POOR PROGNOSIS INDICATOR IN COVID PATIENTS

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ABSTRACT

Whilst COVID-19 infection generally run a mild course in up to 80% of those affected, a number of pre-existing co-morbidities determine the severity of infection and the outcome in an individual patient. The most important of these co-morbidities that have consistently emerged in studies from across the globe, are the patients age and sex. Other important co-morbidities that adversely affect outcomes include pre-existing diabetes, obesity, hypertension, chronic lung disease and malignancy. This comprehensive review discusses the impact of these co-morbidities and the role of laboratory predictors of poor patient outcomes.

When a new disease emerges it is crucial to know who is most at risk. Whilst COVID-19 infection generally runs a mild course in younger patients who havue no other co-morbidities, it is now increasingly clear, 1 year into the pandemic, that patients with certain risk factors are disproportionately affected. This review attempts to analyse and study these factors.

1. **AGE**

   Age is widely observed to be the most important prognostic factor. Advanced age is associated with poor outcome in terms of: death, hospitalization, and Intensive Care Unit (ICU) admission. These findings have been consistent from the earliest studies conducted from the epicentre of this pandemic in Wuhan and continue to be observed in more recent studies.

   a. Death rates are directly co-related with advanced age: One of the earliest retrospective observations from 113 deaths due to SARS-CoV2 in a cohort of 799 patients admitted in Tongji Hospital in Wuhan, showed that the median age of deceased patients was 68 years, which was significantly older than the median age of 51 years in those who recovered. i.e. patients who died were 17 years older than those who recovered. Death rates were 83% in the age group of ≥ 60 years, 17% in 40-60 years, and 0 in patients < 40 years. Another retrospective analysis of 201 patients in Wuhan revealed a statistically significant difference in mean age of the non-survivor and survivor group (i.e. 68 years vs. 50 years respectively with a p value > 0.001). A recent study of 5700 patients in New York also showed that with increasing age there was an increase in the duration of hospital stay, complications, ICU requirement, death and readmission, while there was a decrease in the chance of being discharged alive. Mortality was 0% in those < 19 years, in contrast to 48% in 80-89 years age group. 95% of patients were discharged alive in the 30-39 years age group, while only 36% of those > 90 years of age were discharged alive.
   b. Exponential rise in case fatality ratio over the age of 50: A model-based analysis was done to estimate severity of COVID-19. Individual-case data was collected for patients who died from COVID-19 in Hubei, mainland China, and for cases outside of mainland China.4 This study highlighted that the crude case fatality ratios obtained by dividing the number of deaths by the total number of cases can be misleading. Hence an infection fatality ratio was calculated which accounted for asymptomatic and mildly symptomatic patients who form the major bulk of COVID-19 disease. Here again there was a strong age gradient in the risk of death. Higher age was directly linked to death, with exponential rise over the age of 50 years. On binary division of age groups, death rates were 0.32% in the < 60 years age group and 6.38% in > 60 years age group. Highest death rate (14.8%) was seen in the age group >80 years.
   c. Rate of hospitalization and ICU admission directly co-related with advanced age: In a retrospective, single- centre case series of the 138 consecutive hospitalized patients with confirmed COVID 19 at Zhongnan Hospital, Wuhan, a total of 36 (26%) patients required ICU admission. Median age of patients in the ICU was 66 years compared to 51 years in the non ICU group (p value <0.001).
      Rate of hospitalization was also higher in the older age group. The proportion of infected individuals hospitalized was higher as age advanced (50-59 years: 16%; 60-69 years: 11.8%, 70-79 years: 16.6%, and ≥ 80 years: 18.4%) in a model based

analysis done on 799 patients.4 Similar findings were replicated in a study from the United States.

In conclusion age has consistently emerged as an independent risk factor of poor outcome, and patients above 50 years should be regarded as high risk patients.

2. **SEX**

Male sex has also been consistently observed as a risk factor for poor outcome. Male preponderance has been observed in the total number of cases, complications, and deaths amongst 799 COVID-19 pneumonia patients admitted at Tongji Hospital, Wuhan. Amongst patients who died, M:F ratio was around 7:3 from the 113 deceased.1 In another retrospective cohort study of 201 patients with confirmed COVID-19 pneumonia admitted to Wuhan Jinyintan Hospital in China it was observed that 65.9% of all the deceased were male, while 34.1% were female (p value>0.24). Similarly of all the ARDS cases 71.4% were male and 28.6% were female (p value >0.05).2 Another study including 138 hospitalized patients showed the incidence of ICU admissions was 61% in males and 39% in female (p value 0.34).5 In Italy higher rates of complications were observed in males: 59.8%, compared to 40.2% in female.6 These findings could be only partially confounded by the higher incidence of comorbidities and smoking habits in males.

Possible mechanisms for this sex predilection was explained by the postulate that the biological step required for viral infectivity of the SARS-CoV-2 virus is priming of the spike proteins by transmembrane protease serine 2 (TMPRSS2) which cleaves the Angiotensin converting enzyme-2 (ACE2) receptor. Action of TMPRSS2 is enhanced by androgen, hence viral replication rate can be expected to be higher in males. Male susceptibility to the development of severe COVID-19 symptoms may be further enhanced by X-linked inheritance, since both the androgen receptor gene and the ACE2 genes are located on chromosome X.8 To study this hypothesis two clinical trials have been initiated, one in New York which has commenced treating COVID-19 patients with estrogen, and the other in Los Angeles which will treat male patients with progesterone, which has anti-inflammatory properties, and can potentially prevent harmful overreactions of the immune system.9 Protection in females has been postulated to be either due to XX linkage or estrogens with its role in negative regulation of the serene proteases including TMPRSS2.10 Another postulate attributes the increased male vulnerability to high ACE2 receptor concentrations in the testis.

3. **COMORBITIES**

Up to 63% of death occurred in those who had at least one comorbidity amongst the 113 COVID-19 deaths that occurred at Tongji Hospital in Wuhan.1 Up to 72% (p value <0.001) of 138 patient hospitalized in Zhongnan Hospital, Wuhan requiring intensive care also had some underlying co-morbidities.

Similar results were obtained in a nationwide retrospective study done at 575 hospitals throughout China compiling data of 1590 patients. 25.1% of the total deaths had at least one comorbidity. The most prevalent comorbidity was hypertension (16.9%), followed by diabetes (8.2%). COPD also emerged as an important co-morbidity, even after adjusting for age and smoking status (hazard ratio, HR 2.681) as did diabetes (HR 1.59), hypertension (HR 1.58) and malignancy (HR 3.50). The HR for death was 1.79 among patients with at least one comorbidity and rose to 2.59 among patients with two or more comorbidities (p value<0.05). A meta-analysis of seven studies including 1576 COVID-19 patients also showed the most

prevalent comorbidities to be hypertension (21.1%), diabetes (9.7%), cardiovascular disease (8.4%) and chronic respiratory disease (1.5%).

a. **DIABETES MELLITUS**

Diabetes is a common comorbidity along with hypertension, adversely impacting outcomes in COVID-19 subjects. A recently published meta-analysis of 6452 patients from 30 different studies showed that diabetes was associated with composite poor outcomes in COVID-19 patients with a risk ratio (RR) of 2.38, ($p < 0.001$). In DM the RR for death was 2.12, for severe COVID-19 was 2.45, and for ARDS was 4.64 ($p<0.001$). Strikingly, meta-regression analysis showed that the magnitude of risk linked to DM as a single factor was greater in studies with younger and non-hypertensive patients, suggesting that in this population, younger and non-hypertensive diabetics were at higher risk of poor outcomes in contrast to the expected trend of older patients being at higher risk.A French nationwide study (CORONADO)15 revealed the phenotypes in DM which were more vulnerable to adverse outcomes. In hospitalised COVID-19 patients increased BMI and male sex emerged as important risk factors for adverse outcomes apart from age (odds ratio; OR 2.48), microvascular (OR 2.14) or macrovascular (OR2.54) complications and treated obstructive sleep apnoea (OR 2.8). The biochemical markers such as increased aspartate aminotransferase (AST), C-reactive protein (CRP), low platelet count and estimated glomerular filtration rate (eGFR) appears to be associated with risk of early death in hospitalised COVID-19 patients with DM. The mortality risk was significantly higher in patients with advanced complicated DM and long duration of disease. Oral antidiabetic agents such as thiazolidinedione, sodium glucose transporter2 (SGLT2) inhibitors, glucagon like peptide (GLP1) analogues may have some possible adverse outcomes in management and should be avoided.16 Often severe hyperglycaemia is observed in hospitalised patients and in patients requiring ICU. This warrants tight glycaemic control with intravenous infusion of insulin.Thus it is recommended that oral antidiabetic therapy in hospitalized patients be withheld and Insulin based therapy initiated.

b. **OBESITY**

Increased BMI is emerging as a clear cut independent risk factor in COVID-19 patients and underlying insulin resistance may be contributing to higher mortality.17 In a retrospective analysis of age stratified body mass index (BMI) in 3615 COVID-19 patients it was observed that patients with age < 60 years and BMI ≥ 35 kg/m2 were 3.6 times more likely to require ICU than patients with BMI < 25.18 In a retrospective study amongst 124 patients the odds ratio for requirements of invasive mechanical ventilation in patients with BMI >35 vs patients with BMI <25 kg/m2 was 7.36 ($p=0.02$).18 Currently it is unclear if this is the underlying reason for the higher mortality consistently observed in the ethnic minorities in Black, Asian populations (BAME) in UK and USA, which has been discussed in another section.

c. **RESPIRATORY COMORBITIES**

a. Interstitial lung disease (ILD):

Most patients with ILD due to their poor lung physiology and underlying comorbidities are considered a high risk group. However no data is available on the proportional mortality rate and rate of infection amongst this group of patients.

b. Asthma

In a study conducted during the earlier phase of the pandemic, asthma was not found to increase mortality or complications in COVID-19 patients.12 However a recent cohort study was done using electronic health data to quantify risk factors for COVID-19 death.20 This study included over 17 million (17,425,445) general population enrolled in national health records who were followed up for around 3 months to assess the impact of comorbidities in the 5683 COVID-19 deaths in this cohort. This study uniquely highlighted that asthma was an independent risk factor for COVID-19 deaths (HR 1.23). This risk increased if the patient had a history of recent use of oral corticosteroid (HR 1.70). Deleterious effect of oral corticosteroids was also observed in another study among 600 COVID-19 patient with underlying rheumatological disease.21 It was found that the use of prednisolone ≥10 mg/day was associated with higher odds of hospitalisation (OR 2.05). It was also observed that around half of these patients (55%) required hospitalization and 9% died.

c. TUBERCULOSIS

COVID appears to have both direct and indirect effect on patients of tuberculosis. In a multicentre observational case control study done in 36 COVID-19 patients in Shenyang, China, TB (active or latent) was found to be amongst the most common underlying comorbidities. Of 36 enrolled patients 13 had interferon gamma release assay (IGRA) positive, of which 3 had active TB, 5 were recovered TB patients, 3 had old TB calcifications on chest scans, and 2 patients had latent TB (LTBI). A modelling analysis was done to predict the cumulative incidence and mortality of TB in India, Kenya and Ukraine. This study concluded that in India every month of lockdown would lead to 144,795 excess TB cases and 40,685 excess TB deaths in the next 5 years.

d. **Smoking**

Smoking has been a public health problem since decades however there is some controversy regarding its role in COVID-19 after it emerged that a recent study published from Paris's Pitié-Salpêtrière hospital found smokers had a lower chance of developing SARS-CoV2 compared with the general population.A trial has been initiated in France to study the effects of nicotine patches in COVID-19 patients. Currently one postulate claims smokers have increased numbers of ACE2 receptors but this needs validation.

e. Cancer

Patient with cancer appears to be at higher risk of COVID-19. A study involving 105 cancer patients admitted in 14 hospitals of Wuhan shown that

compared to patients without cancer, the cancer patients had a higher risk of death (OR 2.34; p=0.03), of ICU admission (OR 2.84; p<0.01), and of developing severe/critical symptoms (OR 2.79; p<0.01). With regard to different types of cancer, the study found that patients with hematological malignancy had the highest risk of poor outcomes, followed by those with lung cancers. Patients with metastatic disease had an even higher risk of death (OR 5.58; p=0.01).

4. LABORATORY PARAMETERS

Several routine laboratory indicators have been shown to predict a higher risk of patient mortality.

a. Routine blood investigation

Leukocytosis, lymphocytopenia, neutropenia, and high BUN were all more frequently observed amongst deceased patients than survivors during the second and third week of illness (p value<0.05).5 C-indices of lymphocyte (0.872), prothrombin time (0.858), and CRP (0.844) where observed as strong predictors for death in these patients. 3 Neutrophil-lymphocyte ratio (NLR) was also observed as an independent risk factor for poor outcome (HR 2.52) with a sensitivity of 88% and specificity of 63.6%.

b. D-dimer

A recently published study showed the D-dimer had the highest C-index (0.883) to predict in-hospital mortality in COVID-19 patients. Cut off values established using ROC curve, showed that a D-dimer value on admission greater than 2.0 µg/mL, could effectively predict in-hospital mortality of COVID-19 patients with a sensitivity of 92.3% and specificity of 83.3%.30 Another case series on 18 deaths due to myocardial infarction in COVID-19 patient reported elevated levels of D –dimer as a consistent finding in all 18.31 This was in contrast to a previous study where D-dimer levels were normal amongst 64% of myocardial infarction patients without COVID-19.32 In an analysis of 274 COVID-19 cases in Tongji Hospital in Wuhan, D-dimer concentrations were markedly greater in 113 deceased patients (4.6 µg/mL) as compared to patients who recovered (0.6 µg/mL),emphasizing the role of D-dimer as a predictor of death in COVID-19.

c. Other laboratory markers

Concentrations of procalcitonin [deceased v/s recovered (0.33 v/s 0.5)], high sensitivity CRP (113.0 v/s 26.2) ferritin (1418.3 v/s 481.2), and erythrocyte sedimentation rate (38.5 v/s 28), were significantly higher in deceased patients than in recovered patients (p<0.05). Concentrations of Interleukin (IL) IL2 receptor, IL 6, IL8, IL10, and Tumour necrosis factor (TNFα) were also significantly higher in deceased patients than in recovered patients. Most (91%) deceased patients had undetectable concentrations of IL1β.1 It was observed in various studies that levels of cardiac troponin were raised in patients with severe COVID-19 disease.Similarly N-

terminal pro brain natriuretic peptide (NT-Pro BNP) was recognised as an independent predictor of mortality with sensitivity and specificity of 100% and 66.67% respectively a cut off value of 88.64 pg/mL. These nonspecific elevations of cardiac troponin and NT-Pro BNP could be due to the injury caused by SARS-CoV2 to the ACE-2 receptor rich cardiac tissue.36 This suggests that cardiac troponin and NT-Pro BNP elevations cannot he relied on to diagnose acute myocardial infarction or heart failure in COVID-19 patients.

5. PREGNANCY

Pregnant women do not appear more likely to contract the infection than the general population.However pregnancy is a state of partial immune suppression and it alters the normal physiological and immunological responses of the body uniquely. This may increase the risk of complication and severity of disease.
Studies have reported a mortality rate of 1.4% in pregnant women.There have been case reports of women with severe COVID-19 at the time of birth who have required ventilation and extracorporeal membrane oxygenation. In two retrospective studies from China, analyzing 16 females at term, all deliveries performed by Caesarian section had good outcomes. No data suggest there is an increased risk of preterm or miscarriages in COVID-19 pregnant female. There is no teratogenicity reported to date with Covid-19.

6. ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS

Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin II Receptor Blockers (ARB) are amongst the most important antihypertensive drugs. However, since the Angiotensin Converting Enzyme (ACE)-2 is primarily involved in the entry of the SARS-CoV2 virus into the host cells, and ACEI and ARB drugs could lead to over expression of this cellular receptor, promoting viral replication, the safety of these drugs was initially questioned.
Recent studies have attempted to settle this controversy. A multicenter retrospective study done by the American Heart Association in 1128 hospitalized COVID-19 patients with hypertension concluded that the inpatient use of ACEI/ARB was in fact associated with lower risk of all-cause mortality compared with ACEI/ARB non-users. Unadjusted mortality rate was lower in the ACEI/ARB group versus the non ACEI/ARB group (3.7% vs 9.8%replication). With data accumulated to date, the recommendation is that these drugs should not be discontinued or changed to other antihypertensive drug classes. There are now ongoing trials, (REPLACECOVID46 and CORONACION47), evaluating the possible protective role of ACE/ARB in COVID-19.

7. ETHNICITY

The impact of Corona virus has been disproportionate throughout the globe. This could be attributed to multiple factors, amongst which ethnicity is worth exploring. Ethnicity is a complex mix of genetic constituency, social and cultural practices, and behavioural patterns. Individuals from different ethnic backgrounds vary in behaviours, comorbidities, immune

profiles, and risk of infection, as exemplified by the increased morbidity and mortality in black and minority ethnic (BAME) communities in previous pandemics. The current pandemic appears to be following the same trend. According to most studies, people of BAME communities are most severely and disproportionately affected. In an observational study carried out by the Intensive Care National Audit and Research Centre, it was concluded that as many as one third (nearly 35%) of all ICU admission were from the minority ethnic group. In the United Kingdom of 2249 patients admitted to 201 critical care units in England, 64.8% were white, 13.8% were Asian, 13.6% were black, and 7.8% were from other or mixed ethnic groups.These were unadjusted descriptive data which took no account of factors other than ethnicity that could influence the risk of critical care admission. Similar trends were observed in Chicago where 70% of COVID-19 deaths involve black individuals, although blacks make up only 30% of Chicago's population.These results were consistent across Louisiana, Michigan and New York City. Possible reasons for this disproportionate predilection include socioeconomic, cultural, or lifestyle factors, genetic predisposition, or pathophysiological differences in susceptibility or response to infection. Other factors such as Vitamin D deficiency, vaccination policies in their country, possible but unproven role of BCG vaccination, and higher prevalence of cardiovascular risk factors such as insulin resistance and obesity in the BAME group may also be contributory.

8. GENETIC CONSTITUENCY

As described above, COVID-19 causes complications and deaths mainly in elderly patients with underlying health conditions. But on occasion, it may severely affect young and apparently healthy individuals, with no underlying co-morbidities. Many theories have been proposed to explain this paradox. Some suggest the role of the high viral load to which the patient (often a health care worker) is exposed, which may contribute to mortality even in a younger individual. However many believe that genetic constituency may be the cause of this unexpected vulnerability in a young and seemingly fit individual. Researchers have begun to study patients genomes for DNA variations that could help explain this mystery. This genetic hunt is expected to unmask many determinants of this pandemic, with gene encoding of ACE2 receptors an area of special interest. Apart from the role of ACE2 receptors, genetic studies have also unmasked the possible role of ABO blood groups in determining the outcome of disease. A recent genome association analyses done on 1980 patients with COVID-19 respiratory failure suggested that "A+ve" blood group was associated with higher odds of developing respiratory failure (OR 1.45) whereas blood group "O" had a protective role.(OR 0.65). In this study from Italy and Spain, those with "A+ve" blood group had a 45% higher risk of respiratory failure whilst O blood group had a 35% lower risk.

CONCLUDING REMARKS

As the SARS-Co-V-2 pandemic gathers speed across the globe our understanding of which groups of patients are most vulnerable has crystallised. Knowing that elderly patients, males more than females, hypertensives, diabetics, cardiac patients, those from the BAME group, those with chronic underlying lung disease, and those with cancer are more vulnerable provides extremely important insights. Shielding such high risk groups as best as possible from the ravages of the virus, and working on strategies to improve outcomes in these high-risk patients, will continue to evolve as the pandemic unfolds. As outlined, several laboratory markers such as NLR, D-dimer, procalcitonin, cardiac troponin, CRP and pro-inflammatory interleukins can also help to predict the progression of the disease and predict poor outcomes.

REFERENCES

1. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020. doi:10.1136/bmj.m1091
2. Wu C, Chen X, Cai Y, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020. doi:10.1001/jamainternmed.2020.0994
3. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. Jama 2020;10022:1-8. doi:10.1001/jama.2020.6775
4. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis 2020. doi:10.1016/s1473-3099(20)30243-7
5. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA - J Am Med Assoc 2020. doi:10.1001/jama.2020.1585
6. Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. JAMA 2020. doi:10.1001/jama.2020.4344
7. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. BMJ 2020. doi:10.1136/bmj.m1198.
8. Wambier CG, Goren A, Ossimetha A, Nau G, Qureshi AA. Theory Androgen-driven COVID-19 pandemic theory. 2020;(April):1-15. doi:10.13140/RG.2.2.21254.11848
9. Can Estrogen and Other Sex Hormones Help Men Survive Covid-19? - The New York Times. https://www.nytimes.com/2020/04/27/health/coronavirus-estrogen-men.html?referringSource=articleShare. Accessed April 29, 2020.
10. Stopsack KH, Mucci LA, Antonarakis ES, Nelson PS, Kantoff PW, Kettering S. Serendipity or Opportunity for Intervention? Cancer Discov 2020;10:1-4. doi:10.1158/2159-8290.CD-20-0451.
11. Shastri A, Wheat J, Agrawal S, et al. Delayed clearance of SARS-CoV2 in male compared to female patients: High ACE2 expression in testes suggests possible existence of gender-specific viral reservoirs. medRxiv. April 2020:2020.04.16.20060566. doi:10.1101/2020.04.16.20060566.
12. Guan W, Liang W, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. Eur Respir J. 2020. doi:10.1183/13993003.00547-2020.
13. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. Int J Infect Dis 2020; 94:91-95. doi:10.1016/j.ijid.2020.03.017.
14. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia – A systematic review, meta-analysis, and meta-regression: Diabetes and COVID-19. Diabetes Metab Syndr Clin Res Rev 2020; 14:395-403. doi:10.1016/j.dsx.2020.04.018.
15. Cariou B, Hadjadj S, Wargny, Matthieu, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020;IN PRESS:1-16. doi:10.1007/s00125-020-05180-x

16. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol 2020; 8:546-550. doi:10.1016/S2213-8587(20)30152-2
17. Chiappetta S, Sharma AM, Bottino V, Stier C. COVID-19 and the role of chronic inflammation in patients with obesity. Int J Obes May 2020:1-3. doi:10.1038/s41366-020-0597-4.
18. Lighter J, Phillips M, Hochman S, et al. Obesity in Patients Younger Than 60 Years Is a Risk Factor for COVID-19 Hospital Admission. Clin Infect Dis April 2020. doi:10.1093/cid/ciaa415
19. Disease IL, Ild M, Ild N, et al. British Thoracic Society Advice for Managing Interstitial Lung Disease Patients during COVID-19 pandemic. 2020;(Ild):1-6.
20. Williamson E, Walker AJ, Bhaskaran KJ, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv May 2020:2020.05.06.20092999. doi:10.1101/2020.05.06.20092999
21. Gianfrancesco M, Hyrich KL, Al-Adely S, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis May 2020. doi:10.1136/annrheumdis-2020-217871
22. Liu Y, Bi L, Chen Y, et al. Active or latent tuberculosis increases susceptibility to COVID-19 and disease severity. medRxiv March 2020:2020.03.10.20033795. doi:10.1101/2020.03.10.20033795
23. Stop TB partnership. The Potential Impact of the Covid-19 Response on Tuberculosis in High-Burden Countries : A Modelling Analysis. Dev by Stop TB Partnersh Collab with Imp Coll Avenir Heal Johns Hopkins Univ USAID. 2020:1-7.
24. Miyara M, Tubach F, Pourcher V, et al. Low incidence of daily active tobacco smoking in patients with symptomatic COVID-19. Qeios. April 2020. doi:10.32388/wpp19w.3
25. French researchers to test nicotine patches on coronavirus patients | World news | The Guardian. https://www.theguardian.com/world/2020/apr/22/french-study-suggests-smokers-at-lower-risk-of-getting-coronavirus. Accessed April 28, 2020.
26. Leung JM, Yang CX, Tam A, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur Respir J 2020;55(5):2000688. doi:10.1183/13993003.00688-2020.
27. Dai M, Liu D, Liu M, et al. Patients with cancer appear more vulnerable to SARS-COV-2: a multi-center study during the COVID-19 outbreak. Cancer Discov. April 2020:CD-20-0422. doi:10.1158/2159-8290.CD-20-0422.
28. Cancer patients are nearly three times more likely to die of covid-19, study says - The Washington Post. https://www.washingtonpost.com/health/2020/04/28/coronavirus-cancer-deathrates/. Accessed April 29, 2020.
29. Yang AP, Liu J ping, Tao W qiang, Li H ming. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol 2020;84. doi:10.1016/j.intimp.2020.106504.
30. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost 2020:0-3. doi:10.1111/jth.14859.

31. Bangalore S, Sharma A, Slotwiner A, et al. ST-Segment Elevation in Patients with Covid-19 — A Case Series. N Engl J Med 2020;5(50):NEJMc2009020. doi:10.1056/NEJMc2009020.
32. Choi S, Jang WJ, Song Y Bin, et al. D-dimer levels predict myocardial injury in ST-segment elevation myocardial infarction: A cardiac magnetic resonance imaging study. PLoS One 2016. doi:10.1371/journal.pone.0160955.
33. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497-506. doi:10.1016/S0140-6736(20)30183-5.
34. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395:1054-1062. doi:10.1016/S0140-6736(20)30566-3
35. Gao L, Jiang D, Wen XS, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. Respir Res 2020; 21:83. doi:10.1186/s12931-020-01352-w
36. Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated Troponin in Patients With Coronavirus Disease 2019: Possible Mechanisms. 2020. doi:10.1016/j.cardfail.2020.04.009
37. Royal College of Obstetricians and Gynaecologists. Coronavirus (COVID-19) Infection in Pregnancy Information for Healthcare Professionals.; 2020. doi:1037//0033-2909.I26.1.78
38. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet 2020. doi:10.1016/S0140-6736(20)30360-3
39. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020. doi:10.1056/nejmoa2002032
40. Liu Y, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. J Infect 2020. doi:10.1016/j.jinf.2020.02.028
41. Yu N, Li W, Kang Q, et al. Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study. Lancet Infect Dis 2020. doi:10.1016/s1473-3099(20)30176-6.
42. Mullins E, Evans D, Viner RM, O'Brien P, Morris E. Coronavirus in pregnancy and delivery: rapid review. Ultrasound Obstet Gynecol 2020. doi:10.1002/uog.22014.
43. Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 2020. doi:10.1186/s40779-020-00240-0.
44. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med 2020. doi:10.1056/nejmsr2005760.
45. Zhang P, Zhu L, Cai J, et al. Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19. Circ Res 2020:CIRCRESAHA.120.317134. doi:10.1161/CIRCRESAHA.120.317134.
46. Elimination or Prolongation of ACE Inhibitors and ARB in Coronavirus Disease 2019 - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04338009. Accessed June 2, 2020.

47. Coronavirus (COVID-19) ACEi/ARB Investigation - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04330300. Accessed June 2, 2020.
48. Pareek M, Bangash MN, Pareek N, et al. Correspondence Ethnicity and COVID-19 : an urgent public health research priority. Lancet. 2020;6736(20):2019-2020. doi:10.1016/S0140-6736(20)30922-3.
49. ICNARC. ICNARC report on COVID-19 in critical care. 2020;(March):1-9. icnarc.org
50. Khunti K, Singh AK, Pareek M, Hanif W. Is ethnicity linked to incidence or outcomes of covid-19? BMJ. 2020;369(April):m1548. doi:10.1136/bmj.m1548.
51. Thebault R, Tran AB, Williams V. African Americans are at higher risk of death from coronavirus - The Washington Post. Washington Post. https://www.washingtonpost.com/nation/2020/04/07/coronavirus-is-infecting-killing-black-americans-an-alarmingly-high-rate-post-analysis-shows/?arc404=true. Published 2020. Accessed May 29, 2020.
52. Bhala N, Curry G, Martineau AR, Agyemang C, Bhopal R. Sharpening the global focus on ethnicity and race in the time of COVID-19. Lancet. 2020;395(10238):1673-1676. doi:10.1016/s0140-6736(20)31102-8.
53. Yancy CW. COVID-19 and African Americans. JAMA - J Am Med Assoc 2020;323(19):1891-1892. doi:10.1001/jama.2020.6548.
54. Why do some young people die of coronavirus? | World news | The Guardian. https://www.theguardian.com/world/2020/apr/09/why-do-some-young-people-die-of-coronavirus-covid-19-genes-viral-load. Accessed April 30, 2020.
55. How sick will the coronavirus make you? The answer may be in your genes | Science | AAAS. https://www.sciencemag.org/news/2020/03/how-sick-will-coronavirus-make-you-answer-may-be-your-genes. Accessed April 30, 2020.
56. Ellinghaus D, Degenhardt F, Bujanda L, et al. The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis. doi:10.1101/2020.05.31.20114991.