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Comparison of clinical characteristics and outcomes of COVID-19 patients undergoing early versus late intubation from initial hospital admission: A systematic review and meta-analysis

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ABSTRACT

Background: The true impact of intubation and mechanical ventilation in coronavirus disease 2019 (COVID-19) patients remains controversial.

Methods: We searched Pubmed, Cochrane Library, Embase, and Web of Science databases from inception to October 30th, 2021 for studies containing comparative data of COVID-19 patients undergoing early versus late intubation from initial hospital admission. Early intubation was defined as intubation within 48 h of hospital admission. The primary outcomes assessed were all-cause in-hospital mortality, renal replacement therapy (RRT), and invasive mechanical ventilation (IMV) duration.

Results: Four cohort studies with 498 COVID-19 patients were included between February to August 2020, in which 28.6% had early intubation, and 36.0% underwent late intubation. Although the pooled hospital mortality rate was 32.1%, no significant difference in mortality rate was observed (odds ratio [OR] 0.81; 95% confidence interval 0.32–2.00; P = 0.64) among those undergoing early and late intubation. IMV duration (mean 9.62 vs. 11.77 days; P = 0.25) and RRT requirement (18.3% vs. 14.6%; OR 1.19; P = 0.59) were similar regardless of intubation timing. While age, sex, diabetes, and body mass index were comparable, patients undergoing early intubation had higher sequential organ failure assessment (SOFA) scores (mean 7.00 vs. 5.17; P < 0.001).

Conclusions: The timing of intubation from initial hospital admission did not significantly alter clinical outcomes during the early phase of the COVID-19 pandemic. Higher SOFA scores could explain early intubation. With the advancements in COVID-19 therapies, more
The notion that critically ill patients with known or suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with respiratory failure, non-responsive to conventional oxygen therapy should be intubated and mechanically ventilated early in the disease course without the option for non-invasive mechanical ventilation (NIMV) and high-flow nasal cannula (HFNC) has been proposed since the beginning of the ongoing pandemic. Potential concerns exist for the transmission of SARS-CoV-2 from patients to healthcare workers, particularly among those requiring aerosol-generating procedures and treatments involving NIMV and HFNC. In most instances, intubation and mechanical ventilation are instituted preemptively out of fear of an impending respiratory arrest. Early intubation of a patient with respiratory failure from known or suspected SARS-CoV-2 infection could result in unnecessary intubation and treatment in those who would have otherwise improved with a trial of HFNC and NIMV, such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP). Additionally, unnecessary intubation and mechanical ventilation might deny what might be a life-saving treatment for another patient with respiratory failure not improving with NIMV in a medical resource-limited setting, and proposals even exist for sharing a single ventilator for up to four patients [1]. Furthermore, the notion that early intubation avoids NIMV and HFNC, therefore decreasing the risk of viral transmission despite the use of personal protective equipment (PPE), is debatable. With PPE, NIMV has been shown during the 2003 severe acute respiratory syndrome (SARS) epidemic not to be associated with an increased risk of viral transmission to healthcare workers, whereas intubation increased the risk of aerosolization and infection [2]. Wide variations in protocols exist at various medical institutions on the optimal timing of intubation in critically ill coronavirus disease 2019 (COVID-19) patients. During the early course of the COVID-19 pandemic, up to 60% of COVID-19 non-survivors were intubated and mechanically ventilated instead of 1–15% of survivors [3,4]. There remains no clear consensus on the timing of intubation and trial of NIMV and HFNC before intubation. Our systematic review and meta-analysis aimed to determine the clinical outcomes and characteristics among critically ill COVID-19 patients undergoing early versus late intubation from initial hospital admission.

2. Methods

This systematic review was conducted and presented in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. This study did not require ethical approval and informed consent as it was a systematic review of previously published studies. The protocol for this review was registered and published in the International Prospective Register of Systematic Reviews under reference number CRD42021247842.
2.1. Search strategy

A literature search was performed through the Pubmed, Cochrane Library, Embase, and Web of Science databases from inception to October 30th, 2021, using the search term in Medical Subjects Headings (MeSH) and title/abstract: (“coronavirus disease 2019” OR “COVID-19” OR “COVID 19” OR “COVID19” OR “novel coronavirus” OR “2019 novel coronavirus” OR “2019-ncov” OR “2019 nCov” OR “severe acute respiratory syndrome coronavirus 2” OR “SARS-CoV” OR “SARS-CoV-2”) AND (“early intubation” OR “initial intubation” OR “early mechanical ventilation” OR “immediate intubation”) AND (“late intubation” OR “delayed intubation” OR “late mechanical ventilation” OR “non-invasive mechanical ventilation failure” OR “NIMV failure” OR “non-invasive positive pressure ventilation failure” OR “NIPPV failure” OR “high-flow nasal cannula failure” OR “bilevel positive airway pressure failure” OR “BiPAP failure” OR “continuous positive airway pressure failure” OR “CPAP failure”).

2.2. Study selection

Two authors (W.C. and B.S.) independently reviewed the titles and abstracts of all search results for eligibility. If an article was considered potentially eligible, both authors independently examined the full article for inclusion. Disagreements between the authors were resolved by a consensus-based discussion. Moreover, to detect additional studies, we simultaneously searched the reference lists of all retrieved articles for potentially eligible studies. We included studies that 1) enrolled hospitalized critically ill COVID-19 patients aged 18 years and older (population) undergoing early intubation and mechanical ventilation (intervention) who were compared with those undergoing late intubation (comparison) and reported all-cause in-hospital mortality, duration of invasive mechanical ventilation (IMV), and renal replacement therapy (RRT) as outcomes; 2) presented comparative data on the clinical characteristics and outcomes of critically ill COVID-19 patients; 3) had a cross-sectional, case-control or cohort design; and 4) involved diagnosis of SARS-CoV-2 infections made via real-time reverse transcription-polymerase chain reaction from a nasopharyngeal or oropharyngeal swab. We excluded 1) other systematic reviews, literature reviews, meta-analyses, case reports, case series, editorials, and opinion articles; however, references were screened for relevant articles; 2) studies discussing other infectious outbreaks; 3) studies on animals or in vitro studies; and 4) studies published in languages other than English if no translated version of the manuscript was available. We defined early intubation as COVID-19 patients requiring intubation and IMV within 48 h of hospital admission. Patients who failed to meet the criteria above and were intubated after 48 h of hospital admission were classified as late or delayed intubation. Studies that defined early intubation as intubation within 48 h of meeting acute respiratory distress syndrome (ARDS) criteria or late intubation as patients who failed trials of NIMV and HFNC were excluded. Studies by Pandya et al. and Vera et al. defined early intubation within 48 h from hospital admission. [5,6] Two studies by Hernandez-Romieu et al. and Mellado-Artigas et al. defined early intubation as that within 48 h of ICU admission; however, the time to ICU admission from initial hospitalization was within 48 h in the early intubation group. [7,8].

2.3. Data collection and synthesis

Two researchers (W.C. and B.S.) independently screened the titles and abstracts and reviewed the full texts of articles to identify studies meeting the established criteria. The data were extracted using a standardized data extraction form. Descriptive statistics were reported as means and standard deviations (SDs). The following information of clinical characteristics was collected and summarized in Table 1 for hospitalized critically ill COVID-19 patients: type of cohort study (retrospective or prospective, single- or multi-center); enrollment period; country of publication; the number of patients; mean (+/− SD) age of the patient; sex; Sequential Organ Failure Assessment (SOFA) score and body mass index (BMI) on admission; and cardiac disease, chronic lung disease, and diabetes mellitus as comorbidities. The clinical outcomes of critically ill COVID-19 patients are summarized in Table 2: mean (+/− SD) duration of IMV; outcomes of all-cause in-hospital mortality, and RRT requirement. Any disagreements or discrepancies in the extracted data were resolved via discussion between authors.

2.4. Outcomes

The primary outcomes of interest were the difference in clinical outcomes involving all-cause in-hospital mortality, RRT requirement, and IMV duration among hospitalized critically ill COVID-19 patients who undergo early versus late intubation for respiratory failure from initial hospital admission. The secondary outcomes were the differences in clinical characteristics between critically ill COVID-19 patients undergoing early intubation and those who underwent late intubation.

2.5. Quality assessment

Studies selected for inclusion were independently assessed for methodological quality by two independent reviewers (W.C. and B.S.) using the nine-item Newcastle-Ottawa Scale (NOS, Table 3) [9]. The NOS scale assesses three important features of the study such as adequacy of the selection of exposed and non-exposed cohorts, comparability of groups, and adequacy of outcomes assessment with a total score ranging from 0 to 9. Furthermore, the NOS scale was categorized into three groups: low quality “0–3,” moderate quality “4–6,” and high quality “7–9.” During the quality assessment of the included studies, any disagreements were resolved by consensus.

2.6. Statistical analysis

A meta-analysis was performed for the primary and secondary outcomes using the Review Manager (RevMan) software, Version 5.4, The Cochrane Collaboration, 2020. Dichotomous outcomes were assessed using the Mantel-Haenszel statistical method and measured in odds ratios (ORs) and their 95%
confidence intervals (CIs). Continuous outcomes were evaluated by inverse variance statistical method and represented as mean difference (MDs). The inverse variance method accounts for differing sample sizes of individual studies by weighting studies by the variance of their estimates, such that small studies with large variance have less weighting, and large studies with small variance have more weighting. Using DerSimonian and Laird’s random-effects model, pooled ORs, MDs, and 95% CIs were calculated, and extracted outcomes were pooled by weighted averages [10]. The random-effects model was preferred over the fixed-effects model as we suspected that clinical heterogeneity likely occurs across the included studies due to the differences in clinical protocols and patient characteristics. Furthermore, we aimed to assess the mean distribution of results across the four studies with various sample sizes without disregarding the results of small studies and giving extra weightage to results from larger studies. Statistical heterogeneity among studies was assessed using the I² statistic. High heterogeneity being classified as I² statistics of 75% and greater, moderate heterogeneity between

| Table 1 – Clinical characteristics of patients with COVID-19 undergoing early and late intubation from initial hospital admission. |
|----------------------------------|----------------|----------------|----------------|----------------|
| Author                          | Hernandez-Romieu et al. [7] | Mellado-Artigas et al. [8] | Pandya et al. [5] | Vera et al. [6] |
| **Cohort Design** | Multi-center, Retrospective | Multi-center, Prospective | Single-center, Retrospective | Single-center, Prospective |
| **Enrollment Period** | March–May 2020 | March–August 2020 | February–May 2020 | March–July 2020 |
| **Country**                  | USA | Spain | USA | Chile |
| **Total Patients (N)**          | 118 | 122 | 75 | 183 |
| **Early Intubation**          |        |        |        |        |
| **Patients (N)**               | 76 | 61 | 37 | 88 |
| **Demographics**               |        |        |        |        |
| **Age (Y), Mean ± SD**         | 67.00±14.81 | 61.00±11.00 | 65.90±14.79 | 59.00±9.63 |
| **BMI (kg/m2), Mean ± SD**     | 23 (50.0) | 25 (40.9) | 21 (48.8) | 62 (70.5) |
| **SOFA Score, Mean ± SD**      | 10.50±2.59 | 28.80±4.30 | 28.63±9.44 | 30.00±2.96 |
| **Comorbidity**                |        |        |        |        |
| **DM, N (%)**                  | 53 (69.7) | NR | NR | 27 (30.7) |
| **Late Intubation**            |        |        |        |        |
| **Patients (N)**               | 42 | 61 | 38 | 95 |
| **Demographics**               |        |        |        |        |
| **Age (Y), Mean ± SD**         | 67.00±14.81 | 62.00±11.00 | 64.05±13.87 | 64.00±11.90 |
| **BMI (kg/m2), Mean ± SD**     | 25 (59.5) | 34 (55.7) | 22 (51.2) | 70 (73.7) |
| **SOFA Score, Mean ± SD**      | 10.50±2.59 | 28.80±4.30 | 28.63±9.44 | 30.00±2.96 |
| **Comorbidity**                |        |        |        |        |
| **DM, N (%)**                  | 18 (42.9) | NR | NR | 34 (35.8) |

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease; D, days; DM, diabetes mellitus; NR, non-reported; N, numbers; SD, standard deviations; SOFA, sequential organ failure assessment; Y, years.

| Table 2 – Clinical outcomes of patients with COVID-19 undergoing early and late intubation from initial hospital admission. |
|----------------------------------|----------------|----------------|----------------|----------------|
| Author                          | Hernandez-Romieu et al. [7] | Mellado-Artigas et al. [8] | Pandya et al. [5] | Vera et al. [6] |
| **Early Intubation**          |        |        |        |        |
| **Patients (N)**               | 76 | 61 | 37 | 88 |
| **Outcomes**                   |        |        |        |        |
| **IMV Duration, Mean ± SD**    | 10.00±8.15 | NR | 5.86±8.40 | 13.00±12.60 |
| **In-hospital Mortality, N (%)** | 29 (38.2) | 13 (21.3) | 17 (45.9) | 16 (18.2) |
| **RRT, N (%)**                 | 18 (27.7) | NR | NR | 12 (13.6) |
| **Late Intubation**           |        |        |        |        |
| **Patients (N)**               | 42 | 61 | 38 | 95 |
| **Outcomes**                   |        |        |        |        |
| **IMV Duration, Mean ± SD**    | 9.00±5.93 | NR | 10.30±8.78 | 16.00±17.78 |
| **In-hospital Mortality, N (%)** | 16 (38.1) | 6 (9.8) | 20 (54.1) | 43 (45.3) |
| **RRT, N (%)**                 | 8 (19.5) | NR | NR | 12 (12.6) |

Abbreviations: COVID-19, coronavirus disease; D, days; IMV, invasive mechanical ventilation; N, numbers; NR, non-reported; RRT, renal replacement therapy; SD, standard deviations; SOFA, sequential organ failure assessment; Y, years.
50 and 74% and low as I² statistics less than 25% [11]. A P value < 0.05 was considered statistically significant.

3. Results

3.1. Study selection

Following the initial search, 1235 studies were identified from the Pubmed, EMBASE, Cochrane Library, and Web of Science databases (Fig. 1). After methodological quality assessment and removal of duplicates and non-eligible articles, four cohort studies were included in the meta-analysis. The summary of the risk of bias in each of the included studies is listed in Table 3. Their overall quality was excellent, where two studies scored 9/9 on the NOS and the remaining two studies scored 8/9.

3.2. Study characteristics

A total of 498 critically ill COVID-19 patients with comparative data segregating critically ill COVID-19 patients into early versus late intubation groups were assessed in the four observational studies included in our meta-analysis (Table 1). Of these patients, 28.6% (75/262) received early intubation, and 36.0% (85/236) received late intubation from initial hospital admission. All observational studies were cohort, and one-half were retrospectively designed. The majority of patients were enrolled during the first wave of the pandemic between February and August 2020.

3.3. Outcomes

The overall hospital mortality rate for critically ill COVID-19 patients requiring IMV was 32.1% (160/498) (Table 2). The hospital mortality rate was comparable (28.6% vs. 36.0%; OR 0.81; 95% CI 0.52–2.00; I² = 79%; P = 0.64) for patients undergoing early and late intubation from initial hospital admission (Fig. 2). Two studies reported RRT requirement among those undergoing early and late intubation [6,7]. No difference was observed for RRT (18.3% vs. 14.6%; OR 0.81; 95% CI 0.32–2.00; I² = 79%; P = 0.64) (Fig. 2). According to three studies, the duration of IMV was comparable between COVID-19 patients (mean 9.62 vs. 11.77 days; MD -2.00; 95% CI [-5.42, 1.42]; I² = 57%; P = 0.25) undergoing early and late intubation (Fig. 3) [5–7].

3.4. Clinical characteristics

The average age of COVID-19 patients undergoing early intubation versus late intubation from initial hospital admission was similar (63.23 years vs. 64.26 years; MD -1.77; 95% CI [-4.82, 1.29]; I² = 46%; P = 0.26) (Table 1 and Fig. 3). Both groups had similar proportions of male patients (55.7% vs. 63.9%; OR 0.73; 95% CI 0.51–1.06; I² = 0%; P = 0.10) (Fig. 4). The rate of diabetes (48.8% vs. 38.0%; OR 1.53; 95% CI 0.41–5.75; I² = 86%; P = 0.53) were comparable in both groups (Fig. 4). BMI was similar for COVID-19 patients undergoing early intubation compared to those undergoing late intubation (mean 29.58 vs. 30.37 kg/m²; MD -0.19; 95% CI [-2.51, 2.14]; I² = 80%; P = 0.87) (Fig. 3) [5–8,12,13]. In three studies reporting the SOFA scores on admission, the early intubation group had higher score (mean 7.00 vs. 5.17; MD 1.87; 95% CI 0.99–2.75; I² = 58%; P < 0.001) than the late intubation group (Fig. 3) [6–8].

4. Discussion

Our meta-analysis demonstrated that the timing of intubation from initial hospital admission did not significantly affect outcomes of all-cause in-hospital mortality rate, IMV duration, and RRT requirement. COVID-19 patients undergoing early and late intubation from initial hospital admission shared similar clinical characteristics of age, sex, diabetes, and BMI. However, COVID-19 patients who underwent early intubation had higher SOFA scores upon hospital admission.
than those who received late intubation, which might have been a decision-making factor for warranting early intubation.

A meta-analysis of 12 retrospective observational studies by Papoutsi et al. assessed the timing of intubation among 8,944 critically ill COVID-19 patients [14]. Early intubation was defined as the initiation of mechanical ventilation within 24 h of ICU admission. However, several studies included in that meta-analysis described early intubation as intubation within 24 h of hospitalization (initial presentation) or ICU admission, meeting ARDS criteria, or failing NIMV and HFNC [5,15,16]. Our meta-analysis differs from the
Fig. 3 – Forest plot of patients with coronavirus disease (COVID-19) divided into early intubation versus late intubation from initial hospital admission. Clinical characteristics of age, body mass index (BMI), sequential organ failure assessment (SOFA) score upon ARDS diagnosis, and outcomes of invasive mechanical ventilation (IMV) duration are assessed. Mean differences are calculated by inverse variance statistical method with a random-effects model. Abbreviations: CI, confidence interval; df, degree of freedom; IV, inverse variance; SD, standard deviation; Y, years.

Fig. 4 – Forest plot of patients with coronavirus disease (COVID-19) divided into early intubation versus late intubation from initial hospital admission. Clinical characteristics of male sex and diabetes are assessed. The odds ratio is calculated using the Mantel-Haenszel method with a random-effects model. Abbreviations: CI, confidence intervals; df, degree of freedom; M–H, Mantel-Haenszel.
The variability in the timing of intubation and lack of improvement in mortality could be due to multiple etiologies. The high in-hospital mortality rate of 32.1% in our meta-analysis could be due to the lack of proven COVID-19 therapies available during the initial stage of the pandemic and was almost similar to the ICU mortality published from several early observational studies of critically ill COVID-19 patients [17–19]. COVID-19 patients have been described to have “atypical” ARDS where respiratory failure occurs more than 7 days after initial infection (insult) with a high degree of lung compliance and normal lung volume in the setting of severe hypoxemia [20]. Severe hypoxemia occurs in COVID-19 from the loss of lung perfusion regulation and hypoxic vasoconstriction, with a high shunt fraction [20,21]. The application of PEEP early on in the disease course by intubation and mechanical ventilation is unlikely to improve gaseous exchange due to the lack of recruitable lungs. Moreover, applying high levels of PEEP may hyperinflated alveoli, worsen dead-space ventilation, and redirect blood flow away from overstretched, well-ventilated airspaces while accentuating pre-existing microvascular injury [22]. This will further compromise O2 and CO2 gaseous exchange without the benefit of recruitment of functional lung volume.

During the initial stage of the pandemic, the evidence behind early intubation upon admission without a trial of NIMV is based on the expert consensus that early intubation should be prioritized to avoid vigorous spontaneous inspiratory efforts, commonly seen in critically ill patients that can generate injurious transpulmonary pressure swings leading to a decline in respiratory status, termed patient self-induced lung injury (P-SILI) [1,22,23]. P-SILI is thought to parallel ventilator-induced lung injury (VILI) by augmenting the severity of ARDS where intubation and mechanical ventilation facilitate control of an unstable airway and enable precise regulation of oxygen, pressure, and volume delivered with sedation and paralytic administration [21–23]. This consensus was supported by a large observational study in 2016 involving 351 non-COVID-19 ARDS patients in which the early intubation group, defined as intubation within 24 h upon ARDS diagnosis, had a significantly lower 60-day mortality rate (36% vs. 56%; HR 2.37; 95% CI 1.32–4.24; P < 0.01) than the late intubation group, defined as intubation 24 h after ARDS diagnosis. Furthermore, the early intubation group had more ventilator-free days (16 days vs. 7 days; P < 0.01) and shorter ICU LOS (9 days vs. 11.5 days; P < 0.01) than the late intubation group [24]. The use of NIMV and HFNC could explain the delay in intubation received in certain critically ill COVID-19 patients, particularly in settings where the availability of mechanical ventilation was limited, although data on NIMV and HFNC use was not well described among the studies included in our meta-analysis.

The strengths of our meta-analysis were that we included 498 critically ill COVID-19 patients from four studies included during the early stage of the pandemic between February to August 2020. This allowed us to assess for possible associations found to be non-significant in individual studies due to the small sample sizes. We also applied strict inclusion criteria and compared the clinical characteristics among patients undergoing early and late intubation from initial hospital admission. We assessed other outcomes that have important clinical implications, such as RRT requirement. Several limitations were observed in our meta-analysis. The population studies that were predominantly non-randomized and retrospective observational studies would be predisposed to selection and publication bias. Therefore, important clinical characteristics before intubation such as oxygenation scores involving partial pressure of arterial oxygen (PaO2) and partial pressure of arterial oxygen to fractional of inspired oxygen ratio (PaO2/FiO2), and the utility of NIMV and HFNC use, which could be confounding factors affecting the timing of intubation and clinical outcomes, were not well assessed. The limited enrollment period that was confined to the first wave of pandemic between February and August 2020 may not reflect the actual outcomes of COVID-19 patients because of the recent advancements of COVID-19 therapies involving antivirals and immunomodulators, which could reduce the need for mechanical ventilation and improve mortality and IMV duration [25–28]. The high overall hospital mortality rate of 32.1% may be an independent competing risk factor leading to an unintended underestimation of the actual IMV duration. Due to the small number of studies included, publication bias could not be assessed.

As our meta-analysis results are restricted to the first wave of the pandemic, a well-designed large multi-center prospective study is required to assess the outcomes of intubation timing from COVID-19 illness onset rather than initial hospital admission. Moreover, the use of NIMV to avoid and delay intubation has been increasingly applied in various medical institutions based on evidence from previous respiratory viral outbreaks, and more studies are required to assess the implications of early intubation versus NIMV and HFNC. In 2013, a Spanish registry assessing 685H1N1 patients revealed that a trial of NIMV avoided intubation in up to 41% of patients and was not associated with increased mortality compared with patients intubated early in the disease course [29]. In 2018, Middle East Respiratory Syndrome Syndrome patients sharing similar demographics had no difference in IMV duration and mortality when comparing a trial of NIMV with early intubation [30]. Additionally, future well-designed studies are needed that focus on how intubation timing affects post-intubation complications such as ventilator-associated pneumonia and pneumothorax and the usefulness of oxygenation scores and serum inflammatory biomarkers such as lactate dehydrogenase, C-reactive protein, D-dimer, ferritin, and procalcitonin as markers of disease severity that may signal impending respiratory failure and warrant intubation during COVID-19 [31–34].
5. Conclusion

Our meta-analysis demonstrated the lack of clinical improvement in mortality, IMV duration, and additional outcomes of RRT requirement between COVID-19 patients undergoing early versus late intubation from initial hospital admission. The advantages and disadvantages of avoiding early intubation should consider the complications associated with intubation and mechanical ventilation, such as aspiration, hypotension, VILI, and difficulty in IMV weaning. Although it is impossible to prove that critically ill COVID-19 patients require early intubation and IMV from initial hospital admission, the decision to intubate should be based on the physician’s judgments influenced clinically by dyspnea, respiratory rate, oxygen saturation, and chest radiograph. With the advancements of pharmacological therapies proven to improve outcomes, a well-designed large multi-center study is required to assess the outcomes of intubation timing among critically ill COVID-19 patients beyond the first wave of the pandemic.

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Conflict of Interest

The authors have no conflicts of interest.

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