Multicentre registry of brain-injured patients with disorder of consciousness: rationale and preliminary data

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Summary

Diagnostic accuracy and reliable estimation of clinical evolution are challenging issues in the management of patients with disorders of consciousness (DoC). Longitudinal systematic investigations conducted in large cohorts of patients with DoC could make it possible to identify reliable diagnostic and prognostic markers. On the basis of this consideration, we devised a multicentre prospective registry for patients with DoC admitted to ten intensive rehabilitation units. The registry collects homogeneous and detailed data on patients' demographic and clinical features, neurophysiological and neuroimaging findings, and medical and surgical complications. Here we present the rationale and the design of the registry and the preliminary results obtained in 53 patients with DoC (vegetative state or minimally conscious state) enrolled during the first seven months of the study. Data at 6-month post-injury follow-up were available for 46 of them.
This registry could be an important tool for collecting high-quality data through the application of rigorous methods, and it could be used in the routine management of patients with DoC admitted to rehabilitation settings.

KEY WORDS: disorders of consciousness, minimally conscious state, neurorehabilitation, outcome, registry, vegetative state.

Introduction

Severely brain-injured patients in clinical conditions of prolonged vegetative state (VS, Multi-Society Task Force on PVS, 1994) or prolonged minimally conscious state (MCS, Giacino et al., 2002; Estraneo et al., 2015) pose challenging diagnostic and prognostic issues. The differential diagnosis between unconscious patients (i.e. patients in VS) and patients with minimal but reproducible clinical signs of consciousness (i.e. patients in MCS) can be difficult, since recognition of non-reflexive

(i.e. conscious) behavioural responses to multisensory stimulation can be limited by co-existing comorbidities (e.g. seizures; Pascarella et al., 2016), neurological deficits (e.g. auditory deficits) or arousal fluctuations. Repeated and accurate behavioural examinations performed using standardised clinical scales, such as the Coma Recovery Scale-Revised (CRS-R, Giacino et al., 2004), complemented by neurophysiological and neuroimaging examinations, can minimise diagnostic error (Schnakers et al., 2009; Trojano et al., 2013; Estraneo et al., 2016).

In addition, VS and MCS, which both come under the umbrella term disorders of consciousness (DoC, Bernat, 2006), can last for an indefinite time and even for an entire lifetime (Estraneo et al., 2014; Estraneo and Trojano, 2017). Moreover, patients with DoC can develop many severe clinical complications, capable of influencing mortality rates and cognitive and functional outcomes (Ganesh et al., 2013; Pistoia et al., 2015; Pascarella et al., 2016), and requiring appropriate expertise for their optimal management (De Tanti et al., 2015).

As a consequence, long-term management of these patients has a growing impact on a number of levels: clinical, economic and ethical (Whyte and Nakase-Richardson, 2013; Moretta et al., 2014, 2017; Sattin et al., 2017). In this context, correct diagnosis, reliable estimations about clinical evolution, and identification of valid prognostic markers are all crucial to allow clinicians and patients' families to take appropriate decisions concerning treatment and care (Fins, 2016; Estraneo and Trojano, 2017).

From this perspective, systematic longitudinal investigation of large cohorts of patients with prolonged DoC could make it possible: i) to identify clinical features and neurophysiological and neuroimaging findings with high diagnostic relevance useful for discriminating between VS and MCS, and possibly for subcategorising patients within the two principal diagnostic groups; ii) to identify clinical, neuroimaging and neurophysiological markers with prognostic value; and iii) to identify factors (e.g., clinical complications, effects of pharmacological therapy) that could influence patients' clinical evolution, independently of predictive markers.

For these purposes, we devised a multicentre prospective registry devoted to prolonged DoC (VS and MCS) patients admitted to ten intensive rehabilitation units for severely brain-injured patients. This registry has been developed to gather homogeneous patient data systematically. Here we present the rationale and the design of the registry and the preliminary results seven months after the start of the study.

Materials and methods

Design and study population

Ten intensive rehabilitation units with expertise in the diagnosis and care of adults with severe brain injuries together formed a network for the purpose of building a registry for patients with prolonged DoC. Each of the participating units is located at a Maugeri Clinical Scientific Institute (ICS), and accordingly the network was called the Maugeri DOC-Network. The study was coordinated by the Maugeri ICS research laboratory for DoC in Telese Terme (BN, Italy) and conducted in three distinct phases. In the first phase, after several meetings, a team of physicians, psychologists and speech therapists from all the participating units identified the clinical and instrumental variables to be collected for the purpose of the registry. Then, a home-built web-based electronic database for data recording was created. In the second phase, 2-5 health professionals from each participating centre received training, from the coordinating centre's team, in administration and scoring of the clinical scales selected for the registry project, in acquiring and analysing standard neurophysiological examinations, and in entering findings in the database. The third phase, that of patient enrolment and data entry, formally began on October 31st, 2016. Patients entered in the registry will be followed up at 6, 9, 12, 18, 24, 30 and 36 months post-injury.

The inclusion criteria for patient enrolment were: adult age (≥18 years); diagnosis of DoC (VS or MCS) due to a severe traumatic or non-traumatic (e.g. anoxic, vascular, encephalitic) brain injury; and a post-injury interval of between 2 weeks and 6 months. Clinical diagnosis was based on standardised clinical criteria for VS, MCS and emergence from MCS (Multi-Society Task Force on PVS, 1994; Giacino et al., 2002), and was confirmed using the Italian version of the CRS-R (Estraneo et al., 2015) across at least three evaluations performed within one week of patient admission. In the event of major medical complications (e.g. fever, respiratory infections), diagnostic clinical evaluation was postponed until the patient's clinical conditions had stabilised.

Seven months after starting the study, the patients' data were analysed to evaluate their uniformity and accuracy, in order to ensure data quality for the ongoing prospective study.

Registry and variables

The data gathered in the registry, called the DoC-Network Registry (DoCNR), are the following: i) demographic information; ii) information about the ICS Maugeri neurorehabilitation stay; iii) medical history: information about the acute phase and comorbidity before onset as assessed by the Cumulative Illness Rating Scale (CIRS) (Salvi et al., 2008) and expressed by a severity index (mean of scores for 14 body system items, each scored 0 to 4 depending on severity; range 0-56), and a comorbidity index (number of scores of 3 points or higher); iv) clinical assessment data; v) data from instrumental examinations: neurophysiological evaluations, standard structural (brain CT/MRI) and functional (fMRI/PET) neuroimaging examinations; vi) laboratory blood test results; vii) details of medical complications grouped into 10 categories (see Appendix 1, supplemental material); viii) details of surgical interventions; ix) details of pharmacological therapy. A detailed list of the variables collected at different time points is given in Table I.

Outcome measures

The main outcome measures were level of responsiveness/consciousness as assessed by CRS-R total score, behavioural responses to nociceptive stimuli as assessed by the Nociception Coma Scale (NCS) (Schnakers et al.,

Table I - Variables and timing of data collection in the registry worksheets.

Worksheets	Variables (measure)	Timing of data collection
Demographic information and ID-Centre	Name, surname, date of birth, sex, address	At study entry (first admission)
Neurorehabilitation stay	Admission and discharge date, setting from which the patient was received (e.g. ICU, rehabilitation unit, chronic care facility), discharge modality (e.g. to a chronic care facility, home), any transfers back to acute care wards indicating number of times and reason (e.g. medical, surgical or neurosurgical complications)	On admission/ discharge
Medical history	Comorbidity before brain injury (CIRS comorbidity and severity index)	At study entry (first admission)
	Acute phase information: brain injury (aetiology and date), cause of brain anoxia (i.e. primary respiratory failure or primary cardiac arrest), resuscitation setting (i.e. in or out of hospital), GCS, neuroimaging, surgical interventions, clinical complications, pharmacological therapy, length of ICU stay	
Clinical assessment	General clinical evaluation: BMI, neurological examination, physical examination (i.e. assessment of respiratory, feeding and urinary function, pressure sores)	On admission; 3, 6, 9, 12, 18, 24, 30 and 36 months post-onset
Clinical assessment	Level of consciousness (CRS-R*)	At study entry; 3, 6, 9, 12, 18, 24, 30 and 36 months post-onset
	Level of responsiveness to nociceptive stimuli (NCS)	
	Clinical functioning (LCF)	
	Functional disability status (GOSE*)	
	Level of disability (DRS, FIM)	
	Clinical complexity (ERBI^)	
Neurophysiological evaluations	EEG, upper limb SEP, ERP, BAEP, VEP, MNCV, SNCV	On admission; 3, 6, 9, 12, 18, 24, 30 and 36 months post-onset
Neuroimaging examinations	Cranial CT, structural and functional brain MRI/PET	On admission and at any changes in neurological evaluations
Laboratory blood tests	Blood count, glucose, creatinine, BUN, AST/ALT, sodium, potassium, calcium, ALP, albumin, total protein, thyroid function	On admission; 3, 6, 9, 12, 18, 24, 30 and 36 months post-onset
Medical complications	Clinical complications classified by registration form°	On admission; 3, 6, 9, 12, 18, 24, 30 and 36 months post-onset
Surgical problems	Surgical interventions (type and date)	On admission; 3, 6, 9, 12, 18, 24, 30 and 36 months post-onset
Pharmacological therapy	AED, DOPA and dopaminergic drugs, amantadine, botulinum toxin, baclofen, analgesic drugs, antidepressant drugs	On admission; 3, 6, 9, 12, 18, 24, 30 and 36 months post-onset

Abbreviations and legend: CIRS= Cumulative Illness Rating Scale; BMI=body mass index; GCS= Glasgow Coma Scale at ICU admission; ICU=intensive care unit; CRS-R= Coma Recovery Scale-Revised; NCS=Nociception Coma Scale; DRS=Disability Rating Scale; GOSE=Glasgow Outcome Scale-Extended, FIM=Functional Independence Measure, LCF=Level of Cognitive Functioning; ERBI=Early Rehabilitation Barthel Index; EEG=electroencephalographic examination; SEP=somatosensory evoked potentials; ERP=event-related potentials; BAEP=brainstem auditory evoked potentials; VEP=visual evoked potentials; MNCV=motor nerve conduction velocity; SNCV=sensory nerve conduction velocity; BUN=blood urea nitrogen; AST=aspartate aminotransferase; ALT=alanine aminotransferase; ALP=alkaline phosphatase; AED=anti-epileptic drugs. *at follow-up periods, level of consciousness and patient status were assessed by direct clinical observation or by structured phone interview based on CRS-R and GOSE items. ^The ERBI contains highly relevant items such as mechanical ventilation, tracheostomy, and dysphagia. °see Appendix. Medical complications, surgical interventions and pharmacological therapy referred to months between two consecutive time points.

2010), level of cognitive performance as classified by the Level of Cognitive Functioning (LCF) score (Hagen et al., 1979), functional disability status as classified by the Glasgow Outcome Scale-Extended (GOS-E) score (Wilson et al., 1997), level of functional disability as assessed by the Disability Rating Scale (DRS) score (Rappaport et al., 1982) and Functional Independence Measure (FIM) total score (Keith et al., 1987), and clinical complexity as classified by Early Rehabilitation Barthel Index (ERBI) total score (Schonle, 1995). The best CRS-R total score obtained one week before study entry and at the follow-up end points was reported in the registry (see Appendix 2, supplemental material).

Neurophysiological data acquisition and analysis

Standard EEG

Standard EEG was recorded by 11 electrodes placed on the scalp according to the international 10-20 system (O1, O2, Pz, C3, C4, Cz, T3, T4, Fz, Fp1 and Fp2). An at-least 35-minute recording was acquired according to the standard procedure of eyes-closed recording during waking rest with filter settings 1-70 Hz, and notch filter on. Eye closure for the analysis of predominant activity was obtained by means of forced eye closing: cotton wool pads secured by paper patches in patient awake condition (spontaneous eye opening). The EEG was recorded at the patients' bed in the morning after customary nursing procedures. In order to analyse EEG reactivity, five kinds of stimuli were randomly administered during EEG recording: i) eye opening and (forced) eye closing; ii) tactile stimuli; iii) noxious stimulation; iv) acoustic stimulation; v) intermittent photic stimulation.
EEG activity and reactivity were classified into five categories of severity in accordance with recently proposed criteria for patients with DoC (Estraneo et al., 2016).
The presence and frequency of interictal sporadic or periodic epileptiform abnormalities were also reported, according to a standardised classification (Hirsch, 2011; Pascarella et al., 2016).

Somatosensory evoked potentials

Somatosensory evoked potentials (SEP) after bilateral median nerve stimulation were recorded with standard 4-channel procedures (Erb's point, CV7 spinous process, C3' and C4') and classified as "present" when the N20 cortical response was recorded on at least one side, or "absent", in the presence of a cervical potential (Estraneo et al., 2013).

Event-related potentials

Event-related potentials (ERP) were obtained by means of a simple "oddball" paradigm using auditory stimulation, and they were classified as "present" when the P300 cortical response was recorded on at least one side, or "absent", in the presence of the N100 component (Duncan et al., 2009).

Definition of outcome

At 6 months post-injury we considered, as the primary clinical outcome, improvement in clinical diagnosis with respect to study entry, according to standardised clinical criteria for VS, MCS and emergence from MCS, confirmed by CRS-R. Patients who showed a substantial change in their clinical diagnosis (i.e. VS patients who progressed to MCS or regained full consciousness and MCS patients who recovered full consciousness) were classified as "recovered" (good outcome), while those whose clinical diagnosis did not substantially change or worsened and patients who died were classified as "unrecovered" (poor outcome).

Data management

All participating health professionals from each rehabilitation unit entered patient data into a home-built web-based electronic data processing system that ensured confidentiality.
The system was developed using AngularJs, a JavaScript-based open source front-end web application framework that allows interactions between client and server. Each participating professional received a personal username (i.e. unique identification code) and password allowing him/her to exclusively access the data of patients hospitalised in his/her own rehabilitation unit. Only the coordinating centre could access the whole data set. These features ensured reduction of opportunities for unauthorised or unintentional modification or misuse of information. In addition, the electronic data processing system, composed of nine worksheets for entry of patient data, was provided with a data quality control system. This system automatically checked the following items: required fields, specific formats and calculated fields. When possible, it also provided multiple choice fields in order to help users and organise the data in a structured way. Free text was allowed only when the information was too complex to be summarised in a structured way (e.g. neuroimaging findings, data on neurosurgical interventions), thus allowing professionals to enter detailed descriptions of them.
The system made demographic data, medical history, clinical assessment, possible clinical and surgical complications, laboratory blood tests, pharmacological therapy and EEG findings mandatory fields, so as to obtain specific diagnostic and potential prognostic information. The remaining neurophysiological (i.e. SEP, ERG) and neuroimaging (i.e. CT, MRI or functional MRI) data were considered optional, since few participating centres were able to record them.

Statistical analysis

We calculated means for continuous variables and percentages for categorical variables.
We compared all collected variables as a function of clinical diagnosis and aetiology at study entry and improvement in clinical diagnosis ("recovered" *vs* "unrecovered") at 6-month follow-up. We used Fisher's Exact Test and Pearson's Chi squared test as appropriate. As regards continuous variables, we first verified, using the Shapiro-Wilk Normality Test, whether the data had a normal or non-normal distribution. In the event of non-normal distributions, we used the non-parametric Wilcoxon-Mann-Whitney test, in the presence of two comparison groups, and the Kruskal-Wallis rank sum test in the presence of more than two comparison groups. All the analyses were performed using the R software and all p-value thresholds were set at 0.05.

Table II - Means (and SD) or distribution of demographic, anamnestic and clinical findings in the two diagnostic groups at study entry

	Available data	Total sample	VS	MCS
N.	53	53	37	16
Mean (SD) age (years)	53	59.2 (19.2)	55.7 (18.9)	67.1 (18.0)*
Sex F/M (n)	53	25/28	15/22	10/6
Aetiology	53			
TBI (n)		12	8	4
Vascular (n)		30	20	10
Anoxic (n)		11	9	2
Time between brain injury and admission to rehabilitation unit, mean and (SD) in days	53	55.5 (35.7)	58.8 (37.9)	47.9 (30.0)
Time between brain injury and study entry, mean and (SD) in days	53	58.2 (35.7)	61.7 (37.8)	50.2 (30.0)
GCS score	27	5.9 (1.9)	5.6 (1.9)	6.7 (1.7)
CRS-R total score	53	6.1 (3.7)	4.3 (2.2)	10.2 (3.3)*
NCS total score	53	3.8 (2.4)	2.9 (2.0)	5.7 (2.4)*
CIRS severity index	53	0.1 (0.3)	0.1 (0.2)	0.3 (0.4)
CIRS comorbidity index	53	2.2 (2.1)	2.2 (2.3)	2.2 (1.6)
ERBI total score	53	-210.8 (38.2)	-211.5 (38.5)	-209.3 (38.5)
DRS total score	53	24.9 (2.2)	25.7 (1.7)	22.9 (1.9)*
Tracheostomy (P/A)	53	47/6	35/2	12/4
Urinary catheter (P/A)	53	53/0	37/0	16/0
Pressure sore(s) (P/A)	53	27/26	19/18	8/8
Respiratory function (Au/nAu)	53	46/7	32/5	14/2
Feeding (PEG/NGT/iv/os)	53	30/23/0/0	22/15/0/0	8/8/0/0
Pupillary reflex (P/A)	49	42/7	27/6	15/1
Corneal reflex (P/A)	34	32/2	22/1	10/1

Abbreviations and legend: VS= Vegetative state; MCS= Minimally conscious state; TBI= traumatic brain injury; GCS= Glasgow Coma Scale; CRS-R= Coma Recovery Scale-Revised; NCS=Nociception Coma Scale; CIRS= Cumulative Illness Rating Scale; ERBI=Early Rehabilitation Barthel Index; DRS=Disability Rating Scale; P=present; A= absent; Au= autonomous; nAu=not autonomous; PEG= percutaneous endoscopic gastrostomy; NGT= nasogastric tube.
Pupillary light reflex is coded as present, if there is an at least unilateral response, or as absent. *Mean significantly differed between MCS and VS.

Standard protocol approvals and patient consent

The present study was conducted after obtaining the approval of the institutional ethics committee. Written informed consent was obtained from the legal guardians of all the patients.

Results

Subjects at study entry

In the first 7 months after starting the study, 53 DoC patients (age range: 18-89 years; post-injury interval range: 14-154 days; CRS-R total score range: 1-17) were enrolled in 9/10 participating centres. All enrolled patients had been transferred from acute units (i.e. intensive care units or intensive neurosurgical units). Thirty-seven subjects were in VS (age range: 18-81 years; CRS-R total score range: 1-8) and 16 in MCS (age range: 21-89 years; CRS-R total score range: 6-17) (Table II). The two diagnostic groups significantly differed in age (W=413; p=.024), CRS-R total score (W=558; p<.001), NCS total score (W=480 p<.001) and DRS total score (W=71.5; p<.001), whereas ERBI score did not differ significantly between them (Table II).
None of the variables except one (gender) differed significantly as a function of the three aetiologies; anoxic and traumatic aetiologies were more frequent in males (p =.004) (See supplemental Table I).

Neurophysiological findings

EEG was recorded in all the patients, but could not be evaluated in 15.1% of them due to the presence of artefacts (e.g. dystonic head movements, bruxism) in more than 50% of the EEG recording time in two consecutive acquisitions. In the remaining 45 patients, “diffuse slowing” (DS) (i.e. predominant diffuse theta or theta/delta rhythms at amplitude ≥20 μV, without an anterior-posterior gradient) was the most frequent predominant EEG activity (43.4% of patients), whereas no patients showed normal background activity (Table III). Moreover, due to the low number of some EEG patterns, in all the following analyses, we combined the “normal” with the “mildly abnormal” (MiA) category, and the “moderately abnormal” (MoA) with the “DS” category. The frequency of normal/MiA, MoA/DS and “low voltage” patterns of background EEG activity did not significantly differ between VS and MCS patients (all p>.05). We found sporadic epileptiform activity in 13/45 patients (28.9%), regardless of diagnostic category (p=.721). In all the patients but one, the epileptiform abnormalities recorded were not generalised; the exception was an anoxic VS patient who showed frequent generalised epileptiform activity.
Among periodic epileptiform patterns, lateralised periodic discharges (LPD) were the only type recorded, whereas generalised periodic discharges (GPD) and bilateral independent periodic discharges (BIPD) were not observed. LPD were observed only in DoC patients with vas-

Table III - Neurophysiological findings: distribution of the two diagnostic groups at study entry.

Available data	VS	MCS	
EEG	53	37	16
Background activity			
Normal		0	0 0
Mildly abnormal	4	1	3
Moderately abnormal	12	7	5
Diffuse slowing	23	19	4
Low voltage	6	6	0
n.e.	8	4	4
Reactivity			
Eye opening and closing (P/A/n.e.)	13/13/27	9/12/20	4/1/15
Tactile (P/A/n.e.)	9/15/29	6/14/17	3/1/12
Acoustic (P/A/n.e.)	9/15/29	6/14/17	3/1/12
Nociceptive (P/A/n.e.)	13/13/27	9/12/16	4/1/11
IPS (P/A/n.e.)	12/15/26	7/14/16	5/1/10
At least one reactivity (P/A/n.e.)	21/24/8	16/21	5/7/4
Epileptiform abnormalities			
Sporadic abnormalities (P/A/n.e.)	13/32/8	9/24/4	4/8/4
Type: Generalized	1	1	0
Not generalized	12	8	4
Frequency: Abundant	1	1	0
Frequent	10	7	3
Occasional	2	1	1
Rare	0	0	0
Periodic patterns (P/A/n.e.)	3/42/8	1/32/4	2/10/4
Type: LPD	3	1	2
GPD	0	0	0
BIPD	0	0	0
SEP (N20 component, P/A)	12/4	9/4	3/0
ERP (P300 component, P/A)	7/2	5/2	2/0

Abbreviations: VS= vegetative state; MCS= minimally conscious state; P=present; A=absent; n.e.=not evaluable; IPS = intermittent photic stimulation; LPD= lateralized periodic discharges; GPD= generalized periodic discharges; BIPD= bilateral independent periodic discharges; SEP= somatosensory evoked potentials; ERP= event-related potentials.

cular aetiology. The presence of the cortical component of SEP on at least one side did not significantly differ between the two diagnostic groups (100% MCS, 69.2% VS, p=0.528). Similarly, the presence of ERP did not significantly differ between two diagnostic groups (100% MCS, 71.4% VS, p=1).

Clinical evolution

Seven months after starting the study, 6-month post-injury follow-up data were available in 42/53 patients (30 in VS and 12 in MCS), since 10 patients (6 VS and 4 MCS) did not reach this time point and one VS patient dropped out of the study, after the informed consent to his participation was revoked by his legal guardian. Five of the 42 patients (11.9%) died within 6 months of injury (see supplemental Table II).

The proportion of patients showing improvements in their clinical diagnosis (i.e. "recovered" patients) was significantly higher among those with a traumatic as opposed to an anoxic or vascular aetiology (p =.028). The number of "unrecovered" patients was significantly larger among those with an anoxic aetiology *versus* a vascular or traumatic aetiology (p = .031) (Table IV). Moreover, clinical complexity, as assessed by ERBI total score, was significantly higher in the "recovered" than in the "unrecovered" patients (df= 11; t= 6.539; p=.009) (Table IV).

EEG recorded at study entry (evaluable in 37 out 42 patients, 88%; Table V) revealed moderately abnormal background activity more frequently in patients who recovered responsiveness/consciousness than in patients who did not (p= 0.0178), whereas diffuse slowing or low voltage background activity was more frequent in unrecovered than in recovered patients, albeit non-significantly (p= .177 and p=.385, respectively).

Sporadic and periodic epileptiform activity did not differ statistically between "recovered" and "unrecovered" patients; sporadic generalised epileptiform abnormalities were recorded only in one anoxic patient with a poor outcome. Periodic epileptiform patterns were not recorded in any patients showing good outcome, whereas only two patients (8.7%) in the group with poor outcome showed LPD (GPD and BIPD were not observed).

Somatosensory evoked potentials, recorded in 15/42 patients, did not significantly differ in the two outcome groups, since N20 cortical components were present in all the "recovered" patients, and in 60% of the "unrecovered" patients. Of note, none of the patients without SEP (2 anoxic VS and 2 vascular VS patients) recovered.

Event-related potentials, investigated at study entry in only 9/42 patients, were found to be present in the three who showed clinical improvement at 6 - month post-injury and in 4/ 6 patients who did not improve, but this difference was not statistically significant.

Discussion

The DoCNR is one of the largest registries designed to collect data on the long-term evolution of patients with DoC admitted to neurorehabilitation units in the post-

Table IV - Patients' demographic, anamnestic and clinical findings at study entry as a function of clinical outcome at 6 months post-onset.

	Available data	Total sample	Recovered	Unrecovered
N.	42	42	17	25
Clinical diagnosis (VS/MCS)	42	30/12	12/5	18/7
Mean (SD) age (years)	42	58.7 (19.2)	52.2 (23.1)	63.1 (14.9)
Sex F/M (n)	42	18/24	4/13	14/11
Aetiology	42			
TBI (n)		11	8	3*
Vascular (n)		21	8	13
Anoxic (n)		10	1	9*
Time between brain injury and admission to rehabilitation mean and (SD) in days		60.8 (37.7)	51.5 (39.5)	67.1 (35.9)
Time between brain injury and study entry mean and (SD) in days		62.4 (37.7)	52.3 (35.5)	69.3 (39.6)
GCS	16	5.9 (1.9)	6.0 (1.8)	5.5 (1.7)
CRS-R total score	42	3.9 (3.7)	4.7 (3.7)	5.9 (3.6)
NCS total score	42	3.8 (2.4)	2.9 (2.6)	3.3 (2.2)
CIRS severity index	42	0.20 (0.30)	0.18 (0.35)	0.23 (0.28)
CIRS comorbidity index	42	2.33 (2.15)	2.52 (2.76)	2.20 (1.66)
ERBI total score	42	-204.8 (36.7)	-213.2 (37.6)	-199.0 (35.7)*
DRS total score	42	24.9 (2.2)	24.6 (2.3)	25.2 (2.1)
Tracheostomy (P/A)	42	37/5	15/2	22/3
Urinary catheter (P/A)	42	42/0	17/0	25/0
Pressure sore (P/A)	42	21/21	6/11	15/10
Respiratory function (Au/nAu)	42	37/5	14/3	23/2
Feeding (PEG/NGT/iv/os)	42	25/17/0/0	9/8/0/0	16/9/0/0
Pupillary reflex (P/A)	39	32/7	12/3	20/4
Corneal reflex (P/A)	27	25/2	14/0	11/2

Abbreviations and legend: VS= vegetative state; MCS= minimally conscious state; TBI= traumatic brain injury; GCS= Glasgow Coma Scale; CRS-R= Coma Recovery Scale-Revised; NCS= Nociception Coma Scale; CIRS= Cumulative Illness Rating Scale; ERBI=Early Rehabilitation Barthel Index; DRS=Disability Rating Scale; P=present; A= absent; Au= autonomous; nAu= not autonomous; PEG= percutaneous endoscopic gastrostomy; NGT= nasogastric tube. Pupillary light reflex is coded as present, in case of at least unilateral response, or absent. *Mean significantly differed between the two groups.

acute phase. The registry has been created in such a way as to minimise missing patient data. Some fields related to diagnostic information (e.g. clinical assessment at study entry, standard EEG, Estraneo et al., 2016; Schnakers and Majerus, 2017) or prognostic information (e.g. demographic and anamnestic data, clinical assessment, Estraneo et al., 2013; Estraneo and Trojano, 2017) are mandatory. Instead, fields related to data not routinely collected in the rehabilitation unit setting (Estraneo et al., 2013) are not mandatory notwithstanding their possible diagnostic (e.g. ERP, Hauger et al., 2017) or prognostic value (SEP, Estraneo et al., 2013). Indeed, there is currently a lack of national/international guidelines/recommendations about diagnostic and prognostic procedures for DoC patients (Formisano et al., 2017), and in a scenario frequently characterised by a dearth of equipment and human resources (Sattin et al., 2017), some potentially useful neurophysiological or neuroimaging examinations are not routinely carried out in rehabilitation units. Against this background, to ensure a homogeneous dataset, we conducted specific training courses on clinical and neurophysiological assessment (e.g. clinical scales and their administration, EEG protocol and classification) and on data entry procedures.

Our preliminary findings provide specific information on a cohort of consecutive severely brain-injured patients with DoC, admitted to nine intensive rehabilitation units located in different (n=5) Italian regions over a period of seven months. The cohort included a higher number of VS than MCS patients and a high proportion of patients with vascular aetiology compared to anoxic and traumatic aetiology. These findings are not consistent with those reported in a recent German multicentre rehabilitation registry (Grill et al., 2013), in which there was a higher number of patients with anoxic than with vascular or traumatic aetiology, and the patients were characterised by a shorter time since injury (i.e. mean 28 days). These discrepancies could likely be related to differences in the criteria for enrolment adopted by the two studies. The German registry included severely affected DoC patients for whom discontinuation of specific medical care or life-support care had been discussed in the acute phase with family members, and whose families supported the patients' transfer to the rehabilitation setting. Instead, in the present registry, we enrolled consecutive patients with DoC transferred from acute units, independently of prognostic markers, since the Italian health system does not provide specific indications on care and medical treatment discontinuation. The relatively longer mean time post-injury (55 *vs* 28 days) could be related to differences in health systems, and also to the insufficient number of specialised structures for post-acute care for patients with DoC in Italy (Sattin et al., 2017).

At study entry, the VS and MCS patients differed in clinical scale scores, consistent with diagnostic criteria, but did not differ significantly in terms of their neurophysiological evaluation, in contrast with the findings of previous studies (Perrin et al., 2006; Estraneo et al., 2016). However, it is very likely that the low availability of rele-

Table V - Neurophysiological findings at study entry as a function of clinical outcome at 6 months post-onset.

	Available data	Recovered	Unrecovered
EEG	42	17	25
Background activity			
Normal	0	0	0
Mildly abnormal	3	1	2
Moderately abnormal	10	7	3*
Diffuse slowing	18	5	13
Low voltage	6	1	5
n.e.	5	3	2
Reactivity			
Eye opening and closing (P/A/n.e.)	13/12/19	7/4/7	4/8/12
Tactile (P/A/n.e.)	7/13/22	3/5/10	4/8/12
Acoustic (P/A/n.e.)	8/12/22	5/3/10	3/9/12
Nociceptive (P/A/n.e.)	11/11/20	6/3/9	5/8/11
IPS (P/A/n.e.)	11/13/18	6/4/8	5/9/10
At least one reactivity (P/A/n.e.)	17/20/5	8/10/3	9/13/2
Epileptiform abnormalities			
Sporadic abnormalities (P/A/n.e.)	10/27/5	2/12/3	8/15/2
Type: Generalized	1	0	1
Not generalized	9	2	7
Frequency: Abundant	1	0	1
Frequent	7	1	6
Occasional	2	1	1
Rare	0	0	0
Periodic patterns (P/A/n.e.)	2/35/5	0/14/3	2/21/2
Type: LPD	2	0	2
GPD	0	0	0
BIPD	0	0	0
SEP (N20 component P/A)	11/4	5/0	6/4
ERP (P300 component P/A)	7/2	3/0	4/2

Abbreviations: VS=vegetative state; MCS=minimally conscious state; P=present; A=absent; n.e.=not evaluable; IPS=intermittent photic stimulation; LPD=lateralized periodic discharges; GPD=generalized periodic discharges; BIPD=bilateral independent periodic discharges; SEP=somatosensory evoked potentials; ERP=event-related potentials.

vant data precluded the identification of specific neurophysiological patterns.

The second aim of the present longitudinal study was to identify possible prognostic factors. Although largely preliminary, the present data on clinical evolution at 6 months post-injury (79% of sample) appear to substantially confirm that clinical outcome is worse in anoxic than in traumatic or vascular DoC patients. This finding is consistent with data reported in previous longitudinal studies (Katz et al., 2009; Estraneo et al., 2010; Luauté et al., 2010; Bruno et al., 2012; Estraneo et al., 2013), and suggests that the severity of anoxic brain damage can hamper clinical recovery in DoC patients. About half of the MCS (41.6%) and VS (40.1%) patients recovered responsiveness/consciousness at 6-months post-injury, thus clinical outcome did not significantly differ between the two diagnostic groups. This finding seems to contrast with the results of previous studies showing a better short- (Bruno et al., 2012, Seel et al., 2013; Steppacher et al., 2014) and long-term outcome (i.e. more than 12 months post-injury) in patients in MCS (Luauté et al., 2010; Bruno et al., 2012). This discrepancy could be attributed to different case mixes (time post-injury, percentage of traumatic or non-traumatic aetiology) among studies, and also related to small sample size in the present study.

The organisation of EEG background activity was less severely impaired in patients who recovered responsiveness/consciousness than in those who did not, in agreement with previous studies (Bagnato et al., 2015). No reliable inferences were possible for SEP and ERP, which were recorded in a low percentage of patients who reached the 6-month observational period (30.2% and 17.0% respectively).

Although the present preliminary data cannot provide definitive diagnostic and prognostic information, they strongly indicate the fact-finding potential of the DoCNR. Indeed, use of this registry in a number of rehabilitation units gathered in a large network for patients with DoC could, through rigorous application of standardised clinical and instrumental tools, allow accurate collection of patient data.

The adoption of homogeneous assessment procedures will provide valuable and reliable data for investigating many clinical questions regarding the diagnosis and prognosis of these conditions, as well as the efficacy of treatment strategies on long-term clinical evolution.

Recruitment of large samples of patients in VS and in MCS across multiple rehabilitation centres located in different regional territories could allow the findings to be generalised the broader population of patients with DoC and allow the development of clinical practice recommendations for the care and management of these complex patients (Formisano et al., 2017).

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Supplemental material

Appendix 1. Checklist for categorisation of medical complications.

CATEGORY	DESCRIPTION
Endocrine-metabolic	Metabolic abnormalities (e.g. hyponatremia, anemia, hypoalbuminemia) and endocrine disorders (e.g. diabetes mellitus, thyroid gland dysfunctions)
Cardiovascular	Heart failure (e.g. acute myocardial infarction, congestive heart failure) and/or acute arrhythmia (e.g. atrial fibrillation, ventricular tachycardia), and/or arterial or venous thrombosis
Musculoskeletal-cutaneous	Hypertonia/spasticity, fractures, arthritis, pressure sores
Gastrointestinal	Bleeding, bowel obstruction, peritonitis, clostridium difficilis enteritis, diarrhoea, biliary lithiasis, hepatitis, pancreatitis
Genitourinary tract	Infections, bleeding, urinary stones, urinary obstructions, renal insufficiency
Respiratory	Pulmonary infections, tracheal stenosis or malacia, tracheo-esophageal fistula, central respiratory drive deficits
Neurological/neurosurgical	Hydrocephalus, new brain injury, ventricular-peritoneal shunt dysfunction, cranioplasty infection, meningitides
Epilepsy/myoclonus	Partial or generalised seizures, spontaneous or reflex myoclonus
Heterotopic ossification (Vandenbossche et al., 2005)	Range of motion limitation and/or joint pain and/or local inflammatory signs in joints due to radiologically evident abnormal mature lamellar bone in extra-skeletal soft tissues
Paroxysmal sympathetic hyperactivity (Baguley et al., 2014)	Paroxysmal episodes characterised by increased heart rate, respiratory rate, diaphoresis, motor hyperactivity with or without increased blood pressure and/or hyperthermia

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Appendix 2. Outcome measures

The Coma Recovery Scale Revised (CRS-R) is the most reliable tool for assessing the responsiveness of patients with DoC. It comprises six subscales that assess auditory, visual, motor, oromotor/verbal, communication and arousal functions (total score from 0 to 23). The presence of intentional (non-reflexive) responses on a single subscale (a score of 3-4 on the auditory subscale, of 2-5 on the visual subscale, of 3-5 on the motor subscale, of 3 on the oromotor/verbal subscale, or of 1 on the communication subscale) can suffice to distinguish MCS from VS patients, whereas the presence of functional communication or functional object use, as measured by the CRS-R communication and motor subscales, indicates patients who regained full consciousness (Giacino et al., 2004).

The Nociception Coma Scale (NCS) is a standardised scale used for assessing pain in uncommunicative severely brain-damaged patients with DoC by evaluating behavioural response to noxious stimulation. It is composed of four subscales (motor, verbal, visual and facial expression responses) which are each scored from 0 to 3, thereby giving a total score ranging from 0 to 12 (Schnakers et al., 2010).

The Level of Cognitive Functioning (LCF) is an instrument used to assess cognitive functioning in post-coma patients, classifying them into eight levels (ranging from no response, corresponding to a score of 1, to purposeful-appropriate responses, corresponding to a score of 8) (Hagen et al., 1979).

The Glasgow Outcome Scale-Extended (GOS-E) is an index of global functional disability outcome that rates patient status into one of eight levels (dead, vegetative state, lower severe disability, upper severe disability, lower moderate disability, upper moderate disability, lower good recovery, and upper good recovery), on the basis of a structured interview focused on social and personal functional ability (Wilson et al., 1997).

The Disability Rating Scale (DRS) discriminates between 10 categories of disability with varying levels of functional disability within each one. It consists of eight items that evaluate arousability, dependence on others, cognitive abilities for self-care activities (feeding, toileting, grooming), psychosocial adaptability and employability, and gives a total ranging from 0 (no disability) to 29 (extreme vegetative state) (Rappaport et al., 1982).

The Functional Independence Measure (FIM) is a widely accepted assessment measure of physical and cognitive disability. It consists of 18 items (grouped into two basic domains: physical, 13 motor tasks, and cognitive, 5 tasks) assessing six areas of function (i.e. self-care, sphincter control, mobility, locomotion, communication and social cognition). Each item is rated on a seven-point ordinal scale (from 1=total assistance to 7=total independence) and the instrument gives a total score ranging from 18 (complete dependence) to 126 (complete independence) (Keith et al., 1987).

The Early Rehabilitation Barthel Index (ERBI) is an extended version of the Barthel Index. It consists of two subscales, Part A and Part B.

The first contains seven items evaluating the presence of clinical conditions requiring intensive supervision (i.e. intensive care supervision, mechanical ventilation, tracheostomy, confusion, behavioral disturbances, communication disorders and dysphagia); each item receives a score of -50 if present (with exception of communication disorders, which are scored -25) or 0 when absent, with a total score ranging from -325 to 0. Part B consists of the ten items of Barthel Index (Mahoney and Barthel, 1965); each item is rated from 0 to 10, giving a total score ranging from 0 to 100.

The final total score (Part A+ Part B) of the ERBI ranges from -325 (greatest disability) to 100 (complete autonomy) (Schonle, 1995).

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Supplemental Table I - Means (and SD) or distribution of demographic, anamnestic, clinical findings of patients as a function of aetiology.

	Available data	Total sample	Traumatic	Vascular	Anoxic
N.	53	53	12	30	11
Mean (SD) age (years)	53	59.2 (19.2)	54.9 (25.5)	62.93(17.2)	53.6 (15.8)*
Sex F/M (n)	53	25/28	2/10	20/10	3/8
Clinical diagnosis VS/MCS	53	37/16	8/4	20/10	9/2
Time between brain injury and admission to rehabilitation unit, mean and (SD) in days	53	55.5 (35.7)	63.2 (42.6)	53.2(34.4)	53.5 (33.4)
Time between brain injury and study entry, mean and (SD) in days	53	58.3 (35.7)	64.1 (43.2)	57.2 (34.0)	54.9 (34.2)
GCS	27	6.2 (2.3)	6.8 (1.5)	6.6 (2.5)	4.5 (1.9)
CRS-R total score	53	6.1 (3.7)	7 (3.1)	5.9 (4.1)	5.3 (3.4)
NCS total score	53	3.8 (2.4)	4.6 (1.7)	3.6 (2.6)	3.4 (2.6)
CIRS severity index	53	0.1 (0.3)	0.4 (0.6)	0.5 (0.3)	0.4 (0.2)
CIRS comorbidity index	53	2.2 (2.1)	1.83 (3.1)	2.4 (1.7)	2.1 (1.9)
ERBI total score	53	-210.8 (38.2)	-200 (33.7)	-220 (42.2)	-197.7 (26.1)
DRS total score	53	24.9 (2.2)	24.2 (1.8)	25 (2.3)	25.1 (2.1)
Tracheostomy (P/A)	53	47/6	10/2	27/3	10/1
Urinary catheter (P/A)	53	53/0	12/0	30/0	11/0
Pressure sore(s) (P/A)	53	27/26	5/7	17/13	4/7
Respiratory function (Au/nAu)	53	46/7	7/5	8/22	5/6
Feeding (PEG/NGT/iv/os)	53	30/23/0/0	6/6/0/0	17/13/0/0	7/4/0/0
Pupillary reflex (P/A)	49	42/7	8/3	26/1	8/3*
Corneal reflex (P/A)	34	32/2	7/0	17/1	8/1

Abbreviations and legend: VS= vegetative state; MCS= minimally conscious state; GCS= Glasgow Coma Scale; CRS-R= Coma Recovery Scale-Revised; NCS=Nociception Coma Scale; CIRS= Cumulative Illness Rating Scale; ERBI=Early Rehabilitation Barthel Index; DRS=Disability Rating Scale; P=present; A=absent; Au= autonomous; nAu=not autonomous; PEG= percutaneous endoscopic gastrostomy; NGT=nasogastric tube. Pupillary light reflex is coded as present, in the case of at least unilateral response, or absent. *Mean significantly differed.

Supplemental Table II - Clinical evolution at 6-month post-injury of the two diagnostic groups as a function of etiology.

Clinical diagnosis at study entry	Clinical diagnosis at 6-month post-injury			
	Dead	VS	MCS	eMCS
VS (n= 30)	3	15	8	4
Traumatic (n= 7)	0	1	3	3
Anoxic (n= 9)	2	6	1	0
Vascular (n= 14)	1	8	4	1
MCS (n= 12)	2	0	5	5
Traumatic (n= 4)	1	0	1	2
Anoxic (n= 1)	0	0	1	0
Vascular (n= 7)	1	0	3	3
Total (n= 42)	5	15	13	9

Abbreviations: VS=vegetative state; MCS=minimally conscious state; eMCS=emergence from minimally conscious state.