The Daily COVID-19 Literature Surveillance Summary

October 19, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

Epidemiology

- Sex differential in COVID-19 mortality varies markedly by age according to collated data from the National Institute for Demographic Studies of pooled aggregate rates of infection and mortality of almost 400 million COVID-19 patients in Europe and Korea. Mortality risk ratio was found to be higher in men (overall RR: 1.35, no measure of significance provided). This risk was increased between the ages of 40-79 (RR: 1.87, no measure of significance provided). Authors suggest their findings corroborate prior data reporting equivalent rates of SARS-CoV-2 infection between men and women but higher rates of mortality in men, and hypothesize that both social and genetic factors contribute to this disparity.

- COVID-19 length of stay (LOS) at the hospital was evaluated in a systematic review of 52 studies (46 in China; 6 outside of China) to find the median LOS to be 14 days in China (interquartile range {IQR} 10-19) and 5 days outside China (IQR 3-9), with median ICU LOS of 8 (IQR 5-13) and 7 (IQR 4-11) days, respectively. Authors suggest that this data may be helpful for predicting when hospitals will reach capacity and determining how to appropriately distribute resources.

Transmission & Prevention

- COVID-19 Precautions Helped Limit Cases Linked to Milwaukee Primary. A Centers for Disease control case report described preventative measures enacted for the primary election in Milwaukee, Wisconsin which suggested that preventative measures such as mail-in ballots (69% of votes), early voting, social distancing, PPE for poll-workers, and frequent disinfection at polling sites (which were crowded due to reduction of polling sites from 181 to 5) resulted in no substantial increase in COVID-19 cases after the event.

Management

- Anaemia is associated with severe illness in COVID-19 according to a retrospective cohort study (n total=222, n anemic=79). Authors found anemic patients developed more severe cases of COVID-19 compared to non-anemic patients (17.7% vs 8.1%, P=0.001; OR 3.77, 95%CI:1.33-10.71, P=0.013), though results were limited by sample size. Anemic patients also had demonstrably elevated inflammatory markers (CRP, ESR, PCT, lymphocyte count), increased incidence of coagulopathies, and greater magnitude of organ damage, though no level of significance was provided for these measures. Based on this, the authors posit anemia as an independent risk factor for progression to the severe form of COVID-19, and urge close attention to hemoglobin levels in confirmed COVID-19 patients.

Adjusting Practice During COVID-19

- Outcomes of COVID-19 in 198 chronic lymphocytic leukemia (CLL) patients with CLL from 43 cancer care centers internationally yielded 90% hospitalized and an overall survival (OS) of 71% and 63% at 14 and 28 days, respectively. OS was not affected by whether patients were receiving CLL directed therapy (hazard ratio [HR], 0.77; 95% CI: 0.47-1.26; p = 0.30) or were on a "watch-and-wait" plan (HR, 0.83; 95% CI, 0.51-1.36; p = 0.47). Rather, age and CIRS score provided the largest impact on OS. Authors suggest that CLL patients are at greater risk for death from COVID-19, but different treatment plans for CLL have no effect on overall survival.

- Musculoskeletal injuries secondary to exercise during confinement by the pandemic COVID-19 was found through an 11 question survey of a convenience sample on Twitter in Spain. 12% of 1902 respondents reported MSK injuries during lockdown, with 35% reporting more physical activity than usual and 45% engaging in high intensity exercises. Based on this, they suggest there is a need for public education on safe exercise to decrease MSK injuries in the absence of supervision by trainers or coaches.

R&D: Diagnosis & Treatments

- Detection and quantification of SARS-CoV-2 by droplet digital PCR (ddPCR) in real-time PCR negative nasopharyngeal swabs from 55 suspected COVID-19 patients found 19 samples (35%) had detectable levels of SARS-CoV-2 by ddPCR (median viral load: 1128 copies/mL), of which 12 had multiple RT-PCR negative results (median number of negative swabs=3). They suggest ddPCR can detect SARS-CoV-2 at low copy numbers in symptomatic cases, which could improve sensitivity of testing where current RT-PCR assays are lacking and allow providers to correctly manage COVID-19 patients.

TABLE OF CONTENTS

SEX DIFFERENTIAL IN COVID-19 MORTALITY VARIES MARKEDLY BY AGE

Bhopal SS, Bhopal R.. Lancet. 2020 Aug 22;396(10250):532-533. doi: 10.1016/S0140-6736(20)31748-7. Epub 2020 Aug 13.
Level of Evidence: 3 - Local non-random sample

BLUF

Using collated data from the National Institute for Demographic Studies, epidemiologists from the United Kingdom pooled aggregate rates of infection and mortality of almost 400 million COVID-19 patients in Europe and Korea through June 21, 2020 (Summary) and found mortality risk ratio was higher in men (overall RR: 1.35, no measure of significance provided). This risk was increased between the ages of 40-79 (RR: 1.87, no measure of significance provided)(Summary, Table 1). Authors suggest their findings corroborate prior data reporting equivalent rates of SARS-CoV-2 infection between men and women but higher rates of mortality in men, and hypothesize that both social and genetic factors contribute to this disparity.

SUMMARY

There were a totoal of 396,064,955 COVID-19 positive patients pooled for this study, of these there were 194,349,591 men and 201,715,364 women. Participating nations include: England, Wales, France, Germany, Italy, Netherlands, Portugal, Korea, and Spain.

Researchers stratified their data by age group and found variance between age groups (Table 1). Overall mortality risk ratio between men and women was 1.35, with risk stratified by age as follows:
ages 0-9 years: 0.81,
ages 10-19 years: 1.46,
ages 20-29: 1.78,
ages 30-39: 1.65,
ages 40-49: 1.87,
ages 50-59: 2.31,
ages 60-69: 2.56,
ages 70-79: 2.36,
ages 80+: 1.65.

Authors hypothesize that occupation, lifestyle, and comorbid conditions are plausible explanations for the mortality disparity noted above. However, they acknowledge that genetic explanations will require a more granular approach that discusses not just geneomics but actual gene expression and epigenetics. They suggest that both social and genetic factors contribute to the increased mortality among men, but sex and age deaggregated data is necessary for further analysis.

FIGURES

Table 1: in 10 year age bands by sex, population, deaths, mortality per 100,000, risk ratio in England & Wales, France, Germany, Italy, Netherlands, Portugal, Korea and Spain

	Population		Deaths		Deaths per 100,000		Sex ratio (M:F)
Age group	Male	Female	Male	Female	Male	Female	
0-9	19923780	18935073	6	7	0.03	0.04	**0.81**
10-19	21333098	20087329	14	9	0.07	0.04	**1.46**
20-29	23719884	22435304	94	50	0.40	0.22	**1.78**
30-39	25310993	25157644	282	170	1.11	0.68	**1.65**
40-49	27912903	27945866	993	531	3.56	1.90	**1.87**
50-59	29327752	29834735	3776	1661	12.9	5.57	**2.31**
60-69	22611177	24271853	9590	4024	42.4	16.6	**2.56**
70-79	15668774	18552985	21830	10940	139.3	59.0	**2.36**
80+	8541230	14494575	41067	42199	480.8	291.1	**1.65**
ALL	194349591	201715364	77652	59591	40.0	29.5	**1.35**

Table 1: in 10 year age bands by sex, population, deaths, mortality per 100,000, risk ratio in England & Wales, France, Germany, Italy, Netherlands, Portugal, Korea and Spain

ADULTS

COVID-19 LENGTH OF HOSPITAL STAY: A SYSTEMATIC REVIEW AND DATA SYNTHESIS

Rees EM, Nightingale ES, Jafari Y, Waterlow NR, Clifford S, B Pearson CA, Group CW, Jombart T, Procter SR, Knight GM.. BMC Med. 2020 Sep 3;18(1):270. doi: 10.1186/s12916-020-01726-3.
Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

Epidemiologists from the London School of Hygiene and Tropical Medicine conducted a systematic review of 52 studies (46 in China; 6 outside of China) published from December 24, 201-April 16, 2020 evaluating hospital length of stay (LOS) for patients with COVID-19. They found median LOS was 14 days in China (interquartile range {IQR} 10-19) and 5 days outside China (IQR 3-9)(Figure 2), with median ICU LOS of 8 (IQR 5-13) and 7 (IQR 4-11) days, respectively (Figure 3, 4). Authors suggest that this data may be helpful for predicting when hospitals will reach capacity and determining how to appropriately distribute resources.

ABSTRACT

BACKGROUND: The COVID-19 pandemic has placed an unprecedented strain on health systems, with rapidly increasing demand for healthcare in hospitals and intensive care units (ICUs) worldwide. As the pandemic escalates, determining the resulting needs for healthcare resources (beds, staff, equipment) has become a key priority for many countries. Projecting future demand requires estimates of how long patients with COVID-19 need different levels of hospital care. METHODS: We performed a systematic review of early evidence on length of stay (LoS) of patients with COVID-19 in hospital and in ICU. We subsequently developed a method to generate LoS distributions which combines summary statistics reported in multiple studies, accounting for differences in sample sizes. Applying this approach, we provide distributions for total hospital and ICU LoS from studies in China and elsewhere, for use by the community. RESULTS: We identified 52 studies, the majority from China (46/52). Median hospital LoS ranged from 4 to 53 days within China, and 4 to 21 days outside of China, across 45 studies. ICU LoS was reported by eight studies-four each within and outside China-with median values ranging from 6 to 12 and 4 to 19 days, respectively. Our summary distributions have a median hospital LoS of 14 (IQR 10-19) days for China, compared with 5 (IQR 3-9) days outside of China. For ICU, the summary distributions are more similar (median (IQR) of 8 (5-13) days for China and 7 (4-11) days outside of China). There was a visible difference by discharge status, with patients who were discharged alive having longer LoS than those who died during their admission, but no trend associated with study date. CONCLUSION: Patients with COVID-19 in China appeared to remain in hospital for longer than elsewhere. This may be explained by differences in criteria for admission and discharge between countries, and different timing within the pandemic. In the absence of local data, the combined summary LoS distributions provided here can be used to model bed demands for contingency planning and then updated, with the novel method presented here, as more studies with aggregated statistics emerge outside China.

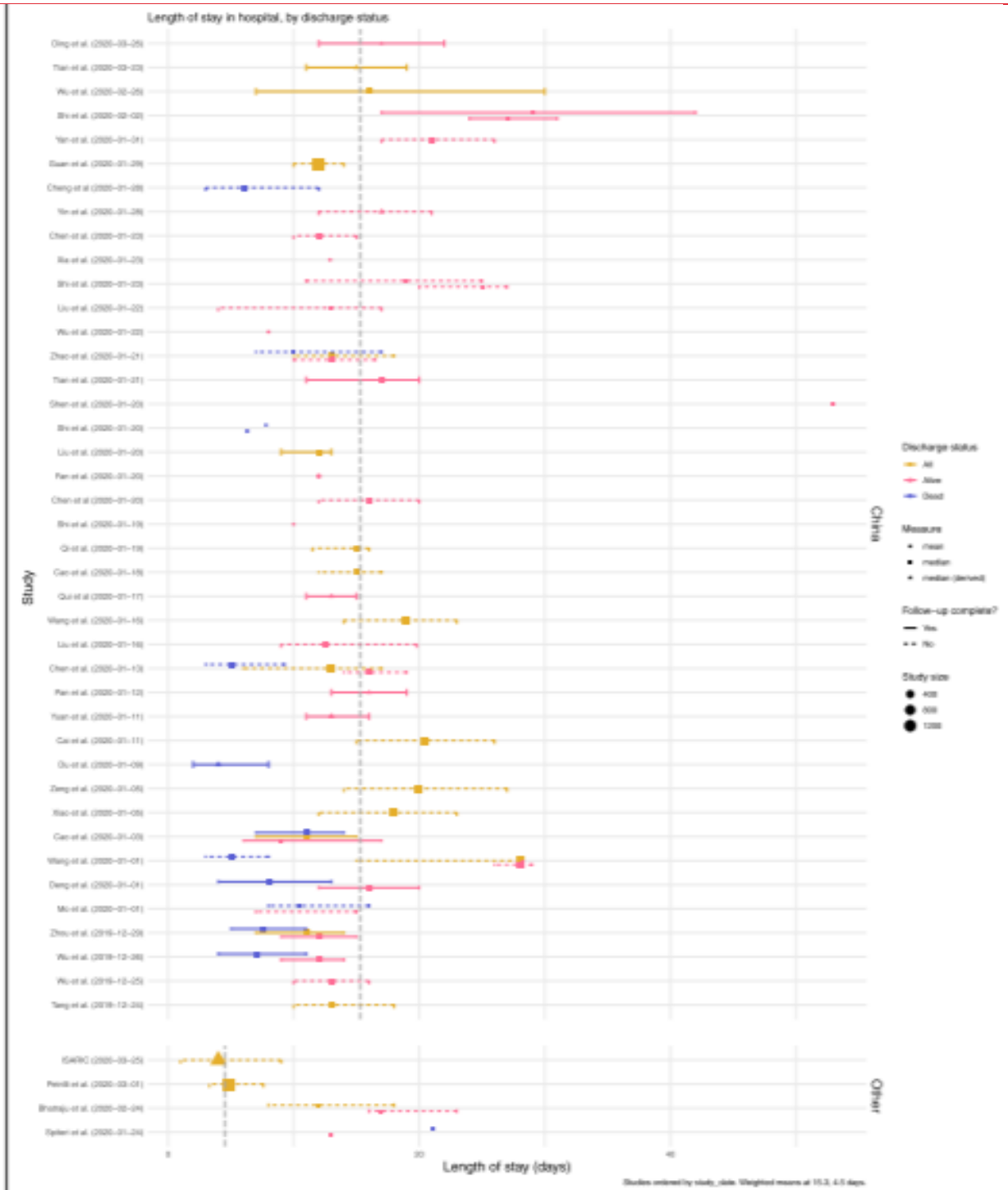


Fig. 2 Hospital length of stay, by discharge status. Medians (square) are presented with interquartile range (IQR). Where estimates were reported as mean and standard deviation, equivalent quantiles have been calculated assuming a Weibull distribution (triangle); if no measure of variation was reported, only the original mean is presented (circle). The grey dashed lines represent the mean value across all point estimates within that setting, weighted by sample size. The studies are ordered by the study start date, with most recent at the top. Two studies (Shi et al. (2020-02-02) and Shi et al. (2020-01-23)) have multiple estimates for the same outcome which represent multiple treatment and comorbidity subgroups, respectively. Details of these are included in Table 1

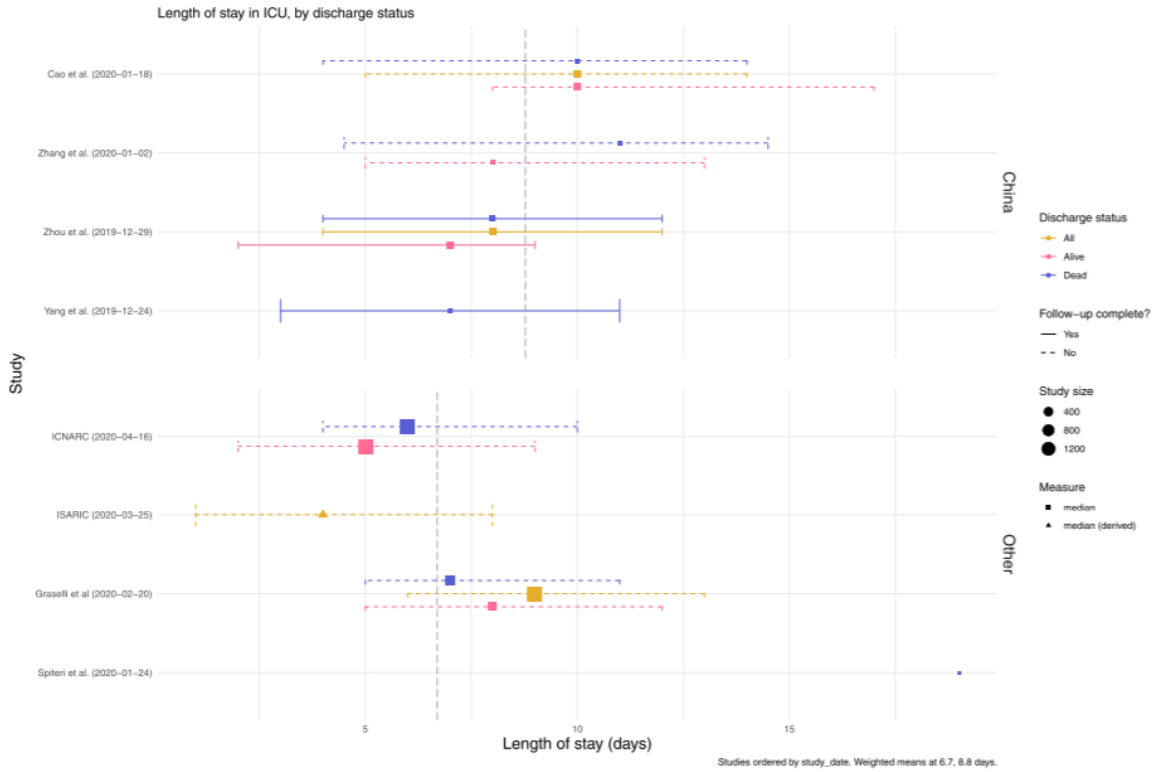


Fig. 3 ICU length of stay, by discharge status. Medians (square) are presented with interquartile range (IQR). Where estimates were reported as mean and standard deviation, equivalent quantiles have been calculated assuming a Weibull distribution (triangle); if no measure of variation was reported, only the original mean is presented (circle). The grey dashed lines represent the mean value across all point estimates within that setting, weighted by sample size. Studies are ordered by the study start date

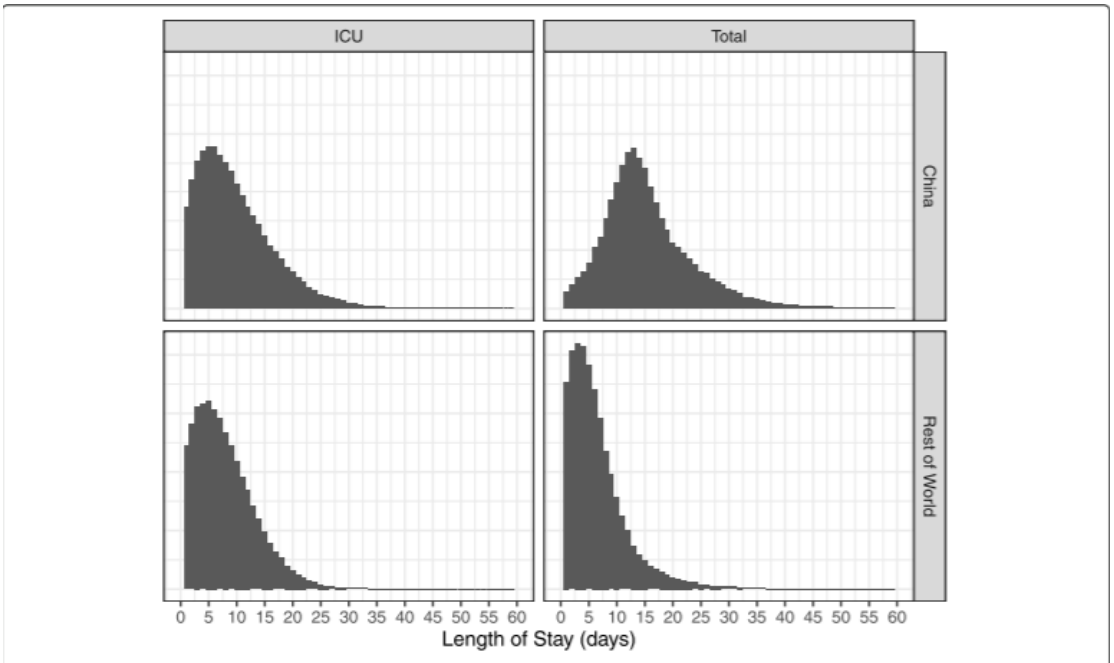


Fig. 4 Combined LOS distributions. Samples from the LoS distributions, split by location (China or rest of world) and type (ICU vs total LoS). For each subset, 100,000 draws were taken. The *x*-axis was cut at days = 60

MANNOSE-BINDING LECTIN IS ASSOCIATED WITH THROMBOSIS AND COAGULOPATHY IN CRITICALLY ILL COVID-19 PATIENTS

Eriksson O, Hultström M, Persson B, Lipcsey M, Ekdahl KN, Nilsson B, Frithiof R.. Thromb Haemost. 2020 Sep 1. doi: 10.1055/s-0040-1715835. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Immunologists from Uppsala University in Sweden conducted a cohort study of 65 critically ill patients with RT-PCR confirmed COVID-19 to investigate the role mannose-binding lectin (MBL) plays in thromboembolic (TE) complications. They found patients with thromboembolic complications (n=9, 14%) had significantly higher MBL levels than those without TE events independent from degree of inflammation and organ dysfunction (Figure 1). The authors suggest MBL contributes to COVID-19 associated coagulopathy (Summary), offering a potential target pathway for novel treatment of thrombosis in COVID-19 and laboratory marker for identifying patients at high risk for TE events.

SUMMARY

Mannose-binding lectin (MBL) is a complement activation factor that typically responds to mannose moieties on certain bacteria and yeast, but SARS-CoV-2 displays affinity for the complement protein. Here, immunologists from Uppsala University in Sweden conducted a cohort study of 65 critically ill patients with RT-PCR confirmed COVID-19 to investigate the role MBL plays in thromboembolic (TE) complications. Patients with elevated MBL were no more likely to die (deceased 717 kU/L [379–1,139] [median and interquartile range] vs. survivors 499 kU/L [282–1,115], p = 0.62), require mechanical ventilation (640 kU/L [302–1,156] vs. 460 kU/L [239–1,064], p = 0.54), or suffer acute kidney injury (p=0.55) compared to those without elevated MBL.

However, elevated MBL levels were associated with increased coagulation (see Figure 1, C-E), measured via elevated D-dimer levels and increased partial thromboplastin time (but not prothrombin time). All of the patients in the cohort were placed on thromboprophylaxis (64 patients with dalteparin sodium and one with apixaban). Nine patients (14%) developed TE despite anticoagulation; 2 with arterial thrombosis and the other 7 with pulmonary embolism. All patients with TE were in the 95th percentile for MBL levels and had increased MBL-dependent C3 deposition, but not increased C3d or C1q, suggesting activation of MBL in COVID-19 does not follow either the classic or alternative pathways of complement activation. Authors suggest their findings point towards a potential mechanism for the increased incidence of TE among COVID-19 patients, and offers a potential target pathway for novel treatment of thrombosis in COVID-19 and laboratory marker for identifying patients at high risk for TE events.

ABSTRACT

The ongoing COVID-19 pandemic has caused significant morbidity and mortality worldwide, as well as profound effects on society. COVID-19 patients have an increased risk of thromboembolic (TE) complications, which develop despite pharmacological thromboprophylaxis. The mechanism behind COVID-19-associated coagulopathy remains unclear. Mannose-binding lectin (MBL), a pattern recognition molecule that initiates the lectin pathway of complement activation, has been suggested as a potential amplifier of blood coagulation during thromboinflammation. Here we describe data from a cohort of critically ill COVID-19 patients (n = 65) treated at a tertiary hospital center intensive care unit (ICU). A subset of patients had strongly elevated MBL plasma levels, and activity upon ICU admission, and patients who developed symptomatic TE (14%) had significantly higher MBL levels than patients without TE. MBL was strongly correlated to plasma D-dimer levels, a marker of COVID-19 coagulopathy, but showed no relationship to degree of inflammation or other organ dysfunction. In conclusion, we have identified complement activation through the MBL pathway as a novel amplification mechanism that contributes to pathological thrombosis in critically ill COVID-19 patients. Pharmacological targeting of the MBL pathway could be a novel treatment option for thrombosis in COVID-19. Laboratory testing of MBL levels could be of value for identifying COVID-19 patients at risk for TE events.

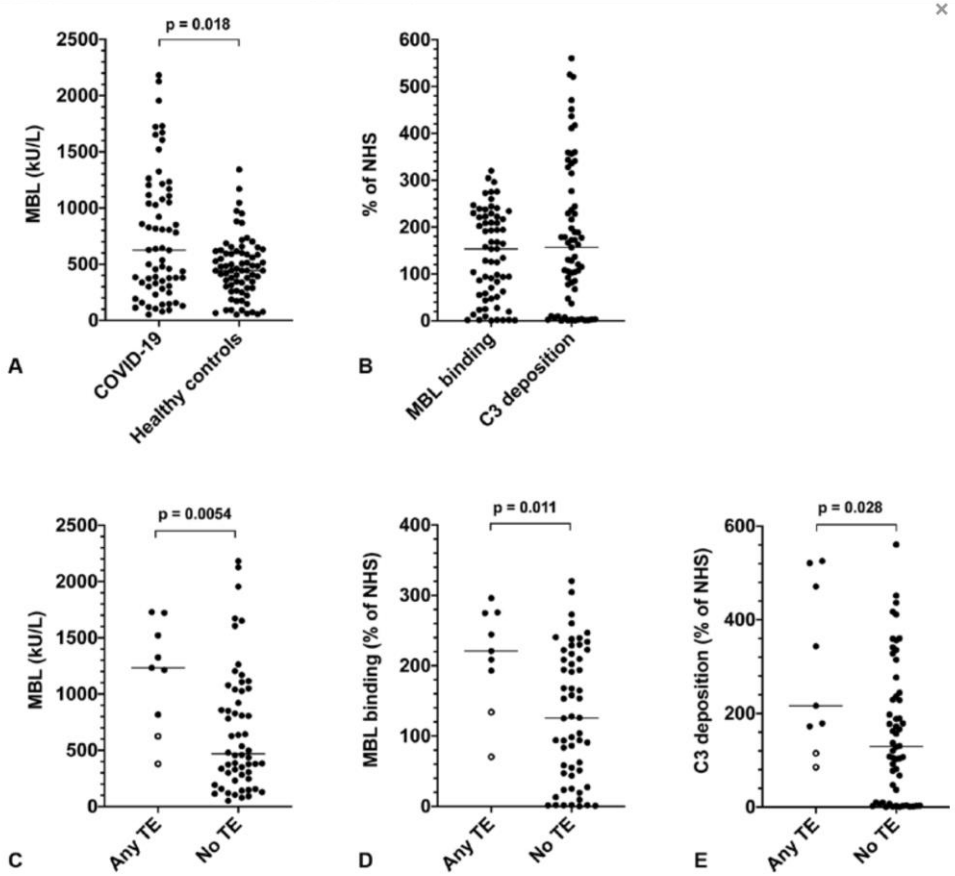


Figure 1. Elevated mannose-binding lectin (MBL) levels and activity in critically ill COVID-19 patients are associated with thromboembolic events. (A) COVID-19 patients have elevated plasma MBL levels compared with healthy controls (625 kU/L [303–1,112] in the patient group [n = 65] vs. 444 kU/L [288–611] in controls [healthy blood donors, n = 72], p = 0.018). MBL was measured by an in-house sandwich enzyme-linked immunosorbent assay (ELISA) using a mouse monoclonal anti-MBL antibody (clone 3E7, Hycult Biotech) as capture antibody. The same antibody was biotinylated and used for detection together with streptavidin-horseradish peroxidase (HRP). (B) Elevated MBL pathway activity in COVID-19 patients measured as MBL binding activity (153% [53–223]), and MBL-dependent C3 deposition (157% [42–296]). MBL pathway activity was measured by a functional ELISA using mannan as MBL ligand. Microtiter plates were coated with 5 µg/mL mannan overnight and then incubated with plasma samples diluted in veronal-buffered saline at 37°C for 30 minutes. After washing, bound MBL and deposited C3 were detected by antibodies from R&D Systems (AF2307) and Complement Technology (A213), respectively, and HRP-conjugated secondary antibodies. Results are expressed as percentage of the activity of pooled normal human serum (NHS). The MBL activity assay showed a very good correlation with the MBL antigen assay (Spearman's r = 0.94, p < 0.0001). (C–E) COVID-19 patients who develop thromboembolic complications have elevated plasma MBL levels and activity. Of the nine patients who developed thrombosis seven had pulmonary embolism (indicated by black dots) and two arterial thromboses (indicated by circles). (C) MBL plasma levels (1,233 kU/L [721–1,623] in the thrombosis group vs. 470 kU/L [256–1,037] in patients with no thrombosis, p = 0.0054); (D) MBL activity (221% [164–275] in the thrombosis group vs. 126% [45–215] in patients with no thrombosis, p = 0.011); (E) C3 deposition (216% [144–496] in the thrombosis group vs. 129% [10–243] in patients with no thrombosis, p = 0.028). Results are expressed as medians and interquartile ranges (IQRs). p-Values were calculated using the Mann–Whitney U test.

COVID-19 PRECAUTIONS HELPED LIMIT CASES LINKED TO MILWAUKEE PRIMARY

Kuehn BM.. JAMA. 2020 Sep 8;324(10):929. doi: 10.1001/jama.2020.16103.
Level of Evidence: 5 - Expert Opinion

BLUF

A journalist for JAMA reports on a Centers for Disease control case report describing preventative measures enacted for the primary election in Milwaukee, Wisconsin which suggested that preventative measures such as mail-in ballots (69% of votes), early voting, social distancing, PPE for poll-workers, and frequent disinfection at polling sites (which were crowded due to reduction of polling sites from 181 to 5) resulted in no substantial increase in COVID-19 cases after the event.

THE FIRST EIGHT MONTHS OF SWEDEN'S COVID-19 STRATEGY AND THE KEY ACTIONS AND ACTORS THAT WERE INVOLVED

Ludvigsson JF.. Acta Paediatr. 2020 Sep 20. doi: 10.1111/apa.15582. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A Swedish epidemiologist at the Karolinska Institutet reviews the first eight months of Sweden's response to the COVID-19 pandemic, which did not involve a general lockdown or universal masking and instead focused on interventions to slow transmission (Summary, Figure 1). Between March and April, 2020, 0.06% of the population died from COVID-19 (Figure 2c), and there was an overall 11% increase in mortality compared to the same dates in 2015-2019 (Figure 3). Because the mortality rate was lower than certain European countries but higher than surrounding Nordic countries, the author suggests these data are not sufficient to either support or refute the success of Sweden's strategy.

SUMMARY

Interventions implemented in Sweden to curb COVID-19 transmission:
- limited visits to the elderly and inpatient facilities
- identification of at risk groups for stricter isolation
- sick leave pay incurred by government
- implementation of travel restrictions
- encouraging work from home
- wearing face masks only in hospitals, unless working in nursing homes or caring for at-risk groups
- promoting physical distancing of at least one meter between people
- distance learning for students over age 17 and college-aged
- mobilizing hospitals to prepare for increased patients
- creating public health information campaigns
- aggressive testing for COVID-19

ABSTRACT

AIM: COVID-19 has affected millions of people worldwide. This paper reviews the Swedish pandemic response. METHODS: A narrative review was carried out and a timeline constructed. RESULTS: By 1 September 2020, 0.8% of Swedish residents had tested positive for the virus and 0.06% of the population had died, which was higher than neighbouring Nordic countries, but lower than some European countries with general lockdowns. The main actors were the Public Health Agency, the National Board of Health and Welfare, the Civil Contingencies Agency and the Government. County councils and regions implemented policies, in conjunction with the Department of Education and county administrative boards. Sweden's response was less invasive than many other countries, with no general lockdown. It focused on mitigation: slowing, but not stopping, the pandemic. Physical distancing was recommended in public spaces, but mandatory in bars, restaurants and at events. Visits to nursing facilities were banned. Kindergartens and schools for children up to 16 stayed open, but closed for older children for three months. There were no enforced quarantines for infected households or geographical regions and facemasks were not

recommended outside healthcare. CONCLUSION: Sweden chose a different pandemic strategy to its peer nations. This paper examines the first eight months.

FIGURES

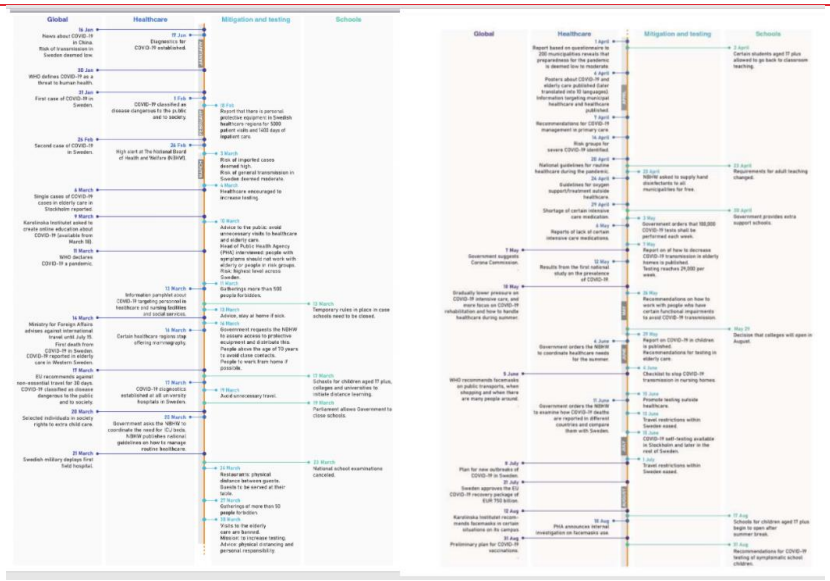
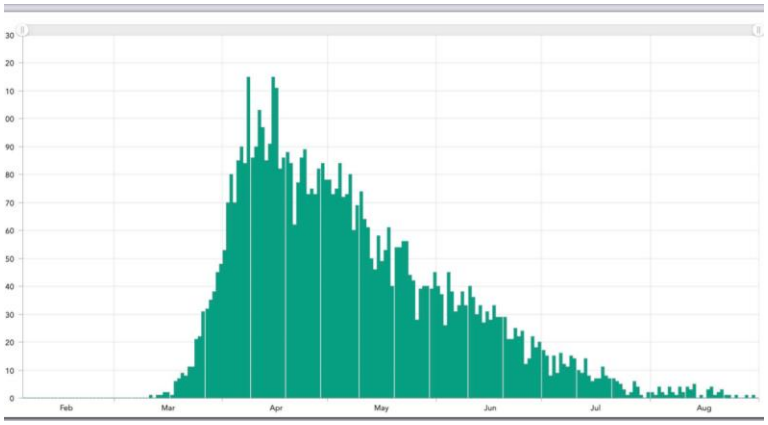
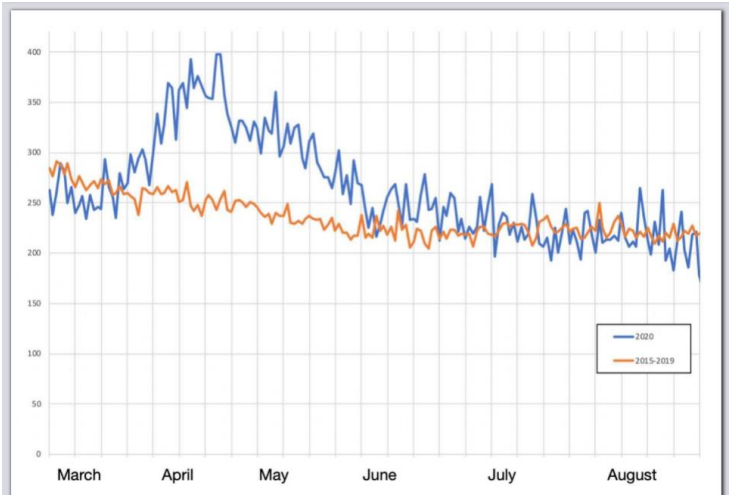


Figure 1: Timeline of the Swedish COVID-19 strategy (parts 1 and 2). ICU, intensive care unit; NBHW, Swedish National Board of Health and Welfare; PHA, Swedish Public Health Agency Data sources: NBHW, PHA, and the Department of Education



'Fig. 2c.' Deaths from COVID-19 in Sweden from 1 February to 31 August 2020 (source: Swedish Public Health Agency)



'Fig. 3.' Number of deaths per day from 1 March to 31 August 2020, compared with the average rates for 2015-2019. The excess mortality rate during these 6 months was 11%. (Source: Statistics Sweden)

APPROPRIATE USAGE OF FACE MASKS TO PREVENT SARS-COV-2: SHARPENING THE MESSAGING AMID THE COVID-19 PANDEMIC

Escandón K, Martin GP, Kuppalli K, Escandón K.. Disaster Med Public Health Prep. 2020 Sep 10:1-8. doi: 10.1017/dmp.2020.336. Online ahead of print.
Level of Evidence: Other - Opinion

BLUF

A letter to the editor written by anthropologists and healthcare professionals as part of the Cambridge Coronavirus Collection argue that confusing public messaging has led to inappropriate mask wearing (Figure 1), and suggest implementation of improved public education strategies regarding the benefits, degree of protection, and appropriate use of masks to ensure the highest benefit possible from their use (Table 1).

FIGURES

Table 1 Instructions for optimal mask wearing, storage, and disposal.[6,8–10]

- Wash hands thoroughly with water and soap for at least 20 seconds or clean them using an alcohol-based hand sanitizer (only if hands are not visibly dirty) before wearing a mask and after touching or removing the mask.
- Put the mask on and ensure it fits snugly around the face and covers nose, mouth, and chin completely at all times while wearing it.
- Avoid touching the face and the mask. If you touch the mask, wash or sanitize your hands.
- Do not fiddle with the mask. Do not share a mask with others.
- Remove the mask from the tie straps behind the head or elastic ear loops, without grabbing the front.
- Discard single-use masks immediately upon removal or when it becomes damaged, moist (e.g., contaminated with bodily fluids and secretions), or visibly dirty. Routinely wash reusable cloth masks with regular detergent and let them dry before wearing again.
- Keep masks in a clean, dry place (e.g., a clean plastic or paper bag)
- Since moisture from breathing inside masks may affect their effectiveness, it should be cautioned against the use of a single mask for extended periods. It is recommended to change to a fresh mask when the mask being worn becomes damp.
- Masks should not be worn by children under 2 years, people who may have baseline breathing difficulties, and people unconscious, incapacitated, or otherwise unable to wear a mask correctly. Alternatively, these people should rely on keeping the respiratory etiquette along with all other personal and environmental hygienic measures.
- Primary school-aged children should have adult supervision when wearing a mask.
- Masks should not be seen as an alternative to physical distancing.

Figure 1 Appropriate and inappropriate mask wearing amid the COVID-19 pandemic.

MANAGEMENT

ACUTE CARE

STEROIDS AND COVID-19: WE NEED A PRECISION APPROACH, NOT ONE SIZE FITS ALL

Waterer GW, Rello J.. Infect Dis Ther. 2020 Sep 16. doi: 10.1007/s40121-020-00338-x. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Referencing the increasing number of studies suggesting steroids benefit patients with COVID-19, intensivists from Spain and Australia caution against their universal application, citing a paucity of evidence supporting their utility in longer durations (>28 days) and patients over 70 years old, with diabetes, and/or mild disease. Authors suggest clinicians should weigh risks and benefits when considering steroids to treat COVID-19 in these groups until more research is available.

ABSTRACT

COVID-19 is a new infectious disease causing severe respiratory failure and death for which optimal treatment is currently unclear. Many therapies have been proven to be ineffective; however, promising findings related to corticosteroid therapy have been published. Analysis of published data including in this issue suggests that therapy with corticosteroids in the range of 6 mg of dexamethasone (or equivalent) per day likely has a positive effect in patients requiring mechanical ventilation but there remains considerable doubt in patients over the age of 70, in patients with diabetes and patients with milder disease. Clinicians must consider the individual potential risks and benefits of corticosteroid in patients with COVID-19 rather than routinely using them until more data is available.

MEDICAL SUBSPECIALTIES

HEMATOLOGY AND ONCOLOGY

ANAEMIA IS ASSOCIATED WITH SEVERE ILLNESS IN COVID-19: A RETROSPECTIVE COHORT STUDY

Tao Z, Xu J, Chen W, Yang Z, Xu X, Liu L, Chen R, Xie J, Liu M, Wu J, Wang H, Liu J.. J Med Virol. 2020 Aug 19. doi: 10.1002/jmv.26444. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective observational study conducted by critical care and emergency medicine physicians in Wuhan, China investigated disease progression of COVID-19 in patients with anemia (n total=222, n anemic=79). Authors found anemic patients developed more severe cases of COVID-19 (see Summary for definition) compared to non-anemic patients (17.7% vs 8.1%, P=0.001; OR 3.77, 95%CI:1.33-10.71, P=0.013), though results were limited by sample size. Anemic patients also had demonstrably elevated inflammatory markers (CRP, ESR, PCT, lymphocyte count), increased incidence of coagulopathies, and greater magnitude of organ damage (see Figures 1 and 2), though no level of significance was provided for these measures. Based on this, the authors posit anemia as an independent risk factor for progression to the severe form of COVID-19, and urge close attention to hemoglobin levels in confirmed COVID-19 patients.

SUMMARY

For the purposes of this paper "Severe COVID-19" is defined as positive COVID-19 meeting one of the following criteria:

1) respiratory distress, respiratory rate (RR) ≥30/min
2) oxyhemoglobin saturation (SpO2) <93% at rest;
3) partial pressure of oxygen/fraction of inspiration O2 (PaO2/FiO2) ≤300mmHg
4) have respiratory failure and need for mechanical assistance; shock; “extra pulmonary” organ failure, intensive care unit is

needed.

Otherwise, the patients were diagnosed as non-severe cases.

ABSTRACT

BACKGROUND AND OBJECTIVE: Anaemia commonly aggravates the severity of respiratory diseases, whereas thus far, few study has elucidated the impact of anaemia on Corona Virus Disease 2019 (COVID-19). The aim of this study was to evaluate the clinical characteristics of patients with anaemia, and to further explore the relationship between anaemia and the severity of COVID-19. METHODS: In this single-center, retrospective, observational study, a total of 222 confirmed patients admitted to Wuhan Ninth Hospital from December 1, 2019 to March 20, 2020 were recruited, including 79 patients with anaemia and 143 patients without anaemia. Clinical characteristics, laboratory findings, disease progression and prognosis were collected and analyzed. Risk factors associated with the severe illness in COVID-19 were established by univariable and multivariable logistic regression models. RESULT: In our cohort, compared to patients without anaemia, patients with anaemia were more likely to have one or more comorbidities and severe COVID-19 illness. More patients demonstrated elevated levels of C-reactive protein (CRP), procalcitonin (PCT) and creatinine in anaemia group. Levels of erythrocyte sedimentation rate (ESR), D-dimer, myoglobin, T-pro brain natriuretic peptide (T-pro-BNP) and urea nitrogen (BUN) in patients with anaemia were significantly higher than those without. In addition, the proportion of patients with dyspnoea, elevated CRP and PCT was positively associated with the severity of anaemia. The Odd Ratio (OR) of anaemia related to the severe condition of COVID-19 was 3.47(95% CI: 1.02-11.75, P=0.046) and 3.77 (95% CI:1.33-10.71, P=0.013) after adjustment for baseline date and laboratory indices, respectively. CONCLUSION: Anaemia is an independent risk factor associated with the severe illness of COVID-19, and healthcare professionals should be more sensitive to the haemoglobin levels of COVID-19 patients on admission. Awareness of anemia as a risk factor for COVID-19 was of great significance. TRIAL REGISTRATION: Ethics committee of Wuhan University People's Hospital (wdry2020-k064) This article is protected by copyright. All rights reserved.

FIGURES

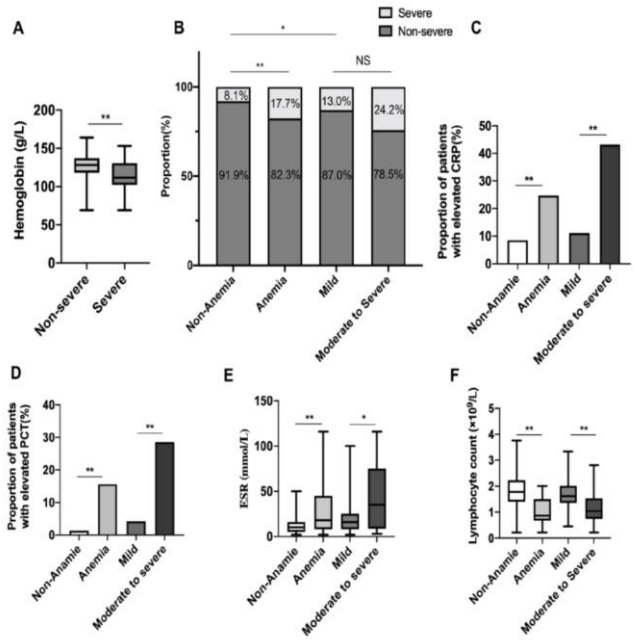


Figure 1. A: Haemoglobin levels between severe and non-severe group. B: Prevalence of clinical subtypes of COVID-19 severity among patients with and without anaemia as well as patients with different severity of anaemia. C, D, E, F: Significant laboratorial findings including c-reactive protein, erythrocyte sedimentation rate and lymphocyte count among patients with and without anaemia as well as patients with different severity of anaemia. *: p<0.05; **: p<0.01; ***p<0.001

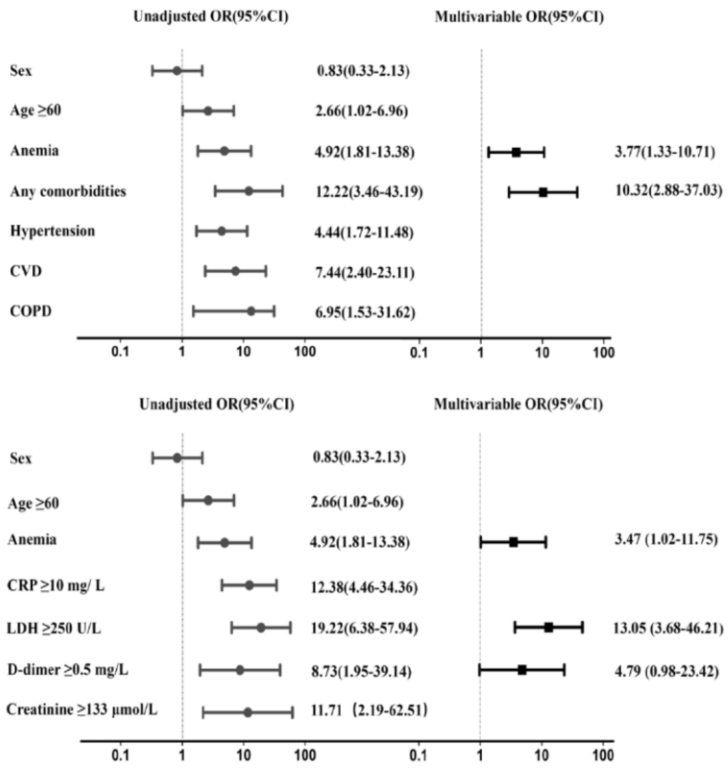


Figure 2. Univariate and multivariate logistic analysis associated with severe illness in COVID-19. Odds ratios were calculated by univariate and multivariate logistic regression. The x-axis is on a log scale. Variables with P <0.05 were defined as potential risk factors and included in multivariate regression analysis by a backward elimination procedure. CVD: Chronic Cardiovascular Disease; COPD: Chronic Obstructive Pulmonary Disease; CRP:C-reactive protein; LDH: Lactate Dehydrogenase

OUTCOMES OF COVID-19 IN PATIENTS WITH CLL: A MULTICENTER INTERNATIONAL EXPERIENCE

Mato AR, Roeker LE, Lamanna N, Allan JN, Leslie L, Pagel JM, Patel K, Osterborg A, Wojenski D, Kamdar M, Huntington SF, Davids MS, Brown JR, Antic D, Jacobs R, Ahn IE, Pu J, Isaac KM, Barr PM, Ujjani CS, Geyer MB, Berman E, Zelenetz AD, Malakhov N, Furman RR, Koropsak M, Bailey N, Hanson L, Perini GF, Ma S, Ryan CE, Wiestner A, Portell CA, Shadman M, Chong EA, Brander DM, Sundaram S, Seddon AN, Seymour E, Patel M, Martinez-Calle N, Munir T, Walewska R, Broom A, Walter H, El-Sharkawi D, Parry H, Wilson MR, Patten PEM, Hernández-Rivas JÁ, Miras F, Fernández Escalada N, Ghione P, Nabhan C, Lebowitz S, Bhavsar E, López-Jiménez J, Naya D, Garcia-Marco JA, Skånland SS, Cordoba R, Eyre TA.. Blood. 2020 Sep 3;136(10):1134-1143. doi: 10.1182/blood.2020006965.
Level of Evidence: 3 - Local non-random sample

BLUF

An international team of oncologists conducted a cohort study to evaluate outcomes of 198 chronic lymphocytic leukemia (CLL) patients infected with SARS-CoV-2 between February 17-April 30, 2020 in 43 cancer care centers internationally. They found 90% were hospitalized and overall survival (OS) was 71% and 63% at 14 and 28 days, respectively (Figure 1). OS was not affected by whether patients were receiving CLL directed therapy (hazard ratio [HR], 0.77; 95% CI: 0.47-1.26; p = 0.30) or were on a "watch-and-wait" plan (HR, 0.83; 95% CI, 0.51-1.36; p = 0.47). Rather, age and CIRS score provided the largest impact on OS (Figure 2). Authors suggest that CLL patients are at greater risk for death from COVID-19, but different treatment plans for CLL have no effect on overall survival.

ABSTRACT

Given advanced age, comorbidities, and immune dysfunction, chronic lymphocytic leukemia (CLL) patients may be at particularly high risk of infection and poor outcomes related to coronavirus disease 2019 (COVID-19). Robust analysis of outcomes for CLL patients, particularly examining effects of baseline characteristics and CLL-directed therapy, is critical to optimally manage CLL patients through this evolving pandemic. CLL patients diagnosed with symptomatic COVID-19 across 43 international centers (n = 198) were included. Hospital admission occurred in 90%. Median age at COVID-19 diagnosis was 70.5 years. Median Cumulative Illness Rating Scale score was 8 (range, 4-32). Thirty-nine percent were treatment naive ("watch and wait"), while 61% had received >=1 CLL-directed therapy (median, 2; range, 1-8). Ninety patients (45%) were receiving active CLL therapy at COVID-19 diagnosis, most commonly Bruton tyrosine kinase inhibitors (BTKi's; n = 68/90 [76%]). At a median follow-up of 16 days, the overall case fatality rate was 33%, though 25% remain admitted. Watch-and-wait and treated cohorts had similar rates of admission (89% vs 90%), intensive care unit admission (35% vs 36%), intubation (33% vs 25%), and mortality (37% vs 32%). CLL-directed treatment with BTKi's at COVID-19 diagnosis did not impact survival (case fatality rate, 34% vs 35%), though the BTKi was held during the COVID-19 course for most patients. These data suggest that the subgroup of CLL patients admitted with COVID-19, regardless of disease phase or treatment status, are at high risk of death. Future epidemiologic studies are needed to assess severe acute respiratory syndrome coronavirus 2 infection risk, these data should be validated independently, and randomized studies of BTKi's in COVID-19 are needed to provide definitive evidence of benefit.

FIGURES

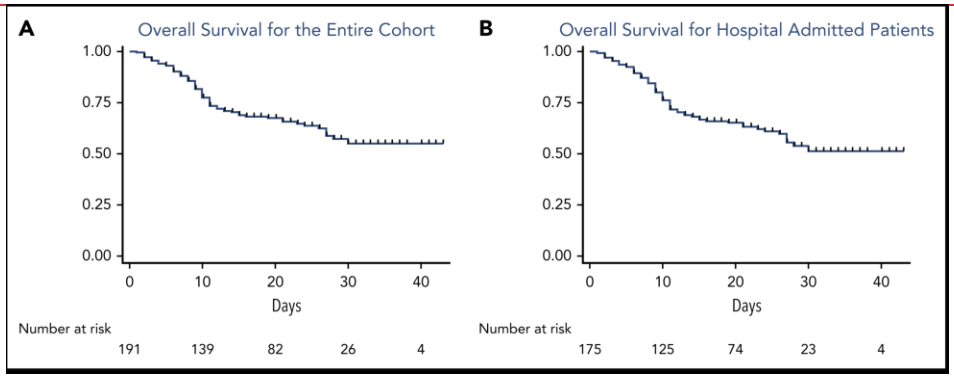


Figure 1: OS from the time of COVID-19 diagnosis of the entire cohort and admitted patients. (A) OS for the entire cohort; (B) OS for admitted patients.

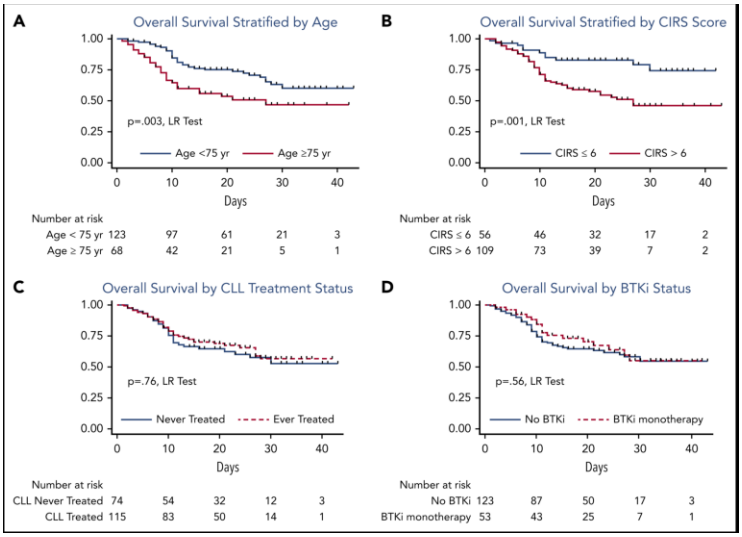


Figure 2: OS from time of COVID-19 diagnosis stratified by age, CIRS score, treatment history, and use of BTKi at time of COVID-19 diagnosis. (A) OS stratified by age; (B) OS stratified by CIRS score; (C) OS by CLL treatment status; (D) OS by BTKi status. LR, log rank.

SURGICAL SUBSPECIALTIES

ORTHOPEDICS

MUSCULOSKELETAL INJURIES SECONDARY TO EXERCISE DURING CONFINEMENT BY THE PANDEMIC COVID-19

Lopez Martinez JJ, Rodríguez-Roiz JM, Salcedo Cánovas C.. Med Clin (Barc). 2020 Sep 11;155(5):221-222. doi: 10.1016/j.medcli.2020.05.016. Epub 2020 Jun 5.
Level of Evidence: 3 - Local non-random sample

BLUF

Spanish orthopedic surgeons deployed an 11 question survey of a convenience sample on Twitter from April 14-April 21, 2020 to evaluate information on musculoskeletal (MSK) injuries occurring during the COVID-19 lockdown in Spain and found 228/1902 respondents (12%) reported MSK injuries during lockdown, with 35% reporting more physical activity than usual and 45% engaging in high intensity exercises (Table 1). Based on this, they suggest there is a need for public education on safe exercise to decrease MSK injuries in the absence of supervision by trainers or coaches.

Table 1.

Eleven questions from a survey conducted via Twitter® with percentage of responses.

Survey question	Percentage of responses
Age	
<30 years	39
30–45 years	38
45–60 years	15
>60 years	8
Sex	
Male	54
Female	46
Did you practice sports before lockdown?	
<2 times a week	39
2–4 times per week	34
>4 times a week	27
Have you been injured during lockdown?	
Yes	12
No	88
Have you done more exercise during lockdown than usual?	
Yes	35
No	65
How did you do the exercise?	
On my own	61
Youtube®	22
Instagram®/Facebook®	7
Mobile app	10
What type of exercise?	
Walk	11
Weight-bearing	30
Intensity	45
Yoga/Pilates	14
What type of injury have you had?	
Knee	25
Tendinous	16
Muscular	50
Sprain	9
What treatment have you had?	
Rest	73
Physiotherapy	21
Doctor	4
Emergency Dpt.	2
Have you required surgery for that injury?	
Yes	5
No	95
Will your way of doing exercise change once lockdown is over?	
More, at home	11
More, generally	33
No	56

ANALYTICAL AND CLINICAL EVALUATION OF THE AUTOMATED ELECSYS ANTI-SARS-COV-2 ANTIBODY ASSAY ON THE ROCHE COBAS E602 ANALYZER

Chan CW, Parker K, Tesic V, Baldwin A, Tang NY, van Wijk XMR, Yeo KJ.. Am J Clin Pathol. 2020 Aug 20:aqaa155. doi: 10.1093/ajcp/aqaa155. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Laboratory scientists from Singapore evaluated the fully automated Roche anti-SARS-CoV-2 antibody assay on Cobas e801/e602 analyzers using samples from RT-PCR-positive confirmed patients. They found it performed with good precision (2.9% for negative control [cut-off index (COI)=0.1], 5.1% for positive control [COI=3.0]), had no cross-reactivity with other viral samples (Figure 2), and demonstrated excellent sensitivity (95%), specificity (100%), and positive (100%) and negative predictive values (99%) in clinical performance (Table 5), suggesting the assay is a highly reliable automated platform for clinical detection of SARS-CoV-2.

ABSTRACT

OBJECTIVES: To evaluate the analytical and clinical performance of the automated Elecsys anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody (Elecsys Ab) assay on the Roche cobas e602 analyzer. With the ongoing global coronavirus disease 2019 (COVID-19) pandemic, widespread and routine serologic testing of SARS-CoV-2 remains a pressing need. To better understand its epidemiologic spread and to support policies aimed at curtailing further infections, reliable serologic testing is crucial for providing insight into the dynamics of the spread of COVID-19 on a population level. METHODS: The presence of anti-SARS-CoV-2 antibodies in polymerase chain reaction-positive, confirmed COVID-19 patient samples was determined using the Elecsys Ab assay on the Roche cobas e602 analyzer. The precision and cross-reactivity of the Elecsys Ab assay were characterized and its performance was compared against the EuroImmun IgA/IgG antibody (EuroImmun Ab) assay. Calculated sensitivity, specificity, and positive and negative predictive values were assessed. RESULTS: The Elecsys Ab assay demonstrated good precision, had no cross-reactivity with other viral samples, and showed 100% concordance with the EuroImmun Ab assay. Excellent clinical performance with respect to sensitivity, specificity, and positive and negative predictive values was observed. CONCLUSIONS: The Elecsys Ab assay is a precise and highly reliable automated platform for clinical detection of seropositivity in SARS-CoV-2 infection.

FIGURES

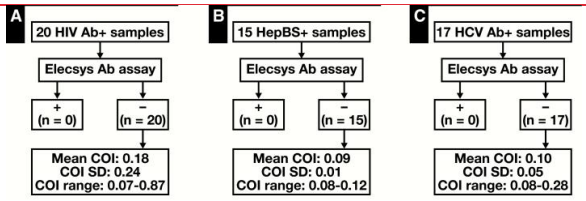


Figure 2

Cross-reactivity with other viral positive samples. A total of 20 human immunodeficiency virus (HIV) (A), 15 hepatitis B surface antigen (HepBS) (B), and 17 hepatitis C (HCV) (C) antibody (Ab)–positive samples were assayed. Reactive (+) and nonreactive (–) Elecsys Ab assay results are defined by a cutoff index (COI) of 1.0 or more or less than 1.0, respectively.

Table 5

Comparison of Clinical Performance of the Elecsys Anti–SARS-CoV-2 Antibody Assay Assuming 3%, 5%, or 10% Disease Prevalence

PCR Positive	3%		5%		10%	
	0-13 Days, %	≥14 Days, %	0-13 Days, %	≥14 Days, %	0-13 Days, %	≥14 Days, %
Sensitivity	77.50	94.74	77.50	94.74	77.50	94.74
Specificity	100	100	100	100	100	100
Positive predictive value	100	100	100	100	100	100
Negative predictive value	99.31	99.84	98.83	99.72	97.56	99.42
Accuracy	99.33	99.84	98.88	99.74	97.75	99.47

PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

CURRENT AND PERSPECTIVE DIAGNOSTIC TECHNIQUES FOR COVID-19

Yuan X, Yang C, He Q, Chen J, Yu D, Li J, Zhai S, Qin Z, Du K, Chu Z, Qin P.. ACS Infect Dis. 2020 Aug 14;6(8):1998-2016. doi: 10.1021/acsinfecdis.0c00365. Epub 2020 Aug 4.
Level of Evidence: Other - Review / Literature Review

BLUF

An interdisciplinary team from China and the United States conducted a literature review comparing and contrasting existing SARS-CoV-2 diagnostics including viral culture, RNA detection with isothermal amplification, RNA detection with CRISPR-Cas system, IgM/IgG combined antibody tests, and radiology (Figure 2, Summary). They recommend technologic solutions such as robots for sample collection, smart toilets, smart phones, and biosensors (Figure 3, summary) to improve efficient COVID-19 diagnosis and suggest use of novel diagnostic techniques such as these will be critical for epidemic control until effective therapeutics and/or vaccines are available.

SUMMARY

The article summarized and provided an overview of the following diagnostic techniques:
-Diagnosis by viral cytopathic effects: the "gold standard" for detection, which uses probes to visualize specific DNA or RNA, but authors claim it is impractical for large scale diagnostics because it requires 3 days for detection and well trained personnel to conduct the test.
-Detection by intact particles: uses a portable platform to capture viruses captured in aerosol based on size, characterized with on-chip spectroscopy using sensors and microbeads to generate a unique pattern of of beads on a smartphone, making it a desirable SARS-CoV-2 detection technique.
-Direct detection of RNA: This technique uses chemiluminescence with a smartphone through RNA-triggered in situ growth of nanoprobes in nucleic acid enzymes.
-Detection by genomic sequencing: droplet-based single cell sequencing technology which enables investigation of the virus as it evolves and can effectively exclude other pathogens as well as identify multiple pathogens in a patient; however, it is expensive, time consuming and requires skilled personnel.
-Detection with quantitative reverse transcription-polymerase chain reaction (qRT-PCR): extracts RNA from patient samples, transcribes viral RNA to cDNA and amplifies the cDNA by PCR, and creates a fluorescent signal; commonly used for clinical diagnosis.
-Detection with CRISPR/Cas System: potent technology for genome editing transformed into a technique for viral detection and assay with isothermal amplification for SARS-CoV-2 detection approved by the US FDA for emergency use; viral RNA and transcribed cDNA passing through nanopores generates peaks for viral nucleic acid characterization, and can be integrated with any nucleic acid amplification system.
-Detection by RNA microarray: detects multiple targets in a sample; has the advantages of needing a small sample volume, a rapid reaction time (15 minutes), and multiple probes per targets.
-Detection by Immunochemistry: single-shot mass spectrometry, sandwich-type electrochemical immunosensor, impedance-based biosensor which detect SARS-CoV-2 carried proteins with epitopes for antibody or nanobody recognition; do not often require virus nucleic acid extraction, which makes it more time efficient, however cannot be used to confirm infection
-Diagnosis by chest computed tomography (CT): based on typical radiographic features (ground-glass opacity, multi focal patchy consolidations, and/or interstitial changes with peripheral distribution) with support of other tests (c-reactive protein, lactate dehydrogenase, or erythrocyte sedimentation rate); limited access to radiologists and technology inhibits widespread use, and variation can be present.

ABSTRACT

Since late December 2019, the coronavirus pandemic (COVID-19; previously known as 2019-nCoV) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been surging rapidly around the world. With more than 1,700,000 confirmed cases, the world faces an unprecedented economic, social, and health impact. The early, rapid, sensitive, and accurate diagnosis of viral infection provides rapid responses for public health surveillance, prevention, and control of contagious diffusion. More than 30% of the confirmed cases are asymptomatic, and the high false-negative rate (FNR) of a single assay requires the development of novel diagnostic techniques, combinative approaches, sampling from different locations, and consecutive detection. The recurrence of discharged patients indicates the need for long-term monitoring and tracking. Diagnostic and therapeutic methods are evolving with a deeper understanding of virus pathology and the potential

for relapse. In this Review, a comprehensive summary and comparison of different SARS-CoV-2 diagnostic methods are provided for researchers and clinicians to develop appropriate strategies for the timely and effective detection of SARS-CoV-2. The survey of current biosensors and diagnostic devices for viral nucleic acids, proteins, and particles and chest tomography will provide insight into the development of novel perspective techniques for the diagnosis of COVID-19.

FIGURES

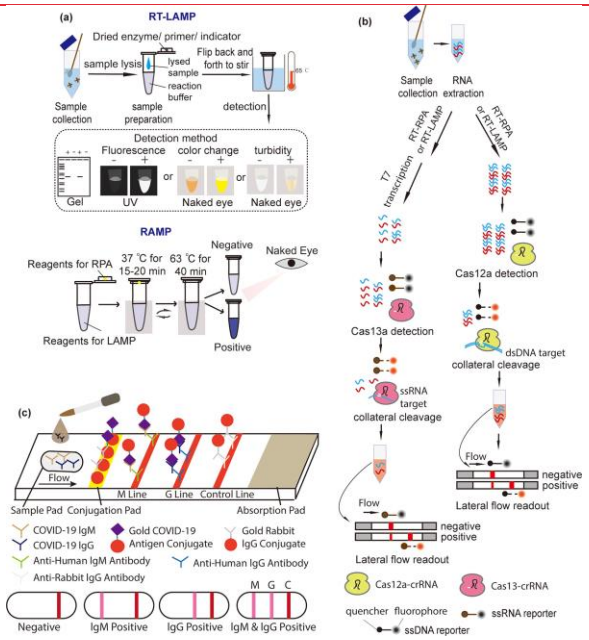


Figure 2. Schematic diagram of current diagnostic approaches of COVID-19: (a) SARS-CoV-2 RNA detection with isothermal amplification;(63,79) (b) SARS-CoV-2 RNA detection with the CRISPR-Cas system;(83,84) (c) SARS-CoV-2 IgM/IgG combined antibody test.(85)

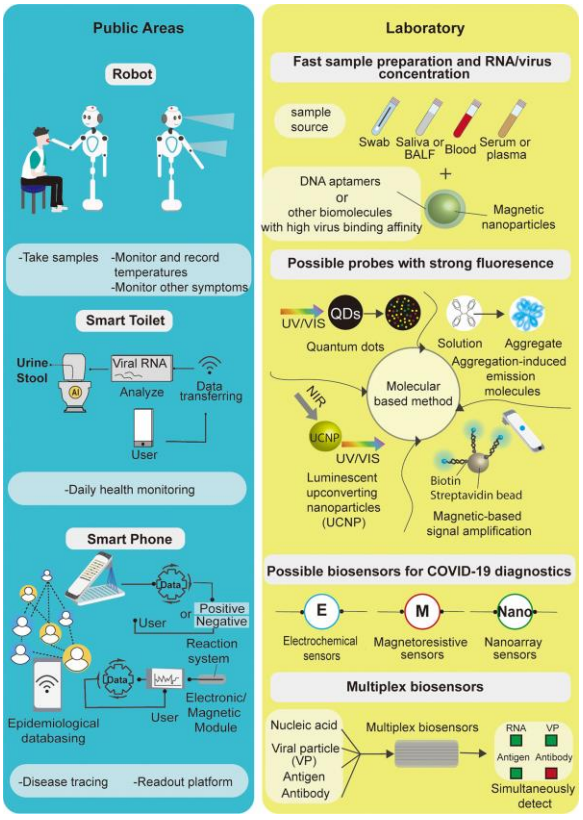


Figure 3. Possible strategies for the timely and efficiency diagnosis of COVID-19 in the future

DETECTION AND QUANTIFICATION OF SARS-COV-2 BY DROPLET DIGITAL PCR IN REAL-TIME PCR NEGATIVE NASOPHARYNGEAL SWABS FROM SUSPECTED COVID-19 PATIENTS

Alteri C, Cento V, Antonello M, Colagrossi L, Merli M, Ughi N, Renica S, Matarazzo E, Di Ruscio F, Tartaglione L, Colombo J, Grimaldi C, Carta S, Nava A, Costabile V, Baiguera C, Campisi D, Fanti D, Vismara C, Fumagalli R, Scaglione F, Epis OM, Puoti M, Perno CF.. PLoS One. 2020 Sep 8;15(9):e0236311. doi: 10.1371/journal.pone.0236311. eCollection 2020.
Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

A multidisciplinary group of Italian physicians evaluated a droplet digital PCR (ddPCR) based assay using samples from 55 suspected but RT-PCR negative COVID-19 cases collected between February and May 2020 (Table 1). They found 19 samples (35%) had detectable levels of SARS-CoV-2 by ddPCR (median viral load: 1128 copies/mL), of which 12 had multiple RT-PCR negative results (median number of negative swabs=3). They suggest ddPCR can detect SARS-CoV-2 at low copy numbers in symptomatic cases, which could improve sensitivity of testing where current RT-PCR assays are lacking and allow providers to correctly manage COVID-19 patients.

ABSTRACT

Since SARS-CoV-2-based disease (COVID-19) spreads as a pandemic, the necessity of a highly sensitive molecular diagnosis that can drastically reduce false negatives reverse transcription PCR (rtPCR) results, raises as a major clinical need. Here we evaluated the performance of a ddPCR-based assay to quantify SARS-CoV-2 titer in 55 suspected COVID-19 cases with negative rtPCR results thanks to in-house ddPCR assay (targeting RdRp and host RNaseP). Samples were collected at ASST-GOM Niguarda between February and May 2020 at hospital admission. Clinical and imaging data were obtained for clinical staging and definition of disease severity. Patients were mainly female (45.5%) with a median age of 73 (57-84) years. ddPCR-based assay detected SARS-CoV-2 genome in nasopharyngeal samples of 19 (34.5%) patients (median viral-load: 128 copies/mL, IQR: 72-345). In 15 of them (78.9%), chest CT showed a classical COVID-19 bilateral interstitial pneumonia; 14 patients (73.7%) showed severe COVID-19 manifestations. ddPCR did not identify any trace of SARS-CoV-2 genome in the respiratory samples of the remaining 36 patients. The serological assay performed in a subgroup of 34 patients at the later stage of illness (from 3 days to 90 days after) confirmed the presence of SARS-CoV-2 antibodies in all patients tested positive for SARS-CoV-2 in ddPCR (100%). Contrariwise, negative tests were observed in 95.0% ddPCR negative patients (P<0.001). Thanks to a ddPCR-based assay, we achieved a rapid and accurate SARS-CoV-2 diagnosis in rtPCR-negative respiratory samples of individuals with COVID-19 suspect, allowing the rapid taking care and correct management of these patients.

FIGURES

	Overall	Paticnts		p-value[a]
		SARS-CoV-2 positive	SARS-CoV-2 negative	
Patients, N	55	19	36	
Males	25 (45.5)	10 (52.6)	20 (55.6)	0.530
Age (years)	73 (57–84)	73 (60–84)	71 (57–84)	0.956
Date of symptoms onset	March 20 (March 5—April 26)	March 14 (March 1-March 25)	April 15 (March 9-April 28)	0.083
Date of Hospital admission	April 20 (March 11-April 29)	March 18 (March 8-April 4)	April 28 (March 9-April 28)	**0.010**
Date of first nasopharingeal swab	April 28 (March 13-May 01)	March 17 (March 8-April 7)	April 30 (April 9-April 28)	**0.003**
Time from symptoms-onset to hospital admission, days	4 (0–9)	4 (0–6)	4 (0–10)	0.425
Time from symptoms-onset to nasopharingeal swab, days	5 (2–10)	5 (1–6)	5 (2–14)	0.210
Positivity to the serological assay[b]	15 (44.1)	14 (100.0)	1[c] (5.0)	**<0.001**
Time from symptoms-onset to serological assay, days[b]	17 (9–33)	22 (13–33)	16 (9–33)	0.495
Symptoms at Hospital admission				
Fever, °C	35 (63.6)	15 (78.9)	20 (55.6)	0.076
Cough	22 (40.0)	11 (57.9)	11 (30.6)	**0.047**
Dyspnea	30 (54.5)	17 (89.5)	13 (36.1)	**<0.001**
Pulmonary involvement	36 (65.5)	18 (94.7)	18 (50.0)	**0.001**
Bilateral interstitial pneumonia	16 (29.1)	15 (78.9)	1[d] (2.8)	**<0.001**
Pneumonia with pleuritis	6 (10.9)	1 (5.3)	5 (13.9)	0.635
Lung cancer	2 (3.6)	1 (5.3)	1 (2.8)	0.986
Lobar pneumonia	6 (10.9)	1 (5.3)	5 (13.9)	0.635
Pneumonia "ab ingestis"	1 (1.8)	0 (0.0)	1 (2.8)	1.000
Bacterial pneumonia	3 (5.5)	0 (0.0)	3 (8.3)	0.544
Fungal pneumonia	1 (1.8)	0 (0.0)	1 (2.8)	1.000

COVID-19, Coronavirus Disease 2019. Data are expressed as median (interquartile range, IQR), or N (%).
[a] Fisher exact test and Wilcoxon test were used for categorical and continuous variables, respectively. Statistically significant p-values are in bold.
[b] Available for 34 patients and tested by Chemiluminescent microparticle immunoassay IgG against SARS-CoV-2 (https://www.corelaboratory.abbott/us/en/offerings/segments/infectious-disease/sars-cov-2).
[c] Patient with a pneumonia with pleuritis, characterized by a time from symptoms-onset to nasopharingeal swab of 28 days, and a time from symptoms-onset to serological assay of 48 days.
[d] Patient with a bilateral interstitial pneumonia, characterized by a time from symptoms-onset to nasopharingeal swab of 11 days, and repeatedly tested negative for SARS-CoV-2. Serological data are not available.

Table 1. Baseline demographic and clinical characteristics of the study population.

MASS SPECTROMETRY FOR COVID-19

SoRelle JA, Patel K, Filkins L, Park JY.. Clin Chem. 2020 Sep 21:hvaa222. doi: 10.1093/clinchem/hvaa222. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

Pathologists in Dallas, Texas review literature regarding the utility of matrix-assisted laser desorption/ionization combined with mass spectrometry (MALDI-MS) for indirect detection of SARS-CoV-2, which the authors argue would be particularly useful in the current resource-limited environment, given the relatively minimal equipment and training required to rapidly analyze an unpurified nasal swab sample with 93.9% accuracy. They suggest that while upfront cost may be prohibitive to widespread use during the current pandemic, investment in indirect detection methods such as MALDI-MS is critical for future pandemic preparedness.

ABSTRACT

In the United States, response to the COVID-19 coronavirus pandemic has been hampered by inadequate testing resources for the causative virus SARS-CoV-2. In the early part of the pandemic, United States laboratories were initially heavily regulated and slow to provide testing. As the pandemic has progressed, the supply chain for instruments and reagents has been inconsistent and has revealed weaknesses in traditional sophisticated infectious disease testing. Testing capabilities of clinical laboratories could be substantially improved by assays that are more simplified and do not require multiple consumable reagents for extraction, purification, amplification and detection. One such technology with the potential to require minimal reagents is matrix-assisted laser desorption/ionization combined with mass spectrometry (MALDI-MS). Recently, Nachtigall and colleagues reported the development of a MALDI-MS method for the diagnosis of SARS-CoV-2 infection (1).

CLINICAL VALIDATION AND PERFORMANCE EVALUATION OF THE AUTOMATED VITROS TOTAL ANTI-SARS-COV-2 ANTIBODIES ASSAY FOR SCREENING OF SEROSTATUS IN COVID-19

Garnett E, Jung J, Tam E, Rajapakshe D, Cheney S, Brown C, Cao J, Muldrew K, Singh I, Versalovic J, Devaraj S.. Am J Clin Pathol. 2020 Aug 31:aqaa157. doi: 10.1093/ajcp/aqaa157. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Clinical chemists from Baylor College of Medicine in Texas performed validation studies of the Vitros Anti–SARS-CoV-2 Total (CoV2T) immunoassay according to Commission of Office Laboratories Accreditation guidelines using 79 blood samples from patients positive for SARS-CoV-2 via RT-PCR and 57 negative controls. The CoV2T assay was acceptably precise (Table 1) with specificity of 100% and sensitivity of 70.9% on initial testing (Table 2). Authors suggest the CoV2T assay may be useful in screening for SARS-CoV-2 exposure but results should be interpreted with caution until more research is performed on cross reactivity with other respiratory viruses (Table 5).

ABSTRACT

OBJECTIVES: Evaluation of serostatus against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as an important tool in identification of exposure to coronavirus disease 2019 (COVID-19). We report on the validation of the Vitros Anti-SARS-CoV-2 Total (CoV2T) assay for qualitative serologic testing of SARS-CoV-2 antibodies. METHODS: We performed validation studies according to Commission of Office Laboratories Accreditation guidelines, using samples previously tested for SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR). We evaluated precision, analytical interferences, and cross-reactivity with other viral infections; evaluated concordance with molecular and other serologic testing; and evaluated seroconversion. RESULTS: The Vitros CoV2T assay exhibited acceptable precision and did not exhibit cross-reactivity with other acute respiratory virus infections. The CoV2T assay exhibited 100% negative predictive agreement (56/56) and 71% positive predictive agreement (56/79) with RT-PCR across all patient samples and was concordant with other serologic assays. Concordance with RT-PCR was 97% more than 7 days after symptom onset. The CoV2T assay was robust to icterus and lipemia but had interference from significant hemolysis. CONCLUSIONS: The Vitros CoV2T assay was successfully validated in our laboratory. We anticipate it will be a useful tool in screening for exposure to SARS-CoV-2; however, the use of the CoV2T and other serologic assays in the clinical management of patients with COVID-19 is unknown and must be evaluated in future studies.

Table 2

Concordance of the CoV2T Assay With Positive or Negative Results by RT-PCR for SARS-CoV-2

	RT-PCR Positive	RT-PCR Negative	Total
CoV2T reactive (Ab positive)	56	0	56
CoV2T nonreactive (Ab negative)	23	57	80
Total	79	57	136

Ab, antibody; Cov2T, Vitros Anti–SARS-CoV-2 Total assay; RT-PCR, reverse transcription–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 5

Analytical Specificity Studies With Interference and Other Respiratory Virus–Positive Specimens

Interferent[a]	Negative Sample	Positive Sample
Positive for influenza A, influenza B, respiratory syncytial virus, adenovirus, rhinovirus, or other coronaviruses (n = 14)	0.15 (0.15; nonreactive)	None
Hemolysate, mg/dL (index value)		
125 (272)	Nonreactive	Reactive
250 (930)	Reactive	Reactive
500 (>1,000)	Reactive	Reactive
Conjugated bilirubin, mg/dL (index value)		
30 (13)	Nonreactive	Reactive
40 (>25)	Nonreactive	Reactive
Triglyceride-rich lipid, mg/dL (index value)		
250 (29)	Nonreactive	Reactive
2,000 (221)	Nonreactive	Reactive

[a]For interference studies, known concentrations of interferent were spiked into either a known nonreactive or reactive sample. The instrument index values are provided in parentheses. For each concentration of interferent, the specimen reactivity is reported. For other virus-positive specimens, patient specimens previously tested positive for another virus by molecular methods were tested by the Vitros Anti–SARS-CoV-2 Total assay for reactivity.

Table 1

Intra- and Interassay Precision Study Results

Sample	Intra-assay S/Co[a]	Interassay S/Co
Nonreactive (S/Co <1.0)	0.065 (0.007); 10.9	0.171 (0.017); 9.7
Reactive (S/Co >1.0)	245 (3.9); 1.6	3.051 (0.099); 3.3

S/Co, signal-to-cutoff ratio.

[a]Values are mean (SD); percentage of coefficient of variation.

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