The Daily COVID-19 Literature Surveillance Summary

August 6, 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

- A recent case report describes an 18-year old male patient diagnosed with COVID-19 after presenting with fever, anorexia, and headache at a clinic on Reunion Island in the Indian Ocean. He later returned with fever, rash, dyspnea, and arthromyalgias and was discovered to be positive for dengue as well highlighting the importance to test for both conditions when clinically indicated.

Understanding the Pathology

- Single cell RNA sequencing of human kidney cells revealed that the expression of angiotensin converting enzyme 2 was highest in the proximal convoluted tubule cells and glomerular parietal cells providing cellular evidence of the means and location by which SARS-CoV-2 can cause direct kidney injury.

Management

- A literature review studied the clinical outcomes of 221 COVID-19 positive kidney transplant patients recipients and found that symptoms were predominantly respiratory with accompanying fever, lymphopenia and elevated CRP were each present in roughly 80% of patients, and 20% of patients died.
- A study conducted in Spain details the effects of an on-site medicalization program at 4 nursing homes with COVID-19 outbreaks in Spain. After implementation, COVID-19 mortality was decreased by 10-15% in the facilities that implemented the programs when compared to other outbreaks in long-term care facilities. These data suggest that medicalization programs such as this can greatly reduce the impact of COVID-19 on long term care facilities.

Adjusting Practice During COVID-19

- A cross-sectional study of adult emergency department visits across 7 medical centers in the United States found that the onset of the pandemic was associated with a decrease in ED visits of roughly 25% as well as reductions in diagnosis of cardiac, surgical, neurological, orthopedic, gastrointestinal, and chronic respiratory emergencies. These data add to the large amount of existing evidence that individuals may be avoiding care, even emergency care, during the pandemic.

R&D: Diagnosis and Treatment

- A group of clinicians from the University of Utah discuss the conflicting data that has emerged regarding corticosteroid use in treatment of COVID-19, citing studies that showed either mortality reduction of COVID-19 when treated with steroids, harm caused by steroid use, or no association between steroid use and mortality. They caution against use of steroids for COVID-19 until randomized clinical trials can be performed to clarify their impact on COVID-19.
- A study conducted in China found several differences in peripheral blood parameters between people infected with COVID-19, influenza, and a healthy control group. Among the differences, monocyte count and percentage of basophils were the key differences between COVID-19 and influenza, indicating their utility in differentiating between COVID-19 and influenza.
- A laboratory study investigating COVID-19 RT-PCR false negatives found that increased SARS-CoV-2 positive RNA levels are correlated with high levels of a housekeeping gene ribonuclease P/MRP subunit p30. Due to the high frequency of false negative tests associated with SARS-CoV-2 RT-PCR, these results suggest measurement of this gene product could help predict false negative tests.
- Investigators effectively isolated and cloned an antibody from a recovering COVID-19 patient that was found to have a high affinity to a highly conserved epitope of the viral spike protein along with effective neutralization of the virus suggesting potential use for this antibody as a COVID-19 therapy.

TABLE OF CONTENTS

ADULTS

CO-INFECTION OF DENGUE AND COVID-19: A CASE REPORT

Verduyn M, Allou N, Gazaille V, Andre M, Desroche T, Jaffar MC, Traversier N, Levin C, Lagrange-Xelot M, Moiton MP, Hoang S.. PLoS Negl Trop Dis. 2020 Aug 3;14(8):e0008476. doi: 10.1371/journal.pntd.0008476. eCollection 2020 Aug.
Level of Evidence: 5 - Case Report

BLUF

Authors in multiple health-related disciplines from France report a case of an 18-year-old male patient diagnosed with COVID-19 after presenting with fever, anorexia, and headache at a clinic on the Indian Ocean's Reunion Island on April 3, 2020. He later returned with symptoms consistent with a diagnosis of severe dengue (fever, rash, dyspnea, arthomyalgia), suggesting that co-testing for dengue and COVID-19 should be conducted in tropical settings where there is a high risk of arbovirus outbreaks.

SUMMARY

An 18-year-old male patient presented to a Reunion Island hospital with a fever, anorexia and headache on April 3, 2020, which led to a positive COVID-19 test. After discharge he returned to hospital on April 7, after 2 days of an itchy, erythematous rash accompanied by high fever, dyspnea and arthromyalgia (Figures 1 and 2). This second visit led to a positive test for dengue (NS1 antigen), and he was admitted to St. Denis University Hospital Center. Presumptive tracing of his COVID-19 infection implicated a March 18th flight, suggesting he may have been an asymptomatic carrier. The authors theorize dengue triggered COVID-19 findings (ie., persistent fever, thrombocytopenia, leukopenia, lymphopenia, and neutropenia) despite an unremarkable CT scan (Figure 3). This study was the first to document a co-infection case suggesting that, in tropical climates, patients should be tested for both.

FIGURES

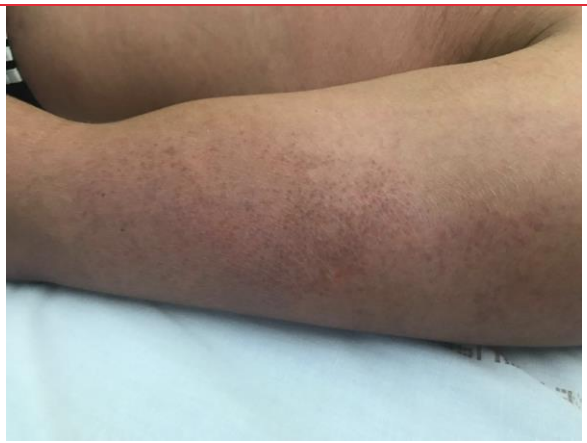

Figure 1. Photograph at hospital admission: roseoliform maculopapular exanthema with healthy skin intervals on left arm.

Figure 2. Photograph during hospitalization: diffuse exanthema with rounded island of sparing ("white island in a sea of red").

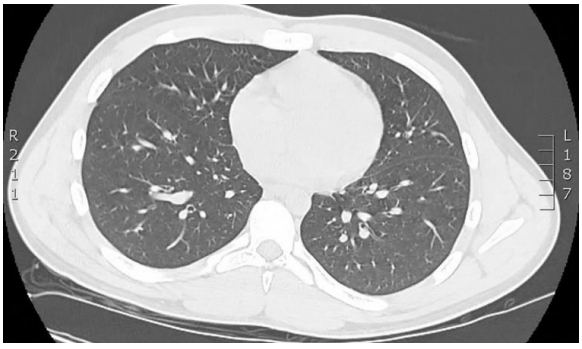

Figure 3. Chest CT confirming findings consistent with COVID-19.

SINGLE-CELL RNA SEQUENCING ANALYSIS OF HUMAN KIDNEY REVEALS THE PRESENCE OF ACE2 RECEPTOR: A POTENTIAL PATHWAY OF COVID-19 INFECTION

He Q, Mok TN, Yun L, He C, Li J, Pan J.. Mol Genet Genomic Med. 2020 Aug 3:e1442. doi: 10.1002/mgg3.1442. Online ahead of print.

Level of Evidence: Other - Mechanism-based reasoning

BLUF

This study used single-cell RNA sequencing of human kidney cells to analyze the genetic expression of angiotensin-converting enzyme 2 (ACE2) in order to elucidate a possible pathogenic mechanism for direct viral kidney injury in COVID-19. The results revealed the majority of ACE2 expression was in the proximal convoluted cells and straight cells (Figure 2). However, a total of 10 different genetic clusters were identified throughout various anatomical regions of renal cells (Figure 1), suggesting multiple areas of possible entry of SARS-CoV-2 into the renal system that could cause damage via an imbalance to the renin-angiotensin system (RAS).

ABSTRACT

BACKGROUND: A novel coronavirus called SARS-Cov-2, which shared 82% similarity of genome sequence with SARS-CoV, was found in Wuhan in late December of 2019, causing an epidemic outbreak of novel coronavirus-induced pneumonia with dramatically increasing number of cases. Several organs are vulnerable to COVID-19 infection. Acute kidney injury (AKI) was reported in parts of case-studies reporting characteristics of COVID-19 patients. This study aimed at analyzing the potential route of SARS-Cov-2 entry and mechanism at cellular level. METHOD: Single-cell RNA sequencing (scRNA-seq) technology was used to obtain evidence of potential route and ACE2 expressing cell in renal system for underlying pathogenesis of kidney injury caused by COVID-19. The whole process was performed under R with Seurat packages. Canonical marker genes were used to annotate different types of cells. RESULTS: Ten different clusters were identified and ACE2 was mainly expressed in proximal tubule and glomerular parietal epithelial cells. From Gene Ontology (GO) & KEGG enrichment analysis, imbalance of ACE2 expression, renin-angiotensin system (RAS) activation, and neutrophil-related processes were the main issue of COVID-19 leading kidney injury. CONCLUSION: Our study provided the cellular evidence that SARS-Cov-2 invaded human kidney tissue via proximal convoluted tubule, proximal tubule, proximal straight tubule cells, and glomerular parietal cells by means of ACE2-related pathway and used their cellular protease TMPRSS2 for priming.

FIGURES

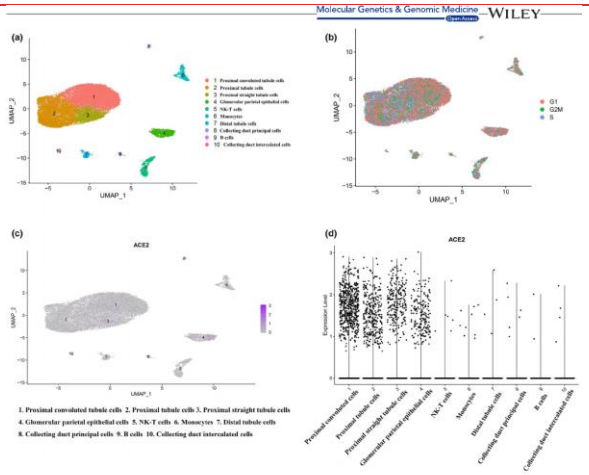

Figure 1. Results from scRNA-seq analysis. (a) Uniform manifold approximation and projection (UMAP) plot of samples revealing the different clusters of renal cells. (b) UMAP plot indicating different cluster with demonstration of different cell

cycles. (c) Expression of ACE2 in different clusters of cells. (d) Violin plot showing the ACE2 expression in different clusters of cells. scRNA, single-cell RNA sequencing.

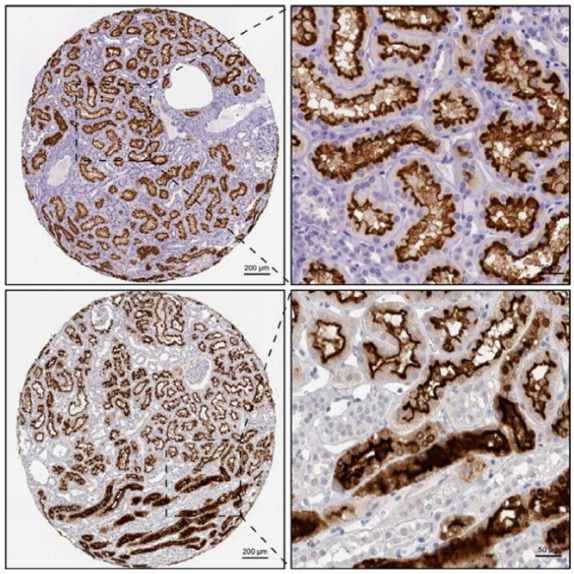

Figure 2. Human protein atlas showing the expression level of ACE2. (Shade of brown indicates the expression level: darker indicates high-level expression and lighter indicates low level expression

MANAGEMENT

ACUTE CARE

KIDNEY TRANSPLANT RECIPIENTS INFECTED BY COVID-19: REVIEW OF THE INITIAL PUBLISHED EXPERIENCE

Moris D, Kesseli SJ, Barbas AS.. Transpl Infect Dis. 2020 Jul 23:e13426. doi: 10.1111/tid.13426. Online ahead of print.
Level of Evidence: 3 - Review / Literature Review

BLUF

A literature review conducted by Duke University School of Medicine of 37 articles between January 1 - June 10, 2020, investigated COVID-19 infection in solid organ kidney transplant (KTx) and found fever, respiratory symptoms, and lymphopenia were common clinical findings (see summary). The researchers report ascertainment bias may affect the true incidence reporting of COVID-19 infection in KTx recipients and believes early use of immunomodulatory therapy may improve outcomes for KTx patients with severe COVID-19; however further research is warranted.

SUMMARY

The review identified 221 KTx recipients mostly from China, USA, and Italy with 87.3% (193/221) treated as inpatient with the following finding:
- Clinical findings were fever (84.5%), cough (64%), and respiratory symptoms (54%).
- Laboratory findings from 33/37 studies included lymphopenia and lymphopenia-associated immunosuppression (84.4%) and elevated CRP (78.8%).
- ICU admission rates for KTx recipients were 33.7% (55/163).
- COVID-related mortality was 19.9% (44/221), 65% (29/44) were of KTx recipients 60 years or older, and 68.1% (30/44) received their transplant greater than 1 year.
- There is no high-level evidence supporting immunomodulatory therapies however early experience suggests potential benefits in KTx patients with severe COVID-19.

ABSTRACT

There is an accumulating body of literature surrounding the impact of COVID-19 infection in solid organ transplant recipients. The aim of this review is to summarize the existing literature specifically in kidney transplant (KTx) recipients, with an emphasis on the epidemiology, clinical presentation, laboratory findings, post-operative outcomes and therapeutic strategies currently employed. We identified thirty-seven studies published between January 1st 2020 to June 10th 2020 that were included in our analysis. As is reported in the general population, there is a wide variation in COVID-19 presentation among KTx patients, ranging from asymptomatic to life-threatening end-organ failure. The most common symptoms are predominantly respiratory and associated with fever. On lab evaluation, many patients present with lymphopenia and increased CRP, which are both associated with inferior outcomes. The majority of patients with severe symptoms have been managed with reduction of immunosuppression, including decreased doses of CNIs and withdrawal of MMF. Lastly, although there is no high-level data supporting the use of immunomodulatory drugs, such as IL-6 inhibitors, early experiences have suggested these drugs may improve outcomes in KTx patients with severe COVID-19.

OBGYN

OBSTETRIC HOSPITAL PREPAREDNESS FOR A PANDEMIC: AN OBSTETRIC CRITICAL CARE PERSPECTIVE IN RESPONSE TO COVID-19

Zalud I, Harvey S.. J Perinat Med. 2020 Aug 3:/j/jpme.ahead-of-print/jpm-2020-0281/jpm-2020-0281.xml. doi: 10.1515/jpm-2020-0281. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

An article by the School of Medicine at the University of Hawaii discusses hospital protocols/preparation plans during COVID-19, with regards to algorithms for patient allocation throughout the hospital (Figure 1), care committees to facilitate a larger

regional volume of obstetric patients (Figure 2), patient management (Figure 3), and how to properly educate staff members about the corresponding protocols/management. This outlines the essential nature of triaging and allocation of resources, including staff, location, and management practices in preparation for the potential of a surge in COVID-19 hospitalizations.

ABSTRACT

The Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic has had a rapid and deadly onset, spreading quickly throughout the world. Pregnant patients have had high mortality rates, perinatal losses, and Intensive Care Unit (ICU) admissions from acute respiratory syndrome Coronavirus (SARS-CoV) and Middle East respiratory syndrome Coronavirus (MERS-CoV) in the past. Potentially, a surge of patients may require hospitalization and ICU care beyond the capacity of the health care system. This article is to provide institutional guidance on how to prepare an obstetric hospital service for a pandemic, mass casualty, or natural disaster by identifying a care model and resources for a large surge of critically ill pregnant patients over a short time. We recommend a series of protocols, education, and simulation training, with a structured and tiered approach to match the needs for the patients, for hospitals specialized in obstetrics.

FIGURES

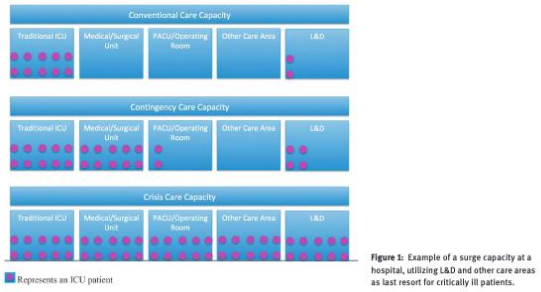

Figure 1:Example of a surge capacity at a hospital, utilizing L&D and other care areas as last resort for critically ill patients.

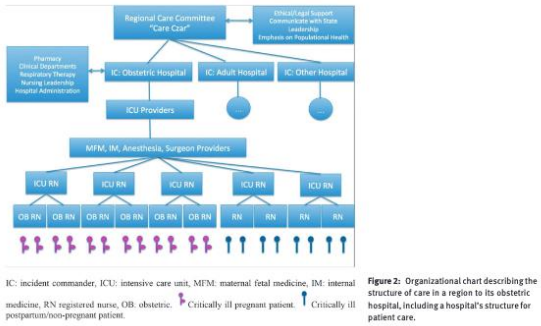

Figure 2: Organizational chart describing the structure of care in a region to its obstetric hospital, including a hospital's structure for patient care.

EFFECTIVENESS OF A ON-SITE MEDICALIZATION PROGRAM FOR NURSING HOMES WITH COVID-19 OUTBREAKS

Bernabeu-Wittel M, Ternero-Vega JE, Nieto-Martín MD, Moreno-Gaviño L, Conde-Guzmán C, Delgado-Cuesta J, Rincón-Gómez M, Díaz-Jiménez P, Giménez-Miranda L, Lomas-Cabezas JM, Muñoz-García MM, Calzón-Fernández S, Ollero-Baturone M.. J Gerontol A Biol Sci Med Sci. 2020 Aug 1:glaa192. doi: 10.1093/gerona/glaa192. Online ahead of print.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

This study by authors affiliated with the Primary Care District of Seville and University of Seville details the effects of an on-site medicalization program (MP) at 4 nursing homes with COVID-19 outbreaks in Spain. After implementation, COVID-19 mortality was decreased in the MP facilities when compared to other outbreaks in long-term care facilities (16% vs 27-33%). The primary composite endpoint of survival or optimal palliative care (SOPC) was independently related to diagnostic verification of COVID-19 at MP facilities (OR=15 [3-81], p=.001) and fewer complications were reported (Table 3), leading the authors to propose widespread implementation of MP's in nursing homes.

SUMMARY

The on-site medicalization program (MP) utilized several processes and interventions:

1. A “clean room” to store medial equipment and maintain electronic records.
2. A secure locker room for health care workers containing adequate personal protective equipment (PPE).
3. Universal SARS-CoV-2 testing for residents and staff.
4. Separating residents with COVID-19 from the other residents via a “clean area” and “contaminated area”.
5. Specific training for staff on obtaining nasopharyngeal swabs and management of COVID-19 patients.
6. Contact tracing.
7. Documentation of all residents via electronic medical records.
8. Providing equipment for all necessary studies and tests, such as portable ultrasound.
9. Staffing of health-care workers such that 24-hour care was possible.
10. Establishment of a common management and treatment algorithm, as well as a protocol to keep family members up to date on their loved one’s progress.

ABSTRACT

BACKGROUND: Nursing homes are highly vulnerable to the occurrence of COVID-19 outbreaks, which result in high lethality rates. Most of them are not prepared to SARS-CoV-2 pandemic. METHODS: A coordinated on-site medicalization program (MP) in response to a sizeable COVID-19 outbreak in four nursing homes was organized, with the objectives of improving survival, offering humanistic palliative care to residents in their natural environment, and reducing hospital referrals. Ten key processes and interventions were established (provision of informatics infrastructure, medical equipment, and human resources, universal testing, separation of 'clean' and 'contaminated' areas, epidemiological surveys, and unified protocols stratifying for active or palliative care approach, among others). Main outcomes were a composite endpoint of survival or optimal palliative care (SOPC), survival, and referral to hospital. RESULTS: 272 out of 457 (59.5%) residents and 85 out of 320 (26.5%) staff members were affected. The SOPC, survival, and referrals to hospital, occurred in 77%, 72.5%, and 29% of patients diagnosed before MP start, with respect to 97%, 83.7% and 17% of those diagnosed during the program, respectively. The SOPC was independently associated to MP (OR=15 [3-81]); and survival in patients stratified to active approach, to the use of any antiviral treatment (OR=28 [5-160]). All outbreaks were controlled in 39 [37-42] days. CONCLUSIONS: A coordinated on-site medicalization program of nursing homes with COVID-19 outbreaks achieved a higher survival or optimal palliative care rate, and a reduction in referrals to hospital, thus ensuring rigorous but also humanistic and gentle care to residents.

PARAMETER (MEAN (SD)-MEDIAN [Q1-Q3] // N (%))	GLOBAL (N=272)	PATIENTS DIAGNOSED WITH COVID-19 BEFORE MP (N=149)	PATIENTS DIAGNOSED WITH COVID-19 DURING MP (N=123) [OR; 95% CI]
Patients with Complications	127 (47%)	83 (56%)	44 (36%) **p=.001 [0.4; 0.3-0.7]**
Acute respiratory failure	106 (39%)	74 (50%)	32 (26%) **p<.001[0.3; 0.2-0.6]**
Persistent or incidental delirium	36 (13%)	21 (14%)	15 (12%)
Immbility and 'bedridden syndrome'	32 (12%)	20 (13.7%)	12 (10%)
LRT bacterial infections	28 (10.3%)	14 (10%)	14 (11.5%)
Acute renal failure	19 (7%)	13 (9%)	6 (5%)
Oropharyngeal dysphagia	16 (6%)	10 (7%)	6 (5%)
Urinary tract infection	15 (5.5%)	8 (5.5%)	7 (5.7%)
Pressure ulcers	14 (5.1%)	9 (6%)	5 (4%)
Number of complications per patient	1.04(1.5)	1.25 (1.6)	0.8 (1.3) **p=.02**
Outcomes			
Composite end point*	234 (86%)	115 (77%)	119 (97%) **p<.001 [9; 3-25]**
Survival	211	108 (72.5%)	103 (84%) **p=.03 [2; 1.1-3.5]**
Patients transferred to hospital	(77.6%)	43 (29%)	21 (17%) **p=.02 [0.5; 0.3-0.9]**
Transfers to Hospital per week	64 (23.5%)	21.5 (2.1)	3.5 (1.9) **p=.02**
	8 (8.5)		

SD= standard deviation; Q1-Q3=quartile1-quartile3; Nº= number; %=percentage; MP=medicalization program; OR=odds ratio; CI= confidence interval; LRT= low respiratory tract; * Composite end -point of survival or optimal end-of-life care.

Table 3. Unadjusted differential complications and outcomes of affected residents during the medicalization program of four nursing homes with COVID-19 outbreaks in Seville, Spain.

EMERGENCY MEDICINE

EMERGENCY DEPARTMENT VISITS FOR SERIOUS DIAGNOSES DURING THE COVID-19 PANDEMIC

Kim HS, Cruz DS, Conrardy MJ, Gandhi KR, Seltzer JA, Loftus TM, Fant AL, McCarthy DM.. Acad Emerg Med. 2020 Aug 1. doi: 10.1111/acem.14099. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Researchers from Chicago, Illinois conducted a cross-sectional study of adult visits to seven Emergency Departments (ED) and measured the visit frequencies for serious diagnoses during the early pandemic period (March 8, 2020 to May 2, 2020) to the pre-pandemic period (December 13, 2019 to March 8, 2020) and found a total decrease in ED visits (4,839/week to 3,709/week) along with diagnoses related to cardiac, surgical, neurological, orthopedic, gastrointestinal, and chronic respiratory emergencies ($p<0.001$, Figure 1). While these results may not represent all medical centers, the researchers believe this study adds to the existing evidence that individuals may be avoiding important critical care due to fears related to COVID-19 at hospitals.

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has significantly affected health care utilization in the United States. Although reductions in routine outpatient visits and elective procedures were intentional in preparation for increases in COVID-19-related volume,1 National Syndromic Surveillance Program data indicate that weekly emergency department (ED) visits decreased 42% during the early stages of the pandemic.2 This reduction may have been driven by a public fear of seeking care,3,4 ultimately delaying interventions for time-sensitive serious conditions.

FIGURES

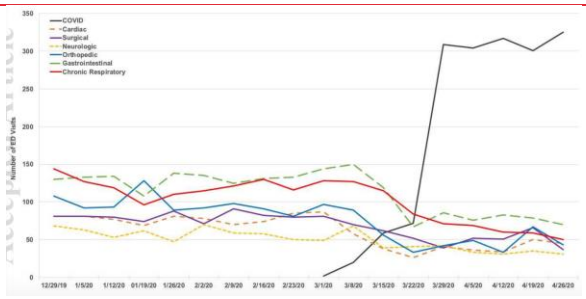

Figure 1: The number of weekly ED visits for each major diagnosis class over the early pandemic and pre-pandemic periods.

R&D: DIAGNOSIS & TREATMENTS

THE UNCERTAIN ROLE OF CORTICOSTEROIDS IN THE TREATMENT OF COVID-19

Liou TG, Adler FR, Hatton ND.. JAMA Intern Med. 2020 Aug 3. doi: 10.1001/jamainternmed.2020.2438. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

In this letter to the editor, experts from University of Utah in Salt Lake City, UT comment on the conflicting data that has emerged regarding corticosteroid use in treatment of COVID-19, citing studies that showed either mortality reduction of COVID-19 when treated with steroids, harm caused by steroid use, or no association between steroid use and mortality. They caution against use of steroids for COVID-19 until randomized clinical trials can be performed to clarify their impact on COVID-19.

DEVELOPMENTS IN DIAGNOSTICS

DISTINGUISHING BETWEEN COVID-19 AND INFLUENZA DURING THE EARLY STAGES BY MEASUREMENT OF PERIPHERAL BLOOD PARAMETERS

Chen J, Pan Y, Li G, Xu W, Zhang L, Yuan S, Xia Y, Lu P, Zhang J.. J Med Virol. 2020 Aug 4. doi: 10.1002/jmv.26384. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

A two-cohort study conducted by the Department of Clinical Laboratory at Zhejiang University School of Medicine in Hangzhou, China found several differences in peripheral blood parameters between people infected with COVID-19 (n=169; 145 "common," 24 severe cases), influenza (n=131; 78 with Influenza A, 53 with Influenza B), and a healthy control group (n=80). Among the differences*, monocyte count and percentage of basophils were the key differences between COVID-19 and Influenza A/B (AUC=0.772), indicating their usefulness in differentiating between COVID-19 and Influenza A/B and making an accurate diagnosis.

SUMMARY

* When comparing peripheral blood parameters of COVID-19 and influenza patients, the study found significant differences in age, white blood cell count, platelet count, neutrophil %, lymphocyte %, monocyte %, eosinophil %, basophil %, neutrophil count and monocyte count.

ABSTRACT

BACKGROUND: Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This study aims to examine the changes in peripheral blood parameters during the early stages of COVID-19 and influenza. METHODS: We analysed the peripheral blood parameters of 169 COVID-19 patients and 131 influenza patients during the early onset stage. Results from the COVID-19 patients were compared with those from healthy controls and influenza patients. In addition, results from patients with common and severe COVID-19 were further compared. RESULTS: There were significant differences between COVID-19 and influenza patients in terms of age, white blood cell count, platelet count, percentage of neutrophils, percentage of lymphocytes, percentage of monocytes, percentage of eosinophils, percentage of basophils, neutrophil count and monocyte count. Two parameters (monocyte count and percentage of basophils) were combined to clarify the diagnostic efficacy of COVID-19 and influenza and the area under the curve was found to be 0.772. CONCLUSION: Comparison of peripheral blood parameters from common COVID-19, severe COVID-19 and influenza patients revealed many differences during the early disease stages. The diagnostic formula developed by this study will be of benefit for physicians in the differentiation of COVID-19 and influenza.

DISCRIMINATION OF FALSE NEGATIVE RESULTS IN RT-PCR DETECTION OF SARS-COV-2 RNAS IN CLINICAL SPECIMENS BY USING AN INTERNAL REFERENCE

Zhang Y, Wang C, Han M, Ye J, Gao Y, Liu Z, He T, Li T, Xu M, Zhou L, Zou G, Lu M, Zhang Z.. Virol Sin. 2020 Aug 4. doi: 10.1007/s12250-020-00273-8. Online ahead of print.
Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

A laboratory study investigating RT-PCR false negatives conducted in a Fuyang, China hospital included multiple sputum and throat swab samples (1152 samples in total) from n=161 confirmed COVID-19 patients, finding increased SARS-CoV-2 positive RNA levels to be correlated with high levels of a housekeeping gene ribonuclease P/MRP subunit p30 (RPP30). Due to the high frequency of false negative tests associated with SARS-CoV-2 RT-PCR, these results suggest the ability to identify and use a cutoff value of RPP30 to predict false negative tests (Figure 6) with high sensitivity (95.03%) and specificity (83.72-95.26%), potentially serving as an indicator for quality of specimen collected, allowing for a reduction in false negative tests.

ABSTRACT

Reverse transcription-polymerase chain reaction (RT-PCR) is an essential method for specific diagnosis of SARS-CoV-2 infection. Unfortunately, false negative test results are often reported. In this study, we attempted to determine the principal causes leading to false negative results of RT-PCR detection of SARS-CoV-2 RNAs in respiratory tract specimens. Multiple sputum and throat swab specimens from 161 confirmed COVID-19 patients were tested with a commercial fluorescent RT-PCR kit targeting the ORF1ab and N regions of SARS-CoV-2 genome. The RNA level of a cellular housekeeping gene ribonuclease P/MRP subunit p30 (RPP30) in these specimens was also assessed by RT-PCR. Data for a total of 1052 samples were retrospectively re-analyzed and a strong association between positive results in SARS-CoV-2 RNA tests and high level of RPP30 RNA in respiratory tract specimens was revealed. By using the ROC-AUC analysis, we identified Ct cutoff values for RPP30 RT-PCR which predicted false negative results for SARS-CoV-2 RT-PCR with high sensitivity (95.03%-95.26%) and specificity (83.72%-98.55%) for respective combination of specimen type and amplification reaction. Using these Ct cutoff values, false negative results could be reliably identified. Therefore, the presence of cellular materials, likely infected host cells, are essential for correct SARS-CoV-2 RNA detection by RT-PCR in patient specimens. RPP30 could serve as an indicator for cellular content, or a surrogate indicator for specimen quality. In addition, our results demonstrated that false negativity accounted for a vast majority of contradicting results in SARS-CoV-2 RNA test by RT-PCR.

FIGURES

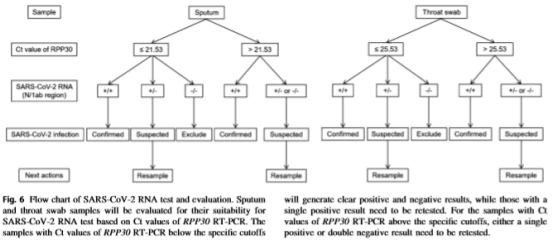

Fig. 6 Flow chart of SARS-CoV-2 RNA test and evaluation. Sputum and throat swab samples will be evaluated for their suitability for SARS-CoV-2 RNA test based on Ct values of *RPP30* RT-PCR. The samples with Ct values of *RPP30* RT-PCR below the specific cutoffs will generate clear positive and negative results, while those with a single positive result need to be retested. For the samples with Ct values of *RPP30* RT-PCR above the specific cutoffs, either a single positive or double negative result need to be retested.

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DEVELOPMENTS IN TREATMENTS

STRUCTURAL BASIS FOR THE NEUTRALIZATION OF SARS-COV-2 BY AN ANTIBODY FROM A CONVALESCENT PATIENT

Zhou D, Duyvesteyn HME, Chen CP, Huang CG, Chen TH, Shih SR, Lin YC, Cheng CY, Cheng SH, Huang YC, Lin TY, Ma C, Huo J, Carrique L, Malinauskas T, Ruza RR, Shah PNM, Tan TK, Rijal P, Donat RF, Godwin K, Buttigieg KR, Tree JA, Radecke

J, Paterson NG, Supasa P, Mongkolsapaya J, Screaton GR, Carroll MW, Gilbert-Jaramillo J, Knight ML, James W, Owens RJ, Naismith JH, Townsend AR, Fry EE, Zhao Y, Ren J, Stuart DI, Huang KA.. Nat Struct Mol Biol. 2020 Jul 31. doi: 10.1038/s41594-020-0480-y. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

A mechanism-based study by authors affiliated with multiple medical institutions isolated and cloned the antibody EY6A from a recovering patient with COVID-19. The antibody was shown to have a high affinity to a highly conserved epitope of the SARS-CoV-2 viral spike glycoprotein along with effective neutralization (Figure 2) as indicated by both quantitative polymerase chain reaction detection (qPCR) as well as plaque reduction assays. These findings suggest that the antibody EY6A has potential as a COVID-19 therapy.

ABSTRACT

The COVID-19 pandemic has had an unprecedented health and economic impact and there are currently no approved therapies. We have isolated an antibody, EY6A, from an individual convalescing from COVID-19 and have shown that it neutralizes SARS-CoV-2 and cross-reacts with SARS-CoV-1. EY6A Fab binds the receptor binding domain (RBD) of the viral spike glycoprotein tightly (KD of 2 nM), and a 2.6-A-resolution crystal structure of an RBD-EY6A Fab complex identifies the highly conserved epitope, away from the ACE2 receptor binding site. Residues within this footprint are key to stabilizing the pre-fusion spike. Cryo-EM analyses of the pre-fusion spike incubated with EY6A Fab reveal a complex of the intact spike trimer with three Fabs bound and two further multimeric forms comprising the destabilized spike attached to Fab. EY6A binds what is probably a major neutralizing epitope, making it a candidate therapeutic for COVID-19.

FIGURES

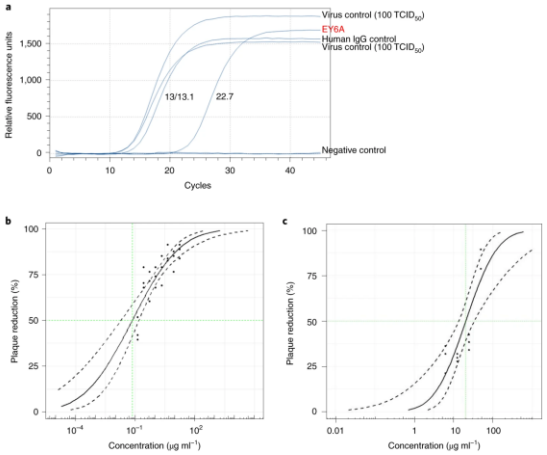

Figure 2 | Neutralization of SARS-CoV-2 by EY6A. a, Neutralization data acquired by measuring the Ct (threshold cycle) value of virus signal in the supernatant of SARS-CoV-2-infected Vero E6 cells in an E gene-based real-time PCR assay with reverse transcription28. An increase indicates a decrease in virus template. Each unit increase suggests a 2× reduction resulting from the presence of Mab. An ~10× increase in Ct corresponds to an ~1,000-fold reduction of viral nucleic acid copies. Virus control was at 100 TCID50 (median tissue culture infectious dose). Anti-influenza H3 MAb BS 1A was included as a human IgG control in the assay, and both this and EY6A were used at 1.5 μg ml−1 . The Ct values are marked in the plot. The neutralization assay was carried out twice with equivalent results. b, Dose–response curve for PRNT with EY6A at a starting concentration of 2.7 mg ml−1 . The probit mid-point is 0.071 μg ml−1 (confidence intervals: 0.019–0.151 μg ml−1). The Excel Spearman-Kärber ND50 (50% neutralizing dose) is 0.39 μg ml−1 . c, Vero-cell-based PRNT assay showing neutralization of SARS-CoV-2 by EY6A and CR3022. The probit mid-point is 20.7 μg ml−1 (confidence intervals: 13.7–34.1 μg ml−1). The Excel Spearman-Kärber ND50 is 10 μg ml−1 . Three technical replicates were done and the confidence limits were calculated as defined in ref. 18.

ACKNOWLEDGEMENTS

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