

Outcomes of SARS-CoV-2 Infections in Patients With Neurodegenerative Diseases in the LEOSS Cohort

The impact of preexisting neurodegenerative diseases on superimposed SARS-CoV-2 infections remains controversial. Here we examined the course and outcome of SARS-CoV-2 infections in patients affected by Parkinson's disease (PD) or dementia compared to matched controls without neurodegenerative diseases in the LEOSS (Lean European Open Survey on SARS-CoV-2-infected patients) cohort, a large-scale prospective multicenter cohort study.¹

The LEOSS scientific data set comprises anonymous data after data quality control, including plausibility checks. Collected data include demographic information, standardized clinical classification of the SARS-CoV-2 severity (hospitalization and discharge), administered medical care (eg, intensive care unit [ICU] stay, and ventilation), preexisting and concomitant signs and symptoms, medication, laboratory parameters, and mortality. The patient sample age is grouped in decades.

Our study population comprised $n = 4310$ SARS-CoV-2-infected patients (59% men). Forty of them had PD (median decade: 76–85 years, 63% men); 290 had dementia (median decade: 76–85 years, 50% men) (Supplementary Tables S1 and S2). Dementia was classified into Alzheimer's disease (22.1%), vascular dementia (13.3%), other dementia (12.4%), and unknown/missing value (52.1%). More than 95% of the patients were from tertiary referral centers in Germany between March 2020 and November 2020.

Using a systematic sampling strategy, we extracted 15 controls randomly from the study population for each PD patient (1:15) and 2 randomly selected controls for each dementia patient (1:2). Any potentially confounding effects resulting from variability in age and sex were fully adjusted for by the matching procedure. To avoid bias, we handled patients and controls the same way according to standard epidemiological principles.

© 2021 International Parkinson and Movement Disorder Society

***Correspondence to:** Günter U. Hoeglinger, MD, Department of Neurology, Hannover Medical School, German Center for Neurodegenerative Diseases (DZNE), Munich, Germany, Carl-Neuberg Str. 1 30625, Hannover Germany. Tel.: +49 511 532 2390. E-mail: hoeglinger.guenter@mh-hannover.de

†M.K.H., C.R., F.H., and G.U.H. contributed equally to this study.

Relevant conflicts of interest/financial disclosures: The authors declare no conflict of interest.

Funding agencies: LEOSS has received funding from the Willy Robert Pitzer Foundation and the German Center for Infection Research (DZIF). This study was funded by intramural funding.

Received: 25 January 2021; **Revised:** 5 February 2021; **Accepted:** 8 February 2021

Published online in Wiley Online Library
(wileyonlinelibrary.com). DOI: 10.1002/mds.28554

The overall SARS-CoV-2-associated mortality in the PD (32.5%) and dementia (32.1%) groups did not significantly differ from their respective control groups (28.7% and 26.5%).

Delirium occurred more frequently in dementia compared to PD and controls, but patient-reported parameters (eg, dry cough and dyspnoe) were less frequent in dementia compared to PD and controls. Interestingly, dementia patients remained in the ICU and were ventilated for a shorter time period than controls. The major SARS-CoV-2 outcome parameters (duration of inpatient stay, duration of ICU stay, and duration of ventilation; SARS-CoV-2-related mortality) were also not significantly different between PD patients, dementia patients, and controls. The age and gender distributions in our patient sample were not significantly different from previously published epidemiological cohort studies reporting the typical characteristics of German PD and dementia patients.^{2–5} This suggests that our sample was representative of the patients observed in the general population. Only the subgroup of female dementia patients had a higher mortality than their female controls (Table 1).

Although prior studies have reported higher SARS-CoV-2-related mortality in patients with PD or dementia compared to patients without preexisting neurodegenerative diseases,^{6,7} encouragingly, our comparably relatively large, well-controlled, standardized data set with prospective patient enrollment does not support the notion of an increased risk for a fatal course of SARS-CoV-2 in PD or dementia patients, when treated in tertiary referral centers. Further research is required to shed light on the impact of gender on the outcome of SARS-CoV-2 infections in dementia patients.

Ethics

Approval for LEOSS was obtained by the applicable local ethics committees of all participating centers and registered at the German Clinical Trials Register (DRKS, number S000 21145). ■

Acknowledgments: We express our deep gratitude to all study teams supporting the LEOSS study. The LEOSS study group contributed at least 5 per mille to the analyses of this study: Tropical Clinic Paul-Lechler Hospital Tübingen (Claudia Raichle), Hospital Ingolstadt (Stefan Borgmann), Technical University of Munich (Christoph Spinner), Hospital Ernst von Bergmann (Lukas Tometten), Kreuzcher Diakonia Hunsrück (Wolfgang Rimili), University Hospital Essen (Sebastian Dölff), Johannes Wesling Hospital Minden (Kai Wille), Hospital Bremen-Center (Christiane Piepel), Hospital Passau (Julia Lanznaster), University Hospital Freiburg (Siegbert Rieg), University Hospital Jena (Maria Madeleine Rührich), University Hospital Ulm (Beate Grüner), University Hospital Würzburg (Nora Isberner), Maria Hilf Hospital (Hendrik Haake), Municipal Hospital Karlsruhe (Christian Degenhardt), University Hospital Tübingen (Silvio Nadalin), Elbland Hospital Riesa (Jörg Schubert), Sophien- and Hufeland Clinic Weimar (Jessica Rüddel), St. Josef-Hospital—Catholic Hospital Bochum (Kerstin Hellwig), Clinic Munich (Wolfgang Guggemos), Petrus Hospital Wuppertal (Sven Stieglitz), Robert-Bosch-Hospital Stuttgart (Katja Rothfuss), Hospital Dortmund (Martin Hower), Hospital St. Joseph-Stift Dresden (Lorenz Walter), University Hospital Augsburg (Christoph Römmele), University Hospital Erlangen (Richard Strauß), Braunschweig Hospital (Jan Kielstein), University Hospital Munich/LMU (Michael von Bergwelt-Baildon), University Hospital Dresden (Katja de With), University Hospital Düsseldorf (Björn Jensen), Agaplesion Diaconia Hospital Rotenburg (David Heigener), Hospital Leverkusen (Lukas Eberwein), University Hospital Saarland (Robert Bals), University Hospital Frankfurt (Maria Vehreschild), University Hospital Cologne (Norma Jung), Preetz Hospital (Helga Peetz), Hospital Fulda (Philipp

TABLE 1. Parameters of SARS-CoV-2 disease course in patients with neurodegenerative comorbidity and controls

Parameter disease course	PD patients vs. controls		Dementia patients vs. controls		PD patients vs. dementia patients	
Duration of inpatient stay	$P = 0.608$	OR: NA*	$P = 0.933$	OR: NA*	$P = 0.503$	OR: NA*
Duration of ICU	$P = 0.215$	OR: NA*	$P = 0.0003$ shorter stay in ICU for D patients	OR: NA*	$P = 0.899$	OR: NA*
Ventilation duration	$P = 0.256$	OR: NA*	$P = 0.0037$ shorter ventilation for D patients	OR: NA*	$P = 0.800$	OR: NA*
Covid death	$P = 0.605$	OR 0.8347 CI [0.4208; 1.6556]	$P = 0.084$ men, $P = 0.448$ women, $P = 0.00036$ higher lethality for women patients with dementia vs. women controls	OR 0.7626 CI [0.5603; 1.0378]	$P = 0.956$	OR 1.02 CI [0.5034; 2.0664]
Death	$P = 0.895$	OR 0.955 CI [0.4821; 1.8922]	$P = 0.057$ men, $P = 0.792$ women, $P = 0.0016$ higher lethality for women patients with dementia vs. women controls	OR 0.7510 CI [0.5587; 1.0094] Men: OR 1.0563 CI [0.7025; 1.5883] Women: OR 0.4964 CI [0.3199; 0.7702]	$P = 0.532$	OR 0.7995 CI [0.3958; 1.6149]
Dry cough	$P = 0.572$	OR 1.237 CI [0.5914; 2.5877]	$P = 0.00014$ D patients with fewer dry cough	OR 2.0252 CI [1.4029; 2.9235]	$P = 0.226$	OR 1.6159 CI [0.7386; 3.5354]
Dyspnoe	$P = 0.708$	OR 0.8794 CI [0.4484; 1.7249]	$P = 0.0085$ D patients with fewer dyspnoe	OR 1.5743 CI [1.1211; 2.2107]	$P = 0.100$	OR 1.8008 CI [0.8854; 3.6624]
Fever	$P = 0.194$	OR 1.6 CI [0.783; 3.2677]	$P = 0.247$	OR 1.2006 CI [0.881; 1.6361]	$P = 0.5439$	OR 0.7935 CI [0.3788; 1.6624]
Delirium	$P = 0.799$	OR 0.7647 CI [0.0962; 6.0767]	$P = 0.00056$ D patients with more frequent delirium	OR 0.3125 CI [0.1563; 0.6249]	$P = 0.223$	OR 0.3028 CI [0.0396; 2.3156]
Headache	$P = 0.423$	OR 2.2348 CI [0.2971; 16.8076]	$P = 0.00177$ D patients with fewer headaches	OR 12.3931 CI [1.6674; 92.1096]	$P = 0.117$	OR 6.8718 CI [0.4212; 112.1193]
Taste disorder	$P = 0.632$	OR 1.6339 CI [0.2149; 12.4198]	$P = 0.0342$ D patients with fewer taste disorders	OR 4.3146 CI [0.9895; 18.8137]	$P = 0.291$	OR 3.4231 CI [0.3032; 38.6459]

Adjusted for age and sex. Univariate statistical analyses were performed to determine the significance between the analyzed subgroups. Odds ratios with the corresponding confidence intervals were generated. Abbreviations: PD, Parkinson's disease patients; D, dementia; controls, SARS-CoV-2 patients without comorbidities, Parkinson's disease or dementia; ICU, intensive care unit; OR, odds ratio; CI, confidence interval; OR, NA*, due to the data structure, multiple ORs are generated for the respective categories. These ORs can be obtained on request.

Markart), Hospital Osbrück (Annika Ritter), Marien Hospital Herne and University Hospital Bochum (Beate Schultheis), Medical University Graz (Jürgen Prattes), University Hospital Heidelberg (Uta Merle). The LEOSS study infrastructure group: Jörg Janne Vehreschild (Goethe University Frankfurt), Lisa Pilgram (Goethe University Frankfurt), Carolin E.M. Jakob (University Hospital of Cologne), Melanie Stecher (University Hospital of Cologne), Max Schons (University Hospital of Cologne), Susana Nunes de Miranda (University Hospital of Cologne), Nick Schulze (University Hospital of Cologne), Sandra Fuhrmann (University Hospital of Cologne), Annika Claßen (University Hospital of Cologne), Bernd Franke (University Hospital of Cologne), Fabian Praßer (Charité, Universitätsmedizin Berlin), and Martin Lablans (University Medical Center Mannheim).

Meret K. Huber, MD,^{1†} Claudia Raichle, MD,^{2†}
Paul Lingor, MD,^{3,4}  Matthias Synofzik, MD,^{5,6} 
Stefan Borgmann, MD,⁷ Johanna Erber, MD,⁸
Lukas Tometten, MD,⁹ Wolfgang Rimili, MD,¹⁰
Sebastian Dölff, MD,¹¹ Kai Wille, MD,¹²
Samuel Knauss, MD,¹³ Christiane Piepel, MD,¹⁴
Julia Lanznaster, MD,¹⁵ Siegfert Rieg, MD,¹⁶
Fabian Prasser, PhD,¹⁷ Lisa Pilgram, MD,¹⁸
Annika Spottke, MD,^{19,20} Thomas Klockgether, MD,^{19,20}
Christine Klein, MD,²¹ Franziska Hopfner, MD,^{1†}  and
Günter U. Höglinger, MD,^{1,4†}  the LEOSS Study Group

¹Department of Neurology, Hannover Medical School, Hannover, Germany, ²Tropical Clinic Paul-Lechler Hospital, Tübingen, Germany, ³Department of Neurology, School of Medicine, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany, ⁴German Center for Neurodegenerative Diseases (DZNE), Munich, Germany, ⁵Department of Neurodegenerative Diseases, Centre for Neurology and Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany, ⁶German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany, ⁷Department of Infectious Diseases and Infection Control, Hospital of Ingolstadt, Ingolstadt, Germany, ⁸School of Medicine, University Hospital Rechts der Isar, Technical University of Munich, Munich, Germany, ⁹Department I for Internal Medicine, University Hospital of Cologne, University of Cologne, Cologne, Germany, ¹⁰Department of Internal Medicine, Stiftung Kreuznacher Diakonie, Rhaunen, Germany, ¹¹Department of Infectious Diseases, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, ¹²University Clinic for Hematology, Oncology, Hemostaseology and Palliative Care, Johannes Wesling Medical Center Minden, UKRUB, University of Bochum, Minden, Germany, ¹³Department of Neurology and Experimental Neurology, Charité—Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt Universität zu Berlin, Berlin Institute of Health, Berlin, Germany, ¹⁴Department of Hemato-Oncology and Infectious Diseases, Klinikum Bremen-Mitte, Bremen, Germany, ¹⁵Department of Internal

Medicine, Hospital Passau, Passau, Germany, ¹⁶Medical Center—University of Freiburg, Division of Infectious Diseases, Department of Medicine II, Faculty of Medicine, University of Freiburg, Freiburg, Germany, ¹⁷Charité—Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany, ¹⁸Department of Internal Medicine, Hematology and Oncology, Goethe University Frankfurt, Frankfurt am Main, Germany, ¹⁹German Center for Neurodegenerative Diseases, Bonn, Germany, ²⁰Department of Neurology, University of Bonn, Bonn, Germany, and ²¹Institute of Neurogenetics, University of Lübeck, Lübeck, Germany

References

1. Jakob CEM, Borgmann S, Duygu F, Behrends U, Hower M, Merle U, et al. First results of the “lean European open survey on SARS-CoV-2-infected patients (LEOSS)”. *Infection* 2021;49:63–73. <https://doi.org/10.1007/s15010-020-01499-0>.
2. Enders D, Balzer-Geldsetzer M, Riedel O, Dodel R, Wittchen HU, Sensken SC, et al. Prevalence, duration and severity of Parkinson’s disease in Germany: a combined meta-analysis from literature data and outpatient samples. *Eur Neurol* 2017;78(3–4):128–136. <https://doi.org/10.1159/000477165>.
3. Trenkwalder C, Schwarz J, Gebhard J, Ruland D, Trenkwalder P, Hense HW, et al. Starnberg trial on epidemiology of parkinsonism and hypertension in the elderly. Prevalence of Parkinson’s disease and related disorders assessed by a door-to-door survey of inhabitants older than 65 years. *Arch Neurol* 1995;52(10):1017–1022. <https://doi.org/10.1001/archneur.1995.00540340109020>.
4. Bickel H. Demenzsyndrom und Alzheimer Krankheit: Eine Schätzung des Krankenbestandes und der jährlichen Neuerkrankungen in Deutschland. *Das Gesundheitswesen* 2000;62(04):211–218. <https://doi.org/10.1055/s-2000-10858>.
5. Jessen, F. Handbuch Alzheimer-Krankheit: Grundlagen – Diagnostik – Therapie – Versorgung – Prävention, De Gruyter; 1. Edition, ISBN-10: 3110403455
6. Del Prete E, Francesconi A, Palermo G, Mazzucchi S, Frosini D, Morganti R, et al. Prevalence and impact of COVID-19 in Parkinson’s disease: evidence from a multi-center survey in Tuscany region. *J Neurol* 2020. <https://doi.org/10.1007/s00415-020-10002-6>.
7. Zhang Q, Schultz JL, Aldridge GM, Simmering JE, Narayanan NS. Coronavirus disease 2019 case fatality and Parkinson’s disease. *Mov Disord* 2020;35(11):1914–1915. <https://doi.org/10.1002/mds.28325>.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.

SGML and CITI Use Only

DO NOT PRINT

Author Roles

(1) Research project: A. Conception: F.H., M.K.H., P.L., M.S., C.R., A.S., T.G., C.K., G.U.H. B. Organization: F.H., M.K.H., P.L., M.S., A.S., T.G., C.K., G.U.H., C.R., L.P. C. Execution: M.K.H., C.R., P.L., M.S., S.B., J.E., L.T., W.R., S.D., K.W., S.K., C.P., J.L., S.R., F.P., L.P., A.S., T.K., C.K., F.H., G.U.H. (2) Statistical analysis: A. Design: F.H., M.K.H., P.L., M.S., A.S., T.G., C.K., G.U.H. B. Execution: F.H., M.K.H. C. Review and critique: F.H., M.K.H., P.L., M.S., S.K., A.S., T.G., C.K., G.U.H. (3) Manuscript preparation: A. Writing of the first draft: F.H., M.K.H., P.L., M.S., C.R., A.S., T.G., C.K., G.U.H. B. Review and critique: M.K.H., C.R., P.L., M.S., S.B., J.E., L.T., W.R., S.D., K.W., S.K., C.P., J.L., S.R., F.P., L.P., A.S., T.K., C.K., F.H., G.U.H.

Financial Disclosures

Meret K. Huber, Claudia Raichle, Matthis Synofzik, Stefan Borgmann, Johanna Erber, Lukas Tometten, Wolfgang Rimili, Sebastian Dolff, Kai Wille, Samuel Knauss, Christiane Piepe, Julia Lanznaster, Siegbert Rieg, Fabian Prasser, Annika Spottke, and Thomas Klockgether report no disclosure. Paul Lingor is supported by the NUM research network of the BMBF (B-FAST) and the Bavarian Staatsministerium für Wissenschaft und Kunst, and Lisa Pilgram is funded by the Willy Robert Pitzer Foundation. Christine Klein is supported by the B-FAST Program (BMBF). Franziska Hopfner receives grants from the German Research Council (DFG), EASI-Genomics Consortium (Horizon 2020), the Erwin-Röver-Foundation, and the Else Kröner-Fresenius Foundation. Günter U. Höglinger is supported by the German Federal Ministry of Education and Research (BMBF: 01KU1403A EpiPD), Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy—ID 390857198), DFG grants (HO2402/6-2, HO2402/18-1 MSAomics), the NOMIS foundation (FTLD project), the EU/EFPIA/Innovative Medicines Initiative, Joint Undertaking (IMPRIND grant number 116060) and by the Volkswagen Stiftung/Lower Saxony Ministry for Science/Petermax-Müller Foundation (Niedersächsisches Vorab - Etiology and Therapy of Synucleinopathies and Tauopathies). All authors are government employees.