

# The Daily COVID-19 Literature Surveillance Summary

**October 16, 2020**



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# COVID-19 Daily Literature Surveillance

COVID19LST



Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

# LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

| Question   | Step 1<br>(Level 1*)  | Step 2<br>(Level 2*)   | Step 3<br>(Level 3*)   | Step 4<br>(Level 4*)   | Step 5 (Level 5)          |
|--|---|--|--|--|---------------------------|
| <b>How common is the problem?</b>                                  | 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                       |
| <b>Is this diagnostic or monitoring test accurate? (Diagnosis)</b> | 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 |
| <b>What will happen if we do not add a therapy? (Prognosis)</b>    | 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                       |
| <b>Does this intervention help? (Treatment Benefits)</b>           | 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 |
| <b>What are the COMMON harms? (Treatment Harms)</b>                | 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 |
| <b>What are the RARE harms? (Treatment Harms)</b>                  | Systematic review of randomized trials or n-of-1 trial  | Randomized trial or (exceptionally) observational study with dramatic effect                 |  |  |                           |
| <b>Is this (early detection) test worthwhile? (Screening)</b>      | 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

- Decreased air pollution reported during the [global shutdown due to the COVID-19 pandemic was "a brief respite" from the impacts of climate change](#), but in light of the global recession, governments and individuals will likely prioritize the economy and their health rather than the environment (decreased use of public transportation, more fossil fuel consumption, increased use of single use plastics), suggesting these behaviors will contribute to even worse air quality moving forward.

## Epidemiology

- Italian sports medicine physicians conducted a cohort study of 30 male professional soccer players, all of whom were negative for acute SARS-CoV-2 infection via RT-PCR and reported histories of either no or mild symptoms of COVID-19, however 18 (60%) were positive for SARS-CoV-2 IgG and demonstrated a [statistically significant decrease in spirometry parameters](#) ( $p<0.05$ ). Because no other relevant differences in cardiopulmonary function testing were found, the authors suggest extensive cardiovascular and hematologic screening for male professional athletes who test positive for SARS-CoV-2 IgG is of limited utility.

## Transmission & Prevention

- A retrospective cohort study of 2888 residents in a Guangzhou community with RT-PCR and genome sequencing of samples collected from the environment and residents found that working in [waste management](#) ( $RR=13$ , 95% CI: 2.3-180), failing to change into clean shoes at home ( $RR=7.4$ , 95% Clexact: 1.8-34), and coming home and cleaning shoes daily ( $RR=6.3$ , 95% Clexact: 1.4-30) were significantly associated with SARS-CoV-2 infection.

## Adjusting Practice During COVID-19

- An international consortium of multidisciplinary cancer care experts from the European Society for Medical Oncology present a set of statements encompassing [28 committee-approved guidelines for cancer care best practices](#) during the SARS-CoV-2 pandemic that encompass 10 categories (patient management and follow-up, infection prevention, use of specific therapies [GC-SF, thromboembolism prophylaxis, targeted TKI, chemotherapy, radiation], immunotherapy utilization, COVID-19 testing, and clinical trial activity) and suggest that their guidelines offer the best strategy for providing high quality care to cancer patients during the COVID-19 pandemic while minimizing potential harm.

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## CLIMATE

### GLOBAL

#### **COVID-19 AND AIR POLLUTION: THE WORST IS YET TO COME**

Dutheil F, Baker JS, Navel V.. Environ Sci Pollut Res Int. 2020 Oct 6. doi: 10.1007/s11356-020-11075-6. Online ahead of print.

Level of Evidence: Other - Opinion

#### **BLUF**

In this letter to the editor published in October 2020, physicians and a physiologist from France and Hong Kong argue that the decreased air pollution reported during the global shutdown due to the COVID-19 pandemic was "a brief respite" from the impacts of climate change. They warn that, in light of the global recession, governments and individuals will likely prioritize the economy and their health rather than the environment (decreased use of public transportation, more fossil fuel consumption, increased use of single use plastics) and suggest these behaviors will contribute to even worse air quality moving forward.

## EPIDEMIOLOGY

### SYMPTOMS AND CLINICAL PRESENTATION

#### ADULTS

#### IS EXTENSIVE CARDIOPULMONARY SCREENING USEFUL IN ATHLETES WITH PREVIOUS ASYMPTOMATIC OR MILD SARS-COV-2 INFECTION?

Gervasi SF, Pengue L, Damato L, Monti R, Pradella S, Pirroni T, Bartoloni A, Epifani F, Saggese A, Cuccaro F, Bianco M, Zeppilli P, Palmieri V.. Br J Sports Med. 2020 Oct 5:bjssports-2020-102789. doi: 10.1136/bjssports-2020-102789. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

#### BLUF

Italian sports medicine physicians recently (exact timeline unclear) conducted a cohort study of 30 male professional soccer players, all of whom were negative for acute SARS-CoV-2 infection via RT-PCR and reported histories of either no or mild symptoms of COVID-19. They evaluated results of physical exam, laboratory studies, spirometry, ECG (resting, stress, and 24-hour), echocardiogram, and chest CT and found 18 (60%) were positive for SARS-CoV-2 IgG and these IgG positive players demonstrated a statistically significant decrease in spirometry parameters ( $p<0.05$ ). However, because no other relevant differences in cardiopulmonary function testing were found, the authors suggest extensive cardiovascular and hematologic screening for male professional athletes who test positive for SARS-CoV-2 IgG is of limited utility.

#### ABSTRACT

**OBJECTIVE:** During the COVID-19 pandemic, it is essential to understand if and how to screen SARS-CoV-2-positive athletes to safely resume training and competitions. The aim of this study is to understand which investigations are useful in a screening protocol aimed at protecting health but also avoiding inappropriate examinations. **METHODS:** We conducted a cohort study of a professional soccer team that is based on an extensive screening protocol for resuming training during the COVID-19 pandemic. It included personal history, antigen swabs, blood tests, spirometry, resting/stress-test ECG with oxygen saturation monitoring, echocardiogram, Holter and chest CT. We also compared the findings with prior data from the same subjects before infection and with data from SARS-CoV-2-negative players. **RESULTS:** None of the players had positive swab and/or anti-SARS-CoV-2 IgM class antibodies. Out of 30 players, 18 (60%) had IgG class antibodies. None had suffered severe SARS-CoV-2-related disease, 12 (66.7%) had complained of mild COVID-19-related symptoms and 6 (33.3%) were asymptomatic. None of the players we examined revealed significant cardiovascular abnormalities after clinical recovery. A mild reduction in spirometry parameters versus pre-COVID-19 values was observed in all athletes, but it was statistically significant ( $p<0.05$ ) only in SARS-CoV-2-positive athletes. One SARS-CoV-2-positive player showed increased troponin I level, but extensive investigation did not show signs of myocardial damage. **CONCLUSION:** In this small cohort of athletes with previous asymptomatic/mild SARS-CoV-2 infection, a comprehensive screening protocol including blood tests, spirometry, resting ECG, stress-test ECG with oxygen saturation monitoring and echocardiogram did not identify relevant anomalies. While larger studies are needed, extensive cardiorespiratory and haematological screening in athletes with asymptomatic/mild SARS-CoV-2 infection appears unnecessary.

## FIGURES

| N  | IgG index (<1.4) | Previous COVID-19-related symptoms                     | Pre-COVID-19 spirometry                  | Post-COVID-19 spirometry                 | Pre-COVID-19 resting ECG                                | Post-COVID-19 resting ECG                               | Pre-COVID-19 stress-test ECG       | Post-COVID-19 stress-test ECG           | Pre-COVID-19 echocardiogram | Post-COVID-19 echocardiogram | Post-COVID-19 Holter ECG monitoring                 |
|----|------------------|--|--|--|---|---|------------------------------------|---|-----------------------------|------------------------------|---|
| 1  | 4.65             | None   | Normal                                   | Normal                                   | Sinus bradycardia<br>AVB I (PR 220 ms); incomplete RBBB | Sinus bradycardia<br>AVB I (PR 220 ms); incomplete RBBB | Normal                             | Normal                                  | Normal                      | Normal                       | Rare, isolated SVBP                                 |
| 2  | 1.75             | Ageusia  | Normal                                   | Normal                                   | n.a.  | n.a.  | Sinus bradycardia; incomplete RBBB | n.a.                                    | Normal                      | Mild MV regurgitation        | Occasional, isolated SVPB; rare, isolated VBP       |
| 3  | 2.36             | None   | n.a.                                     | Normal                                   | Mild reduction in PEF (7% of the theor)                 | Incomplete RBBB   | Incomplete RBBB                    | Normal                                  | n.a.                        | Normal                       | Occasional, isolated SVPB; rare, isolated VBP       |
| 4  | 1.65             | None   | Normal                                   | Mild reduction in PEF (7% of the theor)  | Incomplete RBBB   | Incomplete RBBB   | Normal                             | Rare VPB                                | Mild MV regurgitation       | Mild MV regurgitation        | Occasional, isolated SVPB; rare, isolated VBP       |
| 5  | 2.46             | Ageusia, anosmia                                       | Normal                                   | Normal                                   | Sinus bradycardia; incomplete RBBB                      | Sinus bradycardia; incomplete RBBB                      | Normal                             | Normal                                  | Mild MV regurgitation       | Mild MV regurgitation        | Rare, isolated SVPB; rare, isolated VBP             |
| 6  | 4.42             | Fever >37.5°C, arthromyalgia                           | Normal                                   | Normal                                   | Sinus bradycardia; incomplete RBBB                      | Incomplete RBBB   | Normal                             | Normal                                  | Mild MV regurgitation       | Mild MV regurgitation        | Rare, isolated SVPB                                 |
| 7  | 4.11             | Ageusia, sore throat                                   | Normal                                   | Normal                                   | Sinus bradycardia; incomplete RBBB                      | Incomplete RBBB   | Normal                             | Rare SVPB                               | Normal                      | Normal                       | Occasional SVPB                                     |
| 8  | 2.46             | None   | Normal                                   | Normal                                   | Normal  | Normal  | Normal                             | Normal                                  | Normal                      | Normal                       | Occasional SVPB                                     |
| 9  | 2.96             | Fever >37.5°C, asthenia                                | n.a.                                     | Normal                                   | n.a.  | Sinus bradycardia; incomplete RBBB                      | n.a.                               | Rare VPB, non-significant ST depression | n.a.                        | Mild MV regurgitation        | Rare, isolated SVPB; occasional, isolated VBP       |
| 10 | 2.19             | Asthenia, headache                                     | Normal                                   | Normal                                   | Sinus bradycardia<br>AVB I (PR 220 ms)                  | AVB I (PR 222 ms)                                       | Normal                             | Normal                                  | Mild MV regurgitation       | Mild MV regurgitation        | Rare, isolated SVPB; rare, isolated VBP             |
| 11 | 2.85             | None   | Normal                                   | Normal                                   | Sinus bradycardia; AVB I (PR 215 ms)                    | AVB I (PR 222 ms)                                       | Normal                             | Normal                                  | Normal                      | Normal                       | Occasional, isolated SVPB; occasional, isolated VBP |
| 12 | 7.35             | Fever >37.5°C, cough, asthenia, ageusia, arthromyalgia | Mild reduction in PEF (71% of the theor) | Mild reduction in PEF (74% of the theor) | Normal  | Normal  | Non-significant ST depression      | Non-significant ST depression           | Normal                      | Normal                       | Occasional, isolated SVPB                           |
| 13 | 5.11             | Fever >37.5°C, anosmia, ageusia, nocturnal dyspnoea    | Normal                                   | Normal                                   | Sinus bradycardia; incomplete RBBB                      | Incomplete RBBB   | Normal                             | Normal                                  | Normal                      | Normal                       | Rare, isolated SVPB                                 |
| 14 | 1.64             | Fever >37.5°C  | n.a.                                     | Normal                                   | n.a.  | Sinus bradycardia; AVB I (PR 215 ms)                    | n.a.                               | Normal                                  | n.a.                        | Mild MV regurgitation        | Occasional, isolated SVPB; rare, isolated VBP       |
| 15 | 5.24             | None   | Normal                                   | Normal                                   | Sinus bradycardia; incomplete RBBB                      | Incomplete RBBB   | Normal                             | Normal                                  | Normal                      | Normal                       | Occasional, isolated SVPB; rare, isolated VBP       |
| 16 | 4.73             | Asthenia   | Normal                                   | Normal                                   | Incomplete RBBB   | Incomplete RBBB   | Normal                             | Normal                                  | Normal                      | Normal                       | Rare, isolated SVPB; occasional, isolated VBP       |
| 17 | 5.8              | Fever >37.5°C  | Normal                                   | Normal                                   | Sinus bradycardia                                       | Normal  | Normal                             | Normal                                  | Normal                      | Normal                       | Rare, isolated SVPB; occasional, isolated VBP       |
| 18 | 2.43             | Fever >37.5°C, cough, asthenia, anosmia                | Normal                                   | Normal                                   | Normal  | Normal  | Occasional SVPB                    | Occasional SVPB                         | Normal                      | Normal                       | Occasional, isolated SVPB                           |

AVB I, first-degree atrioventricular block; MV, mitral valve; N.A., not available; PEF, peak expiratory flow; PR, PR interval; RBBB, right bundle branch block; SVPB, supraventricular premature beats; Theor, theoretical for age and body size; VPB, ventricular premature beats.

Table 2: Detailed description of clinical symptoms and instrumental findings in COVID-19+ athletes

|                                 | COVID-19+         |                    | P value |
|---------------------------------|-------------------|--------------------|---------|
|                                 | n                 | 18                 |         |
| <b>Spirometry</b>               |                   |                    |         |
| FVC (L)                         | 5.68 (5.06–6.21)  | 5.62 (4.80–5.83)   | 0.31    |
| % of the theor                  | 102.5 (92–112)    | 103.5 (95–105)     | 0.69    |
| FEV <sub>1</sub> (L)            | 4.62 (4.02–4.77)  | 4.4 (3.87–5.11)    | 0.95    |
| % of the theor                  | 96.5 (91–104)     | 102.5 (94.5–108.5) | 0.39    |
| PEF (L)                         | 9.25 (8.7–10.45)  | 9.38 (8.34–10.39)  | 0.85    |
| % of the theor                  | 89.5 (84–100)     | 89 (82.5–99.5)     | 0.92    |
| MVV (L/min)                     | 161.7 (139.7–167) | 154 (135.3–178.9)  | 0.98    |
| % of the theor                  | 98 (91–104)       | 99.5 (90.5–110)    | 0.72    |
| <b>Stress-test ECG</b>          |                   |                    |         |
| Resting HR (bpm)                | 61.5 (54–69)      | 60.5 (55–62.5)     | 0.33    |
| Max HR (bpm)                    | 180 (172–185)     | 178 (170–181.5)    | 0.44    |
| % of the theor                  | 91 (89–92)        | 90.5 (87.5–92)     | 0.63    |
| Resting SBP (mm Hg)             | 102.5 (100–110)   | 110 (100–120)      | 0.22    |
| Resting DBP (mm Hg)             | 62.5 (60–70)      | 62.5 (60–72.5)     | 0.55    |
| Max SBP (mm Hg)                 | 190 (170–200)     | 190 (175–195)      | 1.00    |
| Max DBP (mm Hg)                 | 77.5 (70–85)      | 75 (70–80)         | 0.63    |
| <b>Echocardiogram</b>           |                   |                    |         |
| LV EDD (mm)                     | 55.5 (51.5–58)    | 53.5 (52.5–55.5)   | 0.39    |
| LV ESD (mm)                     | 33 (31–37)        | 33 (32.5–34.5)     | 0.85    |
| IVSd (mm)                       | 10 (9.5–10)       | 10 (9–10.25)       | 0.92    |
| PWd (mm)                        | 10 (9.5–10)       | 10 (9–10.25)       | 0.78    |
| LV EDV (mL)                     | 153 (126–168)     | 137 (131.5–153)    | 0.25    |
| LV EDV ind (mL/m <sup>2</sup> ) | 73.5 (63.1–85.3)  | 71 (63.9–75.2)     | 0.35    |
| LV ESV (mL)                     | 43.5 (37–60)      | 45 (43.5–48.5)     | 0.82    |
| LV ESV ind (mL/m <sup>2</sup> ) | 22.2 (18.8–27.7)  | 23.5 (20.7–24.7)   | 0.78    |
| FS %                            | 37 (35–41)        | 38 (36.5–41)       | 0.55    |
| EF %                            | 61 (58–63)        | 60.5 (56.5–62.5)   | 0.76    |
| Mitral E:A ratio                | 1.71 (1.45–1.88)  | 1.76 (1.58–2)      | 0.47    |
| RVD1 (mm)                       | 44 (41–45)        | 43 (39.5–45.5)     | 0.69    |
| RVD2 (mm)                       | 32.5 (30–34)      | 31 (29–35.5)       | 0.79    |
| TAPSE (mm)                      | 19.5 (19–22)      | 20.5 (19–21)       | 0.69    |

Data are presented as median (IQR).

BPM, beats per minute; DBP, diastolic blood pressure; LV EDD, left ventricle end-diastolic diameter; LV EDV, left ventricle end-diastolic volume; EF, ejection fraction; LV ESD, left ventricle end-systolic diameter; LV ESV, left ventricle end-systolic volume; FEV<sub>1</sub>, forced expiratory volume in the first second; FS, fractional shortening; FVC, forced vital capacity; HR, heart rate; ind, indexed for body surface area; IVSd, end-diastolic interventricular septum thickness; MVV, maximal voluntary ventilation; PEF, peak expiratory flow volume; PWd, end-diastolic posterior wall thickness; RVD1, right ventricle end-diastolic diameter at the base (4ch); RVD2, right ventricle end-diastolic mid-cavity diameter (4ch); SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; Theor, theoretical for the age and body size.

Table 3: Comparison between COVID-19+ and COVID-19– players

|                                 | COVID-19+ pre       | COVID-19+ post      | P value |                                 | COVID-19- pre       | COVID-19- post    | P value |
|---------------------------------|---------------------|---------------------|---------|---------------------------------|---------------------|-------------------|---------|
| n                               | 15                  | 15                  |         | n                               | 9                   | 9                 |         |
| <b>Spirometry</b>               |                     |                     |         |                                 |                     |                   |         |
| FVC (L)                         | 5.64 (5.44–6.15)    | 5.35 (5.01–6.20)    | <0.05*  | FVC (L)                         | 5.76 (5.24–5.86)    | 5.66 (5.03–5.8)   | 0.95    |
| % of the theor                  | 101 (98–107.5)      | 96 (92–106.5)       | 0.18    | % of the theor                  | 103 (90–111)        | 104 (97–105)      | 0.33    |
| FEV <sub>1</sub> (L)            | 4.91 (4.77–5.02)    | 4.62 (4.08–4.86)    | <0.05*  | FEV <sub>1</sub> (L)            | 4.77 (4.5–5.22)     | 4.52 (4.17–5.03)  | 0.09    |
| % of the theor                  | 104 (99–109)        | 95 (91.5–103)       | <0.05*  | % of the theor                  | 101 (99–105)        | 102 (97–109)      | 0.83    |
| PEF (L)                         | 11.15 (9.59–11.34)  | 9.26 (8.65–10.58)   | <0.05*  | PEF (L)                         | 11.2 (8.9–11.8)     | 9.52 (8.85–10.36) | 0.05    |
| % of the theor                  | 103 (97.5–109.5)    | 89 (83–100.5)       | <0.05*  | % of the theor                  | 106 (95–112)        | 91 (85–97)        | 0.09    |
| MVV (L/min)                     | 180.9 (151.6–197.9) | 161.7 (141.3–170.2) | <0.05*  | MVV (L/min)                     | 183.3 (171.1–202.2) | 158.2 (146–176.1) | 0.17    |
| % of the theor                  | 110 (90.5–122)      | 97 (91.5–104)       | <0.05*  | % of the theor                  | 116 (99–119)        | 100 (95–109)      | 0.17    |
| <b>Stress-test ECG</b>          |                     |                     |         |                                 |                     |                   |         |
| Resting HR (bpm)                | 53 (48–60)          | 65 (58–69)          | <0.05*  | Resting HR (bpm)                | 60 (57–62)          | 61 (55–62)        | 0.86    |
| Max HR (bpm)                    | 176 (174–181)       | 180 (172–185)       | 0.89    | Max HR (bpm)                    | 178 (177–182)       | 179 (173–182)     | 0.09    |
| % of the theor                  | 90 (88–92)          | 91 (89–92)          | 0.73    | % of the theor                  | 90 (88–92)          | 91 (89–92)        | 0.26    |
| Resting SBP (mm Hg)             | 105 (100–110)       | 110 (100–110)       | 0.91    | Resting SBP (mm Hg)             | 110 (105–120)       | 110 (110–120)     | 0.86    |
| Resting DBP (mm Hg)             | 65 (65–70)          | 65 (60–70)          | 0.53    | Resting DBP (mm Hg)             | 70 (60–70)          | 65 (60–70)        | 0.67    |
| Max SBP (mm Hg)                 | 190 (185–200)       | 190 (180–205)       | 0.72    | Max SBP (mm Hg)                 | 200 (195–200)       | 190 (180–195)     | 0.23    |
| Max DBP (mm Hg)                 | 75 (65–80)          | 75 (70–80)          | 0.26    | Max DBP (mm Hg)                 | 75 (70–75)          | 75 (75–80)        | 0.60    |
| <b>Echocardiogram</b>           |                     |                     |         |                                 |                     |                   |         |
| LV EDD (mm)                     | 56 (53.8–58)        | 55 (51.8–57.8)      | 0.14    | LV EDD (mm)                     | 53.3 (52–54.5)      | 53 (52–55)        | 0.49    |
| LV ESD (mm)                     | 35 (32–37.5)        | 34 (31–37.5)        | 0.54    | LV ESD (mm)                     | 32.5 (30–35)        | 33 (32–35)        | 0.89    |
| IVSd (mm)                       | 9.9 (9.6–10)        | 10 (9.75–10)        | 0.95    | IVSd (mm)                       | 9.63 (9–10.3)       | 10 (9–10.5)       | 0.40    |
| PWd (mm)                        | 9.9 (9.6–10)        | 10 (9.75–10)        | 0.59    | PWd (mm)                        | 9.63 (9–10)         | 10 (9–10.5)       | 0.36    |
| LV EDV (mL)                     | 153.7 (139.7–166.6) | 151 (126.5–168)     | 0.47    | LV EDV (mL)                     | 136.5 (130–144.4)   | 134.5 (131–146)   | 0.84    |
| LV EDV ind (mL/m <sup>2</sup> ) | 75.5 (67.5–82.9)    | 73.5 (61.6–84.9)    | 0.41    | LV EDV ind (mL/m <sup>2</sup> ) | 68.1 (63.2–73.1)    | 68.8 (62.9–71.6)  | 0.88    |
| LV ESV (mL)                     | 50.9 (40.9–59.9)    | 46 (37.5–62)        | 0.89    | LV ESV (mL)                     | 42.5 (35–51)        | 45 (42–45)        | 0.96    |
| LV ESV ind (mL/m <sup>2</sup> ) | 26.1 (19.8–28.7)    | 23.6 (18.3–30)      | 0.78    | LV ESV ind (mL/m <sup>2</sup> ) | 22.3 (17.6–25.9)    | 22.9 (20–24.6)    | 0.88    |
| FS %                            | 36 (35–39.5)        | 37 (34.5–40)        | 0.58    | FS %                            | 36.5 (36–41)        | 37 (36–40)        | 0.83    |
| EF %                            | 57 (57–62.5)        | 60 (58–63)          | 0.81    | EF %                            | 58 (56–60)          | 62 (56–63)        | 0.24    |
| Mitral E:A ratio                | 1.87 (1.63–2)       | 1.6 (1.45–1.86)     | 0.21    | Mitral E:A ratio                | 1.88 (1.64–2.25)    | 1.74 (1.5–2)      | 0.24    |

Data are presented as median (IQR).

\*statistically significant difference.

BPM, beats per minute; DBP, diastolic blood pressure; LV EDD, left ventricle end-diastolic diameter; LV EDV, left ventricle end-diastolic volume; EF, ejection fraction; LV ESD, left ventricle end-systolic diameter; LV ESV, left ventricle end-systolic volume; FEV<sub>1</sub>, forced expiratory volume in the first second; FS, fractional shortening; FVC, forced vital capacity; HR, heart rate; ind, indexed for body surface area; IVSd, end-diastolic interventricular septum thickness; MVV, maximal voluntary ventilation; PEF, peak expiratory flow volume; PWd, end-diastolic posterior wall thickness; SBP, systolic blood pressure; Theor, theoretical for the age and body size.

Table 4: Comparison between pre-COVID-19 and post-COVID-19 parameters in COVID-19+ and COVID-19- players

## TRANSMISSION & PREVENTION

### SEWAGE AS A POSSIBLE TRANSMISSION VEHICLE DURING A CORONAVIRUS DISEASE 2019 OUTBREAK IN A DENSELY POPULATED COMMUNITY: GUANGZHOU, CHINA, APRIL 2020

Yuan J, Chen Z, Gong C, Liu H, Li B, Li K, Chen X, Xu C, Jing Q, Liu G, Qin P, Liu Y, Zhong Y, Huang L, Zhu BP, Yang Z.. Clin Infect Dis. 2020 Oct 12:ciaa1494. doi: 10.1093/cid/ciaa1494. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

#### BLUF

Epidemiologists from the Guangzhou Center for Disease Control and Prevention explain findings from a COVID-19 outbreak of eight cases in a Guangzhou community in April 2020. They performed a retrospective cohort study ( $n=2888$  residents) and RT-PCR and genome sequencing of samples collected from the environment and residents and found that working in waste management ( $RR=13$ , 95% CI: 2.3-180), failing to change into clean shoes at home ( $RR=7.4$ , 95% CI exact: 1.8-34), and coming home and cleaning shoes daily ( $RR=6.3$ , 95% CI exact: 1.4-30) were significantly associated with SARS-CoV-2 infection (Table 1). Because the two individuals who transmitted SARS-CoV-2 to six other individuals had not come into physical contact, authors conclude transmission occurred via an apartment sewage pipe which leaked in front of adjacent buildings (Table 2, Figure 1). This suggests sewage can spread SARS-CoV-2 and that safe sanitation practices may be necessary to prevent its transmission.

#### ABSTRACT

**BACKGROUND:** SARS-CoV-2 has been identified in the fecal matter of COVID-19 patients. However, sewage transmission has never been shown. In April 2020, a COVID-19 outbreak occurred in a densely populated community in Guangzhou, China. We investigated this outbreak to identify the mode of transmission. **METHOD:** A home quarantined order was issued in the community. We collected throat swab samples from the residents and environmental samples from the surfaces inside and around the houses, and conducted RT-PCR testing and genome sequencing. We defined a case as a resident in this community with a positive RT-PCR test, with or without symptoms. We conducted a retrospective cohort study of all residents living in the same buildings as the cases to identify exposure risk factors. **RESULT:** We found eight cases (four couples) in this community of 2888 residents (attack rate=2.8/1000), with onset during April 5-21, 2020. During their incubation periods, Cases 1-2 frequented market T with an ongoing outbreak. Cases 3-8 never visited market T during incubation period, lived in separate buildings from, and never interacted with, Cases 1-2. Retrospective cohort study showed that working as cleaners or waste picker ( $RR=13$ , 95% CI exact: 2.3-180), not changing to clean shoes after returning home ( $RR=7.4$ , 95% CI exact: 1.8-34), collating and cleaning dirty shoes after returning home ( $RR=6.3$ , 95% CI exact: 1.4-30) were significant exposure risk factors. Of 63 samples collected from street-sewage puddles and sewage-pipe surfaces, 19% tested positive for SARS-CoV-2. Of 50 environmental samples taken from cases' apartments, 24% tested positive. Viral genome sequencing showed that the viruses identified from the squat toilet and shoe-bottom dirt inside the apartment of Cases 1-2 were homologous with those from Cases 3-8 and those identified from sewage samples. The sewage pipe leading from the apartment of Cases 1-2 to the drainage had a large hole above ground. Rainfalls after the onset of Cases 1-2 flooded the streets. **CONCLUSION:** Our investigation has for the first time pointed to the possibility that SARS-CoV-2 might spread by sewage. This finding highlighted the importance of sewage management, especially in densely-populated places with poor hygiene and sanitation measures, such as urban slums and other low-income communities in developing countries.

## FIGURES

Table 1. Risk factors significantly associated with SARS-CoV-2 infection during a COVID-19 outbreak: Guangzhou, China, April 2020\*

| Risk factors with significant associations†   | n  | Num. cases | Attack rate (%) | RR (95% CI <sub>exact</sub> )‡ |
|---|----|------------|-----------------|--------------------------------|
| Age (years)                                   |    |            |                 |                                |
| ≥50   | 11 | 5          | 46              | 10 (1.6-130)                   |
| <50   | 22 | 1          | 4.6             |                                |
| Household income (yuan/month)                 |    |            |                 |                                |
| <2500§  | 18 | 6          | 33              | ∞ (1.5-∞)                      |
| ≥2500   | 15 | 0          |                 |                                |
| Occupation                                    |    |            |                 |                                |
| Cleaner/Waste picker                          | 9  | 5          | 56              | 13 (2.3-180)                   |
| Other   | 24 | 1          | 4.2             |                                |
| Changing shoes upon returning home            |    |            |                 |                                |
| Not changing to clean shoes                   | 7  | 4          | 57              | 7.4 (1.8-34)                   |
| Changing to clean shoes                       | 26 | 2          | 7.7             |                                |
| Collating/cleaning shoes after returning home |    |            |                 |                                |
| Yes   | 8  | 4          | 50              | 6.3 (1.4-30)                   |
| No  | 25 | 2          | 8.0             |                                |
| Frequency of leaving the house                |    |            |                 |                                |
| ≥2 times/day                                  | 11 | 4          | 36              | 4.0 (0.95-19)                  |
| 0-1 time/day                                  | 22 | 2          | 9.1             |                                |

\* Results of a retrospective cohort study conducted among 33 residents of buildings B and C in a low-income community.

† Other potential risk factors explored included sex, education, handwashing in various situations and frequency; usual mode of leaving the house (walking or bicycling); facemask use; air conditioner use; frequency of opening windows for ventilation, frequency of cleaning floors, and frequency of changing, collating, or washing shoes. These factors were not significantly associated with COVID-19.

‡ RR = risk ratio; CI<sub>exact</sub> = Fisher's exact confidence interval.

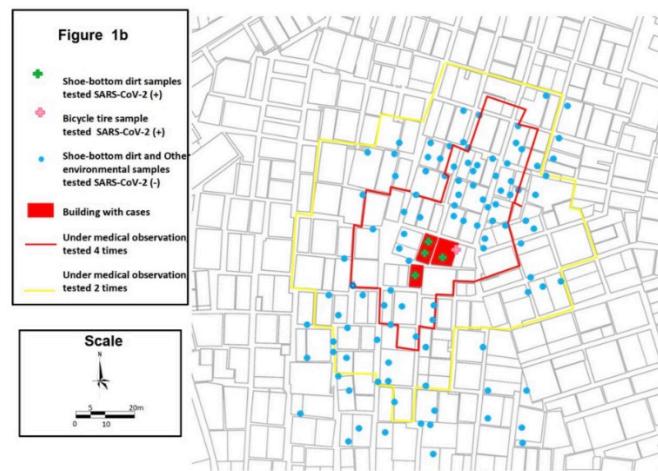
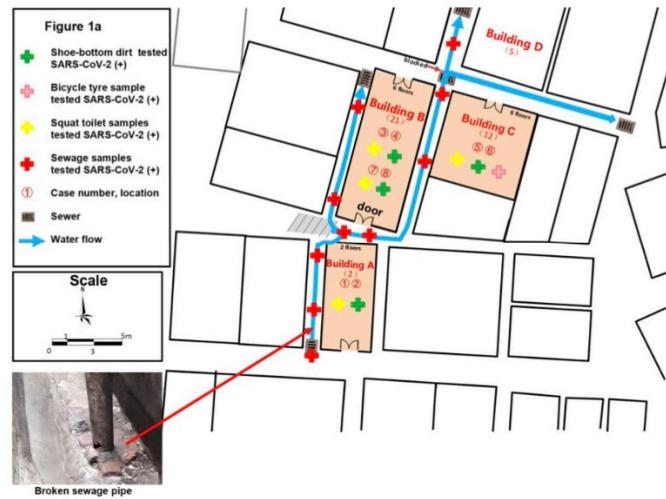
§ 2500 yuan ≈ US\$360

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Table 2. SARS-CoV-2 test results of environmental samples during a COVID-19 outbreak: Guangzhou, China, April 2020

| Location and objects where samples were taken            | Num. samples collected | Num. SARS-CoV-2 (+) samples | % Positive |
|--|------------------------|-----------------------------|------------|
| <b>All samples</b>                                       | <b>199</b>             | <b>25</b>                   | <b>13</b>  |
| <b>Sewage-related samples</b>                            | <b>63</b>              | <b>12</b>                   | <b>19</b>  |
| Swabs of sewage pipes around building A-C                | 7                      | 3                           | 43         |
| Sewage collected on the street near building A-C         | 20                     | 8                           | 40         |
| Sewage collected in buildings besides A-C                | 36                     | 1                           | 2.8        |
| <b>Apartments in Buildings A-C where Cases 1-8 lived</b> | <b>50</b>              | <b>12</b>                   | <b>24</b>  |
| Squat toilet   | 8                      | 4                           | 50         |
| Shoe bottom dirt   | 6                      | 4                           | 67         |
| Other  | 36                     | 4                           | 11         |
| <b>Apartments in Buildings A-C without cases</b>         | <b>14</b>              | <b>1</b>                    | <b>7.1</b> |
| Squat toilet swabs                                       | 1                      | 0                           | 0          |
| Shoe-bottom dirt   | 7                      | 0                           | 0          |
| Bicycle-tire dirt  | 1                      | 1                           | 100        |
| Other  | 5                      | 0                           | 0          |
| <b>Apartments in other buildings besides A-C</b>         | <b>72</b>              | <b>0</b>                    | <b>0</b>   |
| Squat-toilet swabs                                       | 10                     | 0                           | 0          |
| Shoe-bottom dirt   | 29                     | 0                           | 0          |
| Bicycle-tire dirt  | 3                      | 0                           | 0          |
| Other  | 30                     | 0                           | 0.0        |

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### OUTCOMES OF CRITICALLY ILL PREGNANT WOMEN WITH COVID-19 IN THE UNITED STATES

Easter SR, Gupta S, Brenner SK, Leaf DE.. Am J Respir Crit Care Med. 2020 Oct 7. doi: 10.1164/rccm.202006-2182LE. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

#### **BLUF**

A cohort study conducted by a multidisciplinary group of physicians from Brigham and Women's Hospital in Boston, USA compared outcomes of 32 critically ill pregnant women and 64 non-pregnant controls with COVID-19 admitted to 67 US hospitals March 4-May 2, 2020 (Table 2). Findings summarized below suggest that delivery may not be required for non-obstetric indications in pregnant patients critically ill with COVID-19.

#### **SUMMARY**

While no fetuses or pregnant women died, the mortality difference was not statistically significant when matched by age and disease severity (0% vs. 9.4% [n=6] in non-pregnant women, p=0.17). Most women delivered during their hospitalization (n=19, 59.4%) with high rates of cesarean sections and preterm delivery (17% and 94.7% of births, respectively)(Table 1). Authors suggest the relatively high proportion of women who did not deliver and survived may indicate delivery is not required for non-obstetric indications among critically ill pregnant women with COVID-19, though they recommend more research to better inform future decision making.

## FIGURES

| Characteristic   | Pregnant (N=32)  | Non-Pregnant (N=64) | p-value |
|--|------------------|---------------------|---------|
| Age (years) – median (IQR)   | 32 (27-35)       | 32 (27-35)          | 0.99    |
| qSOFA score on ICU admission   |                  |                     | 0.99    |
| 0-1  | 12 (37.5)        | 24 (37.5)           |         |
| 2-3  | 20 (62.5)        | 40 (62.5)           |         |
| Race – no. (%)   |                  |                     | 0.49    |
| White  | 10 (31.2)        | 23 (35.9)           |         |
| Black  | 7 (21.9)         | 20 (31.2)           |         |
| Asian  | 3 (9.4)          | 4 (6.2)             |         |
| More than one or not reported  | 12 (37.5)        | 17 (26.5)           |         |
| Hispanic ethnicity – no. (%)   | 9 (28.1)         | 20 (31.3)           | 0.75    |
| Body mass index (kg/m <sup>2</sup> ) – median (IQR) <sup>a</sup>         | 33.7 (27.0-38.2) | 36.7 (29.9-42.2)    | 0.10    |
| Coexisting conditions – no. (%)  |                  |                     |         |
| Diabetes mellitus  | 4 (12.5)         | 22 (34.4)           | 0.02    |
| Hypertension   | 3 (9.4)          | 16 (25.0)           | 0.07    |
| Asthma   | 9 (28.1)         | 16 (25.0)           | 0.74    |
| Chronic kidney disease   | 1 (3.1)          | 2 (3.1)             | 0.99    |
| Days from symptoms to ICU admission – median (IQR)                       | 7 (5-10)         |                     |         |
| Vital signs on day of ICU admission – median (IQR)                       |                  |                     |         |
| Temperature – °C <sup>a</sup>  | 37.5 (37.0-38.0) | 38.4 (37.3-39.3)    | <0.01   |
| Systolic blood pressure – mmHg   | 99 (91-110)      | 99 (89-106)         | 0.64    |
| Heart rate – beats per min   | 116 (108-128)    | 119 (102-132)       | 0.81    |
| Respiratory rate – breaths per min                                       | 28 (23-37)       | 34 (27-40)          | 0.02    |
| Laboratory findings on day of ICU admission – median (IQR) <sup>a</sup>  |                  |                     |         |
| White blood cell count – per ×10 <sup>9</sup> /L                         | 9.4 (7.8-12.7)   | 7.6 (5.3-11.1)      | 0.04    |
| Creatinine – mg/dl   | 0.5 (0.5-0.7)    | 0.7 (0.6-0.9)       | <0.01   |
| D-dimer – ng/mL  | 890 (640-1374)   | 845 (441-1688)      | 0.68    |
| C-reactive protein – mg/L  | 99 (77 - 118)    | 119 (53-237)        | 0.27    |
| Invasive mechanical ventilation on ICU admission – no. (%)               | 18 (56.2)        | 37 (57.8)           | 0.88    |
| PaO <sub>2</sub> :FiO <sub>2</sub> – mm Hg – median (IQR) <sup>b,d</sup> | 183 (108-261)    | 144 (100-230)       | 0.42    |
| Gestational age at ICU admission, weeks – median (IQR)                   | 30.4 (25.8-33.5) | NA                  | -       |
| Treatments & Organ Injury within the first 14 days of ICU admission      |                  |                     |         |
| Interventions for hypoxemia – no. (%)                                    |                  |                     |         |
| Prone position   | 11 (34.4)        | 25 (39.1)           | 0.65    |
| Neuromuscular blockade   | 9 (28.1)         | 28 (43.8)           | 0.14    |
| Inhaled epoprostenol or nitric oxide                                     | 3 (9.4)          | 10 (15.6)           | 0.40    |
| Medical therapy – no. (%)  |                  |                     |         |
| Remdesivir   | 16 (50.0)        | 7 (10.9)            | <0.01   |
| Tocilizumab  | 3 (9.4)          | 15 (23.4)           | 0.10    |
| Convalescent plasma  | 4 (12.5)         | 6 (9.4)             | 0.73    |
| Any experimental therapy <sup>c</sup>                                    | 17 (53.1)        | 25 (39.1)           | 0.19    |
| Therapeutic anticoagulation  | 13 (41.1)        | 28 (43.8)           | 0.77    |
| Acute respiratory distress syndrome – no. (%)                            | 16 (50.0)        | 16 (50)             | 0.03    |
| Invasive mechanical ventilation – no. (%)                                | 23 (71.9)        | 48 (75.0)           | 0.74    |
| Days of mechanical ventilation – median (IQR) <sup>b</sup>               | 11 (6-14)        | 13 (8-14)           | 0.53    |
| Vasopressors – no. (%)   | 23 (71.8)        | 23 (71.9)           | 0.23    |
| Acute kidney injury – no. (%) <sup>d</sup>                               | 4 (12.5)         | 15 (25.0)           | 0.16    |
| Renal replacement therapy  | 0 (0)            | 6 (10.0)            | 0.09    |
| Arrhythmia – no. (%)   | 1 (3.1)          | 1 (1.6)             | 0.99    |
| Extra-corporeal membrane oxygenation – no. (%)                           | 3 (9.4)          | 3 (4.7)             | 0.40    |
| Thrombosis – no. (%)   | 2 (6.2)          | 7 (10.9)            | 0.71    |
| Outcomes   |                  |                     |         |
| In-hospital death – no. (%) <sup>e</sup>                                 | 0 (0)            | 6 (9.4)             | 0.17    |
| ICU length of stay, days – median (IQR) <sup>a</sup>                     | 10 (3-18)        | 13 (5-24)           | 0.28    |
| Hospital length of stay, days – median (IQR) <sup>a</sup>                | 14 (8-24)        | 11 (5-23)           | 0.13    |
| Delivered during hospitalization – no. (%) <sup>f</sup>                  | 19 (59.4)        | NA                  |         |
| Cesarean delivery – no. (%) <sup>f</sup>                                 | 17 (53.1)        | NA                  |         |
| Gestational age at delivery, weeks – median (IQR)                        | 32.9 (30.1-34.4) | NA                  |         |

<sup>a</sup>Data were missing for creatinine for 3 non-pregnant patients, C-reactive protein for 10 pregnant and 21 non-pregnant patients, d-dimer for 8 pregnant and 29 non-pregnant patients, and PaO<sub>2</sub>:FiO<sub>2</sub> for 10 pregnant and 11 non-pregnant mechanically ventilated patients.

<sup>b</sup>PaO<sub>2</sub>:FiO<sub>2</sub> refers to the ratio of the partial pressure of arterial oxygen (PaO<sub>2</sub>) over the fraction of inspired oxygen (FiO<sub>2</sub>) and was only assessed in patients receiving invasive mechanical ventilation. Days of mechanical ventilation were limited to the first 14 days of hospitalization.

<sup>c</sup>Experimental therapies were remdesivir, tocilizumab, and convalescent plasma.

<sup>d</sup>Acute kidney injury was defined as doubling of baseline creatinine or need for renal replacement therapy. Patients with end-stage renal disease (n=4) were excluded.

Table 1. Characteristics, therapies, and outcomes according to pregnancy status

| Case <sup>a</sup> | Gestation at ICU Admission (n weeks) | Delivery During Admission | Gestational Age at Delivery (weeks) | Mode of Delivery | Indication for Delivery   | Indication for Cesarean Delivery | PaO <sub>2</sub> to FiO <sub>2</sub> on Intubation | Duration of Mechanical Ventilation <sup>b</sup> (Days) | ICU Length of Stay <sup>c</sup> (Days) | Hospital Length of Stay <sup>d</sup> (Days) |
|-------------------|--------------------------------------|---------------------------|-------------------------------------|------------------|---------------------------|----------------------------------|--|--|--|---|
| 1                 | 40.7                                 | Yes                       | 40.6                                | Vaginal          | Spontaneous labor         | NA                               | 513  | 1  | 1                                      | 5   |
| 2                 | 36.4                                 | Yes                       | 36.4                                | Cesarean         | Respiratory failure       | Breech                           | NA   | 0  | 5                                      | 8   |
| 3                 | 36.0                                 | Yes                       | 37.0                                | Cesarean         | Fetal status              | Fetal heart rate                 | NA   | 0  | 1                                      | 8   |
| 4                 | 35.6                                 | Yes                       | 35.6                                | Cesarean         | SROM <sup>e</sup>         | Breech                           | 268  | 6  | 7                                      | 13  |
| 5                 | 34.7                                 | Yes                       | 34.3                                | Cesarean         | Fetal status              | Fetal heart rate                 | 117  | 14   | 25                                     | 35  |
| 6                 | 34.3                                 | Yes                       | 34.4                                | Cesarean         | Respiratory failure       | Critical illness                 | 116  | 12   | 12                                     | 24  |
| 7                 | 33.5                                 | Yes                       | 34.4                                | Cesarean         | Preeclampsia              | Critical illness                 | NA   | 0  | 1                                      | 4   |
| 8                 | 33.6                                 | Yes                       | 33.6                                | Cesarean         | Respiratory failure       | Uterine surgery                  | NA   | 0  | 1                                      | 6   |
| 9                 | 33.4                                 | No                        | NA                                  | NA               | NA                        | NA                               | NA   | 0  | 1                                      | 3   |
| 10                | 33.4                                 | Yes                       | 33.4                                | Cesarean         | Respiratory failure       | Critical illness                 | 101  | 5  | 6                                      | 14  |
| 11                | 32.6                                 | Yes                       | 32.9                                | Cesarean         | Respiratory failure       | Breech                           | 158  | 14   | 15                                     | 24  |
| 12                | 31.6                                 | Yes                       | 31.6                                | Cesarean         | Respiratory failure       | Critical illness                 | 232  | 14   | 18                                     | 22  |
| 13                | 31.3                                 | Yes                       | 32.7                                | Cesarean         | SROM <sup>e</sup> & labor | Fetal heart rate                 | 184  | 6  | 14                                     | 21  |
| 14                | 30.7                                 | Yes                       | 30.7                                | Cesarean         | Respiratory failure       | Critical illness                 | 62   | 14   | 25                                     | 28  |
| 15                | 30.7                                 | No                        | NA                                  | NA               | NA                        | NA                               | NA   | 0  | 1                                      | 7   |
| 16                | 30.6                                 | Yes                       | 31.4                                | Cesarean         | Respiratory failure       | Critical illness                 | 102  | 11   | 15                                     | 18  |
| 17                | 30.1                                 | Yes                       | 30.1                                | Cesarean         | Respiratory failure       | Critical illness                 | 576  | 9  | 9                                      | 13  |
| 18                | 29.4                                 | Yes                       | 29.4                                | Cesarean         | Respiratory failure       | Critical illness                 | 68   | 14   | 36                                     | 44  |
| 19                | 28.4                                 | No                        | NA                                  | NA               | NA                        | NA                               | NA   | 0  | 5                                      | 8   |
| 20                | 27.3                                 | No                        | NA                                  | NA               | NA                        | NA                               | NA   | 0  | 3                                      | 23  |
| 21                | 26.1                                 | Yes                       | 30.0                                | Vaginal          | SROM <sup>e</sup> & labor | NA                               | 161  | 14   | 29                                     | 38  |
| 22                | 26.0                                 | No                        | NA                                  | NA               | NA                        | NA                               | 420  | 7  | 10                                     | 23  |
| 23                | 25.9                                 | Yes                       | 26.0                                | Cesarean         | Fetal status              | Fetal heart rate                 | 92   | 10   | 12                                     | 13  |
| 24                | 25.9                                 | No                        | NA                                  | NA               | NA                        | NA                               | NA   | 13   | 15                                     | 21  |
| 25                | 25.6                                 | No                        | NA                                  | NA               | NA                        | NA                               | 254  | 6  | 8                                      | 12  |
| 26                | 25.4                                 | No                        | NA                                  | NA               | NA                        | NA                               | 183  | 14   | 41                                     | 61  |
| 27                | 25.1                                 | Yes                       | 26.1                                | Cesarean         | Fetal status              | Fetal heart rate                 | 417  | 8  | 21                                     | 38  |
| 28                | 24.9                                 | No                        | NA                                  | NA               | NA                        | NA                               | 348  | 7  | 10                                     | 12  |
| 29                | 23.6                                 | No                        | NA                                  | NA               | NA                        | NA                               | 197  | 1  | 1                                      | 7   |
| 30                | 23.1                                 | No                        | NA                                  | NA               | NA                        | NA                               | 252  | 13   | 19                                     | 30  |
| 31                | 19.3                                 | No                        | NA                                  | NA               | NA                        | NA                               | 310  | 13   | 19                                     | 25  |
| 32                | 18.1                                 | No                        | NA                                  | NA               | NA                        | NA                               | NA   | 0  | 2                                      | 5   |

<sup>a</sup>Five patients were included as cases in references 4 and 5.

<sup>b</sup>Median ICU length of stay was 5 days (IQR, 2-12) for those without delivery versus 12 days (IQR, 5-21) for those delivered during admission. Median hospital length of stay was 11 days (IQR, 6-22) for those without delivery versus 18 days (IQR, 8-28) for those delivered during admission. Median days of mechanical ventilation was 6 days (IQR, 0-13) for those without delivery versus 9 days (IQR, 1-14) for those delivered during admission.

<sup>c</sup>SROM refers to spontaneous rupture of membranes.

Table 2. Case Details of Critically Ill Pregnant Patients with Covid-19

## ADJUSTING PRACTICE DURING COVID-19

### MEDICAL SUBSPECIALTIES

#### HEMATOLOGY AND ONCOLOGY

##### MANAGING CANCER PATIENTS DURING THE COVID-19 PANDEMIC: AN ESMO MULTIDISCIPLINARY EXPERT CONSENSUS

Curigliano G, Banerjee S, Cervantes A, Garassino MC, Garrido P, Girard N, Haanen J, Jordan K, Lordick F, Machiels JP, Michielin O, Peters S, Tabernero J, Douillard JY, Pentheroudakis G; Panel members.. Ann Oncol. 2020 Oct;31(10):1320-1335.  
doi: 10.1016/j.annonc.2020.07.010. Epub 2020 Jul 31.

Level of Evidence: Other - Guidelines and Recommendations

#### BLUF

An international consortium of 62 multidisciplinary cancer care experts from the European Society for Medical Oncology present a set of statements encompassing 28 committee-approved guidelines for cancer care best practices during the SARS-CoV-2 pandemic (Table 1). The guidelines encompass 10 categories: patient management and follow-up, infection prevention, use of specific therapies (GC-SF, thromboembolism prophylaxis, targeted TKI, chemotherapy, radiation), immunotherapy utilization, COVID-19 testing, and clinical trial activity. These authors suggest their guidelines offer the best strategy for providing high quality care to cancer patients during the COVID-19 pandemic while minimizing potential harm.

#### ABSTRACT

We established an international consortium to review and discuss relevant clinical evidence in order to develop expert consensus statements related to cancer management during the severe acute respiratory syndrome coronavirus 2-related disease (COVID-19) pandemic. The steering committee prepared 10 working packages addressing significant clinical questions from diagnosis to surgery. During a virtual consensus meeting of 62 global experts and one patient advocate, led by the European Society for Medical Oncology, statements were discussed, amended and voted upon. When consensus could not be reached, the panel revised statements until a consensus was reached. Overall, the expert panel agreed on 28 consensus statements that can be used to overcome many of the clinical and technical areas of uncertainty ranging from diagnosis to therapeutic planning and treatment during the COVID-19 pandemic.

## FIGURES

| WP   | Main statements  |
|--|--|
| Strategies for patient management and follow-up  | <b>STATEMENT 1:</b> Telehealth and digital health in oncology can be an excellent tool for real-time video consultations for primary care triage and interventions such as counselling, medication prescribing and management, management of long-term treatment and post-discharge coordination supported by remote-monitoring capabilities. It can also be an excellent tool for wellness interventions and in areas such as health education, physical activity, diet monitoring, health risk assessment, medication adherence and cognitive fitness.   |
| Prevention of SARS-CoV-2 infection in cancer patients and prioritisation of cancer care  | <b>STATEMENT 2:</b> Cancer care prioritisation and cancer care intensity should be adapted to the pandemic scenario (from 1 to 4 according to the ECDC), to local RD index and to health facilities and resources.<br><b>STATEMENT 3:</b> When feasible in the context of available resources, cancer patients requiring admission to hospital for cancer treatment should be tested for SARS-CoV-2 regardless of symptoms or chest radiological findings if considered at high risk of mortality in case of SARS-CoV-2 infection.<br><b>STATEMENT 4:</b> Perform a point-of-care risk assessment to assess the likelihood of SARS-CoV-2 infection, including the clinical presentation of the patient and a review of clinical, epidemiological and travel history. This should aim to achieve a rapid evaluation of the risk of infectiousness based on signs, symptoms and the procedures likely to result in infectious respiratory droplets and aerosols.<br><b>STATEMENT 5:</b> PPE should be provided to all health care professionals and used meticulously. Health care workers in enclosed spaces should wear eye protection, a gown and a surgical mask or, if available, an FFP, and practice hand hygiene or protection (gloves). Swab testing should be offered to all symptomatic health professionals.   |
| G-CSF use and thromboprophylaxis in cancer patients during the COVID-19 pandemic: benefits, risks and impact in COVID-19-negative and COVID-19-positive cancer patients<br>COVID-19 testing: who, when and how (PCR, serology) | <b>STATEMENT 6:</b> To lower the risk of febrile neutropenia, consider expanding the indication of G-CSF for patients with intermediate (10%–20%) and high risk of febrile neutropenia (>20%) and specifically for elderly patients with comorbidities.<br><b>STATEMENT 7:</b> In patients with cancer and COVID-19, there is an increased risk of thromboembolic events and associated complications such as lung vessel obstructive thrombo-inflammatory syndrome. Prophylaxis using LMWH or NOACs is recommended.<br><b>STATEMENT 8:</b> Detection of SARS-CoV-2 RNA by means of RT-PCR is the current gold standard for diagnosis of acute infection with the causative organism of COVID-19.<br><b>STATEMENT 9:</b> Serological Ab tests cannot replace testing for the SARS-CoV-2 nucleic acid. They can be used for longitudinal detection of seroconversion and seroprevalence in individuals previously positive for SARS-CoV-2.<br><b>STATEMENT 10:</b> Patients' infectivity for SARS-CoV-2 is determined by the presence of the virus in different body fluids, secretions and excreta. The persistence and clearance of viral RNA from different specimens of patients with COVID-19 remain unclear. We need longitudinal studies to distinguish early asymptomatic patients testing positive from patients recovered from COVID-19 who still test positive by RT-PCR as their infectivity may differ.  |
| Use of immunotherapy   | <b>STATEMENT 11:</b> For the approved indication of (neo)adjuvant treatment, where there is a significant survival benefit, IOs should not be withheld or delayed in the absence of SARS-CoV-2 infection. In patients who have tested positive for SARS-CoV-2, the (neo)adjuvant IO should be postponed until recovery.<br><b>STATEMENT 12:</b> For patients with metastatic melanoma, intermediate/poor-risk mRCC, PD-L1-positive NSCLC and hepatocellular carcinoma, where there is a clear survival benefit, ICI treatment should be interrupted because of COVID-19. Restarting ICI treatment should be considered after complete resolution of COVID-19 following negative RT-PCR testing. A combination of ICI with cytotoxic ChT can be considered and discussed with patients when the cost–benefit ratio is favourable (OS gain) according to patient risk factors and preference.<br><b>STATEMENT 13:</b> High-dose steroids may represent a potential risk factor for mortality in cancer patients who are infected with SARS-CoV-2. In case of the need to manage a G3–4 irAE, if possible, switch to another immunosuppressive agent.<br><b>STATEMENT 14:</b> The combination of anti-CTLA4 plus anti-PD-(L)1 should be given if the patient's disease requires such ICI treatment (in case of an approved indication), in view of the lack of evidence that sequencing anti-PD-(L)1 and anti-CTLA4 agents is as effective or less toxic.<br><b>STATEMENT 15:</b> For the differential diagnosis of an irAE from SARS pneumonitis, a nasopharyngeal swab should be obtained for PCR and a high-resolution thoracic CT scan should be carried out. If negative, a BAL should be considered [increased risk for pulmonary oncology team] for differential diagnosis of irAEs versus COVID-19. |
| Use of targeted TKI therapies  | <b>STATEMENT 16:</b> TKIs of the PI3K/AKT/mTOR or RAS/RAF/MEK axis can interfere with critical pathways involved in innate or adaptive immune responses. The decision to withhold therapy with these TKIs depends on the risk–benefit balance. Consequently, the magnitude of benefit (ESMO-MCBS) from the TKI should be considered in a tumour-specific context in the decision-making process until more clinical data are available.<br><b>STATEMENT 17:</b> Due to the acute kinetics of COVID-19, it is reasonable to withhold TKI therapy in patients with oncologically stable disease until the patient recovers. TKIs may not be interrupted in patients with less severe COVID-19 or in those with targetable, oncogene-addicted high-volume tumours at high risk of flare upon TKI discontinuation.   |
| Implementation of adjuvant/neoadjuvant ChT   | <b>STATEMENT 18:</b> For breast cancer patients in the curative setting, regimens and doses of adjuvant/neoadjuvant systemic therapies should be followed, always preceded by a multidisciplinary discussion, risk–benefit analysis and discussion with the patient. Significant delays should be avoided and protective/supportive measures implemented (growth factor support, less immunosuppressive regimen selection).<br><b>STATEMENT 19:</b> In stage II–III NSCLC, adjuvant ChT (with concurrent or sequential RT in stage III) is recommended for fit, young patients without significant comorbidities, after an informed discussion with the patient. In the event of lack of surgical resources, neoadjuvant ChT followed by surgery may be considered in highly selected subsets of patients.<br><b>STATEMENT 20:</b> Switching to SCPRT (5 × 5 Gy) in rectal cancer rather than standard long-course CRT schedules should be considered.   |
| RT strategies during the COVID-19 pandemic   | <b>STATEMENT 21:</b> Patients undergoing adjuvant or definitive lung RT are at risk of severe complications from COVID-19. In order to reduce the risks of treatment and hospital attendances during the COVID-19 pandemic, the use of reduced-fractionation RT should be discussed by the multidisciplinary tumour board as well as with the patient in order to balance the risk–benefit of the approach.<br><b>STATEMENT 22:</b> In the case of a diagnosed COVID-19 patient with lung cancer, we recommend continuing curative-intent thoracic RT, taking into consideration the severity of the COVID-19 clinical syndrome, the risk of tumour recurrence/progression with treatment interruption and the local resources.  |

Continued

| WP   | Main statements   |
|--|---|
| Prioritisation of cancer care and ICU triage in cancer patients/ rehabilitation after COVID-19 infection | <b>STATEMENT 23:</b> Active and progressing status of cancer, advanced age, poor PS, smoking status, comorbidities and possibly type of cancer (haematological, thoracic malignancies) and administration of cytotoxic ChT have been initially identified as significant risk factors for severity and mortality of COVID-19.<br><b>STATEMENT 24:</b> A decision on ICU transfer depends on the ICU resource strain and is to be adapted according to the RD index and ECDC pandemic scenario; the ethical value of maximising the number of patients who survive COVID-19 with a reasonable life expectancy has the highest priority.  |
| Clinical trials activities in the COVID-19 era   | <b>STATEMENT 25:</b> The risk–benefit profile for including an individual patient in a clinical trial should be adapted to the RD index and case load of the pandemic as well as health care organisation characteristics and resources.<br><b>STATEMENT 26:</b> During the COVID-19 pandemic, deviations from a clinical trial protocol (for risk–benefit reasons) may be considered provided there is rigorous documentation in the medical record of the patient and that this is communicated as soon as possible to the sponsor. There are no acceptable deviations in safety reporting.<br><b>STATEMENT 27:</b> During the COVID-19 pandemic, we should continue lobbying for promoting clinical cancer research to find better therapeutic options for patients with neoplasms. Cancer is and will continue to be one of the most significant causes of morbidity and mortality.<br><b>STATEMENT 28:</b> While we globally continue promoting clinical cancer research as the only way to find better therapeutic options and to improve cancer prognosis, we should continue ranking priorities in terms of value for the most appropriate clinical research. |

Ab, antibody; BAL, broncho-alveolar lavage; ChT, chemotherapy; COVID-19, severe acute respiratory syndrome coronavirus 2-related disease; CRT, chemoradiotherapy; CT, computed tomography; CTLA4, cytotoxic T-lymphocyte-associated protein 4; ECDC, European Centre for Disease Prevention and Control; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; FFP, filtering face piece; G, grade; G-CSF, granulocyte colony-stimulating factor; ICI, immune checkpoint inhibitor; ICU, intensive care unit; irAE, immune-related adverse event; LMWH, low molecular weight heparin; mRCC, metastatic renal cell carcinoma; mTOR, mammalian target of rapamycin; NOAC, novel oral anticoagulant; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; PPE, personal protective equipment; PS, performance status; RT, radiotherapy; SARS-CoV2, severe acute respiratory syndrome coronavirus 2; SCPRT, short-course preoperative radiotherapy; TKI, tyrosine kinase inhibitor; WP, working package.

## R&D: DIAGNOSIS & TREATMENTS

### DEVELOPMENTS IN TREATMENTS

#### APPLICATION OF METHYLENE BLUE -VITAMIN C -N-ACETYL CYSTEINE FOR TREATMENT OF CRITICALLY ILL COVID-19 PATIENTS, REPORT OF A PHASE-I CLINICAL TRIAL

Alamdari DH, Moghaddam AB, Amini S, Keramati MR, Zarmehri AM, Alabdari AH, Damsaz M, Banpour H, Yarahmadi A, Koliakos G. Eur J Pharmacol. 2020 Oct 15;885:173494. doi: 10.1016/j.ejphar.2020.173494. Epub 2020 Aug 20.

Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

#### BLUF

A phase 1 clinical trial conducted by physicians at Mashhad University of Medical Sciences in Mashhad, Iran evaluated outcomes of critically ill COVID-19 patients with evidence of oxidative stress treated with methylene blue-vitamin C-N-acetyl cysteine (MCN). The authors identified 25 severely-ill COVID-19 patients with high nitrite, nitrates, methemoglobin (met-Hb), prooxidant-antioxidant-balance (PAB) levels compared to healthy controls ( $p<0.05$ , Table 1) and treated five with MCN. They found a significant decrease ( $p<0.05$ ) in levels of nitrates, met-Hb, PAB, CRP, and LDH (Table 2) in four patients (80%, Table 2) who were ultimately discharged from the intensive care unit without evidence of adverse effects. The authors suggest MCN is a safe therapy for management of severe COVID-19 disease, with promising preliminary data from a mechanistic standpoint suggesting it reduces inflammatory molecules which warrants progression to randomized trials.

#### ABSTRACT

COVID-19 is a global catastrophic event that causes severe acute respiratory syndrome. The mechanism of the disease remains unclear, and hypoxia is one of the main complications. There is no currently approved protocol for treatment. The microbial threat as induced by COVID-19 causes the activation of macrophages to produce a huge amount of inflammatory molecules and nitric oxide (NO). Activation of macrophages population into a pro-inflammatory phenotype induces a self-reinforcing cycle. Oxidative stress and NO contribute to this cycle, establishing a cascade inflammatory state that can kill the patient. Interrupting this vicious cycle by a simple remedy may save critical patients' lives. Nitrite, nitrate (the metabolites of NO), methemoglobin, and prooxidant-antioxidant-balance levels were measured in 25 ICU COVID-19 patients and 25 healthy individuals. As the last therapeutic option, five patients were administered methylene blue-vitamin C-N-acetyl Cysteine (MCN). Nitrite, nitrate, methemoglobin, and oxidative stress were significantly increased in patients in comparison to healthy individuals. Four of the five patients responded well to treatment. In conclusion, NO, methemoglobin and oxidative stress may play a central role in the pathogenesis of critical COVID-19 disease. MCN treatment seems to increase the survival rate of these patients. Considering the vicious cycle of macrophage activation leading to deadly NO, oxidative stress, and cytokine cascade syndrome; the therapeutic effect of MCN seems to be reasonable. Accordingly, a wider clinical trial has been designed. It should be noted that the protocol is using the low-cost drugs which the FDA approved for other diseases. TRIAL REGISTRATION NUMBER: NCT04370288.

#### FIGURES

**Table 1**  
Demographic characterizations of patients, healthy individuals (HI), and laboratory results.

|                           | HI (n = 25)   | Patients group (n = 25) | P value             |
|---------------------------|---------------|-------------------------|---------------------|
| Age (years)               | 56.6 ± 11.4   | 59.9 ± 13.6             | 0.22                |
| Male/Female               | 12/13         | 11/14                   | 0.74                |
| NO <sup>2</sup> (µmol/l)  | 7.6 ± 3.9     | 10.7 ± 7.9              | 0.01 <sup>a</sup>   |
| NOS <sup>3</sup> (µmol/l) | 22.4 ± 15.3   | 44.7 ± 30.1             | 0.002 <sup>a</sup>  |
| Met-Hb (%)                | 2.5 ± 0.9     | 16.4* ± 9.1             | 0.0001 <sup>a</sup> |
| PAB (HK)                  | 35.8 ± 15.3   | 88.4* ± 28.4            | 0.0001 <sup>a</sup> |
| CRP (mg/dl)               | 8.7 ± 4.5     | 94.3* ± 49.5            | 0.0001 <sup>a</sup> |
| LDH (U/l)                 | 251.6 ± 139.9 | 1036.6* ± 348.8         | 0.0001 <sup>a</sup> |

The data are presented as mean ± S.D.

<sup>a</sup> There was a significant difference between patients and HI ( $p < 0.05$ ).

**Table 2**  
The data of 4 patients before and after treatment.

|  | Before Treatment (n = 4) | After Treatment (n = 4) | P value            |
|--|--------------------------|-------------------------|--------------------|
| NO <sub>2</sub> <sup>·</sup> ( $\mu\text{mol/l}$ ) | 2.8 ± 13.1               | 7.0 ± 1.4               | 0.009 <sup>a</sup> |
| NO <sub>3</sub> <sup>·</sup> ( $\mu\text{mol/l}$ ) | 68.2 ± 44.7              | 40.7 ± 25.2             | 0.05 <sup>a</sup>  |
| Met-Hb (%)   | 14.7 ± 2.2               | 4.5 ± 0.5               | 0.001 <sup>a</sup> |
| PAB (HK)   | 90.5 ± 6.4               | 51.7 ± 21.7             | 0.001 <sup>a</sup> |
| CRP (mg/dl)  | 99.0 ± 31.0              | 17.7 ± 2.9              | 0.005 <sup>a</sup> |
| LDH (U/l)  | 859.75 ± 219.6           | 245.0 ± 100.7           | 0.002 <sup>a</sup> |

The data are presented as mean ± S.D.

<sup>a</sup> There was a significant difference between patients and HI ( $p < 0.05$ ).

## CYSTEINE FOCUSED COVALENT INHIBITORS AGAINST THE MAIN PROTEASE OF SARS-COV-2

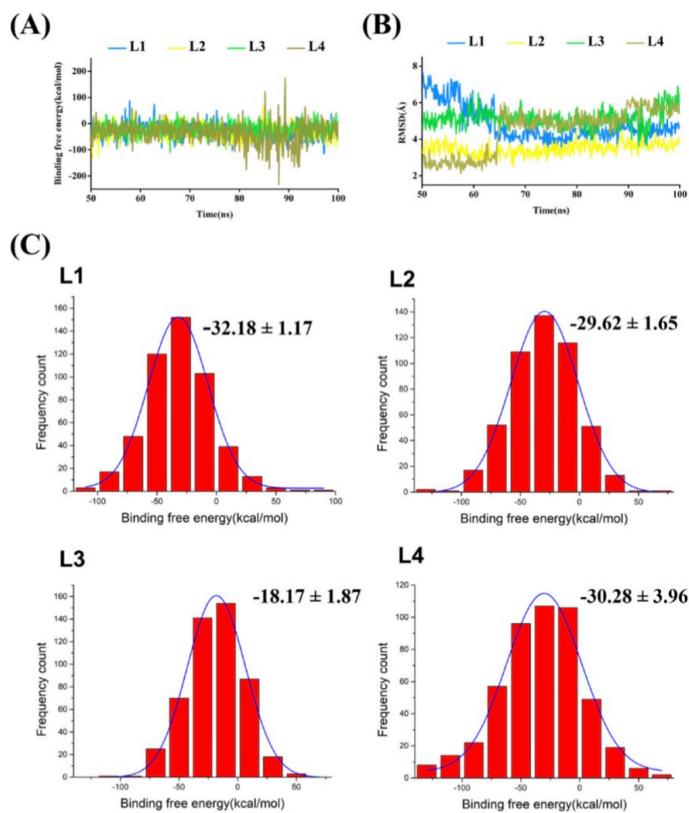
Paul AS, Islam R, Parves MR, Mamun AA, Shahriar I, Hossain MI, Hossain MN, Ali MA, Halim MA.. J Biomol Struct Dyn. 2020 Oct 13:1-20. doi: 10.1080/07391102.2020.1831610. Online ahead of print.

Level of Evidence: Other - Modeling

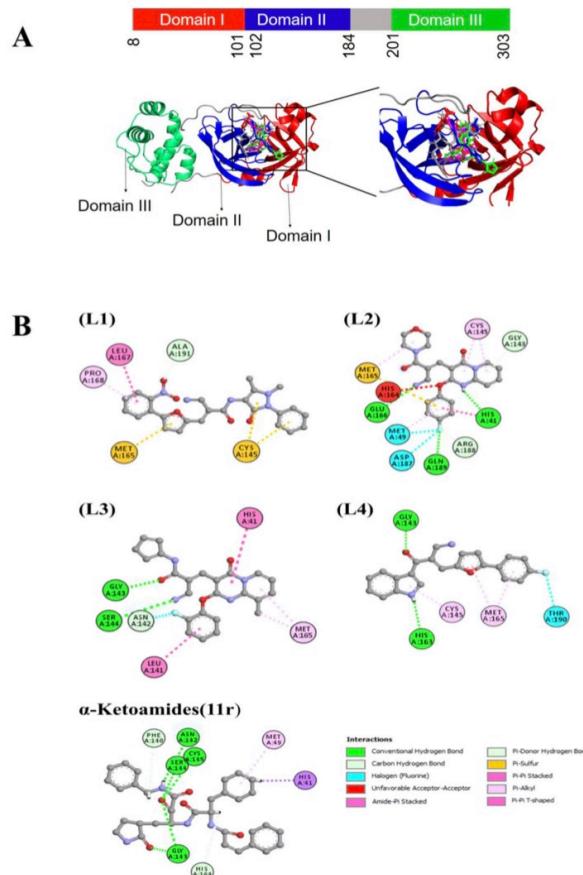
### BLUF

A computer modeling study conducted by chemists from the Red-Green Research Centre in Dhaka, Bangladesh studied a possible mechanism for inhibiting the SARS-CoV-2 main protease (Mpro) by targeting the interactions between ligands and cysteine 145 on Mpro. Using Autodock Vina, authors screened 1400 ligands and chose four (L1, L2, L3, L4) plus a-ketoamide (control) to undergo a molecular docking analysis (Figure 7), which found that L1 had the highest binding affinity (-9.2 kcal/mol) and that the apo form of Mpro was structurally similar to L1, L3, L4 and a-ketoamide (Figure 4). The authors suggest these focused ligands could be utilized to create a therapeutic agent for COVID-19 (Table 5).

### FIGURES



**Figure 7.** (A) Binding free energy (kcal/mol) of each snapshot was calculated by MM-PBSA analysis. (B) Time evolution of RMSDs of Ligand for selected four complexes. (C) Histogram of binding free energy for selected four ligands with Mpro.



**Figure 4.** (A) Domain organization and interaction of the protein with ligands. (B) Non-bonding interactions of selected four ligands and  $\alpha$ -ketoamide (11r) with the Mpro of SARS-CoV-2 (Pose predicted by AutoDock Vina).

**Table 5.** Pharmacokinetic parameters of the selected four ligands and  $\alpha$ -ketoamide (11r).

| Drugs                      | Carcinogenicity  | Rat acute toxicity (LD <sub>50</sub> , mol/kg) | P-glycoprotein Inhibitor | Blood-brain barrier | Human intestinal absorption | Renal organic cation transporter | P-glycoprotein substrate |
|----------------------------|------------------|--|--------------------------|---------------------|-----------------------------|----------------------------------|--------------------------|
| ZINC952688<br>L1           | Non-carcinogenic | 2.2770   | Non-inhibitor            | Positive            | Positive                    | Non-inhibitor                    | Non-substrate            |
| ZINC2441194<br>L2          | Non-carcinogenic | 2.6471   | Non-inhibitor            | Positive            | Positive                    | Non-inhibitor                    | Non-substrate            |
| ZINC224381<br>L3           | Non-carcinogenic | 2.6456   | Non-inhibitor            | Negative            | Positive                    | Non-inhibitor                    | Substrate                |
| ZINC4483162<br>L4          | Non-carcinogenic | 2.6070   | Inhibitor                | Positive            | Positive                    | Non-inhibitor                    | Non-substrate            |
| $\alpha$ -ketonamide (11r) | Non carcinogenic | 2.3318   | Non inhibitor            | Negative            | Positive                    | Non-inhibitor                    | substrate                |

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