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EVIDENCE SEARCH REPORT

RESEARCH QUESTION: How well does the presence and level of antibodies predict the clinical course of disease?	UNIQUE IDENTIFIER: LAB041501-01 ESR
REQUESTED RESOURCES: • medRxiv • Google • Google Scholar • Medline • PubMed • WHO Global Research on COVID-19 • PHAC COVID-19 • BMJ Best Practice	
LIMITS/EXCLUSIONS/INCLUSIONS: 2019-2020	
DATE: APRIL 15, 2020	TIME OF DAY: 16:49
LIBRARIAN: Brianna Howell-Spooner brianna.howell-spooner@saskhealthauthority.ca	REQUESTOR: Dr. Bruce Reeder
TEAM: EOC – LAB GROUP	SEARCH TIME: 8 HOURS
CITE AS: Howell-Spooner, B. How well does the presence and level of antibodies predict the clinical course of disease? 2020 Apr 15; Document no.: LAB041501-01 ESR In: COVID-19 Rapid Evidence Reviews [Internet]. SK: SK COVID Evidence Support Team, c2020. 22 p. (CEST evidence search report)	

LIBRARIAN NOTES/COMMENTS

Hello Hui,
Here are the results of my search on "How well does the presence and level of antibodies predict the clinical course of disease?"
Please let me know if you have any questions or have ideas of different search strategies that I haven't tried.
Cheers,
Brianna

SEARCH RESULTS

To obtain full-text articles email library@saskhealthauthority.ca.

ARTICLES FROM LIBRARY DATABASES

Note: References are sorted by year (newest to oldest)

Pre-printed articles

1. Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J (Engl). 2020. DOI: 10.1097/cm9.0000000000000824

ABSTRACT: BACKGROUND: The 2019 novel coronavirus (2019-nCoV) has caused the outbreak of the acute respiratory disease in Wuhan, Hubei Province of China since December 2019. This study is performed to analyze the clinical characteristics of patients who succumbed to and who recovered from 2019 novel coronavirus disease (COVID-19). METHODS: Clinical data were collected from two tertiary hospitals in Wuhan. A retrospective investigation was conducted to analyze the clinical characteristics of fatal cases of COVID-19 (death group) and compare them with recovered patients (recovered group). Continuous variables were analyzed using the Mann-Whitney U test. Categorical variables were analyzed by chi test or Fisher's exact tests as appropriate. RESULTS: Our study enrolled 109 COVID-19 patients who died during hospitalization and 116 recovered patients. The median age of the death group was older than the recovered group (69 [62, 74] years vs. 40 [33, 57] years, Z = 9.738, P < 0.001). More patients in the death group had underlying diseases (72.5% vs. 41.5%, chi = 22.105, P < 0.001). Patients in the death group had a significantly longer time of illness onset to hospitalization (10.0 [6.5, 12.0] days vs. 7.0 [5.0, 10.0] days, Z = 3.216, P = 0.001). On admission, the proportion of patients with symptoms of dyspnea (70.6% vs. 24.7%, chi = 60.905, P < 0.001) and expectoration (32.1% vs.15.7%, chi = 13.250, P < 0.001) was significantly higher. The blood oxygen saturation was significantly lower in the death group (85 [77, 91]% vs. 97 [95, 98]%, Z = 10.625, P < 0.001). The white blood cell (WBC) in death group was higher on admission (7.23 [4.87, 11.17] x 10/L vs. 4.52 [3.62, 5.88] x 10/L, Z = 7.618, P < 0.001). Patients in the death group exhibited significantly lower lymphocyte count (0.63 [0.40, 0.79] x 10/L vs. 1.00 [0. 72, 1.27] x 10/L, Z = 8.037, P < 0.001) and lymphocyte/WBC ratio (7.10 [4.45, 12.73]% vs. 23.5 [15.27, 31.25]%, Z = 10.315, P < 0.001) on admission, and the lymphocyte/WBC ratio continue to decrease during hospitalization (7.10 [4.45, 12.73]% vs. 2.91 [1.79, 6.13]%, Z = 5.242, P < 0.001). Alanine transaminase (ALT) (22.00 [15.00, 34.00] U/L vs. 18.70 [13.00, 30.38] U/L, Z = 2.592, P = 0.010), aspartate transaminase (AST) (34.00 [27.00, 47.00] U/L vs. 22.00 [17.65, 31.75] U/L, Z = 7.308, P < 0.001), and creatinine levels (89.00 [72.00, 133.50] mumol/L vs.65.00 [54.60, 78.75] mumol/L, Z = 6.478, P < 0.001) were significantly higher in the death group that those in the recovered group. C-reactive protein (CRP) levels were also significantly higher in the death group on admission (109.25 [35.00, 170.28] mg/L vs.3.22 [1.04, 21.80] mg/L, Z = 10.206, P < 0.001) showed no significant improvement after treatment (109.25 [35.0, 170.28] mg/L vs. 81.60 [27.23, 179.08] mg/L, Z = 1.219, P = 0.233). The patients in the death group had more complications such as acute respiratory distress syndrome (89.9% vs. 7.6%, chi = 148.105, P < 0.001), acute cardiac injury (59.6% vs. 0.8%, chi = 93.222, P < 0.001), acute kidney injury (18.3% vs. 0, chi = 23.257, P < 0.001), shock (11.9% vs. 0, chi = 14.618, P < 0.001), and disseminated intravascular coagulation (DIC) (6.4% vs. 0, chi = 7.655, P = 0.006). CONCLUSIONS: Compared to the recovered group, more patients in the death group exhibited characteristics of advanced age, pre-existing comorbidities, dyspnea, oxygen saturation decrease, increased WBC count, decreased lymphocytes, and elevated CRP levels. More patients in the death groups had complications such as ARDS, acute cardiac injury, acute kidney injury, shock, and DIC.

URL:
https://journals.lww.com/cmj/Abstract/publishahead/Clinical_characteristics_of_fatal_and_recovered.99319.aspx

DOI: 10.1097/cm9.0000000000000824
Librarian's Note: other potential serological markers (besides antibodies) of disease progression and fatality studied, could be useful

2. Fu L, Wang B, Yuan T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. J Infect. 2020. DOI: 10.1016/j.jinf.2020.03.041
ABSTRACT: OBJECTIVE: To better inform efforts to treat and control the current outbreak with a comprehensive characterization of COVID-19. METHODS: We searched PubMed, EMBASE, Web of Science, and CNKI (Chinese Database) for studies published as of March 2, 2020, and we searched references of identified articles. Studies were reviewed for methodological quality. A random-effects model was used to pool results. Heterogeneity was assessed using I(2). Publication bias was assessed using Egger's test. RESULTS: 43 studies involving 3600 patients were included. Among COVID-19 patients, fever (83.3% [95% CI 78.4-87.7]), cough (60.3% [54.2-66.3]), and fatigue (38.0% [29.8-46.5]) were the most common clinical symptoms. The most common laboratory abnormalities were elevated C-reactive protein (68.6% [58.2-78.2]), decreased lymphocyte count (57.4% [44.8-69.5]) and increased lactate dehydrogenase (51.6% [31.4-71.6]). Ground-glass opacities (80.0% [67.3-90.4]) and bilateral pneumonia (73.2% [63.4-82.1]) were the most frequently reported findings on computed tomography. The overall estimated proportion of severe cases and case-fatality rate (CFR) was 25.6% (17.4-34.9) and 3.6% (1.1-7.2), respectively. CFR and laboratory abnormalities were higher in severe cases, patients from Wuhan, and older patients, but CFR did not differ by gender. CONCLUSIONS: The majority of COVID-19 cases are symptomatic with a moderate CFR. Patients living in Wuhan, older patients, and those with medical comorbidities tend to have more severe clinical symptoms and higher CFR.
URL: https://www.journalofinfection.com/article/S0163-4453(20)30170-5/pdf
DOI: 10.1016/j.jinf.2020.03.041

3. Gao HX, Li YN, Xu ZG, et al. Detection of serum immunoglobulin M and immunoglobulin G antibodies in 2019-novel coronavirus infected cases from different stages. Chinese medical journal. 2020;26.
ABSTRACT: The epidemic caused by 2019 novel coronavirus (2019-nCoV) has drawn public attention (1) . Huge infected population and enormous economic loss make it the urgent public health event to deal with. Confirmatory test targeting virus RNA was established at the early stage of outbreak and then used for 2019-nCoV infection diagnosis (2) . However, high risk of laboratory infection, high-qualified personnel and strict operation condition hampered its application into primary hospitals and community clinics (3) . In this study, the serum immunoglobulin (Ig) M and IgG antibodies were detected in 2019-nCoV confirmed cases of different stages. Furthermore, three different immunological assays, chemiluminescent immunoassay (CLIA), gold immunochromatographic assay (GICA), and enzyme-linked immunosorbent assay (ELISA) were used for IgM and IgG detection.
URL:
https://journals.lww.com/cmj/Citation/publishahead/Detection_of_serum_immunoglobulin_M_and.99317.aspx

4. Liu L, Liu W, Wang S, et al. A preliminary study on serological assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 238 admitted hospital patients. medRxiv. 2020:2020.03.06.20031856. DOI: 10.1101/2020.03.06.20031856
ABSTRACT: Background The outbreak of the recently emerged novel corona virus disease 2019 (COVID-19) poses a challenge for public health laboratories. We aimed to evaluate the diagnostic value of serological assay for SARS-CoV-2. Methods A newly-developed ELISA assay for IgM and IgG antibodies against N protein of SARS-CoV-2 were used to screen the serums of 238 admitted hospital patients with confirmed or suspected SARS-CoV-2 infection from February 6 to February 14, 2020. SARS-CoV-2 RNA was detected by real time RT-PCR on pharyngeal swab specimens. Findings Of the 238 patients, 194 (81.5%) were detected to be antibody (IgM and/or IgG) positive, which was significantly higher than the positive rate of viral RNA (64.3%). There was no difference in the positive rate of antibody between the confirmed patients (83.0%, 127/153) and the suspected

patients (78.8%, 67/85) whose nucleic acid tests were negative. After the patients were defined to the different stages of disease based on the day when the test samples were collected, the analysis results showed that the antibody positive rates were very low in the first five days after initial onset of symptoms, and then rapidly increased as the disease progressed. After 10 days, the antibody positive rates jumped to above 80% from less than 50%. On the contrary, the positive rates of viral RNA kept above 60% in the first 11 days after initial onset of symptoms, and then rapidly decreased. In addition, half of the suspected patients with symptoms for 6-10 days were detected to be antibody positive. Interpretation The suspected patients were most likely infected by SARS-CoV-2. Before the 11th day after initial onset of symptoms, nucleic acid test is important for confirmation of viral infection. The combination of serological assay can greatly improve the diagnostic efficacy. After that, the diagnosis for viral infection should be majorly dependent on serological assay. Keywords. SARS-CoV-2; diagnosis; serological assay; nucleic acid testCompeting Interest StatementThe authors have declared no competing interest.Funding StatementThis work was supported by the National Natural Science Foundation of China (81801984, 81830003); the National Key Research and Development Program of China (2019YFC130030); and the China Postdoctoral Science Foundation (2019M664008).Author DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesThe data used to support the findings of this study are included within the article.
URL: http://medrxiv.org/content/early/2020/03/08/2020.03.06.20031856.abstract
DOI: 10.1101/2020.03.06.20031856

5. Liu Z, Long W, Tu M, et al. Lymphocyte subset (CD4+, CD8+) counts reflect the severity of infection and predict the clinical outcomes in patients with COVID-19. J Infect. 2020. DOI: 10.1016/j.jinf.2020.03.054
ABSTRACT: We read with interest the recent article by Chen J et al., which found lower CD4+ T cells count was associated with ICU admission in patients with the coronavirus disease 2019 (COVID-19).(1) Among the clinical and laboratory features of COVID-19, a number of abnormalities have been observed and described, the most prominent of which is total lymphopenia. Through routine blood analysis, a significant reduction in lymphocytes is frequently observed; however, there still lacks thoroughly research about the lymphocyte subset counts. Here, we aimed to investigate the changes of lymphocyte subset counts in COVID-19 patients and determine if these changes are associated with disease severity and prognosis.
URL: https://www.journalofinfection.com/article/S0163-4453(20)30182-1/pdf
DOI: 10.1016/j.jinf.2020.03.054

6. Lou B, Li T, Zheng S, et al. Serology characteristics of SARS-CoV-2 infection since the exposure and post symptoms onset. medRxiv. 2020:2020.03.23.20041707. DOI: 10.1101/2020.03.23.20041707
ABSTRACT: Background Timely diagnosis of SARS-CoV-2 infection is the prerequisite for treatment and preventive quarantine. The serology characteristics and complement diagnosis value of antibody test to RNA test needs to be demonstrated. Method A patient cohort study was conducted at the first affiliated hospital of Zhejiang University, China. Serial sera of COVID-19 patients were collected and total antibody (Ab), IgM and IgG antibody against SARS-CoV-2 were detected. The antibody dynamics during the infection were described. Results The seroconversion rate for Ab, IgM and IgG in COVID-19 patients was 98.8% (79/80), 93.8% (75/80) and 93.8% (75/80), respectively. The first detectible serology marker is total antibody and followed by IgM and IgG, with a median seroconversion time of 15, 18 and 20 day post exposure (d.p.e) or 9, 10 and 12 days post onset,

separately. The antibody levels increased rapidly since 6 d.p.o and accompanied with the decline of viral load. For patients in the early stage of illness (0-7d.p.o),Ab showed the highest sensitivity (64.1%) compared to the IgM and IgG (33.3% for both, p<0.001). The sensitivities of Ab, IgM and IgG detection increased to 100%, 96.7% and 93.3% two weeks later, respectively. Conclusions Typical acute antibody response is induced during the SARS-CoV-2 infection. The serology testing provides important complementation to RNA test for pathogenic specific diagnosis and helpful information to evaluate the adapted immunity status of patient. It should be strongly recommended to apply well-validated antibody tests in the clinical management and public health practice to improve the control of COVID-19 infection.Competing Interest StatementThe authors have declared no competing interest.Funding StatementThis study was supported by China National Mega-Projects for Infectious Diseases (2017ZX10103008), and the Science and Technology Major Project of Xiamen (3502Z2020YJ01).Author DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesWe will share individual participant data that underlie the results reported in this article after deidentification (text, tables, figures and appendices). The data will be available beginning 6 months after the major findings from the final analysis of the study were published, ending 2 years later. The data will be shared with investigators whose proposed use of the data has been approved by an independent review committee identified for individual participant data meta-analysis. Proposals should be directed to chenyuzy@zju.edu.cn. To gain access, data requestors will need to sign a data access agreement.
URL: https://www.medrxiv.org/content/medrxiv/early/2020/03/27/2020.03.23.20041707.full.pdf
DOI: 10.1101/2020.03.23.20041707

7. Nikolich-Zugich J, Knox KS, Rios CT, et al. SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. GeroScience. 2020. DOI: 10.1007/s11357-020-00186-0
ABSTRACT: SARS-CoV-2 virus, the causative agent of the coronavirus infectious disease-19 (COVID-19), is taking the globe by storm, approaching 500,000 confirmed cases and over 21,000 deaths as of March 25, 2020. While under control in some affected Asian countries (Taiwan, Singapore, Vietnam), the virus demonstrated an exponential phase of infectivity in several large countries (China in late January and February and many European countries and the USA in March), with cases exploding by 30-50,000/day in the third and fourth weeks of March, 2020. SARS-CoV-2 has proven to be particularly deadly to older adults and those with certain underlying medical conditions, many of whom are of advanced age. Here, we briefly review the virus, its structure and evolution, epidemiology and pathogenesis, immunogenicity and immune, and clinical response in older adults, using available knowledge on SARS-CoV-2 and its highly pathogenic relatives MERS-CoV and SARS-CoV-1. We conclude by discussing clinical and basic science approaches to protect older adults against this disease.
URL: https://link.springer.com/article/10.1007/s11357-020-00186-0
DOI: 10.1007/s11357-020-00186-0

8. Pan Y, Li X, Yang G, et al. Serological immunochromatographic approach in diagnosis with SARS-CoV-2 infected COVID-19 patients. J Infect. 2020;10:10.
ABSTRACT: An outbreak of new coronavirus SARS-CoV-2 was occurred in Wuhan, China and rapidly spread to other cities and nations. The standard diagnostic approach that widely adopted in the clinic is nucleic acid

detection by real-time RT-PCR. However, the false-negative rate of the technique is unneglectable and serological methods are urgently warranted. Here, we presented the colloidal gold-based immunochromatographic (ICG) strip targeting viral IgM or IgG antibody and compared it with real-time RT-PCR. The sensitivity of ICG assay with IgM and IgG combinatorial detection in nucleic acid confirmed cases were 11.1%, 92.9% and 96.8% at the early stage (1-7 days after onset), intermediate stage (8-14 days after onset), and late stage (more than 15 days), respectively. The ICG detection capacity in nucleic acid-negative suspected cases was 43.6%. In addition, the concordance of whole blood samples and plasma showed Cohen's kappa value of 0.93, which represented the almost perfect agreement between two types of samples. In conclusion, serological ICG strip assay in detecting SARS-CoV-2 infection is both sensitive and consistent, which is considered as an excellent supplementary approach in clinical application.
URL: https://www.journalofinfection.com/article/S0163-4453(20)30175-4/fulltext

9. Rokni M, Ghasemi V, Tavakoli Z. Immune responses and pathogenesis of SARS-CoV-2 during an outbreak in Iran: Comparison with SARS and MERS. Rev Med Virol. 2020. DOI: 10.1002/rmv.2107
ABSTRACT: The beginning of 2020 has seen the emergence of COVID-19, an outbreak caused by a novel coronavirus, SARS-CoV-2, an important pathogen for humans. There is an urgent need to better understand this new virus and to develop ways to control its spread. In Iran, the first case of the COVID-19 was reported after spread from China and other countries. Fever, cough, and fatigue were the most common symptoms of this virus. In worldwide, the incubation period of COVID-19 was 3 to 7 days and approximately 80% of infections are mild or asymptomatic, 15% are severe, requiring oxygen, and 5% are critical infections, requiring ventilation. To mount an antiviral response, the innate immune system recognizes molecular structures that are produced by the invasion of the virus. COVID-19 infection induces IgG antibodies against N protein that can be detected by serum as early as day 4 after the onset of disease and with most patients seroconverting by day 14. Laboratory evidence of clinical patients showed that a specific T-cell response against SARS-CoV-2 is important for the recognition and killing of infected cells, particularly in the lungs of infected individuals. At present, there is no specific antiviral therapy for COVID-19 and the main treatments are supportive. In this review, we investigated the innate and acquired immune responses in patients who recovered from COVID-19, which could inform the design of prophylactic vaccines and immunotherapy for the future.
URL: https://onlinelibrary.wiley.com/doi/full/10.1002/rmv.2107
DOI: 10.1002/rmv.2107

10. Tan W, Lu Y, Zhang J, et al. Viral Kinetics and Antibody Responses in Patients with COVID-19. medRxiv. 2020:2020.03.24.20042382. DOI: 10.1101/2020.03.24.20042382
ABSTRACT: Background A pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been spreading over the world. However, the viral dynamics, host serologic responses, and their associations with clinical manifestations, have not been well described in prospective cohort. Methods We conducted a prospective cohort and enrolled 67 COVID-19 patients admitting between Jan 26 and Feb 5, 2020. Clinical specimens including nasopharyngeal swab, sputum, blood, urine and stool were tested periodically according to standardized case report form with final follow-up on February 27. The routes and duration of viral shedding, antibody response, and their associations with disease severity and clinical manifestations were systematically evaluated. Coronaviral particles in clinical specimens were observed by transmission electron microscopy (TEM). Results The median duration of SARS-CoV-2 RNA shedding were 12 (3-38), 19 (5-37), and 18 (7-26) days in nasopharyngeal swabs, sputum and stools, respectively. Only 13 urines (5.6%) and 12 plasmas (5.7%) were viral positive. Prolonged viral shedding was observed in severe patients than that of non-severe patients. Cough but not fever, aligned with viral shedding in clinical respiratory specimens, meanwhile the positive stool-RNA appeared to align with the proportion who concurrently had cough and sputum production, but not diarrhea. Typical coronaviral particles could be found directly in sputum by TEM. The anti-nucleocapsid-protein IgM started on day 7 and positive rate peaked on day 28, while that of IgG was on day 10 and day 49 after illness onset. IgM and IgG appear earlier, and their titers are significantly higher in

severe patients than non-severe patients (p<0.05). The weak responders for IgG had a significantly higher viral clearance rate than that of strong responders (p= 0.011). Conclusions Nasopharyngeal, sputum and stools rather than blood and urine, were the major shedding routes for SARS-CoV-2, and meanwhile sputum had a prolonged viral shedding. Symptom cough seems to be aligned with viral shedding in clinical respiratory and fecal specimens. Stronger antibody response was associated with delayed viral clearance and disease severity.Competing Interest StatementThe authors have declared no competing interest.Funding StatementThis work was partly supported by Chongqing Health Commission COVID-19 Project 2020NCPZX01, Youth Talent Medical Technology Program of PLA (17QNP010), the Chinese Key Project Specialized for Infectious Diseases (2018ZX10723203), the TMMU key project for medical research (2018XYY10), and the Southwest Hospital Medical Science Innovation Plan (SWH2018BJKJ-01, SWH2018QNLC-04). We thank for the supports the Youth Talent Program from Third Military Medical University (Tan W and Sun F) and the Academy of Medical Sciences Newton International Fellowship (Tan W). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.Author DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesRelevant anonymized data will be made available on reasonable request from the corresponding author at gh_deng@hotmail.com or yaokaichen@hotmail.com.
URL: http://medrxiv.org/content/early/2020/03/26/2020.03.24.20042382.abstract
DOI: 10.1101/2020.03.24.20042382

11. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol. 2020. DOI: 10.1002/ajh.25829
ABSTRACT: COVID-19 is a systemic infection with a significant impact on the hematopoietic system and hemostasis. Lymphopenia may be considered as a cardinal laboratory finding, with prognostic potential. Neutrophil/lymphocyte ratio and peak platelet/lymphocyte ratio may also have prognostic value in determining severe cases. During the disease course, longitudinal evaluation of lymphocyte count dynamics and inflammatory indices, including LDH, CRP and IL-6 may help to identify cases with dismal prognosis and prompt intervention in order to improve outcomes. Biomarkers, such high serum procalcitonin and ferritin have also emerged as poor prognostic factors. Furthermore, blood hypercoagulability is common among hospitalized COVID-19 patients. Elevated D-Dimer levels are consistently reported, whereas their gradual increase during disease course is particularly associated with disease worsening. Other coagulation abnormalities such as PT and aPTT prolongation, fibrin degradation products increase, with severe thrombocytopenia lead to life-threatening Disseminated intravascular coagulation (DIC) which necessitates continuous vigilance and prompt intervention. COVID-19 infected patients whatever hospitalized or ambulatory are at high risk for VTE and an early and prolonged pharmacological thromboprophylaxis with low molecular weight heparin is highly recommended. Last but not least, the need for assuring blood donations during the pandemic is also highlighted.
URL: https://onlinelibrary.wiley.com/doi/abs/10.1002/ajh.25829
DOI: 10.1002/ajh.25829

12. Thevarajan I, Nguyen THO, Koutsakos M, et al. Breadth of concomitant immune responses underpinning viral clearance and patient recovery in a non-severe case of COVID-19. medRxiv. 2020:2020.02.20.20025841. DOI: 10.1101/2020.02.20.20025841

ABSTRACT: We report the kinetics of the immune response in relation to clinical and virological features of a patient with mild-to-moderate coronavirus disease-19 (COVID-19) requiring hospitalisation. Increased antibody-secreting cells, follicular T-helper cells, activated CD4+ and CD8+ T-cells and IgM/IgG SARS-CoV-2-binding antibodies were detected in blood, prior to symptomatic recovery. These immunological changes persisted for at least 7 days following full resolution of symptoms, indicating substantial anti-viral immunity in this non-severe COVID-19.Competing Interest StatementSRLÂ's institution has received funding for investigator initiated research grants from Gilead Sciences, Merck, Viiv Healthcare and Leidos. She has received honoraria for participation in advisory boards and educational activities for Gilead Sciences, Merck, Viiv Healthcare and Abbvie.Clinical TrialN/AFunding StatementThis work was funded by the Australian National Health and Medical Research Council (NHMRC) Investigator Grant to KK (#1173871). CES has received funding from the European UnionÂ's Horizon 2020 research and innovation programme under the Marie SkÅ,odowska-Curie grant agreement No 792532 and University of Melbourne McKenzie Fellowship laboratory support. KK is supported by a NHMRC Senior Research Fellowship Level B (#1102792) and SRL is supported by an NHMRC Practitioner Fellowship and an NHMRC program grant. SYCT is supported by a NHMRC Career Development Fellowship (#1145033). XJ is supported by China Scholarship Council-University of Melbourne joint Scholarship. Author DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesData availability The data that support the findings of this study are available from the corresponding author upon request. Raw FACS data are shown in the manuscript.
URL: http://medrxiv.org/content/early/2020/02/23/2020.02.20.20025841.abstract
DOI: 10.1101/2020.02.20.20025841

13. Xiao DAT, Gao DC, Zhang DS. Profile of Specific Antibodies to SARS-CoV-2: The First Report. J Infect. 2020. DOI: 10.1016/j.jinf.2020.03.012
ABSTRACT: A novel coronavirus (COVID-19) epidemic threatens the world.1 , 2 Before this study, some studies reported cases of viral detection by RT-PCR at different timepoints throughout the disease course.3 , 4 However, these reports monitored SARS-CoV-2 in the acute phase of infection. Currently no study reported the profile of specific antibodies to SARS-CoV-2 infection. Profile of specific antibodies in patients' blood can assist diagnosis and reflect the disease course. Here, we first studied the profile of IgM and IgG for SARS-CoV-2 from 34 COVID-19 patients.
URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7118534/
DOI: 10.1016/j.jinf.2020.03.012

14. Zeng F, Dai C, Cai P, et al. A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: a possible reason underlying different outcome between gender. medRxiv. 2020:2020.03.26.20040709. DOI: 10.1101/2020.03.26.20040709
ABSTRACT: Objective: To compare the difference of SARS-CoV-2 IgG antibody between male and female COVID-19 patients and figure out a possible explanation for different outcome between male and female patients. Methods: A total number of 331 patients confirmed SARS-CoV-2 infection were enrolled. The plasma of these patients were collected during hospitalization and were detected for SARS-CoV-2 IgG antibody. Afterwards, the difference of IgG antibody between male and female patients was analyzed. Results: The level of IgG antibody in mild, general and recovering patients showed on difference between male and female. In severe status, the

average IgG antibody level in female patients tended to be higher than that of in male patients. Compared with male patients, most of the female patients generated a relatively high level of SARS-CoV-2 IgG antibody in severe status. In addition, the generation of IgG antibody in female tended to be stronger than male patients in disease early phase. Conclusions: The inconsistent of SARS-CoV-2 IgG antibody generation in male and female patients may account for the different outcome of COVID-19 between gender.Competing Interest StatementThe authors have declared no competing interest.Funding StatementThere was no funding support in this work.Author DeclarationsAll relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.YesAll necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.YesI understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable.YesThe data are available from the author upon request.
URL: http://medrxiv.org/content/early/2020/03/27/2020.03.26.20040709.abstract
DOI: 10.1101/2020.03.26.20040709

15. Zhao J, Liao X, Wang H, et al. Early virus clearance and delayed antibody response in a case of COVID-19 with a history of co-infection with HIV-1 and HCV. Clin Infect Dis. 2020. DOI: 10.1093/cid/ciaa408
ABSTRACT: The effect of host immune status on SARS-CoV-2 infection remains unknown. Here, we report the first case of COVID-19 with HIV-1 and HCV co-infection, who showed a persistently negative SARS-CoV-2 RNA test, but delayed antibody response in the plasma. This case highlights the influence of HIV-1-induced immune dysfunction on the early SARS-CoV-2 clearance.
URL: https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa408/5818121
DOI: 10.1093/cid/ciaa408

16. Zhao J, Yuan Q, Wang H, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019 (preprint). medRxiv. 2020:2020.03.02.20030189. DOI: 10.1101/2020.03.02.20030189
ABSTRACT: Summary Background The novel coronavirus SARS-CoV-2 is a newly emerging virus. The antibody response in infected patient remains largely unknown, and the clinical values of antibody testing have not been fully demonstrated. Methods A total of 173 patients with confirmed SARS-CoV-2 infection were enrolled. Their serial plasma samples (n = 535) collected during the hospitalization period were tested for total antibodies (Ab), IgM and IgG against SARS-CoV-2 using immunoassays. The dynamics of antibodies with the progress and severity of disease was analyzed. Findings Among 173 patients, the seroconversion rate for Ab, IgM and IgG was 93.1% (161/173), 82.7% (143/173) and 64.7% (112/173), respectively. Twelve patients who had not seroconverted were those only blood samples at the early stage of illness were collected. The seroconversion sequentially appeared for Ab, IgM and then IgG, with a median time of 11, 12 and 14 days, respectively. The presence of antibodies was < 40% among patients in the first 7 days of illness, and then rapidly increased to 100.0%, 94.3% and 79.8% for Ab, IgM and IgG respectively since day 15 after onset. In contrast, the positive rate of RNA decreased from 66.7% (58/87) in samples collected before day 7 to 45.5% (25/55) during days 15 to 39. Combining RNA and antibody detections significantly improved the sensitivity of pathogenic diagnosis for COVID-19 patients ($p < 0.001$), even in early phase of 1-week since onset ($p = 0.007$). Moreover, a higher titer of Ab was independently associated with a worse clinical classification ($p = 0.006$). Interpretation The antibody detection offers vital clinical information during the course of SARS-CoV-2 infection. The findings provide strong empirical support for the routine application of serological testing in the diagnosis and management of COVID-19 patients. Competing Interest Statement The authors have declared no competing interest. Clinical Trial Not a study of clinical trial Funding Statement This study was supported by Bill & Melinda Gates Foundation. The

funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Author Declarations All relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript. Yes All necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived. Yes I understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).Yes I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable. Yes We will share individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures and appendices). Also redacted Study Protocol and Statistical Analysis Plan will be shared. The data will be available beginning 6 months after the major findings from the final analysis of the study were published, ending 2 years later. The data will be shared with investigators whose proposed use of the data has been approved by an independent review committee identified for individual participant data meta-analysis. Proposals should be directed to zhangzheng1975@aliyun.com or zhangj@xmu.edu.cn. To gain access, data requestors will need to sign a data access agreement.
URL: http://medrxiv.org/content/early/2020/03/02/2020.03.02.20030189.abstract
DOI: 10.1101/2020.03.02.20030189

Journal articles

17. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. The Journal of Clinical Investigation. 2020;130(5). DOI: 10.1172/JCI137244
ABSTRACT: BACKGROUND Since December 2019, an outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, and is now becoming a global threat. We aimed to delineate and compare the immunological features of severe and moderate COVID-19.METHODS In this retrospective study, the clinical and immunological characteristics of 21 patients (17 male and 4 female) with COVID-19 were analyzed. These patients were classified as severe (11 cases) and moderate (10 cases) according to the guidelines released by the National Health Commission of China.RESULTS The median age of severe and moderate cases was 61.0 and 52.0 years, respectively. Common clinical manifestations included fever, cough, and fatigue. Compared with moderate cases, severe cases more frequently had dyspnea, lymphopenia, and hypoalbuminemia, with higher levels of alanine aminotransferase, lactate dehydrogenase, C-reactive protein, ferritin, and D-dimer as well as markedly higher levels of IL-2R, IL-6, IL-10, and TNF-α. Absolute numbers of T lymphocytes, CD4+ T cells, and CD8+ T cells decreased in nearly all the patients, and were markedly lower in severe cases (294.0, 177.5, and 89.0 × 106/L, respectively) than moderate cases (640.5, 381.5, and 254.0 × 106/L, respectively). The expression of IFN-γ by CD4+ T cells tended to be lower in severe cases (14.1%) than in moderate cases (22.8%).CONCLUSION The SARS-CoV-2 infection may affect primarily T lymphocytes, particularly CD4+ and CD8+ T cells, resulting in a decrease in numbers as well as IFN-γ production by CD4+ T cells. These potential immunological markers may be of importance because of their correlation with disease severity in COVID-19.TRIAL REGISTRATION This is a retrospective observational study without a trial registration number.FUNDING This work is funded by grants from Tongji Hospital for the Pilot Scheme Project, and partly supported by the Chinese National Thirteenth Five Years Project in Science and Technology for Infectious Disease (2017ZX10202201).
URL: https://doi.org/10.1172/JCI137244
DOI: 10.1172/JCI137244

18. Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. J Biol Regul Homeost Agents. 2020;34(2):07.

ABSTRACT: CoV-19/SARS-CoV-2 is a highly pathogenic virus that causes coronavirus-19 disease (COVID-19) an acute respiratory distress syndrome which provokes serious problems for global health. Studies suggest that there are many differences between men and women in the immune response to CoV-19 infection and inflammatory diseases. Women, compared to men, are less susceptible to viral infections based on a different innate immunity, steroid hormones and factors related to sex chromosomes. The presence of two X chromosomes in women emphasize the immune system even if one is inactive. The immune regulatory genes encoded by X chromosome in female gender causes lower viral load levels, and less inflammation than in man, while CD4+ T cells are higher with better immune response. In addition, women generally produce higher levels of antibodies which remain in the circulation longer. The levels of activation of the immune cells are higher in women than in men, and it is correlated with the trigger of TLR7 and the production of IFN. TLR7 is higher in women than in men and its biallelic expression leads to higher immune responses and increases the resistance to viral infections. TLR7 is expressed in innate immune cells which recognizes single strand RNA virus by promoting the production of antibodies against the virus and the generation of pro-inflammatory cytokines including IL-6 and IL-1 family members. Moreover, in women the production of inflammatory IL-6 after viral infection is lower than in males and is often correlated with a better longevity. In addition, on the X chromosome there are loci that code for the genes involved in the regulation of immune cells such as FOXP3, and transcription factor for Treg involved in virus pathogenesis. The X chromosome influences the immune system by acting on many other proteins, including TLR8, CD40L and CXCR3 which can be over-expressed in women, and influence the response to viral infections and vaccinations. However, the biallelic expression of the X-linked genes can promote harmful autoimmune and inflammatory responses. Cardiovascular diseases are more frequent in males and subjects without cardiovascular dysfunctions infected by CoV-19 have a better prognosis. ACE2 is a receptor for CoV-19 and protects lung damage. CoV-19 infection and the virus's Spike protein inhibit the expression of ACE2, abolishing its protective function. Inhibitors of the angiotensin converting enzyme (ACEI) are used to stem the devastating effects of CoV-19, to increase the number of CD3 and CD8 T cells and to reduce the viral load and IL-6 levels that control CoV-19 replication via NF-B, but these effects are still under study. It is hoped that certain drugs, such as CoV-19 receptor blockers, anti-inflammatories (against rheumatic diseases), monoclonal antibodies, anti-IL-1 and anti-IL-6, the remdesevir drug (analogue adenosine, effective against ebola), hydroxychloroquine (for the treatment of malaria) and vaccines, will open up new strategies and new therapeutic ways to combat this terrible virus.

URL: https://www.biolifesas.org/biolife/2020/04/07/coronavirus-cov-19-sars-cov-2-affects-women-less-than-men-clinical-response-to-viral-infection/

19. Du Z, Zhu F, Guo F, et al. Detection of antibodies against SARS-CoV-2 in patients with COVID-19. J Med Virol. 2020. DOI: 10.1002/jmv.25820

ABSTRACT: Testing for SARS-CoV-2 RNA has become the standard for COVID-19 diagnosis.1, 2 However, a number of false negative results have been reported,2 resulting in a failure to quarantine infected patients. If unchecked, this could cause a major setback in containing viral transmission.3

Titers of SARS-CoV-2 antibodies can reflect the progress of viral infection. Around 60 convalescent patients (with an onset time of 6-7 weeks) in a ward in the Wuhan Tongji Hospital were tested for specific antibodies against SARS-CoV-2. All patients tested positive for the IgG against the virus, while 13 patients tested negative for immunoglobulin M (IgM), with the immunoglobulin G (IgG) titer being greater than the IgM titer (Table 1 and Figure 1). Meanwhile, the IgM and IgG titers in 10 convalescent patients were tested twice (1 week a part); both titers showed a decrease, with the IgG titer being greater than the IgM titer (Table 2 and Figure 1). In these patients, two consecutive SARS-CoV-2 RNA tests were negative and the chest computed tomography findings indicated improvement. Considering this, their antibody titers and consistent clinical manifestations suggested that antibody detection could act as an indicator of the stage of COVID-19 progression and that the antibodies in convalescent patients are not always maintained at a high level. The immune status fitted both, the clinical and

general characteristics of the humoral response. In one report, while 38 patients in the acute phase of the infection tested positive for SARS-CoV-2, 31 (81.6%) of them tested negative for IgM and IgG in serological assays,4 thereby demonstrating that these patients were in the early stages of infection, as both the antibody titers were relatively low (Supplemental table 1). COVID-19 patients will develop immunity after recovery; however, the persistence, attenuation, and duration of protection of SARS-CoV-2 antibodies requires further investigation.
URL: https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25820
DOI: 10.1002/jmv.25820

20. Gorse GJ, Donovan MM, Patel GB. Antibodies to coronaviruses are higher in older compared with younger adults and binding antibodies are more sensitive than neutralizing antibodies in identifying coronavirus-associated illnesses. J Med Virol. 2020;92(5):512-7.
ABSTRACT: Human coronaviruses (HCoV) are common causes of respiratory illnesses (RI) despite preexisting humoral immunity. Sera were obtained near the onset of RI and 3 to 4 weeks later as part of a prospective study of 200 subjects evaluated for RI from 2009 to 2013. Antibodies against common HCoV strains were measured by enzyme-linked immunosorbent assay and neutralization assay comparing older adults with cardiopulmonary diseases (99 subjects) to younger, healthy adults (101 subjects). Virus shedding was detected in respiratory secretions by polymerase chain reaction. Of 43 HCoV-associated illnesses, 15 (35%) occurred in 14 older adults (aged >=60 years) and 28 (65%) in 28 younger adults (aged 21-40 years). Binding and neutralizing antibodies were higher in older adults. Only 16 (35.7%) of RI with increases in binding antibodies also had increases in neutralizing antibodies to HCoV. Increases in binding antibodies with RI were more frequent than increased neutralizing antibodies and virus shedding, and more frequent in younger compared to older adults. Functional neutralizing antibodies were not stimulated as often as binding antibodies, explaining in part a susceptibility to reinfection with HCoV. Monitoring binding antibodies may be more sensitive for the serologic detection of HCoV infections.
URL: https://onlinelibrary-wiley-com.shal.idm.oclc.org/doi/pdfdirect/10.1002/jmv.25715

21. Guo L, Ren L, Yang S, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). Clin Infect Dis. 2020;21:21.
ABSTRACT: BACKGROUND: Emergence of coronavirus disease 2019 (COVID-19) is a major healthcare threat. Current method of detection involves qPCR-based technique, which identifies the viral nucleic acids when present in sufficient quantity. False negative results can be achieved and failure to quarantine the infected patient would be a major setback in containing the viral transmission. We here aim to describe the time kinetics of various antibodies produced against the 2019 novel coronavirus (SARS-CoV-2) and evaluate the potential of antibody testing to diagnose COVID-19.
METHODS: The host humoral response against SARS-CoV-2 including IgA, IgM and IgG response were examined by using an ELISA based assay on the recombinant viral nucleocapsid protein. Total 208 plasma samples were collected from 82 confirmed and 58 probable cases (qPCR negative but had typical manifestation). The diagnostic value of IgM was evaluated in this cohort.
RESULTS: The median duration of IgM and IgA antibody detection were 5 days (IQR 3-6), while IgG was detected on 14 days (IQR 10-18) after symptom onset, with a positive rate of 85.4%, 92.7% and 77.9% respectively. In confirmed and probable cases, the positive rates of IgM antibodies were 75.6% and 93.1%, respectively. The detection efficiency by IgM ELISA is higher than that of qPCR method after 5.5 days of symptom onset. The positive detection rate is significantly increased (98.6%) when combined IgM ELISA assay with PCR for each patient compare with a single qPCR test (51.9%).
CONCLUSIONS: Humoral response to SARS-CoV-2 can aid to the diagnosis of COVID-19, including subclinical cases.
URL: https://academic-oup-com.shal.idm.oclc.org/cid/article/doi/10.1093/cid/ciaa310/5810754

22. Haveri A, Smura T, Kuivanen S, et al. Serological and molecular findings during SARS-CoV-2 infection: the first case study in Finland, January to February 2020. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin. 2020;25(11):03.
ABSTRACT: The first case of coronavirus disease (COVID-19) in Finland was confirmed on 29 January 2020. No secondary cases were detected. We describe the clinical picture and laboratory findings 3-23 days since the first symptoms. The SARS-CoV-2/Finland/1/2020 virus strain was isolated, the genome showing a single nucleotide substitution to the reference strain from Wuhan. Neutralising antibody response appeared within 9 days along with specific IgM and IgG response, targeting particularly nucleocapsid and spike proteins.
URL: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.11.2000266

23. Li G, Fan Y, Lai Y, et al. Coronavirus infections and immune responses. J Med Virol. 2020;92(4):424-32.
ABSTRACT: Coronaviruses (CoVs) are by far the largest group of known positive-sense RNA viruses having an extensive range of natural hosts. In the past few decades, newly evolved Coronaviruses have posed a global threat to public health. The immune response is essential to control and eliminate CoV infections, however, maladjusted immune responses may result in immunopathology and impaired pulmonary gas exchange. Gaining a deeper understanding of the interaction between Coronaviruses and the innate immune systems of the hosts may shed light on the development and persistence of inflammation in the lungs and hopefully can reduce the risk of lung inflammation caused by CoVs. In this review, we provide an update on CoV infections and relevant diseases, particularly the host defense against CoV-induced inflammation of lung tissue, as well as the role of the innate immune system in the pathogenesis and clinical treatment. Copyright © 2020 Wiley Periodicals, Inc.
URL: https://onlinelibrary-wiley-com.shal.idm.oclc.org/doi/pdfdirect/10.1002/jmv.25685

24. Thevarajan I, Nguyen THO, Koutsakos M, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nat Med. 2020;26(4):453-5. DOI: 10.1038/s41591-020-0819-2
ABSTRACT: We report the kinetics of immune responses in relation to clinical and virological features of a patient with mild-to-moderate coronavirus disease 2019 (COVID-19) that required hospitalization. Increased antibody-secreting cells (ASCs), follicular helper T cells (TFH cells), activated CD4+ T cells and CD8+ T cells and immunoglobulin M (IgM) and IgG antibodies that bound the COVID-19-causing coronavirus SARS-CoV-2 were detected in blood before symptomatic recovery. These immunological changes persisted for at least 7 d following full resolution of symptoms.
URL: https://www.nature.com/articles/s41591-020-0819-2
DOI: 10.1038/s41591-020-0819-2

25. To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020. DOI: 10.1016/s1473-3099(20)30196-1
ABSTRACT: BACKGROUND: Coronavirus disease 2019 (COVID-19) causes severe community and nosocomial outbreaks. Comprehensive data for serial respiratory viral load and serum antibody responses from patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are not yet available. Nasopharyngeal and throat swabs are usually obtained for serial viral load monitoring of respiratory infections but gathering these specimens can cause discomfort for patients and put health-care workers at risk. We aimed to ascertain the serial respiratory viral load of SARS-CoV-2 in posterior oropharyngeal (deep throat) saliva samples from patients with COVID-19, and serum antibody responses. METHODS: We did a cohort study at two hospitals in Hong Kong. We included patients with laboratory-confirmed COVID-19. We obtained samples of blood, urine, posterior oropharyngeal saliva, and rectal swabs. Serial viral load was ascertained by reverse transcriptase quantitative PCR (RT-qPCR). Antibody levels against the SARS-CoV-2 internal nucleoprotein (NP) and surface spike protein receptor binding domain (RBD) were measured using EIA. Whole-genome sequencing was done to identify possible mutations arising during infection. FINDINGS: Between Jan 22, 2020, and Feb 12, 2020, 30 patients were screened for inclusion, of whom 23 were included (median age 62 years [range 37-75]).

The median viral load in posterior oropharyngeal saliva or other respiratory specimens at presentation was 5.2 log10 copies per mL (IQR 4.1-7.0). Salivary viral load was highest during the first week after symptom onset and subsequently declined with time (slope -0.15, 95% CI -0.19 to -0.11; R(2)=0.71). In one patient, viral RNA was detected 25 days after symptom onset. Older age was correlated with higher viral load (Spearman's rho=0.48, 95% CI 0.074-0.75; p=0.020). For 16 patients with serum samples available 14 days or longer after symptom onset, rates of seropositivity were 94% for anti-NP IgG (n=15), 88% for anti-NP IgM (n=14), 100% for anti-RBD IgG (n=16), and 94% for anti-RBD IgM (n=15). Anti-SARS-CoV-2-NP or anti-SARS-CoV-2-RBD IgG levels correlated with virus neutralisation titre (R(2)>0.9). No genome mutations were detected on serial samples. INTERPRETATION: Posterior oropharyngeal saliva samples are a non-invasive specimen more acceptable to patients and health-care workers. Unlike severe acute respiratory syndrome, patients with COVID-19 had the highest viral load near presentation, which could account for the fast-spreading nature of this epidemic. This finding emphasises the importance of stringent infection control and early use of potent antiviral agents, alone or in combination, for high-risk individuals. Serological assay can complement RT-qPCR for diagnosis. FUNDING: Richard and Carol Yu, May Tam Mak Mei Yin, The Shaw Foundation Hong Kong, Michael Tong, Marina Lee, Government Consultancy Service, and Sanming Project of Medicine.
URL: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30196-1/fulltext
DOI: 10.1016/s1473-3099(20)30196-1

26. Wynants L, Van Calster B, Bonten MMJ, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. BMJ. 2020;369:m1328. DOI: 10.1136/bmj.m1328
ABSTRACT: OBJECTIVE: To review and critically appraise published and preprint reports of prediction models for diagnosing coronavirus disease 2019 (covid-19) in patients with suspected infection, for prognosis of patients with covid-19, and for detecting people in the general population at risk of being admitted to hospital for covid-19 pneumonia. DESIGN: Rapid systematic review and critical appraisal. DATA SOURCES: PubMed and Embase through Ovid, Arxiv, medRxiv, and bioRxiv up to 24 March 2020. STUDY SELECTION: Studies that developed or validated a multivariable covid-19 related prediction model. DATA EXTRACTION: At least two authors independently extracted data using the CHARMS (critical appraisal and data extraction for systematic reviews of prediction modelling studies) checklist; risk of bias was assessed using PROBAST (prediction model risk of bias assessment tool). RESULTS: 2696 titles were screened, and 27 studies describing 31 prediction models were included. Three models were identified for predicting hospital admission from pneumonia and other events (as proxy outcomes for covid-19 pneumonia) in the general population; 18 diagnostic models for detecting covid-19 infection (13 were machine learning based on computed tomography scans); and 10 prognostic models for predicting mortality risk, progression to severe disease, or length of hospital stay. Only one study used patient data from outside of China. The most reported predictors of presence of covid-19 in patients with suspected disease included age, body temperature, and signs and symptoms. The most reported predictors of severe prognosis in patients with covid-19 included age, sex, features derived from computed tomography scans, C reactive protein, lactic dehydrogenase, and lymphocyte count. C index estimates ranged from 0.73 to 0.81 in prediction models for the general population (reported for all three models), from 0.81 to more than 0.99 in diagnostic models (reported for 13 of the 18 models), and from 0.85 to 0.98 in prognostic models (reported for six of the 10 models). All studies were rated at high risk of bias, mostly because of non-representative selection of control patients, exclusion of patients who had not experienced the event of interest by the end of the study, and high risk of model overfitting. Reporting quality varied substantially between studies. Most reports did not include a description of the study population or intended use of the models, and calibration of predictions was rarely assessed. CONCLUSION: Prediction models for covid-19 are quickly entering the academic literature to support medical decision making at a time when they are urgently needed. This review indicates that proposed models are poorly reported, at high risk of bias, and their reported performance is probably optimistic. Immediate sharing of well documented individual participant data from covid-19 studies is needed for collaborative efforts to develop more rigorous prediction models and validate existing ones. The predictors identified in included studies could be considered as candidate predictors for new models. Methodological

guidance should be followed because unreliable predictions could cause more harm than benefit in guiding clinical decisions. Finally, studies should adhere to the TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) reporting guideline. SYSTEMATIC REVIEW REGISTRATION: Protocol https://osf.io/ehc47/, registration https://osf.io/wy245.
URL: https://www.bmj.com/content/369/bmj.m1328.long
DOI: 10.1136/bmj.m1328

27. Zhao J, Yuan Q, Wang H, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis. 2020;28:28.
ABSTRACT: BACKGROUND: The novel coronavirus SARS-CoV-2 is a newly emerging virus. The antibody response in infected patient remains largely unknown, and the clinical values of antibody testing have not been fully demonstrated.
METHODS: A total of 173 patients with SARS-CoV-2 infection were enrolled. Their serial plasma samples (n=535) collected during the hospitalization were tested for total antibodies (Ab), IgM and IgG against SARS-CoV-2. The dynamics of antibodies with the disease progress was analyzed.
RESULTS: Among 173 patients, the seroconversion rate for Ab, IgM and IgG was 93.1%, 82.7% and 64.7%, respectively. The reason for the negative antibody findings in 12 patients might due to the lack of blood samples at the later stage of illness. The median seroconversion time for Ab, IgM and then IgG were day-11, day-12 and day-14, separately. The presence of antibodies was <40% among patients within 1-week since onset, and rapidly increased to 100.0% (Ab), 94.3% (IgM) and 79.8% (IgG) since day-15 after onset. In contrast, RNA detectability decreased from 66.7% (58/87) in samples collected before day-7 to 45.5% (25/55) during day 15-39. Combining RNA and antibody detections significantly improved the sensitivity of pathogenic diagnosis for COVID-19 ($p<0.001$), even in early phase of 1-week since onset ($p=0.007$). Moreover, a higher titer of Ab was independently associated with a worse clinical classification ($p=0.006$).
CONCLUSIONS: The antibody detection offers vital clinical information during the course of SARS-CoV-2 infection. The findings provide strong empirical support for the routine application of serological testing in the diagnosis and management of COVID-19 patients.
URL: https://academic-oup-com.shal.idm.oclc.org/cid/article/doi/10.1093/cid/ciaa344/5812996

SEARCH STRATEGIES

MEDLINE – April 15, 2020, 11:30am

#	Searches	Results
1	coronavirus/ or exp betacoronavirus/ or coronavirus infections/	10535
2	(coronavirus* or corona virus* or coronovirus* or coronaviral or (wuhan adj1 virus) or (wuhan adj1 viral) or cov or covid or WN-CoV or ncov or 2019ncov or ncov2019 or ncovid or ncovid2019 or 2019ncovid or covid-19 or covid19 or covid 19 or corvid 19 or HCov-19 or HCov-2019 or hcov19 or hcov2019 or severe acute respiratory syndrome coronavirus 2 or severe acute respiratory syndrome corona virus 2 or SARS Coronavirus 2 or SARS Corona virus 2 or SARS-COV-2 or SARSCOV2 or SARSCOV 2 or SARS2 or SARS-2 or coronavirus disease 2019 or corona virus disease 2019 or 2019 novel coronavirus infection* or 2019 novel coronavirus disease or 2019-nCoV infection* or coronavirus disease-19 or new coronavirus or novel corona virus).mp,kf,hw,rn,in.	19248

3	1 or 2	20705
4	antibodies/ or antibodies, viral/ or antibody specificity/	208568
5	(antibody or antibodies or antibody specificit* or antibody course).tw,kf.	852946
6	4 or 5	913767
7	disease progression/	159838
8	(disease course or clinical course or disease progression or disease cycle or clinical manifestation?).tw,kf.	209591
9	7 or 8	345188
10	3 and 6 and 9	41
11	limit 10 to yr="2019 -Current"	4
12	3 and 6	3254
13	12 not 11	3250
14	limit 13 to yr="2019 -Current"	258

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CINAHL – April 15, 2020, 1:51pm

#	Query	Results
S1	TX (coronavirus* or corona virus* or coronovirus* or coronaviral or (wuhan w1 virus) or (wuhan w1 viral) or cov or covid or WN-CoV or ncov or 2019ncov or ncov2019 or ncovid or ncovid2019 or 2019ncovid or covid-19 or covid19 or covid 19 or corvid 19 or HCov-19 or HCov-2019 or hcov19 or hcov2019 or severe acute respiratory syndrome coronavirus 2 or severe acute respiratory syndrome corona virus 2 or SARS Coronavirus 2 or SARS Corona virus 2 or SARS-COV-2 or SARSCOV2 or SARSCOV 2 or SARS2 or SARS-2 or coronavirus disease 2019 or corona virus disease 2019 or 2019 novel coronavirus infection* or 2019 novel coronavirus disease or 2019-nCoV infection* or coronavirus disease-19 or new coronavirus or novel corona virus)	7,984
S2	TX (antibody or antibodies or antibody specificit* or antibody course)	110,891
S3	TX (disease course or clinical course or disease progression or disease cycle or clinical manifestation?)	102,878
S4	S1 AND S2 AND S3	82
S5	S1 AND S2 AND S3 [Limit to 2019-2020]	5

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Embase – April 15, 2020, 1:46pm

#	Searches	Results

1	coronavirus/ or exp betacoronavirus/ or coronavirus infections/	14246
2	(coronavirus* or corona virus* or coronovirus* or coronaviral or (wuhan adj1 virus) or (wuhan adj1 viral) or cov or covid or WN-CoV or ncov or 2019ncov or ncov2019 or ncovid or ncovid2019 or 2019ncovid or covid-19 or covid19 or covid 19 or corvid 19 or HCov-19 or HCov-2019 or hcov19 or hcov2019 or severe acute respiratory syndrome coronavirus 2 or severe acute respiratory syndrome corona virus 2 or SARS Coronavirus 2 or SARS Corona virus 2 or SARS-COV-2 or SARSCOV2 or SARSCOV 2 or SARS2 or SARS-2 or coronavirus disease 2019 or corona virus disease 2019 or 2019 novel coronavirus infection* or 2019 novel coronavirus disease or 2019-nCoV infection* or coronavirus disease-19 or new coronavirus or novel corona virus).mp,hw,rn,in.	23102
3	1 or 2	23228
4	antibodies/ or antibodies, viral/ or antibody specificity/	233827
5	(antibody or antibodies or antibody specificit* or antibody course).tw,hw.	1402886
6	4 or 5	1402886
7	disease progression/	82045
8	(disease course or clinical course or disease progression or disease cycle or clinical manifestation?).tw,hw.	665755
9	7 or 8	729516
10	3 and 6 and 9	125
11	limit 10 to yr="2019 -Current"	9

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Pubmed – April 15, 2020, 10:19am
(((coronavirus [tiab] OR "2019-nCoV"[tiab] OR "2019nCoV"[tiab] OR "COVID-19"[tiab] OR "SARS-CoV-2"[tiab] OR (wuhan[tiab] AND coronavirus[tiab]) OR "Novel Coronavirus"[tiab] OR "new coronavirus"[tiab] OR "COVID-19" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "coronavirus infections" [mesh]) AND ((immunology[tiab] OR immunopathology[tiab] OR "Immune response"[tiab] OR "immune responses"[tiab] OR "immune evasion"[tiab] OR "immune system"[tiab] OR immunity[tiab] OR humoral[tiab] OR antibodies[tiab] OR antibody[tiab] OR lymphocyte*[tiab] OR macrophage*[tiab] OR "Immune System Phenomena"[Mesh] OR (("Macrophages"[Mesh]) OR "Leukocyte Count"[Mesh]) OR "Lymphocytes"[Mesh])) AND ((disease course[tiab] OR clinical course[tiab] OR disease progression[tiab] OR disease cycle[tiab] OR clinical manifestation[tiab] OR clinical manifestations[tiab]))) Filters: Publication date from 2019/11/01 to 2020/12/31
Results – 25

Pubmed – April 15, 2020, 10:46am
(((coronavirus [tiab] OR "2019-nCoV"[tiab] OR "2019nCoV"[tiab] OR "COVID-19"[tiab] OR "SARS-CoV-2"[tiab] OR (wuhan[tiab] AND coronavirus[tiab]) OR "Novel Coronavirus"[tiab] OR "new coronavirus"[tiab] OR "COVID-19"

[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "coronavirus infections" [mesh]) AND ((immunology[tiab] OR immunopathology[tiab] OR "Immune response"[tiab] OR "immune responses"[tiab] OR "immune evasion"[tiab] OR "immune system"[tiab] OR immunity[tiab] OR humoral[tiab] OR antibodies[tiab] OR antibody[tiab] OR lymphocyte*[tiab] OR macrophage*[tiab] OR "Immune System Phenomena"[Mesh] OR (("Macrophages"[Mesh]) OR "Leukocyte Count"[Mesh]) OR "Lymphocytes"[Mesh])))
Results - 315

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Google Scholar – April 15, 2020, 1:57pm
(2019 novel coronavirus disease OR 2019 novel coronavirus infection OR 2019-ncov disease OR 2019-ncov infection OR coronavirus disease 2019 OR coronavirus disease-19 OR coronavirus* OR coronovirus*) AND (antibod*) AND (disease course|clinical course)

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Search terms for other resources used in various combinations:
disease course
disease progression
disease cycle
clinical course
clinical manifestation
COVID-19 antibody disease course

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