The Daily COVID-19 Literature Surveillance Summary

December 16, 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

Understanding the Pathology

- Researchers from the Department of Health & Exercise Science at Appalachian State University analyze the vascular impact of SARS-CoV-2 on 20 healthy young adults 3-4 weeks post-infection by doppler ultrasound of arterial blood flow in the upper and lower extremities (markers of vascular function) and pulse wave velocity (indicator of arterial stiffness). Results demonstrated that brachial artery flow-mediated dilation (FMD) was 6% lower after COVID-19 infection, which is clinically significant because each 1% decrease in FMD is associated with a 13% higher risk of cardiovascular events, suggesting that systemic vascular dysfunction and arterial stiffness may be a potential mechanism of COVID-19 vasculopathy.

Management

- A single-center observational cohort study from Turin, Italy analyzed coagulopathy in 36 hospitalized pediatric patients (ages birth to 21 years) with COVID-19 (n=30) and Multisystem Inflammatory Syndrome in Children (MIS-C) (n=6) and found that D-dimer values were not useful in predicting disease severity. Significant differences between D-dimer and CRP values were observed between COVID-19 and MIS-C patients, however there was no difference in coagulopathy incidence in these groups (as measured by fibrinogen levels). They recommend against universal pharmacologic prophylaxis in pediatric COVID-19 patients except in cases of multiple concurrent pro-thrombotic risk factors such as obesity, active malignancy, and sickle cell disease.

TABLE OF CONTENTS

UNDERSTANDING THE PATHOLOGY

VASCULAR ALTERATIONS AMONG YOUNG ADULTS WITH SARS-COV-2

Ratchford SM, Stickford JL, Province VM, Stute N, Augenreich MA, Koontz LK, Bobo LK, Stickford ASL.. Am J Physiol Heart Circ Physiol. 2020 Dec 11. doi: 10.1152/ajpheart.00897.2020. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Researchers from the Department of Health & Exercise Science at Appalachian State University analyze the vascular impact of SARS-CoV-2 on 20 healthy young adults 3-4 weeks post-infection. They utilized doppler ultrasound of arterial blood flow in the upper and lower extremities as markers of vascular function, using pulse wave velocity (PWVcf) as an indicator of arterial stiffness. Results demonstrated that brachial artery flow-mediated dilation (FMD) was 6% lower after COVID-19 infection, which is clinically significant because each 1% decrease in FMD is associated with a 13% higher risk of cardiovascular events. The authors conclude that systemic vascular dysfunction and arterial stiffness may be a potential mechanism of COVID-19 vasculopathy, and they call for further investigation on long term vascular function following infection.

ABSTRACT

BACKGROUND: While SARS-CoV-2 primarily affects the lungs, the virus may be inflicting detriments to the cardiovascular system, both directly through angiotensin converting enzyme 2 receptor as well as initiating systemic inflammation. Persistent systemic inflammation may be provoking vascular dysfunction, an early indication of cardiovascular disease risk. METHODS: In order to establish the potential effects of SARS-CoV-2 on the systemic vasculature in the arms and legs, we performed a cross-sectional analysis of young healthy adults (Control: 5M/15F, 23.0+-1.3y, 167+-9cm, 63.0+-7.4kg) and young adults who, 3-4 weeks prior to testing, had tested positive for SARS-CoV-2 (SARS-CoV-2: 4M/7F, 20.2+-1.1y, 172+-12cm, 69.5+-12.4kg) (mean+-SD). Using Doppler ultrasound, brachial artery flow-mediated dilation (FMD) in the arm and single passive limb movement (sPLM) in the leg were assessed as markers of vascular function. Pulse wave velocity (PWVcf) was assessed as a marker of arterial stiffness. RESULTS: FMD was lower in the SARS-CoV-2 group (2.71+-1.21%) compared to the Control group (8.81+-2.96%) (P<0.01) and when made relative to the shear stimulus (SARS-CoV-2: 0.04+-0.02AU, Control: 0.13+-0.06AU, P<0.01). The femoral artery blood flow response, as evidenced by the area under the curve, from the sPLM was lower in the SARS-CoV-2 group (-3+-91ml) compared with the Control group (118+-114ml) (P<0.01). PWVcf was higher in the SARS-CoV-2 group (5.83+-0.62m/s) compared with the Control group (5.17+-0.66m/s) (P<0.01). CONCLUSIONS: Significantly lower systemic vascular function and higher arterial stiffness are evident weeks after testing positive for SARS-CoV-2 among young adults compared to controls.

CUTTING EDGE: SEVERE SARS-COV-2 INFECTION IN HUMANS IS DEFINED BY A SHIFT IN THE SERUM LIPIDOME, RESULTING IN DYSREGULATION OF EICOSANOID IMMUNE MEDIATORS

Schwarz B, Sharma L, Roberts L, Peng X, Bermejo S, Leighton I, Casanovas-Massana A, Minasyan M, Farhadian S, Ko AI; Yale IMPACT Team, Dela Cruz CS, Bosio CM.. J Immunol. 2020 Dec 4:ji2001025. doi: 10.4049/jimmunol.2001025. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Investigators from Yale University analyzed serum from 38 COVID-19 patients presenting to Yale-New Haven Hospital between March 18 and May 9, 2020 (18 with moderate respiratory symptoms and 20 with severe symptoms requiring ICU admission) against serum from 19 healthy control patients, in order to evaluate dysregulated immunomodulatory and pro-inflammatory lipid mediators (LMs) with corresponding COVID19 severity, as well as associated metabolic comorbidities such as hypertension and heart disease (Figure 4). They found that increased LM products, specifically ALOX5 (Figure 3B) and CYP (Figure 2G), corresponded to increased severity of COVID-19, suggesting potential targets for immune modulation of LM products when treating severe COVID-19.

ABSTRACT

The COVID-19 pandemic has affected more than 20 million people worldwide, with mortality exceeding 800,000 patients. Risk factors associated with severe disease and mortality include advanced age, hypertension, diabetes, and obesity. Each of these risk factors pathologically disrupts the lipidome, including immunomodulatory eicosanoid and docosanoid lipid mediators (LMs). We hypothesized that dysregulation of LMs may be a defining feature of the severity of COVID-19. By examining LMs and polyunsaturated fatty acid precursor lipids in serum from hospitalized COVID-19 patients, we demonstrate that moderate and severe disease are separated by specific differences in abundance of immune-regulatory and proinflammatory LMs. This difference in LM balance corresponded with decreased LM products of ALOX12 and COX2 and an increase LMs products of ALOX5 and cytochrome p450. Given the important immune-regulatory role of LMs, these data provide mechanistic insight into an immuno-lipidomic imbalance in severe COVID-19.

FIGURES

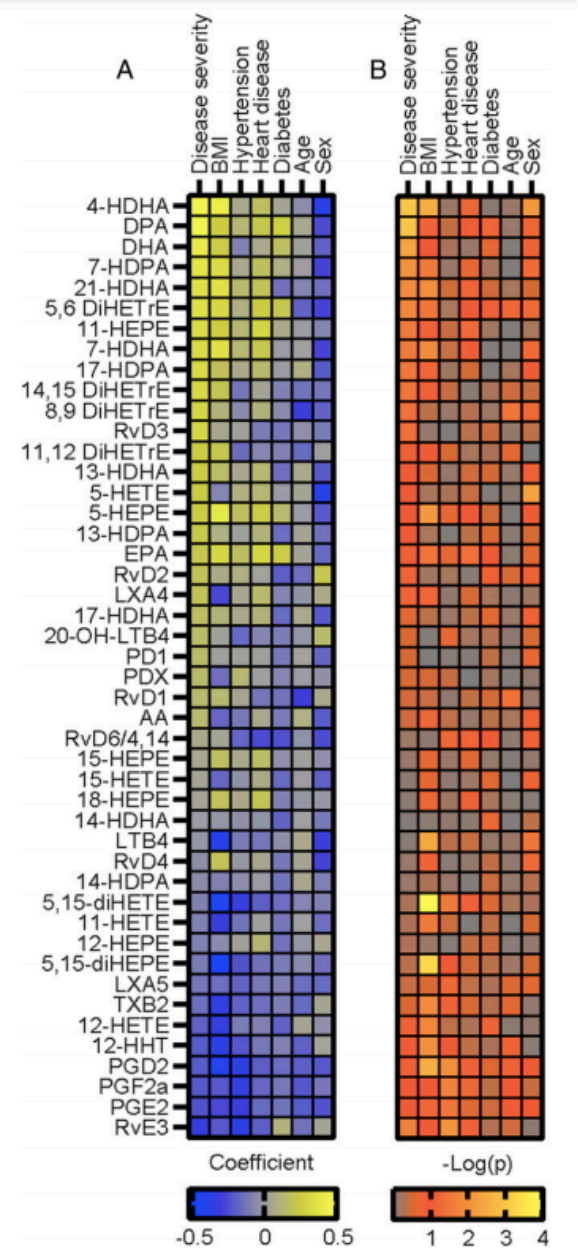

Figure 4. Correlation of comorbidities with LMs and severe COVID-19. (A) Correlation plot of spearman (BMI and age) or point biserial Pearson (disease severity, hypertension, heart disease, diabetes, and gender) correlation coefficient of each LM with disease severity or patient demographics and comorbidities. LMs are ordered by the strength of correlation with disease severity. For gender, a positive correlation is correlated with male. (B) Corresponding p values of each LM patient condition correlation displayed as 2log(p).

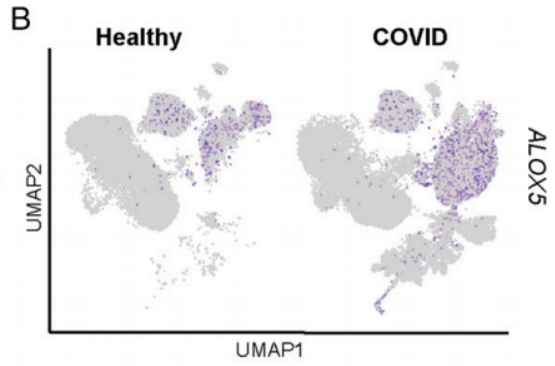

Figure 3. Human PBMCs from COVID-19 patients are enriched for ALOX5 expressing cells and express higher levels of ALOX5. (B) UMAP depicting ALOX5 expressing cells in blue.

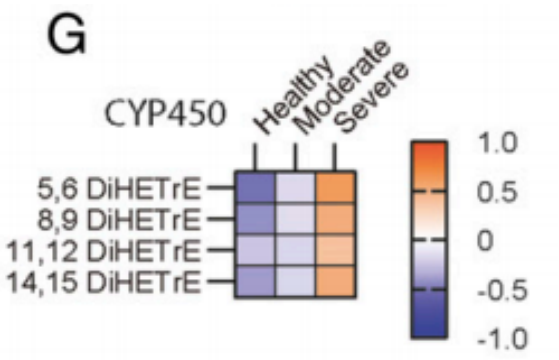

Figure 2. Heatmap of the autoscaled mean for each patient group across molecules synthesized by ALOX5. (G) CYP.

GENETIC MECHANISMS OF CRITICAL ILLNESS IN COVID-19

Pairo-Castineira E, Clohisey S, Klaric L, Bretherick AD, Rawlik K, Pasko D, Walker S, Parkinson N, Fourman MH, Russell CD, Furniss J, Richmond A, Gountouna E, Wrobel N, Harrison D, Wang B, Wu Y, Meynert A, Griffiths F, Oosthuyzen W, Kousathanas A, Moutsianas L, Yang Z, Zhai R, Zheng C, Grimes G, Beale R, Millar J, Shih B, Keating S, Zechner M, Haley C, Porteous DJ, Hayward C, Yang J, Knight J, Summers C, Shankar-Hari M, Klenerman P, Turtle L, Ho A, Moore SC, Hinds C, Horby P, Nichol A, Maslove D, Ling L, McAuley D, Montgomery H, Walsh T, Pereira A, Renieri A; GenOMICC Investigators; ISARIC Investigators; COVID-19 Human Genetics Initiative; 23andMe Investigators; BRACOVID Investigators; Gen-COVID Investigators, Shen X, Ponting CP, Fawkes A, Tenesa A, Caulfield M, Scott R, Rowan K, Murphy L, Openshaw PJM, Semple MG, Law A, Vitart V, Wilson JF, Baillie JK.. Nature. 2020 Dec 11. doi: 10.1038/s41586-020-03065-y. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Results from the GenOMICC (Genetics of Mortality in Critical Care) genome-wide association study (GWAS) of 2,244 critically ill COVID-19 patients identified eight possible genetic variants (Table 1) that were associated with severe COVID-19 (Table 2). Specifically, they found that the IFNAR2 gene (related to innate antiviral defenses) and TYK2 gene (related to host-driven inflammation in the lung) had a significant role in severe host response. Additionally, a transcriptome-wide study in lung tissue found that high expression of the macrophage chemotactic receptor CCR2 is associated with severe COVID-19 (Figure 2). Knowledge of these gene targets may inform researchers in the development of new and repurposed medications that modulate expression of proteins along these pathways.

ABSTRACT

Host-mediated lung inflammation is present,1 and drives mortality,2 in critical illness caused by Covid-19. Host genetic variants associated with critical illness may identify mechanistic targets for therapeutic development.3 Here we report the results of the GenOMICC (Genetics Of Mortality In Critical Care) genome-wide association study(GWAS) in 2244 critically ill Covid-19 patients from 208 UK intensive care units (ICUs). We identify and replicate novel genome-wide significant associations, on chr12q24.13 (rs10735079, p=1.65 [Formula: see text] 10-8) in a gene cluster encoding antiviral restriction enzyme activators (OAS1, OAS2, OAS3), on chr19p13.2 (rs2109069, p=2.3 [Formula: see text] 10-12) near the gene encoding tyrosine kinase 2 (TYK2), on chr19p13.3 (rs2109069, p=3.98 [Formula: see text] 10-12) within the gene encoding dipeptidyl

peptidase 9 (DPP9), and on chr21q22.1 (rs2236757, p=4.99 [Formula: see text] 10-8) in the interferon receptor gene IFNAR2. We identify potential targets for repurposing of licensed medications: using Mendelian randomisation we found evidence in support of a causal link from low expression of IFNAR2, and high expression of TYK2, to life-threatening disease; transcriptome-wide association in lung tissue revealed that high expression of the monocyte/macrophage chemotactic receptor CCR2 is associated with severe Covid-19. Our results identify robust genetic signals relating to key host antiviral defence mechanisms, and mediators of inflammatory organ damage in Covid-19. Both mechanisms may be amenable to targeted treatment with existing drugs. Large-scale randomised clinical trials will be essential before any change to clinical practice.

FIGURES

SNP	chr:pos(b37)	Risk	Alt	RAF_{gcc}	RAF_{ukb}	OR	CI	$P_{gcc.ukb}$	$P_{gcc.gs}$	$P_{gcc.100k}$	Locus
rs73064425	3:45901089	T	C	0.15	0.07	2.1	1.88-2.45	4.8×10^{-30}	2.9×10^{-27}	3.6×10^{-32}	*LZTFL1*
rs9380142	6:29798794	A	G	0.74	0.69	1.3	1.18-1.43	3.2×10^{-8}	0.00091	1.8×10^{-8}	*HLA-G*
rs143334143	6:31121426	A	G	0.12	0.07	1.9	1.61-2.13	8.8×10^{-18}	2.6×10^{-24}	5.8×10^{-18}	*CCHCR1*
rs3131294	6:32180146	G	A	0.9	0.86	1.5	1.28-1.66	2.8×10^{-8}	1.3×10^{-10}	2.3×10^{-8}	*NOTCH4*
rs10735079	12:113380008	A	G	0.68	0.63	1.3	1.18-1.42	1.6×10^{-8}	2.8×10^{-9}	4.7×10^{-6}	*OAS1/3*
rs2109069	19:4719443	A	G	0.38	0.32	1.4	1.25-1.48	4×10^{-12}	4.5×10^{-7}	2.4×10^{-8}	*DPP9*
rs74956615	19:10427721	A	T	0.079	0.05	1.6	1.35-1.87	2.3×10^{-8}	2.2×10^{-13}	3.9×10^{-6}	*TYK2*
rs2236757	21:34624917	A	G	0.34	0.28	1.3	1.17-1.41	5×10^{-8}	8.9×10^{-5}	8.3×10^{-7}	*IFNAR2*

chr:pos - chromosome and position of the top SNP (build 37); Risk – risk allele; Alt - other allele; RAF - risk allele frequency; OR - effect size (odds ratio) of the risk allele in the GenOMICC EUR analysis; CI - 95% confidence interval for the odds ratio in the GenOMICC EUR cohort; P - p-value, Locus – gene nearest to the top SNP. Subscript identifiers indicate the cohorts used for cases: gcc - GenOMICC EUR; and controls: ukb - UK Biobank; gs - Generation Scotland; 100k - 100,000 genomes.

Table 1. Lead variants from independent genome-wide significant regions

SNP	chr:pos(b37)	Risk	Alt	OR_{gcc}	CI_{gcc}	P_{gcc}	OR_{meta}	CI_{meta}	P_{meta}	Locus
rs71325088	3:45862952	C	T	2.1	1.87-2.43	9.3×10^{-30}	1.9	1.73-2	2.5×10^{-54}	*LZTFL1*
rs143334143	6:31121426	A	G	1.8	1.61-2.13	8.8×10^{-18}	1.3	1.27-1.48	1.5×10^{-10}	*CCHCR1*
rs6489867	12:113363550	T	C	1.3	1.15-1.37	6.9×10^{-7}	1.2	1.14-1.25	9.7×10^{-10}	*OAS1*
rs2109069	19:4719443	A	G	1.4	1.25-1.48	4×10^{-12}	1.2	1.19-1.31	7×10^{-13}	*DPP9*
rs11085727	19:10466123	T	C	1.3	1.17-1.4	1.3×10^{-7}	1.2	1.18-1.31	1.2×10^{-13}	*TYK2*
rs13050728	21:34615210	T	C	1.3	1.15-1.38	3×10^{-7}	1.2	1.16-1.28	5.1×10^{-12}	*IFNAR2*

Since this is a meta-analysis of all available data, external replication cannot be attempted, so SNPs are included in this table if they meet a more stringent p-value threshold of $p<10^{-8}$. SNP – the strongest SNP in the locus, ; Risk – risk allele; Alt - alternative allele; OR - odds ratio of the risk allele; CI - 95% confidence interval for odds ratio; Locus – gene nearest to the top SNP. Subscript identifiers show gcc - GenoMICC study, European ancestry, comparison with UK Biobank; meta - combined meta-analysis of all three studies (GenOMICC, HGI and 23andMe) for cases of European ancestry.

Table 2. Meta-analysis of overlapping SNPs between GenOMICC (EUR) and HGI (hospitalized Covid-19 vs. population) and 23andMe studies

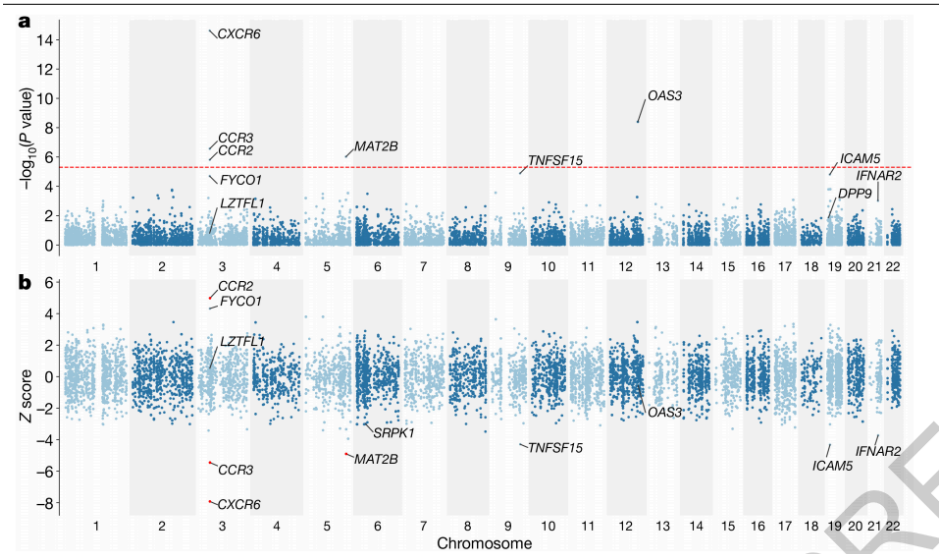

Figure 2. Summary of TWAS results. a. Gene-level Manhattan plot showing raw p-value results from meta-TWAS analysis across tissues (see Methods). Red horizontal line shows gene-level genome-wide significance at −log10(5 × 10) −6 b. z-scores showing direction of effect for genotype-inferred expression of transcripts encoding protein-coding genes in lung tissue (GTEX v8). Red highlighting indicates genome-wide significance at p < 5 × 10-6.

NEONATAL/PEDIATRIC INTENSIVE CARE

SARS-COV-2 ASSOCIATED COAGULOPATHY AND THROMBOEMBOLISM PROPHYLAXIS IN CHILDREN: A SINGLE CENTRE OBSERVATIONAL STUDY

Del Borrello G, Giraudo I, Bondone C, Denina M, Garazzino S, Linari C, Mignone F, Pruccoli G, Scolfaro C, Spadea M, Pollio B, Saracco P.. J Thromb Haemost. 2020 Dec 11. doi: 10.1111/jth.15216. Online ahead of print.
Level of Evidence: 4 - Case-series or case-control studies, or poor quality prognostic cohort study

BLUF

A single-center observational cohort study from Turin, Italy analyzed coagulopathy in 36 hospitalized pediatric patients (ages birth to 21 years) with COVID-19 (n=30) and Multisystem Inflammatory Syndrome in Children (MIS-C) (n=6) and found that D-dimer values were not useful in predicting disease severity. Significant differences between D-dimer and CRP values were observed between COVID-19 and MIS-C patients (Table 2 and Figure 1), however there was no difference in coagulopathy incidence in these groups (as measured by fibrinogen levels). They recommend against universal pharmacologic prophylaxis in pediatric COVID-19 patients except in cases of multiple concurrent pro-thrombotic risk factors such as obesity, active malignancy, and sickle cell disease.

ABSTRACT

BACKGROUND: Multiple investigators have described an increased incidence of thromboembolic events in SARS-CoV-2 infected individuals. Data concerning haemostatic complications in children hospitalised for COVID-19/MIS-C are scant. OBJECTIVES: To share our experience in managing SARS-CoV-2 associated pro-coagulant state in hospitalised children. METHODS: D-dimer values were recorded at diagnosis in children hospitalised for SARS-CoV-2 related manifestations. In moderately to critically ill patients and MIS-C cases, coagulation and inflammatory markers were checked at multiple time-points and median results were compared. Pro-thrombotic risk factors were appraised for each child and thromboprophylaxis was started in selected cases. RESULTS: 35 patients were prospectively enrolled. D-dimer values did not discriminate COVID-19 of differing severity, whereas were markedly different between the COVID-19 and the MIS-C cohorts. In both cohorts, D-dimer and C Reactive Protein levels increased upon clinical worsening but were not accompanied by decreased fibrinogen or platelet values, with all parameters returning to normal upon disease resolution. 6 patients had multiple thrombotic risk factors and were started on pharmacological thromboprophylaxis. No deaths, thrombotic or bleeding complications occurred. CONCLUSIONS: COVID-19 pediatric patients show mildly altered coagulation and inflammatory parameters; on the other hand, MIS-C cases show laboratory signs of an inflammatory driven pro-coagulant status. Universal anticoagulant prophylaxis in hospitalised children with SARS-CoV-2 related manifestations is not warranted, but may be offered to patients with other pro-thrombotic risk factors in the context of a multi-modal therapeutic approach.

Table 2

Clinical category	Age	Gender (F/M)	Comorbidities (Y/N)	D-Dimer# (ng/mL)	CRP* (mg/L)
Mild COVID-19 (14)	9 m (10 d - 17 y)	4/10	2/16	800 (200-1800*)	4 (0-20)
Moderate COVID-19 (10)	3,5 y (2 m - 5,5 y)	2/8	3/7	900 (200-1700)	5 (0-76)
Severe-critical COVID-19 (6)	7,5 y (9 m - 19 y)	3/3	6/0	800 (100-2750**)	25 (3-42)
MIS-C (6)	6,8 y (4,5 - 12,5 y)	3/3	0/6	1900 (1300-4400)	215 (120-300)

Table 2. Clinical and demographic characteristics of pediatric hospitalised patients with SARS- CoV-2 related manifestations. # values recorded upon hospital admission, data displayed as median and overall range; * the D-dimer value of 1800 ng/mL was recorded in a mildly-affected newborn; **the D- dimer value of 2750 ng/mL was recorded in a critically-affected sickle cell disease patient.
Abbreviations used: CRP = C Reactive Protein; MIS-C = Multi-Inflammatory Syndrome in Children.

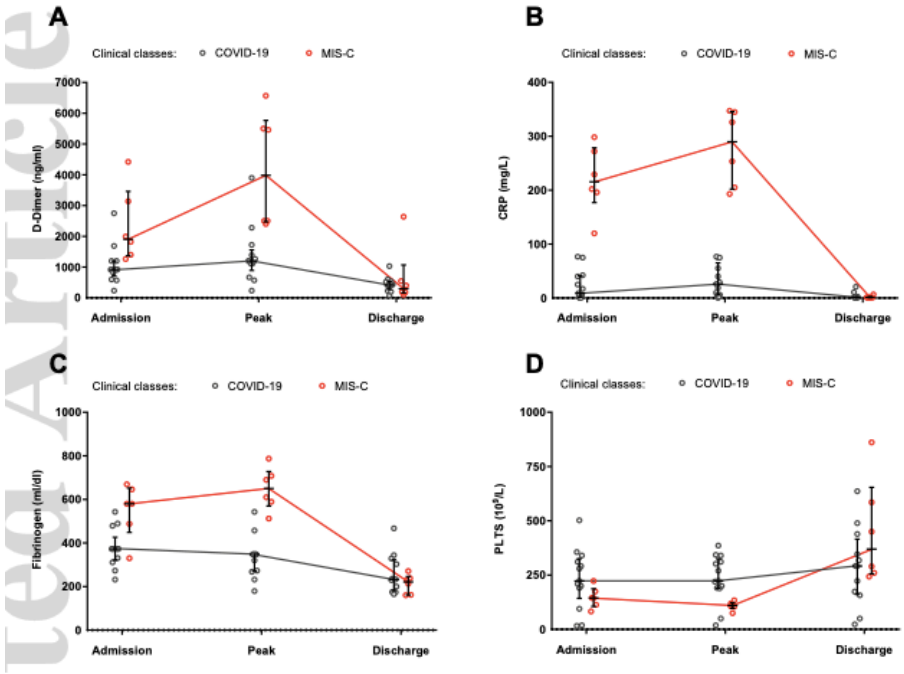

Figure 1

Table 3

	Totale score	Description
Patient 1	3	14 years old post-pubertal girl (TS 4) with COVID-19-driven respiratory exacerbation of underlying cystic fibrosis,who scored 2 on the BQM in the early course of her hospital admission
Patient 2	8	7 years old boy with MIS-C, severe myocardial involvement requiring continuous inotropic support and placement of a non-tunnelled right-jugular CVC, who scored 1 on the BQM over the first 10 days of his hospital admission
Patient 3	3	15 years old obese post-pubertal boy (TS 5) with moderate COVID-19, who scored 3 on the BQS over the course of his hospitalisation
Patient 4	6	19 years old boy (TS 5) with critical COVID-19 requiring mechanical ventilation, who had recently undergone matched unrelated donor Hematopoietic Stem Cell Transplantation due to relapsed Acute Lymphoblastic Leukemia and had suffered from multiple transplant-related complications (including EBV reactivation and fungal pneumonia). A tunnelled CVC had been inserted approximately 6 weeks before the current presentation.
Patient 5	3	a 6 years old obese girl with MIS-C and reduced ejection fraction (40%) but preserved mobility
Patient 6	6	9 month-old with a previously undiagnosed Sickle Cell Disease with critical COVID-19-induced acute chest syndrome who required mechanical ventilation and was later escalated to veno-venous extra-cardiac circulation (switching at that point from PA to full therapeutic anticoagulation)

Table 3. Clinical description of patients who received prophylactic anticoagulation.
Abbreviations used: BQM = Braden Q Mobility score; CVC = Central Venous Catheter; TS = Tanner Stage.

NOVEL CORONA VIRUS (COVID-19) PANDEMIC: CURRENT STATUS AND POSSIBLE STRATEGIES FOR DETECTION AND TREATMENT OF THE DISEASE

Bhagat S, Yadav N, Shah J, Dave H, Swaraj S, Tripathi S, Singh S.. Expert Rev Anti Infect Ther. 2020 Dec 7:1-24. doi: 10.1080/14787210.2021.1835469. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

In this extensive review, authors from various institutions throughout India including Ahmedabad University, Indian Institute of Science, and Centre for Infectious Disease Research, detail several aspects of SARS-CoV-2, including suspected origin, replication (Figure 1), structure, genome and genomic variation (Figure 2), and comparison with other coronaviruses. They also outline events leading up to the initial outbreak, etiology and symptoms, plans for infection control and prevention, detection, details of treatments (including favipiravir, hydroxychloroquine, azithromycin, lopinavir, ritonavir, chloroquine, plasma, and antibody treatment), strategies for viable vaccines (Figure 5), and call for continued research in order to help end the pandemic.

ABSTRACT

INTRODUCTION: In December 2019, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak occurred and caused the coronavirus disease of 2019 (COVID-19), which affected ~ 190 countries. The World Health Organization (WHO) has declared COVID-19 a pandemic on 11th March 2020. AREA COVERED: In the review, a comprehensive analysis of the recent developments of the COVID-19 pandemic has been provided, including the structural characterization of the virus, the current worldwide status of the disease, various detection strategies, drugs recommended for the effective treatment, and progress of vaccine development programs by different countries. This report was constructed by following a systematic literature search of bibliographic databases of published reports of relevance until 1st September 2020. EXPERT OPINION: Currently, the countries are opening businesses despite a spike in the number of COVID-19 cases. The pharmaceutical industries are developing clinical diagnostic kits, medicines, and vaccines. They target different approaches, including repurposing the already approved diagnosis and treatment options for similar CoVs. At present, over ~200 vaccine candidates are being developed against COVID-19. Future research may unravel the genetic variations or polymorphisms that dictate these differences in susceptibilities to the disease.

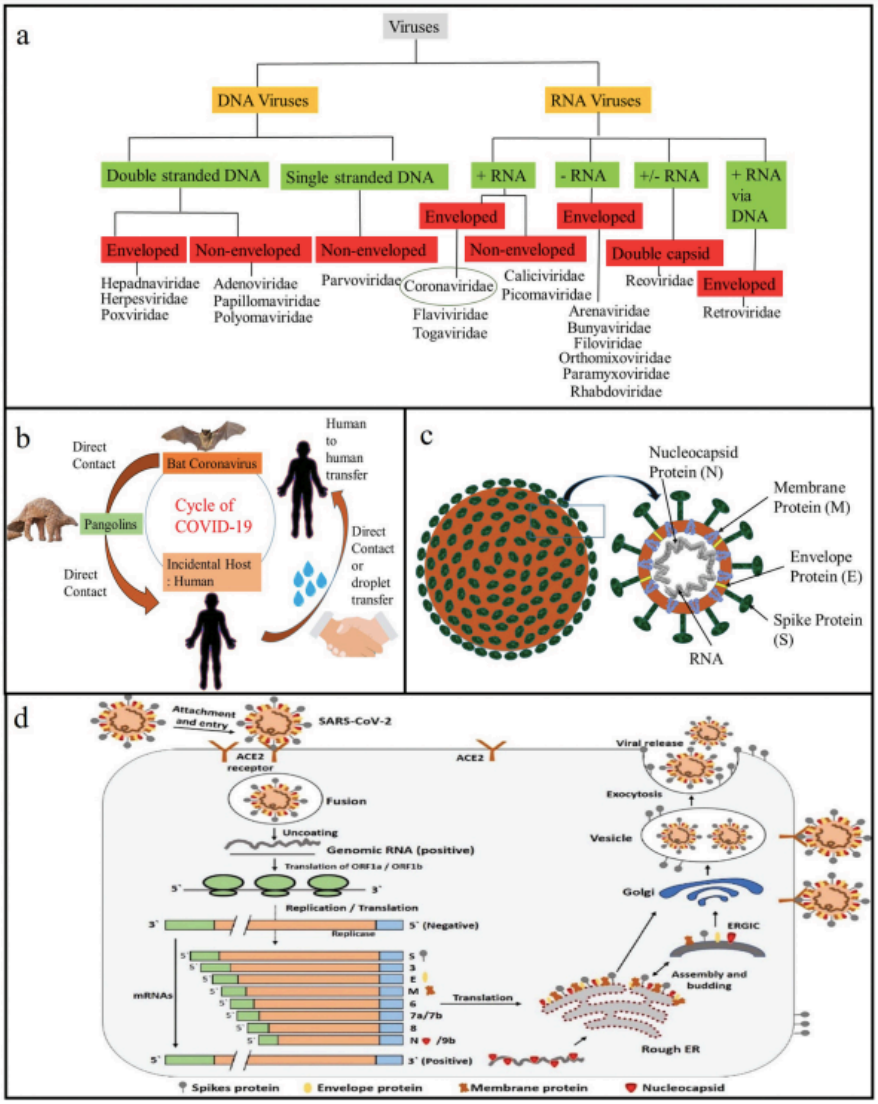

Figure 1. Classification, origin, morphology and replication mechanism of SARS-CoV-2. (a) Schematic representation of the classification of viruses on the basis of their genetic material. (b) The transmission cycle of CoVs from bats to human beings and humans to humans, (c) Structure of CoVs showing envelope and projecting spikes, Cross-sectional view of the virus showing different proteins, (d) Replication cycle of SARS-CoV-2 inside the human body. For binding with the host's cellular receptor angiotensin-converting enzyme 2 (ACE2), the virus utilizes its spike (S)protein and after binding, the conformational changes in S protein facilitates the entry of the virus via the endosomal pathway or by fusion at the cell surface. Inside the host cell, virus releases its RNA which gets translated using host machinery and produces viral polyprotein 1a and polyprotein 1ab. The viral proteases cleave the polyproteins into individual proteins (non-structural proteins, nsps). The subgenomic RNAs are produced by replication-transcription complex (RTC). The assemblage of virions occurs in the endoplasmic reticulum (ER) and Golgi apparatus. The transportation and release of the virus outside the cell is performed by vesicles. Reprinted [Figure 1(d)] with permission from reference [26] Copyright© Elsevier 2020.

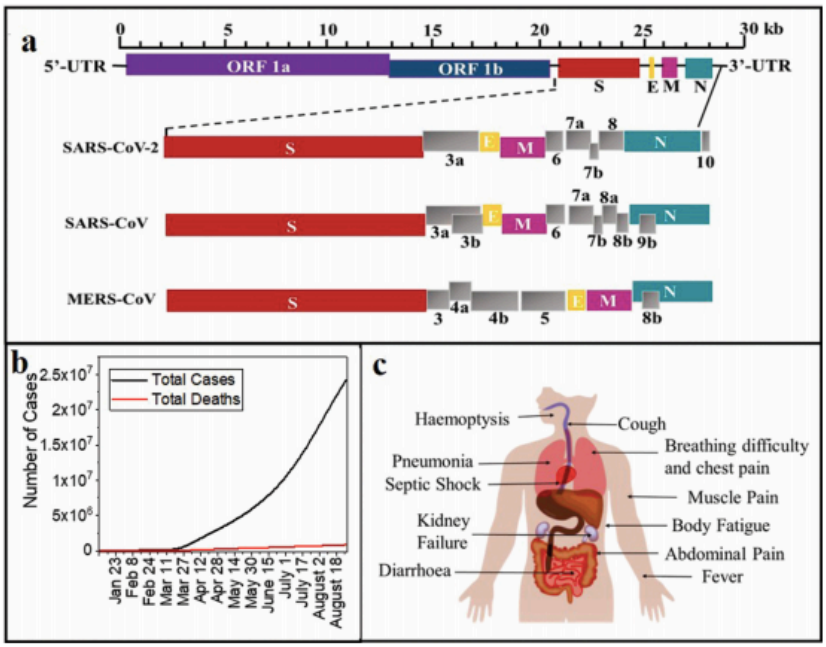

Figure 2. Genomic organization of CoVs, outbreak and symptoms of the COVID-19. (a) Schematic diagram of genomic organization of SARS-CoV-2, SARS-CoV, and MERS-CoV. The genomic regions or ORFs are compared. Structural proteins, including S, E, M and N proteins, as well as non-structural proteins translated from ORF1a and ORF1b and accessory proteins, including 3a, 6, 7a, 7b, 8, and 10 (SARS-CoV-2), 3a, 3b, 6, 7a, 7b, 8a, 8b, and 9b (for SARS-CoV) and 3, 4a, 4b, 5, and 8b (for MERS-CoV) are indicated. 5′-UTR and 3′-UTR, untranslated regions at the N- and C-terminal regions, respectively. kb- kilobase pair (b) Graph showing an increase in the number of cases of COVID-19 and the total number of deaths from 20 January 2020 to 1 September 2020 worldwide, (c) Possible symptoms in humans after of COVID-19 infection.

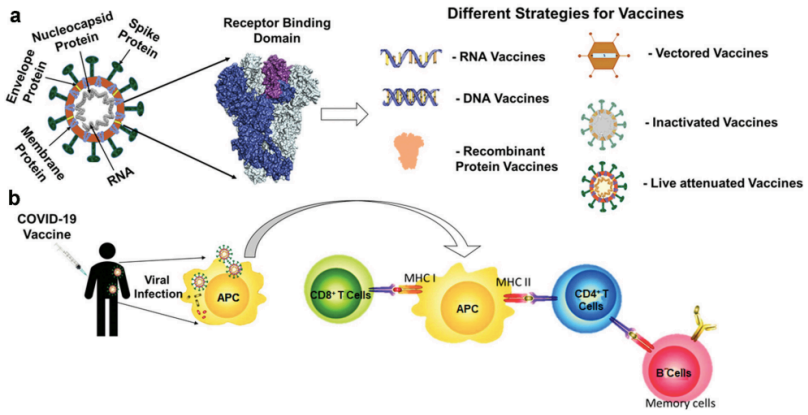

Figure 5. Strategies followed to develop SARS-CoV-2 vaccine: Schematic representation of plausible strategies to develop (a) viral vaccine and (b) process to build immunity in humans against COVID-19.

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