Epidemiological and clinical characteristics of 492 patients in a vegetative state in 29 Italian rehabilitation units. What about outcome?

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Summary

Recent studies on recovery of consciousness of subjects in a vegetative state (VS) admitted to rehabilitation units have focused mainly on the identification of prognostic factors, whereas few studies have focused on outcome.
The aim of this study was to compare demographic and clinical data and report functional outcome of patients in a VS due to severe acquired brain injury (ABI) of different aetiologies.
The study was a retrospective multicentre cohort study and involved 492 patients in a VS due to traumatic (TBI) or non-traumatic (NTBI) severe ABI admitted to 29 Italian rehabilitation units. Demographic and clinical data recorded included age, gender, aetiology, Glasgow Coma Scale score; onset-to-admission interval; length of stay in the rehabilitation unit; the department from which they were referred; and the presence of percutaneous endoscopic gastrostomy or tracheostomy. Recovery of consciousness and disability were evaluated using a discharge Disability Rating Scale.
At discharge, 53.11% patients had emerged from VS, with TBI subjects significantly more likely to recover consciousness than NTBI ones. Subjects with NTBI had a significantly worse prognosis than those with TBI, and within the NTBI group, subjects with a cerebrovascular aetiology had a better outcome than those with an anoxic aetiology. Among the patients who emerged from VS, 71.30% of TBI and 83.06% of NTBI subjects presented extremely severe disability. Only 37.93% of subjects affected by TBI and 17.44% of those affected by NTBI who presented extremely severe disability returned home after their rehabilitation stay.
Even though almost a half of the patients emerged from VS, a large number of these subjects showed severe disability, often making it impossible for them to return home. This situation has a major impact on the healthcare system.

KEY WORDS: acquired brain injury, disorders of consciousness, outcome, rehabilitation.

Introduction

Disorders of consciousness are among the most problematic conditions in the rehabilitation of patients with acquired brain injury (ABI). The rate of recovery of consciousness in patients in a vegetative state (VS) after a severe ABI varies widely (Estraneo et al., 2013; Kang et al., 2014) and predictors of recovery of responsiveness have remained elusive (Estraneo et al., 2010; Luautè et al., 2010; Estraneo et al., 2013; Howell et al., 2013; Klein et al., 2013).
On the other hand, previous studies have mainly focused on the acute phase of the illness and/or have used instruments not readily available in clinical practice (Faugeras et al., 2011; Gosseries et al., 2011; Von Wild et al., 2012; Estraneo et al., 2013; Steppacher et al., 2013; Vogel et al., 2013; Bagnato et al., 2014; Lupi et al., 2014; Stender et al., 2014), such as, for example, the prognostic score system recently proposed by Kang et al, based on a combination of clinical and electrophysiological tools (Boccagni et al., 2011; Bagnato et al., 2013; Bodart et al., 2014; Kang et al., 2014).
The aims of this retrospective study were to compare demographic and clinical characteristic of patients in a VS following severe ABI of different aetiologies, and assess the recovery of consciousness in these patients and their outcome at rehabilitation discharge.
This focus should improve decision making in allocation of resources, provide a basis for realistic goal-setting during rehabilitation, and help families adjust their expectations for the future (Bagnato et al., 2010; Godbolt et al., 2013; Klein et al., 2013; Bodart et al., 2014; Kang et al., 2014).

Materials and methods

Patients

For this retrospective multicentre cohort study, medical records of ABI patients were retrieved from the Italian National Registry of severe ABI (this registry involved 29 Italian rehabilitation units and was closed in 2011). The enrolment period was from June 2008 to December 2011, and the total number of patients involved was 1469.
The inclusion criteria were: age > 18 years, severe ABI as documented by clinical history and a computed tomography scan or magnetic resonance imaging (Hammond et al., 2010), a Glasgow Coma Scale (GCS) score ≤ 8 (corresponding to a state of coma) within 24 hours of the onset of ABI (Zafonte et al., 1996), a Disability Rating Scale (DRS) score > 21 (corresponding to a vegetative state) at the time of rehabilitation unit admission (Rappaport et al., 1982).
Exclusion criteria were: admission to other rehabilitation units after ABI and before the participating one, a history of previous brain injuries, other neurological (neoplastic or inflammatory) or psychiatric disorders.
Brain injury aetiology was traumatic or non-traumatic, in the second case classified as cerebrovascular or anoxic damage. In the participating rehabilitation units, we selected a group of 492 patients in VS; all had been admitted to intensive care departments after brain injury.
Multidisciplinary rehabilitation treatment consisted of individualised training lasting 3 hours/day for 5 days a week (Monday to Friday). Treatment was based on the patient's primary needs and rehabilitation goals and complied with ABI rehabilitation guidelines (Gigli et al., 2008; De Tanti et al., 2014).
The local ethics committee approved the study protocol.

Evaluation procedures

The patients included in the study were divided into two main groups by aetiology: traumatic and non-traumatic. The non-traumatic group was divided into two subgroups: cerebrovascular and anoxic aetiology. The following demographic and clinical information was collected for each patient: age, gender, onset-to-admission interval (OAI) defined as the time from ABI onset to rehabilitation unit admission (in days), length of stay (LOS) in the rehabilitation unit (in days), department from which they were referred (intensive care *vs* acute care), type of hospital discharge (home *vs* other destinations).
Percutaneous endoscopic gastrostomy (PEG), as well as tracheostomy and/or polytrauma in the traumatic group, documented at the time of admission to the rehabilitation unit, were considered as indicators of severity of ABI (Ng et al., 2005).
The GCS score within 24 hours of onset of ABI was recorded. The GCS is a validated scoring system grading the severity of central nervous system involvement in head injury. It measures three parameters (motor response, verbal response and eye opening response) with a total score ranging from 3 (brain death) to 15 (normal cerebral function).
Functional disability was evaluated using the DRS both on admission to the rehabilitation unit and at discharge, and expressed as the DRS score. The DRS is a validated tool for quantifying the degree of residual disability. It assesses a wide range of functional levels from coma through to community living. It consists of 8 items (eye opening, communication ability, motor response, cognitive ability for feeding, toileting and grooming, level of functioning and employability), each rated with a maximum score ranging from 3 to 5 points. The total score is the sum of all the items and it may range from 0 (no disability) to 30 (death). A score >21 denotes VS (Gouvier et al., 1987; Nichol et al., 2011) Scores are grouped in 10 Disability Categories: none (score 0), mild (score 1), partial (score 2-3), moderate (score 4-6), moderately severe (score 7-11), severe (score 12-16), extremely severe (score 17-21), VS (score 22-24), extreme VS (score 25-29), dead (score 30) (Rappaport et al., 1982).
The DRS score is a valid instrument for measuring the level of general disability and therefore not only the level of consciousness (Rappaport et al., 1982; Hall et al., 1985; Gouvier et al., 1987). It was recorded in all the rehabilitation units involved in this study.

Statistical analysis

The statistical analysis was performed using ANOVA and a post-hoc t-test, Holm-Bonferroni corrected, for DRS score analysis and a generalized mixed model for poissonian distributed data and, as post hoc tests, pairwise X^2 for binomial data (number of patients with PEG, tracheostomy) with Holm-Bonferroni correction.

Results

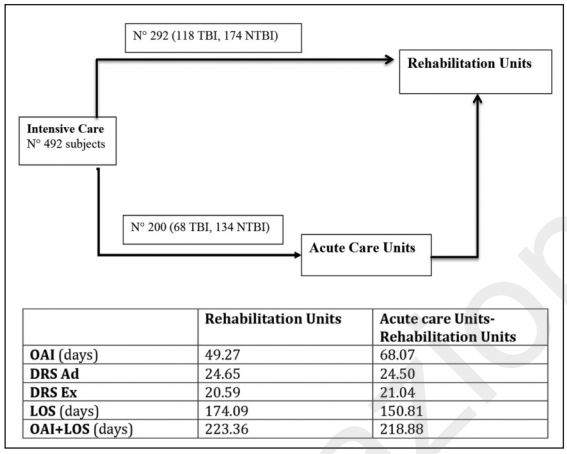
A total of 492 medical records of adult patients (333 males and 159 females) in VS after severe ABI were reviewed. The patients affected by TBI and NTBI accounted for 37.39% (n.184) and 62.61% (n.308), respectively (Table I).

Table I - Epidemiological and clinical data of the patients included in the study.

		Total				Male				Female			
		Subjects (N°)	Age (yrs)	PEG (N°)	Trach. (N°)	Subjects (N°)	Age (yrs)	PEG (N°)	Trach. (N°)	Subjects (N°)	Age (yrs)	PEG (N°)	Trach (N°)
TBI		184	44.72	117	174	155	43.17	97	146	29	46.27	20	28
	A	110	53.18	82	103	70	53.98	49	66	40	52.37	33	37
NTBI	V	198	59.18	134	177	108	58.77	79	98	90	59.58	55	79

Abbreviations: TBI=traumatic brain injury; NTBI=non-traumatic brain injury; A=anoxic; V=vascular; N°=number; PEG= percutaneous endoscopic gastrostomy; Trach.=tracheostomy

The mean age of the sample was 52.1 years. In the TBI group the males had a mean age of 43.17 years (range 18-79) and the females a mean age of 46.27 years (range 20-90), while in NTBI group, the mean age was 56.05 years (range 19-84 age) for the males and 57.70 (range 19-84 age) for the females. Patients with vascular brain injury had a higher mean age than the anoxic group.
The mean GCS score recorded within 24 hours of injury was 4.94 for the TBI group and 4.82 for the NTBI group.
With regard to the presence of devices on admission, 94.56 and 63.58% of the TBI patients had tracheostomy and PEG, respectively, as opposed to 90.90 and 70.12% of the NTBI subjects (Table I).
At discharge from the rehabilitation unit, 60.30% of the whole sample had tracheostomy and 74.50% PEG.
Globally, the proportion of patients with tracheostomy decreased significantly at discharge ($x^2_{(1.978)}$=27.78, p<0.001), whereas the presence of tracheostomy was not significantly related to aetiology ($x^2_{(2.979)}$=3.68, p=0.16) (Figure 1).
The proportion of patients with PEG did not change significantly during the rehabilitation stay (all x^2=5.74, p>0.05). In the TBI group, 73.91% (n. 136) of the patients were affected by polytrauma.
With regard to the referring units, 292 of the patients (118 TBI and 174 NTBI) were admitted to rehabilitation units directly from intensive care units (ICUs), while 200 subjects (68 TBI and 132 NTBI) had been temporarily hospitalised in other acute care units (neurosurgery, general medicine, other) before entering the rehabilitation units. The OAI on admission to rehabilitation units was 49.27 for patients coming directly from an ICU and 68.07 days for those coming from other wards, while the LOS was 174.09 and 150.81 days, respectively. The mean DRS score on admission was 24.65 and 24.50 for the first and second group respectively. The number of hospitalisation days (OAI+LOS) was 223.36 and 218.88 days for the 292 and 200 patients respectively (Figure 2); no statistically significant difference in the length of hospitalisation was found between the different aetiologies ($F_{(2.488)}$=2.93, p>0.05, n^2=0.01).
At discharge, 239 (53.11%) of the whole sample had emerged from VS; most of these patients were affected by TBI; 41 subjects (8.53%) died during the rehabilitation unit stay. Patients in a VS at discharge presented predominantly anoxic brain damage. Within the groups, 115 (66.47%) patients affected by TBI emerged from VS during the rehabilitation stay and 11 died; in the non-traumatic group, 124 (44.76%) had emerged from VS at discharge (30 patients affected by anoxic injury and 94 by cerebrovascular damage), while 31 died during the rehabilitation stay. Analysis of differences between groups revealed that patients affected by TBI were significantly more likely to recover consciousness during the rehabilitation stay those with NTBI, and, within this group, a significantly higher proportion of patients with vascular, as opposed to anoxic, brain damage emerged from VS (Figure 3).
With regard to functional outcome, 71.30% of the TBI group who emerged from VS showed severe or extremely severe disability (DRS Disability Categories 6-7). In the NTBI group, 83.06% of the patients who emerged from VS presented an extremely severe or severe disability (DRS Disability Categories 6-7) (Table II). Statistical analysis showed a significantly better out-



	Rehabilitation Units	Acute care Units-Rehabilitation Units
OAI (days)	49.27	68.07
DRS Ad	24.65	24.50
DRS Ex	20.59	21.04
LOS (days)	174.09	150.81
OAI+LOS (days)	223.36	218.88

Figure 2 - Vegetative state patients' medical pathways: from ICU to rehabilitation unit.
Abbreviations: OAI=onset-to-admission to rehabilitation unit; LOS=length of stay in rehabilitation unit; DRS Ad=Disability Rating Scale score on admission to rehabilitation unit; DRS Ex=Disability Rating Scale score on discharge from rehabilitation unit

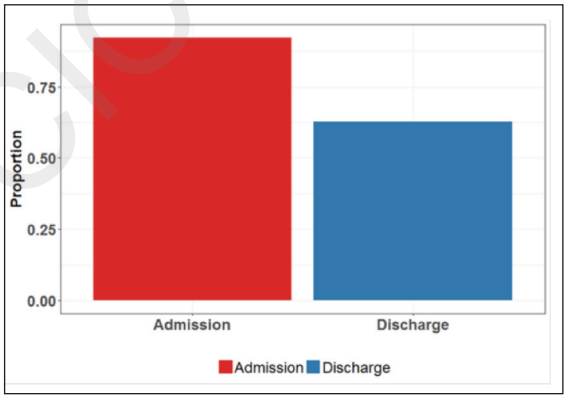


Figure 1 - Proportion of whole patient sample with tracheostomy on admission and at discharge.

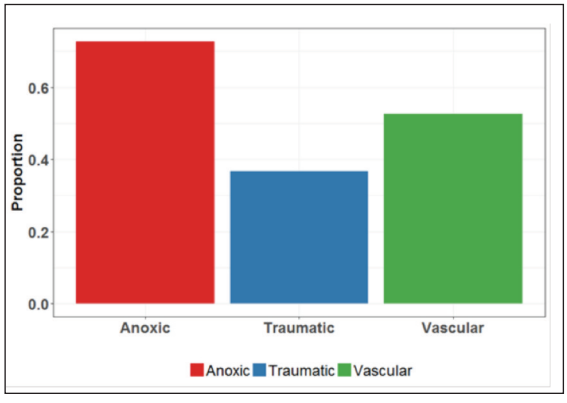


Figure 3 - Proportion of patients with a DRS score >21 at discharge: comparison of the anoxic, vascular and traumatic aetiologies.

Table II - DRS Disability Categories at discharge in the different brain injury groups.

DRS Disability Category	1	2	3	4	5	6	7	8	9	10
DRS score	(0)	(1)	(2-3)	(4-6)	(7-11)	(12-16)	(17-21)	(22-24)	(25-29)	(30)
TBI (N°)	0	1	6	13	13	24	58	34	24	11
NTBI (N°)	2	0	0	2	17	17	86	95	58	30

Abbreviations: DRS=Disability Rating Scale; TBI=traumatic brain injury; NTBI=non-traumatic brain injury; N°=number of patients

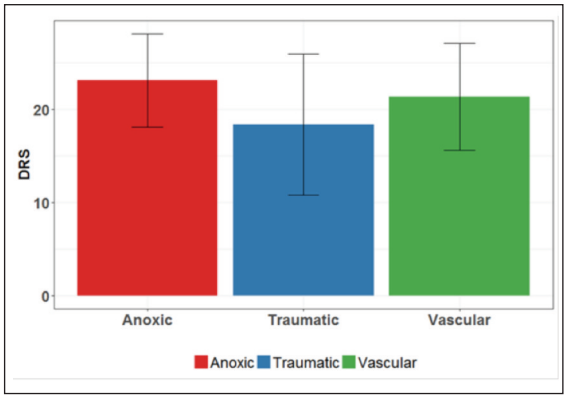


Figure 4 - Outcome of the different groups at discharge measured by DRS score.

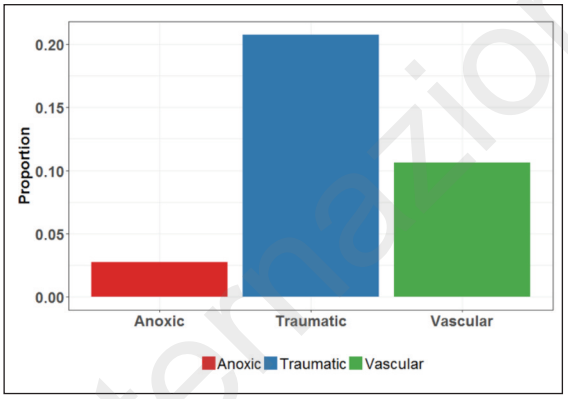


Figure 5 - Proportions of patients returning home after rehabilitation stay.

come at discharge ($F_{(2.488)}$=21.14, p< 0.001, n^2=0.08), measured by DRS score, in TBI *versus* anoxic and vascular ABI patients (p<0.001 in both cases, Holm-Bonferroni corrected). In addition, vascular ABI patients had a better outcome compared with anoxic brain injury patients (p<0.01, Holm-Bonferroni corrected) (Figure 4).
Table III shows the numbers of subjects returning home after discharge from the rehabilitation unit; only 41.84% of subjects affected by TBI returned home after rehabilitation as opposed to 15.25% of those with NTBI; among those with extremely severe residual disability, the percentage was 37.90% for TBI and 17.44% for NTBI patients.All patients affected by TBI and NTBI classified as DRS Disability Category ≤ 4 returned home after their rehabilitation stay. Among the more severely affected patients (Disability Category > 4), the number and percentage of subjects returning home decreased with increasing disability (Table III).
Analysing the between-group differences in the proportion of patients returning home after rehabilitation, we observed a significant result ($x^2_{(2.488)}$=21.28, p<0.001). Post-hoc x^2 showed that those with a traumatic aetiology were significantly more likely to return home than the NTBI group (*vs* anoxic p<0.001, *vs* vascular p<0.05, Holm-Bonferroni corrected). Within the NTBI sample, the proportion returning home was found to be significantly higher among the vascular brain damage patients than the anoxic subjects (p<0.05, Holm-Bonferroni corrected) (Figure 5).
The mean age of the patients affected by TBI who returned home was 34.5 years, *versus* 46.03 years for those not returning home; the mean age of patients the NTBI patients who went home was 46.43 years, *versus* 56.77 years for those who did not.

Discussion

In this retrospective study of disorders of consciousness following ABI of different aetiologies the majority of patients admitted to rehabilitation units with a diagnosis of VS belonged to the NTBI group, confirming the higher incidence of consciousness disorders due to vascular or anoxic brain injury compared to traumatic causes (God-

Table III - DRS Disability Category and returning home.

DRS Disability Category		1	2	3	4	5	6	7	8	9
Home subjects N° (%)	TBI	0 (100)	1 (100)	6 (100)	13 (100)	9 (69,23)	16 (66,66)	22 (37,93)	7 (20,58)	3 (12,50)
	NTBI	2 (100)	0	0	2 (100)	11 (64.70)	12 (70.58)	15 (17.44)	4 (4.21)	1 (1.72)

Abbreviations: DRS=Disability Rating Scale; TBI=traumatic brain injury; NTBI=non-traumatic brain injury.

bolt et al., 2013). The epidemiological data were consistent with previously published data; non-traumatic aetiology of brain injury was predominant and, within this group subjects affected by vascular brain damage were more represented. The mean age was lower in the TBI group compared with the non-traumatic group, and higher in cerebrovascular patients than in anoxic brain injury subjects. Male gender was predominant in all groups (Avesani et al., 2013; Godbolt et al., 2013; Pisa et al., 2013; Smania et al., 2013).

Patients with consciousness disorders are clinically complex and often present respiratory and swallowing problems that necessitate the use of devices such as tracheostomy and/or PEG (Ng et al., 2005; Wheatley-Smith et al., 2013).

In our study, 454 (92.07%) of the subjects presented tracheostomy on admission to the rehabilitation unit, and 334 (67.88%) had PEG; at discharge we observed a decrease in the percentage of patients presenting tracheostomy (60.30%) and an increase in the percentage with PEG (74.50%) in all aetiology groups. While removing tracheostomy is related to better clinical conditions, the variation in PEG use is difficult to interpret due to the lack of data about the presence, on admission, of a nasogastric tube, a device often replaced by PEG during the rehabilitation stay.

The post-acute medical care pathways of patients in VS is influenced by many variables; furthermore, literature data tend to be scarce and show high variability.

In our study, the mean OAI time was similar to data reported by Goldbolt et al. (2013), while DeFina et al. (2010) and Wheatley-Smith et al. (2013) found longer mean OAI times (200 days for TBI and 120 days for NTBI); this variability is probably due to differences in healthcare organisation between countries (Smania et al., 2013). The number of days of hospitalisation (OAI+LOS) was similar in subjects coming to rehabilitation units directly from ICUs and in those who went to an additional acute care ward before being admitted to the rehabilitation unit. In most cases, these temporary transfers were due to a momentary lack of availability of places in rehabilitation units. Thus, outcome, measured by DRS score, was similar between these two groups and consequently seems to be related to the initial severity of the brain injury and not to the different hospital pathways. Although nearly half of the patients had emerged from the VS at the time of their discharge from the rehabilitation unit (53.11%), only 7 patients with TBI and 2 NTBI had a DRS score of between 1 and 3 (mild or partial disability), while the majority presented extremely severe or severe disability. Subjects who did not emerge from the VS mostly had an NTBI aetiology, confirming a worse outcome in these patients than in those with traumatic injury (Estraneo et al., 2010; Whyte et al., 2013; Kang et al., 2014).

As regards disability after recovery of consciousness, Godbolt et al. (2013) conducted a multicenter study in patients with TBI and reported that none of those who emerged from a VS had a Glasgow Outcome Scale score greater than 4 and all presented severe disability. Estraneo et al. (2010) found that, although late recovery of awareness is not exceptional in SV patients, all those who emerged had severely impaired residual functional abilities.

Tang et al. (2017) found that the prevalence of persistent vegetative state (PVS) at six month after severe TBI has not changed significantly over the past four decades; in the study conducted by Baricich et al. (2017), it emerged that 14.29% of the patients in a VS due to a severe brain injury showed, within a period of 4 years after the damage, a recovery of consciousness, transitioning from VS to minimally conscious state (MCS).

All these data underline the poor prognosis and outcome of patients in VS and in PVS; severe outcomes have physical, mental, social and economic consequences for family members and caregivers, with the result that only a small proportion of these patients return home after their rehabilitation stay, the majority being transferred to other care facilities (Goudarzi et al., 2015).

In our study only 41.84% of subjects affected by TBI and 15.25% of patients affected by NTBI returned home; the main characteristics of these subjects, compared with those not returning home, were a younger age and lower DRS score at discharge, confirming that the burden of care is lower for patients with a lower level of disability and a younger age.

The limitation of our study is that we used the DRS to define VS, whereas a large number of studies assess patients with the Coma Recovery Scale-Revised (CRS-R). The CRS-R is the scale usually used for patients affected by disorders of consciousness (Giacino et al., 2004). The CRS-R scale, specifically used to reduce misdiagnosis between VS and MCS, could not be used in the present study because all the rehabilitation units involved used the DRS. No validated Italian version of the CRS-R was available at the time the patients were assessed (Sacco et al., 2011). Furthermore, in our experience, supported by results reported in the study conducted by Sattin et al. (2014), subjects in VS and MCS after an ABI have similar functional outcomes and care needs.

Further studies using other evaluation tools are needed in order to confirm our results.

The severity of the outcomes observed in the population examined in our study and the evidence that only a small proportion of patients return home after a rehabilitation stay suggest that there is a need to define care pathways for subjects in a VS after ABI. Better consideration of rehabilitation indications, but also care needs, could promote more effective allocation of healthcare resources and also better support families in the optimal management of their relatives.

In conclusion, most ABI patients who are in a VS at the time of admission to rehabilitation units after an ABI have a severe or very severe outcome that prevents them from retuning home.

The possibility of identifying, in the acute and sub-acute setting, factors able to predict the recovery of consciousness and outcome of these patients should be investigated, in order to allow better evaluation and planning of rehabilitation and lifelong care pathways — goals that have implications from the ethical perspective but also from that of health economics.

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