Characteristics Associated with Poor COVID-19 Outcomes in Individuals with Systemic Lupus Erythematosus: Data from the COVID-19 Global Rheumatology Alliance

Authors:

Manuel F Ugarte-Gil MD, MSc
School of Medicine. Universidad Cientifica del Sur, Lima, Peru;
Rheumatology Department, Hospital Guillermo Almenara Irigoyen, EsSalud, Lima, Peru
ORCID ID: 0000-0003-1728-1999
Twitter: @mugartegil
Email: mugarte@cientifica.edu.pe

Graciela S. Alarcón MD, MPH
School of Medicine. University of Alabama at Birmingham. AL. USA
School of Medicine. Universidad Peruana Cayetano Heredia, Lima, Peru
ORCID ID: 0000-0001-5190-9175
Twitter:
Email: galarcon@uab.edu

Zara Izadi MPharm MAS
Department of Epidemiology and Biostatistics, University of California, San Francisco
Division of Rheumatology, Department of Medicine, University of California, San Francisco
ORCID ID: 0000-0002-1867-0905
Twitter: none
Email: zara.izadi@ucsf.edu

Alí Duarte-García MD MSc
Division of Rheumatology and Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, Minnesota
ORCID: 0000-0003-1749-5719
Twitter: @AliDuarteMD
Email: duarte.ali@mayo.edu

Cristina Reategui-Sokolova, MD
Rheumatology Department, Hospital Guillermo Almenara Irigoyen, EsSalud, Lima, Perú.
Unidad de Investigación Para La Generación y Síntesis de Evidencias en Salud, Universidad San Ignacio de Loyola, Lima, Perú.
ORCID ID: 0000-0003-3421-2717
Twitter:none
Email: cristina.reateguis@gmail.com

Ann E. Clarke,

Cumming School of Medicine. University of Calgary, Division of Rheumatology Department of Medicine, Calgary, Alberta, Canada
ORCID ID:0000-0002-3112-9646
Email: aeclarke@ucalgary.ca

Leanna Wise MD, MPH
Division of Rheumatology, Department of Internal Medicine, University of Southern California, Los Angeles, CA
ORCID ID: 0000-0002-6172-9474
Twitter: @LeannaWiseMD
Email; Leanna.wise@med.usc.edu

Guillermo Pons-Estel, MD, PHD
Centro Regional de Enfermedades Autoinmunes y Reumáticas (GO-CREAR), Rosario, Argentina;
Research Unit, Argentine Society of Rheumatology, Buenos Aires, Argentina.
ORCID ID: 0000-0002-0647-929X
Twitter: @gponsestel
Email: gponsestel@hotmail.com

Maria José Santos, MD, PhD
Rheumatology Research Unit, Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa, Rheumatology Department Hospital Garcia de Orta, Almada and Reuma.pt, Portugal
ORCID ID: 0000-0002-7946-1365
Twitter: None
Email: mjps1234@gmail.com

Sasha Bernatsky,
McGill University Health Centre, Divisions of Rheumatology and Clinical Epidemiology, Quebec, Canada
ORCID ID:
Twitter:
Email: sasha.bernatsky@mcgill.ca

Sandra Lucia Euzebio Ribeiro
Faculdade de Medicina, Federal University of Amazonas(UFAM), Amazonas, Brazil
ORCID ID: https://orcid.org/0000-0002-4777-8659
Twitter: none
Email: sandraler04@gmail.com

Samar Al Emadi MBBS FRCPC FACR
Rheumatology Department, Hamad Medical Corporation, Doha -Qatar
ORCID ID: 0000-0001-7942-4831
Twitter: @Dr_samaralemadi
Email: salemadi@hamad.qa

Jeffrey A Sparks MD MMSc

Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
ORCID ID: 0000-0002-5556-4618
Twitter: @jeffsparks
Email: jsparks@bwh.harvard.edu

Tiffany Y-T Hsu MD PhD
Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital and Harvard Medical School, Boston
ORCID ID: 0000-0003-1041-8040
Twitter: none
Email: tyhsu@bwh.harvard.edu

Naomi J Patel MD
Rheumatology Unit, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
ORCID ID: 0000-0002-6038-0346
Twitter: @NaomiRheumMD
Email: njpatel@mgh.harvard.edu

Emily L. Gilbert MD PhD
Division of Rheumatology, Mayo Clinic, Jacksonville, Florida
ORCID ID: none
Twitter: none
Email: gilbert.emily@mayo.edu

Maria O Valenzuela-Almada MD
Division of Rheumatology, Mayo Clinic, Rochester, Minnesota
ORCID ID: none
Twitter: none
Email: valenzuelaalmada.maria@mayo.edu

Andreas Jönsen
Lund University, Lund, Sweden
ORCID ID:
Twitter:
Email:andreas.jonsen@med.lu.se

Gianpiero Landolfi, PhD
Epidemiology Research Unit, Italian Society for Rheumatology, Milan, Italy.
ORCID ID:
Twitter:
Email: g.landolfi@reumatologia.it

Micaela Fredi, MD
Rheumatology and Clinical Immunology, ASST Spedali Civili and Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
ORCID ID: 0000-0002-6511-4936

Twitter: @micaela_fredi
Email: fredi.micaela@gmail.com

Tiphaine Goulenok
Internal Medicine Department, Bichat Claude Bernard Hospital, APHP, Paris, France
Université de Paris
ORCID ID: 0000-0003-3680-6682
Twitter: none
Email: tiphaine.goulenok@aphp.fr

Mathilde Devaux, MD
Internal Medicine Department, Poissy Saint-Germain-en-Laye Hospital, Poissy, France
ORCID ID: 0000-0002-4244-5417
Twitter: none
Email: mathilde.devaux@ght-yvelinesnord.fr

Xavier Mariette
Department of Rheumatology, Université Paris-Saclay, Assistance Publique - Hôpitaux de Paris, Le Kremlin Bicêtre, France
ORCID ID: 0000-0002-4244-5417
Twitter:
Email: xavier.mariette@aphp.fr

Viviane Queyrel
Department of Rheumatology, Pasteur 2 Hospital, University of Nice -Sophia-Antipolis, FRANCE,
ORCID ID: 0000-0002-9757-0274
Twitter: @MoranneQueyrel
Email: queyrel-moranne.v@chu-nice.fr

Vasco C. Romão
Rheumatology Department, Hospital Santa Maria, Centro Hospitalar Universitário Lisboa Norte and Rheumatology Research Unit, Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa
ORCID ID: 0000-0002-5603-9436
Twitter: @romaovc
Email: vascoromao@gmail.com

Graça Sequeira
Centro Hospitalar Universitário do Algarve, Unidade de Faro, Faro, Portugal
ORCID ID:
Twitter:
Email: mmunoz@chalgarve.min-saude.pt

Rebecca Hasseli
Department of Rheumatology and Clinical Immunology, Campus Kerckhoff, Justus Liebig University Giessen, Bad Nauheim, Germany.
ORCID ID: 0000-0002-2982-8253

Twitter: none
Email: R.Hasseli-Fraebel@kerckhoff-klinik.de

Bimba F. Hoyer
Department of Rheumatology and Clinical Immunology, Clinic for Internal Medicine I, University Hospital Schleswig-Holstein, Campus Kiel, Germany.
ORCID ID: 0000-0002-5252-1719
Twitter: @rheuma_doktorin
Email: bfhoyer@rheuma.uni-kiel.de

Reinhard E. Voll
Department of Rheumatology and Clinical Immunology, University Medical Center Freiburg, Faculty of Medicine, Albert-Ludwigs-University of Freiburg, Freiburg, Germany.
ORCID ID: 0000-0002-5542-9133
Twitter: none
Email: reinhard.voll@uniklinik-freiburg.de

Christof Specker
Department of Rheumatology & Clinical Immunology, Kliniken Essen-Mitte, Essen, Germany
ORCID ID: 0000-0003-2504-3229
Twitter: @ChSpecker
Email: specker@uni-duesseldorf.de

Roberto M. Baez
Hospital Francisco Lopez Lima, General Roca, Argentina
ORCID ID:
Twitter:
Email: robertobaez58@gmail.com

Vanessa V. Castro-Coello
Sanatorio Güemes, Argentina
ORCID ID: 0000-0002-1448-7732
Twitter: @vane_castro_c
Email: vanytavi@hotmail.com

Hernán Maldonado-Ficco
Hospital San Antonio de Padua, Río Cuarto. Argentina
ORCID ID:
Twitter:
Email: nanmaldonado@msn.com

Edgard Torres dos Reis-Neto
Hospital São Paulo, Universidade Federal de São Paulo (UNIFESP), Brazil
ORCID ID:
Twitter:

Email: edgardtr@hotmail.com

Gilda Aparecida Ferreira
Hospital das Clínicas, Universidade Federal de Minas Gerais (UFMG), Brazil
ORCID ID: 0000-0002-1352-7261
Twitter: NONE
Email: gildaferreira9@gmail.com

Odirlei André Monticielo, MD PhD
Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul (UFRGS), Brazil
ORCID ID: 0000-0003-0720-2097
Twitter: NONE
Email: omonticielo@gmail.com

Emily Sirotich BSc
Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada, and Canadian Arthritis Patient Alliance, Toronto, ON, Canada
ORCID ID: 0000-0002-7087-8543
Twitter: @emilysirotich
Email: sirotie@mcmaster.ca

Jean W Liew MD MS
Section of Rheumatology, Department of Medicine, Boston University School of Medicine, Boston, MA
ORCID ID: 0000-0002-8104-2450
Twitter: @rheum_cat
Email: jwliew@bu.edu

Jonathan S Hausmann MD
Program in Rheumatology, Boston Children's Hospital;
Division of Rheumatology and Clinical Immunology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA.
ORCID ID: 0000-0003-0786-8788
Twitter: @hausmannMD
Email: jonathan.hausmann@childrens.harvard.edu

Paul Sufka MD
Healthpartners, St. Paul, MN, USA
ORCID ID: 0000-0003-3131-7919
Twitter: @psufka
Email: psufka@gmail.com

Rebecca Grainger MBChB BMedSci PhD
Department of Medicine, University of Otago Wellington, New Zealand
ORCID ID: 0000-0001-9201-8678
Twitter: @Drbeckyg
Email: rebecca.grainger@otago.ac.nz

Suleman Bhana MD FACR
Pfizer, Inc, New York, NY, USA
ORCID ID: 0000-0003-3805-0946
Twitter: @Drbhana
Email: suleman.bhana@gmail.com

Wendy Costello
Irish Children's Arthritis Network (iCAN)
Twitter: @wendycostello2
ORCID ID: none
Email: icanireland@gmail.com

Zachary Wallace MD MSc
Clinical Epidemiology Program, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School
ORCID ID: 0000-0003-4708-7038
Twitter: @zach_wallace_md Chara
Email: zswallace@mgh.harvard.edu

Lindsay Jacobsohn BA
Division of Rheumatology, Department of Medicine, University of California, San Francisco
ORCID ID: none
Twitter: none
Email: lindsay.jacobsohn@ucsf.edu

Tiffany Taylor MPH
Division of Rheumatology, Department of Medicine, University of California, San Francisco
ORCID ID: none
Twitter: none
Email: Tiffany.Taylor@ucsf.edu

Clairissa Ja
Division of Rheumatology, Department of Medicine, University of California, San Francisco
ORCID ID: 0000-0002-7101-1474
Twitter: none
Email: cja@ucdavis.edu

Anja Strangfeld MD PhD
German Rheumatism Research Center (DRFZ Berlin), Epidemiology and Health Services
Research, Berlin, Germany
ORCID ID: 0000-0002-6233-022X
Twitter: none

Email: strangfeld@drfz.de

Elsa F Mateus PhD
Portuguese League Against Rheumatic Diseases (LPCDR), Lisbon, Portugal;
European League Against Rheumatism (EULAR) Standing Committee of People with Arthritis/Rheumatism in Europe (PARE), Kilchberg, Switzerland
ORCID ID: 0000-0003-0059-2141
Twitter: none
Email: elsafrazaomateus@gmail.com

Kimme L Hyrich MD PhD
Centre for Epidemiology Versus Arthritis, The University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom;
National Institute of Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom
ORCID ID: 0000-0001-8242-9262
Twitter: @khyrich
Email: kimme.hyrich@manchester.ac.uk

Loreto Carmona MD PhD
Instituto de Salud Musculoesquelética, Madrid, Spain
ORCID ID: 0000-0002-4401-2551
Twiter: @carmona_loreto
Email: loreto.carmona@inmusc.eu

Saskia Lawson-Tovey BA
Centre for Genetics and Genomics Versus Arthritis, Centre for Musculoskeletal Research, University of Manchester, Manchester, United Kingdom;
National Institute of Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom
ORCID ID: 0000-0002-8611-162X
Twitter: @saskiaamber
Email: saskia.lawson-tovey@manchester.ac.uk

Lianne Kearsley-Fleet PhD
Centre for Epidemiology Versus Arthritis, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
ORCID ID: 0000-0003-0377-1575
Twitter: @KearsleyFleet
Email: lianne.kearsley-fleet@manchester.ac.uk

Martin Schaefer
German Rheumatism Research Center (DRFZ Berlin), Epidemiology and Health Care Research, Berlin, Germany
ORCID ID: 0000-0001-6487-3634
Twitter: none

Email: martin.schaefer@drfz.de

Pedro M Machado MD PhD
Centre for Rheumatology & Department of Neuromuscular Diseases, University College London, London, UK;
National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre, University College London Hospitals NHS Foundation Trust, London, UK;
Department of Rheumatology, Northwick Park Hospital, London North West University Healthcare NHS Trust, London, UK
ORCID ID: 0000-0002-8411-7972
Twitter: @pedrommcmachado
Email: p.machado@ucl.ac.uk

Philip C. Robinson MBChB PhD
University of Queensland School of Clinical Medicine, Herston, Queensland;
Department of Rheumatology, Royal Brisbane and Women's Hospital, Metro North Hospital and Health Service, Queensland, Australia.
ORCID ID: 0000-0002-3156-3418
Twitter: @philipcrobinson
Email: philip.robinson@uq.edu.au

Milena Gianfrancesco MPH PhD
Division of Rheumatology, Department of Medicine, University of California, San Francisco
ORCID ID: 0000-0002-8351-4626
Twitter @MilenaGianfran
Email: Milena.Gianfrancesco@ucsf.edu

Jinoos Yazdany MD MPH
Division of Rheumatology, Department of Medicine, University of California, San Francisco
ORCID ID: 0000-0002-3508-4094
Twitter: @JYazdanyMD
Email: Jinoos.yazdany@ucsf.edu

Collaborators:

Name	Institution/Affiliation	Country/Region
Brahim Dahou	Association Rhumatologues Algériens Privés (ARAP)	Algeria
Rosana Quintana	Argentine Society of Rheumatology	Argentina
Gimena Gómez	Argentine Society of Rheumatology	Argentina
Karen Roberts	Argentine Society of Rheumatology	Argentina
Vanessa Castro Coello	Argentine Society of Rheumatology	Argentina
María J. Haye Salinas	Argentine Society of Rheumatology	Argentina
Federico Nicolas Maldonado	Argentine Society of Rheumatology	Argentina

Alvaro Andres Reyes Torres	Argentine Society of Rheumatology	Argentina
Gelsomina Alle	Argentine Society of Rheumatology	Argentina
Romina Tanten	Argentine Society of Rheumatology	Argentina
Hernán Maldonado Ficco	Argentine Society of Rheumatology	Argentina
Romina Nieto	Argentine Society of Rheumatology	Argentina
Carla Gobbi	Argentine Society of Rheumatology	Argentina
Yohana Tissera	Argentine Society of Rheumatology	Argentina
Cecilia Pisoni	Argentine Society of Rheumatology	Argentina
Alba Paula	Argentine Society of Rheumatology	Argentina
Juan Alejandro Albiero	Argentine Society of Rheumatology	Argentina
Maria Marcela Schmid	Argentine Society of Rheumatology	Argentina
Micaela Cosatti	Argentine Society of Rheumatology	Argentina
Maria Julieta Gamba	Argentine Society of Rheumatology	Argentina
Carlevaris Leandro	Argentine Society of Rheumatology	Argentina
María Alejandra Cusa	Argentine Society of Rheumatology	Argentina
Noelia German	Argentine Society of Rheumatology	Argentina
Veronica Bellomio	Argentine Society of Rheumatology	Argentina
Lorena Takashima	Argentine Society of Rheumatology	Argentina
Mariana Pera	Argentine Society of Rheumatology	Argentina
Karina Cogo	Argentine Society of Rheumatology	Argentina
Maria Soledad Gálvez Elkin	Argentine Society of Rheumatology	Argentina
María Alejandra Medina	Argentine Society of Rheumatology	Argentina
Veronica Savio	Argentine Society of Rheumatology	Argentina
Ivana Romina Rojas Tessel	Argentine Society of Rheumatology	Argentina
Rodolfo Perez Alamino	Argentine Society of Rheumatology	Argentina
Marina Laura Werner	Argentine Society of Rheumatology	Argentina
Sofía Ornella	Argentine Society of Rheumatology	Argentina
Luciana Casalla	Argentine Society of Rheumatology	Argentina
Maria de la Vega	Argentine Society of Rheumatology	Argentina
María Severina	Argentine Society of Rheumatology	Argentina
Mercedes García	Argentine Society of Rheumatology	Argentina
Luciana Gonzalez Lucero	Argentine Society of Rheumatology	Argentina
Cecilia Romeo	Argentine Society of Rheumatology	Argentina
Sebastián Moyano	Argentine Society of Rheumatology	Argentina
Tatiana Barbich	Argentine Society of Rheumatology	Argentina
Ana Bertoli	Argentine Society of Rheumatology	Argentina
Andrea Baños	Argentine Society of Rheumatology	Argentina
Sandra Petruzzelli	Argentine Society of Rheumatology	Argentina
Carla Matellan	Argentine Society of Rheumatology	Argentina
Silvana Conti	Argentine Society of Rheumatology	Argentina
Ma. Alicia Lazaro	Argentine Society of Rheumatology	Argentina

Gustavo Fabián Rodriguez Gil	Argentine Society of Rheumatology	Argentina
Fabian Risueño	Argentine Society of Rheumatology	Argentina
Maria Isabel Quaglia	Argentine Society of Rheumatology	Argentina
Julia Scafati	Argentine Society of Rheumatology	Argentina
Natalia Lili Cuchiaro	Argentine Society of Rheumatology	Argentina
Jonathan Eliseo Rebak	Argentine Society of Rheumatology	Argentina
Susana Isabel Pineda	Argentine Society of Rheumatology	Argentina
María Elena Calvo	Argentine Society of Rheumatology	Argentina
Eugenia Picco	Argentine Society of Rheumatology	Argentina
Josefina Gallino Yanzi	Argentine Society of Rheumatology	Argentina
Pablo Maid	Argentine Society of Rheumatology	Argentina
Debora Guaglianone	Argentine Society of Rheumatology	Argentina
Julieta Silvana Morbiducci	Argentine Society of Rheumatology	Argentina
Sabrina Porta	Argentine Society of Rheumatology	Argentina
Natalia Herscovich	Argentine Society of Rheumatology	Argentina
José Luis Velasco Zamora	Argentine Society of Rheumatology	Argentina
Boris Kisluk	Argentine Society of Rheumatology	Argentina
Maria Sol Castaños Menescardi	Argentine Society of Rheumatology	Argentina
Rosana Gallo	Argentine Society of Rheumatology	Argentina
María Victoria Martire	Argentine Society of Rheumatology	Argentina
Carla Maldini	Argentine Society of Rheumatology	Argentina
Cecilia Goizueta	Argentine Society of Rheumatology	Argentina
sabrina solange de la vega fernandez	Argentine Society of Rheumatology	Argentina
Carolina Aeschlimann	Argentine Society of Rheumatology	Argentina
Gisela Subils	Argentine Society of Rheumatology	Argentina
Eva Rath	Hanusch Krankenhaus, Vienna	Austria
Yves Piette	AZ Sint-Jan Brugge	Belgium
Mieke Devinck	AZ Sint-Lucas Brugge	Belgium
Bea Maeyaert	AZ Sint-Lucas Brugge	Belgium
Francinne Machado Ribeiro	Hospital Universitário Pedro Ernesto Universidade do Estado do Rio de Janeiro	Brazil
Sandra Lucia Euzebio Ribeiro	Federal University of Amazonas	Brazil
Marcelo Pinheiro	Universidade Federal De São Paulo Escola Paulista de Medicina e Escola Paulista de Enfermagem	Brazil
Sebastián Ibáñez	Clínica Alemana de Santiago	Chile
Anne-Marie Chassin-Trubert	Complejo Hospitalario San José	Chile
Lingli Dong	Tongji Hospital	China

Lui Cajas	Clinica Universitaria Colombia - Centro Medico Providencia Sanitas	Colombia
Marko Barešić	University Hospital Center Zagreb	Croatia
Branimir Anić	Div Clin Immunol Rheumatol; Dept Int Med, School of Med Zagreb, University Hospital Center Zagreb	Croatia
Melanie-Ivana Čulo	University Hospital Dubrava, Zagreb	Croatia
Tea Ahel Pavelić	Clinical Hospital Center Rijeka	Croatia
Kristina Kovačević Stranski	University hospital Osijek	Croatia
Boris Karanovic	UHC Zagreb	Croatia
Jiri Vencovsky	Institute of Rheumatology, Prague	Czechia
Marta Píchová	Medipont plus s.ro. , České Budějovice	Czechia
Maria Filkova	Institute of Rheumatology, Prague	Czechia
Hesham Hamoud	Al Azhar University Hospitals	Egypt
Dimitrios Vassilopoulos	Hippokration General Hospital, Athens	Greece
Gabriela Maria Guzman Melgar	Hospital del Valle, Honduras	Honduras
Ho So	Chinese University of Hong Kong	Hong Kong
Márta Király	Petz Aladár University Teaching Hospital, Győr	Hungary
Mahdi Vojdanian	Iran Rheumatology Center	Iran
Alexandra Balbir-Gurman	Rambam Rheumatology Institute, Haifa	Israel
Fatemah Abutiban	Kuwait Rheumatology Association	Kuwait
Julija Zepa	Pauls Stradins Clinical University Hospital, Riga	Latvia
Inita Bulina	Pauls Stradins Clinical University hospital, Riga	Latvia
Loreta Bukauskiene	Klaipeda university hospital	Lithuania
Beatriz Zaueta	Centro Medico del Angel	Mexico
Angel Alejandro Castillo Ortiz	Centro Medico Las Americas	Mexico
Erick Zamora Tehozol	Centro Medico Pensiones	Mexico
David Vega	Hospital General de Zona #17	Mexico
Diana Cervántes Rosete	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán	Mexico
Eduardo Martín Nares	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán	Mexico
Tatiana Sofia Rodriguez-Reyna	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán	Mexico
Marina Rull Gabayet	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán	Mexico
Deshiré Alpízar-Rodríguez	Mexican College of Rheumatology	Mexico
Fedra Irazoque	Private Practice	Mexico
Xochitl Jimenez	Centro Medico Naval	Mexico

Lenny Geurts-van Bon	Ziekenhuisgroep Twente	Netherlands
Theo Zijlstra	Isala Hospital, Zwolle	Netherlands
Monique Hoekstra	Isala Hospital, Zwolle	Netherlands
Nasra Al-Adhoubi	Royal Hospital	Oman
Babur Salim	Fauji Foundation Hospital	Pakistan
Enrique Giraldo	Complejo Hospitalario	Panama
Ariel Salinas	Hospital Essalud Alberto Sabogal Sologuren	Peru
Manuel Ugarte-Gil	Universidad Científica del Sur-Hospital Guillermo Almenara Irigoyen	Peru
Jarosław Nowakowski	University Hospital, Krakow	Poland
Samar Al-Emadi	Hamad Medical Corporation	Qatar
Richard Conway	St James' Hospital, Dublin	Republic of Ireland
Rachael Flood	Tallaght University Hospital	Republic of Ireland
Geraldine McCarthy	Mater Misericordiae University Hospital	Republic of Ireland
Ioana Felea	County Emergency Hospital, Cluj Napoca	Romania
Ileana Filipescu	County Emergency Hospital, Cluj Napoca	Romania
Simona Rednic	County Emergency Hospital, Cluj Napoca	Romania
Laura Groseanu	Sf Maria Clinical Hospital, Bucharest	Romania
Maria Magdelena Tamas	County Emergency Hospital, Cluj Napoca	Romania
Vanda Mlynarikova	National Institute of Rheumatic Diseases, Piešťany	Slovak Republic
Martina Skamlova	FNSPFDR, Banská Bystrica	Slovak Republic
Martin Zlnay	National Institute of Rheumatic Diseases, Piešťany	Slovak Republic
Dagmar Mičeková	National Institute of Rheumatic Diseases, Piešťany	Slovak Republic
Lubica Capova	University Hospital, Bratislava	Slovak Republic
Zelmira Macejova	University Hospital, Košice	Slovak Republic
Emőke Šteňová	University Hospital Bratislava	Slovak Republic
Helena Raffayova	National Institute of Rheumatic Diseases, Piešťany	Slovak Republic
Gabriela Belakova	Medman s.r.o., Martin	Slovak Republic
Eva Strakova	Faculty hospital Prešov	Slovak Republic
Marieta Senčarová	Louis Pasteur University Hospital, Košice	Slovak Republic
Soňa Žlnayová	Poliklinika MarMedico, s.r.o., Nové Mesto nad Váhom	Slovak Republic
Anna Sabová	súkromná reumatologická ambulancia, Vranov nad Topľou	Slovak Republic
Daniela Spisakova	University Hospital od L. Pasteur Kosice	Slovak Republic
Mária Oetterová	Safarik University hospital, Kosice	Slovak Republic

Olga Lukacova	National Institute of Rheumatic Diseases, Piešťany	Slovak Republic
Martina Bakosova	UNB Nemocnica Stare Mesto, Bratislava	Slovak Republic
Alojzija Hocevar	UMC Ljubljana	Slovenia
Natalia de la Torre-Rubio	Hospital Universitario Puerta de Hierro Majadahonda	Spain
Juan José Alegre Sancho	Hospital Universitari Dr Peset, Valencia	Spain
Montserrat Corteguera Coro	Complejo Asistencial Avila	Spain
Juan Carlos Cobeta Garcia	Hospital Ernest Lluch, Calatayud	Spain
Maria Carmen Torres Martin	Hospital Nuestra Senora Sonsoles, Avila	Spain
Jose Campos	Hospital Universitario Puerta de Hierro	Spain
Jose A Gomez Puerta	Hospital Clinic Barcelona	Spain
Gozd Kubra Yardımcı	Hacettepe University Faculty of Medicine, Ankara	Turkey
Servet Akar	Izmir Katip Celebi University Atatürk Training and Research Hospital, Izmir	Turkey
Ozan Cemal Icacan	Bakırköy Dr. Sadi Konuk Research And Training Hospital, Istanbul	Turkey
Selda ÇELİK	BAKIRKOY DR SADI KONUK EDUCATIONAL AND RESEARCH HOSPITAL, RHEUMATOLOGY DEPARTMENT, Istanbul	Turkey
Viktoriia Vasylets	Multifield Medical Centre, Odessa	Ukraine
Su-Ann Yeoh	University College London Hospital, London	United Kingdom
Claire Vandevelde	Leeds Teaching Hospitals NHS Trust	United Kingdom
Sasha Dunt	Countess of Chester NHS Foundation Trust	United Kingdom
Jane Leeder	Norfolk & Norwich University Hospital	United Kingdom
Elizabeth Macphie	Lancashire and South Cumbria NHS Foundation Trust	United Kingdom
Rosaria Salerno	King's College Hospital	United Kingdom
Christine Graver	Hampshire Hospitals NHS Trust	United Kingdom
Katie Williams	York District Hospital	United Kingdom
Sheila O'Reilly	Royal Derby Hospital	United Kingdom
Kirsty Devine	York/Scarborough Hospitals	United Kingdom
Jennifer Tyler	Royal United Hospital, Bath	United Kingdom
Elizabeth Warner	Lister Hospital	United Kingdom
James Pilcher	University Hospital Lewisham	United Kingdom
Samir Patel	Queen Elizabeth hospital Woolwich	United Kingdom
Elena Nikiphorou	King's College Hospital	United Kingdom
Laura Chadwick	St Helens & Knowsley NHS Foundation Trust	United Kingdom
Caroline Mulvaney Jones	Llandudno Hospital	United Kingdom
Beverley Harrison	Salford Royal NHS FT	United Kingdom
Lucy Thornton	Bradford Royal Infirmary	United Kingdom

Diana O'Kane	RNHRD at Royal United Hospital Bath	United Kingdom
Lucia Fusi	King's College Hospital	United Kingdom
Audrey Low	Salford Royal NHS FT	United Kingdom
Sarah Horton	Minerva Health Centre	United Kingdom
Shraddha Jatwani	Albert Einstein Medical Center, PA	United States of America
Sara Baig	Arthritis and Rheumatology Consultants, PA	United States of America
Hammad Bajwa	Arthritis and Rheumatology Consultants, PA	United States of America
Vernon Berglund	Arthritis and Rheumatology Consultants, PA	United States of America
Angela Dahle	Arthritis and Rheumatology Consultants, PA	United States of America
Walter Dorman	Arthritis and Rheumatology Consultants, PA	United States of America
Jody Hargrove	Arthritis and Rheumatology Consultants, PA	United States of America
Maren Hilton	Arthritis and Rheumatology Consultants, PA	United States of America
Nicholas Lebedoff	Arthritis and Rheumatology Consultants, PA	United States of America
Susan Leonard	Arthritis and Rheumatology Consultants, PA	United States of America
Jennifer Morgan	Arthritis and Rheumatology Consultants, PA	United States of America
Emily Pfeifer	Arthritis and Rheumatology Consultants, PA	United States of America
Archibald Skemp	Arthritis and Rheumatology Consultants, PA	United States of America
Jeffrey Wilson	Arthritis and Rheumatology Consultants, PA	United States of America
Anne Wolff	Arthritis and Rheumatology Consultants, PA	United States of America
Eduardo Cepeda	Austin Diagnostic Clinic	United States of America
Kristin D'Silva	Brigham and Women's Hospital	United States of America
Tiffany Hsu	Brigham and Women's Hospital	United States of America
Naomi Serling-Boyd	Brigham and Women's Hospital	United States of America
Jeffrey Sparks	Brigham and Women's Hospital	United States of America

Derrick Todd	Brigham and Women's Hospital	United States of America
Zachary Wallace	Brigham and Women's Hospital	United States of America
Denise Hare	Capital Health Rheumatology	United States of America
Cassandra Calabrese	Cleveland Clinic	United States of America
Christopher Adams	East Alabama Medical Center	United States of America
Arezou Khosroshahi	Emory University	United States of America
Adam Kilian	George Washington University	United States of America
Douglas White	Gundersen Health System	United States of America
Melanie Winter	Gundersen Health System	United States of America
Theodore Fields	Hospital for Special Surgery	United States of America
Caroline Siegel	Hospital for Special Surgery	United States of America
Nicole Daver	Institute of Rheumatic and Autoimmune Diseases	United States of America
Melissa Harvey	Institute of Rheumatic and Autoimmune Diseases	United States of America
Neil Kramer	Institute of Rheumatic and Autoimmune Diseases	United States of America
Concetta Lamore	Institute of Rheumatic and Autoimmune Diseases	United States of America
Suneya Hogarty	Integrative Arthritis and Pain Consultants	United States of America
Karen Yeter	Kaiser Permanente	United States of America
Leanna Wise	Los Angeles County + USC Medical Center	United States of America
Faizah Siddique	Loyola University Medical Center	United States of America
Byung Ban	Medstar Georgetown University Hospital	United States of America
Tamar Tanner	Montefiore Medical Center	United States of America
Eric Ruderman	Northwestern Memorial	United States of America

William Davis	Ochsner Medical Center Rheumatology Department	United States of America
Robert Quinet	Ochsner Medical Center Rheumatology Department	United States of America
Evangeline Scopelitis	Ochsner Medical Center Rheumatology Department	United States of America
Karen Toribio Toribio	Ochsner Medical Center Rheumatology Department	United States of America
Tameka Webb-Detiege	Ochsner Medical Center Rheumatology Department	United States of America
Jerald Zakem	Ochsner Medical Center Rheumatology Department	United States of America
Khurram Abbass	Private Practice	United States of America
Gilbert Kepecs	Private Practice	United States of America
Lilliam Miranda	Rheumatology Center INC	United States of America
Michael Guma	Riverside Medical Group	United States of America
Ammar Haikal	Riverside Medical Group	United States of America
Sushama Mody	Riverside Medical Group	United States of America
Daric Mueller	Shores Rheumatology PC	United States of America
Arundathi Jayatilleke	Temple University Hospital	United States of America
JoAnn Zell	University of Colorado	United States of America
Alison Bays	University of Washington, Seattle	United States of America
Kathryn Dao	UT Southwestern Medical Center	United States of America
Ezzati Fatemeh	UT Southwestern Medical Center	United States of America
Deborah Parks	Washington University Div of Rheumatology	United States of America
David Karp	UT Southwestern Medical Center	United States of America
Guillermo Quiceno	UT Southwestern Medical Center	United States of America

Characteristics Associated with Poor COVID-19 Outcomes in Individuals with Systemic Lupus Erythematosus: Data from the COVID-19 Global Rheumatology Alliance

Aim: To determine characteristics associated with more severe outcomes in a global registry of people with systemic lupus erythematosus (SLE) and COVID-19.

Methods: People with SLE and COVID-19 reported in the COVID-19 Global Rheumatology Alliance registry from March 2020 to June 2021 were included. The ordinal outcome was defined as: 1) not hospitalized, 2) hospitalized with no oxygenation, 3) hospitalized with any ventilation or oxygenation, and 4) death. A multivariable ordinal logistic regression model was constructed to assess the relationship between COVID-19 severity and demographic characteristics, comorbidities, medications, and disease activity.

Results: A total of 1606 people with SLE were included. In the multivariable model, older age (OR 1.03 95% CI 1.02-1.04), male sex (1.50, 1.01-2.23), prednisone dose (1-5 mg/d 1.86, 1.20-2.66, 6-9 mg/d 2.47, 1.24-4.86, and ≥10 mg/d 1.95, 1.27-2.99), no current treatment (1.80, 1.17-2.75), comorbidities (e.g. kidney disease 3.51, 2.42-5.09, cardiovascular disease/hypertension 1.69, 1.25-2.29), and moderate or high SLE disease activity (vs. remission; 1.61, 1.02-2.54 and 3.94, 2.11-7.34, respectively) were associated with more severe outcomes. In age and sex-adjusted models, mycophenolate, rituximab and cyclophosphamide were associated with worse outcomes compared to hydroxychloroquine; outcomes were more favorable with methotrexate and belimumab.

Conclusions: More severe COVID-19 outcomes in individuals with SLE are largely driven by demographic factors, comorbidities, and untreated or active SLE. Patients using glucocorticoids also experienced more severe outcomes.

What is already known about this subject?

Demographic factors as well as comorbidities have been associated with poorer COVID-19 outcomes in the general population.

The COVID-19 Global Rheumatology Alliance has reported glucocorticoid dose (≥10 mg/d), some immunosuppressive drugs and disease activity as predictors of poorer COVID-19 outcomes in individuals with different rheumatic diseases.

What does this study add?

More severe COVID-19 outcomes in individuals with SLE are mainly driven by demographic factors, comorbidities, and untreated or active SLE.

Individuals using glucocorticoids (even low dose) experienced more severe outcomes.

How might this impact on clinical practice or future developments?

Individuals with lupus and these characteristics should be prioritized for close monitoring, counseled to receive vaccination, and receive preventive therapies if infected with SARS-Cov2.

Introduction

During the COVID-19 pandemic, individuals with systemic lupus erythematosus (SLE) have been of particular concern. SLE disproportionately impacts populations most severely affected by COVID-19, including those from non-white racial and ethnic groups, and those with low socioeconomic status (1). Moreover, individuals with SLE are often heavily immunosuppressed and have a high comorbidity burden with multiple risk factors for more severe COVID-19. Although previous analyses have evaluated outcomes of infection with SARS-Cov-2 in rheumatic diseases as a group, data on individuals with SLE are limited, and it remains unclear which risk factors are associated with worse COVID-19 outcomes in this population.

Data from the COVID-19 Global Rheumatology Alliance (C19-GRA) registry, a large physician reported registry of individuals with rheumatic diseases and COVID-19, suggest that those with moderate or high disease activity, as well as those receiving specific medications, including moderate or high doses of prednisone, rituximab, immunosuppressive drugs (i.e., mycophenolate mofetil/mycophenolic acid (MMF), tacrolimus, azathioprine, and cyclophosphamide) compared to a reference group of individuals receiving methotrexate have poorer outcomes (2). Furthermore, in an analysis of patients in the C19-GRA registry with rheumatoid arthritis (RA), treatment with rituximab or Janus Kinase (JAK) inhibitors was associated with poorer outcomes compared to treatment with tumor necrosis factor inhibitors (3). However, medications associated with more severe COVID-19 outcomes in SLE have not been extensively examined.

OpenSAFELY, a large analysis of primary care records of more than 17 million adults linked to 10,926 COVID-19-related deaths, reported that after adjustment for a wide variety of factors such as demographic characteristics and comorbidities, those with autoimmune disease (SLE, RA, or psoriasis as a group) had a higher risk of mortality, but this study did not adjust for medication use, nor did it evaluate SLE as a discrete or separate disease (4). Several case series or single center/country studies suggest that some individuals with SLE can have a severe disease course, but the small size of these studies has precluded a comprehensive analysis of risk factors for poor COVID-19 outcomes (5-10).

We used the C19-GRA registry to identify sociodemographic and clinical factors associated with more severe COVID-19 outcomes in individuals with SLE.

Methods

Data Source

Subjetcs with rheumatic disease and COVID-19 from the C19-GRA registry and European Alliance of Associations for Rheumatology (EULAR) COVID-19 registry were included in the analyses, which covered the period from 12 March 2020 to 01 June 2021. Data entry portals include one limited to European countries (eular.org/eular_covid19_database.cfm; hosted by The University of Manchester, UK) and a second for all other countries (rheum-covid.org/provider-global/; hosted by the University of California, San Francisco (UCSF), California, USA) (11, 12). Cases are entered into these registries by their treating clinicians. This study includes all individuals from these registries with SLE diagnosed with COVID-19 by 01 June 2021. Prior studies using C19-GRA and EULAR databases have included some individuals also reported in this study (2, 13, 14), but the number of individuals in this analysis is significantly higher than reported in previous publications.

Data quality was assessed by the data coordinating centers at UCSF and the University of Manchester and included procedures to identify and remove any duplicate cases.

COVID-19 outcomes

We used an ordinal severity outcome in the analyses, with mutually exclusive categories including: 1) not hospitalized, 2) hospitalized with no oxygenation, 3) hospitalized with any ventilation or oxygenation, or 4) death. These outcomes were chosen so that the analyses could reflect the full spectrum of disease associated with COVID-19 and are analogous to outcome measures used in many trials evaluating COVID-19 therapeutics. Only the highest severity level of the outcome occurring during the patient's disease course was included, and all individuals were required to have a resolved clinical course.

Covariates, including medication exposure

Covariates included demographic characteristics, including age, sex, and region (Europe, U.S. & Canada, Latin America, and other), as well as clinical characteristics, including number of comorbidities (including lung, liver or neurological diseases, cancer, diabetes, obesity, among others), specific comorbidities (chronic renal insufficiency or end stage renal disease and hypertension or cardiovascular disease), disease activity (assessed by a physician global assessment categorized as remission, low, moderate or high), dose of glucocorticoids (GCs; entered as daily oral prednisone equivalents), and use of immunosuppressive or immunomodulating medications. Additionally, the date of the case report was analyzed in three time periods: 24 March 2020 to 15 June 2020, 16 June 2020 to 30 September 2020, and 1 October 2020 to 01 June 2021. The first period ended at the release of the RECOVERY study, which changed COVID-19 treatment protocols to incorporate glucocorticoids (15). The second cut-off was based on the beginning of the second wave in many countries around the world.

Medications taken by patients prior to COVID-19 were categorized as: conventional synthetic drugs [antimalarials (hydroxychloroquine, chloroquine), conventional disease-modifying monotherapies generally considered to represent less intensive immunosuppression (sulfasalazine, methotrexate, and leflunomide), conventional

disease-modifying monotherapies with more intense immunosuppressive drugs (MMF, tacrolimus, cyclophosphamide, cyclosporine, azathioprine)]; biologics [abatacept, belimumab, rituximab, IL-6 inhibitors, IL-12/IL-23 inhibitors, IL-17 inhibitors, tumor necrosis factor inhibitors (anti-TNF)] and targeted synthetic drugs, specifically JAK inhibitors, and glucocorticoids. In analyses, we divided medications into five groups: no SLE medications, antimalarial only, conventional disease-modifying monotherapies generally considered to represent less intensive immunosuppression (sulfasalazine, methotrexate, and leflunomide), conventional disease-modifying monotherapies with more intense immunosuppressive drugs (MMF, tacrolimus, cyclophosphamide, cyclosporine, azathioprine), biologic/targeted synthetic drug monotherapy, and finally combination therapy with conventional and biologic disease-modifying immunosuppressive drugs. Glucocorticoids were categorized into four groups by dose: prednisone dose=0mg/d, between 1-5 mg/d, between 6-9 mg/d and >=10mg/d.

Statistical analyses

We used proportional odds logistic regression with severity as dependent variable, and covariates as described below. This is similar to using binary logistic regression for each of the three possible dichotomizations of the four-category dependent variable, with the assumption that the odds ratio is the same for each cut off. The parallel lines test for proportional odds ordinal logistic regression confirmed that this assumption was not violated.

Models included demographic variables and clinical characteristics as well as the time period in the pandemic during which the case was reported. Random effects were included for country and time. These variables were applied to capture the significant variability in regulations enforcing personal protective equipment, hospital resource allocation, and quarantine procedures between countries and over the course of the pandemic.

We assumed that missing data were “missing at random” and missing data were handled using multiple imputation, with 50 imputed data sets.

In all models, we included sex, age, region, glucocorticoids as a categorical variable (0, 1-5, 6-9, >= 10 mg/day), immunosuppressive medication category, time period, and random effects of country and time. To assess the additional impact of comorbidities, we constructed an additional model that included the number of comorbidities and, separately, that included key comorbidities in SLE, including renal disease and hypertension/cardiovascular disease. Finally, we constructed a model that included the above variables but additionally included SLE disease activity.

We conducted several additional analyses to examine associations of six medications of interest in SLE with COVID-19 outcomes: methotrexate (N=173), azathioprine (N=235), MMF (N=332), cyclophosphamide (N=29), rituximab (N=68), and belimumab (N=104). In these analyses, the drug of interest was excluded from the medication category of monotherapies with immunosuppressive drugs or from the biologics/targeted synthetic only category, and their effects were estimated separately. Four models were constructed for each medication: 1) unadjusted, 2) age and sex-adjusted, 3) adjusted for age, sex, renal disease, hypertension/cardiovascular disease, comorbidity count, disease activity, region, time period, and 4) confirmed cases (diagnosis made by PCR, antibody or antigen) adjusted for age, sex, renal disease, hypertension/cardiovascular

disease, comorbidity count, disease activity, region and time period. Additionally, to evaluate the interaction between glucocorticoid therapy and disease activity, an additional analysis was done adding this multiplicative interaction term.

A sensitivity analysis combining mechanical ventilation or death in the highest category was also performed.

Results were considered statistically significant using a two-sided $p<0.05$. Analyses were conducted in R version 4.0.2 (R Core Team, 2020). The C19-GRA physician-reported registry was defined as 'not human subjects research' by the UK Health Research Authority and The University of Manchester, as well as under US Federal Guidelines assessed by the UCSF Institutional Review Board. Due to the de-identified and non-interventional nature of the study, it was determined to be exempt by each institutional review board.

Results

As of 01 June 2021, 1922 subjects with SLE and COVID-19 were reported in the C19-GRA and EULAR registries. Baseline demographic and clinical characteristics are shown in Table 1. Individuals were predominantly female (90.4%) and the mean age was 44.4 years (SD = 14.1). Of the 1922 cases, 555 (28.9%) were reported from the U.S. and Canada, 543 (28.3%) from Europe, 643 (33.5%) from Latin America and 181 (9.4%) from other regions. The majority were non-white (57.3%).

Antimalarials were used as monotherapy by 665 individuals (34.6%), more intense immunosuppressive monotherapies (MMF, tacrolimus, cyclophosphamide, cyclosporine, azathioprine, with or without antimalarials) were used by 630 individuals (32.8%) at the time of COVID-19 onset. Two hundred and thirty (12.0%) did not take immunosuppressive drugs or antimalarials. Eight hundred and forty-six (44.0%) did not take prednisone, 467 (24.3%) took between 1-5 mg/d, 78 (4.1%) between 6-9 mg/d and 280 (14.6%) took a dose $\geqslant$ 10 mg/d.

Clinical outcomes, as well as outcomes as a function of treatment, for 1606 individuals were captured and are shown in Table 2. The majority of individuals (69.6%) were not hospitalized. In the model including demographics, clinical characteristics, medications and disease activity there were significant associations between demographic factors [older age, male sex, geographic location (being from outside of Europe, U.S. & Canada and Latin America), time period of the pandemic] and the ordinal severity outcome. Among comorbidities, chronic renal insufficiency or end stage renal disease, hypertension/cardiovascular disease and the number of other comorbidities were associated with more severe outcomes. Glucocorticoid use was also associated with more severe outcomes compared to those without glucocorticoids. Those who were not being treated for their SLE, or had moderate or high SLE disease activity also experienced more severe outcomes compared to those on remission (Table 3). These findings were consistent across various sensitivity analysis models (supplementary table 1).

Finally, additional analyses were performed to assess the associations of methotrexate, azathioprine, MMF, cyclophosphamide, rituximab and belimumab separately with the

ordinal severity outcome, demonstrating that there was no independent association of these drugs with the ordinal severity outcome in the fully adjusted model; however, rituximab was associated with poorer outcomes and belimumab with better outcomes in the unadjusted as well as the age and sex-adjusted model, and MMF and cyclophosphamide were associated with poorer outcomes and methotrexate was associated with better outcomes only in the age and sex-adjusted model (Table 4). There was no statistically significant interaction between glucocorticoid dose and disease activity or between DMARD use and disease activity (data not shown).

The results were nearly identical (supplementary table 2 and 3) in the alternative model in which mechanical ventilation and death were combined to constitute the highest category.

Discussion

During the COVID-19 pandemic, rheumatologists have been particularly concerned about individuals with SLE. These individuals are often significantly immunosuppressed, commonly use moderate or high doses of glucocorticoids, and have a high comorbidity burden. Moreover, many types of immune dysregulation occur in SLE, including in the interferon pathway, which is critical to the innate immune response during SARS-CoV-2 infection (16). However, SLE is a relatively uncommon disease and it has been difficult to accumulate a sufficient number of cases to examine risk factors for poor COVID-19 outcomes in this vulnerable population. Here we report the largest study of SLE and COVID-19 to date. In our analyses of over 1600 cases, we found that the use of glucocorticoids, having untreated or active SLE, or using rituximab was associated with more severe COVID-19 outcomes. In addition to these factors specific to SLE, our findings also highlight that many factors associated with more severe COVID-19 outcomes in the general population are important in SLE, including male gender (15, 17, 18), age (17-20), and comorbidity burden (17-19).

Prednisone use, even at relatively low doses of less than 5 mg daily, was associated with poorer outcomes in our analysis. In the C19-GRA registry, which included a wide array of rheumatic diseases, only prednisone at doses ≥10mg/d was associated with hospitalization or mortality (4, 13). Interestingly, in additional analyses of the registry we found that in the absence of disease activity, the relationship between glucocorticoid and mortality diminished (21). However, in SLE, even low doses of glucocorticoids were associated with more severe COVID-19 outcomes, including in those with low disease activity. Like our results, in a small study from Belgium, glucocorticoid dose was positively associated with a higher risk of hospitalization in SLE patients (22). These findings suggest that glucocorticoids are of special concern during the pandemic for people with SLE.

Our analyses also demonstrated that individuals not receiving treatment for their SLE at the time of COVID-19 diagnosis had poorer outcomes. The poor outcomes seen in this group may be multifactorial, and it is plausible that social risk factors play a role, such as lack of access to SLE care or treatment, or poor adherence with medications. Consistent with these results, individuals outside Europe, the U.S. & Canada had a poorer outcome, possibly related to healthcare access; but it was not statistically significant for Latin American individuals. Poverty and inequality have been associated with a higher risk and severity of COVID-19 globally (14, 23), and it is likely that health disparities in SLE may be exacerbated by the pandemic.

Rituximab has been associated with poorer outcomes in RA patients (2). We also found this association in SLE in our analysis, but it was present only in the unadjusted and age and sex-adjusted models; this may be due to the smaller number of individuals on rituximab in our study and resultantly low power in statistical analyses (n = 68). In fully adjusted models (including confirmed cases and those diagnosed based on symptoms and epidemiological criteria) there was a trend for an association between rituximab and poorer outcomes. It is important to point out that in the age and sex-adjusted models MMF, cyclophosphamide were associated with poorer outcomes. Cyclophosphamide was not evaluated in a fully adjusted model due to a small sample size. These findings are similar to what has been reported in other studies. For example, in a recent meta-regression including several rheumatic diseases, glucocorticoid use and

immunosuppressive drugs use in monotherapy or combination were associated with hospitalization and death from COVID-19 (24). Patients using belimumab generally had more favorable outcomes in our study; it is unclear if this may partly reflect confounding by health care access or socioeconomic status, as this drug is more commonly used in high income nations. The association between methotrexate and better outcomes in the age and sex-adjusted model could be related to a better disease activity control, as it did not remain significantly associated in the fully adjusted model. Because there were multiple comparisons, significance should be interpreted with caution. Given that there were six statistical comparisons made, one approach is to adjust the p value to a 0.01 level of significance. Using this more conservative approach, belimumab still remains statistically associated with less severe COVID-19 outcomes in the age and sex-adjusted model.

Previous investigators have found an association between SLE disease activity and serious infections (25). It is likely that both underlying immune dysfunction and the use of immunosuppressive therapies increase the risk of infection in SLE, which would explain the association between SLE disease activity and the severity of SARS-CoV-2 infection reported here.

The prognosis of patients with COVID-19 has improved over the course of the pandemic, which may be the result of many factors, including more widespread testing (leading to diagnosis of milder cases), improved pharmacologic therapy, and a better understanding of the timing, method of ventilatory support in critically ill patients and vaccination status for the most recent cases. Our findings suggest that patients with SLE diagnosed in later periods of the pandemic had better outcomes relative to the first part of the pandemic, which is consistent with the overall trends in the general population (26).

It is important to note that chronic kidney disease, a common and serious complication of SLE, has one of the strongest associations with poor COVID-19 outcomes. Chronic kidney disease is also an important risk factor for severe COVID-19 in the general population and may even pose a greater risk than the presence of diabetes (27). In addition to renal disease, our findings indicate that other comorbidities also increase the risk of severe outcomes, which is consistent with numerous previous studies (4, 19, 21). In SLE, medications, particularly glucocorticoids, can impact important comorbidities such as hypertension, diabetes, or obesity (28), which likely increases vulnerability to severe COVID-19 outcomes.

Several limitations of this study should be noted. First, the C19-GRA is a registry that is predicated on physician reporting of COVID-19 in rheumatic disease patients, and as such, may be skewed to include more severe COVID-19 cases. Patients with more severe COVID-19 are more likely to come to the attention of their rheumatology provider. Second, even though we were able to examine the relationship of several factors with more severe outcomes, we cannot exclude other confounders like access to healthcare or socioeconomic status. Third, although the physician global assessment is a valid, responsive and feasible instrument, given its less than optimal reliability it is not ideal to just assess it to the exclusion of the patient's assessment or other measures of disease activity; this is a limitation of our study. Finally, we were underpowered to look at some important treatments for SLE, such as cyclophosphamide, in our fully adjusted models;

data on voclosporin and anifrolumab, two newly approved therapies for SLE, was not available in the registry at the time of our analyses.

In conclusion, we found that in addition to age, male sex and comorbidities, the use of glucocorticoids and having untreated or active disease, were associated with more severe COVID-19 outcomes in individuals with SLE. Individuals with these characteristics should be prioritized for close monitoring, counseled to receive vaccination, and receive preventive therapies such as monoclonal antibodies (when available) if exposed to SARS-CoV-2.

Competing interests

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GSA has nothing to disclose.

ZI has nothing to disclose.

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LW has received consulting fees and speaker's honoraria from Aurinia Pharma unrelated to this manuscript.

GPE reports no competing interests related to this work. Outside of this work, he reports personal consulting and/or speaking fees from Pfizer, GSK, Janssen and Sanofi (all < $10,000).

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AJ has nothing to disclose.

GL has nothing to disclose.

MF has nothing to disclose.

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MD has nothing to disclose.

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VR has nothing to disclose.

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RV reports no competing interests related to this work. He has received personal consulting and/or speaking fees from Abbvie, Amgen, Boehringer-Ingelheim, BMS, Janssen-Cilag, GSK, Hexal, Neutrolis, Novartis, Pfizer (all < 10,000 USD). Institutional research grants were received from Amgen, BMS, Novartis, Pfizer.

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Contributorship

MFU-G, GSA, MG and JY had access to the study data, developed the figures and tables, and vouch for the data and analyses. AMG performed the statistical analyses and contributed to data quality control, data analysis and interpretation of data. All authors contributed to data collection, data analysis and interpretation of data. MFU-G, GSA, MG and JY directed the work, designed the data collection methods, contributed to data collection, data analysis and interpretation of data, and had final responsibility for the decision to submit for publication. All authors contributed intellectual content during the drafting and revision of the work and approved the final version to be published.

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Ethical approval information

The C19-GRA physician-reported registry was determined 'not human subjects' research' by the UK Health Research Authority and the University of Manchester, as well as under US Federal Guidelines assessed by the University of California, San Francisco Institutional Review Board. Due to the de-identified and non-interventional nature of the study, it was determined to be exempt by each institutional review board.

Data sharing statement

Data are available upon reasonable request. Applications to access the data should be made to the C19-GRA Steering Committee.

Patient and Public Involvement

Patient representatives were involved in planning the registry, interpreting results and writing/reviewing the paper.

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Table 1. Characteristics of SLE patients at the time of COVID-19 diagnosis (n=1922).

Characteristics	Mean (SD) or number (percentage)
Age, years, mean (SD)	44.4 (14.1)
Female, n (%)	1734 (90.4%)
Race/Ethnicity, n (%)	
White	639 (33.3%)
Non-white	1102 (57.3%)
Missing	181 (9.4%)
Region, n (%)	
Europe	543 (28.3%)
U.S. & Canada	555 (28.9%)
Latin America	643 (33.5%)
Other	181 (9.4%)
Time period, n (%)	
≤ June 15, 2020	733 (38.1%)
June 16-Sept 30, 2020	444 (23.1%)
Oct 1, 2020- April 12, 2021	745 (38.8%)
Comorbidities, n (%)	
0	1098 (57.1%)
1	511 (26.6%)
≥ 2	313 (16.3%)
Specific Comorbidities, n (%)	
Chronic renal insufficiency or ESRD	223 (11.8%)
Hypertension or cardiovascular disease	597 (31.1%)
Disease Activity, n (%)	
Remission	587 (30.5%)
Minimal or low	700 (36.4%)
Moderate	229 (11.9%)
Severe or high	77 (4.0%)
Missing	329 (17.1%)
Prednisone dose, n (%)**	
0 mg/day	846 (44.0%)
1-5 mg/day	467 (24.3%)
6-9 mg/day	78 (4.1%)
≥10 mg/day	280 (14.6%)
Missing	251 (13.1%)
Medication Category, n (%)	
Antimalarials only	665 (34.6%)
No SLE therapy	230 (12.0%)
Oral synthetic drug monotherapy with methotrexate, leflunomide, OR sulfasalazine only*	175 (9.1%%)
Oral synthetic drug monotherapy with (mycophenolate/mycophenolic acid, tacrolimus,	630 (32.8%)

cyclophosphamide, cyclosporine, OR azathioprine)*	
Biologic/targeted synthetic monotherapy	45 (2.3%)
Biologic/targeted and immunosuppressive drug combination therapy*	177 (9.2%)

ESRD: End-stage renal disease. SLE: Systemic lupus erythematosus IS: immunosuppressive. *These patients could be also on antimalarials. **All glucocorticoids were converted to prednisone-equivalent doses.

Table 2. Ordinal COVID-19 severity outcome as a function of medication class in individuals with SLE (n=1606)

	Total (N=1606)	Antimalarial only (N = 532)	No DMARD (N = 182)	Monotherapy with methotrexate, leflunomide, or sulfasalazine only* (N = 152)	Monotherapy with mycophenolate / mycophenolic acid, tacrolimus, cyclophosphamide, cyclosporine, or azathioprine* (N = 539)	Biologic/ targeted monotherapy* (N = 40)	Biologic/ targeted + immunosuppressive drug combination therapy* (N = 161)
Not hospitalized	1118 (69.6%)	401 (75.4%)	102 (56.0%)	117 (77.0%)	358 (66.4%)	27 (67.5%)	113 (70.2%)
Hospitalized with no oxygenation	169 (10.5%)	50 (9.4%)	26 (14.3%)	14 (9.2%)	62 (11.5%)	4 (10.0%)	13 (8.1%)
Hospitalized with any ventilation/ oxygenation	214 (13.3%)	53 (10.0%)	34 (18.7%)	14 (9.2%)	84 (15.6%)	6 (15.0%)	23 (14.3%)
Death	105 (6.5%)	28 (5.3%)	20 (11.0%)	7 (4.6%)	35 (6.5%)	3 (7.5%)	12 (7.5%)

IS: immunosuppressive *These patients could be also on antimalarials

Table 3: Multivariable ordinal regression model examining characteristics associated with more severe COVID-19 outcomes in individuals with SLE.

Covariate	OR (95% CI)	p-value
Age (years)	1.03 (1.02, 1.04)	<0.001**
Sex		
Male	1.50 (1.01, 2.23)	0.042*
Region		
Europe	Ref.	
U.S. & Canada	0.82 (0.22, 3.02)	0.76
Latin America	1.97 (0.87, 4.48)	0.11
Other	4.79 (2.21, 10.37)	<0.001**
Time period		
≤ June 15, 2020	Ref.	
June 16-Sept 30, 2020	0.50 (0.35, 0.72)	<0.001**
Oct 1, 2020- April 12, 2021	0.40 (0.29, 0.57)	<0.001**
GC Dose		
0 mg/day	Ref.	
1-5 mg/day	1.86 (1.30, 2.66)	<0.001**
6-9 mg/day	2.47 (1.25, 4.86)	0.009**
=>10 mg/day	1.95 (1.27, 2.99)	0.002**
Medication Category		
Antimalarial only	Ref.	
No SLE therapy	1.80 (1.17, 2.75)	0.007**
Monotherapy with methotrexate, leflunomide, or sulfasalazine only[#]	0.74 (0.44, 1.24)	0.25
Monotherapy with mycophenolate/mycophenolic acid, tacrolimus, cyclophosphamide, cyclosporine, or azathioprine[#]	1.01 (0.71, 1.43)	0.95
Biologic/targeted synthetic drug monotherapy	1.38 (0.58, 3.26)	0.47

Biologic/targeted synthetic drug and immunosuppressive drug combination therapy[#]	1.17 (0.72, 1.91)	0.52
Number of Comorbidities (excluding Renal and Cardiovascular disease/Hypertension)	1.60 (1.24, 2.07)	<0.001**
Chronic renal insufficiency or end stage renal disease	3.51 (2.42, 5.09)	<0.001**
Cardiovascular/Hypertension	1.69 (1.25, 2.29)	<0.001**
Disease Activity		
Remission	Ref.	
Minimal or low	0.86 (0.61, 1.21)	0.38
Moderate	1.61 (1.02, 2.54)	0.041*
Severe or high	3.94 (2.11, 7.34)	<0.001**

Each model adjusted for all variables listed, and random effects for country and time.

GC: Glucocorticoids IS: immunosuppressive; OR: Odd ratio; CI: confidence interval
#These patients could be also on antimalarials
* p<0.05
**p<0.01

Table 4. Ordinal regression models examining the association between individual medications and more severe COVID-19 outcomes in individuals with SLE.

		Unadjusted N= 1606		Age and Sex-Adjusted N= 1606		Fully Adjusted Model# N= 1606		Fully Adjusted Model# + Confirmed COVID^ N= 1283	
	Number of individuals taking medication prior to COVID-19 diagnosis with observed outcome	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Methotrexate	173	0.71 (0.50, 1.01)	0.06	0.67 (0.47, 0.97)	0.032*	0.71 (0.43, 1.16)	0.17	0.71 (0.40, 1.25)	0.23
Azathioprine	235	0.88 (0.66, 1.19)	0.42	0.95 (0.70, 1.29)	0.75	0.87 (0.57, 1.34)	0.53	0.89 (0.54, 1.47)	0.65
Mycophenolate/ mycophenolic acid	332	1.20 (0.93, 1.55)	0.15	1.36 (1.05, 1.76)	0.021*	1.08 (0.73, 1.59)	0.72	1.27 (0.82, 1.98)	0.29
Cyclophosphamide	29	1.92 (0.95, 3.91)	0.07	2.55 (1.23, 5.28)	0.012*	-	-	-	-
Rituximab	68	1.62 (1.00, 2.63)	0.049*	1.69 (1.04, 2.75)	0.036*	1.56 (0.84, 2.90)	0.16	1.91 (0.97, 3.79)	0.063
Belimumab	104	0.52 (0.32, 0.86)	0.011*	0.51 (0.31, 0.85)	<0.001**	0.66 (0.34,1.28)	0.22	0.65 (0.31, 1.34)	0.24

Model adjusted for age, sex, renal disease, hypertension/cardiovascular disease, comorbidity count, disease activity, region, time period, glucocorticoid and and other DMARD medication categories; random effects applied for country and time. Reference group = antimalarial only.

^ Confirmed cases were defined as having a diagnosis made by PCR, antibody or antigen test, or a CT scan

OR: Odds ratio; CI: confidence interval

* p<0.05

**p<0.01

Supplementary Table 1: Ordinal regression models examining characteristics associated with more severe COVID-19 outcomes in individuals with SLE.

	Model 1		Model 2 (Adding comorbidity count)		Model 3 (Adding specific comorbidities)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (continuous)	1.04 (1.03, 1.05)	$1.2x10^{-15}$	1.02 (1.01, 1.03)	$1.9x10^{-5}$**	1.03 (1.02, 1.04)	$1.1x10^{-6}$**
Sex						
Female	Ref					
Male	1.55 (1.06, 2.27)	$2.3x10^{-2}$*	1.59 (1.08, 2.35)	$1.9x10^{-2}$*	1.50 (1.02, 2.21)	$3.9x10^{-2}$*
Region						
Europe	Ref					
U.S & Canada	1.22 (0.34, 4.43)	0.76	0.96 (0.26, 3.61)	0.95	0.92 (0.25, 3.44)	0.90
Latin America	2.23 (0.99, 5.02	$5.4x10^{-2}$	1.97 (0.86, 4.52)	0.11	1.93 (0.84, 4.43)	0.12
Other	5.30 (2.47, 11.36)	$1.8 x10^{-5}$**	4.71 (2.16, 10.27)	$9.8x10^{-5}$**	4.97 (2.29, 10.80)	$5.0x10^{-5}$**
Time period						
<=June 15, 2020	Ref					
June 16-Sept 30, 2020	0.50 (0.36, 0.71)	$1.1x10^{-4}$**	0.49 (0.34, 0.71)	$1.2x10^{-4}$**	0.50 (0.35, 0.71)	$1.4x10^{-4}$**
Oct 1, 2020- April 12, 2021	0.38 (0.28, 0.53)	$9.2x10^{-9}$**	0.39 (0.28, 0.55)	$5.8x10^{-8}$**	0.39 (0.28, 0.55)	$4.8x10^{-8}$**
GC Dose						

0 mg/day	Ref					
1-5 mg/day	2.06 (1.45, 2.92)	$4.8x10^{-5}$**	1.93 (1.35, 2.77)	$3.0x10^{-4}$**	1.86 (1.39, 2.66)	$6.4x10^{-4}$**
6-9 mg/day	2.86 (1.50, 5.46)	$1.4x10^{-3}$**	2.66 (1.37, 5.17)	$3.9x10^{-3}$**	2.82 (1.45, 5.47)	$2.2x10^{-3}$**
=>10 mg/day	3.25 (2.21, 4.76)	$1.9x10^{-9}$**	2.78 (1.87, 4.12)	$4.2x10^{-7}$**	2.58 (1.74, 3.82)	$2.6x10^{-6}$**
Medication Category						
Antimalarial only	Ref					
No SLE therapy	2.11 (1.40, 3.18)	$3.3x10^{-4}$**	2.02 (1.33, 3.07)	$1.1x10^{-3}$**	1.95 (1.28, 2.96)	$1.8x10^{-3}$**
Monotherapy with methotrexate, leflunomide, or sulfasalazine only[#]	0.68 (0.41, 1.12)	0.13	0.73 (0.44, 1.22)	0.23	0.72 (0.43, 1.21)	0.21
Monotherapy with mycophenolate/mycophenolic acid, tacrolimus, cyclophosphamide, cyclosporine, or azathioprine[#]	1.29 (0.93, 1.79)	0.13	1.12 (0.80, 1.58)	0.50	1.05 (0.75, 1.47)	0.79
Biologic/targeted synthetic drug monotherapy	1.46 (0.66, 3.25)	0.36	1.43 (0.62, 3.30)	0.40	1.43 (0.62, 3,30)	0.40
Biologic/targeted synthetic drug and immunosuppressive drug combination therapy[#]	1.28 (0.80, 2.05)	0.30	1.18 (0.73, 1.92)	0.50	1.19 (0.73, 1.92)	0.49
Number of Comorbidities (continuous)	_	_	1.94 (1.65, 2.27)	$4.7x10^{-16}$**	_	_
Number of Comorbidities (excluding Renal and	_	_	_	_	1.60 (1.23,2.06)	$2.5x10^{-4}$**

Cardiovascular disease/Hypertension)						
Chronic renal insufficiency or end stage renal disease	_	_	_	_	3.72 (2.57, 5.36)	$2.4x10^{-12}$**
Cardiovascular/Hypertension	_	_	_	_	1.65 (1.23, 2.23)	$9.6x10^{r}$**

GC: Glucocorticoids IS: immunosuppressive; OR: Odd ratio; CI: confidence interval

#These patients could be also on antimalarials

Each model is adjusted for all variables listed; random effects applied for country and time.

* p<0.05

**p<0.01

Supplementary Table 2. Ordinal COVID-19 severity outcome with mechanical ventilation or death combined as highest category

	Total (N=1606)
Not hospitalized	1118 (69.6%)
Hospitalized with no oxygenation	169 (10.5%)
Hospitalized with any ventilation/ oxygenation	179 (11.2%)
Mechanical ventilation or Death	140 (8.7%)

Supplementary Table 3. Ordinal regression model examining characteristics associated with more severe COVID-19 outcomes in individuals with SLE with mechanical ventilation or death combined as highest category

	OR (95% CI)	p-value
Age (continuous)	1.03 (1.02, 1.04)	<0.001**
Sex		
Male	1.48 (1.00, 2.20)	0.05.1
Region		
Europe	Ref.	
U.S. & Canada	0.86 (0.22, 3.28)	0.82
Latin America	2.01 (0.87, 4.66)	0.10
Other	4.96 (2.26, 10.92)	<0.001**
Time period		
≤ June 15, 2020	Ref.	
June 16-Sept 30, 2020	0.50 (0.35, 0.72)	<0.001**
Oct 1, 2020- April 12, 2021	0.41 (0.29, 0.57)	<0.001**
GC Dose		
0 mg/day	Ref.	
1-5 mg/day	1.90 (1.33, 2.72)	<0.001**
6-9 mg/day	2.41 (1.23, 4.72)	0.01**
=>10 mg/day	1.92 (1.26, 2.94)	0.003**
Medication Category		
Antimalarial only	Ref.	
No SLE therapy	1.80 (1.17, 2.74)	0.007**
Monotherapy with methotrexate, leflunomide, or sulfasalazine only[#]	0.73 (0.43, 1.24)	0.24
Monotherapy with mycophenolate/mycophenolic acid, tacrolimus, cyclophosphamide, cyclosporine, or azathioprine[#]	1.04 (0.73, 1.47)	0.83

Biologic/targeted synthetic drug monotherapy	1.31 (0.55, 3.11)	0.54
Biologic/targeted synthetic drug and immunosuppressive drug combination therapy[#]	1.22 (0.75, 1.98)	0.43
Number of Comorbidities (excluding Renal and Cardiovascular disease/Hypertension)	1.56 (1.21, 2.02)	<0.001**
Chronic renal insufficiency or end stage renal disease	3.34 (2.31, 4.85)	<0.001**
Cardiovascular/Hypertension	1.71 (1.27, 2.31)	<0.001**
Disease Activity		
Remission	Ref.	
Minimal or low	0.86 (0.61, 1.21)	0.39
Moderate	1.54 (0.98, 2.43)	0.063
Severe or high	3.67 (1.96, 6.86)	<0.001**

Each model adjusted for all variables listed, and random effects for country and time.

GC: Glucocorticoids IS: immunosuppressive; OR: Odd ratio; CI: confidence interval
#These patients could be also on antimalarials
* p<0.05
**p<0.01