The Daily COVID-19 Literature Surveillance Summary

September 30, 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

- Age-specific COVID-19 case-fatality rates show no evidence of changes over time. Members of the University Vita-Salute San Raffaele School of Medicine in Milan, Italy looked at national-level COVID-19 surveillance data in Italy and found that case fatality rates were 3% in people younger than 60 years compared to 30% in people over 80 years old. This is consistent with higher rates of chronic comorbidities in older populations. These fatality rates remaining consistent over 4 months of monitoring suggests that COVID-19 mortality has not improved or worsened, and younger age groups tend to have less severe COVID-19 outcomes.

Adjusting Practice During COVID-19

- Ocular findings in COVID-19 patients with severe systemic disease, including conjunctival congestion, epiphora, and chemosis, appeared to be common in a review by an ophthalmologist from the Department of Ophthalmology, John Hopkins University School of Medicine. Citing a study of 276 patients admitted to the hospital with COVID-19 in Hubei, China reporting that their eyeglass usage was lower than the general population, the ophthalmologist hypothesizes the possibility of ocular transmission of SARS-CoV-2 and encourages use of personal protective equipment (face shield, goggles, eyeglasses) to prevent ocular transmission during this pandemic.

R&D: Diagnosis & Treatments

- A web visualization tool using T cell subsets as the predictor to evaluate COVID-19 patient's severity: A study conducted at the Wuhan Pulmonary Hospital analyzing COVID-19 positive patients (n=340) found T-cell subsets analyzed upon initial diagnosis (Total T-cells, Helper T-cells [TH], Suppressor T-cells [TSC], and TH/TSC) differed significantly in patients that were discharged (n=310) compared to death cases (n=30); while age, underlying disease status, Helper T-cell count, and TH/TSC ratio were significant predictors of either death or discharge, but a well-functioning immune system at time of hospitalization indicated a higher chance of recovery. These findings suggest T-cell subset monitoring may be useful to detect changes in condition and predict prognosis of patients with COVID-19.

- Targeting the endolysosomal host-SARS-CoV-2 interface by clinically licensed functional inhibitors of acid sphingomyelinase (FIASMA) including the antidepressant fluoxetine showed that fluoxetine successfully inhibits the entry/propagation of SARS-CoV-2 in cell culture without cytotoxic effects. It also exhibits antiviral activity against two subtypes of Influenza A virus via a mechanism that impairs endolysosomal acidification and leads to accumulation of cholesterol in endosomes. Similar effects were also observed with amiodarone and imipramine, two other FIASMA drugs. These findings suggest endolysosomal lipid balance as a potential efficacious FIASMA drug target of the host-virus interface for SARS-CoV-2 and other enveloped viruses.

TABLE OF CONTENTS

DISCLAIMER **2**

NOW LIVE! 2

LEVEL OF EVIDENCE **3**

EXECUTIVE SUMMARY **4**

TABLE OF CONTENTS **5**

EPIDEMIOLOGY **6**

SYMPTOMS AND CLINICAL PRESENTATION 6

Age-specific COVID-19 case-fatality rate: no evidence of changes over time 6

UNDERSTANDING THE PATHOLOGY **7**

IN VITRO 7

Liquid-based cytological and immunohistochemical study of nasopharyngeal swab from persons under investigation for SARS-CoV-2 infection 7

MANAGEMENT **9**

Oral favipiravir for patients with delayed SARS-CoV-2 viral RNA clearance: a case series 9

ADJUSTING PRACTICE DURING COVID-19 ..... **10**

OPHTHALMOLOGY 10

Ophthalmology and COVID-19 10

R&D: DIAGNOSIS & TREATMENTS **11**

DEVELOPMENTS IN DIAGNOSTICS 11

A web visualization tool using T cell subsets as the predictor to evaluate COVID-19 patient's severity 11

Future developments in biosensors for field-ready SARS-CoV-2 virus diagnostics 13

DEVELOPMENTS IN TREATMENTS 14

Targeting the endolysosomal host-SARS-CoV-2 interface by clinically licensed functional inhibitors of acid sphingomyelinase (FIASMA) including the antidepressant fluoxetine 14

ACKNOWLEDGEMENTS **17**

AGE-SPECIFIC COVID-19 CASE-FATALITY RATE: NO EVIDENCE OF CHANGES OVER TIME

Signorelli C, Odone A.. Int J Public Health. 2020 Sep 25. doi: 10.1007/s00038-020-01486-0. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A letter to the editor conducted by members of the University Vita-Salute San Raffaele School of Medicine in Milan, Italy regarding national-level COVID-19 surveillance data in Italy from April 16 - August 18th, 2020 found that case fatality rates were 3% in people younger than 60 years compared to 30% in people over 80 years old (Table 1); this is consistent with higher rates of chronic comorbidities in older populations. These fatality rates staying consistent over 4 months of monitoring suggests that COVID-19 mortality has not improved/worsened, and younger age groups tend to have less severe COVID-19 outcomes.

FIGURES

Table 1 COVID-19 cumulative deaths and case-fatality rates (CFRs) per age group at three different time points (Italy 2020)

	By April 16th			By June 16 th			By August 18th		
Age group	Deaths (*n*)	CFR (%)	Cases (*n*)	Deaths (*n*)	CFR (%)	Cases (*n*)	Deaths (*n*)	CFR (%)	Cases (*n*)
0-19	1	0.0	2.927	4	0.1	5.843	4	0.1	8.516
20-29	7	0.1	7.737	15	0.1	13.673	16	0.1	16.757
30-39	40	0.3	11.686	65	0.3	18.755	67	0.3	21.293
40-49	178	0.9	20.519	286	0.9	31.057	313	0.9	33.462
50-59	756	2.5	29.858	1.159	2.7	42.704	1.241	2.8	44.775
60-69	2.284	9.5	24.040	3.367	10.6	31.777	3.592	10.9	33.097
70-79	6.203	24.1	25.717	8.830	26.0	33.916	9.335	26.7	34.925
≥ 80	10.525	28.8	36.519	19.483	32.3	60.317	21.275	34.6	61.436
Total	**19.996**	**12.6**	**159.107**	**33.209**	**13.9**	**238.082**	**35.843**	**14.1**	**254.283**

Table 1 COVID-19 cumulative deaths and case-fatality rates (CFRs) per age group at three different time points (Italy 2020)

LIQUID-BASED CYTOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY OF NASOPHARYNGEAL SWAB FROM PERSONS UNDER INVESTIGATION FOR SARS-COV-2 INFECTION

Parada D D, Peña KB, Gumá J, Guilarte C, Riu F.. Histopathology. 2020 Sep 24. doi: 10.1111/his.14257. Online ahead of print.
Level of Evidence: 4 - Case-control studies, or "poor or non-independent reference standard

BLUF

A cohort study conducted by pathologists at Hospital Universitari de Sant Joan in Spain between April 1, 2020 and July 30, 2020 found cytology from nasopharyngeal swabs of patients being investigated for SARS-CoV-2 (n=100) showed no viral inclusions or cytopathic effects in squamous cells (Figure 1), while immunohistochemical study was positive for anti-SARS-CoV-2 nucleoprotein antibody in squamous cells in both positive and presumptive positive cases (Table 2, Figure 4; see summary). The results indicate predominant localization of SARS-CoV-2 in nasopharyngeal squamous cells initially, with subsequent spread to lower airways.

SUMMARY

This prospective and descriptive cohort study of 100 consecutive nasopharyngeal swab samples from 54 male and 46 female patients who were investigated for SARS-CoV-2 via RT-PCR (including 40 negative, 33 positive, 27 presumptive positive) revealed the following cytological and immunohistochemical findings from Universal Transport Medium (UTM):
- Liquid-based cytology showed squamous cells with no virus inclusions or cytopathic effects (i.e. hyperchromatic nucleus or multinucleation).
- SARS-CoV-2 positive patients via RT-PCR (n=33) showed 43.74+19.81 squamous cells and 38.01+18.48 ciliated respiratory type cells, whereas presumptive positive patients (n=27) showed 44.93+22.69 squamous cells and 51.84+21.01 ciliated respiratory type cells (Figure 1A,1B).
- SARS-CoV-2 negative patients via RT-PCR (n=40) showed 45.08+19.34 squamous cells and 67+20 ciliated respiratory-type cells.
- No significant cytological differences were noted among the 3 groups (p=0.97).
- Immunohistochemical study showed immunoreactivity for anti-SARS-CoV-2 nucleoprotein antibody in squamous cells among SARS-CoV-2 RT-PCR positive and presumptive positive patients with no statistically significant difference between the two groups. Immunoreactivity was observed only in 3 SARS-CoV-2 RT-PCR negative patients (Table 2, Figure 4).

ABSTRACT

INTRODUCTION: We describe cytologic and immunohistologic findings in virus transport medium on cases under investigation of SARS-CoV-2 infection. METHODS: Cytologic findings in cases under investigation of SARS-CoV-2 infection from one hundred consecutive nasopharyngeal swab were reviewed. Immunohistochemistry and SARSCoV-2 RT-PCR determination were performed to detect virus. RESULTS: No viral inclusions were noted in squamous cells obtained from virus transport medium. Immunohistochemestry with monoclonal antibodody against SARS-CoV-2 viral nucleoprotein was present in squamous cells. No positivity was present in others cellular components. CONCLUSIONS: SARS-CoV-2 predominantly localizes squamous cells in cytology samples of patients with RT-PCR positive determination of SARSCoV-2. The results of the current study support the notion that the nasopharyngeal region is the anatomical station that SARS-CoV-2 infects first, and the infection can lead to the migration of the virus into the lower airways.

	RT-PCR SARS-CoV-2 test negative (40)	RT-PCR SARS-CoV-2 test positive (33)	RT-PCR SARS-CoV-2 test presumptive positive (27)
ICC positive	3	33	27
ICC Negative	37	0	0
Asymptomatic	28	15	21
Symptomatic	12	18	6
Alive	40	29	27

Table 2: RT-PCR SARS CoV-2 test results, immunohistochemical study, clinical symptoms and evolution from persons under investigation for SARS-CoV-2 infection (N=100).

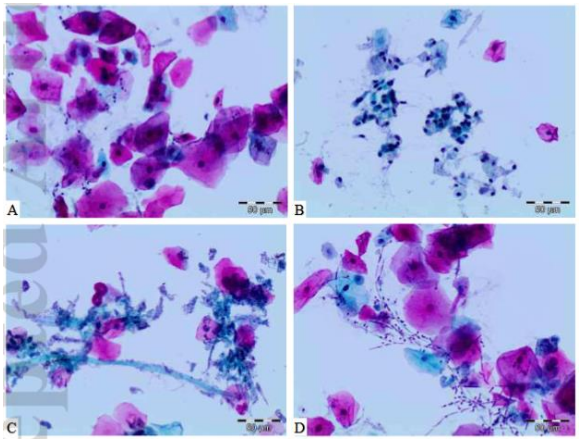


Figure 1. Cytological findings in cases under investigation for SARS-CoV-2 infection from nasopharyngeal swabs. (A) Characteristic finding of squamous cells. No viral cytopathic effect was present. (B) Ciliated respiratory-type epithelial cells, with no evidence of any viral cytopathic effect. (C) Isolated squamous cell metaplasia is present. (D) Candida sp pseudohyphal, and hyphal forms are seen. (Papanicolau staining. DA 20x).

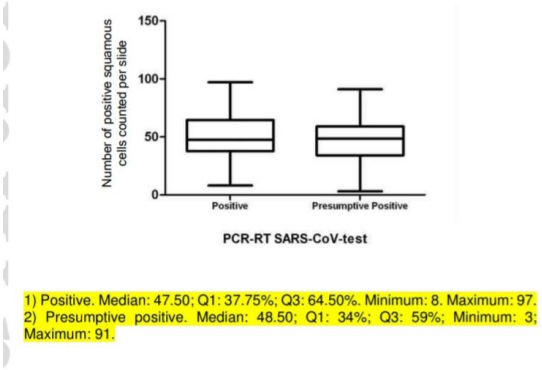


Figure 4: Immunohistological positive squamous cells in cases of RT-PCR SARS-CoV-2 infection positive and presumptive positive. (No significative differences was observed between groups).

MANAGEMENT

ORAL FAVIPIRAVIR FOR PATIENTS WITH DELAYED SARS-COV-2 VIRAL RNA CLEARANCE: A CASE SERIES

Fu D, Cao R, Zhao L, Li W, Zhong W, Wen J.. Crit Care. 2020 Sep 25;24(1):578. doi: 10.1186/s13054-020-03288-5.
Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

BLUF

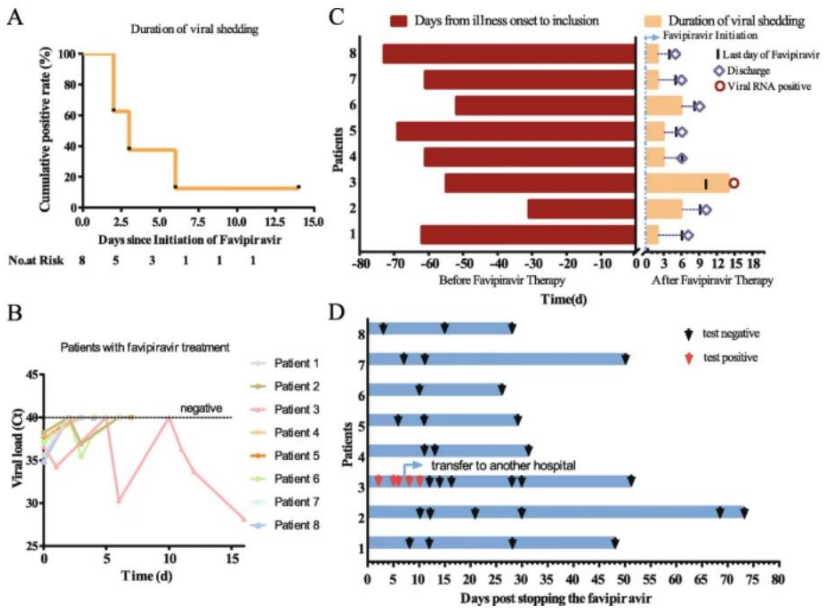
A case series conducted at Jinling Hospital in Nanjing, China by Nanjing University School of Medicine from March 26, 2020 onward found that of 8 asymptomatic COVID-19 positive rehabilitation patients with delayed viral RNA clearance who received oral favipiravir (dosing below), seven experienced a viral clearance within 6 days with a median duration of viral shedding of 3 days, whereas only one patient remained SARS-CoV-2 RNA-positive after 14 days (Figure 1). The authors conclude that favipiravir is worth further investigation as a treatment method for patients with COVID-19.

SUMMARY

Dosage of favipiravir: two doses of 1600 mg on day 1 and 600 mg twice per day on days 2–10 or until SARS-CoV-2 RNA negative

FIGURES

Fig. 1



The status of SARS-CoV-2 viral RNA detection in patients. **a** The Kaplan-Meier estimates of the duration of SARS-CoV-2 RNA detection after starting favipiravir. **b** The change from baseline of SARS-CoV-2 viral RNA load by quantitative real-time RT-PCR. **c** The detection of SARS-CoV-2 viral RNA in individual patients. Day 0 is the day on which treatment with favipiravir was initiated. For each patient, the red bar shows the duration of positive SARS-CoV-2 RNA in throat swabs from illness onset to inclusion, and the yellow bar shows the duration of viral shedding after starting favipiravir. The vertical line segment and diamond represent the last day of favipiravir treatment and the day of discharge, respectively. The red circle indicates that viral RNA was detected in the patient's swab at the end of the 14-day follow-up period. **d** Follow-up results after favipiravir stopped

OPHTHALMOLOGY

OPHTHALMOLOGY AND COVID-19

Bressler NM.. JAMA. 2020 Sep 22;324(12):1143-1144. doi: 10.1001/jama.2020.17595.
Level of Evidence: Other - Review / Literature Review

BLUF

A review by an ophthalmologist from the Department of Ophthalmology, John Hopkins University School of Medicine highlights ocular findings in COVID-19 patients with severe systemic disease; conjunctival congestion, epiphora, and chemosis appeared to be common in these populations. Citing a study of 276 patients admitted to the hospital with COVID-19 in Hubei, China reporting that their eyeglass usage was lower than the general population, the ophthalmologist hypothesizes the possibility of ocular transmission of SARS-CoV-2 and encourages use of personal protective equipment (face shield, goggles, eyeglasses) to prevent ocular transmission during this pandemic.

A WEB VISUALIZATION TOOL USING T CELL SUBSETS AS THE PREDICTOR TO EVALUATE COVID-19 PATIENT'S SEVERITY

Liu Q, Fang X, Tokuno S, Chung U, Chen X, Dai X, Liu X, Xu F, Wang B, Peng P.. PLoS One. 2020 Sep 24;15(9):e0239695. doi: 10.1371/journal.pone.0239695. eCollection 2020.

Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

A study conducted at the Wuhan Pulmonary Hospital analyzing COVID-19 positive patients (n=340) found T-cell subsets analyzed upon initial diagnosis (Total T-cells, Helper T-cells [TH], Suppressor T-cells [TSC], and TH/TSC) differed significantly in patients that were discharged (n=310) compared to death cases (n=30); while age, underlying disease status, Helper T-cell count, and TH/TSC ratio were significant predictors of either death or discharge, but a well-functioning immune system at time of hospitalization indicated a higher chance of recovery (Figures 2,3,4). These findings suggest T-cell subset monitoring may be useful to detect changes in condition and predict prognosis of patients with COVID-19.

ABSTRACT

Wuhan, China was the epicenter of the 2019 coronavirus outbreak. As a designated hospital for COVID-19, Wuhan Pulmonary Hospital has received over 700 COVID-19 patients. With the COVID-19 becoming a pandemic all over the world, we aim to share our epidemiological and clinical findings with the global community. We studied 340 confirmed COVID-19 patients with clear clinical outcomes from Wuhan Pulmonary Hospital, including 310 discharged cases and 30 death cases. We analyzed their demographic, epidemiological, clinical and laboratory data and implemented our findings into an interactive, free access web application to evaluate COVID-19 patient's severity level. Our results show that baseline T cell subsets results differed significantly between the discharged cases and the death cases in Mann Whitney U test: Total T cells ($p < 0.001$), Helper T cells ($p < 0.001$), Suppressor T cells ($p < 0.001$), and TH/TSC (Helper/Suppressor ratio, $p<0.001$). Multivariate logistic regression model with death or discharge as the outcome resulted in the following significant predictors: age (OR 1.05, 95% CI, 1.00 to 1.10), underlying disease status (OR 3.42, 95% CI, 1.30 to 9.95), Helper T cells on the log scale (OR 0.22, 95% CI, 0.12 to 0.40), and TH/TSC on the log scale (OR 4.80, 95% CI, 2.12 to 11.86). The AUC for the logistic regression model is 0.90 (95% CI, 0.84 to 0.95), suggesting the model has a very good predictive power. Our findings suggest that while age and underlying diseases are known risk factors for poor prognosis, patients with a less damaged immune system at the time of hospitalization had higher chance of recovery. Close monitoring of the T cell subsets might provide valuable information of the patient's condition change during the treatment process. Our web visualization application can be used as a supplementary tool for the evaluation.

FIGURES

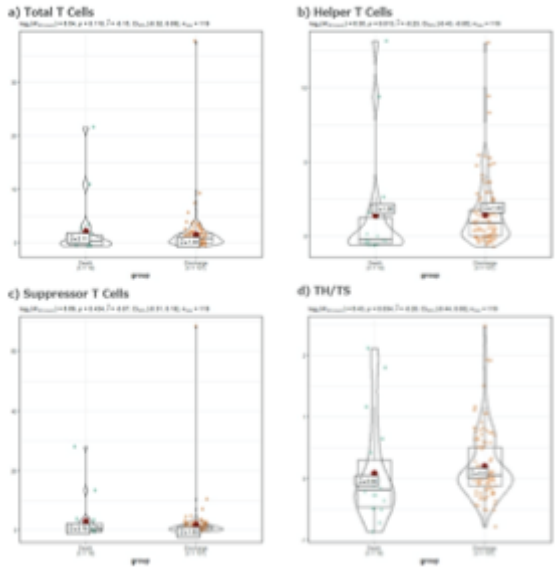


Fig 3. Comparison of the change rates of the T-cell Subsets between the last and first T cell subsets tests. a) Violin plot of the total T cells change rates between the last and the first T-cell Subsets tests during the hospitalization. Wilcoxon-Mann-Whitney test comparing the means of the two groups yielded a p value of 0.110. b) Violin plot of the helper T cells change rates between the last and the first T-cell Subsets tests during the hospitalization. Wilcoxon- Mann-Whitney test comparing the means of the two groups yielded a p value of 0.013. c) Violin plot of the suppressor T cells change rates between the last and the first T-cell Subsets tests during the hospitalization. Wilcoxon-Mann- Whitney test comparing the means of the two groups yielded a p value of 0.434. d) Violin plot of the total TH/TSC ratio change rates between the last and the first T-cell Subsets tests during the hospitalization. Wilcoxon-Mann- Whitney test comparing the means of the two groups yielded a p value of 0.034.

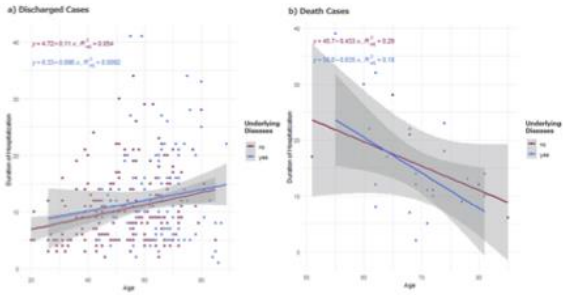


Fig 2. Duration of hospitalization vs age. a) Duration of the hospitalization plotted vs Age, for the discharged group. Pink dots indicate the patients with underlying medical conditions and the blue dots indicate those without. There are two observations from this chart: 1. Elderly patients tend to have underlying diseases than the younger ones; 2. The duration of the hospitalization tends to be longer among the elderly patients. The straight lines and the shaded areas show the regression line and the 95% confidence interval. The parameter estimates as well as the adjusted R squared values were also indicated in the plots. b) Duration of the hospitalization plotted vs Age, for the death group. Pink dots indicate the patients with underlying medical conditions and the blue dots indicate those without. Elderly patients die more quickly than the younger ones. The straight lines and the shaded areas show the regression line and the 95% confidence interval. The parameter estimates as well as the adjusted R squared values were also indicated in the plots.

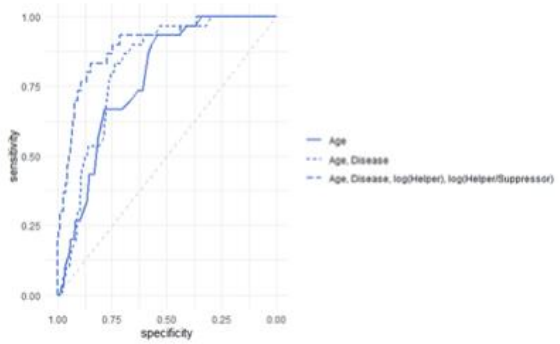


Fig 4. ROC Curves for three different logistic regression models. a) Model 1: logit(Probability of Death) = intercept + aAge. b)Model 2: logit(Probability of Death) = intercept + aAge + bDisease. c) Model 3: logit(Probability of Death) = intercept + aAge + bDisease + clog(Helper) + dlog(Helper/Suppressor).

FUTURE DEVELOPMENTS IN BIOSENSORS FOR FIELD-READY SARS-COV-2 VIRUS DIAGNOSTICS

Fani M, Zandi M, Soltani S, Abbasi S.. Biotechnol Appl Biochem. 2020 Sep 24. doi: 10.1002/bab.2033. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A review article by Iranian virologists and medical researchers examined current methods for SARS-CoV-2 detection including their limitations (i.e. difficulty detecting early infection via serological assays, equipment requirements of RT-PCR, and low specificity of CT scan), new developments in biosensing research (Figure 1; a platform sensor that detects SARS-CoV-2 N-gene at concentrations as low as 0.18 ng/µL within 10 minutes), and potential biosensor advantages (i.e. rapid response, high sensitivity and low cost). Authors conclude that further research should be conducted on the development of DNA biosensors for SARS-CoV-2 detection to improve upon current diagnostic practices.

ABSTRACT

According to the evidence, the Coronavirus disease 19 (COVID-19) is caused by a zoonotic pathogen named respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus can spread through personal contact, respiratory droplets, and also through airborne transmission. A rapid, low-cost, and effective biosensor platform is essential to diagnose patients with COVID-19 infection, predominantly the asymptomatic individuals, and prevent the spread of the SARS-CoV-2 via transmission routes. The objective of this review is to provide a comparative view among current diagnostic methods, focusing on recently suggested biosensors for the detection of SARS-CoV2 in clinical samples. A capable SARS-CoV-2 biosensor can be designed by the holistic insights of various biosensor studies.

FIGURES

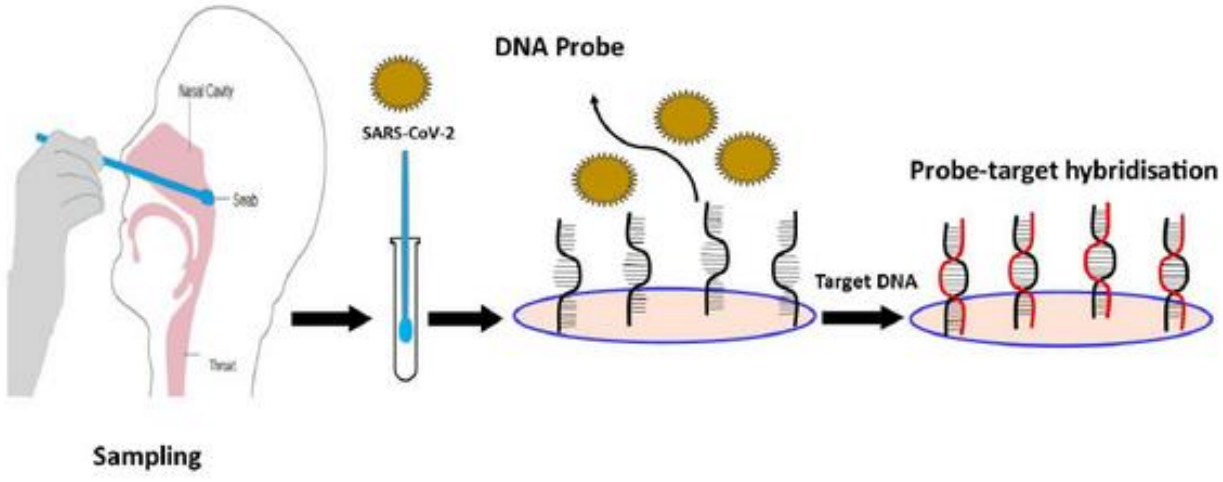


Figure 1. Schematic illustration of the DNA biosensor

TARGETING THE ENDOLYSOSOMAL HOST-SARS-COV-2 INTERFACE BY CLINICALLY LICENSED FUNCTIONAL INHIBITORS OF ACID SPHINGOMYELINASE (FIASMA) INCLUDING THE ANTIDEPRESSANT FLUOXETINE

Schloer S, Brunotte L, Goretzko J, Mecate-Zambrano A, Korthals N, Gerke V, Ludwig S, Rescher U.. Emerg Microbes Infect. 2020 Sep 25:1-26. doi: 10.1080/22221751.2020.1829082. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

An in-vitro study performed by clinical researchers in Germany investigated functional inhibitors of acid sphingomyelinase (FIASMA) drugs and found that fluoxetine successfully inhibits the entry/propagation of SARS-CoV-2 in cell culture without cytotoxic effects, as well as exhibits antiviral activity against two subtypes of Influenza A virus via a mechanism that impairs endolysosomal acidification and leads to accumulation of cholesterol in endosomes (Figure 5). Similar effects were also observed with amiodarone and imipramine (Figure 3), two other FIASMA drugs. These findings suggest endolysosomal lipid balance as a potential efficacious FIASMA drug target of the host-virus interface for SARS-CoV-2 and other enveloped viruses.

ABSTRACT

The Coronavirus Disease 2019 (COVID-19) pandemic caused by the Severe Acute Respiratory Syndrome Related Coronavirus 2 (SARS-CoV-2) is a global health emergency. As only very limited therapeutic options are clinically available, there is an urgent need for the rapid development of safe, effective, and globally available pharmaceuticals that inhibit SARS-CoV-2 entry and ameliorate COVID-19 severity. In this study, we explored the use of small compounds acting on the homeostasis of the endolysosomal host-pathogen interface, to fight SARS-CoV-2 infection. We find that fluoxetine, a widely used antidepressant and a functional inhibitor of acid sphingomyelinase (FIASMA), efficiently inhibited the entry and propagation of SARS-CoV-2 in the cell culture model without cytotoxic effects and also exerted potent antiviral activity against two currently circulating influenza A virus subtypes, an effect which was also observed upon treatment with the FIASMAs amiodarone and imipramine. Mechanistically, fluoxetine induced both impaired endolysosomal acidification and the accumulation of cholesterol within the endosomes. As the FIASMA group consists of a large number of small compounds that are well-tolerated and widely used for a broad range of clinical applications, exploring these licensed pharmaceuticals may offer a variety of promising antivirals for host-directed therapy to counteract enveloped viruses, including SARS-CoV-2 and COVID 19.

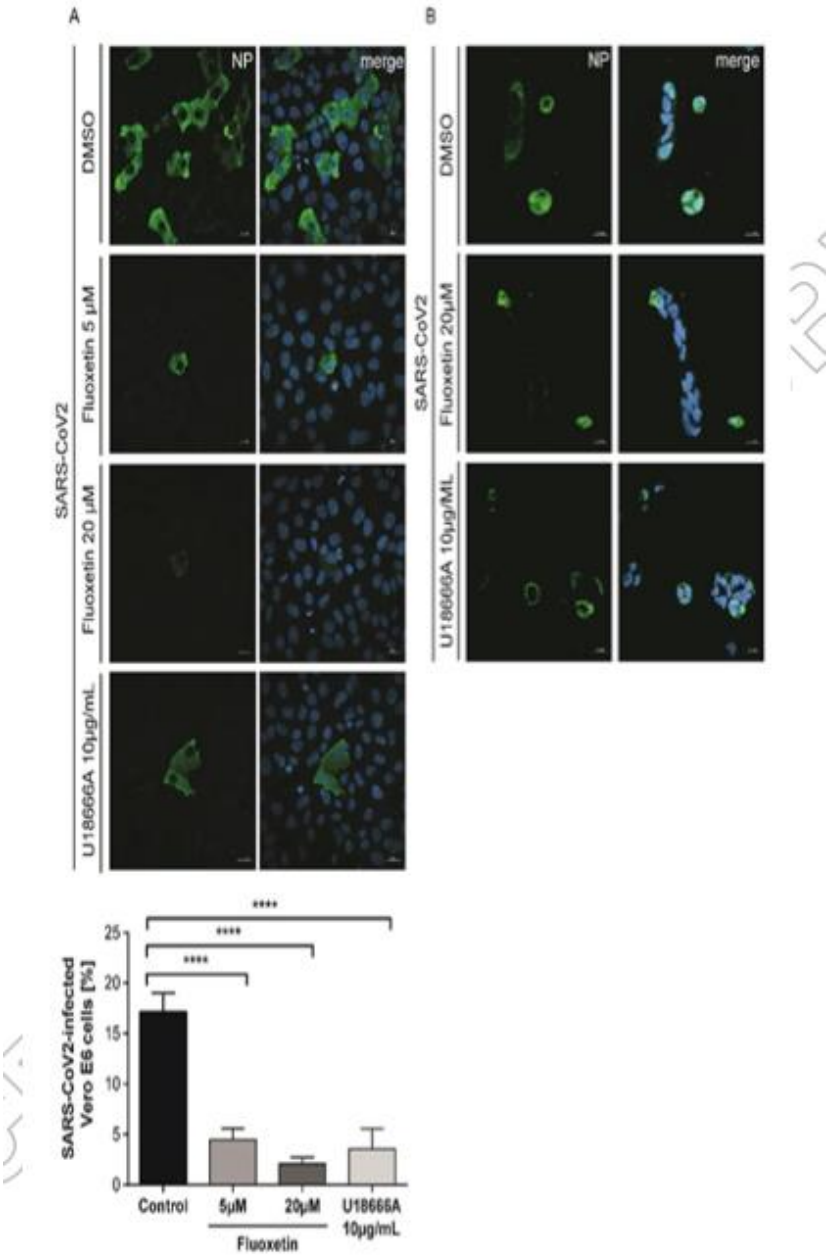


Figure 5. Impact of fluoxetine and U18666A on SARS-CoV-2 infection success within the first cycle of replication. (A) Vero E6 and (B) Calu-3 cells preatreated with the drugs at the indicated concentrations were infected with SARS-CoV-2 at 1 MOI for 1 h. Nuclei were visualized with DAPI. To determine infection rates, NP-positive cells were detected by immunofluorescence imaging. Mean percentages ± SEM of NP-positive cells were calculated from 3 independent experiments. One-way ANOVA followed by by Dunnett's multiple comparison test. ****p ≤ 0.0001.

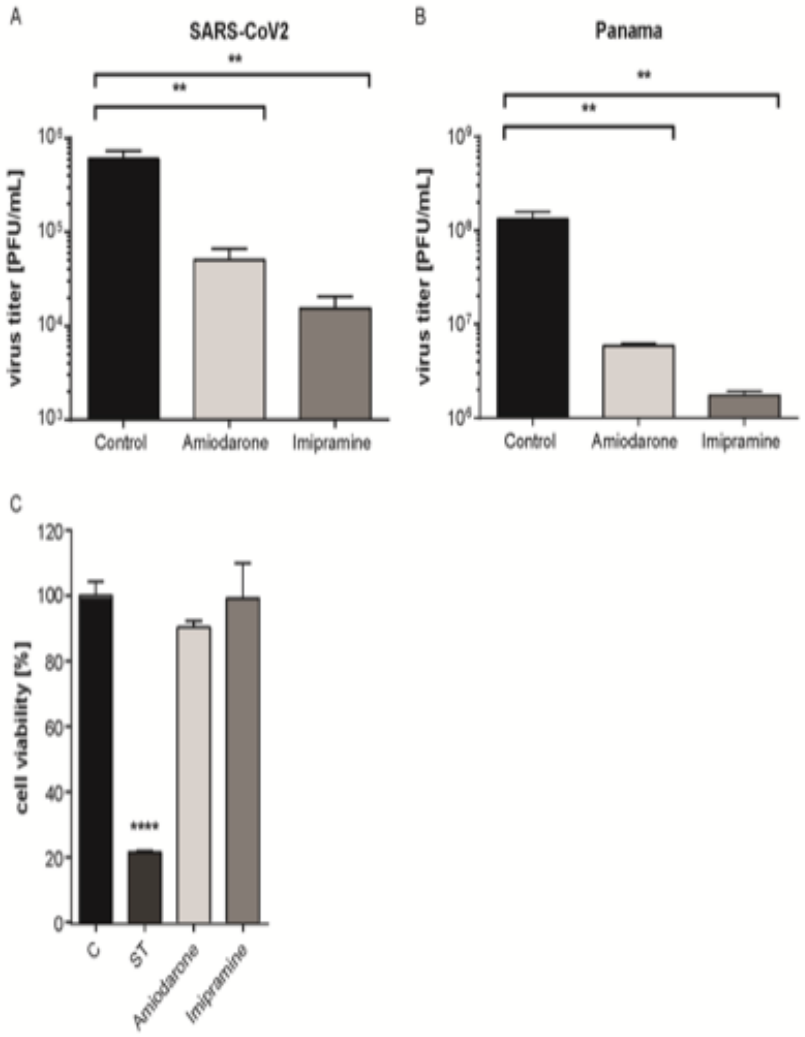


Figure 3. Amiodarone and imipramine as two classic representative of the FIASMA group reduced SARS-CoV-2 and IAV Panama titer. Virus titers determined in Calu-3 cells infected with (A) SARS-CoV-2 at 0.1 MOI for 48 h or (B) with the IAV strain Panama at 0.01 MOI for 24 h. Treatment of infected cells with solvent or amiodarone (5 μM) or imipramine (50 μM) was started 1 h p.i. Data points present mean virus titers ± SEM of three independent experiments. (C) Analysis of cell viability. MTT assay of Calu-3 cells treated with the solvent DMSO (C), amiodarone (5 μM) or imipramine (50 μM) for 48 h. The protein kinase inhibitor staurosporine (ST), a strong inducer of cytotoxicity, served as a positive control. Bar graphs represent the mean viral titers ± SEM of three independent experiments. One-way ANOVA followed by Dunnett's multiple comparison test; **p ≤ 0.01, ****p ≤ 0.0001.

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