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TO THE EDITOR:

COVID-19 and hairy-cell leukemia: an EPICOVIDEHA survey

Sylvain Lamure,[1,*] Jon Salmanton-García,[2,3,*] Elena Robin-Marieton,[4,*] Ozren Jaksic,[5] Milena Kohn,[6] Francesco Marchesi,[7] Monia Marchetti,[8] Shaimaa El-Ashwah,[9] Fatih Demirkan,[10] Toni Valković,[11] Noemí Fernández,[12] Maria Chiara Tisi,[13] Zlate Stojanoski,[14] Guldane Cengiz Seval,[15] Osman Ilhan,[15] Lucia Prezioso,[16] Maria Merelli,[17] Alberto López-García,[18] Marie-Pierre Ledoux,[19] Austin Kulasekararaj,[20] Tomás-José González-López,[21] Maria Gomes da Silva,[22] Ziad Emarah,[23] Rafael F. Duarte,[24] Chiara Cattaneo,[25] Ola Blennow,[26] Yavuz M. Bilgin,[27] Rui Bergantim,[28] Josip Batinić,[29] Raul Cordoba,[30] Jenna Essame,[31] Anna Nordlander,[32] Raquel Nunes Rodrigues,[33] Maria Vittoria Sacchi,[34] Sofia Zompi,[35] Alessandro Busca,[35] Paolo Corradini,[36] Martin Hoenigl,[37] Nikolai Klimko,[38] Philipp Koehler,[2,3] Antonio Pagliuca,[39] Francesco Passamonti,[40] Rémy Duléry,[41] Oliver A. Cornely,[42-46] Caroline Besson,[47,†] and Livio Pagano[48,†]

[1]Department of Clinical Hematology, Montpellier University Hospital, IGMM UMR5535 Centre National de la Recherche Scientifique (CNRS), University of Montpellier, Montpellier, France; [2]Faculty of Medicine and University Hospital Cologne, Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany; [3]Department I of Internal Medicine, Faculty of Medicine and University Hospital Cologne, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology (ECMM), University of Cologne, Cologne, Germany; [4]Service d'Hématologie Oncologie, Centre Hospitalier de Versailles, Le Chesnay, France; [5]University Hospital Dubrava, Zagreb, Croatia; [6]Service d'Hématologie Oncologie, Centre Hospitalier de Versailles, Le Chesnay, France; [7]Hematology and Stem Cell Transplant Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Regina Elena National Cancer Institute, Rome, Italy; [8]Azienda Ospedaliera Nazionale SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; [9]Oncology Center, Mansoura University, Mansoura, Egypt; [10]Division of Hematology, Dokuz Eylul University, Izmir, Turkey; [11]University Hospital Centre Rijeka, and Croatian Cooperative Group for Hematological Diseases (CROHEM), Faculty of Medicine and Faculty of Health Studies University of Rijeka, Rijeka, Croatia; [12]Hospital Universitario Marqués de Valdecilla, Santander, Spain; [13]Department of Hematology, Ospedale San Bortolo, Vicenza, Italy; [14]University Clinic of Hematology, Skopje, Republic of North Macedonia; [15]Department of Hematology, Ankara University School of Medicine, Ankara, Turkey; [16]Hematology and Bone Marrow Unit, University of Parma Hospital, Parma, Italy; [17]Azienda Sanitaria Universitaria del Friuli Centrale, Udine, Italy; [18]Fundacion Jimenez Diaz University Hospital, Health Research Institute IIS-FJD, Madrid, Spain; [19]Institut de Cancérologie de Strasbourg Europe, Strasbourg, France; [20]King's College Hospital, London, United Kingdom; [21]Department of Hematology, Hospital Universitario de Burgos, Burgos, Spain; [22]Departamento de Hematologia, Instituto Português de Oncologia, Lisboa, Portugal; [23]Oncology Center, Mansoura University, Mansoura, Egypt; [24]Hospital Universitario Puerta de Hierro, Majadahonda, Spain; [25]Hematology Unit, ASST-Spedali Civili, Brescia, Italy; [26]Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden; [27]Department of Internal Medicine, Adrz, Goes, The Netherlands; [28]Centro Hospitalar e Universitário São João, Porto, Portugal; [29]School of Medicine, University of Zagreb, and Croatian Cooperative Group for Hematological Diseases (CROHEM), Zagreb, Croatia; [30]Health Research Institute IIS-FJD, Fundacion Jimenez Diaz University Hospital, Madrid, Spain; [31]King's College Hospital, London, United Kingdom; [32]Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden; [33]Departamento de Hematologia, Instituto Português de Oncologia, Lisboa, Portugal; [34]Azienda Ospedaliera Nazionale SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; [35]Stem Cell Transplant Center, AOU Citta' della Salute e della Scienza, Turin, Italy; [36]University of Milan and Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy; [37]Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California San Diego, San Diego, and Clinical and Translational Fungal Research-Working Group, University of California San Diego, La Jolla, CA, and Division of Infectious Diseases, Department of Internal Medicine, Medical University of Graz, Graz, Austria; [38]North-Western State Medical University named after Iliá Ilich Méchnikov, Saint-Petersburg, Russia; [39]Department of Hematological Medicine, Kings College Hospital NHS Foundation Trust, London, United Kingdom; [40]Department of Medicine and Surgery, University of Insubria and ASST Sette Laghi, Ospedale di Circolo of Varese, Varese, Italy; [41]Service d'Hématologie Clinique et de Thérapie Cellulaire, Hôpital Saint Antoine, Assistance Publique-Hôpitaux de Paris, Sorbonne University, INSERM UMRS 938, Paris, France, Faculty of Medicine, University of Cologne, and Department I of Internal Medicine, University Hospital Cologne, Excellence Center for Medical Mycology (ECMM), Cologne, Germany; [42]Faculty of Medicine and University Hospital Cologne, Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany; [43]Department I of Internal Medicine, Faculty of Medicine and University Hospital Cologne, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD) and Excellence Center for Medical Mycology (ECMM), and [44]Faculty of Medicine and University Hospital Cologne, Clinical Trials Centre Cologne (ZKS Köln), University of Cologne, Cologne, Germany; [45]German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany; [46]Faculty of Medicine, University of Cologne, and Translational Research, University Hospital Cologne, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany; Faculty of Medicine, University of Cologne, and Clinical Trials Centre Cologne (ZKS Köln), University Hospital Cologne, Cologne, Germany, Faculty of Medicine, University of Cologne, and University Hospital Cologne, Center for Molecular Medicine Cologne (CMMC), Cologne, Germany, German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany; [47]Service d'Hématologie Oncologie, Centre Hospitalier de Versailles, Le Chesnay, France, Université Paris-Saclay, UVSQ, INSERM, Équipe Exposome et Hérédité, CESP, Villejuif, France; and [48]Hematology Unit, Fondazione Policlinico Universitario Agostino Gemelli–IRCCS, Rome, Italy, Hematology Unit, Università Cattolica del Sacro Cuore, Rome, Italy

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*S.L., J.S.-G., and E.R.-M. are joint junior authors.

†C.B. and L. Pagano are joint senior authors.

The data that support the findings of this study are available from the corresponding author (e-mail: jon.salmanton-garcia@uk-koeln.de) and senior author (e-mail: livio.pagano@unicatt.it) upon reasonable request.

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

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Hairy cell leukemia (HCL) is a rare B lineage malignancy with a high frequency of infection-related mortality. It represents 2% of leukemias[1] and 2% of lymphoid neoplasms.[2] Patients often present with bacterial, viral, or fungal opportunistic infections favored by the monocytopenia, neutropenia, and lymphopenia featuring the diagnosis.[3,4] Immune deficiency is worsened by HCL treatments[5] such as cladribine, a purine analog that depletes $CD4^+$ T cells,[6] or anti-CD20, which depletes B cells,[7] both for a long period. Despite recent guidelines on HCL management in the context of the coronavirus disease 2019 (COVID-19) pandemic,[8] data regarding outcomes of HCL patients with COVID-19 are scarce. In a cohort study including 111 patients with lymphoma who were hospitalized for COVID-19 in France, 2 patients (2%) had HCL.[9] Furthermore, recent single case reports described either a concomitant diagnosis of COVID-19 and HCL[10] or critical COVID-19 in a context of HCL.[11] In this study, we aim to report the characteristics and outcomes of patients with HCL and COVID-19 from the EPICOVIDEHA survey,[12] with a focus on patients with concomitant diagnosis of HCL and COVID-19.

The EPICOVIDEHA registry is an online survey collecting cases of COVID-19 in the context of a hematological malignancy since April 2020, and the registration of new cases is still active. The survey is promoted by the European Hematology Association - Infectious Diseases Working Party (EHA-IDWP) and has been approved centrally by the Institutional Review Board and Ethics Committee of Fondazione Policlinico Universitario A. Gemelli – IRCCS – Università Cattolica del Sacro Cuore, Rome, Italy (Study ID: 3226). The survey is registered at clinicaltrials.gov (#NCT04733729). The data are collected online using an electronic case report form available at www.clinicalsurveys.net (EFS Summer 2021, TIVIAN, Cologne, Germany). The following clinical and epidemiological data from patients with a laboratory-based diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are collected: underlying conditions before SARS-CoV-2, hematological malignancy status, and management before SARS-CoV-2 infection. The severity of COVID-19 is graded according to the China Centers for Disease Control and Prevention and the cause of mortality.[13]

Until January 26, 2022, 40 patients with HCL and COVID-19 were reported out of the 2 422 lymphoproliferative neoplasms in the database (1.7%). Their median age was 60 years (interquartile range [IQR]: 53-67; range, 43-89), 7 patients were >70 years (18%), and 34 were male (85%; Table 1). Thirteen patients had any comorbidity (33%), mostly a cardiovascular condition. Median time between HCL and COVID-19 diagnosis was 14 months (range 0-660 months). The 7 cases diagnosed <1 month before COVID-19 were considered concomitant. HCL was diagnosed >1 month before COVID-19 for 33 patients (83%), including 5 under frontline therapy (13%), 11 in remission (28%), 15 with untreated stable disease (35%), 1 with a refractory disease (3%), and 1 with an unknown situation (3%). Regarding HCL treatments received before COVID-19, 17 patients had received cladribine (43%) at any time, including 16 as last treatment, and 3 were exposed to rituximab (8%). Time between cladribine treatment and COVID-19 was documented for 13 patients and ranged from 7 days to 18 years (median, 3 months); 8 of the patients had received cladribine <6 months before COVID-19. Due to the period covered by this study, only 5 patients were vaccinated against SARS-CoV-2 (13%), and variants were not documented. COVID-19 was severe for 19 cases (48%) and critical

Table 1. Baseline characteristics of patients with HCL and COVID-19

Characteristics	Sample (n = 40)
Demographic characteristics	
Age, y	
Median (IQR | range)	60 (52-67 | 43-89)
≥70, n (%)	7 (18)
Male sex, n (%)	34 (85)
Comorbidities, n (%)	
Obesity	2 (5)
Smoking history	3 (8)
Chronic cardiovascular disease	9 (23)
Diabetes	2 (5)
Chronic pulmonary disease	5 (13)
HCL characteristics	
Status at COVID-19 diagnosis, n (%)	
Onset: concurrent diagnosis	7 (15)
Frontline therapy	5 (13)
Remission	11 (28)
Untreated stable disease	15 (41)
Refractory disease	1 (3)
Unknown	1 (3)
Last treatment before COVID-19, n (%)	
No treatment	19 (48)
Cladribine	17 (43)
Rituximab	2 (5)
Chlorambucil	1 (3)
Corticosteroids	1 (3)
COVID-19 characteristics	
Time between HCL diagnosis and COVID-19 (mo), median (IQR | range)	14 (1-42 | 0-660)
Time between cladribine and COVID-19 (months), median (IQR | range)	3 (2-32 | 0-223)
Vaccination	5 (13)
SARS-CoV-2 variant	
Unknown	32 (80)
Alpha	2 (5)
Delta	1 (3)
COVID-19 symptoms	
Pulmonary	22 (55)
Extrapulmonary	4 (10)
Pulmonary and extrapulmonary	8 (20)
Severity*	
Asymptomatic	3 (8)
Mild	3 (8)
Severe	19 (48)
Critical	14 (35)
Neutrophiles at onset	
≤500	6 (15)
501-999	6 (15)
≥1000	26 (65)

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Table 1. (continued)

Characteristics	Sample (n = 40)
Lymphocytes at onset	
≤200	8 (20)
201-499	8 (20)
≥500	21 (52)
Mortality	
Overall	10 (26)
COVID-19 related	9 (23)
Unknown reason	1 (3)

*Asymptomatic is for patients without clinical signs or symptoms, mild for those with non-pneumonia and mild pneumonia, severe for those with dyspnea, respiratory frequency ≥30 breaths/min, SpO_2 ≤ 93%, PaO_2/FiO_2 < 300, or lung infiltrates >50% on tomography, and critical for patients admitted in intensive care for respiratory failure, septic shock, or multiple organ dysfunction or failure.

for 14 (35%). The median length of in-hospital stay was 15 days (IQR: 8-26, range 1-84), and 8 patients were still hospitalized after 30 days (20%). Fourteen patients (35%) were admitted to an intensive care unit (ICU), of whom 10 (24%) were intubated, and the median stay at the ICU was 15 days (IQR: 6-30, range 1-57). A total of 10 patients died, amounting to a 25% overall mortality, and of these, 9 (90%) died due to the COVID-19, 1 case for an undetermined reason. Among the 22 patients who were treatment-free for HCL, 5 had died (23%), which is similar to the proportion of 5 deaths out of 17 patients (29%) who received cladribine (Figure 1), and no death was reported among the 5 patients who were vaccinated. We found a decrease in mortality along time: in 2020, 8 deaths were observed out of 27 patients (30%) vs 2 out of 13 in 2021 (15%).

Six out of 7 patients for whom HCL was diagnosed at the time of COVID-19 infection are described in the supplemental Table. Most of them did not suffer from any preexisting condition that could favor severe COVID-19 infection. Most of the patients required a hospitalization, and 2 of them were admitted in the ICU to receive noninvasive ventilation. All cases of HCL were diagnosed because of blood counts showing cytopenia, of which neutropenia and monocytopenia were constant. Physical examination and/or computed tomography scan showed enlarged spleen in most of patients. HCL diagnosis was confirmed by proving the coexpression of CD25, CD11c, and CD123 by the abnormal cells and/or by demonstration of BRAF V600E mutation. These findings highlight the importance of simple exams such as blood count and thorough physical examination when a patient presents with severe symptoms of COVID-19 because HCL diagnosis can be suspected when cytopenias and/or splenomegaly is present.

Here we report the first cohort of patients with HCL and COVID-19. The incidence in the survey is close to the previously reported 2% proportion of HCL among lymphoproliferative neoplasm.[2] In the EPICOVIDEHA study, 64% of cases were severe/critical, and the overall mortality was 31%. The 83% of severe/critical patients reported here suggests a more severe presentation of COVID-19, but the percentage of patients who died was comparable to the entire EPICOVIDEHA cohort.[14] Former studies revealed a negative impact of antitumoral treatment on infection outcomes[9]; however, in this study that included a limited number of cases with variable

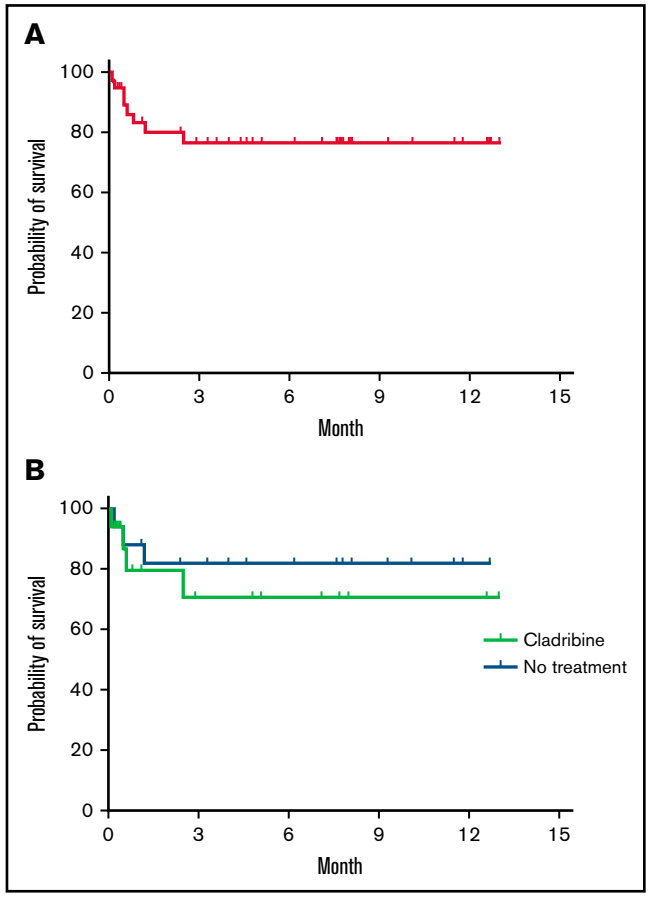


Figure 1. Overall survival of patients with COVID-19 and HCL. Probability of overall survival of 39 patients with hairy cell leukemia after COVID-19 diagnosis (A) and comparison of the survival of 17 patients who had a previous treatment with cladribine with 19 patients who received no treatment (B). Kaplan-Meier survival analysis made with Prism 9 version 9.3.1 (GraphPad 2021).

treatment-free period, we did not observe any effect of HCL treatment on mortality, with the limitation of the heterogeneity of our study population concerning the treatments received. The 20% of patients who stayed longer than 30 days in hospital suggests the frequent persistence of COVID-19 as reported previously.[9] Besides, we observed a significant proportion of new diagnoses of HCL, revealed by splenomegaly and/or cytopenia in the situation of severe COVID-19, highlighting the importance of investigating cytopenia when present at COVID-19 diagnosis. Actually, it is common for patients with HCL to be affected by atypical and severe life-threatening infections because they present with complex immune defects affecting both cellular- and humoral-mediated immunity.[15] Furthermore, the high risk of infections occurring during the initial phase of treatment is a frequent clinical challenge, and the incidence of infectious complications prior to the advent of COVID-19 ranged from 30% to 50%.[4]

Even if not reaching statistical significance, we observed a lower mortality over time because most of the deaths related to COVID-19 occurred in 2020. This could be explained by improvements in therapeutic management of COVID-19, including early corticosteroid therapy[16] as well as the protective effects of vaccination,[17] because the 5 vaccinated patients survived.

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This cohort suggests that HCL may be a risk factor for severe or critical COVID-19, and future work will evaluate the protective effect of vaccination and improvement of outcomes with monoclonal antibodies and antiviral therapies recently developed.

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ORCID profiles: S.L., 0000-0001-5980-305X; J.S-G., 0000-0002-6766-8297; O.J., 0000-0003-4026-285X; F.M., 0000-0001-6353-2272; M.Marchetti, 0000-0001-7615-0572; S.E.-A., 0000-0003-2210-1534; F.D., 0000-0002-1172-8668; T.V., 0000-0001-6083-8815; M.C.T., 0000-0001-8231-6700; Z.S., 0000-0001-7502-8356; G.C.S., 0000-0001-9433-2054; L.P., 0000-0003-1660-4960; M.Merelli, 0000-0003-3352-1163; A.L.-G., 0000-0002-5354-5261; M-P.L., 0000-0002-3261-3616; A.K., 0000-0003-3180-3570; M.G.d.S., 0000-0002-6993-2450; Z.E., 0000-0003-0622-2598; R.F.D., 0000-0002-5240-9815; C.C., 0000-0003-0031-3237; O.B., 0000-0002-7167-7882; Y.M.B., 0000-0003-4854-5424; R.B., 0000-0002-7811-9509; J.B., 0000-0001-5595-9911; R.C., 0000-0002-7654-8836; J.E., 0000-0003-0926-5577; R.N.R., 0000-0002-8347-4281; M.V.S., 0000-0001-8133-3357; S. Z., 0000-0002-4075-8727; A.B., 0000-0001-5361-5613; P.C., 0000-0002-9186-1353; M.H., 0000-0002-1653-2824; N.K., 0000-0001-6095-7531; P.K., 0000-0002-7386-7495; A.P., 0000-0003-2519-0333; F.P., 0000-0001-8068-5289; R.D., 0000-0002-5024-1713; O.A.C., 0000-0001-9599-3137; C.B., 0000-0003-4364-7173; L.Pagano, 0000-0001-8287-928X.

Correspondence: Jon Salmanton-García, Faculty of Medicine and University Hospital Cologne, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany; Department I of Internal Medicine, Excellence Center for Medical Mycology (ECMM), Herderstraße 52-54, 50931 Cologne, Germany; e-mail: jon.salmanton-garcia@uk-koeln.de; and Sylvain Lamure, Department of Clinical Hematology, Montpellier University Hospital, IGMM UMR1535 CNRS, University of Montpellier, Montpellier, France; e-mail: sylvain.lamure@gmail.com.

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