1 Risk prediction: the 4C Mortality Score

BMJ 9 Mar 2020

Using data from 57, 824 hospital admissions, we developed and validated an easy-to-use risk stratification score based on commonly available parameters at hospital presentation. The 4C Mortality Score outperformed existing scores, showed utility to directly inform clinical decision making, and can be used to stratify patients admitted to hospital with covid-19 into different management groups.

The 4C Mortality Score can be found here: isaric4c.net/risk

The 4C Mortality Score has been extensively validated in independent studies across the world. Validation of the 4C score showed similar discrimination in the following countries:

- France
- The Netherlands
- Italy
- Pakistan
- Turkey
- Canada, Toronto
- Canada, Ontario

Altmetric score: 665[1]

2 Characterisation of hospitalised cases of COVID-19

BMJ: 2020; 369

Within weeks of being funded, we produced the largest study anywhere in the world of COVID-19 cases, enabling us to produce the most accurate risk prediction models for the UK population. These will continue to improve. The first one shows that obesity is an important risk factor amongst many. This finding will help to protect people at high risk of death from COVID-19. Our preprint is now online **Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol**. We have also produced an interactive infographic to help communicate these findings.

Altmetric score: 1974[2]

3 Genetic mechanisms of severe Covid-19

MedRxiv September 2020; Nature online December 2020

In collaboration with the ISARIC GenOMICC study we discovered multiple genes that underlie critical illness in Covid-19, including several that led directly to potential therapeutic targets.

In 2244 Covid cases, we compared severely ill patients with matched members of the population from three other studies (UK Biobank, Generation Scotland and 100,000 Genomes). We found genes involved in two molecular processes - antiviral immunity and lung inflammation - were important in determining the development of severe Covid-19. We replicated our findings in additional studies (Covid-19 HGI and 23andme). The associations with disease are robustly confirmed in these studies.

Although we know the DNA associations are real, we can't always be sure exactly how these variants lead to disease. The most likely genes underlying each of the four new discoveries are IFNAR2, TYK2, OAS1, DPP9.

The action of some genetic variants is similar the the action of drugs - either increasing or decreasing the amount of a particular molecule or signal. We can use this to predict new treatments. This evidence has already influenced the inclusion of new therapies in the RECOVERY trial.

Altmetric score: 2730[3]

4 Clinical characterisation of Covid-19 in children

BMJ 2020;370:m3249

We have comprehensively characterised the burden and patterns of disease in children in the UK, demonstrating that life-threatening disease in otherwise healthy children is extremely rare. This had direct impact on public health policy in the UK and abroad.

Altmetric score: 2823[4]

5 Long Covid in adults discharged from UK hospitals after Covid-19

MedRxiv pre-prints 25 March 2021

It is emerging that long-term symptoms are often present in people who have had acute Covid-19 disease. We found that over half of patients reported not feeling fully recovered several months after onset of Covid-19 symptoms. The symptoms reported include fatigue, followed by breathlessness. These findings were present in young, previously healthy working age adults, and were most common in younger females.

Altmetric score: 932[https://doi.org/10.1101/2021.03.18.21253888]

6 Non-steroidal anti-inflammatory drug use and outcomes of COVID-19

The Lancet: Rheumatology May 07, 2021

Early in the pandemic it was suggested that pre-existing use of non-steroidal anti-inflammatory drugs (NSAIDs) could lead to increased disease severity in patients with COVID-19. NSAIDs are an important analgesic, particularly in those with rheumatological disease, and are widely available to the general public without prescription.

Using data from 78,674 patients in ISARIC4C, we showed that NSAID use is not associated with higher mortality or increased severity of COVID-19. To our knowledge, our prospective study includes the largest number of patients admitted to hospital with COVID-19 to date, and adds to the literature on the safety of NSAIDs and in-hospital outcomes. NSAIDs do not appear to increase the risk of worse in-hospital outcomes. NSAIDs are an important analgesic modality and have a vital opioid-sparing role in pain management. Patients and clinicians should be reassured by these findings that NSAIDs are safe in the context of the pandemic.

Altmetric score: 2654[https://doi.org/10.1016/S2665-9913(21)00104-1]

7 Role of blood cytokines IL-6 and GM-CSF in severe COVID-19

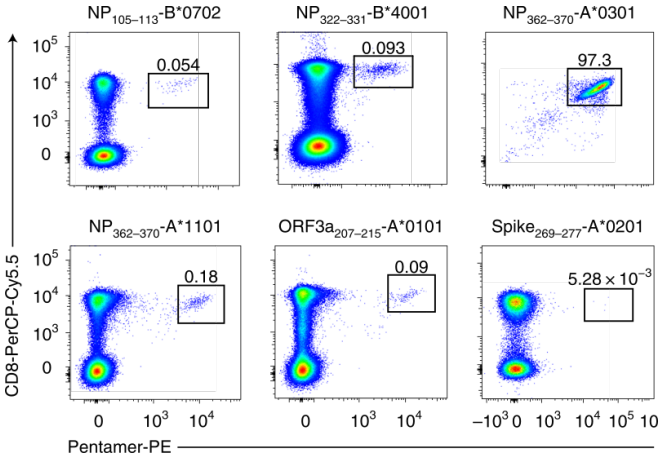
Science Immunology 10 Mar 2021

We have identified new biomarkers of inflammation that both reveal the severity of COVID-19 and set it apart from severe influenza. Many inflammatory cytokines were found in greater numbers in severe COVID-19 and that these levels generally indicate severe disease. We identified patterns within the data that were the most clearly linked to severe cases of COVID-19; two cytokines in particular, IL-6 (interleukin 6) and GM-CSF (granulocyte-macrophage colony stimulating factor) play central roles. With more research, we can see if GM-CSF could be used as a marker in early disease to identify those at risk of going on to develop more severe symptoms.

Altmetric score: 1264[5]

8 T cells target many different parts of the virus

Nature Immunology (4th September 2020))



This study by Yanchung Peng, Alex Mentzer, Tao Dong and colleagues reveals that the immune system responds to many different parts of the SARS-CoV-2 virus. This will influence vaccine design, which often focuses only on the most prominent parts of the virus. It also reveals key differences in the way immune cells fight the virus in patients who have mild disease, helping us to better understand how some people are able to fight it off without becoming very sick.

Altmetric score: 579[6]

9 Setting Serology Standards

10 Setting the standard

ISARIC 4C defined the international reference standard for SARS-CoV-2 serology by providing the first samples to the National Institute for Biological Standards and Control (NIBSC) from COVID-19 cases. These were used to make the WHO International Standard for SARS-CoV-2 serology, which will be used all over the world to compare results from blood tests for COVID-19. 7 of the 11 patients who contributed to the standard were recruited by ISARIC 4C.

11 Viral spike variants evading antibody-mediated immunity

Cell 4 Mar 2021

We showed that the N439K viral mutation has enhanced binding affinity to the ACE2 receptor and that this variant cause infections with similar clinical outcomes compared to the wild type. This mutation is resistant against neutralising monoclonal antibodies and from polyclonal sera from persons recovered from infection. Our findings have highlighted how this virus can mutate and the need for ongoing molecular surveillance to guide development and usage of vaccines and therapeutics.

Altmetric score: 449[7]

12 SARS-CoV-2 surface and air contamination in a healthcare setting

Clinical Infectious Diseases 8 Jul 2020

We have explored the mechanisms of viral transmission. Our findings of extensive viral RNA contamination of surfaces and air across a range of acute healthcare settings in the absence of cultured virus highlighted the potential risk from surface and air contamination in managing COVID-19, and the need for effective use of PPE, social distancing, and hand/surface hygiene.

Altmetric score: 33[8]

13 Impact of ethnicity

SSRN July 2020

We have carefully studied the effect of ethnicity on outcomes in hospitalised patients, revealing the effect of comorbidities in mediating part of the increased susceptibility in some ethic groups.

Altmetric score: 15[http://dx.doi.org/10.2139/ssrn.3618215]

14 ICECAP autopsy study

American Journal of Respiratory and Critical Care Medicine 2021

ISARIC 4C resources and consortium partners supported the COVID-19 post-mortem case series. This is one of several pieces of evidence that changes the model of COVID pathogenesis, supporting a primary role for the host immune system in causing fatal disease.

Altmetric score: 63[9]

15 Using a double binding antigen assay to detect and measure SARS-CoV-2 antibodies

5 Jan 2021

Hybrid DABA displayed attributes necessary for accurate and sensitive detection of antibody to SARS-CoV-2 to predict neutralising activity and the vaccine response.

[https://doi.org/10.2139/ssrn.3739821]

16 Viral RNA found in blood is not infectious

Wellcome Open Research 29 Jul 2020

Laboratory diagnosis of SARS-CoV-2 infection uses PCR to detect viral RNA (vRNA) in respiratory samples. While SARS-CoV-2 RNA has been detected in other sample types, there is very little understanding about its clinical or laboratory significance. This has implications for testing and for safe working in a laboratory setting. To answer this, we undertook a systematic review for evidence of viral RNA in blood. We also attempted viral isolation from PCR-positive blood samples. Viral RNA was detectable at very low levels, but this was not associated with infectious SARS-CoV-2. This work will help to inform biosafety precautions for handling blood from COVID-19 patients.

Altmetric score: 18[https://doi.org/10.12688/wellcomeopenres.16002.1]

17 Developing methods of sequencing the virus

Viruses 14 Oct 2020

Sequencing the viral genome as the outbreak progresses is important, particularly the identification of new variants and to identify whether any changes in the genome will impair clinical testing. Using the MinION/GridIONS platform, we developed a sensitive protocol to rapidly sequence the viral genome. With this study, we showed that amplicon-based detection and subsequent sequencing are feasible for identifying the SARS-CoV-2 genome or nucleic acid in samples from patients with COVID-19.

Altmetric score: 9[10]

18 Adverse outcomes in COVID-19 patients with underlying respiratory conditions

Lancet Respiratory Medicine 4 March 2021

Characterisation of 75 463 hospitalised COVID-19 patients from 258 participating health-care facilities showed that underlying respiratory symptoms is common and patients with asthma were more likely, and those with chronic pulmonary disease less likely, to receive critical care than patients without an underlying respiratory condition.

Altmetric score: 219[https://doi.org/10.1016/s2213-2600(21)00013-8]

19 Pulmonary Microthrombosis and Vasculitis in Life-Threatening Respiratory Virus Diseases

Open Forum Infectious Diseases 28 Dec 2020

This study, with support and resources provided by ISARIC4C, found evidence of thrombosis present in adults with fatal influenza and SARS, with vasculitis also reported.

[11]

20 Using imaging in COVID-19 – UK National COVID-19 Chest Imaging Database

European Respiratory Journal 13 Aug 2020

The National COVID-19 Chest Imaging Database (NCCID) is a repository of chest radiographs, CT and MRI images and clinical data from COVID-19 patients across the UK, to support research and development of AI technology and give insight into COVID-19 disease. To maximise efficient resource utilisation in busy hospitals during the course of the pandemic, NCCID are linking imaging data to the ISARIC4C dataset, and aim to link to the Intensive Care National Audit and Research Centre (ICNARC). ISARIC investigators are collating clinical information and biological samples for COVID-19 cases of all ages admitted to hospitals, while ICNARC collates detailed data from adults in the intensive care setting. The study has also been supported by Health Data Research UK as part of its UK response to COVID-19.

Altmetric score: 46[12]

21 Outcomes of hospitalised COVID-19 patients with interstitial lung disease

American Journal of Respiratory and Critical Care 15 Dec 2020

We completed an international multicentre audit of patients with prior diagnosis of Interstitial Lung Diseases (ILD) admitted to hospital with COVID-19. We showed that these patients are at increased risk of death, particularly those with poor lung function and obesity. Data from this study showed that patients with ILD should follow self-isolation guidelines for vulnerable individuals and be prioritised for vaccinations.

Altmetric score: 104[13]

22 Outcomes of COVID-19 hospitalisation among patients with HIV

Clinical Infectious Diseases 23 Oct 2020

Providing data and support to the British HIV Association, presentation characteristics and outcomes of adults with and without HIV who were hospitalized with COVID-19 at 207 centers across the UK, were compared. HIV-positive status was associated with an increased risk of day-28 mortality among patients hospitalised for COVID-19.

Altmetric score: 22[14]

23 Co-Infections, Secondary Infections, and Antimicrobial Usage

Lancet Microbe (accepted)

Using microbiological investigations recorded for 8649 hospitalised COVID-19 patients, we found that microbiologically-confirmed bacterial/fungal infections is rare, and more likely to be secondary infections. Gram-negative organisms and S. aureus are the predominant pathogens. The frequency and nature of antimicrobial usage is concerning, but tractable targets for stewardship interventions exist.

[https://dx.doi.org/10.2139/ssrn.3786694]

24 Testing the tests

MedRxiv May 2020

We proposed and established a Diagnostic Evaluation Platform at the University of Oxford (led by Dr Alex Mentzer) which is already being used to provide evidence to the UK government about the performance of new diagnostic and antibody tests. This work is essential because if tests work well they can save lives; if they don't, they can cause enormous damage.

Altmetric score: 28[15]

25 Detection of antibodies to determine population exposure

Eurosurveillance 22 Oct 2020

ISARIC4C provided support to this study looking at population exposure in the beginning of the outbreak showing that it is likely that SARS-CoV-2 began circulating in Scotland in late February 2020 and potentially earlier.

Altmetric score: 16[16]

26 Symptom clusters

MedRxiv August 16th 2020.

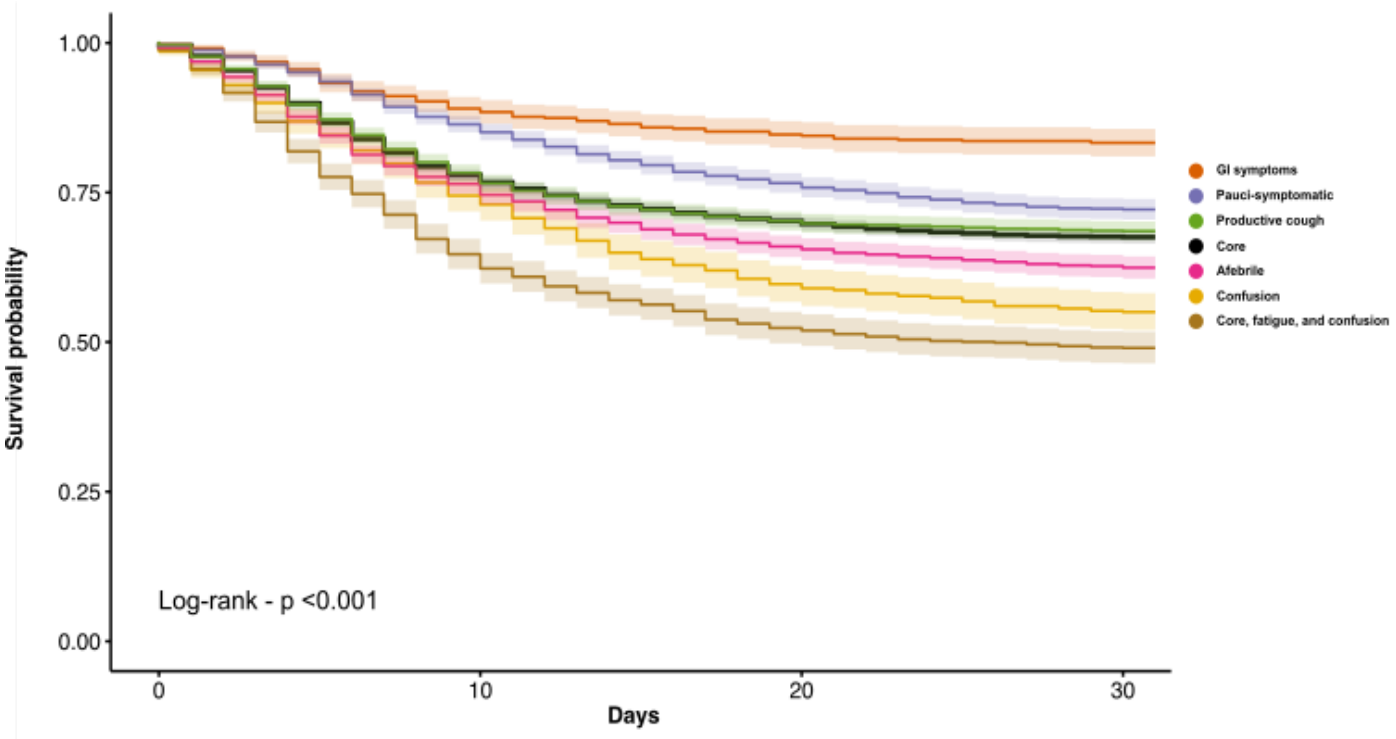


Figure 1: Different outcomes among patients presenting with different patterns of symptoms

Because of the large scale of the ISARIC-4C study, we were able to detect robust groupings of patients with different patterns of symptoms. We found four patterns that are strikingly differnet from the core symptom groups: gastro-intestinal disease, productive cough, confusion, and pauci-symptomatic presentations. Each of these has a different clinical course and a different chance of death.

These observations deepen our understanding of COVID-19 and will influence clinical diagnosis, risk prediction, and future mechanistic and clinical studies.

Altmetric score: 10[https://doi.org/10.1101/2020.08.14.20168088]

27 Vulnerability of Down's syndrome (DS) patients to severe COVID-19

EClinical Medicine 22 Feb 2021)

Providing data and support to the Trisomy 21 Society, a study was conducted to determine if health conditions, immune dysfunction, and premature aging associated with trisomy 21 (Down syndrome, DS) may impact the clinical course of COVID-19. Whilst signs/symptoms of COVID-19 and risk factors for severe disease course are similar to the general population, individuals with DS present significantly higher rates of medical complications and mortality, especially from age 40.

Altmetric score: 470[17]

28 Modelling the association of tiered restrictions with COVID-19 deaths and hospital admissions

Lancet Infectious Diseases 23 Dec 2020

To look at the impact of tiered restrictions, the team fitted a mathematical model of transmission to data on hospital admissions. Results showed that lockdown measures outperformed less stringent restrictions in reducing cumulative deaths.

Altmetric score: 233[https://doi.org/10.1016/s1473-3099(20)30984-1]

29 Multi-model forecasts to inform the response to COVID-19 in the UK

MedRxiv pre-print 4 Dec 2020

Groups of multi-model forecasts can inform the policy response to the Covid-19 pandemic by assessing future resource needs and expected population impact of morbidity and mortality.

Altmetric score: 19[https://doi.org/10.1101/2020.11.11.20220962]

30 Remdesivir Statistical Analysis Plan

The Remdesivir Statistical Analysis Plan was approved on 16 December 2020.

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