The Daily COVID-19 Literature Surveillance Summary

October 14, 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

- Outcomes of COVID-19 in living donor liver transplant (LDLT) recipients are studied by hepatologists and leading liver transplant surgeons from the Institute of Liver Transplantation & Regenerative Medicine in Gurugram, India through a case series of 12 living donor liver transplant patients who tested positive for SARS-CoV-2 via RT-PCR. Most were symptomatic (n=11, 91.7%) with evidence of pneumonia on radiologic imaging (n=9, 75%) and with median duration of detectable virus of 12 days. While the majority (n=10, 83.3%) were on tacrolimus-based immunosuppression, all but one patient (n=11, 91.7%) survived with only supportive care. Because the patient who died had multiple other risk factors for severe COVID-19 (quadruple immunosuppression, hypertension, metabolic syndrome, diabetes), these authors suggest that liver transplant patients as a whole are not at particularly increased risk for mortality from COVID-19.

- Hematological manifestations of SARS-CoV-2 in children are explored in a review of 15 articles meeting study criteria and found children with SARS-CoV-2 were less likely to be lymphopenic compared to adults, with the most common abnormalities being leukopenia in older children and lymphocytosis in infants/neonates. Thrombotic complications and platelets and erythrocytes abnormalities were relatively uncommon and more likely in children with multisystem inflammatory syndrome. Authors suggest these findings, which contrast hematologic changes observed in adults, may be a result of pediatric patients' immature ACE-2 expression and immune systems.

Understanding the Pathology

- Mechanisms by Which SARS-CoV-2 May Impact Male Fertility are discussed in a letter to the editor based on Dutta and Sengupta's article "SARS-CoV-2 and male infertility: possible multifaceted pathology." They propose viral binding to angiotensin-converting enzyme 2 receptors on spermatogonia, Leydig cells, and Sertoli cells may cause overactivation and negatively impact spermatogenesis. Additionally, they urge further studies on SARS-CoV-2's ability to disrupt sperm formation and function because SARS-CoV-2 seems to disproportionately impact males in some studies.

R&D: Diagnosis & Treatments

- REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in certain species based on virologists from Regeneron Pharmaceuticals results from an in vivo study of their proprietary therapeutic cocktail REGN-COV2's (human antibodies REGN10933, REGN10987) ability to reduce viral load via SARS-CoV-2 spike protein binding in resus macaques and golden hamsters. They found a 50 mg/kg dose significantly reduced SARS-CoV-2 gRNA ($p<0.0001$) and sgRNA ($P=0.0012$) in rhesus macaques on oral swab and that 0.5-50 mg/kg prophylactic doses prevented weight loss and reduced lung findings associated with pneumonia in Golden hamsters ($p<0.0001$). Authors suggest this REGN-COV2 regimen shows potential for prevention and treatment of SARS-CoV-2 in humans and express optimism regarding ongoing clinical trials.

TABLE OF CONTENTS

ADULTS

OUTCOMES OF COVID-19 IN LIVING DONOR LIVER TRANSPLANT (LDLT) RECIPIENTS

Dhampalwar S, Saigal S, Choudhary N, Saraf N, Bhangui P, Rastogi A, Thiagrajan S, Soin AS.. Liver Transpl. 2020 Oct 5. doi: 10.1002/lt.25909. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

Hepatologists and leading liver transplant surgeons from the Institute of Liver Transplantation & Regenerative Medicine in Gurugram, India report a case series of 12 living donor liver transplant patients who tested positive for SARS-CoV-2 via RT-PCR. Most were symptomatic (n=11, 91.7%) with evidence of pneumonia on radiologic imaging (n=9, 75%) and with median duration of detectable virus of 12 days. While the majority (n=10, 83.3%) were on tacrolimus-based immunosuppression, all but one patient (n=11, 91.7%) survived with only supportive care. Because the patient who died had multiple other risk factors for severe COVID-19 (quadruple immunosuppression, hypertension, metabolic syndrome, diabetes), these authors suggest that liver transplant patients as a whole are not at particularly increased risk for mortality from COVID-19.

ABSTRACT

The Corona Virus Disease - 2019 (COVID-19) outbreak started in China in December 2019 and rapidly spread all over the world infecting more than 20 million people and causing more than 700,000 deaths. Overall mortality in COVID-19 is 3-4%1 ; the mortality generally happens in patients with older age and comorbidities. No evidence-based treatment has been approved so far.2 Outcomes of COVID-19 in Liver Transplant (LT) recipients are not well known at present. In a single center report from United States, Lee et al. reported overall mortality of 18.4% (7 of 38) in LT recipients; all patients who died had co-morbidities3 . Polak et al. reported 15% mortality in 244 LT recipients in an internet-based survey of European countries.

PEDIATRICS

HEMATOLOGICAL MANIFESTATIONS OF SARS-COV-2 IN CHILDREN

Kosmeri C, Koumpis E, Tsabouri S, Siomou E, Makis A.. Pediatr Blood Cancer. 2020 Oct 3:e28745. doi: 10.1002/pbc.28745. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Greek physicians from the University of Ioannina conducted a review of studies on hematological manifestations of SARS-CoV-2 in children published up to July 27, 2020. The authors identified 15 articles meeting study criteria (Table 1) and found children with SARS-CoV-2 were less likely to be lymphopenic compared to adults, with the most common abnormalities being leukopenia in older children and lymphocytosis in infants/neonates. Thrombotic complications and platelets and erythrocytes abnormalities were relatively uncommon and more likely in children with multisystem inflammatory syndrome (Table 2). Authors suggest these findings, which contrast hematologic changes observed in adults, may be a result of pediatric patients' immature ACE-2 expression and immune systems.

ABSTRACT

Infection from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), though mainly a respiratory disease, can impair many systems, including causing hematological complications. Lymphopenia and hypercoagulability have been reported in adults with coronavirus disease 2019 (COVID-19) and are considered markers of poor prognosis. This review summarizes the hematological findings in children with SARS-CoV-2 infection. The majority of infected children had a normal leukocyte count, while the most common white blood cell abnormality was leukopenia. Lymphopenia, which may be a marker

of severe disease, was rarer in children than in adults, possibly due to their immature immune system or due to the less severe manifestation of COVID-19 in this age group. Age may have an impact, and in neonates and infants the most common abnormality was lymphocytosis. Abnormalities of red blood cells and platelets were uncommon. Anemia and hypercoagulability were reported mainly in children presenting the novel multisystem inflammatory syndrome (MIS) associated with SARS-CoV-2.

FIGURES

TABLE 1 Studies on hematological laboratory findings in children with COVID-19, December 2019 to April 2020

First author	Region	Study period	Number of children	Main hematological findings			
				WBC	Hemoglobin	Platelets	D-dimer
Lu X, et al[12]	Wuhan Children's Hospital, China	January 28 to February 26, 2020	171	Decreased in 26.3% Lymphopenia in 3.5% (these children had either URTI or pneumonia)	Normal		Increased D-dimer in 16% of children with URTI and 17.5% of children with pneumonia
Parri N, et al[13]	Italy, 17 pediatric emergency departments, the CONFIDENCE study	March 3-27, 2020	100	Decreased in 17.7% Lymphopenia in 28.5%	Normal		
Chao J, et al[14]	Single tertiary children's hospital, New York City	March 15 to April 13, 2020	67	Increased in children admitted to ICU	Mean 12.4 g/dL in patients admitted to ICU	Decreased in children admitted to ICU	Mean 0.8 μg/mL in patients admitted to ICU
Qiu H, et al[15]	3 Hospitals, Zhejiang, China	January 17 to March 1, 2020	36	Decreased in 19% Lymphopenia in 31%			Increased D-dimer were associated with severity of COVID-19
Xia W, et al[16]	Wuhan Children's Hospital, inpatients	January 23 to February 8, 2020	20	Normal in 70% Decreased in 20% Increased in 10% Lymphopenia in 35%			
Zheng F, et al[17]	10 Hospitals, Hubei, China	February 1-10, 2020	25	Lymphopenia in 40%			
Sun D, et al[18]	ICU of Wuhan Children's Hospital, China	January 24 to February 24, 2020	8	Normal or increased	Decreased in 3 children	$<100 \times 10^9$/L in 1 patient	Increased in 2 children
Liu W, et al[19]	3 Branches of Tongji Hospital, Wuhan, China	January 7-15, 2020	6	All had lymphopenia	Decreased in 1 patient	Normal	Increased in 3 children
Zheng G, et al[20]	11 Hospitals from South China	January 21 to February 29, 2020	52	Decreased in 6% Lymphopenia in 6% Lymphocytosis in 46.2%			
Romani L, et al[21]	1 Hospital, Italy	March 15 to May 6, 2020	43	Lymphopenia in 37% Neutropenia in 26%		Transient and self-limited thrombocytopenia (112×109/L) in 1 child with respiratory	

TABLE 1 (Continued)

First author	Region	Study period	Number of children	Main hematological findings			
				WBC	Hemoglobin	Platelets	D-dimer
Chen Z, et al[22]	7 Hospitals in Zhejiang province, China	January 15 and March 15, 2020	32	Normal			
Bhumbra S, et al[23]	Riley Hospital for Children, Indianapolis, USA	February 26 to May 4, 2020	19	Median 5700/mm^3 in critically ill Median 8500/mm^3 in general ward		Thrombocytoper in 66% of critically ill patients 0% In general ward	
Zhang L, et al[24]	10 Hospitals in Anhui, China	December 2019 to February 2020	33	Lymphopenia in 75.7%			
Korkmaz M, et al[25]	Bursa City Hospital, Turkey	March 5 to May 5, 2020	79	Lymphopenia in 2.5% Leukopenia in 5%,		Normal	Increased in 12.3%
Xu H, et al[26]	4 Provinces in Western China	January 24 and February 12, 2020	32	Significant negative correlation between lymphocyte count and the time until the first negative nucleic acid, after adjusting for age, gender, and length of stay			

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; URTI, upper respiratory tract infection; WBC, white blood cell.

TABLE 2 Studies on hematological laboratory findings of multistystem inflammatory syndrome in children associated with SARS-CoV-2 (February-June 2020)

First author	Region	Study period	Number of children	Main hematologic findings			
				WBC	Hemoglobin	Platelets	Coagulation studies
Feldstein LR, et al[56]	Pediatric health centers across 26 US States	March 15 to May 20, 2020	186	Neutrophilia Lymphopenia	Anemia	Thrombocytopenia	Increased D-dimers Prolonged INR Increased fibrinogen level
Duforf E, et al[57]	Hospitals in New York	March 1 to May 10, 2020	95	Lymphopenia in 66%			Increased D-dimers in 91%
Davies P, et al[52]	Pediatric ICUs in United Kingdom	April 1 to May 10, 2020	78	Lymphopenia at admission, but median lymphocyte count was normal on day 3 Neutrophilia		Thrombocytopenia at admission, but median platelet count was normal on day 3	Increased D-dimers
Whittaker E, et al[5]	8 Hospitals in England	March 23 to May 16, 2020	58	All had neutrophilia			
Belhadjer Z, et al[58]	14 ICUs in France and Switzerland	March 22 to April 30, 2020	35	Leukocytosis Neutrophilia			Increased D-dimers
Toubiana J, et al[59]	University Hospitalin France	April 27 to May 11, 2020	21	All had leukocytosis, neutrophilia Lymphopenia in 81%	Anemia		Increased D-dimers in 95%
Cheung E, et al[59]	Children's Hospital in New York City	April 18 to May 5, 2020	17	Most had lymphopenia and bandemia			
Verdoni L, et al[60]	Bergamo province, Italy	February 18 to April 20, 2020	10	The majority had neutrophilia, lymphopenia 5 Children had macrophage activation syndrome		Thrombocytopenia	Increased D-dimers
Riphagen S, et al[61]	ICU, UK	10 Days in mid-April, 2020	8				Increased D-dimers
Moraleda C, et al[53]	49 Hospitals in Spain The Epidemiological Study of COVID-19 in Children of the Spanish Society of Pediatrics (EPICO-AEP)	March 1 to June 1, 2020	31				Increased D-dimers in 97%
Lee P, et al[54]	Boston Children's Hospital, USA	March to June, 2020	28	Lymphocytopenia in 75% All patients had at least one inflammatory marker		Thrombocytopenia in 64%	Increased D-dimers in 96%, and 62% had prolonged prothrombin time

SEX DIFFERENCES IN REPORTED ADVERSE DRUG REACTIONS TO COVID-19 DRUGS IN A GLOBAL DATABASE OF INDIVIDUAL CASE SAFETY REPORTS

Zekarias A, Watson S, Vidlin SH, Grundmark B.. Drug Saf. 2020 Sep 25. doi: 10.1007/s40264-020-01000-8. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

A gender-stratified analysis of adverse drug reactions (ADRs) in 2573 COVID-19 reports from VigiBase (Figure 1; WHO global database for individual case safety reports) by experts from the Uppsala Monitoring Centre in Sweden found that the top 10 reported ADRs in males, but not females included acute hepatitis, hepatic enzyme aberrations and renal injury, whereas QT-prolongation (more common in men), nausea, diarrhea, and vomiting were ADRS seen in both sexes (Figure 3). Hydroxychloroquine, azithromycin, lopinavir/ritonavir, remdesivir, and tocilizumab were also statistically significantly used more in males (Figure 2). These findings highlight the potential for significant ADR differences among genders differences in COVID-19 drug usage.

ABSTRACT

INTRODUCTION: In late 2019, a new coronavirus-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-was discovered in Wuhan, China, and the World Health Organization later declared coronavirus disease 2019 (COVID-19) a pandemic. Numerous drugs have been repurposed and investigated for therapeutic effectiveness in the disease, including those from "Solidarity," an international clinical trial (azithromycin, chloroquine, hydroxychloroquine, the fixed combinatio n lopinavir/ritonavir, and remdesivir). OBJECTIVE: Our objective was to evaluate adverse drug reaction (ADR) reporting for drugs when used in the treatment of COVID-19 compared with use for other indications, specifically focussing on sex differences. METHOD: We extracted reports on COVID-19-specific treatments from the global ADR database, VigiBase, using an algorithm developed to identify reports that listed COVID-19 as the indication. The Solidarity trial drugs were included, as were any drugs reported >= 100 times. We performed a descriptive comparison of reports for the same drugs used in non-COVID-19 indications. The data lock point date was 7 June 2020. RESULTS: In total, 2573 reports were identified for drugs used in the treatment of COVID-19. In order of frequency, the most reported ADRs were electrocardiogram QT-prolonged, diarrhoea, nausea, hepatitis, and vomiting in males and diarrhoea, electrocardiogram QT-prolonged, nausea, vomiting, and upper abdominal pain in females. Other hepatic and kidney-related events were included in the top ten ADRs in males, whereas no hepatic or renal terms were reported for females. COVID-19-related reporting patterns differed from non-pandemic reporting for these drugs. CONCLUSION: Review of a global database of suspected ADR reports revealed sex differences in the reporting patterns for drugs used in the treatment of COVID-19. Patterns of ADR sex differences need further elucidation.

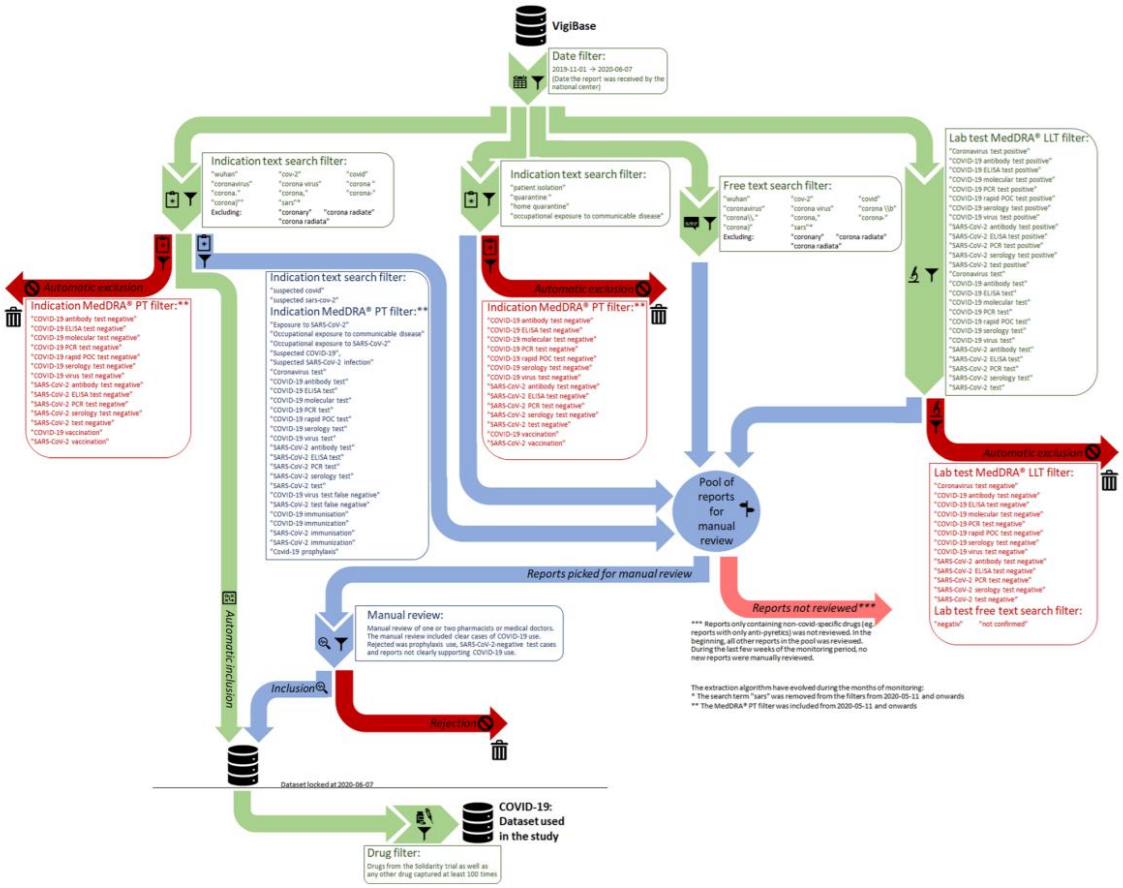
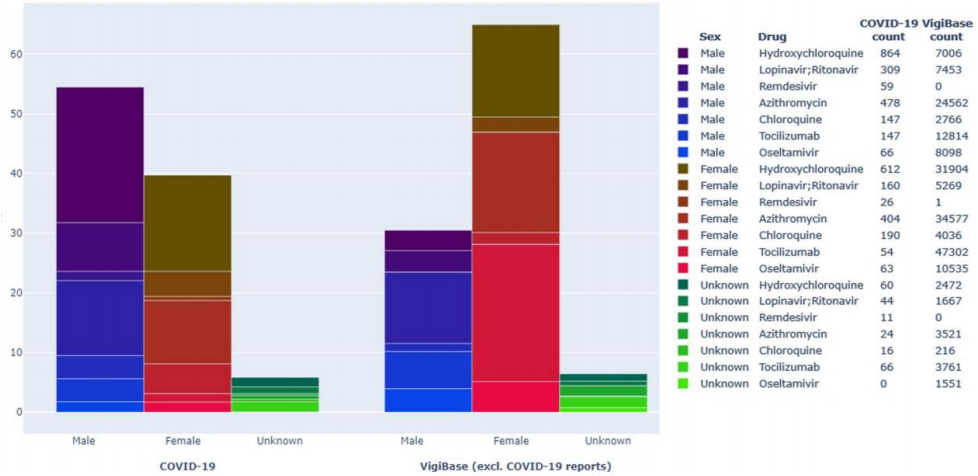


Fig. 1 Flow chart of the scanning algorithm used to create the dataset for the study. All parts above the line were developed iteratively approximately every or every other week, from April 2020, with every iteration adding a batch of reports to the dataset. The flters were adjusted along the way according to (1) needs seen when manually reviewing reports, (2) needs emerging from a growing dataset, (3) new MedDRA® versions released. The fgure represents the algorithm at the point of data lockdown, with major adjustments marked. ELISA enzyme-linked immunosorbent assay, LLT Low Level Term, MedDRA Medical Dictionary for Regulatory Activities, PCR polymerase chain reaction, POC Point of Care, PT preferred term



Sex	Drug	COVID-19 count	VigiBase count
Male	Hydroxychloroquine	864	7006
Male	Lopinavir;Ritonavir	309	7453
Male	Remdesivir	59	0
Male	Azithromycin	478	24562
Male	Chloroquine	147	2766
Male	Tocilizumab	147	12814
Male	Oseltamivir	66	8098
Female	Hydroxychloroquine	612	31904
Female	Lopinavir;Ritonavir	160	5269
Female	Remdesivir	26	1
Female	Azithromycin	404	34577
Female	Chloroquine	190	4036
Female	Tocilizumab	54	47302
Female	Oseltamivir	63	10535
Unknown	Hydroxychloroquine	60	2472
Unknown	Lopinavir;Ritonavir	44	1667
Unknown	Remdesivir	11	0
Unknown	Azithromycin	24	3521
Unknown	Chloroquine	16	216
Unknown	Tocilizumab	66	3761
Unknown	Oseltamivir	0	1551

Fig. 2 Proportions of VigiBase reporting by sex for drugs included in the study. Bars to the left show the COVID-19 subset of VigiBase; bars to the right show the same drugs used for other indications. The legend shows the number of reports for each drug and subset

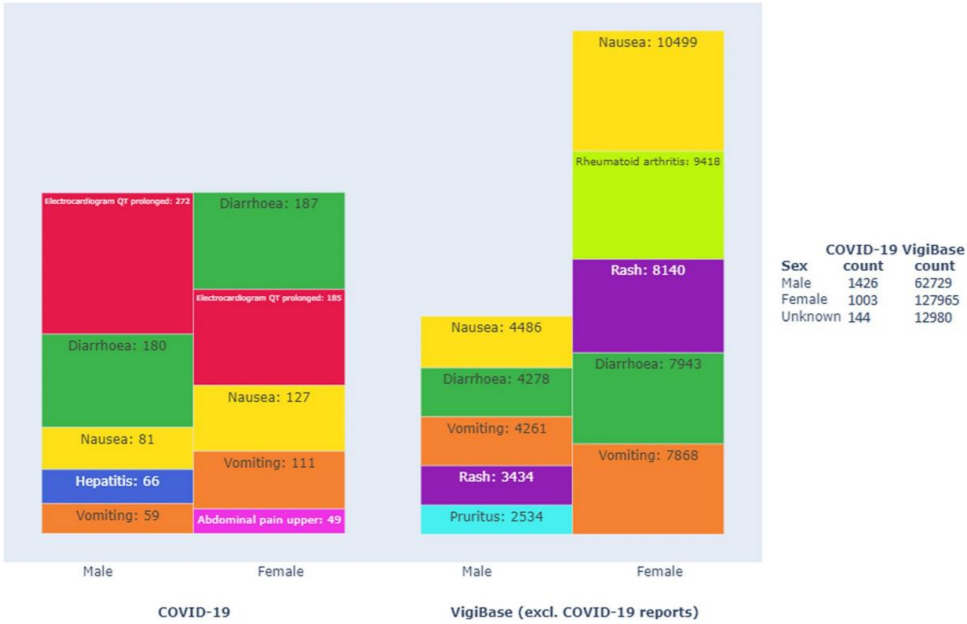


Fig. 3 Top fve reported adverse drug reactions (MedDRA® preferred terms), with number of reported instances, for the included drugs used in treating COVID-19 (left) vs. for the same drugs used in other indications (right), separated by sex. Reports with unknown sex and
the MedDRA® preferred terms of-label use, intentional product use issue, and drug inefective are excluded. The size of the box represents the proportions within the COVID-19 and VigiBase datasets, respectively. Reports may contain more than one reported preferred
term. The legend shows the number of reports for each subset

UNDERSTANDING THE PATHOLOGY

IN VITRO

MECHANISMS BY WHICH SARS-COV-2 MAY IMPACT MALE FERTILITY

Hsu AL, Finlinson A, Warncke K.. Reprod Sci. 2020 Oct 6. doi: 10.1007/s43032-020-00304-5. Online ahead of print.
Level of Evidence: Other - Opinion

BLUF

In this letter to the editor, obstetrician-gynecologists and a medical student from the University of Missouri School of Medicine discuss possible mechanisms of male infertility in SARS-CoV-2 infection described by Dutta and Sengupta in their article "SARS-CoV-2 and male infertility: possible multifaceted pathology." They propose viral binding to angiotensin-converting enzyme 2 receptors on spermatogonia, Leydig cells, and Sertoli cells may cause overactivation and negatively impact spermatogenesis. Additionally, they urge further studies on SARS-CoV-2's ability to disrupt sperm formation and function because SARS-CoV-2 seems to disproportionately impact males in some studies.

ABSTRACT

The COVID-19 pandemic is unlike anything we have experienced in over a century. In the USA, waves of COVID-19 have migrated from the Northeast to the Sun Belt to the Midwest over the past year. Compared with females, males are more susceptible to SARS-CoV-2 infection, have more severe COVID-19 disease, and have higher death rates. In many countries, men are consistently more likely to die by a factor of almost 2. This article describes some of the mechanisms by which COVID-19 may be associated with male infertility, as discussed by Dutta and Sengupta.

EXTRACELLULAR VESICLES RELEASED IN BLOOD OF COVID-19 PATIENTS: MECHANISM FOR DETECTION OF CARDIAC TROPONIN AFTER MYOCARDIAL INJURY?

Wu AHB, Zhang Y, Webber R.. Biomarkers. 2020 Sep 25:1-10. doi: 10.1080/1354750X.2020.1829055. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A literature review from the Department of Laboratory Medicine, UCSF discusses how the most likely mechanism of elevated troponin (cTnI & cTnT) in COVID-19 patients occurs following cardiac injury (due to anoxic stress resulting from acute lung injury or hypoperfusion secondary to bradykinin storm). This injury leads to a Type II myocardial infarct, in which cardiomyocytes experience reversible injury and release extracellular vesicles (EVs) containing cTnI & cTnT. This review suggests analysis of EVs (Figure 1) for cardiac biomarkers could be useful as a diagnostic method for detection of cardiac injury secondary to COVID-19.

FIGURES

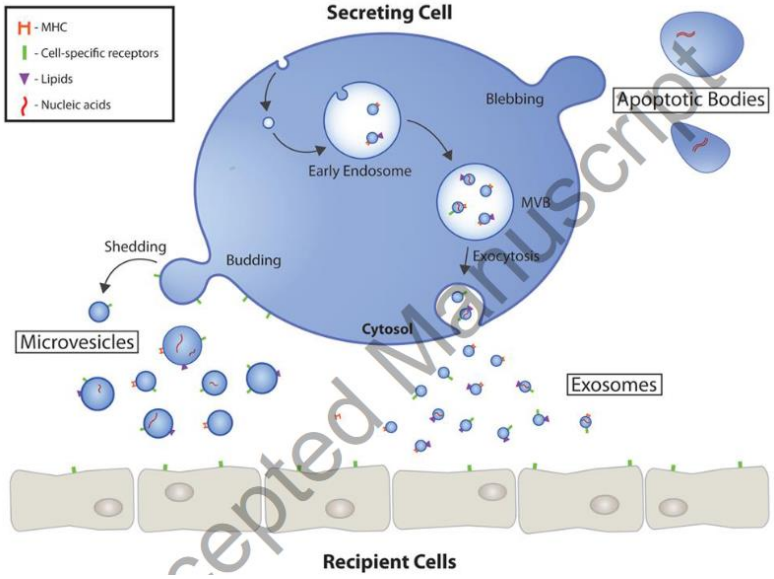


Fig. 1. Intracellular origins of excellular vesicles: exosomes, microvesicles, and apoptotic bodies. Used with permission from Gustafson et al.2017.

ADJUSTING PRACTICE DURING COVID-19

A META-ANALYSIS OF SARS-COV-2 PATIENTS IDENTIFIES THE COMBINATORIAL SIGNIFICANCE OF D-DIMER, C-REACTIVE PROTEIN, LYMPHOCYTE, AND NEUTROPHIL VALUES AS A PREDICTOR OF DISEASE SEVERITY

Singh K, Mittal S, Gollapudi S, Butzmann A, Kumar J, Ohgami RS.. Int J Lab Hematol. 2020 Oct 3. doi: 10.1111/ijlh.13354. Online ahead of print.
Level of Evidence: Other - Modeling

BLUF

Pathologists affiliated with Stanford and UCSF conducted a retrospective meta-analysis of PubMed COVID-19 articles with laboratory blood values of COVID-19 positive patients in May 2020. They developed two predictive equations, one with 4 variables (Equation 1: CRP, D-dimer, lymphocyte, neutrophils) and another with 3 (Equation 2: CRP, lymphocytes, neutrophils) to predict COVID-19 disease severity (Table 1), highlighting the equations' performance in adult and pediatric

respectively (Tables 2, 3). The authors believe their algorithms can efficiently predict disease severity, subsequently leading to improved patient care and decreased mortality in these COVID-19 patients.

SUMMARY

A meta-analysis was performed including 10 qualifying COVID-19 articles from PubMed in May 2020. Multivariate regression analysis and validation tests were performed.
- Equation 1 includes 4 laboratory blood variables and equation 2 includes 3 variables (Table 1).
- The sensitivity, specificity, positive predictive value, negative predictive value, and test yield % were assessed in adult and pediatric populations (Tables 2, 3).
- The equations significantly predicted disease severity. They found a significant power>0.9 by power analysis, sufficient to achieve statistical significance <0.05.
- Neutropenia, lymphocytopenia, elevated CRP and D-dimer levels had an association with the progression of disease.
- The authors clinically implicate the significance of implementing these equations to COVID-19 patients the first day of diagnosis to aid in predicting disease severity.

ABSTRACT

BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known to be the causative agent of COVID-19, has led to a worldwide pandemic. At presentation, individual clinical laboratory blood values, such as lymphocyte counts or C-reactive protein (CRP) levels, may be abnormal and associated with disease severity. However, combinatorial interpretation of these laboratory blood values, in the context of COVID-19, remains a challenge. METHODS: To assess the significance of multiple laboratory blood values in patients with SARS-CoV-2 and develop a COVID-19 predictive equation, we conducted a literature search using PubMed to seek articles that included defined laboratory data points along with clinical disease progression. We identified 9846 papers, selecting primary studies with at least 20 patients for univariate analysis to identify clinical variables predicting nonsevere and severe COVID-19 cases. Multiple regression analysis was performed on a training set of patient studies to generate severity predictor equations, and subsequently tested on a validation cohort of 151 patients who had a median duration of observation of 14 days. RESULTS: Two COVID-19 predictive equations were generated: one using four variables (CRP, D-dimer levels, lymphocyte count, and neutrophil count), and another using three variables (CRP, lymphocyte count, and neutrophil count). In adult and pediatric populations, the predictive equations exhibited high specificity, sensitivity, positive predictive values, and negative predictive values. CONCLUSION: Using the generated equations, the outcomes of COVID-19 patients can be predicted using commonly obtained clinical laboratory data. These predictive equations may inform future studies evaluating the long-term follow-up of COVID-19 patients.

FIGURES

Equation		Multiple *R*	R^2
1	$y = 0.97 - 0.92 \times (\text{LYM K}/\mu\text{l}) + 0.070 \times (\text{NEU K}/\mu\text{l}) + 0.0038 \times (\text{CRP mg/L}) + 0.033 \times (\text{DD mg/L})$	0.86	.75
2	$y = 0.79 - 0.82 \times (\text{LYM K}/\mu\text{l}) + 0.090 \times (\text{NEU K}/\mu\text{l}) + 0.0045 \times (\text{CRP mg/L})$	0.82	.68

Table 1: COVID-19 severity prediction equations.

Equation	Test yield (%)	Positive predictive value	Negative predictive value	Sensitivity	Specificity
1	79	0.73	0.82	0.76	0.79
2	84	0.68	0.83	0.68	0.83

Note: Test yield = percentage of cases that can be classified.

Table 2: Evaluation of the performance of COVID-19 predictor equations in adult patients.

Equation	Test yield (%)	Positive predictive value	Negative predictive value	Sensitivity	Specificity
1	89	1.00	0.64	0.29	1.00
2	92	1.00	0.68	0.13	1.00

Note: Test yield = percentage of cases that can be classified.

Table 3: Evaluation of the performance of COVID-19 predictor equations in pediatric patients.

INCREASED MICROBIAL LOADING IN AEROSOLS PRODUCED BY NON-CONTACT AIR-PUFF TONOMETER AND RELATIVE SUGGESTIONS FOR THE PREVENTION OF CORONAVIRUS DISEASE 2019 (COVID-19)

Guo H, Li W, Huang Y, Li X, Li Z, Zhou H, Sun E, Li L, Li J.. PLoS One. 2020 Oct 8;15(10):e0240421. doi: 10.1371/journal.pone.0240421. eCollection 2020.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Ophthalmologists from Qilu Hospital of Shandong University in China conducted a study of device contamination from March 18-25, 2020. They found non-contrast tonometers (NCTs) used to measure intraocular pressure had an increased number of bacterial colonies in air samples taken directly beside the nozzle after air puff than those 1 meter from the nozzle ($p<0.05$)(Table and Figure 1). Decontamination of the nozzle with 75% alcohol demonstrated significantly less colony formation ($p<0.05$)(Figure 2) compared to samples taken prior to decontamination. While they did not perform viral detection studies, authors suggest NCTs may also be a potential source of SARS-CoV-2 transmission in ophthalmology offices, but routine disinfection with 75% alcohol could reduce the risk of viral transmission.

ABSTRACT

OBJECTIVE: To evaluate the microbial loading in aerosols produced after air-puff by non-contact tonometer (NCT) as well as the effect of alcohol disinfection on the inhibition of microbes and thus to provide suggestions for the prevention and control of COVID-19 in ophthalmic departments of hospitals or clinics during the great pandemics. METHODS: A cross-sectional study was carried out in this study. A NIDEK NCT was used for intraocular pressure (IOP) measurement for patients who visited Department of Ophthalmology in Qilu Hospital of Shandong University during March 18-25 2020. After ultra-violate (UV) light disinfection, the room air was sampled for 5 minutes. Before and after alcohol disinfection, the air samples and nozzle surface samples were respectively collected by plate exposure method and sterile moist cotton swab technique after predetermined times of NCT air-puff. Microbial colony counts were calculated after incubation for 48 hours. Finally, mass spectrometry was performed for the accurate identification of microbial species. RESULTS: Increased microbial colonies were detected from air samples close to NCT nozzle after air-puff compared with air samples at a distance of 1 meter from the nozzle ($p = 0.001$). Interestingly, none microbes were detected on the surface of NCT nozzle. Importantly, after 75% alcohol disinfection less microbes were detected in the air beside the nozzle ($p = 0.003$). Microbial species identification showed more than ten strains of microbes, all of which were non-pathogenic. CONCLUSION: Aerosols containing microbes were produced by NCT air-puff in the ophthalmic consultation room, which may be a possible virus transmission route in the department of ophthalmology during the COVID-19 pandemic. Alcohol disinfection for the nozzle and the surrounding air was efficient at decreasing the microbes contained in the aerosols and theoretically this prevention measure could also inhibit the virus. This will give guidance for the prevention of virus transmission and protection of hospital staff and patients.

FIGURES

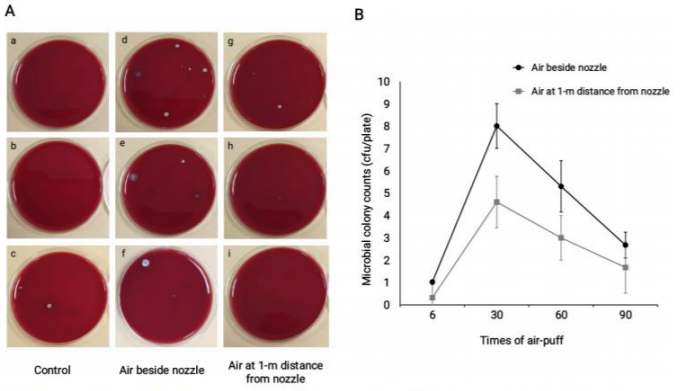


Fig 1. Increased microbial colonies were detected in air samples beside the nozzle after NCT air-puff. A: Representatives of culture plates at different sampling sites after NCT air-puff. a,b,c: room air samples after UV disinfection; d,e,f: air samples beside the nozzle after different times of air-puff; g,h,i: air samples at 1-m distance from the nozzle after different times of air-puff. **B**: More microbial colonies were detected in air samples beside the nozzle compared with samples at 1-m distance (overall difference $p<0.05$). For the difference between groups, a significant difference was observed in the group of 30 times air-puff ($p<0.05$). There were no significant differences between the other three groups.

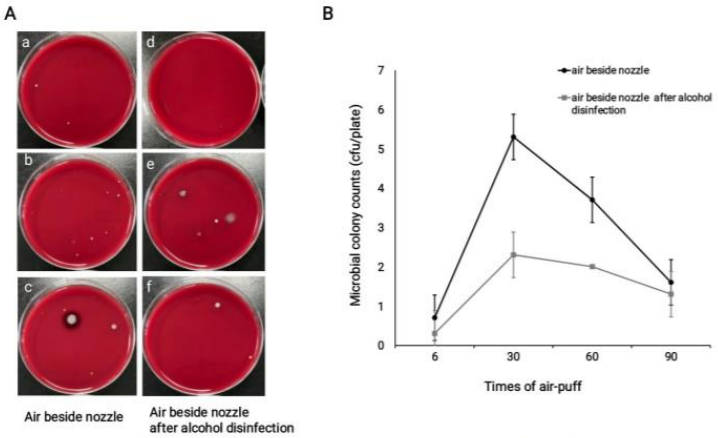


Fig 2. Less microbial colonies were detected in air samples beside the nozzle after 75% alcohol disinfection. A: Representatives of culture plates of air samples beside the nozzle after NCT air-puff before and after 75% alcohol disinfection. a,b,c: air samples besides nozzle after different times of air-puff; d.e.f: air samples besides nozzle after different times of air-puff with alcohol disinfection. **B**: Less microbial colonies were detected in air samples besides nozzle after alcohol disinfection (overall difference $p<0.05$). For the difference between groups, a significant difference was observed in both groups of 30- and 60- times air-puff ($p<0.05$). There were no significant differences between the other two groups.

Table 1. Microbial strains identified by mass spectrometry in room air samples after UV light disinfection and air samples collected beside the nozzle and at 1-m distance from the nozzle after NCT air-puff.

Site	Times of air-puff	Microbial Strains
Room air after ultraviolet light disinfection	N/A	Micrococcus sp, Moraxella osloensis
Air samples beside the nozzle	6	Micrococcus luteus
	30	Micrococcus luteus, Escherichia coli, Kytococcus schroeteri, Pseudarthrobacter oxydans, Bacillus feed
	60	Pseudarthrobacter oxydans, Corynebacterium afermentans, Corynebacterium lipophiloflavum
	90	Staphylococcus xylosus Staphylococcus epidermidis
Air samples at 1-m distance from the nozzle	6	Staphylococcus epidermidis
	30	Micrococcus luteus, Bacillus littoral, Staphylococcus epidermidis
	60	Agrococcus jenensis, Shewanell baltica, Staphylococcus epidermidis
	90	Clostridium bharat

REGN-COV2 ANTIBODIES PREVENT AND TREAT SARS-COV-2 INFECTION IN RHESUS MACAQUES AND HAMSTERS

Baum A, Ajithdoss D, Copin R, Zhou A, Lanza K, Negron N, Ni M, Wei Y, Mohammadi K, Musser B, Atwal GS, Oyejide A, Goez-Gazi Y, Dutton J, Clemmons E, Staples HM, Bartley C, Klaffke B, Alfson K, Gazi M, Gonzalez O, Dick E Jr, Carrion R Jr, Pessaint L, Porto M, Cook A, Brown R, Ali V, Greenhouse J, Taylor T, Andersen H, Lewis MG, Stahl N, Murphy AJ, Yancopoulos GD, Kyratsous CA.. Science. 2020 Oct 9:eabe2402. doi: 10.1126/science.abe2402. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Virologists from Regeneron Pharmaceuticals report results from in vivo study of their proprietary therapeutic cocktail REGN-COV2's (human antibodies REGN10933, REGN10987) ability to reduce viral load via SARS-CoV-2 spike protein binding in resus macaques and golden hamsters. They found a 50 mg/kg dose significantly reduced SARS-CoV-2 gRNA ($p<0.0001$) and sgRNA ($P=0.0012$) in rhesus macaques on oral swab (figures 1,2) and that 0.5-50 mg/kg prophylactic doses prevented weight loss and reduced lung findings associated with pneumonia in Golden hamsters ($p<0.0001$)(Figure 3). Authors suggest this REGN-COV2 regimen shows potential for prevention and treatment of SARS-CoV-2 in humans and express optimism regarding ongoing clinical trials.

ABSTRACT

An urgent global quest for effective therapies to prevent and treat COVID-19 disease is ongoing. We previously described REGN-COV2, a cocktail of two potent neutralizing antibodies (REGN10987+REGN10933) targeting non-overlapping epitopes on the SARS-CoV-2 spike protein. In this report, we evaluate the in vivo efficacy of this antibody cocktail in both rhesus macaques, which may model mild disease, and golden hamsters, which may model more severe disease. We demonstrate that REGN-COV-2 can greatly reduce virus load in lower and upper airways and decrease virus induced pathological sequelae when administered prophylactically or therapeutically in rhesus macaques. Similarly, administration in hamsters limits weight loss and decreases lung titers and evidence of pneumonia in the lungs. Our results provide evidence of the therapeutic potential of this antibody cocktail.

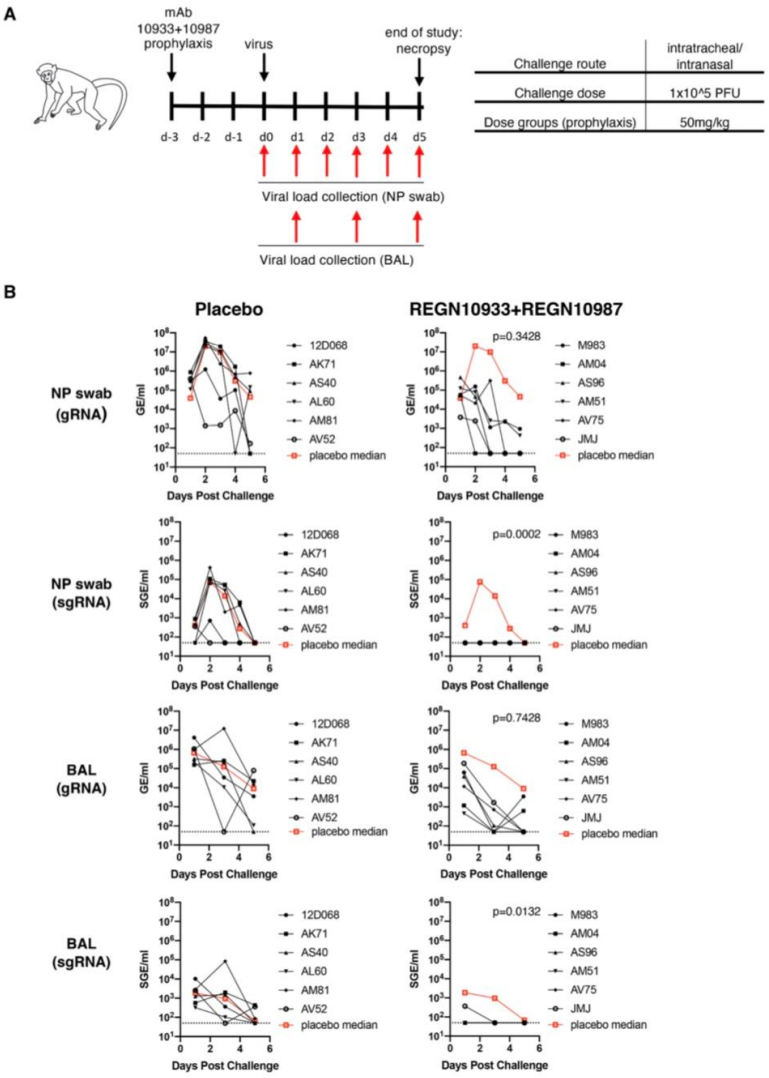


Fig. 1. Prophylactic efficacy of REGN-COV2 in the rhesus macaque model of SARS-CoV-2 infection (NHP Study #1) (**A**) Overview of study design. (**B**) Impact of REGN-COV2 prophylaxis on viral genomic RNA (gRNA) and subgenomic RNA (sgRNA) in nasopharyngeal swabs and bronchioalveolar lavage (BAL) fluid. For detailed statistical analysis refer to tables S2 and S3.

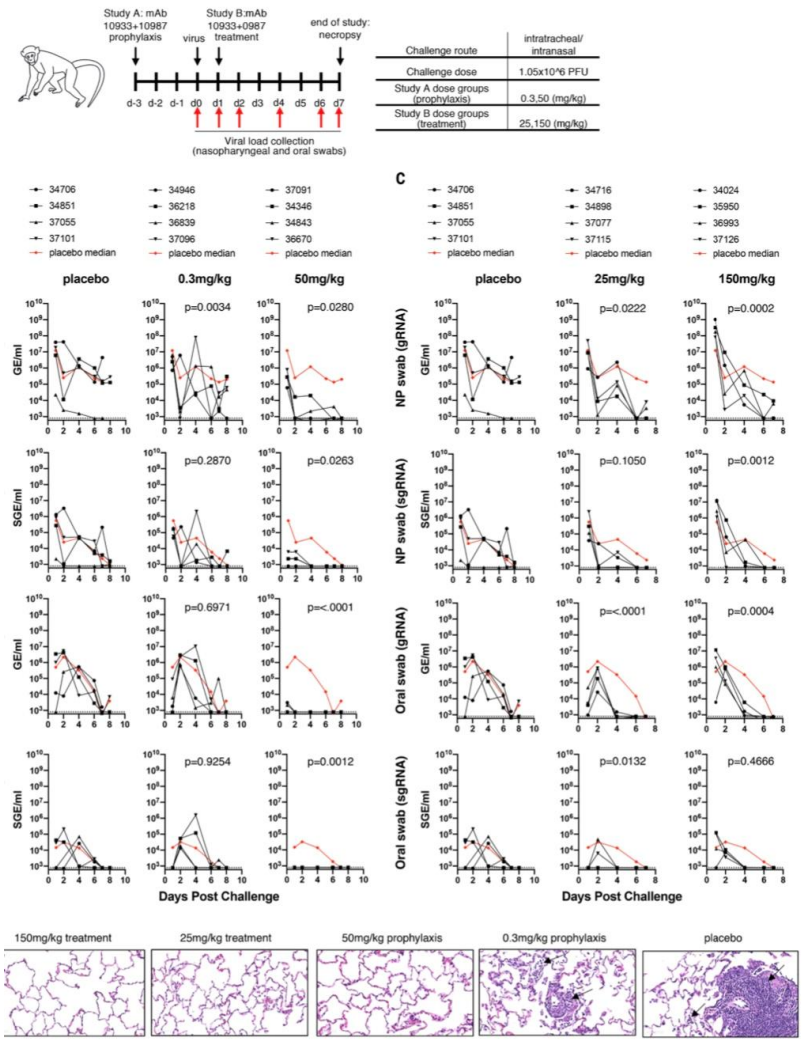


Fig. 2. Prophylactic and therapeutic efficacy of REGN-COV2 in the rhesus macaque model of SARS-CoV-2 infection (NHP Study #2) (**A**) Overview of study design. (**B**) Impact of REGN-COV2 prophylaxis on viral genomic RNA (gRNA) and subgenomic RNA (sgRNA) in nasopharyngeal swabs and oral swabs [Study A, as shown in (A)]. (**C**) Impact of REGN-COV2 treatment on viral genomic RNA (gRNA) and subgenomic RNA (sgRNA) in nasopharyngeal swabs and oral swabs [Study B, as shown in (A)]. (**D**) representative images of histopathology in lungs of treated and placebo animals. For detailed statistical analysis refer to tables S2 and S3.

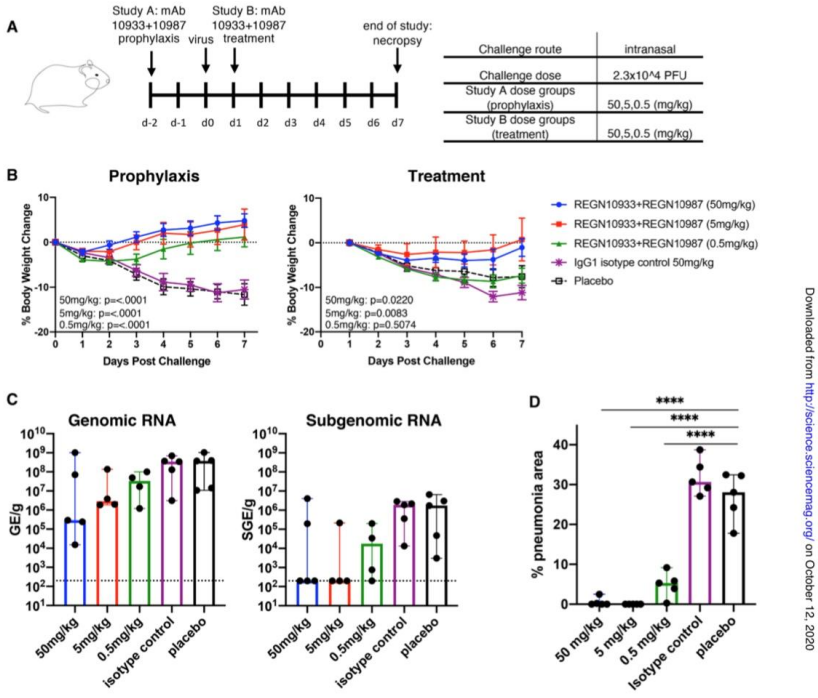


Fig. 3. Efficacy of REGN-COV2 in treatment and prophylaxis in the golden Syrian hamster model of SARS-CoV-2 infection. (**A**) Study design overview. (**B**) Impact of REGN-COV2 on weight loss in prophylaxis and treatment. (**C**) Impact of REGN-COV-2 prophylaxis on levels of gRNA and sgRNA in hamster lungs (7dpi). No statistical significance was observed between any treatment groups and placebo. (**D**) Impact of REGN-COV2 prophylaxis on percent area of lung exhibiting pathology typical of pneumonia (significant differences are denoted by: ****p<0.0001). For detailed statistical analysis refer to tables S4 and S5.

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