

# Endotoxin Adsorbent Therapy in Severe COVID-19 Pneumonia

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## Keywords

Coronavirus disease 19 · Endotoxemia · Endotoxin adsorbent · Acute respiratory distress syndrome · Critical care · Adsorption therapy

## Abstract

**Introduction:** Uncontrolled systemic inflammation may occur in severe coronavirus disease 19 (COVID-19). We have previously shown that endotoxemia, presumably from the gut, may complicate COVID-19. However, the role of endotoxin adsorbent (EA) therapy to mitigate organ dysfunction in COVID-19 has not been explored. **Methods:** We conducted a retrospective observational study in COVID-19 patients who received EA therapy at the King Chulalongkorn Memorial Hospital, Bangkok, Thailand, between March 13 and April 17, 2020. Relevant clinical and laboratory data were collected by inpatient chart review. **Results:** Among 147 hospitalized COVID-19 patients, 6 patients received EA therapy. All of the 6 patients had severe COVID-19 infection with acute

respiratory distress syndrome (ARDS). Among these, 5 of them were mechanically ventilated and 4 had complications of secondary bacterial infection. The endotoxin activity assay (EAA) results of pre-EA therapy ranged from 0.47 to 2.79. The choices of EA therapy were at the discretion of attending physicians. One patient was treated with oXiris<sup>®</sup> along with continuous renal replacement therapy, and the others received polymyxin B hemoperfusion sessions. All patients have survived and were finally free from the mechanical ventilation as well as had improvement in PaO<sub>2</sub>/FiO<sub>2</sub> ratio and decreased EAA level after EA therapy. **Conclusions:** We demonstrated the clinical improvement of severe COVID-19 patients with elevated EAA level upon receiving EA therapy. However, the benefit of EA therapy in COVID-19 ARDS is still unclear and needs to be elucidated with randomized controlled study.

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## Introduction

The emergence of coronavirus disease 19 (COVID-19) has become a devastating condition affecting millions worldwide. Severe COVID-19 infection shares common features with sepsis syndrome and with bacterial coinfection may result in bacterial toxins, which might contribute to disease severity [1]. Furthermore, high level of bacterial DNA and LPS were found in bloodstream of patients with severe COVID-19 [2]. At present, the only therapies for critically ill patients with COVID-19 include supportive care and low-dose corticosteroids. Remdesivir may shorten the disease course and viral shedding duration but may not improve the patient's survival [3]. Many other potential treatments such as favipiravir, chloroquine/hydroxychloroquine, and convalescent plasma are under investigation with unclear efficacy [4].

Many recent reports suggested the high incidence of secondary bacterial infection in severe COVID-19 patients judging from the rate of empirical antibiotics, which varied from 58 to 80.3% [1, 5, 6]. Endotoxin, also known as LPS, is a part of the cell wall of gram-negative bacteria. Endotoxin has been extensively investigated and acknowledged as one of the key triggers of lethal shock during severe sepsis and also one of the primary drivers of systemic inflammation [7–9]. However, the role of endotoxin in severe COVID-19 is still unknown.

Endotoxin adsorbent (EA) therapy is a standard of care to control endotoxemia in many countries, particularly in Asia. This treatment was first introduced in Japan >20 years ago. There is an evidence that removing endotoxin by EA therapy can literally reduce circulating levels of pro-inflammatory cytokines [10]. In addition, previous literature also demonstrated a potential benefit of EA in viral pneumonias such as H1N1 influenza and H5N1 [11–13].

Whether EA therapy may be useful in severe COVID-19 is unknown. However, in this study, we sought to determine whether EA therapy could be associated with pulmonary gas exchange and remote organ dysfunction improvement in patients with COVID-19 pneumonia.

## Materials and Methods

### *Study Population, Setting, and Data Collection*

This was a retrospective observational study in COVID-19 patients who received EA therapy. We included patients who (1) aged >18 years, (2) had laboratory-confirmed COVID-19 pneumonia, (3) received EA therapy, and (4) were admitted to King Chulalongkorn Memorial Hospital, Bangkok, Thailand, during March 13 and April 17, 2020.

We obtained demographic data, information on clinical presentation, laboratory investigation, and radiography at the time of presentation and during ICU admission. All laboratory tests and radiological assessments, including plain chest radiography and chest computed tomography, were performed at the discretion of the treating physician. All patients received standard treatment protocol, whereas other therapeutic treatments were prescribed according to the judgment of treating physician. Patients with COVID-19 acute respiratory distress syndrome (ARDS) who had intermediate to high blood endotoxin activity assay (EAA) level ( $\geq 0.4$ ) were eligible for EA therapy. EAA levels were obtained before and after each EA therapy session and at 7 days after the first session. We followed the clinical course and outcome of the patients until May 20, 2020. The study was approved by the Faculty of Medicine, Chulalongkorn University Ethics Committee (IRB No. 336/63). The informed consent was waived due to retrospective nature of the study. Only deidentified data were used in this study.

### *Definition*

We used the Berlin Criteria [14] to define ARDS. This classified the severity of ARDS by  $\text{PaO}_2/\text{FiO}_2$  (P/F) ratio as mild ( $>200$ – $300$  mm Hg), moderate ( $>100$ – $200$  mm Hg), and severe ( $\leq 100$  mm Hg). Acute kidney injury (AKI) was defined by creatinine and urine output criteria according to the Kidney Disease: Improving Global Outcomes (KDIGO) [15]. Secondary bacterial infection was defined as bacterial infection that occurred during hospital admission.

### *Standard Treatment Protocol*

All patients received the standard treatment protocol. Treating physicians performed thorough evaluation and managed COVID-19 patients with standard care including volume status assessment and hemodynamic and respiratory support. Although currently there is no specific antiviral treatment for COVID-19, this therapy was given to all patients with confirmed COVID-19 pneumonia, as recommended by the Department of Medical Service, Ministry of Public Health of Thailand [16]. The antiviral treatment consists of a combination of favipiravir, lopinavir/ritonavir or darunavir, hydroxychloroquine, and azithromycin.

### *EA Protocol*

Hemoperfusion with endotoxin and/or cytokine adsorbent cartridges were used as adjunctive therapy based on decision of the treating physicians. The treatment protocol used either 2 sessions of 4-h polymyxin B hemoperfusion (Toraymyxin<sup>®</sup>; Toray Medical, Tokyo, Japan) for 2 consecutive days or the hollow-fiber modified AN69 membrane (oXiris<sup>®</sup>; Baxter, Meyzieu, France) for 72 h. Toraymyxin<sup>®</sup> is a polystyrene-based woven fiber coated with immobilized polymyxin B, which has a strong affinity to the lipid A portion of endotoxin through ionic and hydrophobic interactions. oXiris<sup>®</sup> is a surface-treated AN69 membrane with polyethylenimine and grafted with heparin, which could adsorb both endotoxin and cytokines. Selection of adsorbent for each patient was mainly decided by clinical judgment and availability of the devices. Vascular access was placed using a double-lumen catheter inserted through the central vein by Seldinger's method. Blood flow rate was set at 120–150 mL/min. Heparin infusion was the standard anticoagulation. In case heparin was contraindicated, the non-anticoagulation strategy would be applied.

**Table 1.** Patient characteristics

	1	2	3	4	5	6
Age, years	50	59	57	58	64	58
Sex	M	M	M	M	M	F
U/D	DMT2	DMT2	DCM	KT, DMT2, HT, DLP	MM, DMT2, HT, DLP	HIV infection
Fever day at admission <sup>a</sup>	5	3	6	10	3	7
Fever day at EA therapy <sup>b</sup>	10	13	12	12	4	12
ICU admission	Y	Y	Y	Y	Y	Y
APACHE II score at EA therapy	17	10	4	12	22	11
SOFA score at EA therapy	17	11	10	6	11	6
PaO <sub>2</sub> /FiO <sub>2</sub> ratio at EA therapy	186	246	190	212	145	281
Intubation	Y	Y	Y	N	Y	Y
IL-6 level, pg/mL	3,237	496	66	16	438	868
<i>Treatments</i>						
EA therapy	oXiris	PMX-HP	PMX-HP	PMX-HP	PMX-HP	PMX-HP
Darunavir + ritonavir	Y	Y	Y	N	N	Y
Antimalarial drug	Y	Y	Y	N	Y	Y
Favipiravir	Y	Y	Y	Y	Y	Y
Azithromycin	Y	Y	N	N	Y	N
Corticosteroid	Y	Y	N	Y	N	N
Antibiotics	Y	Y	Y	Y	Y	Y

APACHE II score, Acute Physiology and Chronic Health Evaluation II score; DCM, dilated cardiomyopathy; DLP, dyslipidemia; DMT2, type 2 diabetes mellitus; EA, endotoxin adsorbent; F, female; FiO<sub>2</sub>, fractional inspired oxygen; HBV, hepatitis B virus; HP, hemoperfusion; HT, hypertension; ICU, intensive care unit; IL-6, Interleukin-6; KT, kidney transplant; PMX-HP, polymyxin B hemoperfusion; M, male; MM, multiple myeloma; N, no; PaO<sub>2</sub>, partial pressure of arterial oxygen; SOFA score, Sequential Organ Failure Assessment score; U/D, underlying disease; Y, yes. <sup>a</sup> Fever day at admission = duration between fever onset date and admission date. <sup>b</sup> Fever day at EA therapy = duration between fever onset date and EA therapy date.

#### Laboratory Procedures

##### COVID-19 Test Confirmation

COVID-19 tests were performed by qRT-PCR technique using cobas<sup>®</sup> SARS-CoV-2 qualitative test with the cobas<sup>®</sup> 6800 platform (Roche Diagnostics, Indianapolis, IN, USA). The test method was described in detail in online suppl. material 1 (for all online suppl. material, see [www.karger.com/doi/10.1159/000515628](http://www.karger.com/doi/10.1159/000515628)).

##### Endotoxin Activity Assay

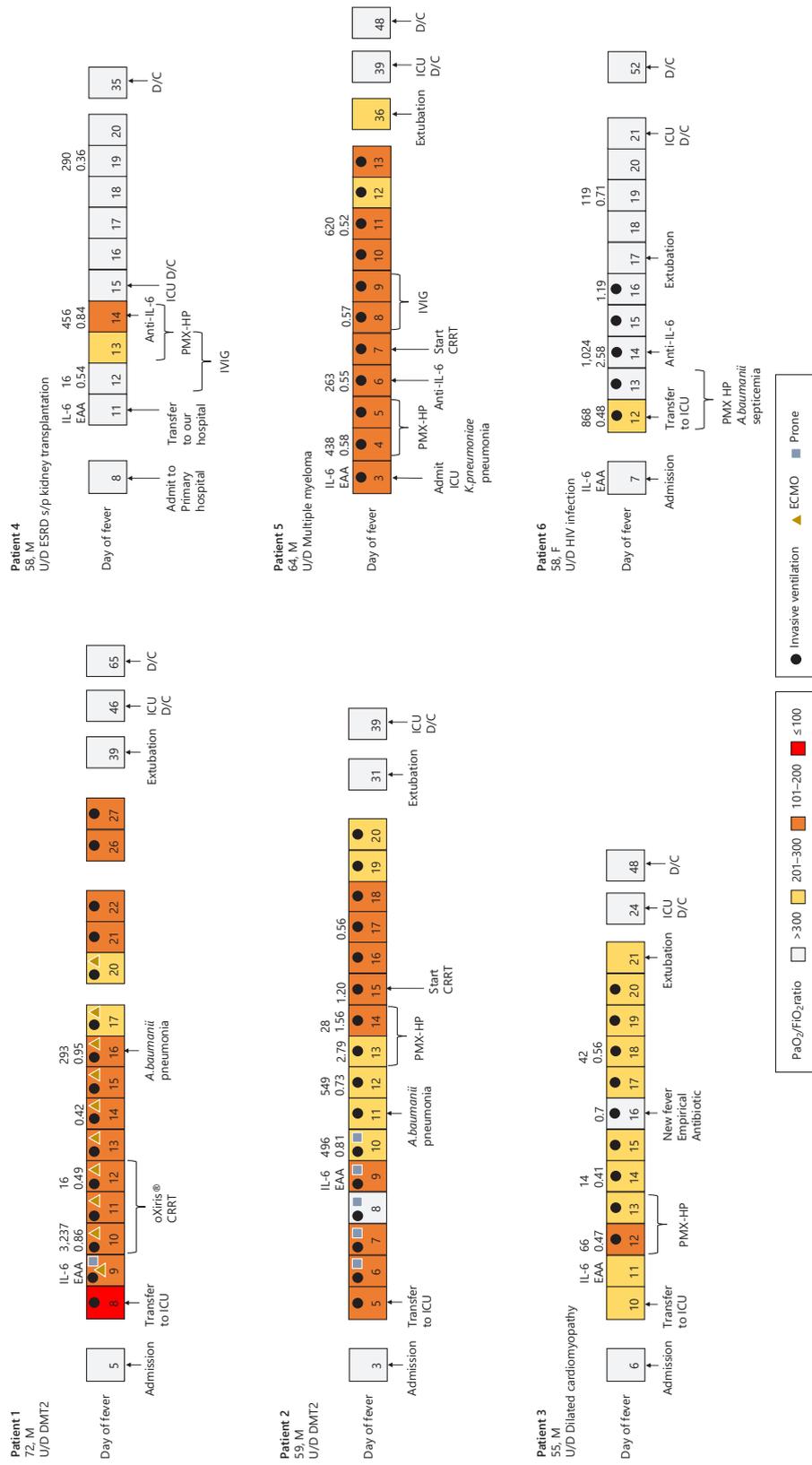
We performed the chemiluminescent-based EAA (Spectral Diagnostics, Ontario, Canada), as described elsewhere [17]. This assay is based on the detection of enhanced respiratory burst activity in neutrophils, following their priming by complexes of endotoxin and a specific antiendotoxin antibody. Briefly, 40 µL of whole blood was incubated with zymosan and antiendotoxin antibody. EAA level of ≥0.40 was considered as intermediate increase [18]. Manufacturer fact sheet was available in online suppl. material 2.

## Results

During the study period, a total of 147 COVID-19 patients were hospitalized. Six patients were diagnosed with ARDS and underwent EA therapy. Of these, 5 patients

received polymyxin B hemoperfusion sessions, and another patient received treatment with oXiris<sup>®</sup> by Prismaflex system. Baseline characteristics are summarized in Table 1. There were 5 male and 1 female patients, with age ranging from 55 to 72 years. All 6 patients had underlying comorbidities – 4 patients with type 2 diabetes mellitus, 1 patient with HIV infection, and 1 patient with history of multiple myeloma (in remission). Days of fever at admission and days of fever at EA therapy were ranging from 3 to 8 days and 4 to 13 days, respectively. Five out of 6 patients were intubated before the initiation of EA therapy. P/F ratios at initiation of EA therapy were ranging from 145 to 281. All patients received antiviral medication and antibiotics.

Clinical courses of 6 patients are depicted in Figure 1, and clinical outcomes are shown in Table 2. EAA level before EA therapy ranged from 0.47 to 2.79. Two patients were placed in prone position and 1 patient underwent extracorporeal membrane oxygenation (ECMO) therapy. Status as of May 20, 2020, all patients have survived and were free from mechanical ventilation. All patients had improvement in P/F ratios and a decrease in EAA level



(For legend see next page.)

after EA therapy. No complication of EA therapy was observed. Three patients developed secondary bacterial infections before EA therapy, while 1 patient developed 7 days afterward.

All 6 patients developed AKI. Three patients (patients 1, 2, and 5) had oliguria with volume overload and required continuous renal replacement therapy (CRRT). As of January 11, 2021, all patients were dialysis independent and recovered from AKI.

## Discussion

We reported clinical courses and outcomes of 6 critically ill COVID-19 patients with ARDS who received EA therapy. Secondary bacterial infections were observed in 4 patients. All patients were survived and free from mechanical ventilation.

High EAA level in viral infection has been demonstrated to be associated with poor outcome in animal study, causing a release of proinflammatory cytokines and interferons [19, 20]. Recently, patients with COVID-19 were found to have high level of proinflammatory cytokines [1]. Similar findings were also reported in patients with severe acute respiratory syndrome [21] and Middle East

respiratory syndrome [22]. This emphasized the existing and impact of so-called “cytokine storm” in viral respiratory infection that deteriorates the clinical course. The mechanisms of endotoxemia in patients with COVID-19 pneumonia or even other viral syndromes have not been well studied. Patients with viral respiratory infection such as influenza often suffer from severe secondary bacterial infections, which are frequently associated with high morbidity and mortality [23, 24]. Previous pandemic outbreak of H1N1 influenza A in 1918–1919, also known as “Spanish flu,” resulted in an estimated death toll of 50 million people, many of which were caused by secondary bacterial pneumonia [25, 26]. About 30% of patients with H1N1 influenza A pandemic in 2009 also had been aggravated with secondary bacterial infection [27, 28]. Previous observational study showed that patients with EAA level of 0.4–0.6 were associated with a higher risk of bacterial infection compared with those who had EAA level of <0.4 [29]. Although all patients in our study had EAA level >0.40, only 3 patients developed concurrent bacterial infection (Fig. 1; patients 2, 5, and 6). This finding indicated that COVID-19 may induce endotoxemia without secondary bacterial infection. It might be possible that viremia results in capillary leakage similar to bacterial sepsis, which causes interstitial edema and dysfunc-

**Table 2.** Clinical outcomes

	1	2	3	4	5	6
Dead	N	N	N	N	N	N
Total ICU admission day	28	28	14	2	28	10
Days of hospitalized after EA therapy	53		35	21	43	39
Total mechanical ventilation day	28	25	9	0	28	6
Use of inotropic drug	Y	Y	N	N	Y	Y
Prone position	Y	Y	N	N	N	N
ECMO	Y	N	N	N	N	N
Bacterial infection	Y	Y	N	N	Y	Y
Site of infection	Pneumonia	Pneumonia	N	N	Pneumonia	Septicemia
Organisms	<i>A. baumannii</i>	<i>A. baumannii</i>	N	N	<i>Klebsiella pneumoniae</i>	<i>A. baumannii</i>
Maximum AKI staging	3	3	1	2	3	2
RRT	Y, renal recovery	Y, no renal recovery	N	N	Y, renal recovery	N

*A. baumannii*, *Acinetobacter baumannii*; AKI, acute kidney injury; EA, endotoxin adsorbent; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; M, male; N, no; RRT, renal replacement therapy; Y, yes.

**Fig. 1.** Six cases of EA therapy. IL-6 was presented as pg/mL. *A. baumannii*, *Acinetobacter baumannii*; anti-IL-6, anti-IL-6 receptor antibody; CRRT, continuous renal replacement therapy; D/C, discharge; DMT2, diabetes mellitus type 2; EA, endotoxin adsorbent; EAA, endotoxin activity assay; ECMO, extracorporeal mem-

brane oxygenation; F, female; IVIG, intravenous immunoglobulin; ICU, intensive care unit; IL-6, interleukin-6; *K. pneumoniae*, *Klebsiella pneumoniae*; M, male; PaO<sub>2</sub>/FiO<sub>2</sub> ratio, arterial partial pressure of oxygen and the fraction of inspired oxygen ratio; PMX-HP, polymyxin B hemoperfusion; U/D, underlying disease.

tion of the intestinal barriers. This phenomenon may promote the translocation of bacteria or bacterial product from the lung and/or gut into the blood circulation and then induce the release of proinflammatory cytokines. We as well recently demonstrated the evidence of bacterial RNA in bloodstream in severe COVID-19 patients with high EAA level [30].

Data showing benefits of polymyxin B hemoperfusion in ARDS are limited to small uncontrolled studies [31–33]. Recently, several studies reported successful hemoperfusion with polymyxin B-immobilized fiber in patients with H1N1 and H5N1 influenza complicated with ARDS by improving oxygenation [11, 12, 34, 35]. Moreover, the latest approval of the Government of Canada on the use of polymyxin B hemoperfusion in severe COVID-19 pneumonia was announced on April 20, 2020 [36]. EA therapy has been proposed to mitigate cytokine burden by cutting the peak of a specific foreign target (endotoxin), resulting in the restoration of immune homeostasis without a prolonged state of immunosuppression [37, 38]. Conversely, other potential therapy for cytokine storm, such as IL-6 receptor inhibitor, may cause serious secondary infection from prolonged immunosuppressive effect. Recently, De Rosa et al. [39] reported a case series from EUPHAS 2 study. They investigated the use of polymyxin B hemoperfusion in COVID-19-infected patients with septic shock from various pathogens and reported the reduction of SOFA score after 2 sessions of polymyxin B hemoperfusion [39].

We used 2 adsorbent devices in this study, Toraymyxin<sup>®</sup> and oXiris<sup>®</sup>. Data from in vitro study [40] demonstrated that oXiris<sup>®</sup> was able to remove endotoxin as effective as Toraymyxin<sup>®</sup>. Due to the negatively charged AN69 membrane, oXiris<sup>®</sup> provides a cytokine-adsorbing property by ionic bonding, which was shown to be as effective as CytoSorb<sup>®</sup>. While Toraymyxin<sup>®</sup> has lower rate of cytokine removal [40]. Practically, oXiris<sup>®</sup> could contemporaneously provide cytokine and endotoxin adsorption with continuous dialysis therapy, meanwhile Toraymyxin<sup>®</sup> could be intermittently performed without dialysis. Thus, oXiris<sup>®</sup> might be preferable in patient requiring CRRT in order to correct metabolic derangement and control fluid balance. In addition, 1 patient in our study (patient 1) underwent ECMO therapy. This patient suffered from ARDS complicated by severe AKI and needed venovenous-ECMO therapy and CRRT for organ support. We then decided to use oXiris<sup>®</sup> for both dialysis and adsorptive therapy. The arterial and venous lines of CRRT machine were connected at post-pump and pre-oxygenator area of the ECMO circuit. Continuous heparin infu-

sion was used for anticoagulation. CRRT was then switched to prolonged intermittent hemodialysis after 3 days, whereas ECMO was able to discontinue after 9 days of support.

Our study has several strengths. First, to our knowledge, this is the first study that explored the role of EA therapy in patients with COVID-19 pneumonia. We believe that this finding will provide the novel insight for management of these patients. Second, we tested EAA level by using the US FDA cleared test kit. This test is one of the most reliable tests to measure the endotoxin level. Third, we also demonstrated the benefits of early use of EA therapy in mild ARDS patients who had ongoing deterioration of the PF ratios (Fig. 1; patients 4 and 6). However, our study was not without limitations. First, we did not include patients with COVID-19 ARDS without EA therapy as a control group. Therefore, it is quite difficult to conclude the benefits of EA therapy in this setting. However, we wish that our study will be a starting point to examine the effect of EA therapy in mitigation of organ dysfunction in severe COVID-19. We strongly encourage further randomized controlled trials exploring this issue. Second, this is a single-center study; hence, generalizability is limited.

## Conclusions

We described the clinical improvement of severe COVID-19 patients with elevated EAA level receiving EA therapy. However, the benefit of EA therapy in COVID-19 ARDS is still unclear and needs to be elucidated with randomized controlled study.

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## Statement of Ethics

The study was reviewed and approved by the Faculty of Medicine, Chulalongkorn University Ethics Committee (IRB No. 336/63). The consent was voided due to retrospective nature of the study. We presented only deidentified data.

## Conflict of Interest Statement

Toray Industries provided the polymyxin B cartridge and endotoxin activity assay kits for use in this study and Baxter company provided oXiris® set. Both companies had no influence on the study design or analysis or on the comment of this article. None of the authors have any conflicts to disclosure.

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## Author Contributions

S.P., P.S., W.K., and N.S. were responsible for study concept and design. S.T. and K.T. were responsible for the acquisition, analysis, or interpretation of data. S.P., P.S., and N.S. were responsible for drafting the manuscript. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors interpreted the findings, contributed to writing the manuscript, and approved the final version for publication.

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