construct									0.947	-	-	-	-	-	-	-
Axi-cel	-	-	-	-	-	-	-	-								
Tisa-cel	0.820	0.888	0.321	2.458	-	-	-	-	-	-	-	-	-	-	-	-
Other	0.986	-	-	-	-	-	-	-	0.382	0.479	0.092	2.494	0.603	1.552	0.296	8.133
ICU stay	0.413	1.529	0.554	4.225	-	-	-	-	0.991	-	-	-	-	-	-	-
Tocilizumab/Steroids after CAR-T	0.484	1.437	0.520	3.972	-	-	-	-	0.870	0.887	0.211	3.729	0.152	3.331	0.643	17.247
Time from CAR-T to COVID-19																
≤ 6 months	-	-	-	-	-	-	-	-								
> 6 months	0.996	0.998	0.359	2.770	-	-	-	-								
Neutrophils at COVID-19 diagnosis																
≤ 500	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
> 500	0.469	0.611	0.161	2.321	-	-	-	-	0.724	0.761	0.167	3.472	-	-	-	-
Lymphocytes at COVID-19 diagnosis																
≤ 200	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
> 200	0.334	0.551	0.164	1.846	-	-	-	-	0.444	0.568	0.133	2.419	0.907	0.872	0.089	8.515

Axi-cel, axicabtagene ciloleucel; **CAR-T**, chimeric antigen receptor T; **CI**, confidence interval; **COVID-19**, coronavirus diseases 2019; **HR**, hazard ratio; **ICU**, intensive care unit; **Tisa-cel**, tisagenlecleucel

Table 1. Characteristics of the 30 patients receiving CAR-T cells therapy and COVID-19

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Other reasons for death: Patient #3, possible IFI; patient #6, pulmonary embolism and heart failure).

ALL, acute lymphoid leukaemia; **Axi-cel**, axicabtagene ciloleucel; **Benda**, bendamustine; **CAR-T**, chimeric antigen receptor T; **COVID-19**, coronavirus disease 2019; **CRS**, cytokine release syndrome; **Cyc**, cyclophosphamide; **d**, day; **LBCL**, diffuse large B-cell lymphoma; **Flu**, fludarabine; **ICANS**, immune effector cell-associated neurotoxicity syndrome; **MM**, multiple myeloma; **NA**, not applicable; **NHL**, non-Hodgkin lymphoma; **NOS**, not otherwise specified; **Tisa-cel**, tisagenlecleucel

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	All patients								CAR-T ≤ 6 months before COVID-19				CAR-T > 6 months before COVID-19			
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			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
Sex																
Female	-	-	-	-	-	-	-	-								
Male	0.093	2.682	0.849	8.474	0.092	2.742	0.848	8.861	-	-	-	-	-	-	-	-
Age									0.141	4.897	0.591	40.604	0.401	1.928	0.417	8.908
< 50 years old	-	-	-	-	-	-	-	-								
≥ 50 years old	0.115	5.119	0.673	38.955	-	-	-	-	-	-	-	-	-	-	-	-
Number of comorbidities									0.580	1.809	0.222	14.742	0.254	42.159	0.068	26050.639
No comorbidities	-	-	-	-	-	-	-	-								
1 comorbidity	0.111	3.093	0.772	12.393	-	-	-	-	-	-	-	-	-	-	-	-
2 comorbidities	0.229	3.021	0.498	18.328	-	-	-	-	0.111	3.093	0.772	12.393	0.218	3.438	0.482	24.537
3 or more comorbidities	0.414	1.880	0.413	8.562	-	-	-	-	0.229	3.021	0.498	18.328	0.558	2.055	0.185	22.871
Malignancy status at COVID-19 diagnosis									0.414	1.880	0.413	8.562	0.077	6.111	0.820	45.529
Controlled disease	-	-	-	-	-	-	-	-								
Active disease	0.067	2.707	0.931	7.870	0.075	2.652	0.907	7.754	-	-	-	-	-	-	-	-
Unknown	0.674	1.579	0.188	13.238	0.958	1.059	0.123	9.132	0.944	2.707	0.931	7.870	0.916	1.121	0.133	9.446
CAR-T construct									0.947	-	-	-	-	-	-	-
Axi-cel	-	-	-	-	-	-	-	-								
Tisa-cel	0.820	0.888	0.321	2.458	-	-	-	-	-	-	-	-	-	-	-	-
Other	0.986	-	-	-	-	-	-	-	0.382	0.479	0.092	2.494	0.603	1.552	0.296	8.132
ICU stay	0.413	1.529	0.554	4.225	-	-	-	-	0.991	-	-	-	-	-	-	-
Tocilizumab/Steroids after CAR-T	0.484	1.437	0.520	3.972	-	-	-	-	0.870	0.887	0.211	3.729	0.152	3.331	0.643	17.247
Time from CAR-T to COVID-19																
≤ 6 months	-	-	-	-	-	-	-	-								
> 6 months	0.996	0.998	0.359	2.770	-	-	-	-								
Neutrophils at COVID-19 diagnosis																

	All patients								CAR-T ≤ 6 months before COVID-19				CAR-T > 6 months before COVID-19			
	Univariable				Multivariable				Univariable				Univariable			
	p value	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
≤ 500	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
> 500	0.469	0.611	0.161	2.321	-	-	-	-	0.724	0.761	0.167	3.472	-	-	-	-
Lymphocytes at COVID-19 diagnosis																
≤ 200	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
> 200	0.334	0.551	0.164	1.846	-	-	-	-	0.444	0.568	0.133	2.419	0.907	0.872	0.089	8.511

Axi-cel, axicabtagene ciloleucel; **CAR-T**, chimeric antigen receptor T; **CI**, confidence interval; **COVID-19**, coronavirus diseases 2019; **HR**, hazard ratio; **ICU**, intensive care unit; **Tisa-cel**, tisagenlecleucel