

The Daily COVID-19 Literature Surveillance Summary

December 03, 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>

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EXECUTIVE SUMMARY

Management

- A systematic review analyzed a set of 45 studies (n= 4,203 patients) published between November 1, 2019 and March 15, 2020 and found that elevated leukocyte count, alanine aminotransferase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), and procalcitonin levels [predicted ICU admission in patients with COVID-19](#). Acute respiratory distress syndrome (ARDS) was predicted by elevated LDH, while mortality was predicted by increased leukocyte count and elevated LDH. Treatment with lopinavir-ritonavir showed no significant benefit across mortality and ARDS rates, while corticosteroids were associated with a higher rate of ARDS. These findings suggest that elevated levels of LDH, leukocytosis, procalcitonin, AST, and ALT may be important early signs of disease severity, though early antiviral and steroid treatments do not appear to offer much clinical benefit.
- Members of the Department of Geriatrics at Peking University First Hospital in China conducted a systematic review and meta-analysis of 25 articles assessing coagulation parameters in 3952 SARS-CoV-2 positive patients published between December 1, 2019 and May 1, 2020 and found significantly higher D-dimer (standardized mean difference [SMD] 0.83, I²=56.9%), prothrombin time (SMD 0.39, I²=79.4%), and fibrinogen (SMD 0.35, I²=42.4%) in patients with more severe COVID-19 compared to those with less severe disease, suggesting that [hypercoagulability is associated with severity of COVID-19](#) and coagulation parameters should be assessed in these patients to monitor progression.

Silver Linings

- A literature review by investigators at McGill University of vaccine trials for 23 different viral infectious diseases from January 2005 through March 2020 showed that these trials historically have a 10% chance of moving from phase 2 through Food and Drug Administration (FDA) licensure within 10 years, and the average timeline from phase 2 to approval was 4.4 years, suggesting an [unparalleled achievement if COVID-19 vaccine is approved](#) within 18 months of the start of the pandemic.

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UNDERSTANDING THE PATHOLOGY

IN VITRO

STRUCTURAL BASIS OF RNA RECOGNITION BY THE SARS-COV-2 NUCLEOCAPSID PHOSPHOPROTEIN

Dinesh DC, Chalupska D, Silhan J, Koutna E, Nencka R, Veverka V, Boura E.. PLoS Pathog. 2020 Dec 2;16(12):e1009100. doi: 10.1371/journal.ppat.1009100. Online ahead of print.

Level of Evidence: Other - Mechanism-based reasoning

BLUF

Chemists from the Institute of Organic Chemistry and Biochemistry at the Czech Academy of Sciences in Prague, Czech Republic utilized NMR spectroscopy to analyze the N protein's N-terminal RNA binding (N-NTD) of SARS-CoV-2. They found a U-shaped canyon of arginines and lysines on the N-NTD which serves as a binding site for RNA (Figures 1-3). Authors suggest this site contributes to the supercoiling and structure of SARS-CoV-2 and that studying this structure could improve understanding of which antivirals may be most effective for treatment.

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the coronavirus disease 2019 (COVID-19). SARS-CoV-2 is a single-stranded positive-sense RNA virus. Like other coronaviruses, SARS-CoV-2 has an unusually large genome that encodes four structural proteins and sixteen nonstructural proteins. The structural nucleocapsid phosphoprotein N is essential for linking the viral genome to the viral membrane. Both N-terminal RNA binding (N-NTD) and C-terminal dimerization domains are involved in capturing the RNA genome and, the intrinsically disordered region between these domains anchors the ribonucleoprotein complex to the viral membrane. Here, we characterized the structure of the N-NTD and its interaction with RNA using NMR spectroscopy. We observed a positively charged canyon on the surface of the N-NTD that might serve as a putative RNA binding site similarly to other coronaviruses. The subsequent NMR titrations using single-stranded and double-stranded RNA revealed a much more extensive U-shaped RNA-binding cleft lined with regularly distributed arginines and lysines. The NMR data supported by mutational analysis allowed us to construct hybrid atomic models of the N-NTD/RNA complex that provided detailed insight into RNA recognition.

FIGURES

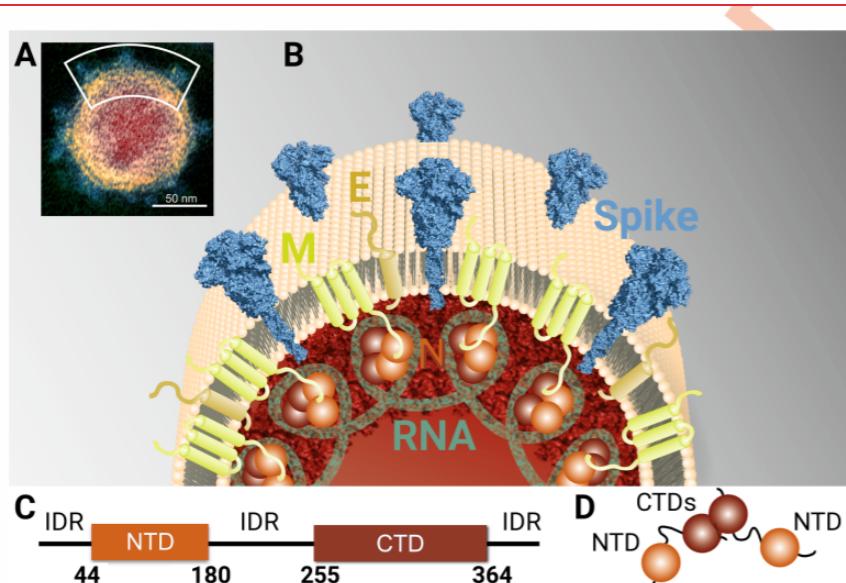


Fig 1. SARS-CoV-2 virion and model of structural proteins. (A) Transmission electron microscopic image of a single SARS-CoV-2 viral particle (image credit: NIH, NIAID-RML, <https://www.niaid.nih.gov/news-events/novel-coronavirus-sarscov2-images>). (B) Enlarged 2D model of the viral membrane showing the four structural proteins: Spike—Spike glycoprotein, M—Membrane protein, E—Envelope protein, and N—Nucleocapsid phosphoprotein along with viral membrane and the RNA genome. (C) Domain organization of the full length N-protein showing structural regions as boxes (NTD and CTD) and the intrinsically disordered regions (IDRs) as a line. (D) Schematic model of the full length N-protein dimer formed through the CTD domains (the N-NTD is shown in brown and the N-CTD in dark brown).

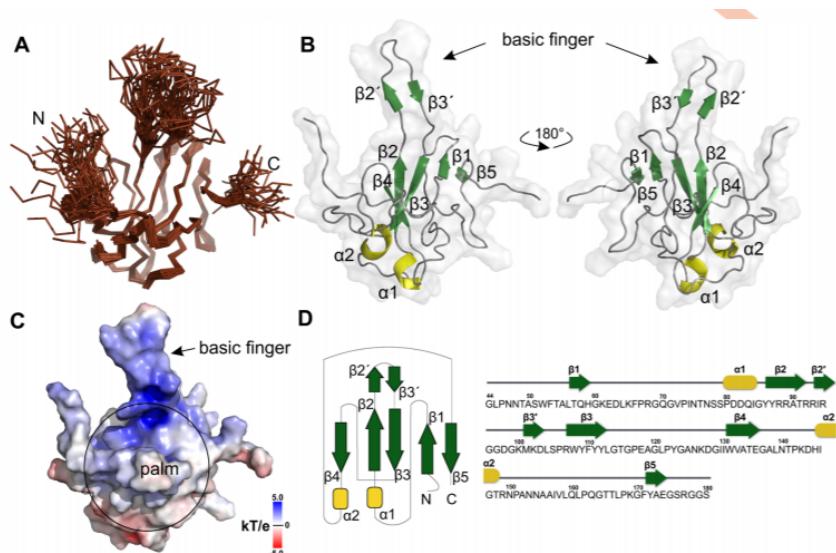


Fig 2. Solution structure of the SARS-CoV-2 N-NTD RNA binding domain. (A) Backbone representation of the 40 converged structures of N-NTD obtained by NMR spectroscopy. (B) Cartoon representation of the lowest energy structure (structural elements are highlighted in color: α_1 - α_2 helices in yellow, β_1 - $(\beta_2$ - $\beta_3)$ - β_5 in green, and loops in gray) show the overall U-shaped antiparallel β -sheet platform (the palm) and a protruding β -hairpin (the basic finger). (C) The N-NTD molecular surface electrostatic potentials revealed a basic patch extended between the finger and the palm, with a positively charged surface shown in blue and negatively charged surface in red. (D) Topology diagram of the N-NTD and protein sequence displaying the secondary structural elements.

<https://doi.org/10.1371/journal.ppat.1009100.g002>

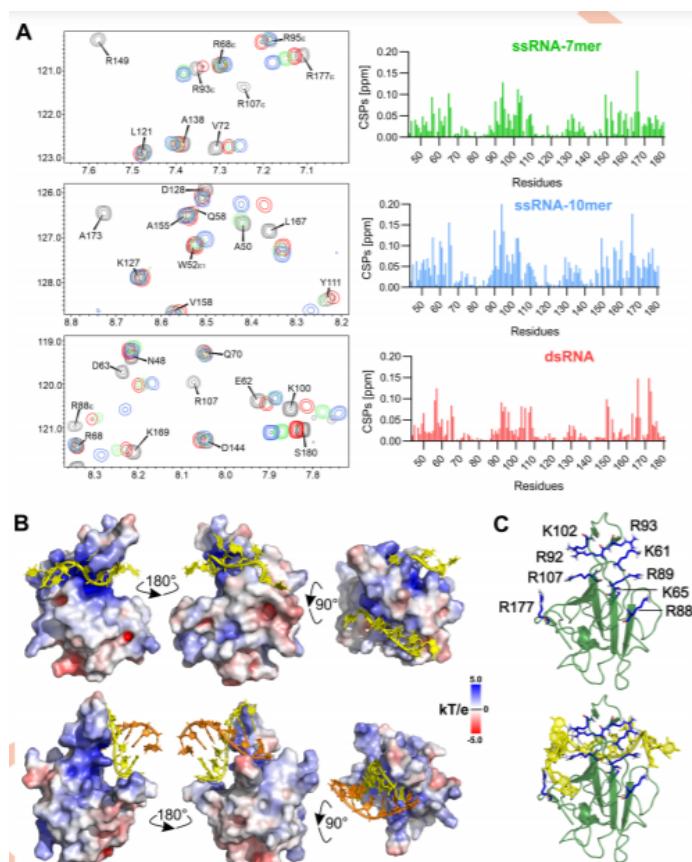


Fig 3. NMR-based mapping and a model of the SARS-CoV-2 N-NTD:RNA complex. (A) Representative regions from the 2D $^{15}\text{N}/^1\text{H}$ HSQC spectra illustrating the effects of addition of the RNA-7mer (green), 10mer (blue) and dsRNA (red) on the side-chain N-NTD amide signals (arginine side-chains are labeled along with NH^+). The $50 \mu\text{M}$ ^{15}N -labeled N-NTD protein construct was titrated with an increasing concentration of RNAs. Corresponding chemical shift perturbations (CSP) of N-NTD residues upon binding ssRNA 7mer ($5'$ -UCUAACG- $3'$) in green, 10mer ($5'$ -UCUCUAAACG- $3'$) in blue from viral genomic 5' UTR containing the conserved transcriptional regulatory sequence (TRS), and a random dsRNA (RNA-7mer duplex, $5'$ -CACUGAC- $3'$ and $5'$ -GUCAAGU- $3'$) in red. (B) N-NTD:RNA complex. The RNA-10mer and dsRNA are shown as a cartoon representation (yellow) over the electrostatic surface of N-NTD shown in three orientations. (C) Cartoon representation of N-NTD highlighting all the available arginine and lysine residues in the interaction interface, shown as blue sticks, and the lower panel displays the

MANAGEMENT

ACUTE CARE

RISK FACTORS FOR SEVERE DISEASE AND EFFICACY OF TREATMENT IN PATIENTS INFECTED WITH COVID-19: A SYSTEMATIC REVIEW, META-ANALYSIS, AND META-REGRESSION ANALYSIS

Zhang JJY, Lee KS, Ang LW, Leo YS, Young BE.. Clin Infect Dis. 2020 Nov 19;71(16):2199-2206. doi: 10.1093/cid/ciaa576.

Level of Evidence: 1 - Systematic review of cross sectional studies with consistently applied reference standard and blinding

BLUF

A systematic review, conducted primarily at National University of Singapore, analyzed a set of 45 studies ($n= 4,203$ patients) published between November 1, 2019 and March 15, 2020 and found that elevated leukocyte count, alanine aminotransferase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), and procalcitonin levels predicted ICU admission (Figure 1). Furthermore, acute respiratory distress syndrome (ARDS) was predicted by elevated LDH (Figure 2), while mortality was predicted by increased leukocyte count and elevated LDH. Treatment with lopinavir-ritonavir showed no significant benefit across mortality and ARDS rates, while corticosteroids were associated with a higher rate of ARDS (Figure 4). These findings suggest that elevated levels of LDH, leukocytosis, procalcitonin, AST, and ALT may be important early signs of disease severity, though early antiviral and steroid treatments do not appear to offer much clinical benefit.

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic spread globally in the beginning of 2020. At present, predictors of severe disease and the efficacy of different treatments are not well-understood. We conducted a systematic review and meta-analysis of all published studies up to March 15, 2020 which reported COVID-19 clinical features and/or treatment outcomes. 45 studies reporting 4203 patients were included. Pooled rates of intensive care unit (ICU) admission, mortality and acute respiratory distress syndrome (ARDS) were 10.9%, 4.3% and 18.4%, respectively. On meta-regression, ICU admission was predicted by raised leukocyte count ($p<0.0001$), raised alanine aminotransferase ($p=0.024$), raised aspartate transaminase ($p=0.0040$), elevated lactate dehydrogenase (LDH) ($p<0.0001$) and increased procalcitonin ($p<0.0001$). ARDS was predicted by elevated LDH ($p<0.0001$), while mortality was predicted by raised leukocyte count ($p=0.0005$) and elevated LDH ($p<0.0001$). Treatment with lopinavir-ritonavir showed no significant benefit in mortality and ARDS rates. Corticosteroids were associated with a higher rate of ARDS ($p=0.0003$).

FIGURES

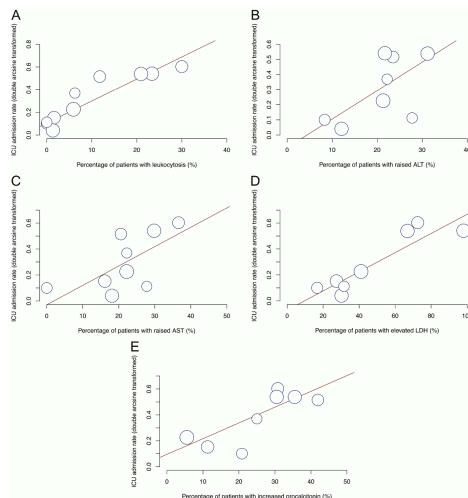


Figure 1. Bubble plot for meta-regression of transformed ICU admission rate against percentages of patients with leukocytosis (A), increased ALT (B), increased AST (C), elevated LDH (D), and increased procalcitonin (E) in each study. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ICU, intensive care unit; LDH, lactate dehydrogenase.

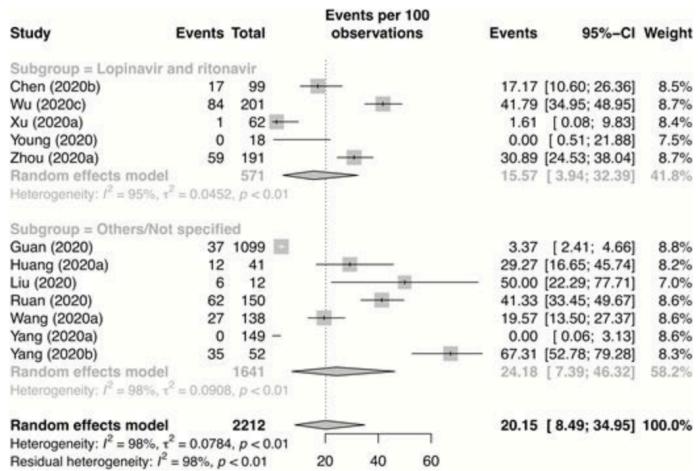


Figure 4. Forest plot for subgroup analysis of ARDS by type of antiviral used. The event rate is the incidence of ARDS in lopinavir and ritonavir recipients (top of figure) versus recipients of other/nonspecified antivirals (bottom of figure). Abbreviations: CI, confidence interval; ARDS, acute respiratory distress syndrome.

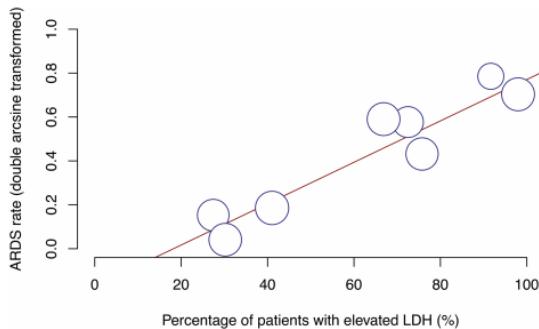


Figure 2. Bubble plot for meta-regression of transformed proportion of ARDS against percentage of patients with elevated LDH in each study. Abbreviations: ARDS, acute respiratory distress syndrome; LDH, lactate dehydrogenase.

DIAGNOSIS, MANAGEMENT, AND PATHOPHYSIOLOGY OF ARTERIAL AND VENOUS THROMBOSIS IN COVID-19

Piazza G, Morrow DA.. JAMA. 2020 Nov 23. doi: 10.1001/jama.2020.23422. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

A vascular medicine specialist and intensivist from Brigham and Women's Hospital in Boston review thrombotic complications (i.e. myocardial infarction, venous thromboembolism [VTE], ischemic stroke, microthrombi in multiple organ systems) that occur in hospitalized COVID-19 patients. They summarize current VTE prophylaxis recommendations from the International Society on Thrombosis and Hemostasis (ISTH) and American College of Chest Physicians (ACCP)(Table). While the guidelines conflict on some points, authors suggest considering thromboprophylaxis for all hospitalized COVID-19 patients without contraindications and continued research regarding appropriateness of prophylactic regimens for discharged and non-hospitalized patients.

FIGURES

Patient/setting	Recommendation	
	American College of Chest Physicians	International Society on Thrombosis and Hemostasis
Critically ill	Prophylactic-dose LMWH	Prophylactic-dose LMWH; half-therapeutic-dose LMWH can be considered if patient is high risk
Non-critically ill	Prophylactic-dose LMWH or fondaparinux	Prophylactic-dose LMWH
After discharge	Extended prophylaxis not recommended	LMWH/DOAC for up to 30 d can be considered if high thrombosis risk and low bleeding risk
Nonhospitalized	Routine prophylaxis not recommended	Routine prophylaxis not recommended

Abbreviations: DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin.

Table 1: "Current Guideline Recommendations for Venous Thromboembolism Prevention in Hospitalized Patients with Coronavirus Disease 2019".

CRITICAL CARE

COAGULOPATHY IN PATIENTS WITH COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS

Zhang X, Yang X, Jiao H, Liu X. Aging (Albany NY). 2020 Nov 24;12. doi: 10.18632/aging.104138. Online ahead of print.
Level of Evidence: 2 - Systematic review of inception cohort studies

BLUF

Members of the Department of Geriatrics at Peking University First Hospital in China conducted a systematic review and meta-analysis of 25 articles assessing coagulation parameters in 3952 SARS-CoV-2 positive patients published between December 1, 2019 and May 1, 2020 (Figure 1). They found significantly higher D-dimer (standardized mean difference [SMD] 0.83, I²=56.9%), prothrombin time (SMD 0.39, I²=79.4%), and fibrinogen (SMD 0.35, I²=42.4%) in patients with more severe COVID-19 compared to those with less severe disease (Table 1, Figure 2). Authors suggest hypercoagulability is associated with severity of COVID-19 and coagulation parameters should be assessed in these patients to monitor progression.

ABSTRACT

COVID-19 patients frequently exhibit coagulation abnormalities and thrombotic events. In this meta-analysis, we investigated the association between coagulopathy and the severity of COVID-19 illness. Using PubMed, Embase, Cochrane, WanFang Database, CNKI, and medRxiv, a systematic literature search was conducted for studies published between December 1, 2019 and May 1, 2020. We then analyzed coagulation parameters in COVID-19 patients exhibiting less severe and more severe symptoms. All statistical analyses were performed using Stata14.0 software. A total of 3,952 confirmed COVID-19 patients from 25 studies were included in the meta-analysis. Patients with severe symptoms exhibited higher levels of D-dimer, prothrombin time (PT), and fibrinogen (FIB) than patients with less severe symptoms (SMD 0.83, 95% CI: 0.70-0.97, I² 56.9%; SMD 0.39, 95% CI: 0.14-0.64, I² 79.4%; and SMD 0.35, 95% CI: 0.17-0.53, I² 42.4%, respectively). However, platelet and activated partial thromboplastin times did not differ (SMD -0.26, 95% CI: -0.56-0.05, I² 82.2%; and SMD -0.14, 95% CI: -0.45-0.18, I² 75.7%, respectively). These findings demonstrate that hypercoagulable coagulopathy is associated with the severity of COVID-19 symptoms and that D-dimer, PT, and FIB values are the main parameters that should be considered when evaluating coagulopathy in COVID-19 patients.

FIGURES

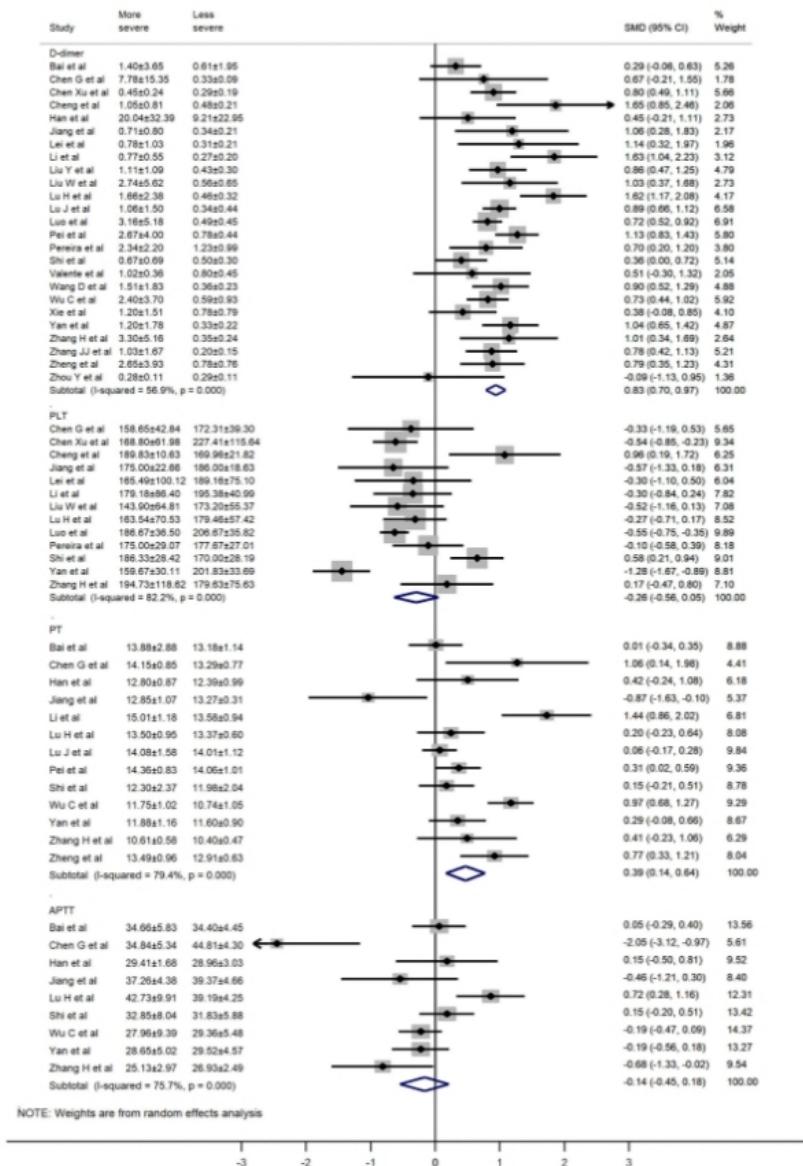


Figure 2: "forest plot of the association between D-dimer, PLT, PT, and APTT in patients with COVID-19 stratified by disease severity".

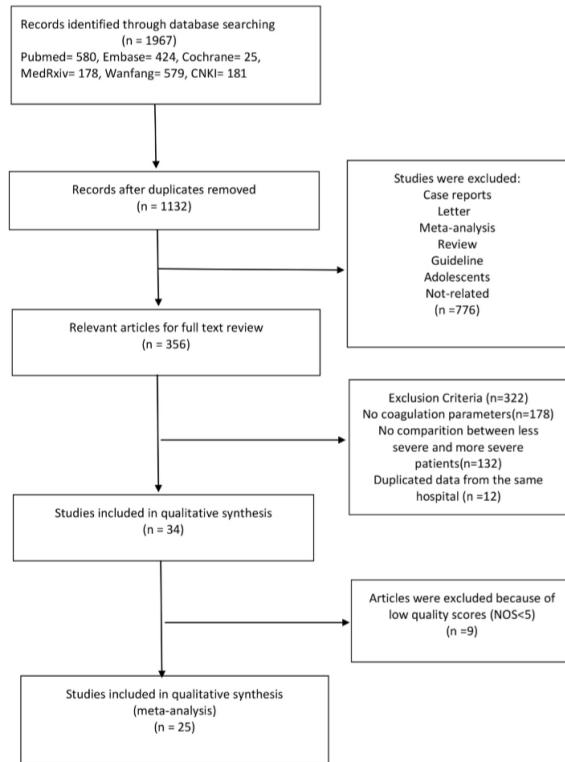


Figure 1: "Schema of literature search".

Test of association					
Groups	Studies	SMD	95%CI	p value	
D-dimer	25	0.83	0.70,0.97	0.000	
PLT	13	-0.26	-0.56,0.05	0.096	
PT	13	0.39	0.14,0.64	0.002	
APTT	9	-0.14	-0.45,0.18	0.384	
FIB	5	0.35	0.17,0.53	0.000	
RE, random effects					
FE, fixed effects					
SMD, standardized mean difference					
CI, confidence interval					

Table 1: "Summary of the meta-analysis results".

ADJUSTING PRACTICE DURING COVID-19

FOR HEALTHCARE PROFESSIONALS

LOW PREVALENCE OF BLOODSTREAM INFECTION AND HIGH BLOOD CULTURE CONTAMINATION RATES IN PATIENTS WITH COVID-19

Yu D, Ininbergs K, Hedman K, Giske CG, Strålin K, Özenci V.. PLoS One. 2020 Nov 23;15(11):e0242533. doi: 10.1371/journal.pone.0242533. eCollection 2020.

Level of Evidence: 4 - Cohort study or control arm of randomized trial

BLUF

This retrospective cohort study by investigators primarily at Karolinska Institutet (Sweden) compared blood cultures (BC) in SARS-CoV-2 patients from March 1 to April 30, 2020 to 2 control patient groups without SARS-CoV-2 from March 1 to April 30, 2019 and 2020 (15,103 total patients; Figure 1). After studying a total of 17,865 BC, they found that the percentage of BC growth in COVID-19 patients (6.5%) was less than the control groups (10.4% in 2019 & 10.8% in 2020) and that contamination in COVID-19 BC samples (8.4%) was higher than in controls (4.3% in 2019 & 5% in 2020; Figure 2), elucidating that guidelines regarding blood culture sampling and empiric therapy should be studied more closely.

ABSTRACT

PURPOSE: In the management of COVID-19, knowledge is lacking on the frequency of secondary bacterial infections and on how empirical antibiotic therapy should be used. In the present study, we aimed to compare blood culture (BC) results of a COVID-19 patient cohort with two cohorts of patients without detected COVID-19. **METHODS:** Using a retrospective cohort study design of patients subjected to BC in six tertiary care hospitals, SARS-CoV-2 positive patients from March 1 to April 30 in 2020 (COVID-19 group) were compared to patients without confirmed SARS-CoV-2 during the same period (control group-2020) and with patients sampled March 1 to April 30 in 2019 (control group-2019). The outcomes studied were proportion of BC positivity, clinically relevant growth, and contaminant growth. **RESULTS:** In total 15,103 patients and 17,865 BC episodes were studied. Clinically relevant growth was detected in 197/3,027 (6.5%) BC episodes in the COVID-19 group compared to 717/6,663 (10.8%) in control group-2020 ($p<0.0001$) and 850/8,175 (10.4%) in control group-2019 ($p<0.0001$). Contamination was present in 255/3,027 (8.4%) BC episodes in the COVID-19 group compared to 330/6,663 (5.0%) in control group-2020 ($p<0.0001$) and 354/8,175 (4.3%) in control group-2019 ($p<0.0001$). **CONCLUSION:** In COVID-19 patients, the prevalence of bloodstream bacterial infection is low and the contamination rate of BC is high. This knowledge should influence guidelines regarding blood culture sampling and empirical antibiotic therapy in COVID-19 patients.

FIGURES

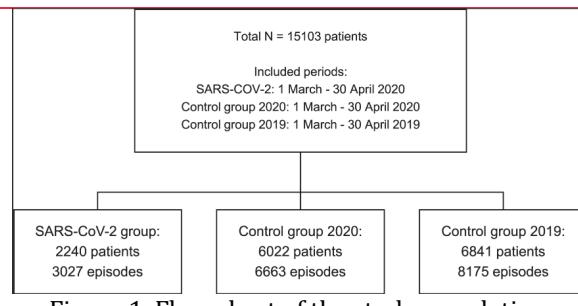


Figure 1. Flow chart of the study population.

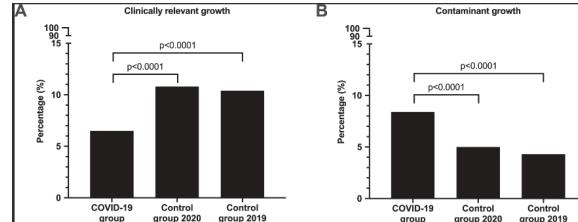


Figure 2. Blood culture episodes with clinically relevant growth (Panel A) and with contaminant growth (Panel B). Total number of episodes included for analysis were COVID-19 group: 3,027, Control group-2020: 6,663, Control group-2019: 8,175.

R&D: DIAGNOSIS & TREATMENTS

CURRENT DIAGNOSTICS

COVID-19 SCREENING IN A HEALTHCARE OR COMMUNITY SETTING: COMPLEXITY OF SALIVA AS A SPECIMEN FOR PCR-BASED TESTING

Sahajpal NS, Mondal AK, Njau A, Ananth S, Ghamande S, Hegde M, Chaubey A, M Rojiani A, Kolhe R.. Future Med Chem. 2020 Nov 24. doi: 10.4155/fmc-2020-0255. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

Investigators primarily from Augusta University (Georgia) review several articles that highlight the benefits and limitations of saliva samples versus nasopharyngeal (NPS) samples in the detection of SARS-CoV-2 by RT-PCR. Saliva samples provide several practical advantages including reduced exposure for collection, reduced wait time, and being less invasive. Limitations of saliva samples include the possibility of reduced diagnostic yield due to oral residues (residual food/beverages, medications, cigarette smoke residues, etc) and reported lower sensitivity when compared to NPS. The authors suggest saliva samples should be further utilized, but call for well-defined collection protocols and additional studies including larger cohorts.

SILVER LININGS

PROBABILITY OF SUCCESS AND TIMELINES FOR THE DEVELOPMENT OF VACCINES FOR EMERGING AND REEMERGED VIRAL INFECTIOUS DISEASES

MacPherson A, Hutchinson N, Schneider O, Oliviero E, Feldhake E, Ouimet C, Sheng J, Awan F, Wang C, Papenburg J, Basta NE, Kimmelman J. Ann Intern Med. 2020 Nov 24. doi: 10.7326/M20-5350. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

A literature review, conducted by investigators at McGill University, of vaccine trials for 23 different viral infectious diseases (Table 1,2) from January 2005 through March 2020 showed that these trials historically have a 10% chance of moving from phase 2 through Food and Drug Administration (FDA) licensure within 10 years. Further, the average timeline from phase 2 to approval was 4.4 years, suggesting an unparalleled achievement if COVID-19 vaccine is approved within 18 months of the start of the pandemic.

ABSTRACT

BACKGROUND: Anticipated success rates and timelines for COVID-19 vaccine development vary. Recent experience with developing and testing viral vaccine candidates can inform expectations regarding the development of safe and effective vaccines. **OBJECTIVE:** To estimate timelines and probabilities of success for recent vaccine candidates. **DESIGN:** ClinicalTrials.gov was searched to identify trials testing viral vaccines that had not advanced to phase 2 before 2005, and the progress of each vaccine from phase 1 through to U.S. Food and Drug Administration (FDA) licensure was tracked. Trial characteristics were double-coded. (Registration: Open Science Framework [<https://osf.io/dmuzx/>]). **SETTING:** Trials launched between January 2005 and March 2020. **PARTICIPANTS:** Preventive viral vaccine candidates for 23 emerging or reemerged viral infectious diseases. **MEASUREMENTS:** The primary end point was the probability of vaccines advancing from launch of phase 2 to FDA licensure within 10 years. **RESULTS:** In total, 606 clinical trials forming 220 distinct development trajectories (267 343 enrolled participants) were identified. The probability of vaccines progressing from phase 2 to licensure within 10 years was 10.0% (95% CI, 2.6% to 16.9%), with most approvals representing H1N1 or H5N1 vaccines. The average timeline from phase 2 to approval was 4.4 years (range, 6.4 weeks to 13.9 years). The probabilities of advancing from phase 1 to 2, phase 2 to 3, and phase 3 to licensure within the total available follow-up time were 38.2% (CI, 30.7% to 45.0%), 38.3% (CI, 23.1% to 50.5%), and 61.1% (CI, 3.7% to 84.3%), respectively. **LIMITATIONS:** The study did not account for preclinical development and relied primarily on ClinicalTrials.gov and FDA resources. Success probabilities do not capture the varied reasons why vaccines fail to advance to regulatory approval. **CONCLUSION:** Success probabilities and timelines varied widely across different vaccine types and diseases. If a SARS-CoV-2 vaccine is licensed within 18 months of the start of the pandemic, it will mark an unprecedented achievement for noninfluenza viral vaccine development. **PRIMARY FUNDING SOURCE:** McGill Interdisciplinary Initiative in Infection and Immunity (MI4) Emergency COVID-19 Research Funding program.

FIGURES

Table 1. Characteristics of EVIDs Included in the Study*

EVID	Virus Family	Trials, n (%)	Trajectories, n (%)	Enrollment, n (%)†	Approved Vaccines, n‡
HIV	Retroviridae	120 (19.8)	60 (27.3)	10 612 (4.0)	0
H5N1	Orthomyxoviridae	117 (19.3)	36 (16.4)	50 385 (18.8)	3
Ebola§	Filoviridae	59 (9.7)	15 (6.8)	34 891 (13.0)	1
H1N1	Orthomyxoviridae	59 (9.7)	15 (6.8)	26 597 (9.9)	5
H7N9	Orthomyxoviridae	30 (5.0)	15 (6.8)	7313 (2.7)	0
Zika	Flaviviridae	19 (3.1)	14 (6.4)	3609 (1.3)	0
Universal flu	Orthomyxoviridae	26 (4.3)	10 (4.5)	14 538 (5.4)	0
EV71	Picornaviridae	22 (3.6)	8 (3.6)	39 507 (14.8)	0
Dengue	Flaviviridae	88 (14.5)	7 (3.2)	73 697 (27.5)	1
West Nile	Flaviviridae	9 (1.5)	6 (2.7)	918 (0.3)	0
Chikungunya	Togaviridae	12 (2.0)	5 (2.3)	1581 (0.6)	0
H3N2v	Orthomyxoviridae	7 (1.2)	4 (1.8)	1235 (0.5)	0
Hepatitis C	Flaviviridae	6 (1.0)	4 (1.8)	622 (0.2)	0
Marburg§	Filoviridae	5 (0.8)	4 (1.8)	305 (0.1)	0
MERS	Coronaviridae	8 (1.3)	4 (1.8)	101 (0)	0
Smallpox	Poxviridae	7 (1.2)	3 (1.4)	1248 (0.5)	2
Yellow fever	Flaviviridae	3 (0.5)	3 (1.4)	152 (0.1)	0
Hantavirus	Hantaviridae	4 (0.7)	2 (0.9)	79 (0)	0
CCHF	Bunyaviridae	1 (0.2)	1 (0.5)	60 (0)	0
H10N8	Orthomyxoviridae	1 (0.2)	1 (0.5)	201 (0.1)	0
Lassa	Arenaviridae	1 (0.2)	1 (0.5)	0 (0)	0
Nipah	Paramyxoviridae	1 (0.2)	1 (0.5)	0 (0)	0
Rift Valley	Bunyaviridae	1 (0.2)	1 (0.5)	20 (0)	0

CCHF = Crimean-Congo hemorrhagic fever; EV71 = enterovirus 71; EVID = emerging or reemerged viral infectious disease; MERS = Middle East respiratory syndrome.

* Four EVIDs did not have any eligible trials (Hendra virus, adenovirus 14, severe acute respiratory syndrome, and monkeypox).

† Trials that did not include only patients in trials that had "actual" enrollment listed on ClinicalTrials.gov.

‡ Number of vaccines approved by the U.S. Food and Drug Administration since 2005. One H1N1 vaccine (Influenza A [H1N1] 2009 Monovalent Vaccine; MedImmune LLC) and the 2 smallpox vaccines (Ymeos; Smallpox and Monkeypox Vaccine, Live, Non-Replicating; Bavarian Nordic AS and ACAM2000; Smallpox [Vaccinia] Vaccine, Live; Emergent Product Development Gaithersburg Inc.) had no eligible trials and were excluded from the analysis.

§ Two trajectories overlap between Marburg and Ebola.

Table 1. Characteristics of EVIDs Included in the Study*

Table 2. Trial and Trajectory Characteristics

Characteristic	Value
Trials	
Total trials, n	606
Median (range) trials per EVID, n	8 (1-120)
Median (range) trials per trajectory, n	1 (1-30)
Trial phase, n (%)	
Phase 1	319 (52.6)
Phase 1/2*	59 (9.7)
Phase 2	154 (25.4)
Phase 2/3*	5 (0.8)
Phase 3	69 (11.4)
Trajectories	
Total trajectories, n	220
Median (range) trajectories per EVID, n	4 (1-60)
Patients	
Total, n†	267 343
Median (range) patients per EVID, n	1248 (20-73 697)
Median (range) patients per trajectory, n	147 (1-44 500)
Vaccine type, n (%)	
Whole-pathogen	53 (24.1)
Split virus	14 (6.4)
Subunit	40 (18.2)
Nucleic acid	103 (46.8)
Multiple	10 (4.5)
Highest phase reached, n (%)	
Phase 1	144 (65.5)
Phase 2	54 (24.5)
Phase 3	22 (10.0)
Sponsorship, n (%)‡	
Large companies	35 (15.9)
Small companies	90 (40.9)
Government	129 (58.6)
Foundation	19 (8.6)
Other	79 (35.9)

EVID = emerging or reemerged viral infectious disease.

* 51 of 59 phase 1/2 trials and 4 of 5 phase 2/3 trials were considered as phase 2 and phase 3 trials, respectively, on the basis of completion status and enrollment.

† Enrollment in trials that overlapped between EVIDs or trajectories was only counted once. Enrollment was not counted if it was listed as "anticipated" on ClinicalTrials.gov.

‡Sponsorship was based on the earliest 2 trials per trajectory. "Large company" was defined as a pharmaceutical company listed among the top 10 companies by sales in the year of trial start on ContractPharma; all other companies were considered to be small companies. The percentage sum exceeds 100% because many trajectories had multiple sponsors.

Table 2. Trial and Trajectory Characteristics

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