Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Racial and ethnic differences in COVID-19 outcomes: a call to action

Published Online
June 8, 2022
https://doi.org/10.1016/
S2665-9913(22)00135-7

See Articles page e490

The COVID-19 pandemic has demanded a huge effort to identify the risks associated with poor outcomes. The focus has been particularly relevant in patients with immune-mediated inflammatory diseases and those on therapies that suppress the immune system. Small early observational studies looked worrisome, but as data from larger studies became available a consistent picture became evident. Demographic risk factors such as age and comorbidity are really the salient factors, with some risk from underlying disease and a few specific therapeutic agents, such as rituximab.

Now that we are 2 years into the pandemic, the initial frenzy to generate data has receded, and we need to make sure that we are asking the right questions and designing studies appropriately to answer those questions. It is against this backdrop that the OPENSafely initiative has examined the question of the risk of poor outcomes in patients with immune-mediated inflammatory disease and those on immune-modifying therapy.[1] In *The Lancet Rheumatology*, Brian MacKenna and colleagues linked primary care data from the UK National Health Service with hospital prescription data for patients with immune-mediated inflammatory diseases.[1] They compared patients with immune-mediated inflammatory diseases with the general population and patients with immune-mediated inflammatory diseases on targeted or biological therapy with those on conventional therapies, such as methotrexate. Two-thirds of the cohort had inflammatory skin diseases, such as psoriasis, and some immune-mediated inflammatory diseases, such as multiple sclerosis, were excluded as well as some drugs, including abatacept, upadacitinib, and integrin inhibitors. The sample sizes of 1·1 million patients with immune-mediated inflammatory diseases and 200 000 patients on immune-modifying drugs are impressive. The authors reassuringly found that patients with immune-mediated inflammatory diseases have a small increased risk of poor outcomes after adjusting for comorbidities (hazard ratio 1·15 [95% CI 1·11–1·18] for COVID-19-related death, 1·16 [1·12–1·19] for COVID-19-related critical care admission or death, and 1·20 [1·17–1·23] for COVID-19-related hospital admission). This finding is in line with data from the US Veterans Affairs administration in patients with rheumatoid arthritis and the COVID-19 Global Rheumatology Alliance registry.[2] However, other groups have shown that the risk for poor outcomes largely disappears after adjusting for comorbidities.[3] MacKenna and colleagues also showed that some agents, notably rituximab, are associated with poor outcomes; this finding has been shown previously by several groups across multiple diseases and further increases our confidence that rituximab has a negative effect on COVID-19 outcomes.[4–7] We can conclude from this and other studies that patients with immune-mediated inflammatory diseases are at an increased risk of poor outcomes definitely attributed to their comorbidities and also potentially to a degree their underlying disease and specific immunosuppressive drugs.

What does this latest study contribute beyond adding robustly collected confirmatory evidence? The authors examined the influence of race and ethnicity on outcomes in patients with rheumatic diseases who had COVID-19. In the general population, non-White individuals, such as those of South Asian and African race, had poorer outcomes than White people. The same is seen when outcomes by race and ethnicity are examined in the immune-mediated inflammatory disease groups. The increased hazard of death and hospital admission was not trivial, with hazard ratios above 1·50 and often above 2·00 depending on the specific analysis. These UK data follow a similar pattern to data published in the USA from the Global Rheumatology Alliance.[8]

Can we unravel these striking health disparities? The US National Institute of Minority Health and Health Disparities provides a useful framework for conceptualising factors relevant to understanding health disparities. Different domains (ie, biological, behavioural, physical or built environment, sociocultural environment, and health-care system) and levels of influence (ie, individual, interpersonal, community, and societal) within these domains are included in this framework.[9] The pandemic has brought to light the many factors across these domains and levels of influence that

Panel: Activating health equity for patients with rheumatic diseases during the COVID-19 pandemic

Individual clinicians

- Counsel patients to have home COVID-19 tests available for prompt diagnosis, if financially feasible. Ensure that patients know where to get tested
- Counsel patients about prevention (personal protective equipment, vaccinations)
- Offer and arrange for pre-exposure prophylaxis for patients at high risk of poor outcomes from COVID-19, such as rituximab
- Counsel patients about available antiviral and monoclonal antibody therapies, time windows for eligibility, and who to call to request these therapies

Clinic or health system

- Collect high-quality data on patient race and ethnicity to identify and monitor health disparities
- Counsel patients about adjusting immunosuppression for vaccination or infection
- Use population health management, including tracking of vaccination rates among vulnerable groups
- Target culturally and linguistically appropriate, evidence-based outreach and education to groups with low vaccination rates

Community organisations

- Conduct outreach activities, including culturally and linguistically tailored COVID-19 prevention campaigns for immunocompromised patients
- Provide educational, social, and other support to people with rheumatic diseases during the pandemic and ensure that this support reaches the most vulnerable populations

Policy makers

- Ensure equitable access to COVID-19 testing and treatment
- Provide free access to effective vaccines
- Fund high-quality research investigating how best to protect immunocompromised patients, including those from vulnerable communities, from severe COVID-19
- Address social determinants of health, including housing and food security

underlie health disparities in COVID-19 outcomes. For example, individuals with rheumatic disease and low socioeconomic status might have greater disease severity and a higher comorbidity burden, both factors that drive more severe COVID-19 outcomes. Similarly, individuals from vulnerable groups might distrust the health-care system or have poor access to care, leading to treatment delays for COVID-19. Front-line jobs and crowded housing conditions increase the risk of SARS-CoV-2 transmission. Limited health literacy and misinformation among social networks might lead to lower vaccination rates and also inability to advocate for pre-exposure prophylaxis or outpatient COVID-19 therapies such as antivirals or monoclonal antibodies. Implicit or even overt bias among health-care professionals could lead to inadequate counselling on these and other important topics.

Given the complexity of the factors underlying these health disparities for people with rheumatic disease during the pandemic, what can we do to activate health equity? In the panel, we outline actions that individual rheumatologists and their clinics and communities can take to address COVID-19 health disparities. Rheumatologists can proactively counsel patients regarding prevention and treatment for COVID-19, filling educational gaps about vaccines, testing, pre-exposure prophylaxis, and treatment for patients who might not otherwise have access to this information. Clinics and health systems should build processes for population health management, including targeting culturally and linguistically appropriate evidence-based materials to patients at high risk. There are also actions that our communities and policy makers should take to protect vulnerable populations, particularly around addressing the many social determinants of health that conspire to put vulnerable populations at risk for poor health outcomes. The root causes of racial and ethnic disparities in COVID-19 outcomes for people with rheumatic diseases are complex, and solutions will need to be multifaceted. We have the skills and knowledge to start to address COVID-19 health disparities, and data from this study and others serve as a call to action to implement strategies to improve health equity for patients with rheumatic disease.

PCR reports personal fees from AbbVie, Atom Biosciences, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Kukdong, Novartis, UCB, Roche, and Pfizer; meeting attendance support from Bristol Myers Squibb, Roche, Pfizer, and UCB; and grant funding from Janssen, Novartis, Pfizer, and UCB Pharma. JY is supported by US National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases grants K24 AR074534 and P30 AR070155. She has received research grants from AstraZeneca, Gilead, and BMS Foundation, and has had consultancy roles with Pfizer, AstraZeneca, and Aurinia.

**Philip C Robinson, Jinoos Yazdany*
philip.robinson@uq.edu.au

Faculty of Medicine, University of Queensland, Brisbane, QLD 4006, Australia (PCR); Royal Brisbane & Women's Hospital, Metro North Hospital and Health Service, Brisbane, QLD, Australia (PCR); Division of Rheumatology, Department of Medicine, University of California, San Francisco, San Francisco, CA, USA (JY)

1 MacKenna B, Kennedy NA, Mehrkar A, et al. Risk of severe COVID-19 outcomes associated with immune-mediated inflammatory diseases and immune-modifying therapies: a nationwide cohort study in the OpenSAFELY platform. *Lancet Rheumatol* 2022; published online June 8. https://doi.org/10.1016/S2665-9913(22)00098-4.

2 England BR, Roul P, Yang Y, et al. Risk of COVID-19 in rheumatoid arthritis: a national Veterans Affairs matched cohort study in at-risk individuals. *Arthritis Rheumatol* 2021; **73:** 2179–88.

3 D'Silva KM, Jorge A, Cohen A, et al. COVID-19 outcomes in patients with systemic autoimmune rheumatic diseases (SARDs) compared to the general population: a US multi-center comparative cohort study. *Arthritis Rheumatol* 2021; **73:** 914–20.

4 Liew DFL, Robinson PC. What does endemic COVID-19 mean for the future of rituximab? *Lancet Rheumatol* 2022; **4:** e3–5.

5 Andersen KM, Bates BA, Rashidi ES, et al. Long-term use of immunosuppressive medicines and in-hospital COVID-19 outcomes: a retrospective cohort study using data from the National COVID Cohort Collaborative. *Lancet Rheumatol* 2022; **4:** e33–41.

6 Strangfeld A, Schäfer M, Gianfrancesco MA, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2021; **80:** 930–42.

7 Avouac J, Drumez E, Hachulla E, et al. COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study. *Lancet Rheumatol* 2021; **3:** e419–26.

8 Gianfrancesco MA, Leykina LA, Izadi Z, et al. Race/ethnicity association with COVID-19 outcomes in rheumatic disease: Data from the COVID-19 Global Rheumatology Alliance Physician Registry. *Arthritis Rheumatol* 2021; **73:** 374–80.

9 US National Institute on Minority Health and Health Disparities. NIMHD research framework. 2018. NIMHD. https://www.nimhd.nih.gov/about/overview/research-framework/nimhd-framework.html (accessed May 4, 2022).

Plasma protein correlates of skin severity in systemic sclerosis

See **Articles** page e507

Systemic sclerosis is an autoimmune disease associated with widespread fibrosis in skin and internal organs. The extent of skin involvement affects quality of life and an improvement in skin thickening predicts better survival.[1] Moreover, skin involvement is the primary or secondary outcome in many systemic sclerosis clinical trials. Currently, the extent of skin fibrosis is measured using a palpitation-based, semi-quantitative scoring system called the modified Rodnan skin score (mRSS). Although the mRSS is a validated outcome measure, it requires extensive training and has a high inter-observer variability. The limited accuracy and reliability of the mRSS has contributed to the fact that there are no US Food and Drug Administration approved medications for skin involvement in systemic sclerosis. Reliable and valid biomarkers that track severity of skin involvement represent an unmet clinical need in systemic sclerosis. Previous studies have shown that skin transcripts correlate highly with the concurrent mRSS[2,3] but it is difficult to obtain longitudinal skin biopsies in clinical settings to track disease severity. Recent studies have indicated that serum and plasma proteins in the circulation more accurately reflect the molecular dysregulations at the end-organ level such as skin rather than molecular dysregulations observed in the surrounding peripheral blood cells in patients with systemic sclerosis.[4,5] Moreover, serum and plasma are an ideal source of biomarker development as they are easily accessible and can be obtained during routine clinical care.

In *The Lancet Rheumatology*, Kristina E N Clark and colleagues[6] have identified four plasma proteins (collagen 4A1 [COL4A1], cartilage oligomatrix protein [COMP], spondin 1 [SPON1], and tenascin C [TNC]) that correlated significantly and independently with mRSS through an integrated and multilevel approach. First in addition to global skin gene expression analysis, the proteomic profile of skin blister fluid was examined, which has been shown to reflect the local microenvironment of skin cells.[7] Subsequently, a weighted gene co-expression network analysis integration of skin transcriptomic and blister fluid proteomic data was performed. Hub analytes belonging to modules that correlated with the diagnosis of early diffuse cutaneous systemic sclerosis and the other tissue modality (skin blister fluid proteome for skin transcriptome and vice versa) were selected for further analysis. This approach increased the likelihood that the selected serum proteins are biologically relevant and reflect the skin disease severity in a multi-compartment disease, in which fibrosis, occurring in other organs, can complicate identification of skin specific surrogate markers. Moreover, a multiplex proteomic platform was used allowing measurement of an extended panel of proteins (ie, 1196 analytes) in the blister fluid and plasma. Ultimately, four plasma proteins were identified that correlated significantly and independently with the concurrent mRSS in a multivariable model, assigning a specific relative weight to each analyte.

These four proteins have all been linked to biological processes underlying systemic sclerosis skin pathology in previous mechanistic studies. Moreover, COMP,[4,8] TNC,[4,5,9] and SPON1[10] have been previously shown to correlate with concurrent mRSS, however, the data on COL4A1 are less consistent.[4,5,11] Discrepancy in correlation results