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.

We declare no competing interests.

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Defining COVID-19-associated hyperinflammatory syndrome in specific populations

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Among the unique characteristics of COVID-19 is a predilection to elicit a maladaptive immune response leading to excessive inflammation and organ injury.[1] This complication of severe COVID-19 is associated with poor outcomes, shares characteristics with other cytokine storm or hyperinflammatory syndromes,[2] and is the target for a variety of immunomodulatory therapeutics. Defining this syndrome and identifying which patient populations are at highest risk of developing hyperinflammation are high clinical priorities.

Identifying this risk is particularly important in patients with underlying systemic rheumatic diseases for several reasons. First, patients with these diseases often have an elevated inflammatory setpoint and might be more likely to develop secondary hyperinflammatory syndromes.[3] Second, immunomodulatory therapies used in patients with systemic rheumatic diseases might variably affect susceptibility to COVID-19 and its associated hyperinflammatory syndrome. For example, some therapies, such as tumour necrosis factor inhibitors, have been posited to temper complications associated with COVID-19 hyperinflammation.[4] Alternatively, drugs that impair humoral immunity, such as anti-CD19 monoclonal antibodies or non-selective antiproliferative drugs, might prolong the active virological phase of COVID-19, leading to perpetuated lung injury, persistent or relapsing inflammation, and poor outcomes.[5] Finally, the interaction between systemic inflammation and immunomodulatory therapy and COVID-19 prognosis is further complicated by the high prevalence of chronic diseases in patients with systemic rheumatic diseases that independently increase risk for poor outcomes in COVID-19.[6]

In *The Lancet Rheumatology*, Tiffany Hsu and colleagues[7] report hyperinflammatory features and outcomes in patients with systemic rheumatic diseases admitted to hospital with severe COVID-19 compared with contemporaneous comparators without rheumatic diseases matched by age, sex, and date of initial PCR positivity for SARS-CoV-2. The authors compared levels of laboratory biomarkers, as well as the COVID-19-associated hyperinflammatory syndrome (cHIS) criteria, an ordinal diagnostic scale based on existing diagnostic criteria for other hyperinflammatory disorders and adapted to features unique to COVID-19.[2] Demographics and comorbid conditions were similar between patients with a rheumatic disease and comparators, with the exception of chronic kidney disease and interstitial lung disease, which were more common in patients. Body-mass index, which is an important contributor to poor outcomes of COVID-19, was similar between groups.

Hsu and colleagues' data showed that patients with systemic rheumatic diseases had higher expression

of many laboratory biomarkers, overall greater peak cHIS scores (median 3 [IQR 1–5] in patients *vs* 2 [1–4] in comparators; p=0·013), and required intensive care (adjusted odds ratio [OR] 2·08, [95% CI 1·09–3·96]) or mechanical ventilation (2·60 [1·32–5·12]) more often than matched comparators. Patients also had numerically higher odds of in-hospital mortality, but this was not statistically significant, most likely because of the small sample size. In subgroup analysis, hyperinflammation (assessed by cHIS) and outcomes in patients with quiescent disease and those not taking immunosuppressive medications were similar to values in comparators, whereas patients with active disease had a greater inflammatory biomarker signature and poorer outcomes. This observation suggests that the baseline inflammatory milieu before development of COVID-19 might affect the subsequent severity of COVID-19; this idea merits additional investigation. Interestingly, use of immunosuppressive medication among patients in the study seemed to be collinear with disease activity, as patients on immunosuppressive therapies also had higher inflammatory biomarkers and poorer outcomes.

Perhaps of most interest, Hsu and colleagues did an independent, external validation of the cHIS criteria. In the study by Webb and colleagues, cHIS showed excellent, temporally dynamic prediction of mechanical ventilation and mortality, and at a threshold of 2 or lower, differentiated patients with very low risk of progressing to severe disease and poor outcomes.[2] In this validation cohort, very similar results were observed; with each incremental increase in peak cHIS score, the risk of progressing to intensive care (adjusted OR 1·74 [95% CI 1·48–2·04]), mechanical ventilation (4·55 [3·11–6·64]), or in-hospital mortality (2·09 [1·63–2·68]) increased. Similarly, in this population, the cutpoint of cHIS score of 2 or more was strongly predictive of poor outcomes. Like the study by Webb and colleagues, the study by Hsu and colleagues is limited by a small sample size. Nevertheless, these findings lend support to the generalisability and accuracy of the cHIS scale and call for additional validation in large, diverse cohorts.

In the integrated health system in the USA, cHIS criteria have been implemented as part of a pragmatic, standardised, risk-targeted approach to COVID-19 management. For example, observational results from multiple studies that included data not captured in RECOVERY UK[8] suggest that the presence of biomarker evidence of clinically significant hyperinflammation (eg, elevated C-reactive protein or ferritin) differentiates benefit versus potential harm of corticosteroid therapy in non-critically ill patients hospitalised with COVID-19.[9,10] Based on these findings and our observation that patients without hyperinflammation have very high rates of recovery with supportive care alone, a cHIS score of 2 or more is being used as the primary indication for corticosteroid use in hospitalised patients without severe hypoxaemia. Similarly, cHIS screening has been implemented in the emergency department during peak surge to preserve hospital capacity by safely triaging patients without resting hypoxaemia or evidence of hyperinflammation to home-based supportive care and remote monitoring. A cHIS score of 3 or more is being incorporated as a threshold to identify patients with persistent hyperinflammation despite corticosteroid therapy or accompanying severe hypoxic respiratory failure who might benefit from adjunct selective cytokine antagonist therapy. Validation of strategies to risk-stratify patients based on objective measures of hyperinflammation, such as cHIS, and to use these measures to tailor anti-inflammatory therapies to patients most likely to benefit are important areas for further clinical investigation in COVID-19.

My institution (Intermountain Healthcare) has participated in COVID-19 trials sponsored by Abbvie, Genentech, Gilead, Regeneron, Roche, and the US National Institutes of Health Accelerating COVID-19 Therapeutic Interventions and Vaccines and Prevention and Early Treatment of Acute Lung Injury clinical trials networks. I was a site investigator on these trials but received no direct or indirect remuneration for my effort. I report partial salary support from a US Federal grant from the Agency for Healthcare Research and Quality.

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Understanding when and how joint injury leads to osteoarthritis

Joint trauma markedly, but variably, increases a person's risk of developing osteoarthritis. The magnitude of the risk is influenced by the severity of the injury, but also by individual endogenous factors. Many of the underlying factors that determine the variable outcomes of knee joint injury remain poorly understood, and reliable prognostic models are scarce. We are often unable to determine an individual's risk and therefore unable to provide personalised, post-injury advice for lifestyle and treatment.

Although reconstructive surgery of the ruptured anterior cruciate ligament or meniscus of an injured knee are common procedures, these interventions have not been proven to diminish the risk of developing posttraumatic osteoarthritis, suggesting that the surgical procedures are unable to faithfully reconstruct the preinjury functional anatomy of the joint, or that the long-term fate of the joint is determined already at the moment of trauma (or both). Further, the forces required to tear a cruciate ligament or meniscus are considerable, and the joint surfaces that serve as the fulcrum of these forces are exposed to equally traumatic loads. Examples of immediate occult injuries not routinely diagnosed are macroscopic or microscopic fractures of the joint cartilage with associated chondrocyte death, and subchondral bone fractures.

To improve our understanding of the immediate biological response to knee joint injury and its potential association with patient-reported outcomes and imaging outcomes over the long term, in *The Lancet Rheumatology*, Cesar Garriga and colleagues quantified a panel of protein biomarkers in synovial fluid and blood collected from patients who had traumatic knee injuries, at a median of 17 days (range 1–59 days) after the injury.[1]

The investigators found that the early, synovial fluid molecular response to the acute knee injury was associated with patient-reported symptomatic outcomes (as measured by the composite Knee Injury and Osteoarthritis Outcome Score 4 [$KOOS_4$]), but not with the development of new radiographic osteoarthritis at 2 years. Of a panel of 12 synovial fluid biomarkers, only monocyte chemoattractant protein 1 (MCP-1) and interleukin (IL)-6 showed independent associations with $KOOS_4$ in a multivariable model (change in $KOOS_4$ of –0·015 [95% CI 0·027 to –0·004]; p=0·011 for MCP-1; –0·0005 [–0·0009 to –0·0001]; p=0·017 for IL-6). However, these biomarkers played only a minor role—accounting for 39% of variability of KOOS4 at 2 years—with knee effusion and synovial fluid blood staining being the major drivers in the predictive model. When tested in the multivariable model, none of the baseline blood biomarkers associated with patient-reported outcomes at 2 years or with new radiographic osteoarthritis.

These and other findings reported in the Article by Garriga and colleagues extend and confirm findings of earlier publications exploring the biology of joint injury, osteoarthritis, and the role of protein biomarkers in predictive models for human osteoarthritis disease development. Studies on protein biomarkers, be they cytokines, growth factors, proteases, proteolytic fragments of connective tissue, or cartilage matrix molecules, have improved our understanding of the upregulation or downregulation of cellular processes associated with joint injury and osteoarthritis. However, it is fair to say that these biomarkers, when included in predictive models with more easily obtainable demographic or clinical variables, have yet to prove their clinical use.[2]

Notably, the investigators found that marked effusion and blood staining of the effusion were independent and dominant predictors in a model that included


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