

# Electroencephalography of mechanically ventilated patients at high risk of delirium

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## Abstract

**Objective:** Neurophysiological exploration of ICU delirium is limited. Here, we examined EEG characteristics of medical-surgical critically ill patients with new-onset altered consciousness state at high risk for ICU delirium.

**Materials and methods:** Pre-planned analysis of non-neurological mechanically ventilated medical-surgical ICU subjects, who underwent a prospective multicenter randomized, controlled EEG study (NCT03129438, April 2017–November 2018). EEG characteristics, according to the 2012 ACNS nomenclature, included background activity, rhythmic periodic patterns/epileptic activity, amplitude, frequency, stimulus-induced discharges, triphasic waves, reactivity, and NREM sleep. We explored EEG findings in delirious versus non-delirious patients, specifically focusing on the presence of burst-suppression and rhythmic periodic patterns (ictal-interictal continuum), and ictal activity.

**Results:** We analyzed 91 patients (median age, 66 years) who underwent EEG because of new-onset altered consciousness state at a median 5 days from admission; 42 patients developed delirium (46%). Burst-suppression (10 vs 0%,  $p = .02$ ), rhythmic/periodic patterns (43% vs 22%,  $p = .03$ ) and epileptiform activity (7 vs 0%,  $p = .05$ ) were more frequent in delirious versus non-delirious patients. The presence of at least one of these abnormal EEG findings (32/91 patients; 35%) was associated with a significant increase in the likelihood of delirium (42 vs 15%,  $p = .006$ ). Cumulative dose of sedatives and analgesics, as well as all other EEG characteristics, did not differ significantly between the two groups.

**Conclusion:** In mechanically ventilated non-neurological critically ill patients with new-onset alteration of consciousness, EEG showing burst-suppression, rhythmic or periodic patterns, or seizures/status epilepticus indicate an increased risk of ICU delirium.

## KEYWORDS

critical care, delirium, EEG

Electroencephalographic characteristics of medical-surgical critically ill patients with new-onset altered consciousness state at high risk for delirium

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## 1 | INTRODUCTION

Electroencephalography is a part of standard diagnostic procedures in critically ill patients with new-onset altered state of consciousness. In these patients, ICU delirium is frequent and may often go undetected, in particular, because of hypo-active forms and the confounding effect of sedative-analgesia. The pathophysiology of delirium remains unclear and is associated with neurotransmitter deficiency, pro-inflammatory cytokines, acute stress responses, and neuronal injury.<sup>1</sup> Delirium is related to functional outcome and mortality<sup>2,3</sup>; nevertheless, a tool that can predict delirium development especially in ICU has not yet been widely established. The use of screening scales is valuable and the Confusion Assessment Method for the ICU (CAM-ICU) has the highest sensitivity in patients in the ICU (64%–100%), but still may miss up to 50% of delirious patients.<sup>4,5</sup>

EEG is part of standard diagnostic procedures of acute alteration of consciousness in the ICU, and may therefore prove useful to contribute to delirium diagnosis.<sup>6–8</sup> Yet, clinical data on EEG in ICU delirium is limited,<sup>9,10</sup> and to our knowledge, a comprehensive analysis of EEG characteristics in mechanically ventilated critically ill patients at high delirium risk has not been explored so far, especially in adults without known acute brain injury. In this study, we aimed at examining EEG characteristics of mechanically ventilated ICU patients with new-onset altered consciousness state, and to evaluate whether in this high-risk population the presence of any abnormal EEG findings, based on the 2012 American Clinical Neurophysiology Society (ACNS) nomenclature,<sup>11</sup> may be indicative of a higher delirium rate.

## 2 | METHODS

### 2.1 | Patients

In this pre-planned analysis of a multicenter randomized controlled EEG study (Continuous EEG Randomized Trial in Adults, CERTA) performed in four Swiss hospitals between April 2017 and November 2018,<sup>12,13</sup> adult inpatients presenting with consciousness disorders of any etiology were randomized to receive continuous EEG (30–48 h) or routine EEG (20 min repeated once within 48 h); 368 patients have been initially included. Only patients from Lausanne University Hospital (CHUV) were kept in the study since comprehensive data concerning delirium were not all recorded in the CERTA trial (n = 287).

Our aim was to study the relationship between delirium and EEG in ICU patients without a brain injury or cardiac arrest, we retrospectively identified patients in whom the primary cause for ICU admission was sepsis or cardio-respiratory failure; patients with a cerebral lesion such as a tumor were admitted in ICU for a non-neurological reason were also included; four patients with a brain tumor (cranio-pharyngioma, glioma, astrocytoma, glioblastoma). We collected data concerning delirium mainly via the CAM-ICU score, which is part of the local routine assessment in the ICU and is performed daily by an experienced ICU nurse. When CAM-ICU score was missing, patients were also categorized as having delirium based on medical

records review and identification of agitation/confusion requiring administration of antipsychotic drugs (haloperidol or quetiapine) for at least 2 days. Haloperidol dosage varied from 0.5 mg to 4 mg/day. Quetiapine dosage varied from 25 to 200 mg per day. Delirium diagnosis was made according to the DSM-5 criteria.<sup>14</sup> Patients without an ICU stay were also excluded (n = 10).

### 2.2 | EEG and clinical data

For the purpose of this study, we considered only the first EEG for each patient, whether continuous or routine. Digital video-EEG were recorded using scalp electrodes placed according to the international 10–20 system. Type of sedation and dosages, duration of hospital stay, duration of mechanical ventilation, reason for EEG request, and main ICU admission diagnosis were prospectively collected. The occurrence of delirium was defined and assessed by means of the CAM-ICU scale for 45 patients, and via medical records and drug administration for the others (n = 46).<sup>15</sup> We also assessed retrospectively the timing of EEG in relationship with delirium diagnosis. EEG interpretation followed the 2012 American Clinical Neurophysiology Society (ACNS) nomenclature.<sup>11</sup> It prospectively assessed background activity (frequency, amplitude, reactivity) and continuity: continuous or nearly continuous (suppression <10%), discontinuous (suppression 10%–49%), burst-suppression (suppression ≥50%) and suppressed (<10 μV). Further, sporadic epileptiform activity, lateralized rhythmic delta activity (LRDA), lateralized or generalized periodic discharges (LPD, GPD) (ictal-interictal continuum), sporadic epileptiform activity, presence of triphasic waves, and occurrence of NREM 2 sleep features (spindles, K-complexes).<sup>11</sup> A uniform operational definition of electrographic seizures (≥10 s) and SE (≥5 min) was used for the CERTA study: repetitive, rhythmic, or periodic discharges or spike-waves at greater than 3 Hz or less than 3 Hz with evolution in amplitude, frequency, location, or with electroclinical response to antiseizure drugs (ASD).<sup>11,16,17</sup> EEG reactivity was tested by auditory and nociceptive stimuli.<sup>18</sup> Background reactivity was considered present if a clearly reproducible change in amplitude or frequency was seen immediately after stimulation, excluding stimulus-induced discharges (SIRPIDS) and muscle artifacts. Amplitude was divided into three categories according to voltage: 1 = suppressed <10 μV, 2 = low 10–20 μV, 3 = normal >20 μV.

### 2.3 | Statistical analysis

We explored EEG characteristics among delirious versus non-delirious patients, focusing on specific EEG patterns, including the presence of burst-suppression, rhythmic, or periodic patterns or ictal activity. Continuous, not normally distributed variables were presented using the median and first to third quartile and compared using a Wilcoxon–Mann–Whitney test. Categorical variables were compared using a chi-square test. Statistical analysis of patients' characteristics was conducted with JMP statistics.<sup>19</sup> In explorative analyses, all possible combinations of EEG characteristics were

compared between patients who were delirious and those who were not. Associations were considered statistically significant at a  $p$ -value  $\leq .05$ .<sup>20</sup> Given the exploratory nature of the study, we did not apply corrections for multiple comparisons.

### 3 | RESULTS

#### 3.1 | Patient demographics

The study flow chart is shown in Figure 1. A total of 91 patients were included in the present analysis, of which 42 were diagnosed with ICU delirium (half were diagnosed based on CAM-ICU score, and the other half according to agitation/confusion diagnosis plus antipsychotic therapy). Median age was 66 years and the male gender was predominant (66%) (Table 1). The main primary ICU admission diagnosis was sepsis (42%). EEG was performed when the diagnosis of consciousness disorder was made (within 4 h after clinician request according to the study protocol), which occurred at a median of 5 days (2–10) from hospital admission. Median EEG duration was 0.5 h (0.3–30). The majority of patients (64%) were under continuous sedation during EEG, with propofol and/or midazolam; their median duration of mechanical ventilation was 8 days (4–14) and the median ICU stay was 11 days (6–20).

#### 3.2 | EEG findings

Delirium median duration in ICU was 7 days. EEG was performed during delirium in the majority of patients (81/91; 89%), and before its onset in 10 (Figure 2).

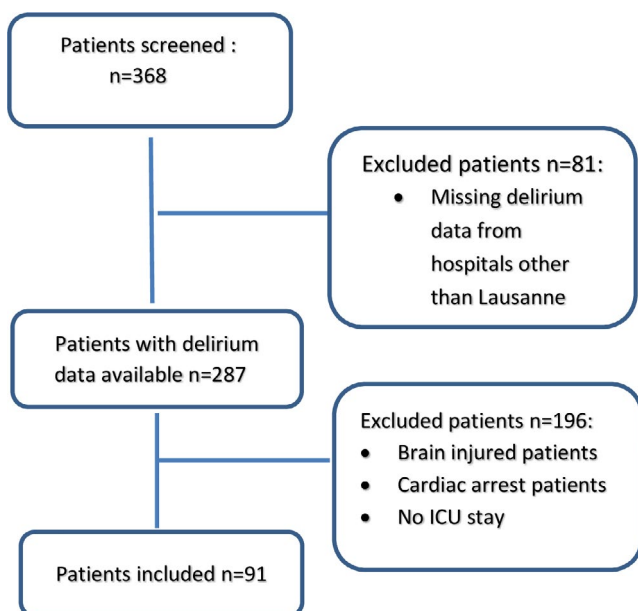


FIGURE 1 Study flow chart

EEG findings according to the ACNS nomenclature were compared between delirious and non-delirious patients (Table 2). While EEG duration and sedation rate and doses/kg (propofol, midazolam) were similar for patients with and without delirium, mechanical ventilation and ICU stay were significantly longer for the delirium group.

Regarding background activity, we found that the majority of the patients had a continuous or discontinuous EEG; however, only in the delirium group, a burst-suppression pattern was observed (10% vs 0%,  $p = .02$ ). Out of these patients ( $n = 4$ ), two were not sedated during EEG, and two were receiving propofol (2.2 and 2.5 mg/kg/h). All were diagnosed with sepsis, and two of them died during their hospital stay. Regarding the best frequency observed, in both groups, theta was dominant; followed by alpha and delta. Reactivity to stimuli (noise, pain, name call) was present in the majority of patients in both groups.

In the delirium group, significantly more patients (43% vs 22.5%) presented rhythmic or periodic patterns not classifying as seizures ( $p = .037$ ). Only in delirious patients, we found seizures or status epilepticus (7% vs 0%,  $p = .05$ ). The presence of triphasic waves was similar in both groups (33 vs 27%). All other EEG variables (amplitude, background activity, best frequency, NREM sleep, rhythmic or periodic patterns, seizures, stimulus-induced epileptiform discharges and triphasic morphology) did not differ between delirious and non-delirious patients.

Out of the four patients with brain tumors included in the study, only one presented delirium during ICU stay (craniopharyngioma) and had a continuous EEG with rhythmic/periodic EEG patterns and no seizures or interictal epileptiform activity.

TABLE 1 Characteristics of the 91 analyzed patients

Age (years)	66 (57–73)
Female gender	31 (34%)
Medical ICU primary diagnosis	
Sepsis	35%
Metabolic dysfunction	9%
Cardiopulmonary dysfunction	24%
Other <sup>a</sup>	32%
Simplified Acute Physiology Score (SAPS) II	39 (33–54)
Delirium <sup>b</sup>	42 (46%)
EEG after hospital admission (latency in days)	5 (2–10)
Median EEG duration (hours)	0.45 (0.3–30)
Any sedation during EEG	58 (64%)
Mechanical ventilation (days)	8 (4–14)
ICU length of stay (days)	11 (6–20)
Hospital length of stay (days)	33 (16–60)
Poor outcome (mRs 4–6)	39 (43%)

Note: Data are expressed as median and quartile 25%–75% or number (%).

<sup>a</sup>Trauma (without brain lesion), digestive hemorrhage, drug intoxication, brain tumor, etc.

<sup>b</sup>Delirium was diagnosed based on CAM-ICU score, or according to medical chart review indicating agitation/confusion requiring >2 days therapy with antipsychotic drugs (haloperidol or quetiapine).

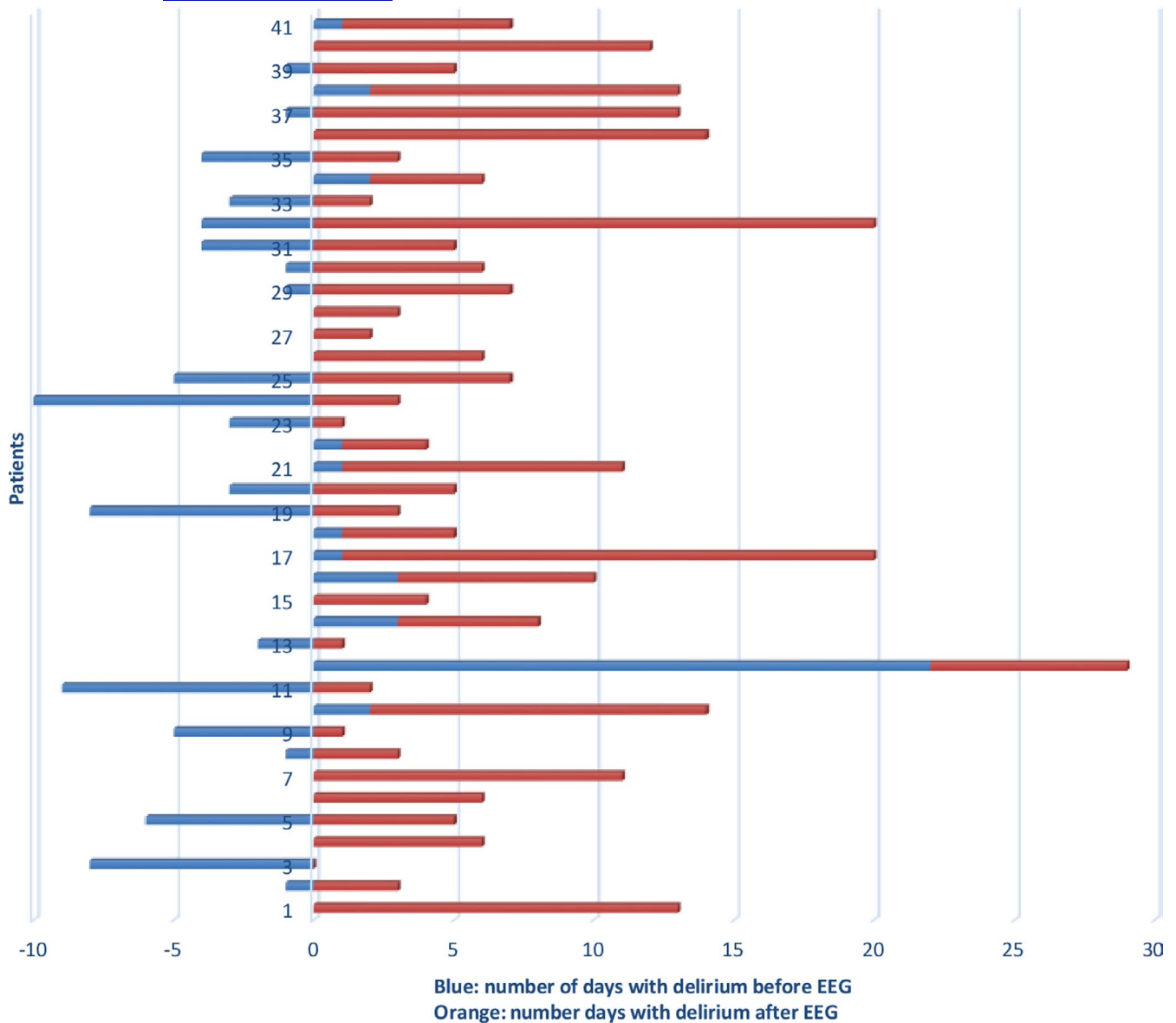


FIGURE 2 EEG chronologic relationship between delirium duration. In blue: number of days with delirium before EEG; in orange, number of days with delirium after EEG

### 3.3 | Specific EEG findings are associated with high delirium risk

The presence of at least one abnormal EEG findings, among burst-suppression, rhythmic or periodic patterns, or seizures/status epilepticus, was associated with a higher rate of ICU delirium (42 vs 15%,  $p = .006$ ). Percentages of specific EEG findings are illustrated in Figure 3.

## 4 | DISCUSSION

Delirium in ICU is frequent with harmful consequences for patients.<sup>21</sup> EEG is a noninvasive, broadly available tool that can provide important information for delirium detection and management.<sup>22</sup>

According to our findings, the presence of burst-suppression, rhythmic or periodic patterns, or epileptic activity, seem associated with a higher likelihood of delirium. Our data suggest that identification of these particular EEG patterns in patients with severe critical illness with altered consciousness state may be indicative of delirium. They support the concept that EEG monitoring is helpful in this setting, and if done at the early phase may prompt preventive or therapeutic anti-delirium strategies.

In our study, a small proportion of patients with delirium had burst-suppression during EEG. Sedation rates were similar in both groups before and during EEG, minimizing sedative drug influence over EEG between both groups. Burst-suppression in ICU may be an independent predictor of delirium as previously suggested by another study using processed EEG,<sup>23</sup> could primarily attributable to critical illness itself,<sup>24</sup> and may be associated with increased

TABLE 2 Characteristics compared between delirium patients and mortality

EEG characteristics	Patients with delirium (n = 42)	Patients without delirium (n = 49)	p value
Age	65 (58–74)	66 (51–73)	.43
ICU primary diagnosis:			.23
Sepsis	43%	27%	
Metabolic dysfunction	5%	13%	
Cardiopulmonary dysfunction	26%	23%	
Other	26%	37%	
SAPS II score	43 (34–57)	37 (30–53)	.11
Dominant background activity:			.02
Continuous/discontinuous	90%	100%	
Burst-suppression	10%	0%	
Suppressed	0%	0%	
Amplitude			.16
Low	33%	20%	
Normal	67%	80%	
Best frequency			.83
delta	7%	6%	
theta	74%	67%	
alpha	17%	25%	
beta	2%	2%	
Lack of background reactivity	7%	6%	.84
NREM sleep EEG features	21%	22%	.9
Sporadic epileptiform discharges	31%	32%	.86
Rhythmic or periodic EEG patterns not classifying as seizures	43%	22%	<b>.03</b>
Seizure or status epilepticus	7%	0%	<b>.05</b>
Stimulus induced rhythmic, periodic or ictal discharges	17%	18%	.91
Triphasic morphology	33%	27%	.73
EEG duration (hours)	21.5 (0.33–40)	0.35 (0.33–30)	.07
Mechanical ventilation (days)	10 (5–16)	6 (2–13)	.02
ICU length of stay (days)	15 (10–22)	8 (5–17)	<b>.002</b>
Sedation during EEG	62%	65%	.73
Propofol total dose mg/kg first 5 days of hospitalization	858 (161–2508)	497 (50–1243)	.11
Midazolam total dose mg/kg first 5 days of hospitalization	13 (0.2–34)	3 (0–59)	.37
Fentanyl total dose mg/kg first 5 days of hospitalization	520 (309–1176)	348 (0–1002)	.09

Note: Data are expressed as median, first and third quartile, or numbers (%). Bold values are significant.

mortality.<sup>25</sup> We observed seizures and status epilepticus in 7% of our patients with delirium compared to none in the group without delirium. Seizures are known to be associated with a poor outcome in patients in ICU<sup>26</sup> and can be found in patients with delirium of any cause and in patients with sepsis like the majority of our patients.<sup>1,27</sup> The co-occurrence of seizures in septic patients may be seen as a potential marker of brain dysfunction with prognostic significance.<sup>1,27,28</sup> On the other hand, the presence of epileptiform activity may worsen and/or may even trigger delirium in some patients.<sup>29</sup> Periodic discharges without seizures were also more prominent in delirium patients; studies in neurologic ICU patients suggest that periodic discharges are independent predictors of poor outcome.<sup>30,31</sup>

Rhythmic or periodic patterns without seizure activity were significantly more prevalent in patients with delirium and are part of the ictal-interictal continuum.<sup>32</sup> Individual management according to each pattern and close monitoring is advised for early detection and treatment of epileptiform activity if present.<sup>32,33</sup>

Generalized EEG slowing (increased delta and theta frequency) is frequently found in patients with delirium.<sup>8,28</sup> However slowing is also common in ICU patients and related to various causes of altered mental status, decreased arousal, including coma, sleep, and sedation.<sup>34</sup> In our study, we did not find any significant differences in slowing when patients were compared for delirium. Triphasic waves evolve from an interplay of pathological neurostructural, metabolic,

## EEG and delirium

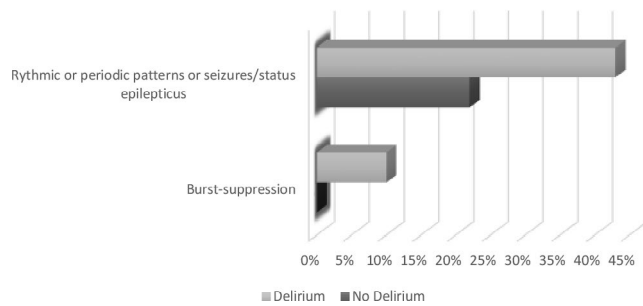


FIGURE 3 EEG characteristics between two groups

and toxic conditions, and are significantly associated with white matter disease, infections, and metabolic derangements.<sup>35</sup> In our study, these were not increased in frequency in patients with delirium, as reported in previous studies.<sup>8,36</sup> NREM stage 1–2 sleep was not differently prevalent between the two groups. It has been hypothesized that the presence of sleep elements, especially K-complexes is associated with good outcome in encephalopathic adults.<sup>37,38</sup>

This study has limitations. The sample size is relatively limited and consisted of a selected population of non-neurological ICU patients, without acute brain injury. Data generalization is therefore limited. In particular, the association between delirium and EEG seizures/status epilepticus was of borderline significance and needs further confirmation by larger studies. Half of the patients with a burst-suppression pattern were sedated with a low dose of propofol during EEG possibly influencing the degree of encephalopathy.

CAM-ICU scores were not available in all patients. EEG timing was not uniform across patients in relationship with their delirium development, but this reflects real clinical practice. Importantly, however, clinical variables and EEG interpretation were completed prior to this analysis and blinded to the development of delirium.

In conclusion, in mechanically ventilated medical-surgical critically ill patients with new-onset alteration of consciousness, EEG showing burst-suppression state and/or ictal-interictal continuum findings indicates a higher risk of ICU delirium, independently of sedation and analgesia.

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#### CONFLICTS OF INTEREST

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#### AUTHOR CONTRIBUTIONS

EE contributed to acquisition and data analysis, statistical analysis, and drafted the manuscript; CI contributed to acquisition and

data analysis, and revised the manuscript; VA, SR, KS contributed to acquisition and data analysis, and revised the manuscript; AOR contributed to acquisition and data analysis, study conception, and critically revised the manuscript. MO conceived the study, supervised acquisition and data analysis, statistical analysis, and critically revised the manuscript.

#### ETHICS APPROVAL

This study was approved by the Ethic's Commission of each participating hospital and was performed in accordance with ethical standards of the 1964 Helsinki Declaration and later amendments.

#### CONSENT TO PARTICIPATE

Informed consent was obtained from all individual participants included in the study.

#### DATA AVAILABILITY STATEMENT

The clinical datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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