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ORIGINAL ARTICLE

Risk factors for 2-year mortality in patients with prolonged disorders of consciousness: An international multicentre study

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Abstract

Background and purpose: Patients with prolonged disorders of consciousness (pDoC) have a high mortality rate due to medical complications. Because an accurate prognosis is essential for decision-making on patients' management, we analysed data from an international multicentre prospective cohort study to evaluate 2-year mortality rate and bedside predictors of mortality.

Methods: We enrolled adult patients in prolonged vegetative state/unresponsive wakefulness syndrome (VS/UWS) or minimally conscious state (MCS) after traumatic and non-traumatic brain injury within 3 months postinjury. At enrolment, we collected demographic (age, sex), anamnestic (aetiology, time postinjury), clinical (Coma Recovery Scale–Revised [CRS-R], Disability Rating Scale, Nociception Coma Scale–Revised), and neurophysiologic

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(electroencephalogram [EEG], somatosensory evoked and event-related potentials) data. Patients were followed up to gather data on mortality up to 24 months postinjury.

Results: Among 143 traumatic (n = 55) and nontraumatic (n = 88) patients (VS/UWS, n = 68, 19 females; MCS, n = 75, 22 females), 41 (28.7%) died within 24 months postinjury. Mortality rate was higher in VS/UWS (42.6%) than in MCS (16%; $p < 0.001$). Multivariate regression in VS/UWS showed that significant predictors of mortality were older age and lower CRS-R total score, whereas in MCS female sex and absence of alpha rhythm on EEG at study entry were significant predictors.

Conclusions: This study demonstrated that a feasible multimodal assessment in the postacute phase can help clinicians to identify patients with pDoC at higher risk of mortality within 24 months after brain injury. This evidence can help clinicians and patients' families to navigate the complex clinical decision-making process and promote an international standardization of prognostic procedures for patients with pDoC.

KEYWORDS
disorders of consciousness, minimally conscious state, mortality, prognosis, vegetative state

INTRODUCTION

After severe acquired brain injury, survivors can remain in prolonged (>28 days from onset) disorders of consciousness (pDoC) [1]. Following a period of coma, patients who recover eyes opening (spontaneously or in response to stimuli) but do not demonstrate signs of awareness are defined as being in vegetative state/unresponsive wakefulness syndrome (VS/UWS) [2], whereas the minimally conscious state (MCS) [3] is defined by the appearance of inconsistent but reproducible intentional behaviours (e.g., visual pursuit, localization to pain, command following).

Patients in MCS and, less frequently, those in VS/UWS can regain full consciousness [4], in some cases even years after the injury [5]. However, a variable but substantial proportion of patients with pDoC (even up to 74%) [4] die within 12 months of brain injury, most often due to severe medical complications such as pneumonia or cardiac failure, with lowest mortality rates following trauma [6–8].

The main predictors for mortality are older age, nontraumatic aetiology, short time postinjury, and diagnosis of VS/UWS compared to MCS [4,7,9]. Moreover, recent studies highlighted that additional clinical variables, such as the Coma Recovery Scale–Revised (CRS-R) [10] total score [7], and electrophysiological markers, such as the absence of somatosensory evoked potentials (SEPs) [11] or event-related potentials (ERPs) [12], and worse electroencephalographic (EEG) background activity [13,14], could predict poor outcome, including mortality, in patients with pDoC. However, most of these prognostic studies evaluated a limited number of predictors, thus precluding detection of the independent predictive value of each variable [15]. Moreover, most studies showed limits in generalization of the results, mainly due to single-centre design and sampling bias.

As an accurate prognostication is essential for assisting clinicians and patients' relatives in decision-making on care and life-sustaining treatment [16], we analysed data from a multicentre longitudinal study on a large cohort of patients with pDoC to evaluate the role of demographic, anamnestic, clinical, and neurophysiological factors in predicting mortality up to 24 months postinjury. This study was initiated by the Special Interest Group on DoC of the International Brain Injury Association (see www.internationalbrain.org).

METHODS

Study design and participants

This study is part of a multicentre prospective project whose goal is to evaluate clinical evolution and identify prognostic factors in a large sample of patients with pDoC [17]. The international framework involved 12 medical centres (intensive care unit, n = 2; intensive specialized rehabilitation unit for postacute patients, n = 8, neurology department, n = 2) with expertise in diagnosis and care of adults with severe acquired brain injury, located in Europe (n = 10), North America (n = 1), and Asia (n = 1). All the participating centres enrolled a sample of patients with pDoC between January and December 2017, and collected longitudinal data on mortality up to 24 months after brain injury (until December 2019).

Inclusion criteria were (i) age ≥ 18 years; (ii) clinical diagnosis of VS/UWS or MCS, according to standard diagnostic criteria [3]; (iii) traumatic or nontraumatic (i.e., vascular or anoxic) aetiology; and (iv) time postinjury (TPI) ranging from 28 days to 3 months. Exclusion criteria were (i) previous history of acquired brain injury, or psychiatric or neurodegenerative diseases; and (ii) coexisting neoplasms, severe organ dysfunction, or unstable clinical condition (e.g., hemodynamic instability or severe respiratory failure).

Of 194 patients screened for the study, 147 patients with pDoC fulfilled the selection criteria.

After hospital discharge, patients were transferred to long-term facilities or home-based care and were followed up to gather data on outcome and mortality at 24 months after brain injury.

Clinical and neurophysiological variables

Based on recent practice guidelines [1], we focused on clinical and electrophysiological markers that could be easily collected in most medical settings. At study entry, each centre collected patient demographic data (i.e., age, sex) and information about medical history (i.e., aetiology, TPI). Within 1 week from study entry, repeated CRS-R assessments (at least three times within a 1-week period) were performed for all patients by skilled investigators to confirm the patients' clinical diagnosis. The CRS-R with the best total score was considered for the statistical analyses [18]. Patients' behavioural responses to nociceptive stimuli were assessed with the Nociception Coma Scale–Revised (NCS-R) [19] and functional disability level with the Disability Rating Scale (DRS) [20].

Multimodal neurophysiological data, including standard EEG, SEPs, and ERPs, were recorded within 2 weeks from study entry. Data were analysed by skilled neurophysiologists blind to the patient's clinical diagnosis.

EEG background activity was classified into five severity patterns (normal, mildly abnormal, moderately abnormal, diffuse slowing, low voltage) according to a recent proposal of EEG categorization for patients with pDoC [21]. For the purpose of multivariate analysis (see below) and based on the previous observation that even residual alpha rhythms on EEG were strongly associated with a high level of intentional behaviour [21], we grouped EEG background activity patterns into two categories. In the first category, we included the normal, mildly abnormal, and moderately abnormal patterns, which showed at least a small percentage of alpha rhythm (8–13 Hz) on posterior regions, whereas we included in the second the diffuse slowing and low-voltage patterns, lacking alpha rhythm.

We also collected EEG reactivity to five types of external stimuli: (i) eye opening and (forced) eye closing; (ii) tactile stimuli (wiping on the back of right and left forearm with cotton wool); (iii) noxious stimulation (pressing fingernail beds on each hand, according to the standardized procedure included in the CRS-R and NCS-R); (iv) acoustic stimulation (hand clapping); and (v) intermittent photic stimulation by 1-, 3-, 6-, 9-, 12-, 15-, 18-, and 21-Hz flashes in 10-s trains presented through closed eyelids with a 5-s interval between two trains. Presence of reactivity was defined as a clear and reproducible change in frequency and/or amplitude in cerebral activity in the 3 s after stimulus onset. SEPs were recorded during bilateral median nerve electrical stimulation, and classified as present if the N20 cortical component was recorded on at least one side [22]. Finally, ERPs were obtained by means of an auditory oddball paradigm [23], during which patients were asked to keep a mental count of the rare (target) tones while ignoring the frequent (nontarget) tones, regardless of level of consciousness. The presence of the P300 component was assessed. Full details about collection of clinical and neurophysiological variables have been previously reported [17].

Statistical analyses

Statistical analyses were performed by the coordinator researcher group (A.E., A.M., L.T.). The cumulative rate of survival for each group (overall sample, VS/UWS, MCS) was calculated using the Kaplan–Meier method. Thereafter, a log-rank (Mantel–Cox) test across strata was used for comparing variables between survivors and deceased. For this purpose, within each group continuous variables were dichotomized based on the median value, and EEG background patterns were grouped into two categories. Variables with a significance level of $p < 0.05$ on the log-rank test were selected, and the independent association of these factors with survival at 24 months postinjury was examined by a multivariate Cox regression analysis (with 95% confidence intervals [CIs]). Missing data were handled by listwise deletion.

Prior to the Cox regression analysis, multicollinearity was tested among the predictors by checking for the variance inflation factor (VIF) and tolerance.

Statistical analyses were performed with SPSS v25 (IBM), with $p < 0.05$ (two-tailed) considered statistically significant.

Ethics

The institutional review board of the coordinating centre and of each centre involved in the study reviewed and approved the same outline of the project, shared by all centres and translated into their respective languages. This study was approved by the ethical standards committee of the coordinator centre (Protocol 2/16 OSS) and each centre involved in the study, as well as its later amendments. The study was conducted according to the ethical standards of the Declaration of Helsinki (1964). The legal surrogate of all patients enrolled in the study provided their written informed consent after a semiformalized interview in which the purposes, procedures, and time points of the longitudinal study were clearly explained. The original forms were collected and stored at each participant centre in accordance with national regulation on the protection of personal data, and anonymized data were then centralized in one secured database for the analysis.

RESULTS

Two-year follow-up was completed and information on mortality was available for 143 of 147 patients (97.3% of the sample; 68 in VS/UWS, 75 in MCS; 41 females; 55 traumatic; mean age = 48.9 ± 19.8 years; mean TPI = 60.0 ± 25.3 days). One patient was lost to follow-up, one dropped out from the study because of withdrawal of life-sustaining

TABLE 1 Demographic, anamnestic, and clinical characteristics at baseline of included patients as a function of 24-month outcome

Characteristic	Overall sample				VS/UWS				MCS			
	Total, $N = 143$	Deceased, $n = 41$	Survivors, $n = 102$	p	Total, $n = 68$	Deceased, $n = 29$	Survivors, $n = 39$	p	Total, $n = 75$	Deceased, $n = 12$	Survivors, $n = 63$	p
Age, years	48.9 (19.8)	61.9 (16.5)	43.6 (18.7)	<0.001[a]	51.1 (19.5)	61.0 (15.3)	43.7 (19.2)	0.002[a]	46.8 (20.0)	64 (19.6)	43.6 (18.5)	0.009[a]
Sex, F/M	41/102	19/22	22/80	0.001[a]	19/49	10/19	9/30	0.199	22/53	9/3	13/50	<0.001[a]
TPI, days	60.0 (25.3)	64.6 (25.5)	58.1 (25.1)	0.420	60.3 (26.0)	65.7 (26.1)	56.2 (25.4)	0.184	59.8 (24.9)	61.8 (20.0)	59.4 (25.0)	0.786
Aetiology, TBI/non-TBI	55/88	6/35	49/53	<0.001[a]	23/45	5/24	18/21	0.021[a]	32/43	1/11	31/32	0.009[a]
CRS-R, total score	7 (7)	5 (4)	9 (9)	<0.001[a]	4.5 (3)	4 (2)	5 (2)	0.010[a]	12 (5)	12 (4)	12 (5)	0.838
NCS-R, total score	3 (2)	2 (3)	3 (2)	0.062	2 (2)	1 (2)	2 (2)	0.025[a]	4 (3)	4 (2)	4 (3)	0.011[a]
DRS, total score	24 (4)	25 (3)	24 (3)	0.041[a]	25 (2)	26 (2)	25 (2)	0.362	22 (3)	22.5 (2)	22 (5)	0.182

Note: Descriptive data are reported as mean (SD) for continuous variables, as median for ordinal variables, and as counts of patients for each level of categorical variables. Univariate statistics are based upon the log-rank (Mantel–Cox) test.

Abbreviations: CRS-R, Coma Recovery Scale–Revised; DRS, Disability Rating Scale; F, female; M, male; MCS, minimally conscious state; NCS-R, Nociception Coma Scale–Revised; TBI, traumatic brain injury; TPI, time postinjury; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

[a]Statistically significant.

therapy, and for two further patients the legal guardians revoked their consent for study participation. Due to logistical issues, neurophysiological findings were not recorded in all patients (available EEG = 94.4%, SEPs = 58.7%, ERPs = 51.7%). Most patients of the study sample had been enrolled in specialized postacute rehabilitation units (112/143, 78.3%), whereas 24 of 143 (16.8%) and seven of 143 (4.9%) had been enrolled in neurology departments and intensive care units, respectively.

Patients in MCS did not differ from patients in VS/UWS in terms of age, sex, aetiology, or TPI (all $p > 0.05$); full demographic, anamnestic, clinical, and neurophysiological data at study entry were reported elsewhere [17].

The 24-month mortality was 28.7% in the whole sample (41/143 deceased) and was significantly higher in the VS/UWS group (29/68 patients, 42.6%) than in the MCS group (12/75 patients, 16.0%; log-rank test, $\chi^2 = 12.5$; $p < 0.001$). In both groups, most patients died within 12 months after onset (VS/UWS: 22/29 deceased patients, 75.9%; MCS: 8/12 deceased patients, 66.7%). Mean time of death did not differ between patients in VS/UWS (296.0 ± 157.6 days) and those in MCS (341.2 ± 215.7 days; $U = 167.5$; $p = 0.85$). Overall mortality rate was not affected significantly by the medical setting at enrolment ($\chi^2 = 3.1$; $p = 0.208$; postacute rehabilitation: 33/112 deceased, 29.5%; neurology departments: 8/24 deceased, 33.3%; intensive care: 0/7 deceased, 0%). The most frequent causes of death were severe medical complications related to immobility (e.g., sepsis, pneumonia).

Within the overall sample, the log-rank test showed that, beyond clinical diagnosis, nontraumatic aetiology ($\chi^2 = 13.2$; $p < 0.001$), and older age ($\chi^2 = 21.7$; $p < 0.001$), lower CRS-R total score ($\chi^2 = 15.3$; $p < 0.001$), higher DRS total score ($\chi^2 = 4.2$; $p = 0.04$), but also female sex ($\chi^2 = 10.2$; $p = 0.001$) and the lack of alpha rhythm on EEG ($\chi^2 = 14.3$; $p < 0.001$) were significant risk factors for mortality (Tables 1 and 2). As no collinearity was identified among the selected predictors (VIF range = 1.06–3.86; tolerance range = 0.25–0.94), we performed a Cox regression analysis on the 135 patients (40 deceased) in whom all data were collected. The analysis provided a significant final model ($\chi^2 = 43.9$, $df = 7$; $p < 0.001$) in which only older age (risk ratio [RR] = 2.8, 95% CI = 1.1–7.0; $p = 0.027$) and female sex (RR = 2.5, 95% CI = 1.3–4.8; $p = 0.004$) were significantly associated with a higher risk of mortality (Figure 1).

Within the VS/UWS subgroup, the log-rank test showed that older age ($\chi^2 = 9.3$; $p = 0.002$), nontraumatic aetiology ($\chi^2 = 5.3$; $p = 0.02$), and lower CRS-R ($\chi^2 = 6.7$; $p = 0.01$) and NCS-R ($\chi^2 = 5.0$; $p = 0.02$) total scores were significant risk factors for mortality (Table 1). VIF among these predictors ranged from 1.00 to 1.38; tolerance ranged from 0.73 to 0.99. Cox regression analysis on all patients of the VS/UWS subgroup provided a significant final model ($\chi^2 = 20.3$, $df = 4$; $p < 0.001$). In this model, older age (RR = 3.2, 95% CI = 1.2–8.4; $p = 0.017$) and lower CRS-R total score (RR = 2.6, 95% CI = 1.2–5.8; $p = 0.019$) were significantly associated with a higher mortality risk (Figure 2).

Within the MCS subgroup, the log-rank test showed that older age ($\chi^2 = 6.9$; $p = 0.009$), female sex ($\chi^2 = 15.6$; $p < 0.001$), nontraumatic aetiology ($\chi^2 = 6.9$; $p = 0.009$), lower NCS-R total score

TABLE 2 Available neurophysiological data at baseline, including EEG (n = 135), SEPs (n = 84), and ERPs (n = 74), as a function of 24-month outcome

	Overall sample				VS/UWS				MCS			
	Total	Deceased	Survivors	p	Total	Deceased	Survivors	p	Total	Deceased	Survivors	p
EEG background activity pattern												
Normal	6	1	5		0	0	0		6	1	5	
Mildly abnormal	26	1	25		5	0	5		21	1	20	
Moderately abnormal	35	8	27		17	6	11		18	2	16	
Diffuse slowing	43	21	22		30	16	14		13	5	8	
Low voltage	25	9	16		14	7	7		11	2	9	
Alpha rhythm on EEG, P/A	67/68	10/30	57/38	<0.001[a]	22/44	6/23	16/21	0.055	45/24	4/7	41/17	0.025[a]
Reactivity to eye opening, P/A	43/91	9/31	34/60	0.118	16/50	7/22	9/28	0.916	27/41	2/9	25/32	0.101
Reactivity to tactile s., P/A	19/107	6/34	13/73	0.977	10/55	6/23	4/32	0.321	9/52	0/11	9/41	0.146
Reactivity to acoustic s., P/A	34/102	9/31	25/71	0.595	12/54	7/22	5/32	0.253	22/48	2/9	20/39	0.279
Reactivity to nociceptive s., P/A	32/93	11/29	21/64	0.866	14/50	8/21	6/29	0.411	18/43	3/8	15/35	0.816
Reactivity to IPS, P/A	25/104	11/29	14/75	0.147	15/50	8/21	7/29	0.422	10/54	3/8	7/46	0.297
N20 on SEPs, P/A	64/20	20/5	44/15	0.552	31/14	13/4	18/10	0.378	33/6	7/1	26/5	0.779
P300 on ERPs, P/A	39/35	7/12	32/23	0.092	11/22	3/9	8/13	0.458	28/13	4/3	24/10	0.438

Note: Data relative to EEG background activity are reported as absolute counts; data for the remaining variables are expressed as counts of patients showing/not showing the respective feature. For the purpose of multivariate analyses, EEG background activity patterns have been classified into two categories: presence of alpha rhythm (including normal, mildly abnormal, and moderately abnormal patterns) and absence of alpha rhythm (including diffuse slowing and low-voltage patterns). Univariate statistics are based upon the log-rank (Mantel–Cox) test. The distribution of EEG background activity patterns significantly differed between survivors and deceased in the whole sample ($p = 0.002$) but not in the two subsamples ($p > 0.1$).

Abbreviations: EEG, electroencephalogram; ERP, event-related potential; IPS, intermittent photic stimulation; MCS, minimally conscious state; P/A, present/absent; s., stimuli; SEP, somatosensory evoked potentials; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

[a]Statistically significant.

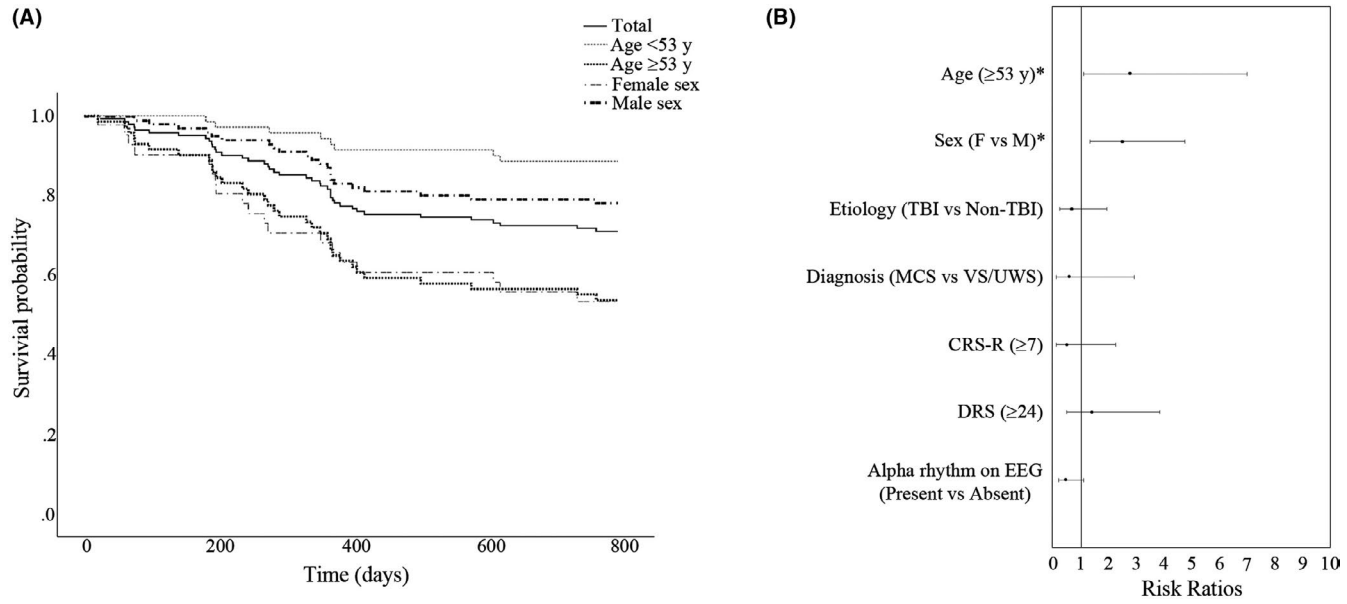

FIGURE 1 Survival curves as a function of the significant predictors in the Cox regression analysis (a) and forest plot of significant predictors of mortality up to 24 months postinjury (b) in the overall sample of patients with disorders of consciousness. *Significant predictors. CRS-R, Coma Recovery Scale–Revised; DRS, Disability Rating Scale; EEG, electroencephalogram; F, female; M, male; MCS, minimally conscious state; TBI, traumatic brain injury; VS/UWS, vegetative state/unresponsive wakefulness syndrome

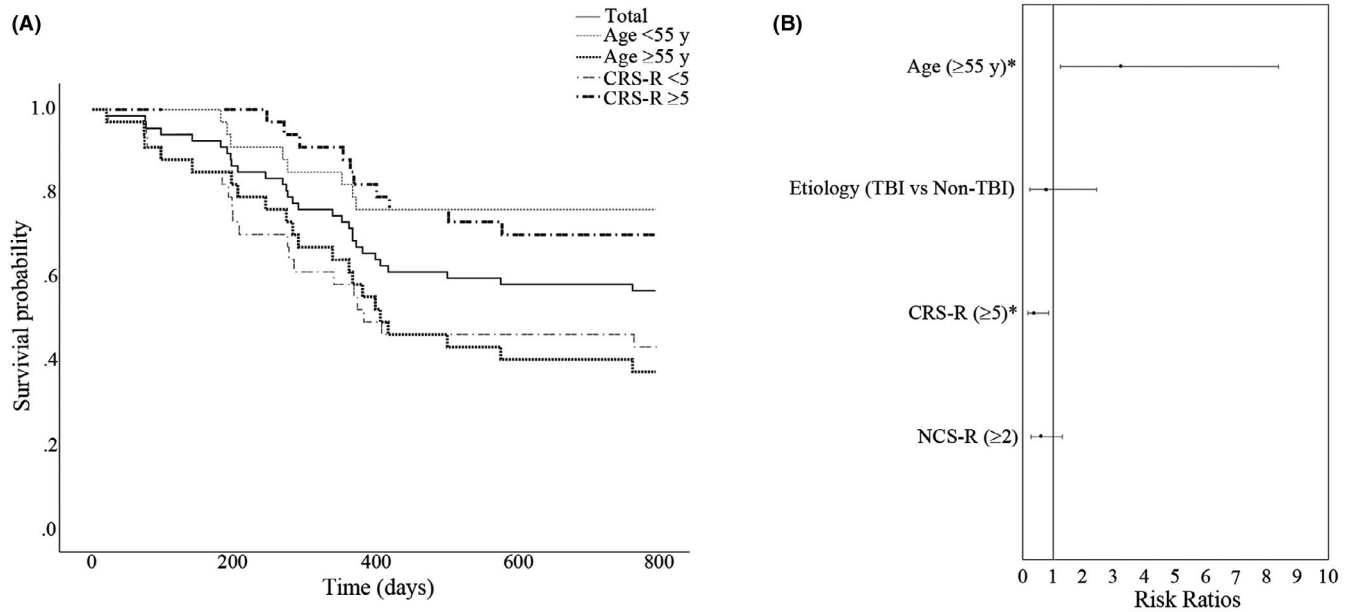

FIGURE 2 Survival curves as a function of the significant predictors in the Cox regression analysis (a) and forest plot of significant predictors of mortality up to 24 months postinjury (b) in the vegetative state/unresponsive wakefulness syndrome group. *Significant predictors. CRS-R, Coma Recovery Scale–Revised; NCS-R, Nociception Coma Scale–Revised; TBI, traumatic brain injury

(χ^2 = 6.5; p = 0.01), and absence of alpha rhythm on EEG (χ^2 = 5.0; p = 0.02) were significant mortality risk factors (Table 2). VIF among these predictors ranged from 1.02 to 1.55; tolerance ranged from 0.64 to 0.98. Cox regression analysis on the MCS subgroup was performed on 69 patients (11 deceased and six with incomplete data). The analysis provided a significant final model (χ^2 = 2739, df = 5; p < 0.001), in which female sex (RR = 7.5, 95% CI = 1.5–36.5; p = 0.013) and absence of alpha rhythm on EEG (RR = 3.7, 95% CI = 1.1–12.8; p = 0.040) were significantly associated with a higher risk of mortality (Figure 3).

DISCUSSION

In this multicentre, large-cohort, longitudinal study on patients in pDoC, we examined the mortality rate and the predictors of

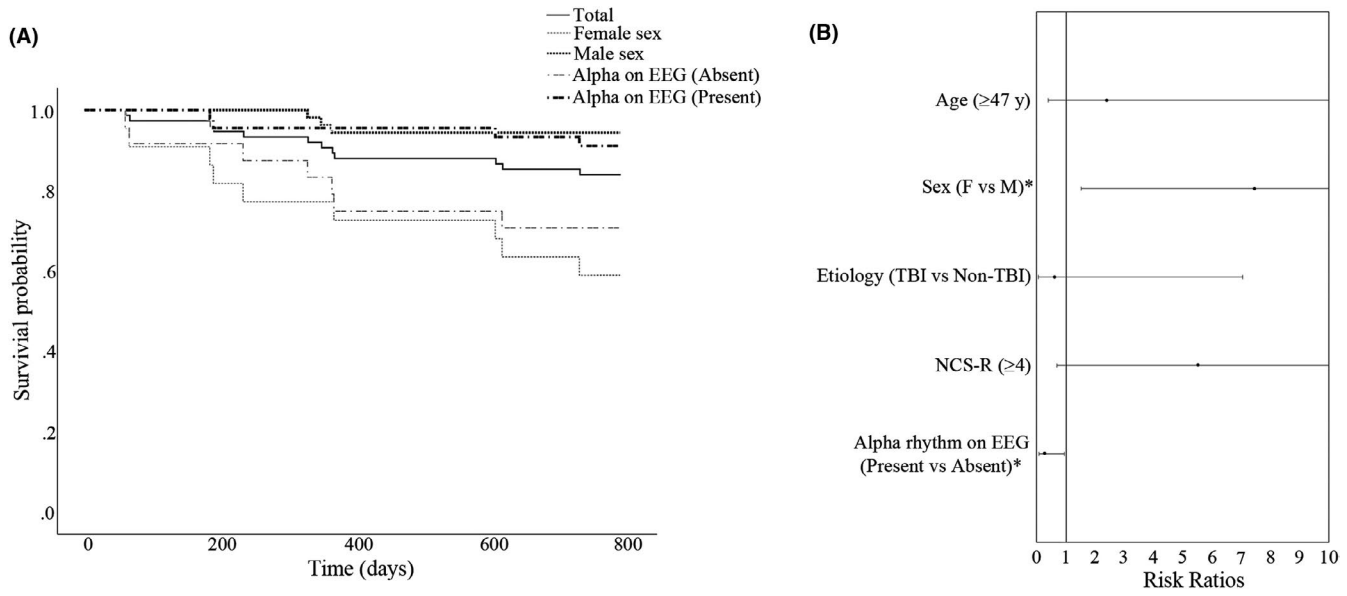

FIGURE 3 Survival curves as a function of the significant predictors in the Cox regression analysis (a) and forest plot of significant predictors of mortality up to 24 months postinjury (b) in the minimally conscious state group. *Significant predictors. EEG, electroencephalogram; F, female; M, male; NCS-R, Nociception Coma Scale–Revised; TBI, traumatic brain injury

mortality within 24 months after severe acquired brain injury. The mortality rate was higher in the VS/UWS group than in the MCS group, consistent with prior studies indicating that clinical outcome is worse in patients with a lower level of consciousness [4,7,12,24]. In both diagnostic groups, the mortality rate was twice as high in the first year compared to the second year after the brain injury. This finding could be ascribed to the higher medical instability during the first year postinjury [25,26].

Although the likelihood of survival was significantly higher for MCS patients compared to VS/UWS patients in the univariate analysis, in the Cox regression analysis on the overall sample, the predictive role of diagnosis at study entry for MCS was not significant and only older age and female sex were significant predictors of mortality. This finding is in contrast with previous studies reporting an association of diagnosis at study entry with mortality [7,24] or with clinical outcome [12]. However, the relationship between clinical diagnosis and mortality (and clinical outcome) in such studies was significant on univariate analyses. Only one study [4] performed a multivariate analysis supporting the association of diagnosis with mortality risk, and it was based on data from patients in intensive care units with a shorter time postinjury who cannot be compared to those included in the present sample of patients in pDoC. Our study recruited most patients (almost 80%) in a postacute rehabilitation setting, at 1–3 months after onset. Our findings suggested that the predictive value of age and sex could reduce the weight of the clinical diagnosis in predicting long-term mortality, but these issues should be addressed by further longitudinal studies. It is worth noting that in our study the mortality rate did not differ as a function of enrolment setting (intensive care vs. postacute rehabilitation or neurology units). Although this finding should be treated with caution because of the large disproportion of enrolments in different settings, it seems to be consistent with previous investigations in pDoC suggesting that the type of care received after discharge in long-term care facilities or at home could affect long-term mortality more than the enrolment setting [24].

The prognostic value of older age and female sex did not apply to the same extent in the two diagnostic groups. The analysis on patients in VS/UWS revealed that older age together with lower CRS-R total score at study entry significantly predicted higher mortality rates.

The impact of age on mortality rates is likely due to frailty and higher occurrence of coexisting or premorbid medical illnesses in the elderly [27], and is consistent with several previous investigations [4,9,12,24]. The significant predictive value of the lower CRS-R total score on mortality at 24 months is a relatively novel finding, as previous studies investigated the predictive role of the CRS-R total score for general clinical improvement but not specifically for survival [7,11,17,28]. The CRS-R total score reflects the sum of the scores of six subscales, in which items are organized hierarchically so that higher scores correspond to higher-level neurologic functioning [29]. As a consequence, the CRS-R total score, which has no diagnostic value, might be considered an indirect index of severity of brain injury [10,29].

In contrast, in the sample of patients in MCS, female sex and absence of alpha rhythm on EEG background activity were significant predictors of mortality. The association of female sex with higher risk of mortality was not observed in previous investigations. Previous prognostic studies in DoC found no differences in mortality rates between sexes [24] or reported a higher risk of mortality for males [6]. Similarly, conflicting data have been reported on patients with moderate and severe traumatic brain injury, with some studies observing a higher mortality risk for men

[30] and others reporting the opposite result [31]. Sex-related disparities in outcomes could be attributable to differences in care pathways [32] or in the level of familial/social caregiving [33] between the two sexes, with family support and care being more feasible for male than for female patients with severe acquired brain injury [34,35]. Further investigations on potential sex-related factors (e.g., influence of sex hormones, differences in haemostasis and inflammatory response, interaction between pharmacological treatment and endocrine or metabolic differences [31]) are needed to clarify the potential role of sex differences in mortality in patients with DoC.

The prognostic value of the EEG dominant background activity for clinical outcomes has been demonstrated in several studies on DoC [13–15,36,37]. However, the association between abnormal EEG background activity and mortality in pDoC, and in patients in MCS specifically, is a relatively novel finding. Previous investigations suggested that slow-wave EEG activity is associated with severe encephalopathy and/or structural lesions [38], and with higher risk of mortality in acute coma [39], but this issue has not been comprehensively addressed in patients with pDoC [38]. Conversely, the presence of residual alpha rhythm could be considered to be an electrophysiological sign of at least relatively preserved thalamocortical connectivity, a system related to cognitive processing [40] and consciousness [41]. Our results suggested that the absence of alpha rhythm on posterior regions with preserved anterior–posterior gradient could have a predictive value for mortality in MCS too, in which reorganization of EEG background activity tends to occur, differently from VS/UWS [21,42]. However, further studies are warranted for confirming and clarifying this finding. Moreover, the analysis conducted on patients in MCS should be interpreted cautiously, because of the low number of deceased patients in this diagnostic group (15.9%). Future studies should enrol a larger MCS sample to confirm these results and to perform subgroup analyses for patients in MCS as a function of complexity of their clinical behaviour (i.e., in MCS+ and MCS− separately [43]).

Of note, here we did not find a significant value of EEG reactivity in predicting long-term mortality. Previous investigations [14,15,17,44] found that presence of EEG reactivity to different stimulation could predict the transition from VS/UWS to MCS and recovery of consciousness. Other studies showed that lack of EEG reactivity in comatose patients was associated with mortality up to 1 year following discharge from the intensive care unit [45]. To our knowledge, no previous studies assessed the predictive value of EEG reactivity for long-term mortality in patients with pDoC. Our findings would suggest that when clinical conditions are stabilized in pDoC, EEG reactivity represents a predictor of clinical improvement, but additional variables could be more strongly related to mortality than EEG reactivity (e.g., older age, presence of comorbidities and complications), and even than SEPs and ERPs, which have been shown to predict recovery of consciousness [11,46].

It is also possible that the lack of predictive value of EEG reactivity in some cases might depend on the particular stimulus used for eliciting reactivity. Here, we administered a standardized noxious stimulus used in the clinical evaluation of nociceptive responsiveness by means of CRS-R and NCS-R, but previous investigations suggested that other noxious stimuli could evoke different EEG and behavioural responses in comatose [47] and in pDoC [48] patients. The comparison of the effect of different stimulation methods on EEG reactivity has to be addressed by specifically designed studies.

The present study has several limitations. First, the relatively low number of deceased patients in the present sample probably accounted for the wide CIs for RRs of the significant predictors, age and sex, in the VS/UWS and in MCS groups, respectively. Wide CIs indicate that further information is needed, but we would emphasize that in the present study sample, no patients died because of withdrawal of life-sustaining therapy; thus, our data outlined the natural clinical history of pDoC patients. Second, neurophysiological findings (i.e., SEPs and ERPs) were not available for all enrolled patients due to logistical constraints or to patients' movement artefacts that hampered analysis. Only a few studies on DoC have collected multimodal clinical and neurophysiological findings in a multicentre longitudinal design [17]. Third, as this study was based on clinical diagnosis and did not have a complete neuroimaging workup, we could not search for signs of covert cognition [49] and analyse mortality in patients showing such signs. Fourth, the multicentre design of the present study made it possible to reduce the sampling biases and idiosyncrasies of single-centre studies, but we could not analyse our data stratified for country, as samples were too small to be representative. Lastly, we could not investigate the impact of therapeutic interventions and of clinical complications that could influence survival of such complex patients [6,25].

Notwithstanding these limitations, this study has provided evidence that demographic (i.e., age and sex), clinical (i.e., CRS-R total score), and neurophysiological (i.e., EEG background activity) factors, which are feasible to collect at most centres in the postacute phase in a standardized manner, have a predictive value for long-term mortality in patients in pDoC. These multimodal clinical and neurophysiological findings can help clinicians to identify patients with pDoC at higher risk of mortality and can guide clinical decision-making and management, providing patients' families with evidence-based prognostic information.

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CONFLICT OF INTEREST

All authors declare no conflict of interest regarding the content of this article.

AUTHOR CONTRIBUTIONS

Anna Estraneo: Conceptualization (lead), data curation (lead), methodology (lead), project administration (lead), resources (equal), supervision (equal), writing–original draft (equal). **Alfonso Magliacano:** Data curation (equal), formal analysis (equal), methodology (supporting), validation (equal), visualization (equal), writing–original draft (lead). **Salvatore Fiorenza:** Data curation (equal), investigation (equal), methodology (equal). **Rita Formisano:** Investigation (equal), resources (equal), writing–review & editing (equal). **Antonello Grippo:** Investigation (equal), resources (equal), writing–review & editing (equal). **Efthymios Angelakis:** Investigation (equal), resources (equal), writing–review & editing (equal). **Helena Cassol:** Investigation (equal), resources (equal), writing–review & editing (equal). **Aurore Thibaut:** Investigation (equal), resources (equal), writing–review & editing (equal). **Olivia Gosseries:** Investigation (equal), resources (equal), writing–review & editing (equal). **Gianfranco Lamberti:** Investigation (equal), resources (equal), writing–review & editing (equal). **Enrique Noé:** Investigation (equal), resources (equal), writing–review & editing (equal). **Sergio Bagnato:** Investigation (equal), resources (equal), writing–review & editing (equal). **Brian L. Edlow:** Investigation (equal), resources (equal), writing–review & editing (equal). **Camille Chatelle:** Investigation (equal), resources (equal), writing–review & editing (equal). **Nicolas Lejeune:** Investigation (equal), resources (equal), writing–review & editing (equal). **Vigneswaran Veeramuthu:** Investigation (equal), resources (equal), writing–review & editing (equal). **Michelangelo Bartolo:** Investigation (equal), resources (equal), writing–review & editing (equal). **Donatella Mattia:** Investigation (equal), resources (equal), writing–review & editing (equal). **Jlenia Toppi:** Investigation (equal), resources (equal), writing–review & editing (equal). **Nathan Zasler:** Investigation (equal), resources (equal), writing–review & editing (equal). **Caroline Schnakers:** Investigation (equal), resources (equal), writing–review & editing (equal). **Luigi Trojano:** Formal analysis (equal), methodology (equal), supervision (supporting), writing–original draft (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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