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Prevalence, semiology and neuroimaging of movements in comatose adults at risk of death by neurologic criteria: a prospective cohort study

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Abstract

Purpose In comatose patients at risk of death by neurologic criteria (DNC), spinal-mediated movements (SMM) and movements of unclear neuroanatomic origin (MUO) are occasionally challenging to discriminate from cerebral-mediated movements. Our objectives were to assess the respective prevalence and semiology of SMM and of MUO in this population and to estimate the associations between these movements with cerebral blood flow and perfusion.

Methods In this prospective cohort study conducted in 15 intensive care units across Canada, we enrolled consecutive, brain-injured adults with an unconfounded Glasgow Coma Scale score of 3. Physicians conducted standardized DNC clinical evaluation, and participants underwent a brain CT-perfusion scan with CT-angiography reconstructions within a 2-h delay. We assessed the prevalence and semiology of SMM and MUO with descriptive statistics. We estimated the associations between SMM and MUO with cerebral blood flow and brain perfusion using generalized linear mixed models with a logit link function, age and sex as covariates, and random intercepts for study sites.

Results We included 282 participants with a median [IQR] age of 60 [47—69] years. The respective prevalence of SMM and MUO were 27% (95% CI: 22—32%) and 12% (95% CI: 9—16%). SMM and MUO were not associated with the presence of cerebral blood flow on CT-angiography (aOR for SMM: 1.14, 95% CI: 0.63—2.05; aOR for MUO: 1.36, 95% CI: 0.61—3.01) or brain perfusion on CT-perfusion (aOR for SMM: 1.44, 95% CI: 0.77—2.68; aOR for MUO: 1.75, 95% CI: 0.77—3.97). Findings were similar in the subgroup of 204 patients fulfilling clinical criteria for DNC.

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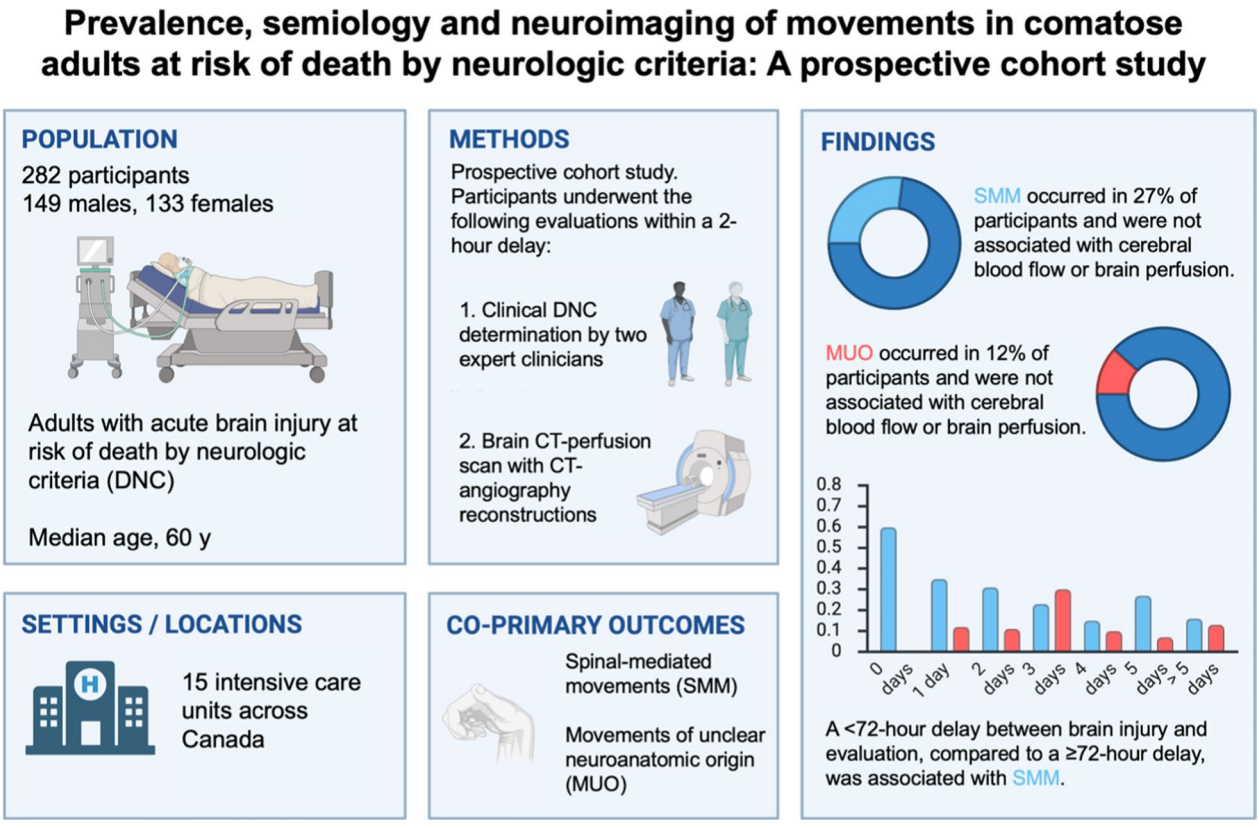
Conclusions SMM and MUO are common among comatose patients at risk of DNC. Their prevalence is similar among alive comatose patients and patients fulfilling clinical criteria for DNC. These movements are not associated with cerebral blood flow on CT-angiography or brain perfusion on CT-perfusion.

Trial registration: Registered on ClinicalTrials.gov: NCT03098511 on March 27, 2017.

Keywords Death by neurologic criteria, Brain death, Spinal movements, Spinal reflexes, Coma

Graphical abstract



Introduction

The cornerstone of death determination by neurologic criteria (DNC) is the demonstration, in an appropriate clinical context, of brainstem areflexia, inability to breathe, and the permanent cessation of consciousness [1, 2]. Spinal-mediated movements (SMM), such as lower extremity triple flexion responses and the Lazarus sign, are automatisms and reflexes mediated by the peripheral nervous system and the spinal cord that can occur in comatose patients, including those who fulfill clinical criteria for DNC. Occasionally, SMM and other movements of unclear neuroanatomic origin (MUO) can be difficult to distinguish from movements mediated by cerebral functions that are incompatible with DNC [3]. The frequency and semiology of SMM among DNC patients have previously been described in cohort studies that reported a 13—79% SMM prevalence [4, 5]. Nevertheless, previous studies relied on no longer recommended ancillary investigations, notably EEG and evoked potentials. It is unclear whether SMM and MUO are associated with cerebral blood flow or brain perfusion on modern neuroimaging modalities [6, 7]. Moreover, clinicians and family members often encounter SMM and MUO prior to DNC determination, but the frequency and semiology of these movements in the broader population of comatose patients at risk of DNC are unknown. This information could prove valuable for clinicians to inform patients' families and allied healthcare professionals on the implications of these movements in patients at risk of DNC.

The primary objectives of this study were to assess the respective prevalence and semiology of SMM and of MUO among deeply comatose patients at risk of DNC, and to estimate the associations between these movements and cerebral blood flow as well as brain perfusion. The secondary objectives were to determine the associations between the delay between brain injury and DNC clinical examination and the occurrence of SMM and MUO.

Methods

Study design

This study is a secondary analysis of the INDex study, a multicentric prospective cohort study evaluating the diagnostic accuracy of CT-perfusion and CT-angiography as ancillary investigations for DNC (ClinicalTrials.gov: NCT03098511, registered on March 27, 2017). Patients were recruited between April 2017 and March 2021 in 15 Canadian intensive care units. The methods and primary analyses of INDex were published previously [6]. Briefly, following enrollment all participants underwent a brain CT-perfusion scan with CT-angiography reconstructions followed by standardized neurological clinical examinations for DNC. CT-perfusion and CT-angiography scans were acquired solely for the purpose of the study and clinicians caring for study participants were not made aware of results from these tests. The study was approved by the Institutional Review Board of the Centre hospitalier de l'Université de Montréal (#MP-02—2017—7010) and each participating site. Informed consent was obtained from each participant's legal representative prior to study enrollment. Study reporting follows guidance from the STROBE statement [8]. The protocol for this secondary analysis was prespecified.

Participants

The target population comprises adult patients who are at risk of DNC following a severe brain injury. Participant selection criteria for the study were the same as for INDex, which included consecutive adults 18 years and older, admitted in the ICU with a severe brain injury, who had a Glasgow Coma Score of 3 and in whom sedation sufficient to affect the validity of the neurological examination had been stopped for at least six hours. The exclusion criteria were contraindications to CT-perfusion (pregnancy, contrast allergy, or clinician refusal to include because of kidney injury) and any of the following factors precluding a complete and valid clinical neurological examination: cervical fracture above C6, significant facial trauma limiting cranial nerve examination, hypothermia < 34 °C, use of intravenous barbiturates at any time since admission, unresuscitated shock, peripheral nerve or muscle dysfunction or neuromuscular blockade potentially accounting for unresponsiveness, anoxic brain injury < 24 h (or 72 h if therapeutic hypothermia was used), attending physician disagreement with the performance of an apnea test, or any other abnormalities deemed by the attending physician to potentially alter the validity of the clinical neurological examination. Potential organ donation was not a selection criterion. Eligibility of all enrolled participants was confirmed by blind central adjudication. Trained research coordinators at each center monitored daily admissions to the ICU to identify all potential participants.

Study procedures

Data was directly collected from the INDex study database, for which baseline information was obtained by site-specific trial research coordinators based on information from each participant's in-hospital medical file. Physicians performing the clinical neurological examination, neuroradiologists interpretating the scans, and the research personnel involved in longitudinal outcome assessment were blinded to the observations of their counterparts. Therefore, physicians did not have access to the CT-angiography or CT-perfusion scans and neuroradiologists did not have access to clinical examination information. Research coordinators recorded longitudinal outcomes, such as vital status (death or survival) at discharge from the ICU and organ donation.

Clinical examination

Two licensed physicians competent in DNC determination (intensivists, neurosurgeons, neurologists), or residents in those specialties who were in their final year of training, applied standardized criteria based on contemporary Canadian DNC guidelines to classify participants as DNC or alive [9]. At least one clinician had to be certified in their specialty. DNC determination included the documentation of a severe structural brain injury etiology compatible with DNC, exclusion of potential confounders to the clinical examination (including measure of plasma concentrations for midazolam, propofol, morphine, hydromorphone, fentanyl and the active metabolites of these compounds) [10], and a complete and reliable neurologic examination including an apnea test consistent with DNC. The neurologic examination comprised bilateral assessment of tympanic membrane integrity; verification of blood pressure, heart rate, and core temperature; determination of the Glasgow Coma Scale score; and evaluation of motor responses to noxious stimulation applied to the frontal skull, maxillary region, trapezius, and upper and lower limbs. Brainstem reflexes were assessed bilaterally, including pupillary light (photomotor), corneal, oculocephalic, oculocaloric, cough, and pharyngeal (gag) reflexes. An apnea test was performed at the conclusion of the examination (eTable 1). The apnea test was not undertaken in patients exhibiting any brainstem reflexes or other signs of life during the examination. An apnea test was positive when no respiratory effort was observed in the presence of a rise in arterial carbon dioxide tension ($PaCO_2$) to ≥ 60 mm Hg and at least 20 mm Hg above the baseline, with a corresponding pH ≤ 7.28, as documented by arterial blood gas measurement. Both clinicians had to agree that all criteria were met for the patient to be classified as DNC. In eventuality of disagreement, a third clinician could be consulted. Since participant selection criteria excluded all indications for ancillary testing in Canadian guidelines, study

participants did not require ancillary testing for DNC determination. When clinicians observed movements during the neurologic examination, they were requested to classify them as a typical spinal reflex, Lazarus sign (arms raise then drop across the chest), atypical movements and other movements (eTable 2). In the absence of a formally recognized classification of movements in this patient population, we complemented this pragmatic classification with a standardized and detailed description of each movement: clinicians determined whether movements occurred spontaneously or could be elicited by stimulation (if so, which type of stimulation elicited the movement, and the time lag between the stimulus and the movement), provided a description of the movement, reported whether the movement was fatigable, the number of times the movement was witnessed and whether the participant was determined not to be deceased due to the presence of the movement. Movement documentation occurred immediately at the bedside. In cases of discrepancies in clinicians' descriptions of the movements observed during neurologic examination, a neurointensivist independently adjudicated descriptions based on the reports provided by both clinicians.

Neuroimaging

Neuroimaging and clinical DNC examinations were instructed to occur within a 2-h delay. Clinical examination could occur before or after neuroimaging. The CT-perfusion and CT-angiography image acquisition protocol in the INDex study was previously published [6]. During image acquisition, we documented any incidence of systolic blood pressure ≥ 180 mmHg or mean arterial blood pressure ≤ 60 mmHg. Two licensed neuroradiologists centrally and independently interpreted the CT-perfusion and CT-angiography scans. Neuroradiologists examined the CT-perfusion scans qualitatively to determine the presence or absence of a matched intracranial decrease in cerebral blood flow and a corresponding decrease in cerebral blood volume. They applied the 10-point scale to interpret CT-angiography images by assessing vessel opacification of the A3 segments of the anterior cerebral arteries, the M4 segments of the middle cerebral arteries, the P2 segments of the posterior cerebral arteries, the two internal cerebral veins, the great vein of Galen, and the basilar artery in late-phase acquisitions [11]. In cases of imaging interpretation disagreements, the images were reviewed again by the two assessors, blinded from the first two interpretations and DNC clinical examination results.

Outcomes

This study's co-primary outcomes were SMM and MUO. SMM included typical spinal reflexes, such as triple flexion response to nociceptive stimulation, and the Lazarus sign. MUO included atypical and other movements. Clinicians performing bedside neurological examination for DNC determined whether participants had SMM and/or MUO. Physicians were not instructed as to what distinguished atypical movements from other movements. SMM and MUO could not include movements involving cerebral functions such as decortication, decerebration, withdrawal and localization to pain.

Statistical analysis

We provide descriptive statistics, reporting continuous variables as medians and interquartile ranges, and dichotomous variables as counts and proportions. We report the respective prevalence of SMM and of MUO with their corresponding 95% confidence intervals, calculated using the Wilson score method. Using generalized linear mixed models, with intercept random effects for the study site, a logit link function, and age and sex as covariates, we assessed the associations between (1) each co-primary outcome and both cerebral blood flow on CT-angiography and brain perfusion on CT-perfusion, and (2) the delay between brain injury and clinical examination, modeled in days, for each co-primary outcome. Analyses were adjusted for age and sex a priori given their potential association with both cerebrovascular perfusion patterns and movement expression, thereby reducing confounding in the assessment of the association between movements and neuroimaging findings. In all models, we determined 95% confidence intervals using robust standard errors (sandwich estimator).

In subgroup analyses, we assessed the prevalence of each co-primary outcome among alive participants and DNC participants. We also estimated the associations between each primary co-outcome and cerebral blood flow, and between each co-primary outcome and brain perfusion, among DNC participants. In sensitivity analyses, we first reran the general linear mixed model above to assess the association between a < 72-h delay between brain injury and clinical examination, compared to a ≥ 72-h delay, and SMM. The dichotomization threshold was chosen based on a prior study that found that SMM disappeared within 72 h of DNC determination [12]. Second, we also ran models estimating associations between SMM and MUO with cerebral blood flow on CT-angiography and brain perfusion on CT-perfusion by adding injury etiology as a covariate, which we categorized as structural (traumatic brain injury, hemorrhagic stroke and ischemic stroke) versus non-structural (anoxic brain injury). All analyses were performed on RStudio, version 2023.06.0 + 421 (Vienna, Austria).

Results

Among 850 patients screened for enrollment, 333 participants were enrolled of whom 282 completed the study protocol and were included in the study (Fig. 1). Baseline characteristics are detailed in Table 1. The sample's median (interquartile range) age was 60 [47—69] years; 133 (47%) were female. The initial brain injury etiologies were intracranial hemorrhages in 150 (53%), anoxic brain injuries in 59 (21%), traumatic brain injuries in 40 (14%),

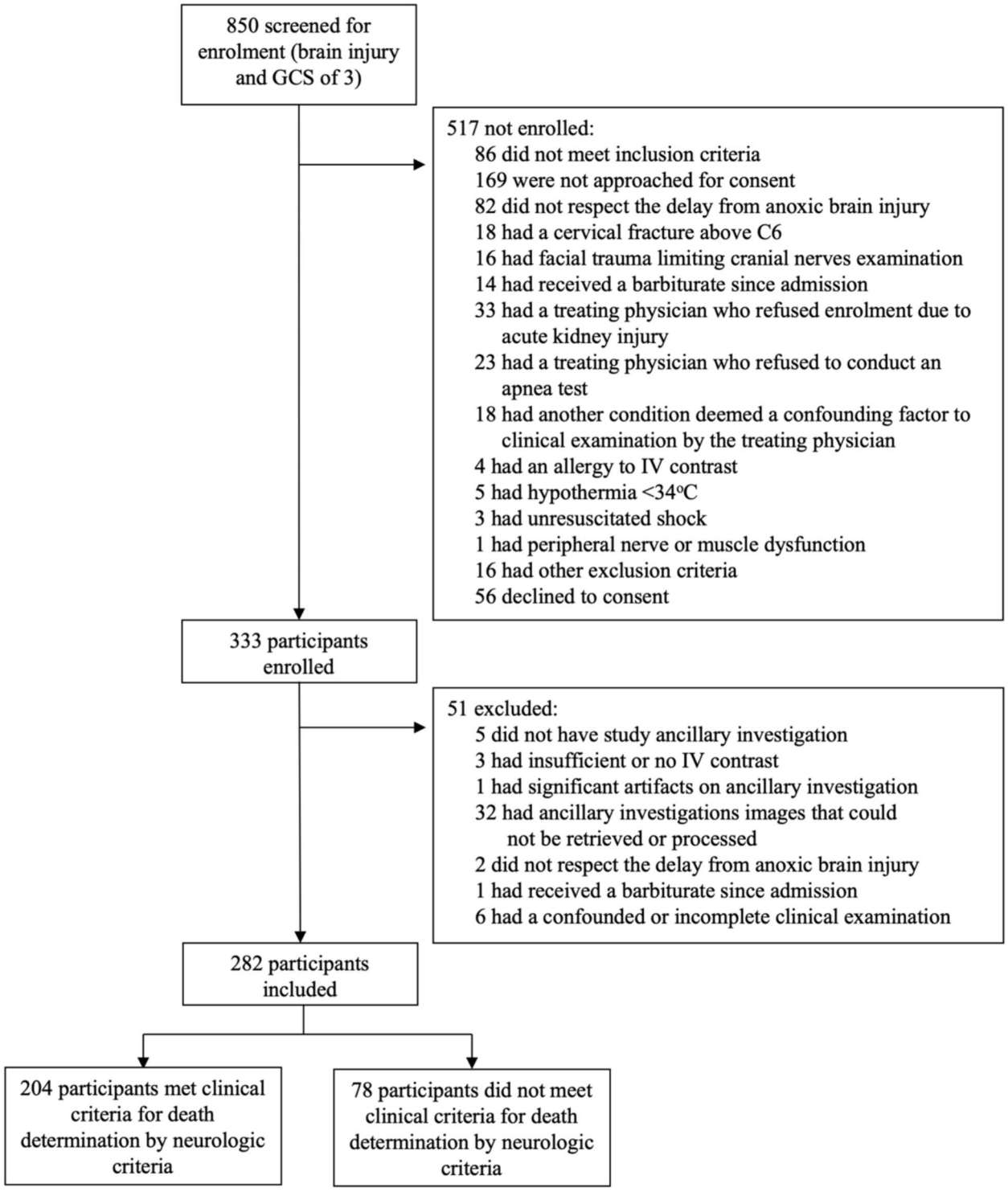


Fig. 1 Flowchart diagram. GCS: Glasgow Coma Scale

Table 1 Baseline participant characteristics

	Entire cohort (n = 282)	Alive participants (n = 78)	Dead/DNC participants (n = 204)	Participants with SMM (n = 76)	Participants without SMM (n = 206)	Participants with MUO (n = 33)	Participants without MUO (n = 249)
Demographics							
Age (median [IQR])	60 [47—69]	62 [51—69]	58 [47—70]	60 [48—71]	60 [47—69]	58 [39—67]	60 [47—70]
Female sex (n, %)	133 (47)	23 (30)	110 (54)	40 (53)	93 (45)	17 (52)	116 (47)
Race (n, %)							
Asian	24 (9)	4 (5)	20 (10)	7 (9)	17 (8)	0 (0)	24 (10)
Black or African American	4 (1)	1 (1)	3 (2)	0 (0)	4 (2)	0 (0)	4 (2)
Caucasian	217 (77)	64 (82)	153 (75)	57 (75)	160 (78)	30 (91)	187 (75)
First Nations	11 (4)	1 (1)	10 (5)	3 (4)	8 (4)	1 (3)	10 (4)
Other or unknown [a]	26 (9)	8 (10)	18 (9)	9 (12)	17 (8)	2 (6)	24 (10)
Comorbidities (n, %)							
Hypertension	114 (40)	36 (46)	78 (38)	29 (38)	85 (41)	14 (42)	100 (40)
Diabetes mellitus	50 (18)	20 (26)	30 (15)	16 (21)	34 (17)	6 (18)	44 (18)
Atherosclerotic cardiovascular disease	60 (21)	20 (26)	40 (20)	12 (16)	48 (23)	10 (30)	50 (20)
Coronary heart disease	40 (14)	17 (22)	23 (11)	7 (9)	33 (16)	7 (21)	33 (13)
Peripheral vascular disease	6 (2)	2 (3)	4 (2)	2 (3)	4 (2)	2 (6)	4 (2)
History of previous stroke	27 (10)	8 (10)	19 (9)	8 (10)	19 (9)	4 (12)	23 (9)
Smoking							
Active smoking	42 (15)	14 (18)	28 (14)	14 (18)	28 (14)	6 (18)	36 (15)
History of smoking	18 (6)	4 (5)	14 (7)	6 (8)	12 (6)	1 (3)	17 (7)
Chronic kidney disease							
Not on dialysis	10 (4)	3 (4)	7 (3)	1 (1)	9 (4)	1 (3)	9 (4)
On dialysis	3 (1)	3 (4)	0 (0)	1 (1)	2 (1)	2 (6)	1 (0)
Liver disease	25 (9)	10 (13)	15 (7)	10 (13)	15 (7)	2 (6)	23 (9)
Brain injury etiology (n, %)							
Ischemic stroke	15 (5)	2 (3)	13 (6)	5 (7)	10 (5)	0 (0)	15 (6)
Intracranial hemorrhage	150 (53)	29 (37)	121 (59)	46 (61)	104 (51)	13 (39)	137 (55)
Intraparenchymal hemorrhage	78 (28)	18 (23)	60 (29)	23 (30)	55 (27)	7 (21)	71 (29)
Aneurysmal subarachnoid hemorrhage	63 (22)	10 (13)	53 (26)	22 (30)	41 (20)	6 (18)	57 (23)
Non-aneurysmal subarachnoid hemorrhage	9 (3)	1 (1)	8 (4)	1 (1)	8 (4)	0 (0)	9 (4)
Traumatic brain injury	40 (14)	12 (15)	28 (14)	15 (20)	25 (12)	3 (9)	37 (15)
Anoxic brain injury	59 (21)	28 (36)	31 (15)	5 (7)	54 (26)	13 (40)	46 (19)
Other	18 (6)	7 (9)	11 (5)	5 (6)	13 (6)	4 (12)	14 (6)

[a] Other/Unknown includes participants identified as Arab, Latin American, or multiracial by surrogate decision makers—or, when no surrogate was available, as recorded in hospital charts—along with individuals who declined to report race/ethnicity or whose race/ethnicity could not be determined by the study team. DNC: death by neurologic criteria, SMM: spinal-mediated movements, MUO: movements of unclear neuroanatomic origin, IQR: interquartile range

ischemic strokes in 15 (5%) and other conditions in 18 (7%) participants.

Clinical neurologic examinations occurred at a median of 2 [1–4] days following the acute brain injury. Physicians performing the neurologic examinations were licensed in intensive care medicine (502/564, 89%), neurology (24/564, 4%), other specialties (13/564, 2%) or were residents in their last year of training in one of those specialties (25/564, 4%). Overall, 204 of 282 (72%) participants fulfilled criteria for DNC on clinical examination. Table 2 summarizes clinical examination and neuroimaging findings. Central adjudication confirmed that none of the participants were under the effect of sedative medications based on the plasma concentrations of common sedatives. On neurologic examination, 129 (46%) participants exhibited movements. Seventy-six of 282 (27%) participants had SMM: 75 (27%) had typical spinal-mediated reflexes, and one (0.4%) participant had the Lazarus sign. Thirty-three of 282 (12%) participants had MUO: 24 (9%) had atypical movements and nine (3%) had other movements. No participant had both SMM and MUO. Neuroimaging occurred a median of 64.5 [40.0—87.8] minutes from clinical examination. On neuroimaging, 121 of 282 (43%) participants had cerebral blood flow on CT-angiography. Eighty-five of 282 (30%) participants had brain perfusion on CT-perfusion.

Among the 78 participants who were alive at the time of clinical examination, 7 (9%) survived to discharge from

Table 2 Clinical examination and neuroimaging findings

	Entire cohort (n = 282)	Alive participants (n = 78)	Dead/DNC participants (n = 204)	Participants with SMM (n = 76)	Participants without SMM (n = 204)	Participants with MUO (n = 33)	Participants without MUO (n = 249)
Clinical examination findings							
Delay from brain injury to clinical examination in days (median [IQR])	2 [1-4]	3 [2-5]	2 [1-3]	2 [1-3]	3 [1-4]	3 [1-3]	2 [1-4]
DNC examination (n, %)							
Consistent with DNC (dead)	204 (72)	0 (0)[a]	204 (100)[a]	54 (71)	150 (73)	18 (55)	186 (75)
Inconsistent with DNC (alive)	78 (28)	78 (100)[a]	0 (0)[a]	22 (29)	56 (27)	15 (46)	63 (25)
Any movement (n, %)	129 (46)	57 (73)	72 (35)	76 (100)[a]	53 (26)	33 (100)[a]	96 (39)
Movements involving cerebral function (n, %)	20 (7)	20 (26)	0 (0)	0 (0)	20 (10)	0 (0)	20 (8)
Localization	1 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	1 (0)
Withdrawal	3 (1)	3 (4)	0 (0)	0 (0)	3 (2)	0 (0)	3 (1)
Decortication posturing	4 (1)	4 (5)	0 (0)	0 (0)	4 (2)	0 (0)	4 (2)
Decerebration posturing	11 (4)	11 (14)	0 (0)	0 (0)	11 (5)	0 (0)	11 (4)
Other (grimacing)	1 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	1 (0)
Spinal mediated movements (n, %)	76 (27)	22 (28)	54 (27)	76 (100)[a]	0 (0)[a]	0 (0)	76 (31)
Typical spinal-mediated reflex	75 (27)	22 (28)	53 (26)	75 (99)	0 (0)[a]	0 (0)	75 (30)
Lazarus sign	1 (0)	0 (0)	1 (1)	1 (0)	0 (0)[a]	0 (0)	1 (0)
Movements of unclear origin (n, %)	33 (12)	15 (19)	18 (9)	0 (0)	33 (16)	33 (100)[a]	0 (0)[a]
Atypical movements	24 (9)	11 (14)	13 (6)	0 (0)	24 (12)	24 (73)	0 (0)[a]
Other movements	9 (3)	4 (5)	5 (3)	0 (0)	9 (4)	9 (27)	0 (0)[a]
Neuroimaging findings							
Delay from brain injury to radiologic examination in days (median [IQR])	2 [1-4]	3 [2-5]	2 [1-3]	2 [1-3]	3 [1-4]	3 [1-3]	2 [1-4]
CT-angiography result (n, %)							
Cerebral blood flow absent	161 (57)	7 (9)	154 (76)	43 (57)	117 (57)	17 (52)	144 (58)
Cerebral blood flow present	121 (43)	71 (91)	50 (25)	33 (43)	88 (43)	16 (49)	105 (42)
CT-perfusion result (n, %)							
Brain perfusion absent	197 (70)	6 (8)	191 (94)	50 (66)	147 (71)	20 (61)	177 (71)
Brain perfusion present	85 (30)	72 (92)	13 (6)	26 (34)	59 (29)	13 (39)	72 (29)

[a] By definition. DNC: death by neurologic criteria, SMM: spinal-mediated movements, MUO: movements of unclear neuroanatomic origin, IQR: interquartile range

the ICU, 52 (67%) were determined deceased by circulatory criteria and 19 (24%) eventually met criteria for DNC.

The prevalence of SMM was 27% (95% CI: 22—32%) among comatose participants at risk of DNC. Table 3 details the semiology of SMM. None of the 75 participants with typical spinal-mediated reflexes was considered alive based on the presence of these movements. One participant had the Lazarus sign: they were not considered alive based on the presence of this reflex. SMM were not associated with cerebral blood flow on CT-angiography (aOR: 1.14, 95% CI: 0.63—2.05) or brain perfusion on CT-perfusion (aOR: 1.44, 95% CI: 0.77—2.68).

The prevalence of MUO was 12% (95% CI: 9—16%) among comatose participants at risk of DNC. Table 4 details the semiology of MUO. Information on a DNC participant who had an atypical movement elicited by painful stimulus above the clavicles are provided in Table 4 and eTable 3. Six of 24 participants (25%) with atypical movements were considered to have movements compatible with life. Details on these six cases are reported in Table 4 and eTable 4. Information on a DNC participant who had leg withdrawal are provided in Table 4 and eTable 5. Two of 9 participants (22%) with other movements were considered to have movements compatible with life. Details on these two cases are reported in Table 4 and eTable 6. MUO were not associated with cerebral blood flow on CT-angiography (aOR: 1.36, 95% CI: 0.61—3.01) or brain perfusion on CT-perfusion (aOR: 1.75, 95% CI: 0.77—3.).

Prevalence of SMM and of MUO are plotted over the delay between brain injury and DNC clinical examination in days in Fig. 2**.** Delays in hours are provided in eFigures 1—2. The delay between brain injury and clinical examination in days was not associated with SMM (aOR: 0.92, 95% CI: 0.82—1.02) or MUO (aOR: 0.95, 95% CI: 0.80—1.03). In sensitivity analysis, a < 72-h delay between brain injury and clinical examination, compared to a ≥ 72-h delay, was associated with SMM (aOR: 2.27, 95% CI: 1.23—4.17).

Table 3 Semiology of spinal mediated movements (SMM)

	Entire cohort	Alive participants	Dead/DNC participants
Typical spinal-mediated reflex	**n = 75**	**n = 22**	**n = 53**
Spontaneous (n, %)[a]	4 (5)	1 (5)	3 (6)
Stimulus-induced (n, %)[a]	75 (100)	22 (100)	53 (100)
Elicited by nail bed pressure to the finger	8 (11)	6 (27)	2 (4)
Elicited by nail bed pressure to the toe	72 (96)	21 (96)	51 (96)
Elicited by plantar stimulation	7 (13)	1 (5)	7 (13)
Time lag between stimulus and response in seconds (median, IQR)	0 [0—1]	0 [0—1]	0 [0—1]
Movement description (n, %)[a]			
Lower extremity triple flexion	70 (93)	21 (96)	49 (93)
Knee extension	3 (4)	0 (0)	3 (6)
Pectoral myoclonus	1 (1)	0 (0)	1 (2)
Leg internal rotation	1 (1)	1 (5)	0 (0)
Ankle flexion	1 (1)	0 (0)	1 (2)
Toe flexion	1 (1)	0 (0)	1 (2)
Toe extension	1 (1)	1 (5)	0 (0)
Toe fanning	1 (1)	0 (0)	1 (2)
Fatigable (n, %)	36 (48)	10 (46)	26 (49)
Number of times witnessed (n, %)			
1	5 (7)	1 (5)	4 (8)
2	12 (16)	2 (9)	10 (19)
> 2	58 (77)	19 (86)	39 (74)
Participant considered alive based on the presence of this movement	0 (0)	0 (0)	0 (0)
Lazarus sign[b]	**n = 1**	**n = 0**	**n = 1**

[a] Not mutually exclusive. [b] One participant had the Lazarus sign: they were not considered alive based on the presence of this reflex, which was stimulus-induced and occurred > 2 times. IQR: interquartile range

Sensitivity analyses reporting estimates adjusted for age, sex and brain injury etiology are reported in eTables 7—8. Association estimates in these analyses were similar to those from primary analyses. In subgroup analyses, prevalence of SMM was 28% (95% CI: 19—39%) among alive participants and 27% (95% CI: 21—33%) among DNC participants. Among DNC participants, SMM were not associated with cerebral blood flow on CT-angiography (aOR: 0.71, 95% CI: 0.29—1.42) or brain perfusion on CT-perfusion (aOR: 1.24, 95% CI: 0.33—3.93). Prevalence of MUO was 19% (95% CI: 12—29%) among alive participants and 9% (95% CI: 6—14%) among DNC participants. Among DNC participants, MUO were not associated with cerebral blood flow on CT-angiography (aOR: 1.35, 95% CI: 0.44—4.13) or brain perfusion on CT-perfusion (aOR: 0.88, 95% CI: 0.11—7.24).

Discussion

In this large, prospective, multicentric cohort study, we observed a 27% prevalence of SMM and a 12% prevalence of MUO in comatose patients at risk of DNC. SMM and MUO occurred as frequently among those who fulfilled clinical criteria for DNC as those who did not. Neither SMM nor MUO were associated with cerebral blood flow on CT-angiography or brain perfusion on CT-perfusion. These findings were replicated in the subgroup of participants fulfilling clinical criteria for DNC, supporting decades of research showing that these movements are unlikely to be mediated by upper motoneurons and other pathways in the brain or brainstem. Whereas previous work was based largely on evoked potentials, EEG and cerebral angiography, our work extends the window of investigation to CT-angiography and CT-perfusion. These neuroimaging modalities offer advantages in terms of accessibility and reliability in the presence of metabolic and chemical confounders to the clinical neurologic examination.

We did not find associations between the brain injury and clinical examination delay and the presence of SMM or MUO. Based on previous clinical observations, SMM are considered to disappear over time, typically within 72 h of fulfilling clinical criteria for DNC [12]. This is consistent with our sensitivity analysis results, which suggest that patients examined within 72 h of their brain injury have higher odds of having SMM on clinical examination than those examined 72 h or later. Nevertheless, our study design did not include serial neurologic examinations after participants met criteria for DNC, such that we could not confirm the timeframe after which SMM are unlikely to occur. The mechanisms leading to a decay in SMM prevalence over time are unknown but could involve progressive rostrocaudal circulatory arrest of the central nervous system, extending from the brain into the spinal cord.

Our study contributes to the literature on SMM among patients fulfilling clinical criteria for DNC by providing a robustly and prospectively assessed prevalence estimate in this population, as well as in a wider population of comatose patients at risk of DNC. Previous studies, which relied mainly on retrospective review of movements observed during DNC determination, have suggested that SMM occur in 13—79% of patients fulfilling clinical criteria for DNC. [4, 5, 12–17] Heterogeneity in study population, sampling, and outcome assessment likely explain the significant variability in prevalence estimates observed in previous work. For instance, some studies enrolled DNC patients based solely on clinical criteria, whereas others enrolled patients who fulfilled

Table 4 Semiology of movements of unclear neuroanatomic origin (MUO)

	Entire cohort	Alive participants	Dead/DNC participants
Atypical movements	**n = 24**	**n = 11**	**n = 13**
Spontaneous (n, %)[a]	4 (17)	2 (18)	2 (15)
Stimulus-induced (n, %)[a]	22 (92)	11 (100)	11 (85)
Elicited by painful stimulus above clavicles	6 (25)	5 (46)	1 (8)[b]
Elicited by nail bed pressure to the finger	11 (46)	6 (55)	5 (39)
Elicited by nail bed pressure to the toe	9 (38)	5 (46)	4 (31)
Elicited by plantar stimulation	1 (4)	0 (0)	1 (8)
Elicited by neck flexion	1 (4)	0 (0)	1 (8)
Elicited by sternal pressure	1 (4)	1 (9)	0 (0)
Elicited by tracheal stimulation	1 (4)	1 (9)	0 (0)
Elicited by caloric testing	1 (4)	1 (9)	0 (0)
Elicited by nasal tickling	1 (4)	1 (9)	0 (0)
Time lag between stimulus and response in seconds (median, IQR)	0 [0—1]	0 [0—1]	0 [0—1]
Movement description (n, %)[a]			
Toe flexion	5 (21)	2 (18)	3 (23)
Head rotation	4 (17)	2 (18)	2 (15)
Lower extremity triple flexion	4 (17)	4 (36)	0 (0)
Leg myoclonus	2 (8)	1 (9)	1 (8)
Finger extension	2 (8)	1 (9)	1 (8)
Thumb flexion	1 (4)	0 (0)	1 (8)
Arm tremor	1 (4)	0 (0)	1 (8)
Arm myoclonus	1 (4)	0 (0)	1 (8)
Elbow extension	1 (4)	1 (9)	0 (0)
Pectoral myoclonus	1 (4)	1 (9)	0 (0)
Axial myoclonus during apnea testing	1 (4)	0 (0)	1 (8)
Toe myoclonus	1 (4)	1 (9)	0 (0)
Toe extension	1 (4)	0 (0)	1 (8)
Knee extension	1 (4)	0 (0)	1 (8)
Leg internal rotation	1 (4)	0 (0)	1 (8)
Fatigable (n, %)	11 (46)	4 (36)	7 (54)
Number of times witnessed (n, %)			
1	2 (8)	1 (9)	1 (8)
2	4 (17)	0 (0)	4 (31)
> 2	18 (75)	10 (91)	8 (62)
Participant considered alive based on the presence of this movement	6 (25)	6 (55)[c]	0 (0)
Other movements	**n = 9**	**n = 4**	**n = 5**
Spontaneous (n, %)[a]	4 (45)	1 (25)	3 (60)
Stimulus-induced (n, %)[a]	7 (78)	4 (100)	5 (60)
Elicited by painful stimulus above clavicles	3 (33)	3 (75)	0 (0)
Elicited by nail bed pressure to the finger	2 (22)	1 (25)	1 (20)
Elicited by nail bed pressure to the toe	2 (22)	1 (25)	1 (20)
Elicited by plantar stimulation	1 (11)	0 (0)	1 (20)
Time lag between stimulus and response in seconds (median, IQR)	1 [0—1]	1 [0—1]	1 [0—1]
Movement description (n, %)[a]			
Toe extension	1 (11)	1 (25)	0 (0)
Hiccup	1 (11)	1 (25)	0 (0)
Arm tremor	1 (11)	0 (0)	1 (20)
Arm withdrawal	1 (11)	1 (25)	0 (0)
Elbow extension	1 (11)	1 (25)	0 (0)
Hand fasciculations	1 (11)	0 (0)	1 (20)
Lower extremity triple-flexion	1 (11)	1 (25)	0 (0)
Knee extension	1 (11)	0 (0)	1 (20)
Leg withdrawal	1 (11)	0 (0)	1 (20)[d]

Table 4 (continued)

	Entire cohort	Alive participants	Dead/DNC participants
Fatigable (n, %)	3 (33)	0 (0)	3 (60)
Number of times witnessed (n, %)			
1	1 (11)	0 (0)	1 (20)
2	0 (0)	0 (0)	0 (0)
> 2	8 (89)	4 (100)	4 (80)
Participant considered alive based on the presence of this movement	2 (22)	2 (50)[e]	0 (0)

[a] Not mutually exclusive. [b] Details on this case are reported in eTable 3. This patient was not considered to be alive based on this movement. CT-angiography showed absence of cerebral blood flow and CT-perfusion showed absence of brain perfusion. [c] Details on these cases are reported in eTable 4. Three of these six participants did not have other signs consistent with life; CT-angiography showed absence of cerebral blood flow and CT-perfusion showed absence of brain perfusion in these three participants. The other three of six participants had cough (3/3) and pharyngeal (2/3) reflexes and did not undergo apnea testing due to signs of life; CT-angiography showed cerebral blood flow and CT-perfusion showed brain perfusion in all three. [d] Details on this case are reported in eTable 5. This patient was not considered to be alive based on this movement. CT-angiography showed absence of cerebral blood flow and CT-perfusion showed absence of brain perfusion. [e] Details on these cases are reported in eTable 6. Both participants had other signs of life; CT-angiography showed cerebral blood flow and CT-perfusion showed brain perfusion in both. IQR: interquartile range

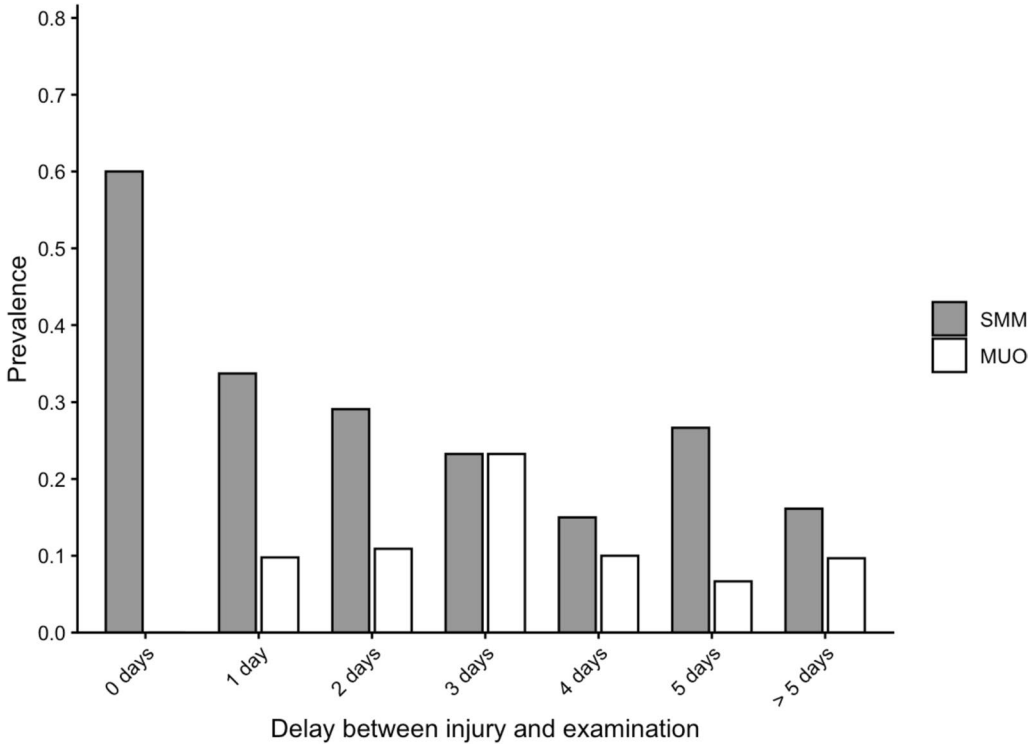


Fig. 2 Prevalence of movements over the delay between brain injury and clinical examination. SMM: spinal-mediated movements, MUO: movements of unclear neuroanatomic origin

clinical and ancillary testing criteria for DNC, typically using EEG or transcranial Doppler ultrasonography. Whereas SMM have traditionally been described as movements elicited by triggers of limited variation, occurring stereotypically, and having invariant time patterns of latency and duration, as well as a refractory period, our findings also reinforce previous observations that these movements are in fact heterogeneous in semiology and do not necessarily comply with traditional characteristics [18]. Our results also show that heterogeneous movements occur in patients fulfilling clinical criteria for DNC and with absent cerebral blood flow on CT-angiography and absent perfusion on CT-perfusion, broadening the semiology of possible movements attributable to the spinal cord and peripheral nervous system. Overall, these data will make clinicians better informants, and allied healthcare professionals and family members better informed, on the frequency and implications of SMM in patients at risk of DNC.

Our study also characterizes the frequency, semiology and neuroimaging of MUO. Many MUO descriptions were similar to those of SMM (e.g. toe flexion and extension, often observed in SMM "undulating toes"), suggesting these MUO may in fact have been misclassified SMM. On the other hand, some MUO had semiology descriptions that do not localize to the brain, such as segmental

myoclonus, which is frequently spinal in origin, and fasciculations, which are lower motoneuron phenomena. Eight participants with MUO had movements that physicians considered to be compatible with life. Five of these eight participants also had some intact brainstem reflexes, as well as present cerebral blood flow on CT-angiography and brain perfusion on CT-perfusion. Conversely, the remaining three of eight individuals were found to fulfill all other clinical criteria for DNC, including complete brainstem areflexia and central apnea, and had absent cerebral blood flow and absent brain perfusion. It is possible that the latter three participants were misclassified as being alive when they were dead. Taken together, our results reinforce prior literature and guidelines stating that SMM and MUO alone should not be assumed to be signs of life in comatose patients at risk of DNC. Furthermore, these data support the potential utility of CT-angiography or CT-perfusion in selected cases where patients have MUO despite fulfilling all other clinical criteria for DNC. Nevertheless, the interpretation of movements in comatose patients at risk of DNC must remain individualized. Clinicians responsible for DNC determination should consider the full spectrum of relevant clinical factors and recognize that the presence of movements may be interpreted differently by families depending on their educational, cultural, and personal backgrounds and values. Clear, factual, and sensitive communication is therefore essential to support families and to ensure compassionate, empathetic care when movements are observed in patients at risk of DNC.

Our study has several methodological strengths. The risk of selection bias at enrollment was mitigated by recruiting a national multicentric prospective and consecutive sample of participants using one set of inclusion criteria. Information bias was minimized since measurements were performed using reliable data sources by trained study personnel and following a uniform protocol applied to all participants. Our study also has some limitations. First, we did not capture all SMM such as deep tendon reflexes and abdominal reflexes. Moreover, clinicians may have applied varying types and quantities of stimuli to elicit movements beyond those included in the standard DNC examination. Therefore, we may have underestimated the prevalence of SMM and MUO. Our SMM estimates remain, however, within the range of previously published prevalence. Second, we did not include pediatric patients, which limits generalizability to infants and children. Third, due to the variability of accepted ancillary investigations for DNC determination across the globe, our findings may be less transposable to jurisdictions that do not recommend CT-angiography or CT-perfusion scans for this purpose. Fourth, clinical examinations were performed by a large group of physicians with likely variable levels of experience in DNC determination. Because the classification of SMM and MUO relied on a pragmatic clinical approach, some degree of misclassification may have occurred. Such misclassification would most likely be non-differential and therefore bias estimates toward the null. However, this approach reflects real-world clinical practice and may enhance the generalizability of our findings.

In conclusion, SMM and MUO are common among comatose patients at risk of DNC. Their prevalence is similar among alive comatose patients and patients fulfilling clinical criteria for DNC. These movements are not associated with cerebral blood flow on CT-angiography or brain perfusion on CT-perfusion.

Abbreviations

DNC	Death by neurologic criteria
EEG	Electroencephalography
ICU	Intensive care unit
SMM	Spinal mediated movement
MUO	Movement of unclear neuroanatomic origin

Supplementary Information

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Additional file 1.

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JNB, JJS and MC designed the study. JNB did the statistical analysis and drafted the manuscript. All other authors revised the manuscript for intellectual content. All authors also reviewed and approved the final version of the manuscript. MC is the senior author and the guarantor of the study.

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Data availability
The sharing of individual patient data is restricted in accordance with applicable local laws of Canada. However, access to the full dataset, including individual patient data, may be possible for audit purposes or for secondary studies if they align with the original study protocol and informed patient consent. Such access would be contingent upon a formal data sharing agreement, ethical review board approval, and will be facilitated within a secure, controlled environment.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Review Board of the Centre hospitalier de l'Université de Montréal (#MP-02—2017—7010) and each participating site. Informed consent was obtained from each participant's legal representative prior to study enrollment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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