The Daily COVID-19 Literature Surveillance Summary

December 01, 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

- Is there SARS-CoV-2 persistence and non-protective immunity in infected haematological patients? Greek infectious disease physicians present a case of 35-year-old with a history of acute lymphoblastic leukemia 14 days status-post chemotherapy with R-hyper-CVAD who presented on April 8, 2020 with pneumonia after positive RT-PCR for SARS-CoV-2 on March 26. The patient eventually recovered after a seven-week hospitalization and developed antibodies suggestive of immunologic memory but was later readmitted on July 22 with severe COVID-19 pneumonia despite serologic testing with continued adequate IgG. Authors suggest defective innate and adaptive immunity in immunocompromised patients may facilitate SARS-CoV-2 infection (i.e. antibodies may be non-neutralizing following chemotherapy) and allow persistence or viral reactivation.

Understanding the Pathology

- There may be postmortem findings of diaphragm pathology related to critically ill patients with COVID-19. Critical care physicians conducted a case-control study using autopsies of 26 deceased critically ill COVID-19 patients from 3 medical centers in the Netherlands to analyze the extent of diaphragm involvement. Findings show increased ACE-2 expression and SARS-CoV-2 viral infiltration in the diaphragm of patients who died of severe COVID-19 compared to control specimens from 8 deceased ICU patients without COVID-19, suggesting that diaphragm fibrosis could be a source of respiratory distress in COVID-19 patients.

Management

- Early short-course corticosteroids have beneficial outcomes in hospitalized patients with COVID-19. A quasi-experimental study, conducted by the Henry Ford COVID-19 Management Task Force at multiple hospitals in Michigan, evaluated the effect of early corticosteroid therapy in 132 hospitalized patients with severe to moderate COVID-19 versus 81 COVID-19 patients on standard care treatment. They found that early corticosteroid group (median time to initiation 2 days, IQR 1-3, range 0-8) had less transfers to the ICU (34.9% vs 54.3%, p=0.005), decreased ARDS occurrences (26.6% vs 38.3%, p=0.04), and spent less days in the hospital (5 vs 8 days, p less than 0.001) compared with the standard of care group. These findings suggest that early methylprednisolone therapy in patients with moderate/severe COVID-19 may help curb the inflammatory response elicited by SARS-CoV-2 and thus lead to better outcomes.

R&D: Diagnosis & Treatments

- What is the role of immunoglobulin G and IgM antibodies against SARS-CoV-2? Investigators from the National Clinical Research Center for Infectious Diseases in Shenzhen, China analyzed 347 serum samples from 41 RT-PCR confirmed COVID-19 patients (15 with mild-moderate symptoms, 16 with severe, and 10 with critical) admitted to The Third People's Hospital of Shenzhen. Results revealed 39% of COVID-19 patients had seroconversion of IgG antibodies against SARS-CoV-2 nucleocapsid (N) protein and spike (S) glycoprotein in an average of 11 days after onset of symptoms, and 51.2% with seroconversion to IgM antibodies in an average of 14 days. Further, critical patients were found to have a delayed, but more robust IgG and IgM response. This understanding of antibody kinetics against SARS-CoV-2 may assist in clinical diagnosis, specifically in utilizing immunoassays as a testing tool during the pandemic.

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RENIN-ANGIOTENSIN SYSTEM INHIBITION AND RISK OF INFECTION AND MORTALITY IN COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS

Koshy AN, Murphy AC, Farouque O, Ramchand J, Burrell LM, Yudi MB.. Intern Med J. 2020 Nov 16. doi: 10.1111/imj.15002. Online ahead of print.

Level of Evidence: 1 - Systematic review of randomized trials, systematic review of nested case-control studies, nof-1 trial with the patient you are raising the question about, or observational study with dramatic effect

BLUF

A systematic review and meta-analysis of 6 publications (Figure 3) conducted by cardiologists in Melbourne, Australia found use of renin-angiotensin system (RAS) inhibitors (including angiotensin-converting enzyme inhibitors [ACEI] or angiotensin receptor blockers [ARB]) was not associated with severity of illness or mortality (Figure 2; p=0.21), nor increased incidence of COVID-19 diagnosis (Figure 1; p=0.48) in study participants (n=73,122). These data suggest use of RAS inhibitors may not increase susceptibility or severity of COVID-19 due to SARS-CoV-2 cell entry through the ACE2 receptor, as previously theorized.

ABSTRACT

BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, enters human cells by binding of its viral protein to the aminopeptidase angiotensin-converting enzyme 2 (ACE2). This has led to speculation whether treatment with renin-angiotensin system (RAS) inhibitors was associated with an increased likelihood of a positive test for COVID-19 and risk of mortality. AIMS: We performed a systematic review and meta-analysis to investigate whether RAS inhibitors increased the likelihood of a positive test or death/severe illness in patients with COVID-19. METHODS: A systematic search of MEDLINE, PubMed and EMBASE was conducted for studies stratified by the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). Pooled analysis was performed using a random-effects model. RESULTS: Seven trials of 73 122 patients were included. Overall, 16 624 (22.7%) patients had a positive COVID-19 test and 7892 (10.8%) were on a RAS inhibitor. RAS inhibitors were not associated with higher likelihood of a positive COVID-19 test result (odds ratio (OR) 0.97 (95% CI 0.97-1.05, P = 0.48) with low heterogeneity. This was comparable when stratifying by use of each medication class. The use of RAS inhibitors was also not associated with mortality or severe illness (OR 0.89, 95% CI 0.73-1.07, P = 0.21) with moderate heterogeneity. CONCLUSION: Use of ACEI or ARB was not associated with a heightened susceptibility for a positive diagnosis of COVID-19. Furthermore, they were not associated with increased illness severity or mortality due to COVID-19. Randomised controlled trials are needed to address definitively the potential benefits or harms of RAS inhibitors in patients with COVID-19.

FIGURES

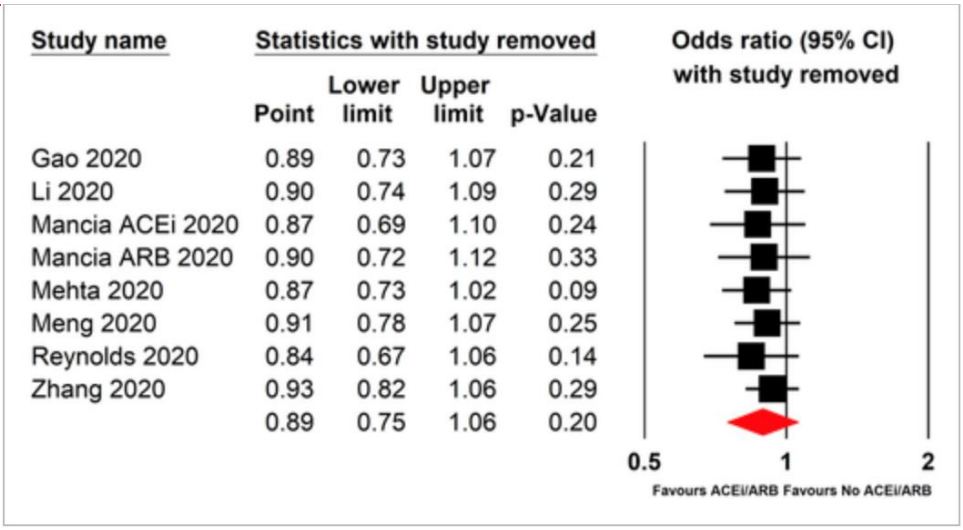


Figure 3. Pooled odds ratios with systematic exclusion of individual studies.

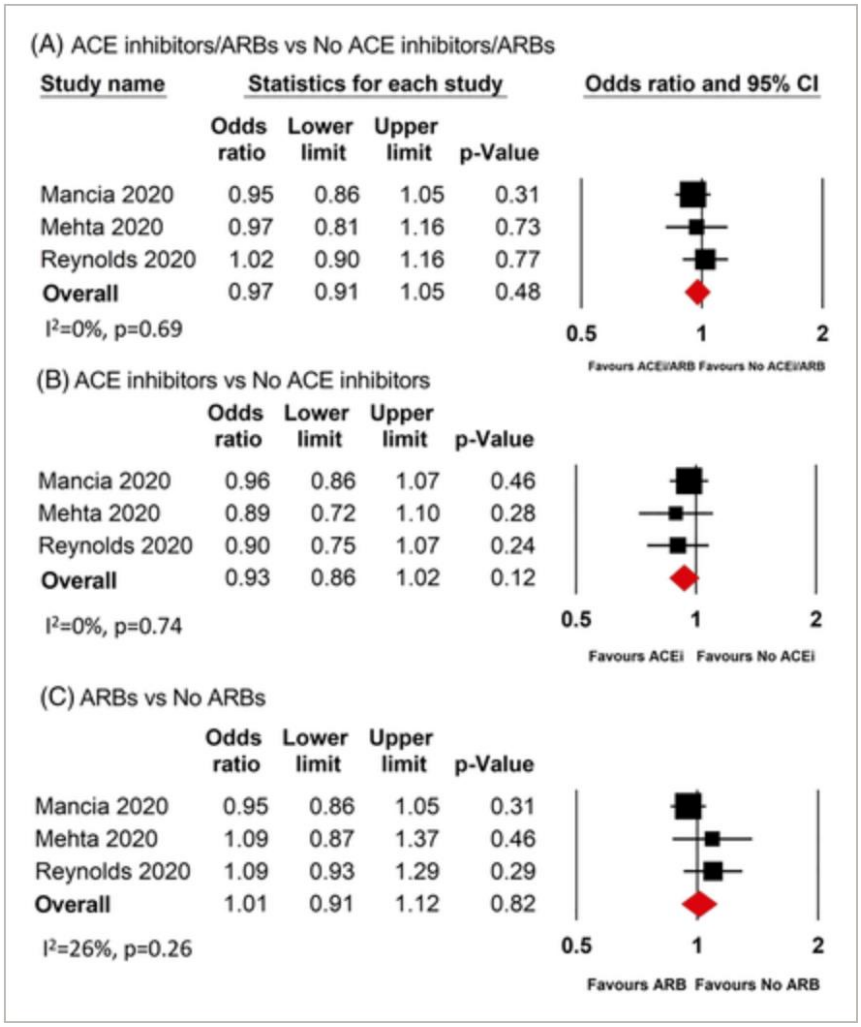


Figure 1. Renin–angiotensin system inhibitors and risk of a positive COVID-19 test.

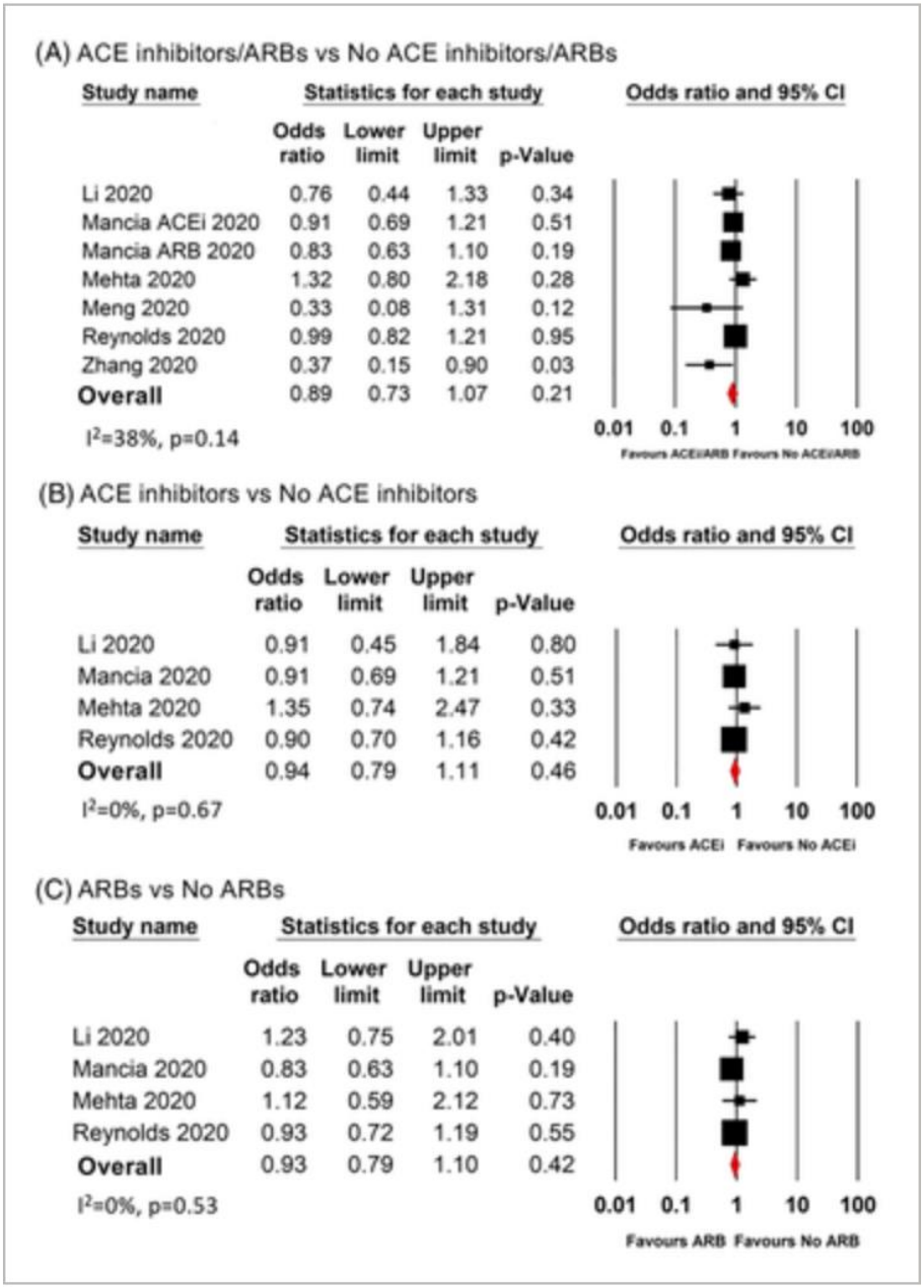


Figure 2. Renin–angiotensin system inhibitors and risk of severe illness/mortality.

PREVALENCE OF ASYMPTOMATIC COVID-19 INFECTION USING A SEROEPIDEMIOLOGICAL SURVEY

Shakiba M, Nazemipour M, Heidarzadeh A, Mansournia MA.. Epidemiol Infect. 2020 Nov 13:1-7. doi: 10.1017/S0950268820002745. Online ahead of print.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

This cross-sectional study by epidemiologists at Guilan University of Medical Sciences in Iran examined individuals using COVID-19 IgM/IgG rapid testing (n=528) and found 57.2% (65/117) had asymptomatic infection, while those who had previous contact with COVID-19 positive individuals showed lower asymptomatic prevalence than those with no contact (12% v. 69%). These data suggest asymptomatic prevalence is highly dependent on contact with COVID-19 positive individuals, so authors urge for more robust contact tracing to better understand transmission dynamics in addition to maintaining current public health protocols.

SARS-COV-2 PERSISTENCE AND NON-PROTECTIVE IMMUNITY IN INFECTED HAEMATOLOGICAL PATIENTS

Akinosoglou K, Paliogianni F, Spyridonidis A, Symeonidis A, Alexopoulos LG, Ziazias D, Kouraklis-Symeonidis A, Marangos M, Gogos C.. Br J Haematol. 2020 Nov 20. doi: 10.1111/bjh.17212. Online ahead of print.
Level of Evidence: Other - Case Report

BLUF

Greek infectious disease physicians present a case of 35-year-old with a history of acute lymphoblastic leukemia 14 days status-post chemotherapy with R-hyper-CVAD who presented on April 8, 2020 with pneumonia after positive RT-PCR for SARS-CoV-2 on March 26. The patient eventually recovered after a seven-week hospitalization and developed antibodies suggestive of immunologic memory (Figure 1, Table 1), but was later readmitted on July 22 with severe COVID-19 pneumonia despite serologic testing with continued adequate IgG. Authors suggest defective innate and adaptive immunity in immunocompromised patients may facilitate SARS-CoV-2 infection (i.e. antibodies may be non-neutralizing following chemotherapy) and allow persistence or viral reactivation.

FIGURES

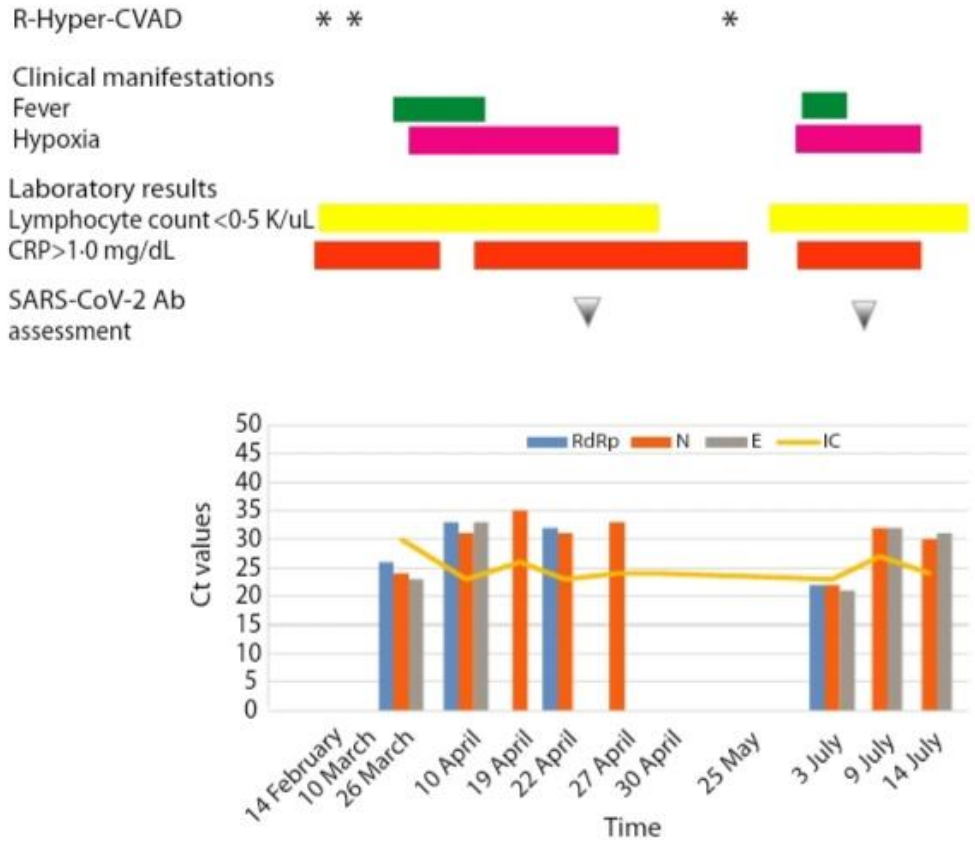


Figure 1: "Timeline of hospital admissions and tests for SARS-CoV-2. Viral gene expression as inversely expressed by a number of Ct values, againstthe presence of an internal positive control (IC) (yellow line). Values below the IC critical cut-off denote detectable gene expression. Clusteredbars indicate expression of RNA-dependent RNA polymerase (RdRp)(blue), nucleocapsid protein (N)(orange) and envelope (E)(grey). Colourblocks indicate the presence of fever (green), hypoxia (pink), lymphocyte count <0.5 K/µl (yellow) and CRP > 1 mg/dl (red). Clinical manifesta-tions and laboratory signs of lower respiratory tract infection occur when viral gene expression appears to be below the IC critical threshold,denoting a positive result. Expression fades as time passes, until it disappears for one or more genes to indicate progressive viral clearance. Greyarrowheads and stars (*) indicate timing of antibody assessment and R-hyper-CVAD (rituximab, cyclophosphamide, vincristine, doxorubicin,adriamycin, dexamethasone) administration, respectively.".

Normalised median fluorescence intensity	Nucleoprotein	Spike S1	Spike RBD	Test interpretation
Cut-off Anti IgA-IgG-IgM	3·8	4·0	4·0	
1st admission serum pooled_Anti IgA-IgG-IgM	1·5	8·6	18·8	Positive
2nd admission serum pooled_Anti IgA-IgG-IgM	0·5	8·5	18·5	Positive
Cut-off Anti IgG	2·3	3·5	4·3	
1st admission serum_Anti IgG	1·1	11·9	56·9	Positive
2nd admission serum_Anti IgG	0·3	8·8	47·4	Positive
Cut-off Anti IgA	3·9	4·7	3·4	
1st admission serum_Anti IgA	4·7	2·0	11·0	Positive
2nd admission serum_Anti IgA	0·9	2·6	16·6	Negative
Cut-off Anti IgM	7·3	4·8	4·8	
1st admission serum_Anti IgM	2·5	9·7	8·6	Positive
2nd admission serum_Anti IgM	0·7	2·4	1·7	Negative

As per manufacturer interpretation rule (Protatonce Ltd), the patient presented positive anti-SARS-CoV-2 antibodies (green shading) against S1 and receptor-binding domain (RBD), but not nucleoprotein. First and second admission sampling was performed on 30 March and 4 July, respectively.

Table 1: "Antibody detection against different SARS-CoV-2 antigens".

DIAPHRAGM PATHOLOGY IN CRITICALLY ILL PATIENTS WITH COVID-19 AND POSTMORTEM FINDINGS FROM 3 MEDICAL CENTERS

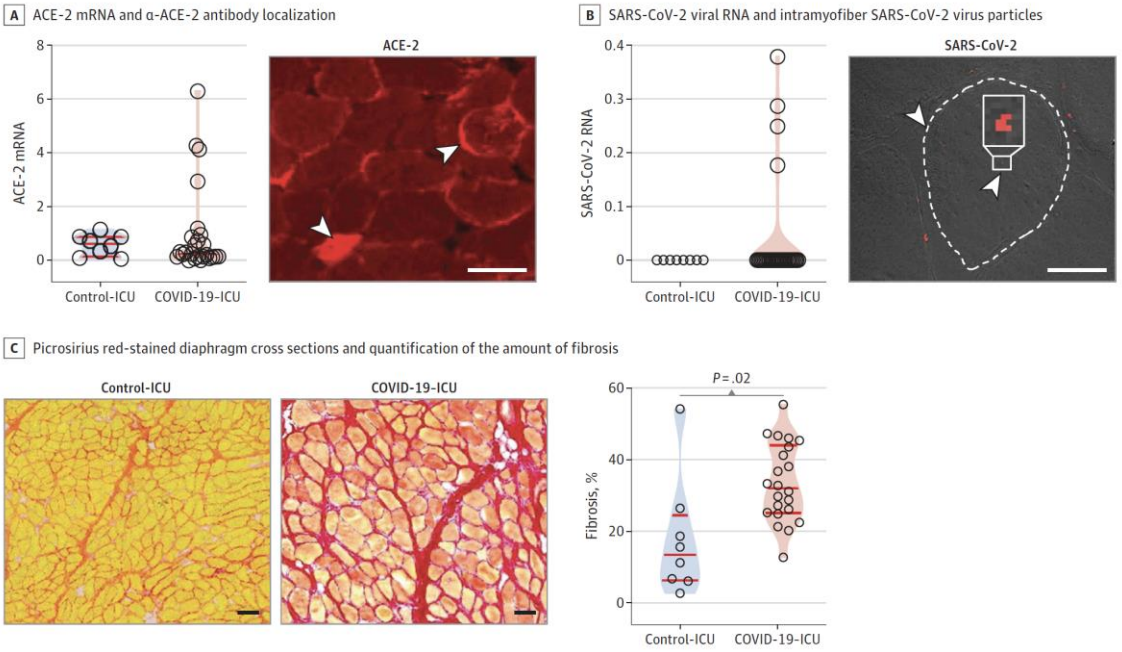
Shi Z, de Vries HJ, Vlaar APJ, van der Hoeven J, Boon RA, Heunks LMA, Ottenheijm CAC; Dutch COVID-19 Diaphragm Investigators.. JAMA Intern Med. 2020 Nov 16. doi: 10.1001/jamainternmed.2020.6278. Online ahead of print.
Level of Evidence: 4 - Local non-random sample

BLUF

Critical care physicians conducted a case-control study using autopsies of 26 deceased critically ill COVID-19 patients from 3 medical centers in the Netherlands during April and May 2020 to analyze the extent of diaphragm involvement. Findings show increased ACE-2 expression and SARS-CoV-2 viral infiltration in the diaphragm of patients who died of severe COVID-19 (Figure) compared to control specimens from 8 deceased ICU patients without COVID-19, suggesting that diaphragm fibrosis could be a source of respiratory distress in COVID-19 patients.

FIGURES

Figure. Angiotensin-Converting Enzyme 2 (ACE-2), SARS-CoV-2, and Fibrosis in the Diaphragms of Patients With COVID-19



A, Left panel: ACE-2 mRNA in diaphragm specimens determined by quantitative polymerase chain reaction (qPCR) and normalized to housekeeping gene *TBP*. Right panel: α-ACE-2 antibody localization with fluoresceine microscopy on diaphragm cross-sections; the arrowheads show membrane and cytosolic localization (bar = 50 µm). B, Left panel: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA, determined by qPCR and normalized to housekeeping gene *TBP*, is detected in the diaphragm of 4 coronavirus disease 2019 (COVID-19)–intensive care unit (ICU) patients (patients 7, 9, 33, and 36). Right panel: in situ hybridization using RNAscope on patient #7 shows intramyofiber SARS-CoV-2 virus particles (red dots, indicated with arrowheads); a myofiber edge is highlighted with dashed line (bar = 30 µm). C, Left panels: representative images of picrosirius red-stained diaphragm cross-sections to highlight fibrosis; patients #22 and 3 are shown (bar = 100 µm). Right panel: quantification of the amount of fibrosis.

EARLY SHORT-COURSE CORTICOSTEROIDS IN HOSPITALIZED PATIENTS WITH COVID-19

Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudhry Z, Bhargava P, Miller J, Kenney RM, Alangaden G, Ramesh MS; Henry Ford COVID-19 Management Task Force.. Clin Infect Dis. 2020 Nov 19;71(16):2114-2120. doi: 10.1093/cid/ciaa601.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

This quasi-experimental study, conducted by the Henry Ford COVID-19 Management Task Force at multiple hospitals in Michigan from March 12 to March 27, 2020, evaluated the effect of early corticosteroid therapy in 132 hospitalized patients with severe to moderate COVID-19 versus 81 COVID-19 patients on standard care treatment (Table 1). They found that early corticosteroid group (median time to initiation 2 days, IQR 1-3, range 0-8) had less transfers to the ICU (34.9% vs 54.3%, p=0.005), decreased ARDS occurrences (26.6% vs 38.3%, p=0.04), and spent less days in the hospital (5 vs 8 days, p less than 0.001) compared with the standard of care group (Table 2, 3). These findings suggest that early methylprednisolone therapy in patients with moderate/severe COVID-19 may help curb the inflammatory response elicited by SARS-CoV-2 and thus lead to better outcomes.

SUMMARY

The corticosteroid therapy group received an early, brief regimen of methylprednisolone 0.5 to 1 mg/kg/day divided in 2 intravenous doses for 3 days.

ABSTRACT

BACKGROUND: There is no proven antiviral or immunomodulatory therapy for COVID-19. The disease progression associated with the pro-inflammatory host response prompted us to examine the role of early corticosteroid therapy in patients with moderate to severe COVID-19. METHODS: We conducted a single pre-test, single post-test quasi-experiment in a multi-center health system in Michigan from March 12 to March 27, 2020. Adult patients with confirmed moderate to severe COVID were included. A protocol was implemented on March 20, 2020 using early, short-course, methylprednisolone 0.5 to 1 mg/kg/day divided in 2 intravenous doses for 3 days. Outcomes of standard of care (SOC) and early corticosteroid groups were evaluated, with a primary composite endpoint of escalation of care from ward to ICU, new requirement for mechanical ventilation, and mortality. All patients had at least 14 days of follow-up. RESULTS: We analyzed 213 eligible subjects, 81 (38%) and 132 (62%) in SOC and early corticosteroid groups, respectively.The composite endpoint occurred at a significantly lower rate in the early corticosteroid group (34.9% vs. 54.3%, p=0.005). This treatment effect was observed within each individual component of the composite endpoint. Significant reduction in median hospital length of stay was also observed in the early corticosteroid group (8 vs. 5 days, p < 0.001). Multivariate regression analysis demonstrated an independent reduction in the composite endpoint at 14-days controlling for other factors (aOR: 0.41; 95% CI [0.22 - 0.77]). CONCLUSION: An early short course of methylprednisolone in patients with moderate to severe COVID-19 reduced escalation of care and improved clinical outcomes.

Characteristics	Total (n=213)	Standard of Care (n=81)	Early CP (n=132)	p-value
Demographics				
Median age (IQR) - yr	62 (51-62)	64 (51.5-3.5)	61 (51-72)	0.400
Male sex – no. (%)	109 (51.2)	41 (50.6)	68 (51.5)	0.899
Black race – no. (%)	155 (72.8)	50 (61.7)	105 (79.5)	0.004
Median body mass index (IQR) - kg/m^2	32 (27.3-38.7)	30 (25-39)	33.2 (28.9-38.5)	0.007
Coexisting conditions – no. (%)				
Asthma	33 (15.5)	16 (19.8)	17 (12.9)	0.180
Chronic kidney disease	98 (46)	41 (51.9)	57 (43.5)	0.240
Chronic obstructive pulmonary disease	27 (12.7)	15 (18.5)	12 (9.1)	0.045
Congestive heart failure	26 (12.2)	10 (12.5)	16 (12.2)	0.951
Coronary artery disease	38 (17.8)	18 (22.2)	20 (15.2)	0.192
Diabetes	105 (49.3)	37 (45.7)	68 (51.5)	0.411
Hypertension	158 (74.2)	62 (76.5)	96 (72.7)	0.925
Malignancy	24 (11.3)	11 (13.6)	13 (9.9)	0.405
Smoking history	88 (41.3)	40 (49.4)	48 (36.4)	0.0615
Symptoms				
Cough – no. (%)	158 (74.2)	62 (76.5)	96 (72.7)	0.536
Fever – no. (%)	150 (70.4)	57 (70.4)	93 (70.5)	0.989
Myalgia – no. (%)	85 (39.9)	32 (39.5)	53 (40.2)	0.926
Shortness of breath – no. (%)	148 (69.5)	50 (61.7)	98 (74.2)	0.054
Median duration of symptoms (IQR) - days	5 (3-7)	5 (2-7)	6 (3-7)	0.107
Severity of illness in emergency department (ED)				
Median qSOFA (IQR)	1 (0-1)	1 (0-1)	1 (0-1)	0.850
Median NEWS (IQR)	7 (4-10)	7 (4-10)	7 (4-9)	0.668
Requiring mechanical ventilation in ED – no. (%)	22 (10.3)	10 (12.3)	12 (9.1)	0.448
Direct admission to ICU – no. (%)	26 (12.2)	11 (13.6)	15 (11.4)	0.631

*IQR denotes Interquartile range, CP denotes corticosteroid group, NEWS denotes National Early Warning Score, qSOFA denotes quick Sequential Organ Failure Assessment (qSOFA), ED denotes

Table 1. Baseline Demographics and Clinical Characteristics of Study Patients

Treatment	Total (n=213)	Standard of Care (n=81)	Early CP (n=132)	p-value
Antimicrobials				
Empiric antibiotic prescribed for pneumonia – no. (%)	163 (76.5)	65 (80.2)	98 (74)	0.316
Median time to empiric antibiotics (IQR) – days	1 (0-1)	1 (0-1)	0 (0-1)	0.631
Median duration of antimicrobials (IQR) - days	4 (2-5)	5 (3-5)	3 (2-5)	0.009
Hydroxychloroquine use - no. (%)	161 (75.6)	57 (70.4)	104 (78.8)	0.167
Median time to hydroxychloroquine initiation (IQR) - days	2 (1-3)	3 (1-4)	1 (0-2)	0.126
Lopinavir/ritonavir and ribavirin use - no. (%)	10 (4.7)	9 (11.1)	1 (0.76)	0.001
Remdesivir use – no. (%)	5 (2.3)	5 (6.2)	0 (0)	0.004
Tocilizumab use – no. (%)	14 (6.6)	8 (10.1)	6 (4.5)	0.126
Corticosteroid treatment				
Median time to steroid initiation from admission (IQR) – days	2 (1-4)	5 (3-7)	2 (1-3)	<0.001
Corticosteroids received in first 48 hours - no. (%)	65 (30.5)	10 (12.4)	55 (41.7)	<0.001
Corticosteroids received at any time - no. (%)*	136 (63.8)	46 (56.8)	90 (68.2)	0.094
Methylprednisolone use - no (%)	129 (94.9)	43 (93.5)	86 (95.5)	0.688
Median methylprednisolone dose (IQR) – mg	40 (40-50)	40 (40-50)	40 (35-50)	0.851
Oral prednisone switch – no. (%)	7 (5.4)	5 (11.6)	2 (2.3)	0.041
Median duration of corticosteroids (IQR) – days#	3 (3-3)	3 (3-3)	3 (3-3)	0.812

CP denotes corticosteroid group, IQR denotes Interquartile range

*Refer to Figure S1, supplemental materials for description of timing

#29 patients received greater than 3 days; Early CP 20 (22.2), 9 SOC (19.5)

Table 2. Treatments Received by Groups

Outcomes	Standard of Care (n=81)	Early CP (n=132)	Odds Ratio (CI)	p-value
Primary Outcome				
Primary composite outcome – no. (%)	44 (54.3)	46 (34.9)	0.45 (0.26 – 0.79)	0.005
Death – no. (%)	21 (26.3)	18 (13.6)	0.45 (0.22 – 0.91)	0.024
Respiratory failure requiring mechanical ventilation – no. (%)*	26 (36.6)	26 (21.7)	0.47 (0.25-0.92)	0.025
Escalation from GMU to ICU – no. (%)+	31 (44.3)	32 (27.3)	0.47 (0.25 – 0.88)	0.017
Secondary Outcomes				
Overall mechanical ventilation – no. (%)	36 (44.4)	38 (28.8)	0.51 (0.28 – 0.90)	0.020
ARDS – no. (%)	31 (38.3)	33 (26.6)		0.040
Mild	3 (3.7)	1 (0.76)		0.125
Moderate	8 (9.9)	9 (6.8)		0.307
Severe	20 (24.7)	23 (17.4)		0.201
Median duration of mechanical ventilation (IQR) - days	8 (4-13)	7 (4-9)		0.558
Median time to extubation (IQR) – days	8 (4-13)	7 (4-9)		0.558
Shock – no. (%)	19 (23.5)	17 (12.6)		0.069
Acute kidney injury – no. (%)	42 (51.9)	59 (44.7)		0.310
Median hospital length of stay (IQR) - days	8 (5-14)	5 (3-7)		<0.001
Discharged from hospital – no. (%)	51 (62.2)	88 (66.7)		0.584
Remain hospitalized – no. (%)	9 (11.1)	26 (19.7)		0.102
Remain intubated – no. (%)	7 (8.6)	13 (9.8)		0.771

CP denotes corticosteroid group, CI denotes confidence interval, ICU denotes intensive care unit, GMU denotes general medical unit, ARDS denotes acute respiratory distress syndrome, IQR denotes Interquartile range

*A total of 10 and 12 patients were not included in this analysis because they required mechanical ventilation in the emergency department in the SOC and early corticosteroid group, respectively.

+A total of 11 and 15 patients were not included in this analysis because they were directly admitted to the intensive care unit in the SOC and early corticosteroid group, respectively.

Table 3. Outcomes in the Pre-Corticosteroid and Corticosteroid Protocol Groups

PROGNOSTIC FACTORS AND PREDICTORS OF OUTCOME IN PATIENTS WITH COVID-19 AND RELATED PNEUMONIA: A RETROSPECTIVE COHORT STUDY

Boari GEM, Chiarini G, Bonetti S, Malerba P, Bianco G, Faustini C, Braglia-Orlandini F, Turini D, Guarinoni V, Saottini M, Viola S, Ferrari-Toninelli G, Pasini G, Mascadri C, Bonzi B, Desenzani P, Tusi C, Zanotti E, Nardin M, Rizzoni D.. Biosci Rep. 2020 Nov 17:BSR20203455. doi: 10.1042/BSR20203455. Online ahead of print.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A retrospective cohort study of patients with COVID-19 pneumonia (n=258; Table 1) conducted in Brescia, Italy from February 28 to April 30, 2020 found preexisting comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease, heart disease, cancer; Figure 2), ACE-Inhibitor or anti-platelet drug use, and radiologic Brixia scores >8 were associated with worse outcomes (n=65 deaths; Figure 1), whereas anticoagulation with enoxaparin (dose >4000 U) was associated with better prognosis. Authors suggest preexisting comorbidities and Brixia scores may be useful prognostic indicators of COVID-19 severity, and advocate for more comprehensive investigation of enoxaparin as a COVID-19 treatment.

ABSTRACT

The aim of the study was to assess simultaneously several potential predictors of outcome (co-morbidity, previous and in-hospital treatment, radiologic Brixia score) in patients with COVID-19. This retrospective cohort study included 258 consecutive patients with confirmed COVID-19 admitted to a medical ward at the Montichiari Hospital, Brescia, Italy from February 28th to April 30th, 2020. Patients had COVID-19 related pneumonia with respiratory failure, and were treated with

hydroxychloroquine, lopinavir plus ritonavir. In some patients additional treatment with tocilizumab, dexamethasone and enoxaparin was adopted. Outcomes (death or recovery) were assessed at the end of the discharge period or at the end the follow-up (August 2020). During hospitalization, 59 patients died, while 6 died after discharge. The following variables were demonstrated to be associated with a worse prognosis: Radiologic Brixia score higher than 8, presence at baseline of hypertension, diabetes, chronic obstructive pulmonary disease, heart disease, cancer, previous treatment with ACE-inhibitors or anti-platelet drugs. Anticoagulant treatment during hospital admission with enoxaparin at a dose higher than 4000 U per was associated to a better prognosis. In conclusion, our study demonstrates that some co-morbidities and cardiovascular risk factors may affect prognosis. The radiologic Brixia score may be a useful tool for stratifying the risk of death at baseline. Anticoagulant treatment with enoxaparin might be associated to a clinical benefit in terms of survival in patients with COVID-19.

FIGURES

Table 1. Demographic and clinical characteristics of the two groups of patients.

	Dead (n=65)	**Alive (n=193)**	**All patients (n=258)**
Age (years)	80.1±7.57 ***	68.6±19.7	71.0±13.8
Gender (males)	49/65 ***	124/193	173/258
Diabetes (yes)	23/65 ***	44/193	67/258
Hypertension (yes)	54/65 ***	107/193	151/258
COPD (yes)	15/65 ***	20/193	35/258
Smoke (yes) (actual or previous)	10/65 ***	30/193	40/258
Obesity (yes)	9/33 ***	31/145	40/178
Cancer (yes)	7/65 ***	5/193	12/258
Time of symptoms before hospitalization (days)	5.75±3.58**	8.60±8.83	7.92±5.51
Previous treatment ACE-inhibitors (yes)	21/65***	32/193	53/258
Angiotensin-receptor blockers (yes)	14/65 ***	40/193	54/258
Statins (yes)	26/65 ***	53/193	79/258
Anti-platelets agents (yes)	27/65 ***	48/193	75/258
Steroids (yes)	5/65 ***	6/193	11/258
Anticoagulants (yes)	11/65 ***	18/193	29/258

***p<0.001 vs. alive.

Table 1. Demographic and clinical characteristics of the two groups of patients.

Fig. 1 - Brixia Score

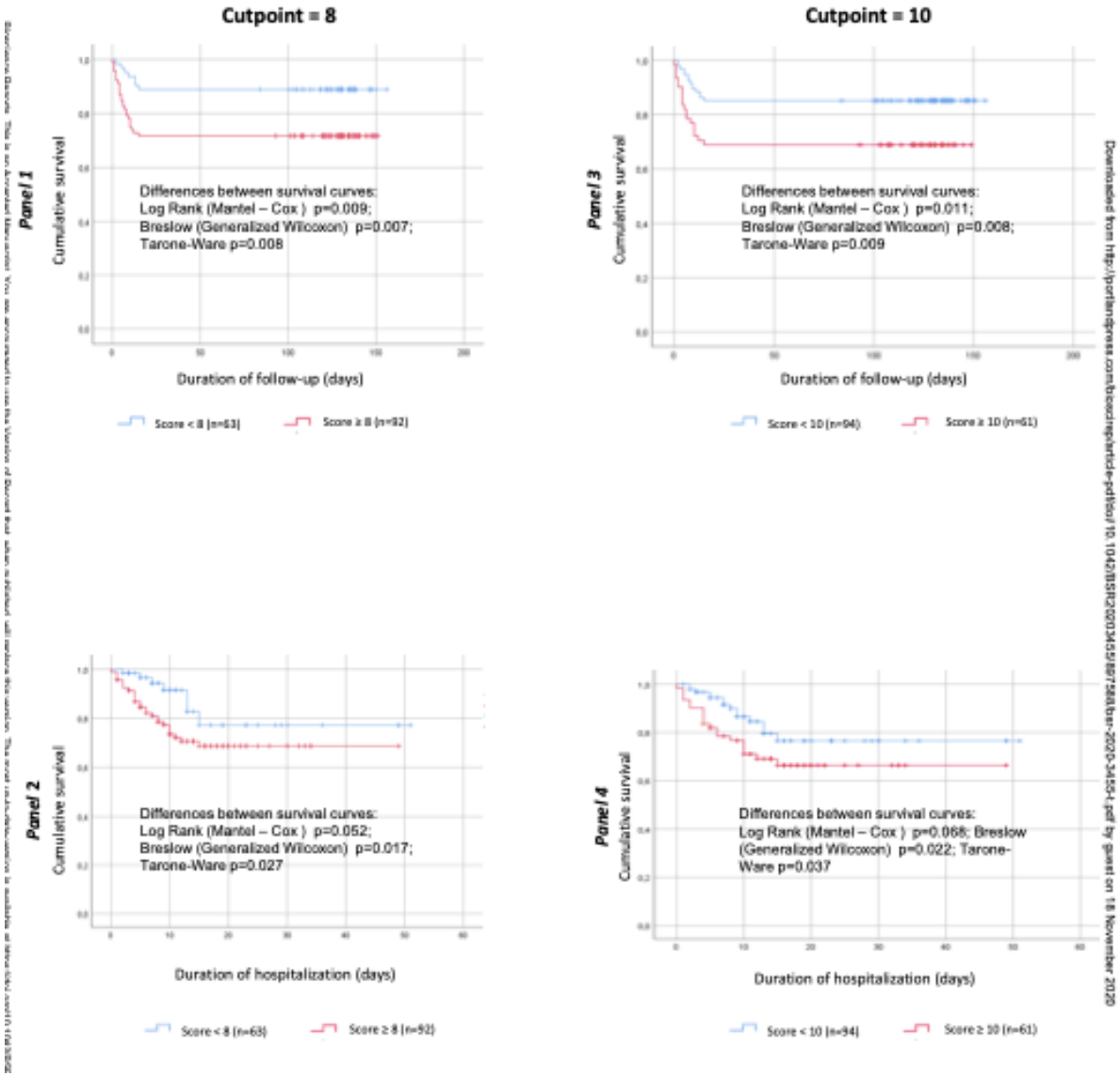


Figure 1. Kaplan-Meier survival curve for the Brixia radiologic score
Analysis run using group as factor; death as event and time to death/discharge or time to death/re- evaluation at follow up as time variable. Panel 1: Brixia score ≥ 8 (red line) or < 8 (blue line), time to death/re-evaluation at follow up as time variable. Panel 2: Brixia score ≥ 8 (red line) or < 8 (blue line), time to death/discharge as time variable. Panel 3: Brixia score ≥ 10 (red line) or < 8 (blue line), time to death/re-evaluation at follow up as time variable. Panel 4: Brixia score ≥ 10 (red line) or < 8 (blue line), time to death/discharge as time variable

Figure 2 – Risk factors

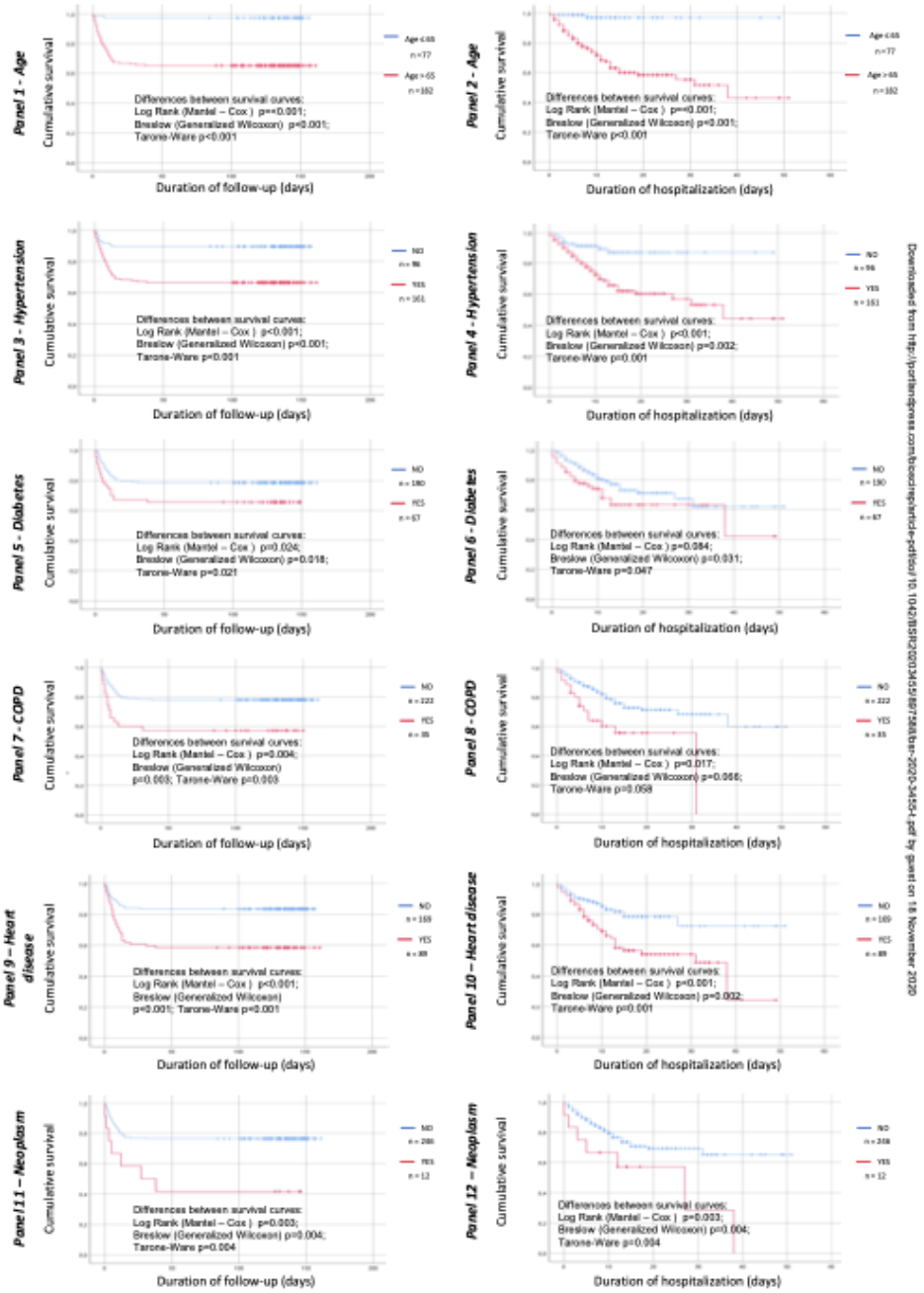


Figure 2. Kaplan-Meier survival curve for the presence or absence of cardiovascular risk factors or comorbidities Analysis run using group as factor; death as event and time to death/discharge or time to death/re- evaluation at follow up as time variable. Panel 1: age ≥ 65 (red line) or < 65 (blue line), time to death/re-evaluation at follow up as time variable. Panel 2: age ≥ 65 (red line) or < 65 (blue line), time to death/discharge as time variable. Panel 3: presence (red line) or absence (blue line) of hypertension at entry, time to death/re- evaluation at follow up as time variable. Panel 4: presence (red line) or absence (blue line) of hypertension at entry, time to death/discharge as time variable. Panel 5: presence (red line) or absence (blue line) of diabetes mellitus at entry, time to death/re- evaluation at follow up as time variable. Panel 6: presence (red line) or absence (blue line) of diabetes mellitus at entry, time to death/discharge as time variable. Panel 7: presence (red line) or absence (blue line) of chronic obstructive pulmonary disease at entry, time to death/re-evaluation at follow up as time variable. Panel 8: presence (red line) or absence (blue line) of chronic obstructive pulmonary disease at entry, time to death/discharge as time variable. Panel 9: presence (red line) or absence (blue line) of any cardiac disease at entry, time to death/re- evaluation at follow up as time variable. Panel 10: presence (red line) or absence (blue line) of any cardiac disease at entry, time to death/discharge as time variable. Panel 11: presence (red line) or absence (blue line) of any active tumor entry at entry, time to death/re-evaluation at follow up as time variable. Panel 12: presence (red line) or absence (blue line) of any active tumor entry, time to death/discharge as time variable

BREAKTHROUGH VENOUS THROMBOEMBOLIC EVENTS IN FIVE PATIENTS WITH COVID-19 ON DIRECT ORAL ANTICOAGULANTS

Lewis P, Tharp JL.. J Clin Pharm Ther. 2020 Nov 20. doi: 10.1111/jcpt.13311. Online ahead of print.
Level of Evidence: 4 - Case-series, case-control, or historically controlled studies

BLUF

Pharmacists from Johnson City Medical Center (Tennessee) present a case series of 5 hospitalized patients with COVID-19 who were taking direct oral anticoagulants (DOACs) and monitored via D-Dimer for detection of venous thromboembolism (VTE; Figure 1). They observed that 4 patients had a prior VTEs and had atrial fibrillation, 4 patients developed acute VTE, and 1 patient was clinically diagnosed with stroke during hospitalization (Table 1). This case series suggests that COVID-19 may lead to higher rates of DOAC failure, leading the authors to propose that patients may be safer using low molecular weight or unfractionated heparin instead of DOACs as they have additional anti-inflammatory properties.

ABSTRACT

WHAT IS KNOWN AND OBJECTIVE: Coronavirus disease 2019 (COVID-19) is associated with increased risk of venous thromboembolism (VTE). Guidance for VTE prophylaxis continues to evolve, including addressing direct oral anticoagulants (DOACs) continued upon hospitalization. CASE SUMMARIES: We present 5 patients hospitalized for COVID-19 while on DOACs. Four patients had atrial fibrillation and had a previous VTE. Four patients developed acute VTE and one developed stroke-like symptoms. Monitoring D-dimer assisted with the detection of VTE. Three patients died, and two were discharged alive. WHAT IS NEW AND CONCLUSION: Therapeutic failure with DOACs appears to be commonplace in COVID-19. Further research is needed to determine whether there is an underlying cause to this association.

FIGURES

TABLE 1 Patient details

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Demographics	77-year-old white male	70-year-old white male	76-year-old white male	80-year-old white male	92-year-old white male
Past medical history	Atrial fibrillation, dyslipidaemia	Atrial fibrillation CAD, CHF, COPD, diabetes type 2, dyslipidaemia, hypertension,	Atrial fibrillation, CHF, dyslipidaemia, hypertension, asthma, diabetes type 2	CAD, CHF, dyslipidaemia, hypertension, history of pulmonary embolus	Atrial fibrillation, CAD, CHF, dyslipidaemia, CLL, CAD s/p CABG, ischaemic cardiomyopathy, sick sinus syndrome s/p PPM, HLD, HLD, paroxysmal Afib, anaemia of chronic disease and chronic pleural effusion.
Home anticoagulant	Apixaban 5 mg twice daily	Apixaban 5 mg twice daily	Rivaroxaban 20 mg daily	Rivaroxaban 20 mg daily	Apixaban 2.5 mg twice daily
Other home medications	Metoprolol Atorvastatin	Aspirin, carvedilol, dulaglutide, furosemide, insulin glargine, lansoprazole, losartan, montelukast, simvastatin	Atorvastatin, bisoprolol, buspirone, digoxin, dulaglutide, escitalopram, esomeprazole, insulin lispro, levothyroxine, losartan, pregabalin, ropinirole, tamsulosin, trazodone	Amiodarone, aspirin, atorvastatin, furosemide, insulin aspart, insulin detemir, levothyroxine, mirtazapine, sertraline	Carvedilol, ferrous sulphate
COVID/ infection-related therapies	Convalescent plasma Dexamethasone Cefepime	Convalescent plasma Dexamethasone	Convalescent plasma Dexamethasone Cefepime, linezolid	Convalescent plasma Dexamethasone Cefepime, linezolid	Convalescent plasma Dexamethasone Remdesivir Cefepime, linezolid
Highest Oxygen requirement prior to VTE	Supplemental oxygen (15 L/min)	Supplemental oxygen (10 L/min)	High flow nasal cannula	Mechanical ventilation	High flow nasal cannula
Reason for VTE workup	D-dimer > 5000 ng/mL	D-dimer 2721 ng/mL	Shortness of breath, D-dimer > 5000 ng/mL	Increasing O2 requirement, unable to safely perform CT	Left-sided facial droop with aphasia, D-dimer 3160 ng/mL
VTE findings	Chest CT demonstrated bilateral upper lobe pulmonary emboli	Venous ultrasound demonstrating partially occluding and soft echogenic material in the lumen of the popliteal and femoral veins	Chest CT demonstrated small pulmonary embolism in distal segmental and subsegmental pulmonary artery branches of right lower lobe	Venous ultrasound demonstrated echogenic material in lumen of femoral vein, appears acute on chronic	Clinical diagnosis of a stroke. Care was withdrawn and no further imaging was performed
Treatment rendered	Change to enoxaparin 1 mg/kg every 12hr	Change to enoxaparin 1 mg/kg every 12 hr	Change to enoxaparin 1 mg/kg every 12 hr	Change to enoxaparin 1 mg/kg every 12 hr	Care withdrawn
Highest oxygen requirement after VTE	Mechanical ventilation	Supplemental oxygen (5 L/min)	Mechanical ventilation	Mechanical ventilation	Care withdrawn
Patient outcome	Deceased	Discharge to skilled nursing facility	Discharge to inpatient rehabilitation	Deceased	Deceased

Table 1. Patient Data

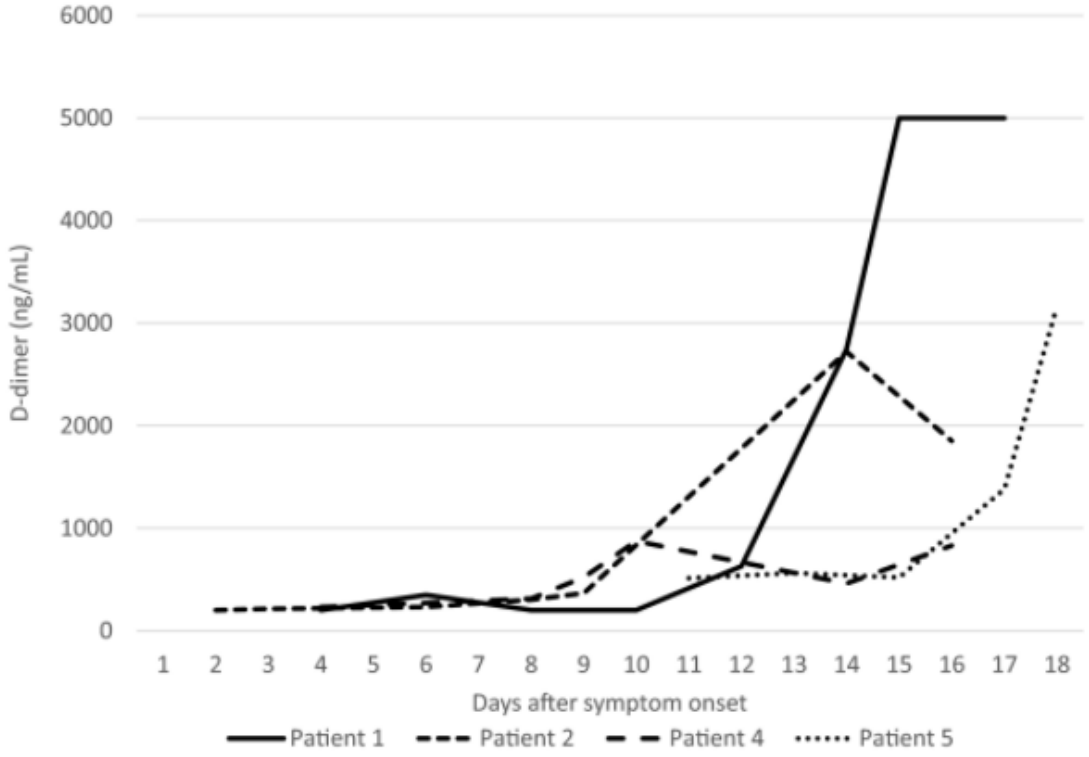


Figure 1. D-dimer trend. Note that patient 3 had a single D-dimer value on day 15 reported as >5000 ng/mL

A CASE OF COVID-19 PATIENT WITH FALSE-NEGATIVE FOR SARS-COV-2 OF PHARYNGEAL SWAB, FROM A CHINESE TRAVELLER RETURNING FROM WUHAN, HUBEI PROVINCE, CHINA, JANUARY 2020

Ishikane M, Miyazato Y, Kustuna S, Suzuki T, Ide S, Nakamura K, Morioka S, Katano H, Suzuki T, Ohmagari N.. Jpn J Infect Dis. 2020 Nov 24;73(6):462-464. doi: 10.7883/yoken.JJID.2020.240. Epub 2020 May 29.
Level of Evidence: 5 - Case report

BLUF

A case report of a man in his early 50's admitted at the National Center for Global Heath and Medicine in Tokyo on January 26, 2020 who presented with a fever, sore throat, and a mild dry cough with bilateral lower lung field infiltrate (Figure 1). On day 1 of admission, a pharyngeal specimen was found to be negative for SARS-CoV-2 via RT-PCR. However, due to clinical and epidemiological reasons to suspect COVID-19, the patient's reserved sputum specimen from days 1 to day 3 of hospital stay was re-tested for SARS-CoV-2 after patient discharge and found to be positive (Table 1). Given the original false negative test, the authors urge clinicians to consider the time period from disease onset to COVID-19 testing and the specimen type used when testing for COVID-19.

ABSTRACT

We report a case of patient in Japan with Coronavirus disease 2019 (COVID-19) with false-negative of reverse transcription polymerase chain reaction for Severe Acute Respiratory Syndrome Coronavirus 2 of pharyngeal swab, from a Chinese traveller returning from Wuhan, Hubei Province, China. If a patient is clinically or epidemiologically suspected of COVID-19, appropriate infection and prevention control measures such as standard, contact, and droplet precaution are needed until the patient is proven to be true-negative.

FIGURES

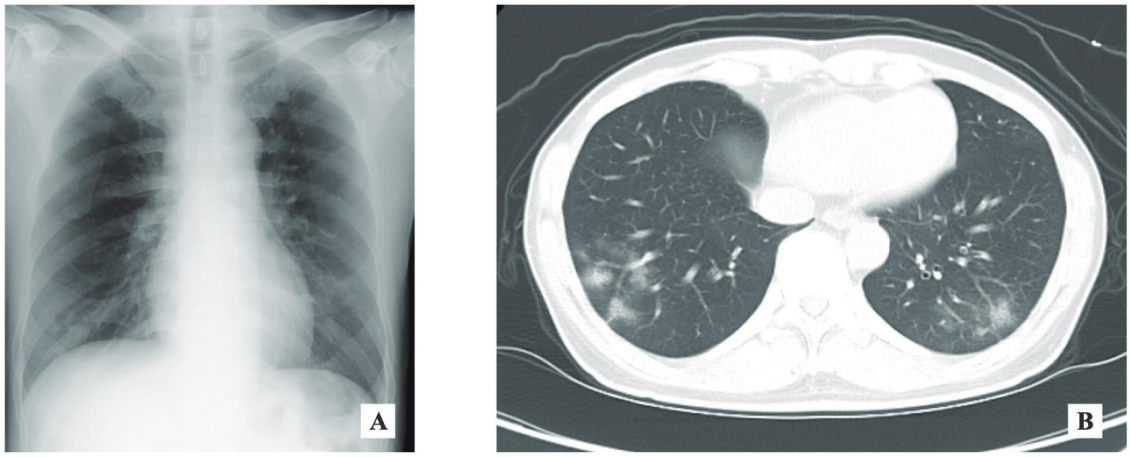


Figure 1. Chest x-ray and computed tomography of the chest on admission. A. Chest x-ray with infiltration in bilateral lower lung fields (A). Computed tomography of the chest with pan lobular centrality ground-glass opacity with bronchial wall thickening on bilateral lower lobes (B).

Specimen	illness Day 1		illness Day 3	
	Real-time RT-PCR (S)	Real-time RT-PCR (N)	Real-time RT-PCR (S)	Real-time RT-PCR (N)
Pharyngeal swab	Negative	Negative	NT	NT
Sputum	Positive 21.3 (37.8)	Positive 4.0 (37.3)	Positive 9.8 (39.0)	Positive 6.6 (36.7)
Serum	Negative	Negative	Negative	Negative
Urine	Negative	Negative	Negative	Negative
Stool	NT	NT	NT	NT

Data are presented as virus copies per 1μL (Ct).
Lower cycle threshold (Ct) values indicate higher viral loads.
Real-time RT-PCR (S and N) detected spike and nucleoprotein genes of SARS-CoV-2, respectively.
NT, denotes not tested.

Table 1. Results of real-time reverse transcriptase-polymerase-chain-reaction testing for the severe and acute respiratory syndrome Coronavirus 2 (SARS-CoV-2).

RECURRENCE OF SARS-COV-2 NUCLEIC ACID POSITIVE TEST IN PATIENTS WITH COVID-19: A REPORT OF TWO CASES

Wu J, Cheng J, Shi X, Liu J, Huang B, Zhao X, Qiu Y, Yu J, Cao H, Li L.. BMC Pulm Med. 2020 Nov 23;20(1):308. doi: 10.1186/s12890-020-01348-8.
Level of Evidence: 5 - Case Report

BLUF

Investigators primarily from Zhejiang University School of Medicine present a case report of 2 COVID-19 patients (a 8-year-old boy with mild COVID-19 and a 46-year-old female with moderate COVID-19) who were considered recovered after 3 consecutive negative nucleic acid SARS-CoV-2 tests in February, 2020 yet tested positive for COVID-19 again within 2 weeks and 1 week, respectively (Figure 1). These two cases highlight the possibility of both reinfection and incomplete recovery of COVID-19 after the first infectious stage, suggesting a need to improve the "discharge standard of care" for COVID-19 patients.

ABSTRACT

BACKGROUND: The recurrence of positive SARS-CoV-2 nucleic acid test results in patients with COVID-19 is becoming more important and warrants more attention. CASE PRESENTATION: This study reports 2 cases, a child with mild COVID-19 and an adult female with moderate COVID-19, who were discharged after three consecutive negative nucleic acid tests and were later readmitted to the hospital for recurrence of SARS-CoV-2 nucleic acid positivity. By tracking the patients' symptoms, serum antibodies, and imaging manifestations after readmission, we found that they showed a trend of gradual improvement and recovery throughout treatment. They were cured without additional treatment, with the appearance of antibodies and the recovery of immune functions. CONCLUSIONS: It is deemed extremely necessary to improve the discharge standard of care. At the same time, nucleic acid detection is recommended to increase the dynamic monitoring of serum antibodies and imaging, strengthen the management of discharged patients, and appropriately extend the home or centralized isolation time.

FIGURES

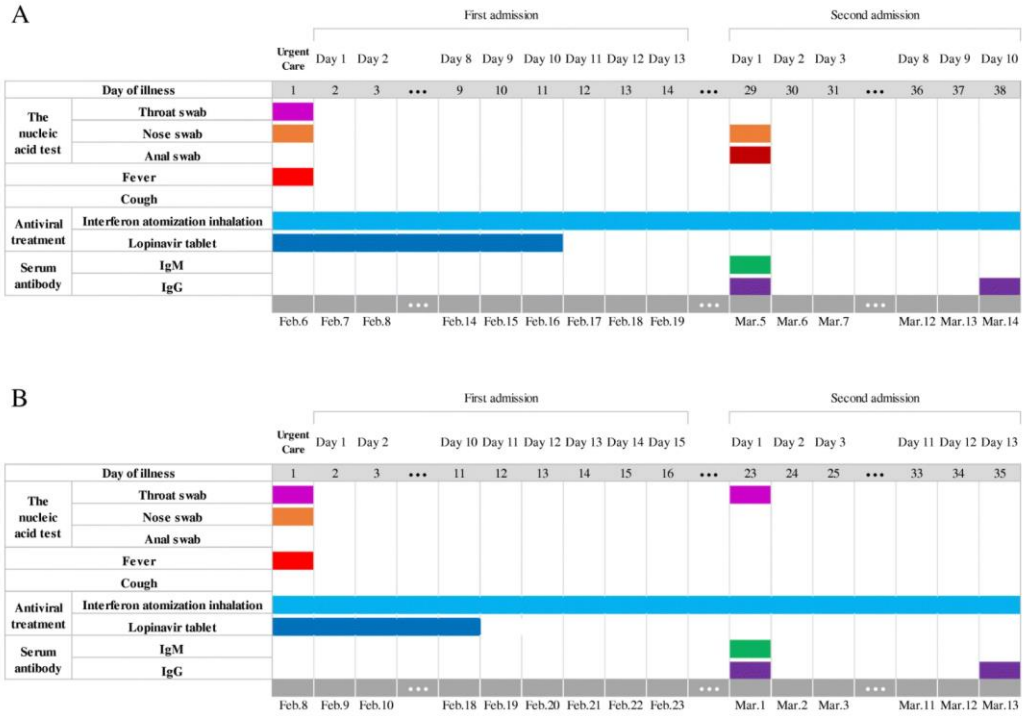


Figure 1. Timeline of the patients with COVID-19 after the onset of illness. a, the 8-year-old boy; b, the 46-year-old woman

PROFILE OF IMMUNOGLOBULIN G AND IGM ANTIBODIES AGAINST SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2)

Qu J, Wu C, Li X, Zhang G, Jiang Z, Li X, Zhu Q, Liu L.. Clin Infect Dis. 2020 Nov 19;71(16):2255-2258. doi: 10.1093/cid/ciaa489.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Investigators from the National Clinical Research Center for Infectious Diseases (Shenzhen, China) analyzed 347 serum samples from 41 RT-PCR confirmed COVID-19 patients (15 with mild-moderate symptoms, 16 with severe, and 10 with critical) admitted to The Third People's Hospital of Shenzhen between January 11 and February 10, 2020. Results revealed 39% of COVID-19 patients had seroconversion of IgG antibodies against SARS-CoV-2 nucleocapsid (N) protein and spike (S) glycoprotein in an average of 11 days after onset of symptoms (Figure 1A), and 51.2% with seroconversion to IgM antibodies in an average of 14 days (Figure 1B). Further, critical patients were found to have a delayed, but more robust IgG and IgM response (Figure 1C and 1D). This understanding of antibody kinetics against SARS-CoV-2 may assist in clinical diagnosis, specifically in utilizing immunoassays as a testing tool during the pandemic.

SUMMARY

The COVID-19 serum samples were compared with control samples of 10 influenza patients and 28 healthy patients completing routine check-ups between February 4 and February 10, 2020, which all tested negative.

ABSTRACT

We profiled the serological responses to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) nucleocapsid (N) protein and spike (S) glycoprotein. The majority of the patients developed robust antibody responses between 17 and 23 days after illness onset. Delayed, but stronger antibody responses were observed in critical patients.

FIGURES

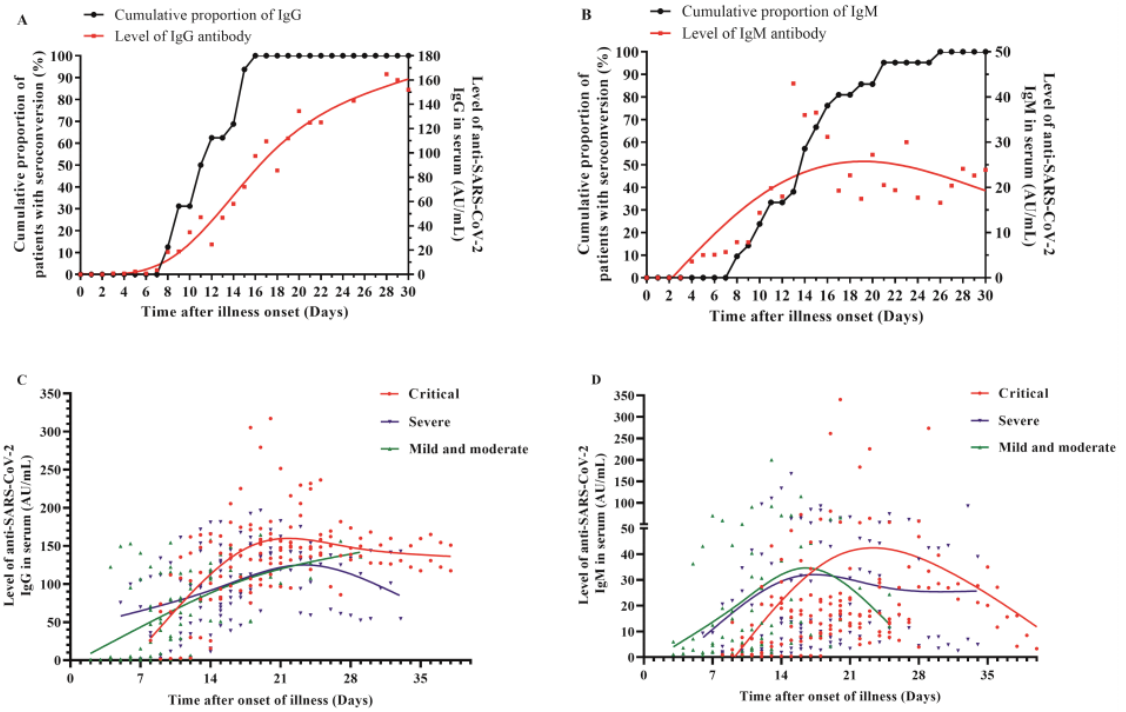


Figure 1. Longitudinal profile of IgG and IgM antibodies to SARS-CoV-2 nucleocapsid protein and spike glycoprotein in patients with COVID-19. A, Cumulative proportion of patients who seroconverted and the concentration level of anti–SARS-CoV-2 IgG in the sera of 16 patients. B, Cumulative proportion of patients who seroconverted and the concentration level of anti–SARS-CoV-2 IgM in the sera of 21 patients. C, The level (AU/mL) of anti–SARS-CoV-2 IgG in patients with mild and moderate, severe, and critical COVID-19 during hospitalization. D, The level (AU/mL) of anti–SARS-CoV-2 IgM in patients with mild and moderate, severe, and critical COVID-19 during hospitalization.

DEVELOPMENTS IN TREATMENTS

REVEALING THE INHIBITION MECHANISM OF RNA-DEPENDENT RNA POLYMERASE (RDRP) OF SARS-COV-2 BY REMDESIVIR AND NUCLEOTIDE ANALOGUES: A MOLECULAR DYNAMICS SIMULATION STUDY

Wakchaure PD, Ghosh S, Ganguly B.. J Phys Chem B. 2020 Nov 15. doi: 10.1021/acs.jpcb.0c06747. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

A molecular dynamics study conducted by computation and simulation specialists at the Academy of Scientific and Innovative Research in Ghaziabad, India investigated remdesivir (an RNA-dependent RNA polymerase [RdRp] enzyme inhibitor) and two similar nucleotide analogues (compound 8 and compound 17; Figure 3) via simulation and found compound 17 had similar hydrogen-bonding and binding energy to remdesivir (Figures 5,6), while also forming hydrogen bonds with catalytic residues. Authors suggest compound 17 may bind strongly with SARS-CoV-2 RdRp and has potential as an antiviral target for COVID-19 treatment.

ABSTRACT

Antiviral drug therapy against SARS-CoV-2 is not yet established and posing a serious global health issue. Remdesivir is the first antiviral compound approved by the US FDA for the SARS-CoV-2 treatment for emergency use, targeting RNA-dependent RNA polymerase (RdRp) enzyme. In this work, we have examined the action of remdesivir and other two ligands screened from the library of nucleotide analogues using docking and molecular dynamics (MD) simulation studies. The MD simulations have been performed for all the ligand-bound RdRp complexes for the 30 ns time scale. This is one of the earlier reports to perform the MD simulations studies using the SARS-CoV-2 RdRp crystal structure (PDB ID 7BTF). The MD trajectories were

analyzed and Molecular Mechanics Poisson-Boltzmann Surface Area (MM-PBSA) calculations were performed to calculate the binding free energy. The binding energy data reveal that compound-17 (-59.6 kcal/mol) binds more strongly as compared to compound-8 (-46.3 kcal/mol) and remdesivir (-29.7 kcal/mol) with RdRp. The detailed analysis of trajectories shows that the remdesivir binds in the catalytic site and forms a hydrogen bond with the catalytic residues from 0 to 0.46 ns. Compound-8 binds in the catalytic site but does not form direct hydrogen bonds with catalytic residues. Compound-17 showed the formation of hydrogen bonds with catalytic residues throughout the simulation process. The MD simulation results such as hydrogen bonding, the center of mass distance analysis, snapshots at a different time interval, and binding energy suggest that compound-17 binds strongly with RdRp of SARS-CoV-2 and has the potential to develop as a new antiviral against COVID-19. Further, the frontier molecular orbital analysis and molecular electrostatic potential (MESP) iso-surface analysis using DFT calculations shed light on the superior binding of compound-17 with RdRp compared to remdesivir and compound-8. The computed as well as the experimentally reported pharmacokinetics and toxicity parameters of compound-17 is encouraging and therefore can be one of the potential candidates for the treatment of COVID-19.

FIGURES

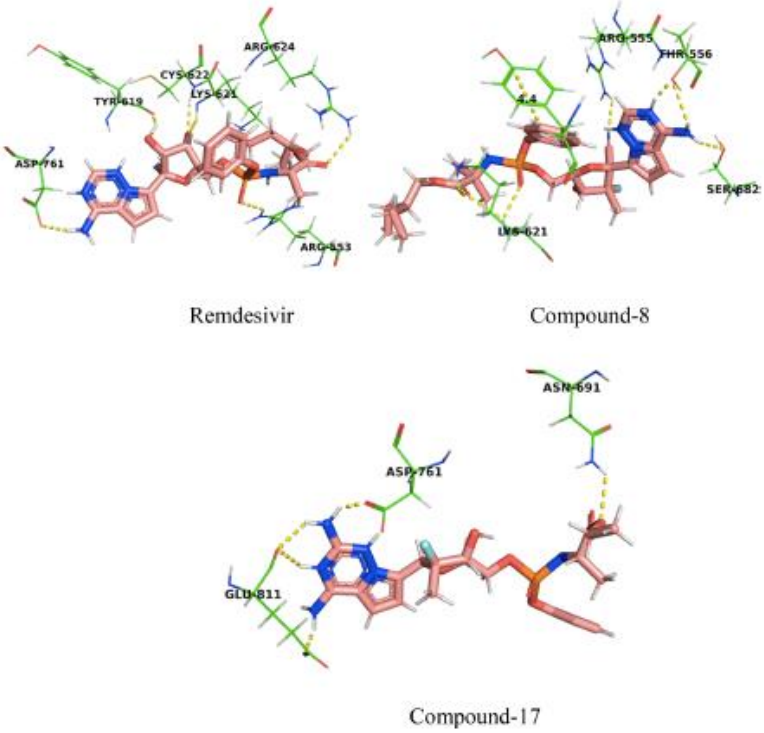


Figure 3. Ligand binding conformations and binding site interactions with RDRP active site.

Figure 3. Ligand binding conformations and binding site interactions with RDRP active site.

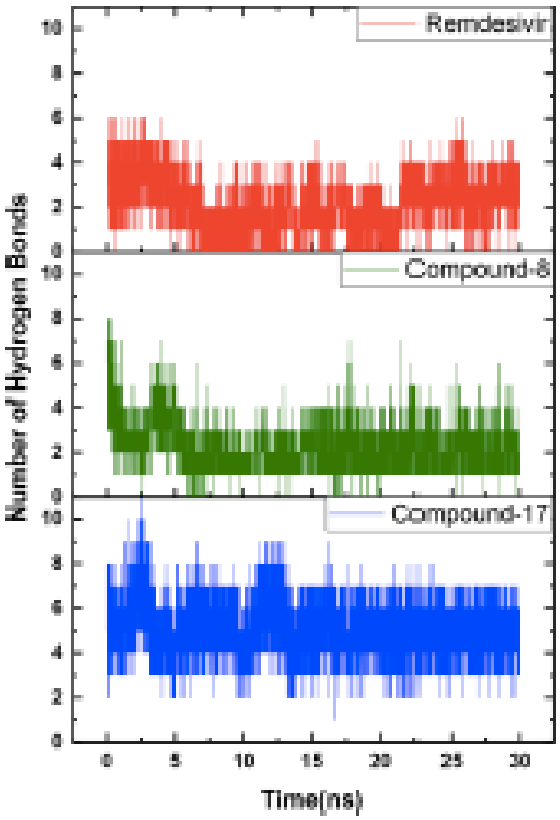


Figure 6. Hydrogen-bonding interactions of ligands with residues during the simulation.

Figure 6. Hydrogen-bonding interactions of ligands with residues during the simulation.

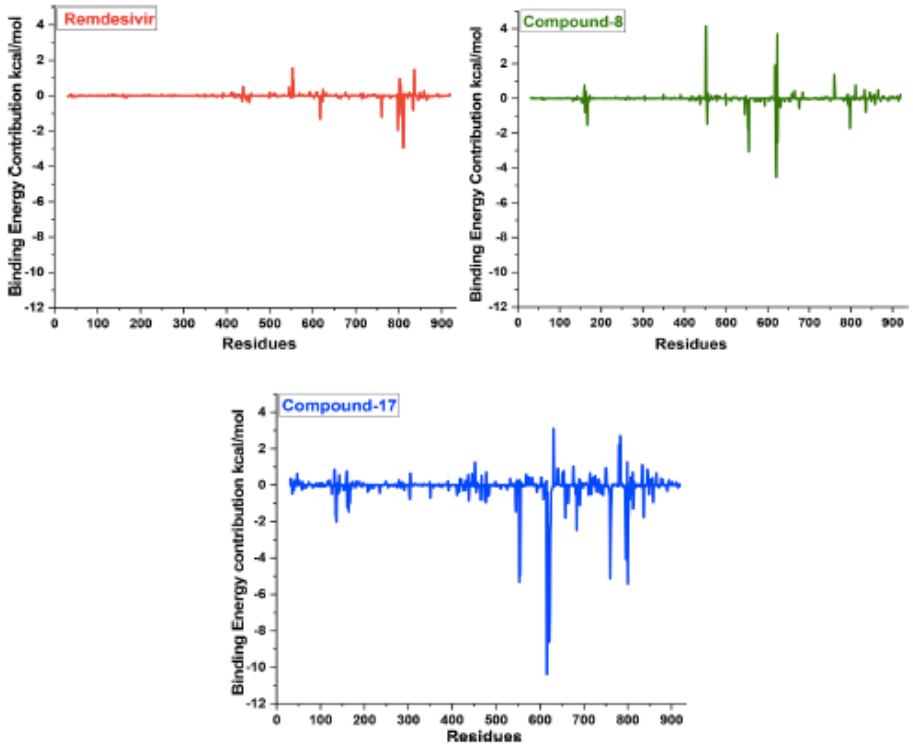


Figure 5. Energy contribution of residues to the average binding energy of the ligands

Figure 5. Energy contribution of residues to the average binding energy of the ligands

ACKNOWLEDGEMENTS

CONTRIBUTORS

Ankita Dharmendran
Ellen Reidy
Eva Shelton
Krithika Kumarasan
Renate Meckl
Sarala Kal
Sokena Zaidi
Veronica Graham
Zainab Awan

EDITORS

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