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# Predictors of Mortality and Effect of Drug Therapies in Mechanically Ventilated Patients With Coronavirus Disease 2019: A Multicenter Cohort Study

We conducted a multicenter cohort study to determine the effect of drug therapies on survival in mechanically ventilated patients with coronavirus disease 2019. All consecutive adult patients admitted to ICU for coronavirus disease 2019 from March 1, 2020, to April 25, 2020, and under invasive mechanical ventilation for more than 24 hours were included. Out of 2,003 patients hospitalized for coronavirus disease 2019, 361 were admitted to ICU, 257 were ventilated for more than 24 hours, and 247 were included in the study. Simple and multiple time-dependent Cox regression models were used to assess the effects of factors on survival. Methylprednisolone administration during the first week of mechanical ventilation was associated with a decrease in mortality rate from 48% to 34% ($p = 0.01$). Mortality was significantly associated with older age, higher creatinine, lower lymphocyte count, and mean arterial pressure lower than 70 mm Hg on the day of admission.

## To the Editor:

Since the start of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, the World Health Organization (WHO) has advocated for trials to assess the benefit of antiviral treatment, anticytokine drugs, anti-inflammatory drugs, convalescent plasma, and hydroxychloroquine. However, evidence of the efficacy of such strategies is still lacking, except for corticosteroid therapy. In particular, a before-after study suggested a beneficial effect of methylprednisolone use in patients with moderate-to-severe coronavirus disease 2019 (COVID-19) (1). The randomized evaluation of COVID-19 therapy (RECOVERY) trial recently showed dexamethasone resulted in lower 28-day mortality among COVID-19 patients receiving either invasive mechanical ventilation or oxygen (2). Following these results, further studies comparing hydrocortisone or dexamethasone and placebo in COVID-19 patients were underpowered to find statistically significant reductions in mortality and stopped early. These studies were then included in the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) meta-analysis pooling data from seven randomized clinical trials and including 1,703 patients (3). This meta-analysis observed administration of systemic corticosteroids compared with usual care or placebo was associated with lower 28-day all-cause mortality (3).

Until now, the COVID-19 patients treated with endotracheal intubation and mechanical ventilation have reported mortality rates of 28–81%, depending on patient characteristics (4–8). In Belgian recommendations, before publication of the RECOVERY trial, the use of corticosteroids was left to the discretion of the ICU clinical team. This cohort study aimed to investigate whether drug therapies used against COVID-19 improved survival and to determine predictors of mortality in mechanically ventilated COVID-19 patients.

## MATERIALS AND METHODS

This cohort study started at the onset of the pandemic in the area of Liège, Belgium. It was performed in the following 12 hospitals in Wallonia, Belgium: Centre Hospitalier Universitaire of Liege, Centre Hospitalier Régional of Liege, Centre Hospitalier Chrétien of Liege, Centre Hospitalier Régional of Verviers, Centre Hospitalier Chrétien of Hermalle, Centre Hospitalier Régional of Huy, Clinique Notre-Dame de Grâce of Gosselies, Centre Hospitalier Universitaire (Université Catholique de Louvain) of Dinant, Klinik St Josef VoG of St Vith, Centre Hospitalier of Malmedy, Centre Hospitalier du Bois de l'Abbaye of Seraing, and Centre Hospitalier André Renard of Herstal. The Ethics Committee of the University Hospital of Liege (Comité d'éthique hospitalo-universitaire de Liège [707]) reviewed the study and approved it (Reference 2020/194). Due to the retrospective nature of the data collected, no consent from patients was required.

All consecutive adult patients admitted to the participating ICUs for acute respiratory failure due to SARS-CoV-2 pneumonia (diagnosed with a chest tomodensitometry suggestive of COVID-19 and with a positive polymerase chain reaction for SARS-CoV-2 in nasal swab) and mechanically ventilated for at least 24 hours from March 1, 2020, to April 25, 2020 were included. The following data were retrospectively collected and entered in a clinical report form transmitted to the participating ICUs: 1) on ICU admission: admission date, age, gender, body mass index, underlying conditions (smoking, chronic kidney disease, diabetes, and hypertension) urine output, mean arterial pressure, $Pao_2$, $FIO_2$, $Pao_2/FIO_2$ ratio, and laboratory blood values (creatinine, bilirubin, ferritin, C-reactive protein [CRP], D-dimer, platelets count, and lymphocytes count), Sequential Organ Failure Assessment (SOFA) score, and Glasgow Coma Score, 2) during ICU stay: the use of drugs to treat COVID-19 (hydroxychloroquine, azithromycin, and

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antivirals) or immune response (anticytokines and corticosteroids), the use of vasopressors, renal replacement therapy, extracorporeal membrane oxygenation, the median time gap between diagnosis and need for mechanical ventilation, the median time gap between diagnosis and steroid use, CRP and ferritin values on day 7, and 3) date of death. Patients were defined as treated with corticosteroid for COVID-19 if the corticosteroid therapy (methylprednisolone or dexamethasone) was started between day 0 and day 7 after ICU admission. In particular, corticosteroid use at a later stage of ICU stay, either for rescue therapy of acute respiratory distress syndrome (ARDS) or prevention of extubation stridor, was not reported.

Patients were followed during their entire stay in the hospital or for a minimum of 42 days in the case of prolonged hospital stay. The primary outcome was the effect of corticosteroid therapy on survival. Secondary outcomes were risk factors for mortality. Quantitative variables were reported as median and interquartile range (IQR) and compared with a Kruskal-Wallis test. Categorical variables were expressed as *n* (%) and compared with a Chi-square test. A Kaplan-Meier plot was used to describe survival rate. Simple and multiple time-dependent Cox regression models were used to assess the effects of corticosteroid therapy and other factors on survival. All variables that had a *p* value lower than a critical level of 0.1 were selected for the multivariate model. A value of $p < 0.05$ was considered significant. Missing data were not replaced. Calculations were performed using SAS (Version 9.4; Analytics Software and Solution, SAS Institute, Cary, NC) and R (Version 3.6.2; R Foundation for Statistical Computing, Vienna, Austria). All statistical analyses were done by the Biostatistics and Medico-economic Information Department of the University Hospital of Liege (Liege, Belgium).

## RESULTS

From March 1, 2020, to April 25, 2020, a total of 2,003 adult patients diagnosed with SARS-CoV-2 pneumonia were hospitalized in the participating hospitals and 361 patients were admitted to ICU for acute respiratory failure. Of these patients, 257 patients were mechanically ventilated for more than 24 hours and 247 patients included in the database. Ten patients were not included, because they were transferred to another hospital ($n = 5$) or from another hospital ($n = 5$) during their ICU stay.

The baseline characteristics of the 247 included patients are shown in **Tables 1** and **2**. As opposed to survivors, nonsurvivors were older and suffered more often from chronic kidney disease (Table 1). On the day of ICU admission, nonsurvivors had higher SOFA score and serum creatinine level, and lower mean arterial pressure and urine output. Nonsurvivors were also more frequently treated with norepinephrine during the first day in ICU. Survivors more frequently received corticosteroids and hydroxychloroquine. The median time gap between diagnosis and need for mechanical ventilation was 3 days (IQR, 2–5 d) in survivors and 2 days (IQR, 1–4 d) in nonsurvivors ($p = 0.003$). There was no difference in the median gap between diagnosis and need for mechanical ventilation between steroid and no-steroid group (median, 2 d; IQR, 1–4 d vs median, 3 d; IQR, 1–5 d; $p = 0.85$).

Corticosteroid therapy was started in 58 patients (23%) between days 0 and 7 of ICU admission. All corticosteroid treatment regimens were given using methylprednisolone with dosages shown in **Table 3**. Indications for methylprednisolone administration differed between clinicians and comprised: all patients (14 patients), all patients with $Pao_2/Fio_2$ ratio less than 150 mm Hg (36 patients), and between days 5 and 7 if patient condition did not improve (eight patients). The median time gap between the diagnosis and steroid use was 3 days (IQR, 2–6). There was no difference between survivors (median, 3.5; IQR, 2–6) and nonsurvivors (median, 2.5; IQR, 1–6) ($p = 0.6$).

Two hundred and twenty-five patients (91%) received hydroxychloroquine alone or in combination with methylprednisolone and/or azithromycin. One patient (0,004%) received antiviral (remdesivir: 200-mg loading dose IV and 100-mg IV once daily from day 2 to day 10) but received no corticosteroid treatment. This patient survived. Five patients (0.02%) received antiinterleukin-6 (Tocilizumab: 164 mg subcutaneously) but no corticosteroid. Three of these five patients treated by tocilizumab survived. Sixty-nine patients (28%) needed renal replacement therapy and 215 patients (87%) were treated with norepinephrine. Four patients (1.6%) were treated with extracorporeal membrane oxygenation.

Patients treated with methylprednisolone had lower SOFA scores, lower D-dimer values, higher mean arterial pressure, higher $Pao_2$, and higher $Pao_2/Fio_2$ ratio on ICU admission than patients who did not receive methylprednisolone (Table 2). Using multiple regression, methylprednisolone use, but not hydroxychloroquine use, was associated with a lower mortality rate. Mortality was also significantly associated with older age, higher creatinine, lower lymphocytes count, and mean arterial pressure lower than 70 mm Hg on the day of ICU admission (Table 1). There was no difference in CRP and ferritin values between the steroid and no-steroid groups on the day of admission to the ICU (Table 2). From the day of admission to the ICU to day 7, CRP values decreased by 23 mg/L (IQR, −130 to +64 mg/L) in the steroid group and by 1 mg/L (IQR, −78 to +67 mg/L) in the no-steroid group ($p = 0.12$). Ferritin values decreased by 443 μg/L (IQR, −503 to −383 μg/L) in the steroid group and by 0 μg/L (IQR, −511 to +28 μg/L) in the no-steroid group ($p = 0.13$).

Overall mortality was 111/247 (45 %). Mortality was 34% (20/58) in patients who received methylprednisolone and 48% (91/189) in patients who did not (adjusted *p* value = 0.01). The survival probability was 75% by day 23 in patients who received methylprednisolone versus 75% by day 10 for those who did not. By day 42, using logistic regression, mortality was lower in patients treated with methylprednisolone (31% vs 48%; $p = 0.028$).

## DISCUSSION

In this multicenter cohort study of 247 consecutive mechanically ventilated COVID-19 patients, methylprednisolone therapy was associated with a lower mortality. Mortality was also significantly associated with older age and higher severity at ICU admission, as assessed by mean arterial pressure less than 70 mm Hg, creatinine values, and lymphocyte count. Mechanically ventilated patients were chosen, because their definition is objective and their predicted mortality is high. Including all consecutive patients from a large area of Belgium and having no missing patients mitigates selection and attrition bias, whereas mimicking standard care as it occurs.

**TABLE 1. Baseline Characteristics and Treatment, and Association With Survival in Mechanically Ventilated Patients With Coronavirus Disease 2019**

| Variable | All *n* = 247 | | Survivors (*n* = 136) | Nonsurvivors (*n* = 111) | Simple Cox–*p* | Multiple Cox–Adjusted *p* |
|---|---|---|---|---|---|---|
| | *n* (%) or Median (Q1–Q3) | *n* Missing | *n* (%) or Median (Q1–Q3) | *n* (%) or Median (Q1–Q3) | | |
| Male sex | 172 (69.6) | – | 95 (69.9) | 77 (69.4) | 0.92 | – |
| Age (yr) | 65 (57–72) | – | 63 (55–69) | 69 (60–77) | < 0.0001 | < 0.0001 |
| Body mass index (kg/m$^2$) | 29 (26–33) | 14 | 29 (26–33) | 30 (26–33) | 0.88 | – |
| Tobacco | 21 (8.5) | 1 | 8 (5.9) | 13 (11.7) | 0.05 | 0.07 |
| Chronic kidney disease | 26 (10.5) | – | 8 (5.9) | 18 (16.2) | 0.0007 | 0.71 |
| Diabetes | 88 (35.8) | 1 | 48 (35.6) | 40 (36.0) | 0.98 | – |
| Hypertension | 141 (57.1) | – | 77 (56.6) | 64 (57.7) | 0.71 | – |
| Chronic obstructive pulmonary disease | 32 (13.0) | – | 13 (9.6) | 19 (17.1) | 0.09 | 0.63 |
| Cancer | 11 (6.1) | 66 | 5 (5.3) | 6 (7.0) | 0.74 | – |
| Immunodeficiency | 16 (6.5) | – | 6 (4.4) | 10 (9.0) | 0.22 | – |
| Sequential Organ Failure Assessment score | 6 (4–8) | – | 5 (3–7) | 7 (5–9) | < 0.0001 | 0.27 |
| $Pao_2$ (mm Hg) | 74 (62–90) | 25 | 72 (62–90) | 75 (64–91) | 0.95 | – |
| $Fio_2$ (%) | 80 (60–90) | 17 | 78 (60–90) | 80 (65–100) | 0.09 | 0.19 |
| $Pao_2/Fio_2$ | 103 (82–132) | 25 | 108 (83–140) | 96 (79–128) | 0.83 | – |
| Platelet count (10$^3$/mm$^3$) | 207 (156–290) | – | 209 (160–285) | 207 (155–293) | 0.79 | – |
| Bilirubin (mg/dL) | 0.64 (0.49–0.94) | 1 | 0.67 (0.50–0.97) | 0.60 (0.42–0.93) | 0.42 | – |
| Glasgow Coma Scale = 15 | 185 (77.4) | 8 | 109 (82.6) | 76 (71.0) | 0.05 | 0.49 |
| Creatinine (mg/dL) | 1.00 (0.78–1.37) | 1 | 0.91 (0.71–1.21) | 1.20 (0.88–1.73) | < 0.0001 | < 0.0001 |
| Mean arterial pressure < 70 mm Hg | 89 (36.0) | – | 37 (27.2) | 52 (46.8) | 0.0004 | 0.01 |
| Norepinephrine use | 128 (51.8) | – | 58 (42.6) | 70 (63.1) | 0.0021 | 0.41 |
| Urine output (mL/d) | | 1 | | | < 0.0001 | 0.25 |
| ≥ 500 | 226 (91.9) | | 132 (97.1) | 94 (85.5) | | |
| 200–500 | 11 (4.5) | | 4 (2.9) | 7 (6.4) | | |
| ≤ 200 | 9 (3.7) | | 0 (0.0) | 9 (8.2) | | |
| C-reactive protein (mg/L) | 175 (108–258) | – | 172 (107–243) | 179 (109–261) | 0.33 | – |
| D-dimer (ng/mL)[a] | 1,500 (868–3,832) | 84 | 1,305 (843–3,190) | 1,938 (990–4,000) | 0.13 | – |
| Lymphocyte count (10$^3$/mm$^3$)[a] | 0.80 (0.55–1.05) | 2 | 0.84 (0.60–1.10) | 0.75 (0.51–1.02) | 0.06 | 0.02 |
| Ferritin (μg/L)[a] | 1,185 (582–3,053) | 163 | 1,281 (578–2,790) | 1,041 (587–3,196) | 0.43 | – |
| Hydroxychloroquine use | 225 (91.1) | – | 128 (94.1) | 97 (87.4) | 0.02 | 0.46 |
| Azithromycin use | 107 (43.3) | – | 59 (43.4) | 48 (43.2) | 0.82 | – |
| Corticosteroid use | 58 (23.5) | – | 38 (27.9) | 20 (18.0) | 0.05 | 0.01 |

[a]Cox model on log-transformed values.

The characteristics of our cohort were consistent with results observed by previous authors (4–8). These series assessed 37–1,150 mechanically ventilated patients and reported 28–81% mortality rates. In most of these studies, the primary outcome was reported as 28-day all-cause mortality, whereas we followed our patients for their entire hospital stay or for a minimum of 42 days in the case of prolonged hospital stay. The therapies used in our patients were consistent with those used during

**TABLE 2. Baseline Characteristics and Treatment in Mechanically Ventilated Patients With Coronavirus Disease 2019 Who Received Methylprednisolone and Those Who Did Not**

| Variable | No Methylprednisolone (*n* = 189) *n* (%) or Median (Q1–Q3) | Methylprednisolone (*n* = 58) *n* (%) or Median (Q1–Q3) | *p*[a] |
|---|---|---|---|
| Male sex | 95 (69.9) | 77 (69.4) | 0.60 |
| Age (yr) | 65 (56–73) | 66 (58–70) | 0.50 |
| Body mass index (kg/m$^2$) | 30 (26–33) | 28 (26–32) | 0.05 |
| Tobacco | 19 (10.1) | 2 (3.5) | 0.12 |
| Chronic kidney disease | 21 (11.1) | 5 (8.6) | 0.59 |
| Diabetes | 69 (36.7) | 19 (32.8) | 0.58 |
| Hypertension | 109 (57.7) | 32 (55.2) | 0.74 |
| Chronic obstructive pulmonary disease | 20 (10.6) | 12 (20.7) | 0.05 |
| Cancer | 6 (4.9) | 5 (8.6) | 0.33 |
| Immunodeficiency | 12 (6.3) | 4 (6.9) | 0.88 |
| Sequential Organ Failure Assessment score | 7 (4–8) | 5 (3–7) | 0.003 |
| $Pao_2$ (mm Hg) | 70 (62–88) | 83 (69–101) | 0.008 |
| $Fio_2$ (%) | 80 (60–94) | 80 (60–90) | 0.49 |
| $Pao_2/Fio_2$ | 100 (76–128) | 109 (91–154) | 0.009 |
| Platelet count (10$^3$/mm$^3$) | 207 (156–291) | 213 (160–273) | 0.78 |
| Bilirubin (mg/dL) | 0.68 (0.50–0.99) | 0.59 (0.44–0.88) | 0.11 |
| Glasgow Coma Scale = 15 | 131 (72.4) | 54 (93.1) | 0.001 |
| Creatinine (mg/dL) | 1.02 (0.79–1.40) | 0.91 (0.75–1.26) | 0.16 |
| Mean arterial pressure < 70 mm Hg | 59 (31.2) | 30 (51.7) | 0.004 |
| Norepinephrine use | 101 (53.4) | 27 (46.6) | 0.36 |
| Urine output (mL/d) | | | 0.91 |
| ≥ 500 | 172 (91.5) | 54 (93.1) | |
| 200–500 | 9 (4.8) | 2 (3.4) | |
| ≤ 200 | 7 (3.7) | 2 (3.4) | |
| C-reactive protein (mg/L) | 179 (108–259) | 165 (109–236) | 0.80 |
| D-dimer (ng/mL) | 1,635 (1,004–4,000) | 990 (599–2,239) | 0.01 |
| Lymphocyte count (10$^3$/mm$^3$) | 0.78 (0.55–1.07) | 0.82 (0.51–1.03) | 0.81 |
| Ferritin (μg/L) | 1,233 (562–3,196) | 1,132 (720–1,779) | 0.62 |
| Hydroxychloroquine use | 171 (90.5) | 54 (93.1) | 0.54 |
| Azithromycin use | 88 (46.6) | 19 (32.8) | 0.06 |

[a]*p* value of Kruskal-Wallis or $\chi^2$ test.

this first phase of the pandemic. Regular use of hydroxychloroquine in our patients was based on initial observational studies, but its efficacy was not confirmed in a subsequent randomized controlled trial (9). No recommendation prompted adjunctive treatments, because no specific treatment had yet been proven to decrease mortality in critically ill COVID-19 patients on mechanical ventilation. The RECOVERY trial recently demonstrated a beneficial effect of dexamethasone in the most severe patients but was ongoing at the time we treated the patients in Belgium in this study (2).

The beneficial role of methylprednisolone in this study is consistent with what was recently anticipated by Fadel et al (1) in a before-after study, which showed a short course of methylprednisolone that was associated with a reduction in the primary composite end point from 54% to 35%. The primary composite end point in the study by Fadel et al (1) was escalation to ICU from a general

**TABLE 3. Methylprednisolone Dosage and Duration of Treatment Used in Mechanically Ventilated Coronavirus Disease 2019 Patients**

| Number of patients ($n = 58$) | Dosage | Duration (d) |
|---|---|---|
| 36 | Methylprednisolone 40 mg/12 hr (5 d) and 40 mg/d (5 d) | 10 |
| 9 | Methylprednisolone 40 mg/d | 10 |
| 8 | Methylprednisolone 2 mg/kg/d (7 d), 1 mg/kg/d (5 d), and 0.5 mg/kg/d (5 d) | 17 |
| 2 | Methylprednisolone 40 mg/d | 5 |
| 2 | Methylprednisolone 1 mg/kg/d | 7 |
| 1 | Methylprednisolone 1.5 mg/kg/d (3 d), 0.5 mg/kg (2 d), 0.2 mg/kg (2 d), and 0.1 mg/kg (3 d) | 10 |

medical unit, progression to respiratory failure requiring mechanical ventilation after hospital admission, or inhospital all cause of mortality. The RECOVERY multicenter randomized controlled trial in the United Kingdom indicated low-dose dexamethasone was associated with a better prognosis in those severely affected patients. RECOVERY trial showed 28-day mortality decreased from 40% to 28% in patients receiving low dose of dexamethasone (2). Subsequently, several ongoing studies were stopped, because it would be unethical to continue corticosteroid versus placebo trials and were thus unable to demonstrate any beneficial effect on outcome.

In a recently published meta-analysis including RECOVERY, those studies ended before completion, and three other trials, 28-day mortality was reduced by systemic corticosteroids from 41% to 31% (3). Dexamethasone was used in three of the seven studies, hydrocortisone in three, and methylprednisolone in one (3). In our study, using methylprednisolone, we observed a 14% crude difference in mortality (34% vs 48% in no-steroid patients). In the glucocorticoid therapy for COVID-19 critically ill patients with severe acute respiratory failure (Steroids-SARI; NCT04244591) included in the meta-analysis of (3), the dosage of methylprednisolone was 40 mg every 12 hours during 5 days. In our cohort, the methylprednisolone dosage was similar, ranging from 40 mg per day to 2 mg/kg/d and lasted from 5 to 10 days (Table 3).

Corticosteroids may act by controlling the intensity of the immune response to SARS-CoV-2 infection. At the start of the SARS-CoV-2 pandemic, based on prior literature about other respiratory viruses, several authors argued against the use of steroids outside research trials in COVID-19 patients, because their use was associated with delay in the clearance of viral RNA from respiratory tract. In contrast, steroids have been shown to improve outcome in ARDS secondary to *Pneumocystis carinii* pneumonia and recently in ARDS of various causes (10).

Although many countries have now adopted the use of dexamethasone for patients receiving either mechanical ventilation or oxygen alone, our results suggest other steroids, such as methylprednisolone, may have a similar or potentially better effect. We believe our results and those of REACT trial support a continuing search for the best molecule among steroids, as well as to determine the optimal dosage and duration of therapy (3). Since there was no evidence that high dose of corticosteroid use was associated with greater benefit than a lower dose of corticosteroid, we suggest a low-dose regimen of dexamethasone (6 mg/d) or a low-weight-based dose of methylprednisolone (0.5 mg/kg/d) during 10 days in COVID-19 patients.

Our study has several limitations. First, it was a retrospective analysis of the cohort due to the rapidity of occurrence of COVID-19 in Belgium and Wallonia. This rate of spread precluded the possibility to make therapy protocols and data assessment homogeneous. As most patients were still in the hospital when data collection started, our approach resulted in very few missing data, and all patients were consistently treated according to conventional intensive care guidelines and in accordance with international guidelines at the time. Second, the study was performed in one part of Belgium (Wallonia) and our results may not be applicable to other regions or countries. However, it is a multicenter study, and we estimate that our hospitals did not suffer shortages of human or material resources, as suggested in several other western countries, which could ameliorate this issue. Third, at the time of the study, there were no required guidelines for specific treatments or protocols for COVID-19. Thus, the practice and approach in caring for these patients could be different from other regions of the world, potentially reducing the external validity of our results. Fourth, due to the lack of consensus about the use of corticosteroid at the beginning of the pandemic, only 23% of patients received corticosteroids with no consistency in steroid use or dosage. These patients were overall less sick at the time of ICU admission than the other cohort. This difference has been considered by using multiple regression analysis in our statistical analysis.

## CONCLUSIONS

In a cohort of 247 unselected, sequential patients with SARS-CoV-2 pneumonia treated with mechanical ventilation, we observed mortality as high as 45%. Within this cohort, methylprednisolone therapy was independently associated with a lower mortality rate of 34%. Our results provide additional evidence to support the use of corticosteroids in COVID-19 patients. As these results are consistent with those obtained with dexamethasone, the choice of the optimal molecule, dosage, and treatment duration requires additional trials.

The authors have disclosed that they do not have any potential conflicts of interest.

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