The Daily COVID-19 Literature Surveillance Summary

November 16, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

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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

Climate

- The International COVID-19 Parental Attitude Study (COVIPAS) group conducted a cross-sectional survey of 1541 caregivers from six countries and found that 65% of caregivers were willing to vaccinate their child against COVID-19 whenever a vaccine became available, and that 52% of those refusing vaccination reported that the newness of the vaccine was a deciding factor. Authors suggest these findings demonstrate the need for effective public health education efforts regarding the safety, efficacy, and utility of any available COVID-19 vaccine.

Epidemiology

- Massive dissemination of a SARS-CoV-2 Spike Y839 variant in Portugal was found. Bioinformatic and surveillance specialists from Portugal reviewed geotemporal spread of SARS-CoV-2 Spike 839Y variant, introduced from Italy to Portugal in February 2020, using 1,516 SARS-CoV-2 genome sequences collected as part of national surveillance. They found relative frequency increased at a rate of 12.1% every three days, and the Spike 839Y variant was associated with 24.8% of confirmed cases by the end of April. This variant has since been detected in 12 other countries, so authors suggest ongoing surveillance of SARS-CoV-2 genetic diversity and epidemiological monitoring of potentially significant variants.

- A retrospective study of 192 COVID-19 patients hospitalized at "Beato Matteo" (Hospital Group San Donato) conducted by internal and emergency medicine specialists in Vigevano, Italy found no significant association between having lupus anticoagulant (95/192, 49.5%) and mortality (47.7% of 130 survivors and 53.2% of 62 non-survivors; p=0.4745) or need for mechanical ventilation. However, worse outcomes were seen in patients with obesity, low oxygen saturation, and high troponin level. Authors suggest lupus anticoagulant is not a strong prognostic marker in COVID-19 patients and it may be a side effect of rather than a cause for thromboembolism.

Management

- What are the SARS-CoV-2 risks in first trimester pregnancy? A cohort study, conducted at Copenhagen University Hospital, examined potential risk caused by SARS-CoV-2 infection for first trimester pregnancies by analyzing double tests, which are blood samples for pregnancy-associated plasma protein A (PAPP-A) and free beta human chorionic gonadotropin (β-hCG), of 1,019 pregnant women for SARS-CoV-2 antibodies. Results indicated SARS-CoV-2 infection early in pregnancy as 18 (1.8%) of the 1,019 pregnant women were positive for SARS-CoV-2 antibodies in their serum. However, there was not a significant correlation with nuchal translucency thickness nor increased risk of pregnancy loss between the women testing positive versus those testing negative for SARS-CoV-2 antibodies. While these results may be limited by sample size, population type, and severity of COVID-19 infection, this study demonstrates no increased risk of low-severity COVID-19 infections during the first trimester of pregnancy.

TABLE OF CONTENTS

CLIMATE

CAREGIVER WILLINGNESS TO VACCINATE THEIR CHILDREN AGAINST COVID-19: CROSS SECTIONAL SURVEY

Goldman RD, Yan TD, Seiler M, Parra Cotanda C, Brown JC, Klein EJ, Hoeffe J, Gelernter R, Hall JE, Davis AL, Griffiths MA, Mater A, Manzano S, Gualco G, Shimizu N, Hurt TL, Ahmed S, Hansen M, Sheridan D, Ali S, Thompson GC, Gaucher N, Staubli G; International COVID-19 Parental Attitude Study (COVIPAS) Group.. Vaccine. 2020 Nov 10;38(48):7668-7673. doi: 10.1016/j.vaccine.2020.09.084. Epub 2020 Oct 10.
Level of Evidence: 3 - Local non-random sample

BLUF

The International COVID-19 Parental Attitude Study (COVIPAS) group conducted a cross-sectional survey of 1541 caregivers from six countries between March 26 and May 31, 2020 and found that 65% of caregivers were willing to vaccinate their child against COVID-19 whenever a vaccine were available, and that 52% of those refusing vaccination reported that the newness of the vaccine was a deciding factor (Table 3). Authors suggest these findings demonstrate the need for effective public health education efforts regarding the safety, efficacy, and utility of any available COVID-19 vaccine.

ABSTRACT

BACKGROUND: More than 100 COVID-19 vaccine candidates are in development since the SARS-CoV-2 genetic sequence was published in January 2020. The uptake of a COVID-19 vaccine among children will be instrumental in limiting the spread of the disease as herd immunity may require vaccine coverage of up to 80% of the population. Prior history of pandemic vaccine coverage was as low as 40% among children in the United States during the 2009 H1N1 influenza pandemic. PURPOSE: To investigate predictors associated with global caregivers' intent to vaccinate their children against COVID-19, when the vaccine becomes available. METHOD: An international cross sectional survey of 1541 caregivers arriving with their children to 16 pediatric Emergency Departments (ED) across six countries from March 26 to May 31, 2020. RESULTS: 65% (n = 1005) of caregivers reported that they intend to vaccinate their child against COVID-19, once a vaccine is available. A univariate and subsequent multivariate analysis found that increased intended uptake was associated with children that were older, children with no chronic illness, when fathers completed the survey, children up-to-date on their vaccination schedule, recent history of vaccination against influenza, and caregivers concerned their child had COVID-19 at the time of survey completion in the ED. The most common reason reported by caregivers intending to vaccinate was to protect their child (62%), and the most common reason reported by caregivers refusing vaccination was the vaccine's novelty (52%). CONCLUSIONS: The majority of caregivers intend to vaccinate their children against COVID-19, though uptake will likely be associated with specific factors such as child and caregiver demographics and vaccination history. Public health strategies need to address barriers to uptake by providing evidence about an upcoming COVID-19 vaccine's safety and efficacy, highlighting the risks and consequences of infection in children, and educating caregivers on the role of vaccination.

	Number of Surveys	Total population (n = 1541)	Not willing to vaccinate child against COVID-19 (n = 509)	Willing to vaccinate child against COVID-19 (n = 1005)	P value
Child's median age in years (SD)	1532	7.50 (4.98)	7.03 (4.94)	7.74 (4.98)	0.009
Child's gender female	1533	733 (47.8%)	248 (48.8%)	477 (47.8%)	0.748
Child has chronic illness	1532	184 (12.0%)	71 (14.0%)	109 (10.9%)	0.096
Child with chronic medication use	1536	205 (13.3%)	59 (11.6%)	143 (14.3%)	0.183
Person completing the survey	1540				0.002
Father		393 (25.5%)	103 (20.2%)	282 (28.1%)	
Mother		1109 (72.0%)	396 (77.8%)	695 (69.2%)	
Other*		38 (2.47%)	10 (1.96%)	27 (2.69%)	
Caregiver's median age in years (SD)	1517	39.9 (7.58)	39.0 (7.22)	40.4 (7.72)	<0.001
Caregivers with higher education**	1517	1217 (80.2%)	406 (80.4%)	792 (80.3%)	1.000
Child's vaccinations up to date	1525	1352 (88.7%)	407 (80.6%)	930 (92.9%)	<0.001
Child received influenza vaccine last 12 months	1522	486 (31.9%)	108 (21.3%)	374 (37.5%)	<0.001
Caregiver received influenza vaccine last 12 months	1529	594 (38.8%)	131 (25.8%)	458 (45.7%)	<0.001
Mean score 10-point Likert scale - caregiver concerned their child has COVID-19 (SD)	1503	1.86 (2.78)	1.36 (2.36)	2.09 (2.93)	<0.001
Mean score 10-point Likert scale- caregiver concerned they have COVID-19 (SD)	1498	1.83 (2.64)	1.37 (2.27)	2.04 (2.77)	<0.001

*grandparents or siblings

**completed more education than high school studies

Table 1: Factors associated with caregiver willingness to vaccinate their children against COVID-19.

	Odds Ratio	OR 95% CI	P value
Child's median age	1.03	(1.00 – 1.05)	0.033
Child has chronic illness	0.66	(0.47–0.95)	0.022
Child vaccinations up to date	2.57	(1.81–3.68)	<0.001
Child vaccinated against influenza in the last 12 months	1.49	(1.09–2.05)	0.013
Mother completing the survey	0.62	(0.47–0.81)	<0.001
Caregiver vaccinated against influenza in the last 12 months	2.08	(1.55–2.8)	<0.001
Mean score 10 point Likert scale - caregiver concerned their child has COVID-19	1.08	(1–1.17)	0.048
Mean score 10 point Likert scale- caregiver concerned they have COVID-19	1.05	(0.97–1.14)	0.220

Table 2: Predictors of caregiver willingness to vaccinate their children against COVID-19 identified by multivariate logistic regression analysis.

Reason to Vaccinate (n = 1005)	Example quote	Number of caregivers	Percent of available comments
Protect the child	"To give her immunity to COVID-19"	492	62.4%
Protect others	""Herd immunity matters"	187	23.7%
General vaccine acceptance	"Vaccines work"	109	13.8%
Perceived pandemic severity	"Seems more deadly of a virus"	66	8.4%
High risk child or family members	"He has pre-existing lung issues"	54	6.8%
Accepting, but concerns of efficacy/safety	"Actually I'd wait to see how most people reacted. So would not get right away but once I was sure it was safe"	38	4.8%
Desire to return to normal life	"To get back to school"	12	1.5%
No comment		216	
Reason not to Vaccinate (n = 509)	Example quote	Number of caregivers	Percent of available comments
Novelty	"Not enough testing"	197	51.6%
Perceived child not at risk to contract COVID-19	"It doesn't affect children as badly as adults"	119	31.2%
Side effects/safety concerns	"Fear of side effects"	84	22.0%
May vaccinate if more information available/recommended by healthcare provider	"I would want to wait until we know more before making such a decision"	65	17.0%
Vaccine refusal in general	"Vaccines need to be abolished"	40	10.5%
Efficacy Concerns	"You don't know if it works"	34	8.9%
Perceived Contraindication*	"I don't think he can have vaccines while receiving chemo"	7	1.8%
No comment		127	

(*) immunosuppression, child is too young, allergy

Table 3: Reasons reported by caregivers for willingness to vaccinate or not vaccinate children against COVID-19.

EPIDEMIOLOGY

MASSIVE DISSEMINATION OF A SARS-COV-2 SPIKE Y839 VARIANT IN PORTUGAL

Borges V, Isidro J, Cortes-Martins H, Duarte S, Vieira L, Leite R, Gordo I, Caetano CP, Nunes B, Sá R, Oliveira A, Guiomar R; Portuguese network for SARS-CoV-2 genomics, Gomes JP.. Emerg Microbes Infect. 2020 Nov 2:1-58. doi: 10.1080/22221751.2020.1844552. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Bioinformatic and surveillance specialists from Portugal review geotemporal spread of SARS-CoV-2 Spike 839Y variant (introduced from Italy to Portugal in February 2020), using SARS-CoV-2 genome sequences (n=1516) collected as part of national surveillance through July 23, 2020. They found relative frequency increased at a rate of 12.1% every three days between March 14 and April 9, 2020, and the Spike 839Y variant was associated with 24.8% of confirmed cases by the end of April (Figures 1,3). This variant has since been detected in 12 other countries (Table 1), so authors suggest ongoing surveillance of SARS-CoV-2 genetic diversity and epidemiological monitoring of potentially significant variants.

ABSTRACT

Genomic surveillance of SARS-CoV-2 was rapidly implemented in Portugal by the National Institute of Health in collaboration with a nationwide consortium of >50 hospitals/laboratories. Here, we track the geotemporal spread of a SARS-CoV-2 variant with a mutation (D839Y) in a potential host-interacting region involving the Spike fusion peptide, which is a target motif of anti-viral drugs that plays a key role in SARS-CoV-2 infectivity. The Spike Y839 variant was most likely imported from Italy in mid-late February and massively disseminated in Portugal during the early epidemic, becoming prevalent in the Northern and Central regions of Portugal where it represented 22% and 59% of the sampled genomes, respectively, by April 30th. Based on our high sequencing sampling during the early epidemics [15.5% (1275/8251) and 6.0% (1500/24987) of all confirmed cases until the end of March and April, respectively)], we estimate that, between March 14th and April 9th (covering the epidemic exponential phase) the relative frequency of the Spike Y839 variant increased at a rate of 12.1% (6.1%-18.2%, CI 95%) every three days, being potentially associated with 24.8% (20.8-29.7%, CI 95%; 3177-4542 cases, CI 95%) of all COVID-19 cases in Portugal during this period. Our data supports population/epidemiological (founder) effects contributing to the Y839 variant superspread. The potential existence of selective advantage is also discussed, although experimental validation is required. Despite huge differences in genome sampling worldwide, SARS-CoV-2 Spike D839Y has been detected in 13 countries in four continents, supporting the need for close surveillance and functional assays of Spike variants.

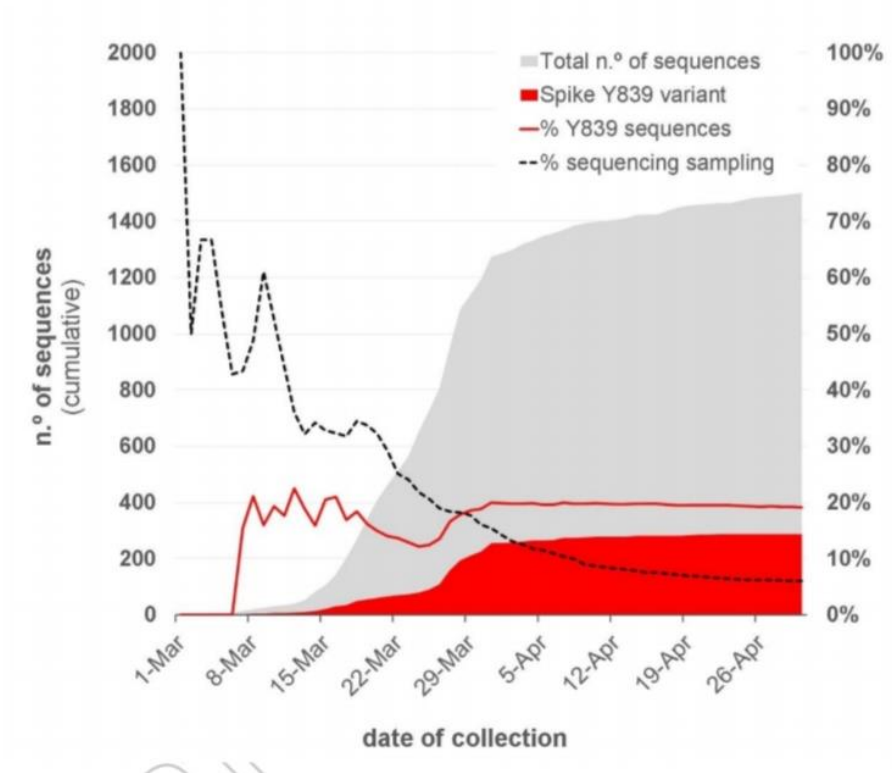


Figure 1. Overview of the SARS-CoV-2 genome sequencing sampling in Portugal and cumulative relative frequency of the circulating Spike Y839 variant, as of April 30th, 2020 (n=1500). Area plots (left y-axis) reflect the cumulative total number of SARS-CoV-2 genome sequences (gray) and Spike Y839 variant sequences (red) obtained in Portugal during the first two months of the epidemic. Lines (right y-axis) display the cumulative percentage of COVID-19 confirmed cases for which SARS-CoV-2 genome data was generated ("sequencing sampling" - black dash line) and the cumulative proportion of the Spike Y839 variant sequences (red line) detected in Portugal during the same period.

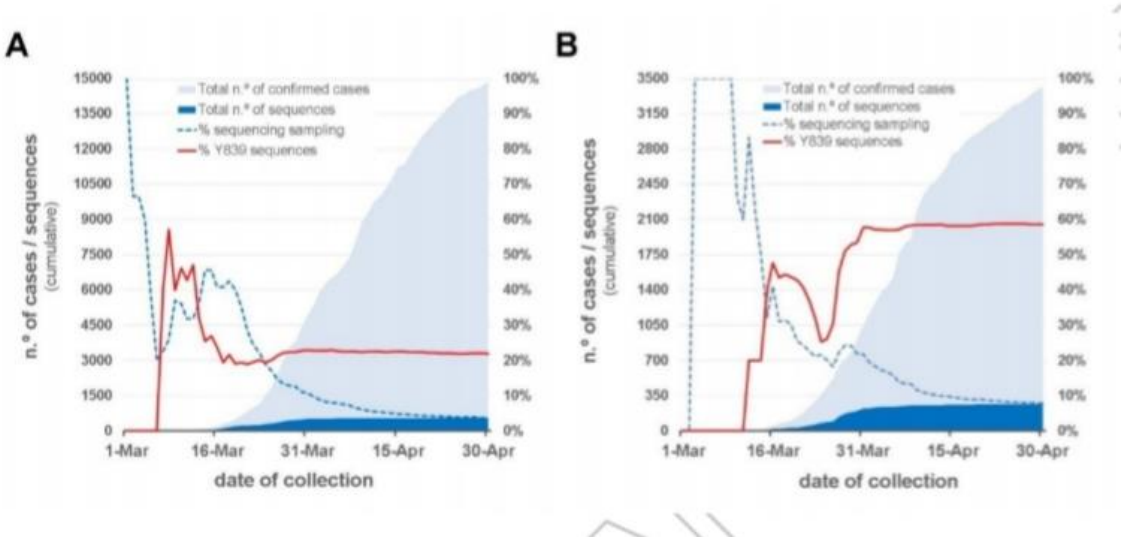


Figure 3. Overview of the SARS-CoV-2 genome sequencing sampling and cumulative relative frequency of the circulating Spike Y839 variant, as of April 30th, 2020 (n=1500), in the Northern (A) and Central (B) regions of Portugal. Area plots (left y-axis) reflect the cumulative total number of COVID-19 confirmed cases (light blue) and SARS-CoV-2 genome sequences (dark blue) detected/generated in each Health Administration region. Lines (right y-axis) display the cumulative percentage of COVID-19 confirmed cases with SARS-CoV-2 genome data, i.e., sequencing sampling (blue dash line) and the cumulative proportion of the Spike Y839 variant sequences (red line) detected in those regions during the same period.

Spike mutation	D614G background	count	countries [a,b]	date of collection range [b]
D839Y	**G614**	382	Italy (1), United Kingdom (51), Iceland (4), **Portugal (290),** Georgia (1), Poland (1), Netherlands (9), New Zealand (14), Switzerland (4), Austria (1), USA (1), Estonia (1), India (4)	21/Feb - 17/Jun
D839E	**G614**	1	Netherlands (1)	28/Feb
D839N	**G614**	1	Australia (1)	20/Jun
D839N	**D614**	1	United Kingdom (1)	25/Mar
D839G	**D614**	2	United Kingdom (2)	24/Mar - 08/May

[a]Countries are ordered by the date of collection of the first reported genome with the Spike 839 site variant. Individual sequences are detailed in Table S1 (Portugal) and S2 (abroad).

[b]The reported case in Estonia has March 2020 as the date of collection (March 31st 2020 was assumed in the Figure 5). Two genomes (one from United Kingdom and another from India) only had the year of sampling available. These were not included in Figure 5.

MANUSCRIPT

Table 1. Overview of the SARS-CoV-2 Spike amino acid sequences with mutations in the 839 site available at GISAID, as of July 23rd, 2020.

SYMPTOMS AND CLINICAL PRESENTATION

ADULTS

INTRACRANIAL HEMORRHAGE IN CORONAVIRUS DISEASE 2019 (COVID-19) PATIENTS

Cheruiyot I, Sehmi P, Ominde B, Bundi P, Mislani M, Ngure B, Olabu B, Ogeng'o JA.. Neurol Sci. 2020 Nov 3. doi: 10.1007/s10072-020-04870-z. Online ahead of print.
Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

Investigators from the University of Nairobi and Kenya Methodist University in Kenya performed a rapid systematic review of 23 studies (Figure 1) reporting intracranial hemorrhage (ICH) in COVID-19 patients published between November 1, 2019 to August 14, 2020. Of the 9 studies who reported incidence among their patients with COVID-19 (n = 13,741), a 0.7% pooled incidence of ICH was observed (Figure 2). Further, a mortality rate of 48.6% in COVID-19 patients with ICH was observed among 14 studies (n = 111 patients). The authors suggest their results guide importance of early ICH recognition in this patient population given the high mortality, albeit a low incidence rate.

ABSTRACT

BACKGROUND: Emerging evidence suggests that a subset of coronavirus disease 2019 (COVID-19) patients may present with or develop cerebrovascular disease during the course of hospitalization. Whereas ischemic stroke in COVID-19 patients has been well described, data on intracranial hemorrhage (ICH) in these patients is still limited. We, therefore, conducted a rapid systematic review of current scientific literature to identify and consolidate evidence of ICH in COVID-19 patients. METHODS: A systematic search of literature was conducted between November 1, 2019, and August 14, 2020, on PubMed and China National Knowledge Infrastructure (CNKI) to identify eligible studies. RESULTS: A total of 23 studies describing ICH in 148 COVID-19 patients were included. The pooled incidence of ICH in COVID-19 patients was 0.7% (95% CI 0.5-0.9), with low levels of inter-study heterogeneity observed (I2 = 33.6%, Cochran's Q = 12.05, p = 0.149). Most of the patients were elderly male patients (65.8%) with comorbidities, the most common being systemic hypertension (54%). Hemorrhage involving multiple cranial compartments was reported in 9.5% of cases. Single compartments were involved in the rest, with intraparenchymal hemorrhage (IPH) being the most common variety (62.6%) and intraventricular hemorrhage (IVH) the least common (1.4%). Half of these patients were on some form of anticoagulation. Overall, the mortality rate in the COVID-19 patients with ICH was about 48.6%. CONCLUSION: Although relatively uncommon among COVID-19 patients, ICH is associated with a high mortality rate. Early identification of patients at risk of developing ICH, particularly with comorbid conditions and on anticoagulant therapy, may be important to improve outcomes.

FIGURES

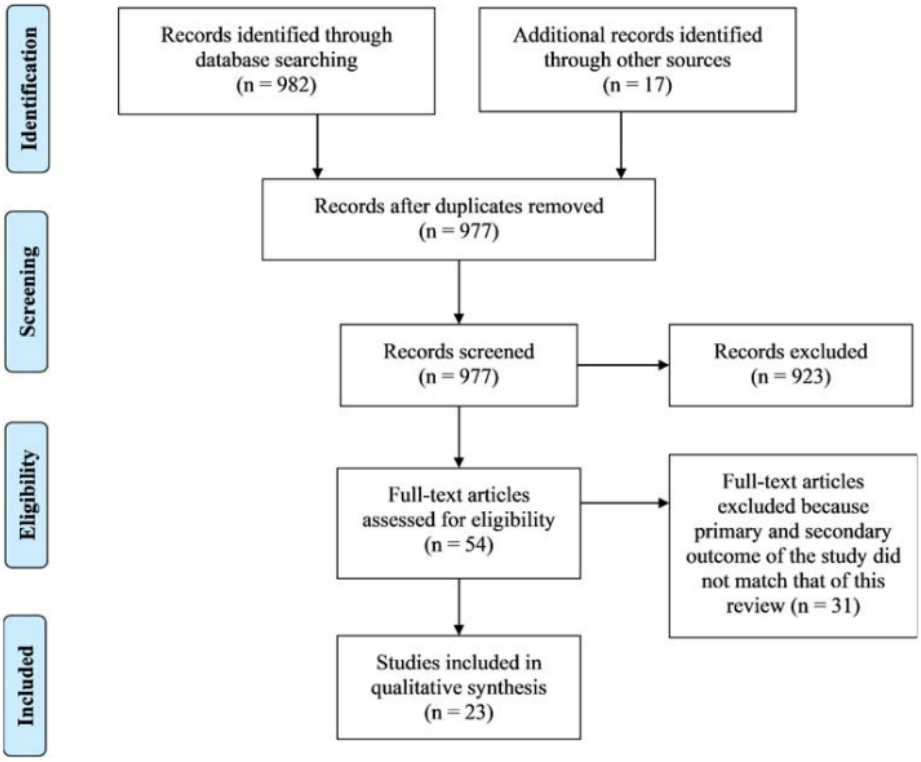


Figure 1. PRISMA flow diagram indicating flow of studies through the review.

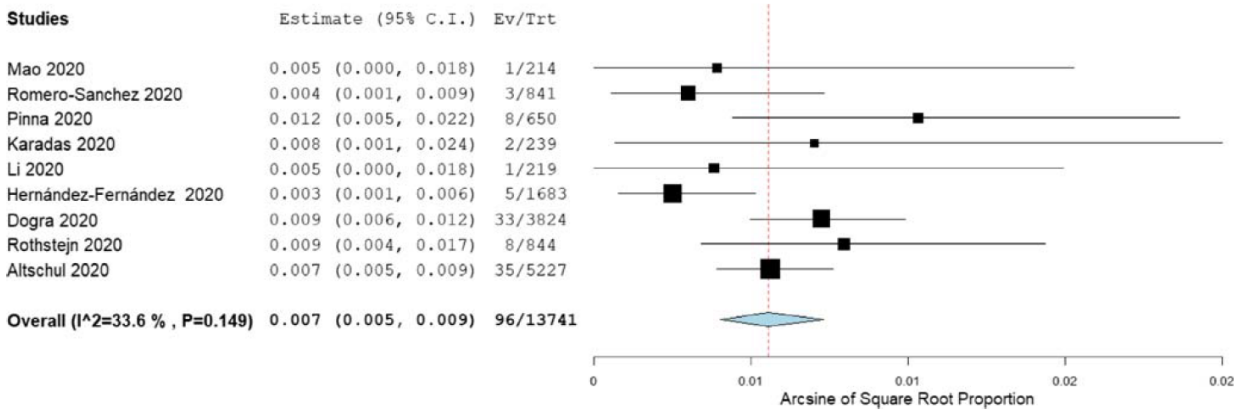


Fig. 2 Forest plot for the pooled incidence of intracranial hemorrhage in COVID-19 patients

LUPUS ANTICOAGULANT AND MORTALITY IN PATIENTS HOSPITALIZED FOR COVID-19

Gazzaruso C, Mariani G, Ravetto C, Malinverni L, Tondelli E, Cerrone M, Sala V, Bevilacqua L, Altavilla T, Coppola A, Gallotti P.. J Thromb Thrombolysis. 2020 Nov 7. doi: 10.1007/s11239-020-02335-w. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective study of COVID-19 patients (n=192) hospitalized at "Beato Matteo" (Hospital Group San Donato) conducted by internal and emergency medicine specialists in Vigevano, Italy found no significant association between having lupus anticoagulant (95/192, 49.5%) and mortality (Figure 1; 47.7% of 130 survivors and 53.2% of 62 non-survivors; p=0.4745) or need for mechanical ventilation, but worse outcomes were seen in patients with obesity, low oxygen saturation, and high troponin level (Tables 2,3). Authors suggest lupus anticoagulant is not a strong prognostic marker in COVID-19 patients and it may be a side effect of rather than a cause for thromboembolism.

ABSTRACT

Coronavirus disease 2019 (COVID-19) is characterized by a procoagulant state that can lead to fatal thromboembolic events. Several studies have documented a high prevalence of lupus anticoagulant that may at least partially explain the procoagulant profile of COVID-19. However, the association between lupus anticoagulant and thrombotic complications in COVID-19 is controversial and no study has specifically evaluated the impact of lupus anticoagulant on mortality. The aim of our study was to investigate the association between lupus anticoagulant and mortality in a large group of 192 consecutive patients hospitalized for COVID-19. Lupus anticoagulant was found in 95 patients (49.5%). No difference in the percentage of patients with lupus anticoagulant was observed between 130 survivors and 62 non-survivors (47.7 versus 53,2%; p = 0.4745). When the combined outcome of death or need for mechanical ventilation in survivors was taken into account, the difference in the prevalence of patients with lupus anticoagulant between the patients with the combined outcome (n = 76) and survivors who did not require mechanical ventilation (n = 116) was not significant (52.6% versus 47.4%; p = 0.4806). In multivariate analysis predictors of mortality or need for mechanical ventilation in survivors were obesity, low oxygen saturation and elevated troponin levels measured on admission. In conclusion, our study did not show any association of lupus anticoagulant with mortality and with need for mechanical ventilation in survivors. The role of obesity, low SaO2 and elevated troponin levels as predictors of a worse prognosis in patients hospitalized for COVID-19 was confirmed.

FIGURES

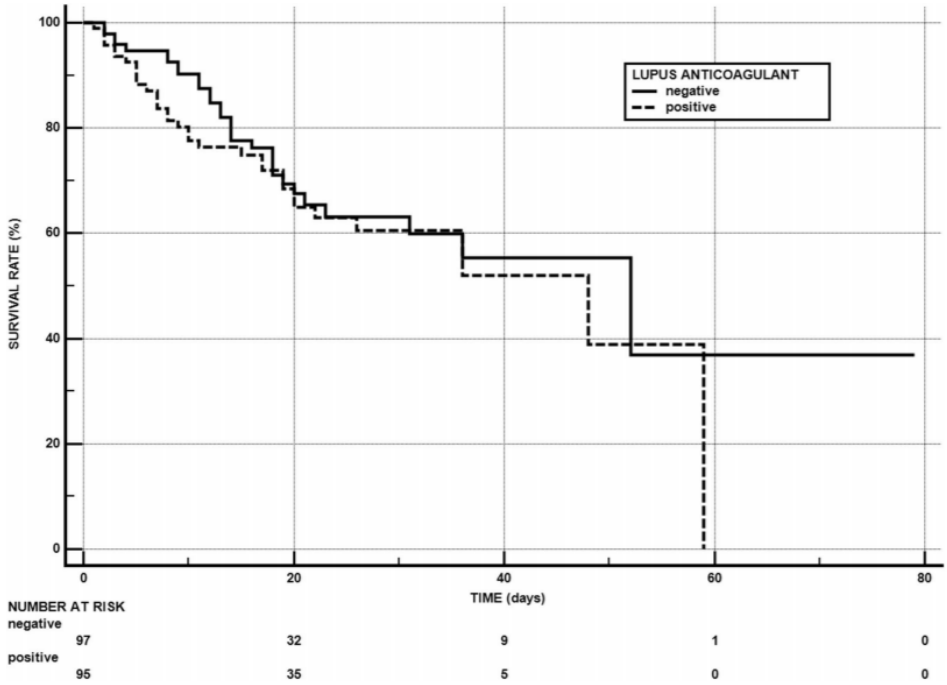


Figure 1. Kaplan–Meier survival curve according to presence/absence of lupus anticoagulant in patients hospitalized for COVID-19 during the follow-up period (18.8±13.2 days—range 1–79). For each time interval, survival probability is calculated as the number of subjects surviving divided by the number of patients at risk ("number at risk"). Subjects who have died are not counted as "at risk"

Variable	Reference range	Total patients (n = 192)	Survivors (n = 130)	Non-survivors (n = 62)	p-value
Age (years)		69.4 ± 14.5	66.6 ± 14.8	75.2 ± 12.1	0.0001
Males (%)		58.3	56.9	61.3	0.5670
History of Diabetes (%)		17.2	17.7	16.1	0.7889
History of Hypertension (%)		45.3	35.4	50.0	0.0540
History of CVD (%)		23.4	23.1	24.2	0.8647
History of Lung Disease (%)		9.9	6.9	16.1	0.0463
BMI		27.9 ± 4.8	26.4 ± 3.8	30.9 ± 5.3	< 0.0001
eGFR (ml/min)	> 90	71.3 ± 27.1	74.2 ± 25.0	65.2 ± 30.5	0.0541
CRP (mg/L)	< 5	142.2 ± 118.0	118.3 ± 88.7	176.6 ± 117.7	0.0342
D-dimer (ng/ml)	< 200	1762.2 ± 5189.6	1049.0 ± 3097.2	3255.7 ± 7790.6	< 0.0001
High-sensitivity Troponin (pg/ml)	< 20	40.0 ± 88.3	14.8 ± 18.7	92.6 ± 139.6	< 0.0001
Lupus anticoagulant (%)	Negative	49.5	47.7	53.2	0.4745
Prothrombin time (s)	9.9–12.9	13.6 ± 3.0	13.4 ± 2.9	14.0 ± 3.1	0.1904
Activated partial-thromboplastin time (s)	25–45	32.0 ± 5.2	32.2 ± 5.4	31.7 ± 4.9	0.5470
SaO2 (%)	> 93	89.9 ± 7.4	91.6 ± 5.8	86.6 ± 9.2	< 0.0001
Lactate dehydrogenase (U/L)	125–300	371.7 ± 229.6	336.0 ± 146.3	446.5 ± 333.5	0.0082
Therapeutic anticoagulation (%)		49.0	34.6	79.0	< 0.0001

CVD cardiovascular disease, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *CRP* C-reactive protein, *SaO2* oxygen saturation

Table 2. Features of the whole population and of survivors and non-survivors

Predictors	Regression coefficient β	Standard error SE	Odds Ratio	95%CI	p-value
Primary outcome (death)					
Age	1.1293	0.4006	3.0935	1.4107–6.7839	0.0048
BMI	1.2871	0.2693	3.6222	2.1368–6.1401	< 0.0001
History of hypertension	− 0.6616	0.2749	0.5160	0.2999–0.8879	0.0169
SaO2	1.1088	0.3676	3.0309	1.4746–6.2296	0.0026
High-sensitivity troponin	0.6539	0.2903	1.9230	1.0887–3.3967	0.0243
Combined outcome (death or need for mechanical ventilation in survivors)					
BMI	0.9808	0.2499	2.6666	1.6338–4.3522	0.0001
SaO2	0.8571	0.2962	2.3563	1.3184–4.2112	0.0038
High-sensitivity troponin	0.6073	0.2419	1.8355	1.1426–2.9486	0.0120

Primary outcome. Variables not included into the model: d-dimer, eGFR, lactate dehydrogenase, history of a lung disease and C-reactive protein

Combined outcome. Variables not included into the model: age, d-dimer, history of hypertension, eGFR, lactate dehydrogenase, history of a lung disease and C-reactive protein

95%CI 95% confidence interval, *BMI* body mass index, *SaO2* oxygen saturation, *eGFR* estimated glomerular filtration rate

Table 3. Predictors of outcomes in patients hospitalized for COVID-19

UNDERSTANDING THE PATHOLOGY

THE CLINICAL VALUE OF MINIMAL INVASIVE AUTOPSY IN COVID-19 PATIENTS

D'Onofrio V, Donders E, Vanden Abeele ME, Dubois J, Cartuyvels R, Achten R, Lammens M, Dendooven A, Driessen A, Augsburg L, Vanrusselt J, Cox J.. PLoS One. 2020 Nov 11;15(11):e0242300. doi: 10.1371/journal.pone.0242300. eCollection 2020.

Level of Evidence: 4 - Case-series

BLUF

A multidisciplinary Belgian infectious disease research group performed minimally invasive autopsies (MIA: consisting of whole-body CT scans and CT-guided biopsies) on 18 deceased patients who were diagnosed with COVID-19 either by PCR (n=15) or radiologically (n=3) between April 14 and May 12, 2020. They found MIA altered the clinically diagnosed cause of death in 29% of these patients and altered the contributing diagnoses in 78% (Table 1); histopathology proved especially useful, contributing to 93% of patients with alterations. Authors suggest their findings demonstrate the utility of MIA and histopathology in more accurately identifying cause of death in COVID-19 patients.

ABSTRACT

BACKGROUND: Minimally invasive autopsy (MIA) is a validated and safe method to establish the cause of death (COD), mainly in low-resource settings. However, the additional clinical value of MIA in Coronavirus disease (COVID-19) patients in a high-resource setting is unknown. The objective was to assess if and how MIA changed clinical COD and contributing diagnoses in deceased COVID-19 patients. METHODS AND FINDINGS: A prospective observational cohort from April to May 2020 in a 981-bed teaching hospital in the epicenter of the COVID-19 pandemic in Belgium was established. Patients who died with either PCR-confirmed or radiologically confirmed COVID-19 infection were consecutively included. MIA consisted of whole-body CT and CT-guided Tru-Cut biopsies. Diagnostic modalities were clinical chart review, radiology, microbiology, and histopathology which were assessed by two independent experts per modality. MIA COD and contributing diagnoses were established during a multi-disciplinary meeting. Clinical COD (CCOD) and contributing diagnosis were abstracted from the discharge letter. The main outcomes were alterations in CCOD and contributing diagnoses after MIA, and the contribution of each diagnostic modality. We included 18 patients, of which 7 after intensive care unit hospitalization. MIA led to an alteration in 15/18 (83%) patients. The CCOD was altered in 5/18 (28%) patients. MIA found a new COD (1/5), a more specific COD (1/5), a less certain COD (1/5), or a contributing diagnosis to be the COD (2/5). Contributing diagnoses were altered in 14/18 (78%) patients: 9 new diagnoses, 5 diagnoses dismissed, 3 made more specific, and 2 made less certain. Overall, histopathology contributed in 14/15 (93%) patients with alterations, radiology and microbiology each in 6/15 (40%), and clinical review in 3/15 (20%). Histopathology was deemed the most important modality in 10 patients, radiology in two patients, and microbiology in one patient. CONCLUSION: MIA, especially histological examination, can add valuable new clinical information regarding the cause of death in COVID-19 patients, even in a high-resource setting with wide access to premortem diagnostic modalities. MIA may provide important clinical insights and should be applied in the current ongoing pandemic. TRIAL REGISTRATION: Clinicaltrials.gov identifier: NCT04366882.

Patient	Disease duration LOS (days)	ICU admission Invasive ventilation		Clinical COD Clinical contributing diagnoses	MIA COD MIA contributing diagnoses	MIA alteration
PCR confirmed COVID-19 patients						
1	21	Yes	COD	Rabdomyolysis with subsequent MOF including renal failure with dialysis	Rabdomyolysis eci with subsequent MOF including renal failure with dialysis	Confirm
	20	Yes	Contributing diagnoses	COVID-19 severe pneumonia clinically improving	COVID-19 severe pneumonia	Confirm
2	51	Yes	COD	Sudden death eci	Sudden death eci	Confirm
	44	Yes	Contributing diagnoses	COVID-19 severe pneumonia clinically improving	COVID-19 severe pneumonia clinically improving	Confirm
					Minor intracerebral bleeding	New
					Sepsis	New
3	41	No	COD	Acute on chronic renal failure	Acute on chronic renal failure due to crescentic glomerulonephritis	More specific
	23	No	Contributing diagnoses	COVID-19 infection, clinical uncertainty if pneumonia	COVID-19 severe pneumonia	More specific
				Bacterial co-infection highly suspected		Dismiss
4	8	No	COD	COVID-19 severe pneumonia	Massive pulmonary embolism	Confirm (Assign as immediate COD)
	7	No	Contributing diagnoses	Massive pulmonary embolism	COVID-19 severe pneumonia	Confirm
				Hepatitis eci	Right sided heart failure leading to severe sinusoidal dilatation in the liver	More specific
5	Unkown	Yes	COD	Intracerebral bleeding	Intracerebral bleeding	Confirm
	20	Yes	Contributing diagnoses	Renal failure eci leading to dialysis	Renal failure due to ATN leading to dialysis	More specific
				COVID-19 severe pneumonia	COVID-19 severe pneumonia	Confirm
					Steatohepatitis	New
6	27	No	COD	COVID-19 severe pneumonia	COVID-19 severe pneumonia	Confirm
	17	No	Contributing diagnoses	Acute on chronic renal failure	*No renal biopsy performed*	-
					Left-and right sided heart failure	New
					Subileus	New
7	18	No	COD	Probable invasive *Aspergillus fumigatus* pulmonary infection	COVID-19 severe pneumonia	Confirm (Assign as immediate COD)
	17	No	Contributing diagnoses	COVID-19 severe pneumonia	Probable invasive *Aspergillus fumigatus* pulmonary infection	Less certain
				Cerebral B-cell lymphoma	Cerebral B-cell lymphoma	Confirm
8	Unkown	No	COD	Small cell lung carcinoma with metastasis	Small cell lung carcinoma with metastasis	Confrim
	4	No	Contributing diagnoses	COVID-19—mild illness	COVID-19—mild illness	Confirm
					Pancreatitis eci	New
9	3	No	COD	COVID-19 severe pneumonia	COVID-19 severe pneumonia	Confirm
	1	No	Contributing diagnoses	Bacterial COPD excacerbation		Dismiss
10	18	Yes	COD	Intracranial bleeding with subdural	Intracranial bleeding with subdural	Confirm
	3	No	Contributing diagnoses	COVID-19 severe pneumonia	COVID-19 severe pneumonia	Confirm
11	32	Yes	COD	Para-tracheal bleeding eci while on anticoagulant therapy for DVT and AF	Para-tracheal bleeding eci while on anticoagulant therapy for DVT and AF	Confirm
	26	No	Contributing diagnoses	COVID-19 severe pneumonia	COVID-19 severe pneumonia	Confirm
12	28	Yes	COD	COVID-19 severe pneumonia	COVID-19 severe pneumonia	Confirm
	24	No	Contributing diagnoses	Hospital acquired pneumonia	Hospital acquired pneumonia	Less certain
13	Unkown	No	COD	Hemorrhagic and semi recent ischemic cerebrovascular accident	Hemorrhagic and semi recent ischemic cerebrovascular accident	Confirm
	19	No	Contributing diagnoses	Depression with refusal of food and medical interventions	Depression with refusal of food and medical interventions	Confirm
				COVID-19—mild illness	COVID-19—mild illness	Confirm
					Bacterial pneumonia	New
14	Unkown	Yes	COD	COVID-19 pneumonia	COVID-19 pneumonia	Confirm
	22	No	Contributing diagnoses	Hospital acquired pneumonia		Dismiss
					Left- and right sides heart failure	New
15	12	No	COD	COVID-19 Pneumonia	COVID-19 Pneumonia	Confirm
	65	No	Contributing diagnoses	Post-anoxic encephalopathy after out-of-hospital cardiac arrest	Post-anoxic encephalopathy after out-of-hospital cardiac arrest	Confirm
				Hospital acquired pneumonia		Dismiss
Radiologivally confirmed COVID-19 patients						
16	Unkown	No	COD	Radiological COVID-19 severe pneumonia with negative SARS-CoV-2 PCR	Left-and right sided heart failure	Dismiss/New
	6	No	Contributing diagnoses	Pseudoaneurysma left femoral artery	Pseudoaneurysma left femoral artery	Confirm
17	1	No	COD	Radiological COVID-19 severe pneumonia with negative SARS CoV-2 PCR	Viral pneumonia	Less certain
	1	No	Contributing diagnoses		Left- and right sided heart failure	New
18	11	No	COD	Bacterial Pneumonia	Bacterial pneumonia	Confirm
	1	No	Contributing diagnoses	Left- and right sided heart failure	Left- and right sided heart failure	Confirm
				Radiological COVID-19 severe pneumonia with negative SARS CoV-2 PCR considered		Dismiss

Per patient, the COD is the first diagnosis given. Following diagnoses are contributing findings. eci: e causa ignota; MOF: multi-organ failure; COVID-19: corona viral disease 2019; ATN: acute tubules necrosis; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; PCR: polymerase chain reaction; COPD: chronic obstructive pulmonary diseases; DVT: deep venous thrombosis; AF: atrial fibrillation

Table 1: Premortem clinical cause of death and contributing diagnoses and postmortem MIA cause of death and contributing diagnosis per patient.

LONG-TERM SURVIVAL OF SARS-COV-2 ON SALMON AS A SOURCE FOR INTERNATIONAL TRANSMISSION

Dai M, Li H, Yan N, Huang J, Zhao L, Xu S, Wu J, Jiang S, Pan C, Liao M.. J Infect Dis. 2020 Nov 12:jiaa712. doi: 10.1093/infdis/jiaa712. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Veterinarians at South China Agricultural University in Guangzhou, China compared the titer of viable SARS-CoV-2 (TCID50/mL) detectable at various temperatures in untreated culture medium versus attached to salmon. They found untreated SARS-CoV-2 survived more than eight days at 4 and 25 degrees Celsius in culture medium while SARS-CoV-2 attached to salmon survived 8 and 2 days in culture medium, respectively (Figures A, B). Authors suggest that SARS-CoV-2 can survive on fish stored at cold temperatures and fish importation should be strictly monitored and inspected in order to reduce COVID-19 transmission.

FIGURES

Figure A

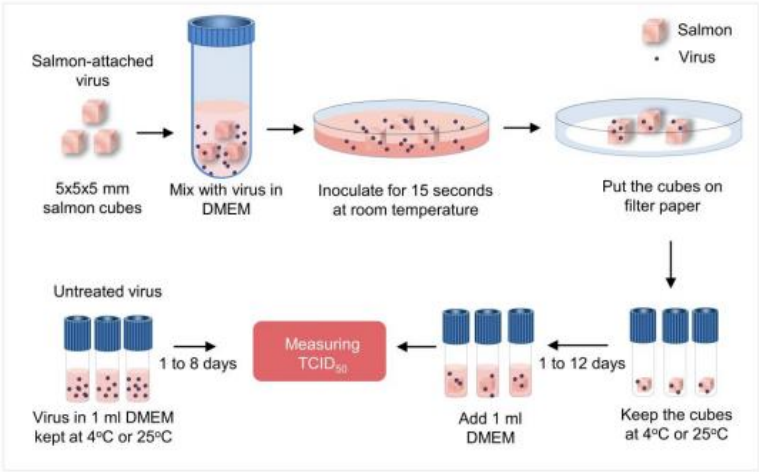
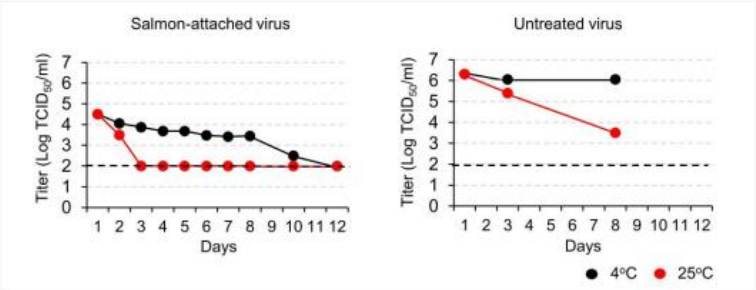


Figure B



'Figure A and B'. Viability of salmon-attached and untreated SARS-CoV-2 in culture medium at 4°C and 25°C. Panel A is the overview of the study design and experimental procedure. Briefly, the individual salmon cubes (5x5x5 mm) were mixed with 13 mL liquid of SARS-CoV-2 at 3.16x106 TCID50/mL by inverting 5 times, transferred into the 10 cm dishes, incubated for 15 seconds at room temperature , and then put on filter paper to remove excess virus liquid. After that, the salmon cubes were transferred to 1.5 mL freezing tubes and stored at 4°C and 25°C for later treatment. On day 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12, freezing tubes was taken out and 1 mL DMEM culture medium was added, oscillated for 5 seconds, and then centrifuged at 6,000 rpm for 5 minutes at 4°C. The liquid was used for virus titer detection.
On day 1, 3, and 8, the virus in culture medium kept at 4°C or 25°C was detected. In panel B, the titer of SARS-CoV-2 was quantified by end-point titration on Vero E6 cells and expressed as log10 TCID50/mL. Plots show the means of data from two or three samples. The dashed lines indicate the limit of detection, which were 102 TCID50 /mL

ASSESSMENT OF AIR AND SURFACES CONTAMINATION IN A COVID-19 NON-INTENSIVE CARE UNIT

Declementi M, Godono A, Mansour I, Milanesio N, Garzaro G, Clari M, Fedele L, Passini V, Bongiorno C, Pira E.. Med Lav. 2020 Oct 31;111(5):372-378. doi: 10.23749/mdl.v111i5.9991.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

A study conducted at University of Turin (Italy), sought to examine the amount of environmental contamination in a COVID-19 non-Intensive Care Unit (ICU) of a Trauma Center in Northern Italy before and after adoption of additional sanitation measures. On May 5th and May 6th 2020, samples were collected from the air and multiple surfaces (Table 1) for RT-PCR testing for SARS-CoV-2. All 24 samples collected were negative for SARS-CoV-2. While more samples should be collected for definitive conclusions, the results of this study indicate that typical hospital cleaning methods and air filtration are sufficient to remove significant levels of SARS-CoV-2 from the environment.

ABSTRACT

BACKGROUND: Severe Acute Respiratory Syndrome - Coronavirus - 2 (SARS-CoV-2) is a virus, primarily transmitted through droplets, able to persist on different surfaces and in the air for several hours. During the COVID-19 pandemic, Health Care Workers should be considered a high risk profession. Beside social distancing rules and the proper use of Personal Protective Equipment, sanitization measures and ventilation system disinfection are essential to reduce viral transmission. OBJECTIVES: This is the first Italian study aiming to assess the magnitude of environmental contamination in a COVID-19 non-Intensive Care Unit. METHODS: In addition to ordinary cleaning procedures, surface and air samplings have been performed before and after the application of two different sanitization devices. Samples have been analyzed with Real Time-Polymerase Chain Reaction in order to find viral RNA. RESULTS: All samples obtained from surfaces and air before and after extra-ordinary sanitization procedures turned out negative for viral detection. DISCUSSION: These findings highlight the efficiency of ordinary cleaning procedures in guaranteeing a safer workplace. The adoption of additional sanitization protocols should be considered in order to further reduce environmental viral contamination.

FIGURES

Patient 1 room surfaces	PPE	HVAC	Air pumps sites
Bed rail[a]	Surgical mask Patient 1[a]	Air Handling Units (AHU) filter of supply air duct.[b]	Patient 1 room[b]
Sheets and pillow[a]	Surgical mask Patient 2[a]	AHU filter nearby return air duct.[b]	Patient 2 room[b]
Floor within 1 m of bed[a]	Disposable Gown Patient 1[a]	Return air vents in Patient 1 room[b]	Empty room near patients rooms[b]
Wall within 1 m of bed[a]	Disposable Gown Patient 2[a]	Return air vents in Patient 2 room[b]	Corridor outside the rooms[b]

(a): sites treated with a hot disinfection system based on a solution with high alcohol concentration and quaternary ammonium salts;
(b): sites treated with hydrogen peroxide atomizer.
PPE: Personal Protective Equipment;
HVAC: Heat,Ventilation and Air Conditioning.

Table 1 - Surface and air sampling sites inside the COVID-19 Unit.

CRITICAL CARE

PRONE POSITIONING IN MECHANICALLY VENTILATED PATIENTS WITH SEVERE ACUTE RESPIRATORY DISTRESS SYNDROME AND CORONAVIRUS DISEASE 2019

Gleissman H, Forsgren A, Andersson E, Lindqvist E, Lipka Falck A, Cronhjort M, Dahlberg M, Günther M.. Acta Anaesthesiol Scand. 2020 Nov 9. doi: 10.1111/aas.13741. Online ahead of print.

Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

BLUF

A case series conducted in Sweden assessed mechanically-ventilated COVID-19 patients (n=44) with severe acute respiratory distress syndrome (ARDS, as defined by a PaO2:FiO2 ratio of <150 mm Hg, with a FiO2 of >0.6) who were treated with prone positioning from March 17, 2020 - May 19, 2020. Findings show that placing patients in the prone position consistently increased PaO2: FiO2 ratio in patients whose initial ratios were <120 mmHg (Figure 1, 2), suggesting the possible benefits of this technique, although they highlight the need for further studies to evaluate whether proning is a viable method to decrease COVID-19 ARDS mortality.

ABSTRACT

BACKGROUND: The management of COVID-19 ARDS is debated. Although current evidence does not suggest an atypical ARDS, the physiological response to prone positioning is not fully understood and it is unclear which patients benefit. We aimed to determine whether proning increases oxygenation and to evaluate responders. METHODS: This case series from a single, tertiary university hospital includes all mechanically ventilated patients with COVID-19 and proning between March 17, 2020 and May 19, 2020. The primary measure was change in PaO2 :FiO2 . RESULTS: 44 patients, 32 males/12 females, were treated with proning for a total of 138 sessions, with median (range) 2 (1-8) sessions. Median (IQR) time for the five sessions was 14 (12-17) hours. In the first session, median (IQR) PaO2 :FiO2 increased from 104 (86-122) to 161 (127-207) mm Hg (p<0.001). 36 out of 44 patients (82%) improved in PaO2 :FiO2 , with a significant increase in PaO2 :FiO2 in the first three sessions. Median (IQR) FiO2 decreased from 0.7 (0.6-0.8) to 0.5 (0.35-0.6) (<0.001). A significant decrease occurred in the first three sessions. PaO2 , tidal volumes, PEEP, mean arterial pressure and norepinephrine infusion did not differ. Primarily, patients with PaO2 :FiO2 approximately <120 mm Hg before treatment responded to proning. Age, sex, BMI, or SAPS 3 did not predict success in increasing PaO2 :FiO2 . CONCLUSION: Proning increased PaO2 :FiO2 , primarily in patients with PaO2 :FiO2 approximately < 120 mmHg, with a consistency over three sessions. No characteristic was associated with non-responding, why proning may be considered in most patients. Further study is required to evaluate mortality.

FIGURES

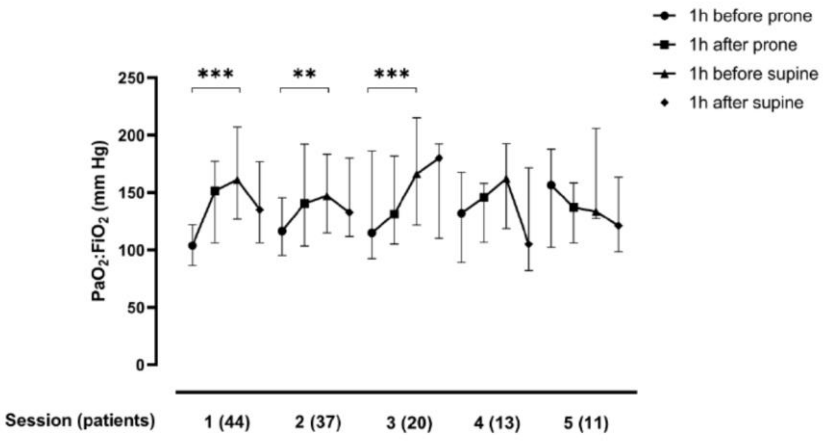


Figure 1: PaO2:FiO2 during five consecutive prone positioning sessions. Displayed as medians with IQR. ***p<0.001, **p<0.005.

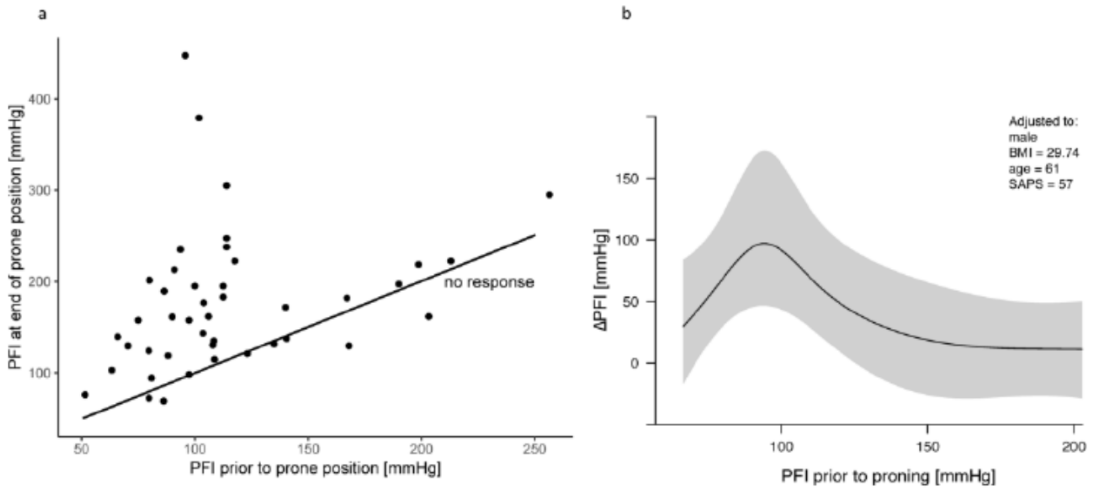


Figure 2: (a) PaO2:FiO2 (PFI) at the end of the first proning session as a function of the initial PaO2:FiO2. The line of no response is shown in grey. (b) The predicted effect of initial PaO2:FiO2 (PFI) on the change in PaO2:FiO2 from the ordinal regression model, taken at the median values of the other covariables.

OBGYN

SARS-COV-2 IN FIRST TRIMESTER PREGNANCY: A COHORT STUDY

la Cour Freiesleben N, Egerup P, Vauvert Römmelmayer Hviid K, Rosenbek Severinsen E, Kolte AM, Westergaard D, Fich Olsen L, Prætorius L, Zedeler A, Hellerung Christiansen AM, Reinhardt Nielsen J, Bang D, Berntsen S, Ollé-López J, Ingham A, Bello-Rodríguez J, Marie Storm D, Ethelberg-Findsen J, Hoffmann ER, Wilken-Jensen C, Stener Jørgensen F, Westh H, Løvendahl Jørgensen H, Nielsen HS.. Hum Reprod. 2020 Nov 4:deaa311. doi: 10.1093/humrep/deaa311. Online ahead of print.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A cohort study, conducted at Copenhagen University Hospital (Denmark), examined potential risk caused by SARS-CoV-2 infection for first trimester pregnancies by analyzing double tests (blood samples for pregnancy-associated plasma protein A (PAPP-A) and free beta human chorionic gonadotropin (β-hCG)) of 1,019 pregnant women between February 17th and April 23, 2020 for SARS-CoV-2 antibodies. Results indicated SARS-CoV-2 infection early in pregnancy as 18 (1.8%) of the 1,019 pregnant women were positive for SARS-CoV-2 antibodies in their serum. However, there was not a significant correlation with nuchal translucency thickness nor increased risk of pregnancy loss between the women testing positive versus those testing negative for SARS-CoV-2 antibodies (Table II, III). While these results may be limited by sample size, population type, and severity of COVID-19 infection, this study demonstrates no increased risk of low-severity COVID-19 infections during the first trimester of pregnancy.

SUMMARY

Additionally, the researchers also investigated 36 women who experienced first trimester pregnancy loss before the double test were performed. None of these 36 women had SARS-CoV-2 antibodies in their serum.

ABSTRACT

STUDY QUESTION: Does maternal infection with SARS-CoV-2 in first trimester pregnancy have an impact on the fetal development as measured by nuchal translucency thickness and pregnancy loss? SUMMARY ANSWER: Nuchal translucency thickness at the first trimester scan was not significantly different in pregnant women with versus without SARS-CoV-2 infection in early pregnancy and there was no significant increased risk of pregnancy loss in women with SARS-CoV-2 infection in the first trimester. WHAT IS KNOWN ALREADY: Pregnant women are more vulnerable to viral infections. Previous coronavirus epidemics have been associated with increased maternal morbidity, mortality and adverse obstetric outcomes. Currently, no evidence exists regarding possible effects of SARS-CoV-2 in first trimester pregnancies. STUDY DESIGN, SIZE, DURATION: Cohort study of 1,019 women with a double test taken between Feb. 17 and Apr. 23, 2020, as a part of the

combined first trimester risk assessment, and 36 women with a first trimester pregnancy loss between Apr. 14 and May 21, 2020, prior to the double test. The study period was during the first SARS-CoV-2 epidemic wave in Denmark. PARTICIPANTS/MATERIALS, SETTING, METHODS: Cohort 1 included pregnant women with a double test taken within the study period. The excess serum from each double test was analyzed for SARS-CoV-2 antibodies. Results were correlated to the nuchal translucency thickness and the number of pregnancy losses before or at the time of the first trimester scan. Cohort 2 included women with a pregnancy loss before the gestational age for double test sample. Serum from a blood test taken the day the pregnancy loss was identified was analyzed for SARS-CoV-2 antibodies. The study was conducted at a public university hospital serving approximately 12% of pregnant women and births in Denmark. All participants in the study provided written informed consent. MAIN RESULTS AND THE ROLE OF CHANCE: Eighteen (1.8%) women had SARS-CoV-2 antibodies in the serum from the double test suggestive of SARS-CoV-2 infection in early pregnancy. There was no significant difference in nuchal translucency thickness for women testing positive for previous SARS-CoV-2 infection (n = 18) versus negative (n = 994) (p = 0.62). There was no significant increased risk of pregnancy loss for women with positive antibodies (n = 1) (OR 3.4, 0.08-24.3 95% CI, p = 0.27). None of the women had been hospitalized due to SARS-CoV-2 infection. None of the women with pregnancy loss prior to the double test (Cohort 2) had SARS-CoV-2 antibodies. LIMITATIONS, REASONS FOR CAUTION: These results may only apply to similar populations and to patients who do not require hospitalization due to SARS-CoV-2 infection. A limitation of the study is that only 1.8% of the study population had SARS-CoV-2 antibodies suggestive of previous infection. WIDER IMPLICATION OF THE FINDINGS: Maternal SARS-CoV-2 infection had no effect on the nuchal translucency thickness and there was no significant increased risk of pregnancy loss for women with SARS-CoV-2 infection in first trimester pregnancy. Evidence concerning Covid-19 in pregnancy is still limited. These data indicate that infection with SARS-CoV-2 in not hospitalized women does not pose a significant threat in first trimester pregnancies. Follow up studies are needed to establish any risk to a fetus exposed to maternal SARS-CoV-2 infection. STUDY FUNDING/COMPETING INTEREST(S): Prof. Henriette Svarre Nielsen (HSN) and colleagues received a grant from the Danish Government for research of Covid-19 among pregnant women. The Danish government was not involved in the study design, data collection, analysis, interpretation of data, writing of the report or decision to submit the paper for publication. AI, JOL, JBR, DMS, JEF, and ERH received funding from a Novo Nordisk Foundation (NNF) Young Investigator Grant (NNF15OC0016662) and a Danish National Science Foundation Center Grant (6110-00344B). AI received a Novo Scholarship. JOL is funded by an NNF Pregraduate Fellowship (NNF19OC0058982). DW is funded by the NNF (NNF18SA0034956, NNF14CC0001, NNF17OC0027594). AMK is funded by a grant from the Rigshospitalet's research fund. Henriette Svarre Nielsen has received speakers fees from Ferring Pharmaceuticals, Merck Denmark A/S and Ibsa Nordic (outside the submitted work). Nina la Cour Freiesleben has received a grant from Gedeon Richter (outside the submitted work). Astrid Marie Kolte has received speakers from Merck (outside the submitted work). The other authors did not report any potential conflicts of interest.

FIGURES

	Negative (n = 994)	**Positive** (n = 18)	***p*-value** *Positive versus negative*
Nuchal translucency thickness (mm), *median (quartiles)*	1.7 (1.5-2.0)	1.8 (1.5-2.0)	0.62
Free β-hCG (IU/L), *median (quartiles)*	51.9 (32.9-80.0)	53.8 (22.1-86.8)	0.63
Free β-hCG (MoM), *median (quartiles)*	1.0 (0.7-1.5)	1.1 (0.7-1.6)	0.81
PAPP-A (IU/L), *median (quartiles)*	1.7 (1.1-2.9)	1.3 (0.8-3.5)	0.64
PAPP-A (MoM), *median (quartiles)*	1.1 (0.8-1.7)	1.0 (0.6-1.5)	0.30

Information on nuchal translucency thickness was available for 982 of the included women and information on free β-hCG and PAPP-A for 1,012. MoM values were available for 978 of the included women.

Table II. Primary outcomes for cohort 1 according to SARS-CoV-2 antibody status. Cohort 1 was included after the double test.

	Cohort 1		Cohort 2	
	Negative (n = 1000)	Positive (n = 18)	Negative (n = 36)	Positive (n = 0)
Ongoing pregnancy, *n*	983	17	0	0
Pregnancy loss, *n*	17	1	36	0

One woman with a negative test result was lost to follow up after double test.

Table III. Pregnancy status after the first trimester according to SARS-CoV-2 antibody status in the double test. The table includes both Cohort 1 and 2.

THE IMPACT OF EXTREME REUSE AND EXTENDED WEAR CONDITIONS ON PROTECTION PROVIDED BY A SURGICAL-STYLE N95 FILTERING FACEPIECE RESPIRATOR

Duncan S, Bodurtha P, Bourgeois C, Dickson E, Jensen C, Naqvi S.. J Occup Environ Hyg. 2020 Nov 9:1-14. doi: 10.1080/15459624.2020.1829633. Online ahead of print.
Level of Evidence: 4 - Guidelines and Recommendations

BLUF

An efficacy analysis conducted by Suffield Research Centre in Alberta, Canada measured inward leakage of aerosol and physical defects of N95 respirator masks and found general respirator protection factor (GRPF) values dropped during a 5 day period with repeated active and passive workplace usage (up to 19 uses; n=7 participants), but remained above the assigned protection factor (APF) threshold of 10 (Figure 1). Authors acknowledge this study lacks generalizability towards other facepiece respirators but suggest N95 masks may be able to maintain protection under extreme usage conditions and hope these data can inform institutions with PPE shortages.

ABSTRACT

Most respirators employed in health care settings, and often in first responder and industrial settings, are intended for single-use: the user dons the respirator, performs a work activity, and then doffs and discards the respirator. However, in the current COVID-19 pandemic, in the presence of persistent shortages of personal protective equipment, extended use and reuse of filtering facepiece respirators are routinely contemplated by many health care organizations. Further, there is considerable current effort to understand the effect of sterilization on the possibility of reuse, and some investigations of performance have been conducted. While the ability of such a respirator to continue to provide effective protection after repeated sanitization cycles is a critical component of implementing its reuse, of equal importance is an understanding of the impact that reusing the respirator multiple times in a day while performing work tasks, and even extending its wear over multiple days, has on the workplace protective performance. In this study, we subjected a stockpiled quantitatively fitted surgical style N95 filtering facepiece respirator device to extreme reuse and extended wear conditions (up to 19 uses over a duration of 5 days) and measured its protective performance at regular intervals, including simulated workplace protection factor measurements using total inward leakage. With this respirator, it was shown to be possible to maintain protection corresponding to an assigned protection factor greater than 10 under extreme usage conditions provided an individual is properly trained in the use of, and expertly fitted in, the respirator. Other factors such as hygiene and strap breakage are likely to place limits on reuse.

FIGURES

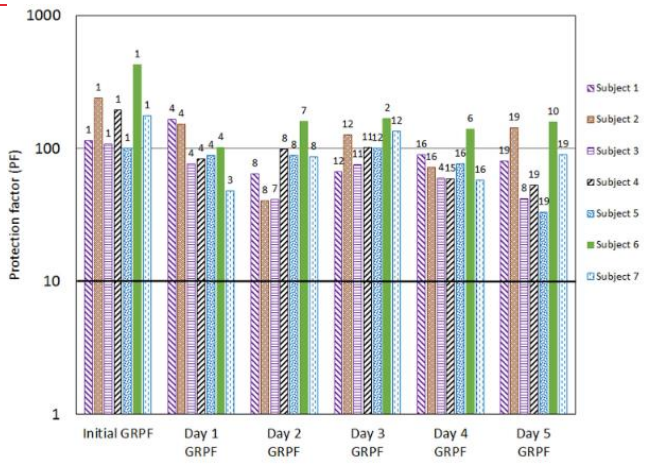


Figure 1. Results of daily measurements of GRPF for each reuse subject. The values above the bars are the total number of FFR wears at the time of the measurement. Subjects 3 and 6 were issued a second, replacement FFR on Day 4 and Day 3, respectively, due to strap failure.

COVID-19 UNFOLDING FILARIASIS: THE FIRST CASE OF SARS-COV-2 AND WUCHERERIA BANCROFTI COINFECTION

Mohamed MFH, Mohamed SF, Yousaf Z, Kohla S, Howady F, Imam Y.. PLoS Negl Trop Dis. 2020 Nov 9;14(11):e0008853. doi: 10.1371/journal.pntd.0008853. eCollection 2020 Nov.
Level of Evidence: Other - Case Report

BLUF

Internists at Hamad Medical Corporation in Qatar present this case of a 37 year-old COVID-19 positive male whose blood smear revealed incidental infection with Wuscheria bancrofti (Figure 1), with subsequent diagnosis of asymptomatic filariasis (see summary). Authors believe this is the first reported case of COVID-19 with incidental discovery of filariasis and recommend that healthcare providers worldwide keep a broad differential diagnosis in patients infected with SARS-CoV-2, particularly those with atypical symptoms or in endemic areas of infectious organisms.

SUMMARY

The 37 year-old Asian male with history of diabetes mellitus and hypertension presented with 10-day history of fever, dyspnea, sore throat, cough, nausea, vomiting, and diarrhea. Physical exam revealed bilateral crackles at the lung bases and chest x-ray revealed bilateral hazy lung infiltrates. The patient then tested positive for SARS-CoV-2 via RT-PCR and was started on hydroxychloroquine and azithromycin upon admission. On hospital day 5, blood smear revealed incidental infection with W. bancrofti (Figure 1) but no associated symptoms. He was administered a single 400-mg dose of diethylcarbamazine and a 6-week oral course of 100-mg doxycycline BID. The patient made a full recovery and had no residual symptoms 3 months following discharge.

ABSTRACT

With the evolution of the Coronavirus Disease 2019 (COVID-19) pandemic, the number of patients brought to medical attention has increased. This has led to the unmasking of many coexisting occult infections and comorbidities such as tuberculosis, dengue, human immunodeficiency viral infection, diabetes, and hypertension. We report the first case of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, unveiling the diagnosis of asymptomatic filariasis. A 37-year-old gentleman presented with shortness of breath, fever, and cough. He was found to have COVID-19 pneumonia. During his stay, microfilaria of Wuchereria bancrofti was detected incidentally on a blood smear exam. Consequently, the patient received appropriate treatment for both conditions. In order not to miss relevant concomitant diagnoses, it is prudent to keep a broad differential diagnosis when faced with SARS-CoV-2-infected patients; this is especially true when atypical symptoms are present or in areas endemic with other infections.

FIGURES

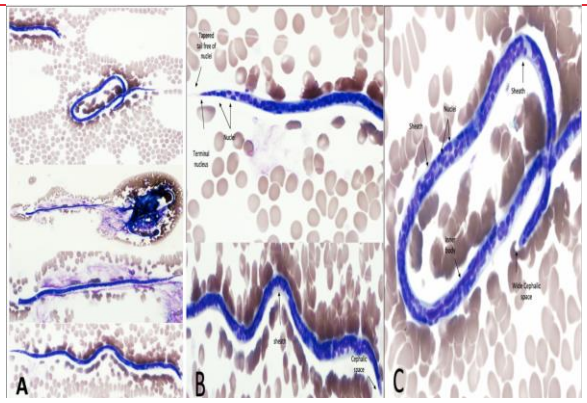


Fig 1. Microphotographs of Wuchereria bancrofti microfilaria in a peripheral blood smear.

Thin blood film Giemsa stain, 100×. (A) Full-size microfilaria × 10 (B) head, body, and tail details. (C) Body and tail details.

VERSATILE AND MULTIVALENT NANOBODIES EFFICIENTLY NEUTRALIZE SARS-COV-2

Xiang Y, Nambulli S, Xiao Z, Liu H, Sang Z, Duprex WP, Schneidman-Duhovny D, Zhang C, Shi Y.. Science. 2020 Nov 5:eabe4747. doi: 10.1126/science.abe4747. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

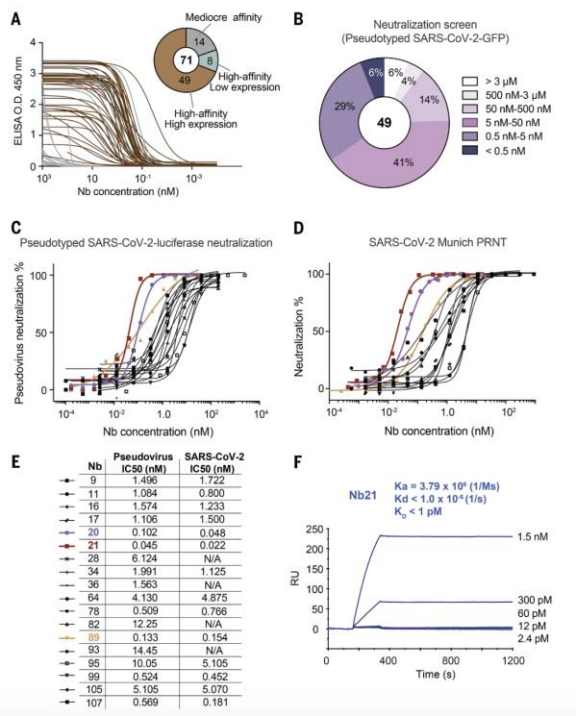
BLUF

Cell biologists and vaccine researchers affiliated with University of Pittsburgh, Pennsylvania identified neutralizing multivalent camelid nanobodies (Nbs; Figure 1) which target the receptor-binding domain (RBD) on SARS-CoV-2 S1 spike glycoprotein and found these single-chain Nbs had the ability to bind the RBD with a high affinity and potency (Figure 3), which blocks SARS-CoV-2 fusion to host cells. Authors suggest these Nbs have potential to be effective COVID-19 therapy (Figure 5) but acknowledge a need for further research to determine their efficacy in humans.

ABSTRACT

Cost-effective, efficacious therapeutics are urgently needed against the COVID-19 pandemic. Here, we used camelid immunization and proteomics to identify a large repertoire of highly potent neutralizing nanobodies (Nbs) to the SARS-CoV-2 spike (S) protein receptor-binding domain (RBD). We discovered Nbs with picomolar to femtomolar affinities that inhibit viral infection at sub-ng/ml concentration and determined a structure of one of the most potent in complex with RBD. Structural proteomics and integrative modeling revealed multiple distinct and non-overlapping epitopes and indicated an array of potential neutralization mechanisms. We constructed multivalent Nb constructs that achieved ultrahigh neutralization potency (IC50s as low as 0.058 ng/ml) and may prevent mutational escape. These thermostable Nbs can be rapidly produced in bulk from microbes and resist lyophilization, and aerosolization.

FIGURES



Nb	Pseudovirus IC50 (nM)	SARS-CoV-2 IC50 (nM)
9	1.496	1.722
11	1.084	0.800
16	1.574	1.233
17	1.106	1.500
20	0.102	0.048
21	0.045	0.022
28	6.124	N/A
34	1.991	1.125
36	1.563	N/A
64	4.130	4.875
78	0.509	0.766
82	12.25	N/A
89	0.133	0.154
93	14.45	N/A
95	10.05	5.105
99	0.524	0.452
105	5.105	5.070
107	0.569	0.181

Figure 1. Production and characterizations of high-affinity RBD Nbs for SARS-CoV-2 neutralization. (A) The binding affinities of 71 Nbs toward RBD by ELISA. The pie chart shows the number of Nbs according to affinity and solubility. (B) Screening of 49 high-affinity Nbs with high-expression level by SARS-CoV-2-GFP pseudovirus neutralization assay. n = 1 for Nbs with neutralization potency IC50 <= 50 nM, n = 2 for Nbs with neutralization potency IC50 > 50 nM. (C) The neutralization potency

of 18 highly potent Nbs was calculated based on the pseudotyped SARS-CoV-2 neutralization assay (luciferase). Purple, red, and yellow lines denote Nbs 20, 21, and 89 with IC50 < 0.2 nM. Two different purifications of the pseudovirus were used. The average neutralization percentage was shown for each data point (n = 5 for Nbs 20, 21; n = 2 for all other Nbs). (D) The neutralization potency of 14 neutralizing Nbs by SARS-CoV-2 plaque reduction neutralization test (PRNT). The average neutralization percentage was shown for each data point (n = 4 for Nbs 20, 21, and 89; n = 2 for other Nbs). (E) A table summary of pseudovirus and SARS-CoV-2 neutralization potencies of 18 Nbs. N/A: not tested. (F) The SPR binding kinetics measurement of Nb21.

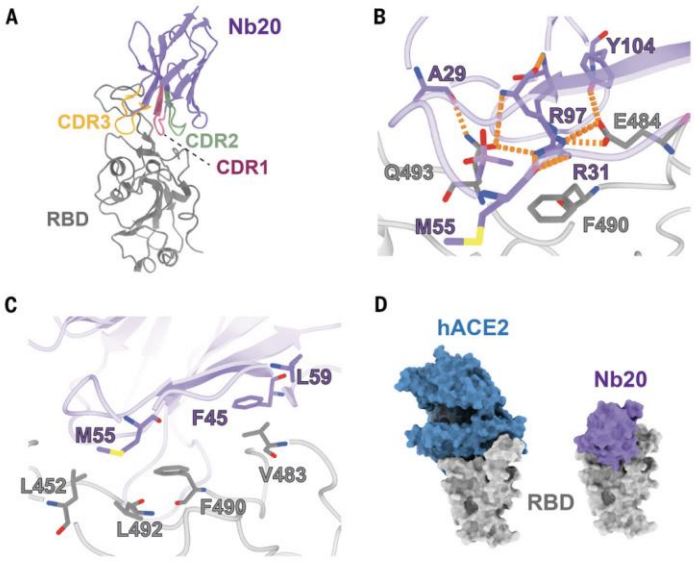
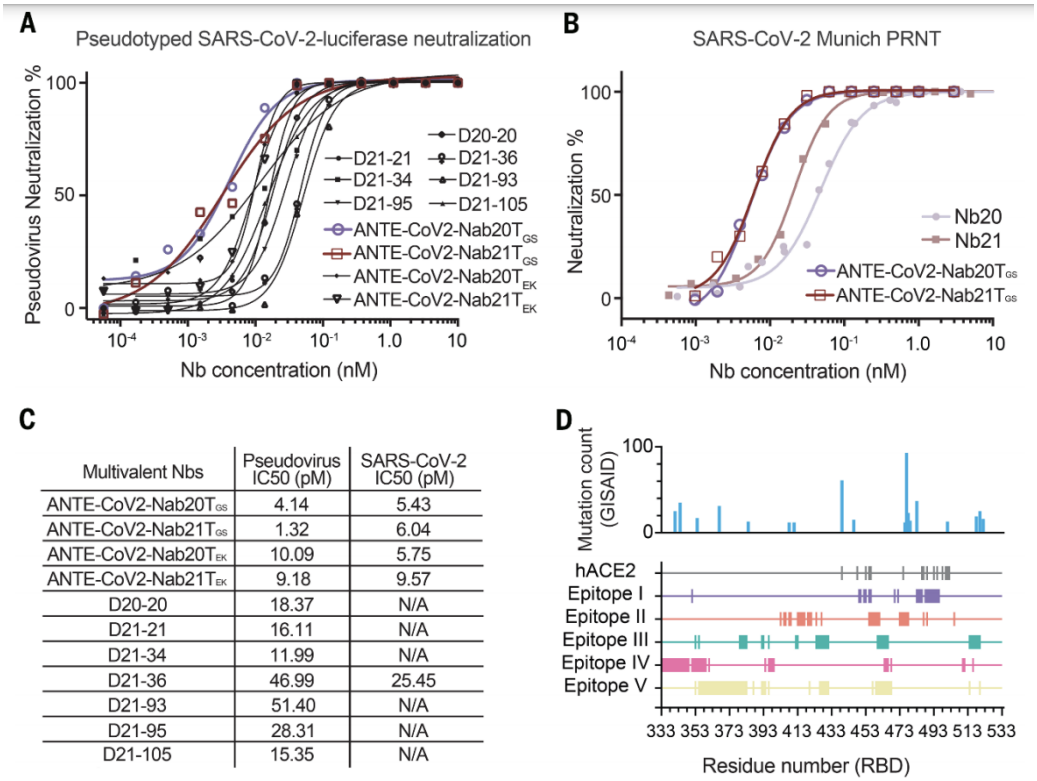


Figure 3. Crystal structure analysis of an ultrahigh affinity Nb in complex with the RBD. (A) Cartoon presentation of Nb20 in complex with the RBD. CDR1, 2, and 3 are in red, green, and orange, respectively. (B) Zoomed-in view of an extensive polar interaction network that centers on R35 of Nb20. (C) Zoomed-in view of hydrophobic interactions. (D) Surface presentation of the Nb20-RBD and hACE2-RBD complex (PDB: 6M0J).



Multivalent Nbs	Pseudovirus IC50 (pM)	SARS-CoV-2 IC50 (pM)
ANTE-CoV2-Nab20TGS	4.14	5.43
ANTE-CoV2-Nab21TGS	1.32	6.04
ANTE-CoV2-Nab20TEK	10.09	5.75
ANTE-CoV2-Nab21TEK	9.18	9.57
D20-20	18.37	N/A
D21-21	16.11	N/A
D21-34	11.99	N/A
D21-36	46.99	25.45
D21-93	51.40	N/A
D21-95	28.31	N/A
D21-105	15.35	N/A

Figure 5. Development of multivalent Nb cocktails for highly efficient SARS-CoV-2 neutralization. (A) Pseudotyped SARS-CoV-2 neutralization assay of multivalent Nbs. The average neutralization percentage of each data point was shown (n = 2). ANTE-CoV2-Nab20TGS/EK: homo-trimeric Nb20 with the GS/EK linker; ANTE-CoV2-Nab21TGS/EK: homo-trimeric Nb21 with the GS/EK linker. (B) SARS-CoV-2 PRNT of monomeric and trimeric forms of Nbs 20 and 21. The average neutralization percentage of each data point was shown (n = 2 for the trimers, n = 4 for the monomers). (C) A summary table of the neutralization potency measurements of the multivalent Nbs. N/A: not tested. (D) Mapping mutations to localization of Nb epitopes on the RBD. The x-axis corresponds to the RBD residue numbers (333 to 533). Rows in different colors represent different epitope residues. Epitope I: 351, 449-450, 452-453, 455-456, 470, 472, 483-486, 488-496; Epitope II: 403, 405-406, 408,409, 413-417, 419-421, 424, 427, 455-461, 473-478, 487, 489, 505; Epitope III: 53, 355, 379-383, 392-393, 396,412-413, 424-431, 460-466, 514-520; Epitope IV: 333-349, 351-359, 361, 394, 396-399, 464-466, 468, 510-511, 516; Epitope V: 353, 355-383, 387, 392-394, 396, 420, 426-431, 457,459-468, 514, 520.

PURCHASING, CONSUMPTION, DEMOGRAPHIC AND SOCIOECONOMIC VARIABLES ASSOCIATED WITH SHIFTS IN ALCOHOL CONSUMPTION DURING THE COVID-19 PANDEMIC

Callinan S, Mojica-Perez Y, Wright CJC, Livingston M, Kuntsche S, Laslett AM, Room R, Kuntsche E.. Drug Alcohol Rev. 2020 Nov 10. doi: 10.1111/dar.13200. Online ahead of print.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

A cross-sectional study sampling 2,307 adults in Australia reported that overall alcohol consumption decreased during the COVID-19 pandemic among individuals who normally drank outside their homes and increased among individuals experiencing increased stress (primarily work and school disruptions) or were of the younger age group (Figure 1, 2). The authors recommend assessing the long-term effects of alcohol consumption after the COVID-19 pandemic.

ABSTRACT

INTRODUCTION AND AIMS: Restrictions introduced to reduce the spread of COVID-19 have had major impacts on the living circumstances of Australians. This paper aims to provide insight into shifts in alcohol consumption and associated factors during the epidemic. DESIGN AND METHODS: A cross-sectional convenience sample of 2307 Australians aged 18 and over who drank at least monthly was recruited through social media. Respondents were asked about their alcohol consumption and purchasing in 2019 prior to the epidemic plus similar questions about their experiences in the month prior to being surveyed between 29 April and 16 May 2020. RESULTS: Reports of average consumption before (3.53 drinks per day [3.36, 3.71 95% confidence interval]) and during (3.52 [3.34, 3.69]) the pandemic were stable. However, young men and those who drank more outside the home in 2019 reported decreased consumption during the pandemic, and people with high levels of stress and those who bulk-bought alcohol when restrictions were announced reported an increase in consumption relative to those who did not. DISCUSSION AND CONCLUSIONS: A reported increase in consumption among those experiencing more stress suggests that some people may have been drinking to cope during the epidemic. Conversely, the reported decrease in consumption among those who drank more outside of their home in 2019 suggests that closing all on-trade sales did not result in complete substitution of on-premise drinking with home drinking in this group. Monitoring of relevant subgroups to assess long-term changes in consumption in the aftermath of the epidemic is recommended.

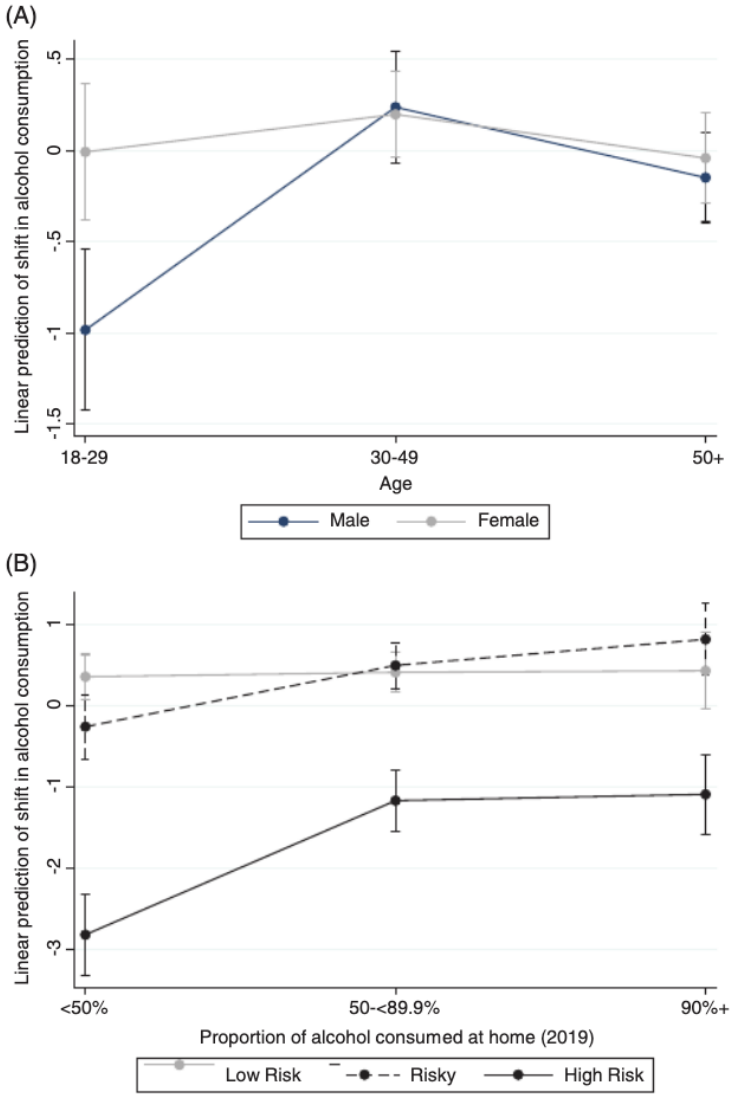


Figure 2. *Estimated marginal means of shifts in consumption by (a) age and sex and by (b) 2019 home drinking categories and 2019 risk categories.*

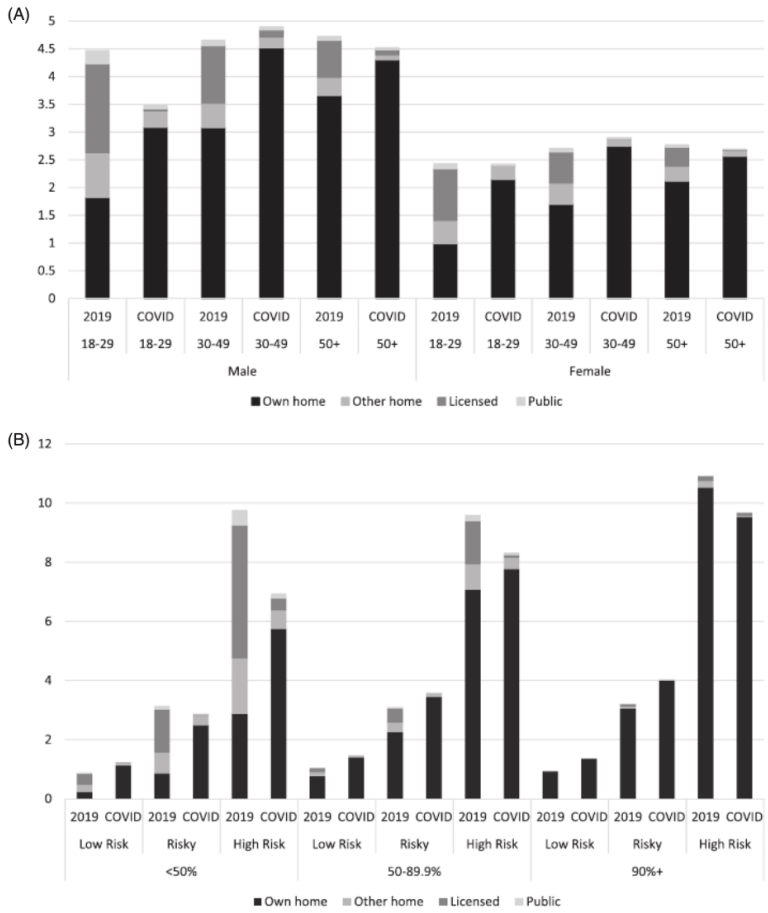


Figure 1. *Mean drinks per day per location in 2019 and during COVID-19 lockdown by (a) age and sex and (b) proportion of alcohol consumed in the home in 2019 and risk category in 2019.*

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