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ORIGINAL COMMUNICATION

Risk factors for mortality in 600 patients in vegetative and minimally conscious states

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Abstract A significant proportion of patients who survive traumatic or nontraumatic severe acquired brain injuries experiences disorders of consciousness. The vegetative state and the minimally conscious state may have different prognoses, and while some patients regain awareness, others have negative outcomes and die. The aim of this work is to identify age-related, medical and behavioural risk factors for mortality in those patients. Participants were enrolled from June 2009 to March 2012 in 107 Italian health care institutions. Univariate and multivariate Cox proportional hazard models were adopted to screen and test candidate risk factors. The study enrolled 600 subjects in vegetative and minimally conscious states for an overall mortality rate of 180.1 per 1,000 person-years. The following traits were associated with a significantly lower chance of survival: age at the acute event higher than 51 years, disease duration less than 1 year, post-anoxic aetiology, absence of visual fixation, and the presence of endocrine, nutritional, and metabolic diseases, and immunity disorders. Clinical history, behavioural assessment, and age-related factors provide important prognostic information on negative outcomes that helps clinicians and researchers to predict patients who are at higher risk of mortality. This knowledge has important clinical, managerial, and ethical implications.

Keywords Vegetative State · Minimally conscious state · Prognosis · Mortality rate

Introduction

Severe acquired brain injuries represent a spectrum of neurological damage and have a strong impact on sensory-motor functions, cognition, and consciousness. Among those patients who survive the acute event, a significant percentage experience disorders of consciousness (DOC) [1]. These include vegetative state (VS), a condition in which patients are unable to show any residual behavioural evidence of awareness of themselves and their environment [2], and minimally conscious state (MCS), a condition in which residual finalistic behavioural signs of awareness are spared [3].

In Italy, the prevalence of patients with DOC in post-acute rehabilitation settings is between 0.5 and 4 cases per 100,000 inhabitants [4], and similar figures are reported in other European countries [5] and the United States [6], although precise epidemiological data on prevalence in the long-term is still missing. One-third of the cases occurs after severe traumatic brain injury, whereas approximately two-thirds occur as a consequence of non-traumatic injuries, including intracranial haemorrhages, tumours, developmental disorders, intoxication, cerebral anoxia, hypoxemia after cardiopulmonary arrest, metabolic abnormalities, or progression of neurodegenerative diseases [7–10]. Patients in VS and MCS might have different prognoses, and while some regain awareness, even years after the acute event [11], others have a negative outcome

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and die. Clinical and instrumental data have provided the scientific community with evidence that several factors are associated with increased or decreased mortality rates in patients with DOC; infections, organ failure, cachexia, and sudden death have been identified as common causes of death, as reported in different studies [5, 12, 13].

A seminal longitudinal epidemiological Japanese study carried out between 1973 and 1976 on 110 subjects revealed that 65 % died within 3 years, with a mean survival time of 38 months [8]. A 5-year follow-up study on the same sample revealed that 73 % of the patients died, whereas 10 % partially recovered form VS. Death was mainly associated with cerebrovascular lesions and brain tumours, whereas better rates of survival were associated with intoxication and traumatic head injuries [14].

An Israeli study conducted on 134 patients with traumatic brain injury who suffered from DOC for more than 1 month and initially rated 7 or less on the Glasgow coma scale reported a median survival time of 15.5 months (ranging from 2 to 115) with cumulative mortality figures of 15 % at 3 months, 40 % at 6 months, 60 % at 1 year, 86 % at 2 years and 94 % at 5 years [15]. Another study from the same research group investigated a sample of 100 nontraumatic patients. Thirty-one patients died within six months following injury, while 49 continued with disorders of consciousness until death. Life expectancy of these 49 patients was between 26 and 34 months, and the prognosis for life or death was not significantly correlated with age or aetiology [16].

In 1994, the Multi-Society Task Force on Persistent Vegetative State produced a consensus publication that summarized the medical knowledge on DOC and reported that the average life expectancy of these patients is approximately 2–5 years, and survival beyond 10 years is uncommon. Within 1 year after the acute event, one-third of traumatic adult patients in a vegetative state and more than a half of those in a vegetative state after a nontraumatic injury had died [6]. Another study reported similar estimates, where the mean survival of 51 patients in VS, mainly following cerebrovascular accidents and dementia, was found equal to 3.3 years [17].

Research from California published between 1994 and 2000 reported median survival for patients with disorders of consciousness. A first study performed in paediatric patients reported that survival varies according to patient age, with patients living longer if their DOC occurs later in their childhood [18]. A second study based on a sample of 1,021 patients of all ages reported higher life expectancy figures, up to 12 years for adolescents of 15 years of age. Interestingly, this study corroborated the independence between survivals and aetiology, but the association between mortality and type of place where the patient is hosted was not confirmed [12]. A third study on children and adolescents, based on 5,075 cases gathered between 1988 and 1997, reported figures of survival at 8 years as high as 60 % for children aged between 3 and 15 years old. Mortality was lower for traumatic brain injury and higher for degenerative disease, suggesting separate prognoses for different aetiologies. Little difference in survival rates between patients in VS and MCS was detected, which was suggestive of a secondary role of diagnosis on life expectancy in children [13].

In brief, the shortened life expectancy of patients with DOC has been related to several factors, but the large majority of data on mortality rates reported in literature are not based on recent studies and do not take into account medical and technological advances in the care of patients in VS and MCS. Research figures are needed for clinicians and researchers, and the present study aims, therefore, to summarise and present recent clinical and demographic data on the risk factors associated with mortality rate in a large sample of traumatic and nontraumatic patients with DOC living in post-acute and long-term care settings, or who live at home.

Materials and methods

Study design and sample characteristics

This was a national, observational, multicentric, longitudinal study involving 107 Italian health care institutions, including hospitals and centres specialising in post-acute rehabilitation treatment or in long-term care of patients with DOC. Data collection on 600 patients with DOC was carried out between June 2009 and March 2010 (enrollment phase), and then longitudinal data on mortality were collected between July 2011 and September 2012 (follow-up). A snowball sampling methodology was used to involve the centres in the study. Experience of authors in the care of patients with DOC suggested that 107 health care institutions were a representative number of facilities, even though no data on total number of Italian facilities hospitalizing patients with DOC are available, nor were data on the number of DOC patients in the whole country available. This study was part of a broader project that aimed at collecting epidemiological and clinical data on patients with DOC to highlight the complex condition of these cases and to develop better management strategies and inclusive health care programs.

Inclusion criteria was a diagnosis of VS or MCS according to internationally recognised diagnostic recommendations suggested by the Aspen Neurobehavioural Conference Workgroup [19], and exclusion criteria was presence of neurological and psychiatric disorders prior to the acute event. The diagnosis of VS and MCS was

performed by qualified medical doctors with expertise in DOC at each participating institution. Also outpatients hosted at domicile were enrolled if they were regularly followed up by specialists from a participating centre. Alegal representative of each patient provided signed informed consent, and privacy procedures were applied to protect patients' sensitive data for both data collections. The study was approved by the ethics committee of the coordinating institution, and the approval was ratified by the participating institutions.

Materials

A research protocol was specifically designed and developed for this study. It included medical and demographic data as well as information collected by standardised assessment. A common training on modalities and procedures to administer the protocol, complete the forms and store the data was provided to health care professionals involved in data collection. The disability rating scale (DRS) was adopted to objectively measure general functioning and disability outcomes in the different stages of the course of recovery. Scores range from 0 to 29, with higher values indicating higher disability [20]. Additional ad hoc behavioural information concerning visual responses and the ability to perform simple tasks was collected using post-coma scale items [21]. The international classification of diseases clinical modification (ICD-9-CM) was used as a standard diagnostic tool to classify patients' comorbidities [22]. Data quality control was performed after the enrollment of the first 60 cases: completeness of data was checked after the enrollment of 60 patients, and a report with corrective recommendations was sent to each centre.

Statistical analysis

Quantitative variables were expressed as mean (and standard deviation, median and range), whereas categorical variables were reported as count (and percentage). Since data was analysed before all the patients died, and patients did not enter the study at the same time, survival analysis for censored observations was used to indicate the number of patients surviving the clinical condition of DOC. The cumulative rate of survival was calculated by the Kaplan–Meier method. In this method the units of analysis are the consecutive months each patient contributes between the starting and ending dates.

The univariate Cox proportional hazard model was adopted to explore hazard ratios with 95 % confidence interval (95 % CI) and significance, and a log-rank test of equality across strata was used to test whether to include each variable in the final multivariate model. The large sample size allowed us to investigate the effect of multiple covariates. To test the predictive power, emphasis has been placed on medical, behavioural response, and age-related factors. The following demographic and medical factors were recorded and tested as candidate risk factors: (1) age at acute event, (2) duration of clinical condition, (3) aetiology, (4) DRS score, (5) visual responses, (6) performing simple tasks, (7) and ICD-9-CM comorbidities which were observed in more than 5 % of the sample. For each category, a reference group was set (age at acute event = less than 20 years; duration of clinical condition = less than 1 year; aetiology = traumatic; visual, performing simple tasks = presence; ICD-9-CM comorbidities = absence) against which the other group's hazard ratios were tested.

Variables with significance level of $p < 0.1$ in univariate analysis were selected for the multivariate Cox proportional hazard model where hazard ratios (with 95 % CI and significance) were calculated. The Breslow method was used to handle tied failures. All the variables met the constant proportional hazards assumption (Supplementary Material). STATA version 11 was adopted for data analysis [23].

Results

A total of 600 subjects where recruited in the enrollment phase of the study, of whom 157 (26.2 %) were living in rehabilitation units, 381 (63.5 %) in long-term care facilities, and 62 (10.3 %) lived at home. 15 patients (2.5 %) were lost in the follow-up, and 2 (0.3 %) were excluded from further analysis due to data unavailability. Overall, this longitudinal study included 13,610 person months drawn from 583 patients (36 children and adolescents under 18), of whom 203 (34.8 %) died during their time in the study, for an overall mortality rate of 180.1 per 1,000 person-years (95 % CI 157.2–206.4). 240 (41.2 %) of the participants were females. 366 (62.8 %) were in VS. 380 (65.2 %) were hosted in long-term care institutions, 157 (26.9 %) in post-acute rehabilitation centres, and 46 (7.9 %) at home. Mean age at recruitment was 51.7 years (SD 20.2, median 54.5, range 0.1–90.8), with a mean DRS score of 23.5 (SD 2.3, median 24, range 17–29). Detailed medical and demographic characteristics of our sample are reported in Table 1. Among comorbidities, the most represented ICD-9-CM categories were diseases of the circulatory system (17.0 %), diseases of the nervous system and sense organs (13.2 %), and endocrine, nutritional, and metabolic diseases and immunity disorders (9.6 %) (Table 2). In details, endocrine, nutritional, and metabolic diseases were composed of nutritional deficiencies (1.9 %), disorders of the thyroid gland (14.8 %), other metabolic and immunity disorders (16.7 %), and diseases of other

Table 1 Distribution of medical and demographic factors of patients with follow-up ($n = 583$), expressed in frequency (and percentage)

Demographic factors	*n* (%)
Age at the acute event (years)	
Less than 20	45 (7.7)
21–30	52 (8.9)
31–40	58 (9.9)
41–50	83 (14.2)
51–60	108 (18.5)
61–70	126 (21.6)
More than 71	111 (19.0)
Duration of clinical condition (years)	
Less than 1	154 (26.4)
1–2	101 (17.3)
2–3	83 (14.2)
3–4	74 (12.7)
4–5	39 (6.7)
More than 5	132 (22.6)
Aetiology	
Traumatic	152 (26.1)
Haemorrhagic	162 (27.8)
Ischemic	39 (6.7)
Post-anoxic	183 (31.4)
Other/not specified	47 (8.1)
Visual responses	
Yes	124 (21.3)
Sometimes	151 (25.9)
No	308 (52.8)
Performing simple tasks	
Yes	34 (5.8)
Sometimes	124 (21.2)
No	425 (72.9)

endocrine glands (66.7 %), with diabetes as the most frequent disease in this last group ($n = 26$).

In unadjusted analyses, medical and demographic characteristics as well as comorbidities were tested as candidate risk factors. Age at the acute event ($\chi^2 = 72.6$; $p < 0.001$), duration of clinical condition ($\chi^2 = 26.70$; $p < 0.001$), aetiology ($\chi^2 = 12.94$; $p = 0.011$), DRS score ($\chi^2 = 30.59$; $p = 0.002$), visual responses, and endocrine, nutritional, and metabolic diseases, immunity disorders ($\chi^2 = 3.14$; $p = 0.076$), and diseases of the circulatory system ($\chi^2 = 4.39$; $p = 0.036$) were selected for multivariate analysis. Performing simple tasks and diseases of the nervous system and sense organs were excluded from multivariate analysis, as they overcame the threshold of significance of $p < 0.1$. For both included and excluded variables, hazard ratios, confidence intervals, and significance are reported in Table 3.

Table 2 Distribution of comorbidities in patients with follow-up, as grouped by ICD-9-CM, expressed in frequency (and percentage)

Comorbidities	*n* (%)
Infectious and parasitic diseases	24 (4.1)
Neoplasms	7 (1.2)
Endocrine, nutritional, and metabolic diseases and immunity disorders	56 (9.6)
Diseases of the blood and blood-forming organs	4 (0.7)
Mental disorders	9 (1.5)
Diseases of the nervous system and sense organs	77 (13.2)
Diseases of the circulatory system	99 (17)
Diseases of the respiratory system	20 (3.4)
Diseases of the digestive system	12 (2.1)
Diseases of the genitourinary system	8 (1.4)
Complications of pregnancy, childbirth, and the puerperium	2 (0.3)
Diseases of the skin and subcutaneous tissue	4 (0.7)
Diseases of the musculoskeletal system and connective tissue	5 (0.9)
Congenital anomalies	1 (0.2)
Certain conditions originating in the perinatal period	1 (0.2)
Symptoms, signs, and ill-defined conditions	8 (1.4)
Injury and poisoning	2 (0.3)

Multivariate analyses showed that age at the acute event, duration of clinical condition, aetiology, visual responses, and presence of endocrine, nutritional, and metabolic diseases, and immunity disorders were significant predictors of mortality. In particular, age at the acute event higher than 51 years, disease duration less than 1 year, post-anoxic aetiology, absence of visual responses, and presence of endocrine, nutritional, and metabolic diseases and immunity disorders were associated to higher risk of mortality (Table 3).

Discussion

This study was based on a large sample of Italian patients in VS and MCS, which allowed us to take into account several relevant medical and demographic risk factors of mortality simultaneously. The main finding is that age over 50 years, time since the acute event of less than 1 year, post-anoxic aetiology, absence of visual responses, presence of endocrine, nutritional, and metabolic diseases and immunity disorders, in particular diabetes, are related to an increased risk of mortality.

Overall, age at acute event is the most critical factor impacting mortality rates. In fact, the mortality risk in patients older than 51 years is almost four times higher than the risk in patients younger than 20, whereas young

Table 3 Frequencies (percentages), unadjusted and multivariate analyses of risk factors for mortality

	Unadjusted analysis			Multivariate analysis		
	HR	95 % CI	*p*	HR	95 % CI	*p*
Age at the acute event (years)						
Less than 20						
21–30	0.45	0.13–1.55	0.208	0.55	0.16–1.91	0.355
31–40	0.76	0.27–2.11	0.605	0.87	0.31–2.44	0.801
41–50	1.25	0.51–3.02	0.617	1.19	0.48–2.94	0.693
51–60	3.37	1.52–7.43	0.003	4.10	1.81–9.29	0.001**
61–70	3.13	1.42–6.89	0.004	3.42	1.51–7.71	0.003**
More than 71	4.31	1.97–9.44	<0.001	4.20	1.87–9.41	0.001**
Duration of clinical condition (years)						
Less than 1						
1–2	0.51	0.33–0.79	0.003	0.51	0.33–0.79	0.003*
2–3	0.70	0.46–1.06	0.098	0.60	0.40–0.94	0.022*
3–4	0.66	0.42–1.02	0.066	0.59	0.41–1.03	0.048*
4–5	0.42	0.22–0.82	0.012	0.44	0.22–0.86	0.016*
More than 5	0.38	0.25–0.58	<0.001	0.43	0.28–0.66	<0.001**
Aetiology						
Traumatic						
Haemorrhagic	1.80	1.18–2.74	0.006	1.11	71–1.72	0.624
Ischemic	2.21	1.25–3.92	0.006	1.36	0.75–2.47	0.306
Post-anoxic	1.92	1.27–2.89	0.002	1.67	1.02–2.35	0.036*
Other/not specified	1.86	1.05–3.30	0.032	1.46	0.81–2.61	0.202
DRS score	1.07	1.01–1.14	0.022	1.02	0.96–1.08	0.387
Visual responses						
Yes						
Sometimes	1.28	0.82–2.00	0.261	1.36	0.88–2.24	0.154
No	1.67	1.14–2.46	0.009	1.87	1.16–3.00	0.010*
Performing simple tasks						
Yes						
Sometimes	1.16	0.56–2.40	0.685			
No	1.57	0.80–3.08	0.185			
Endocrine, nutritional, and metabolic diseases and immunity disorders						
Yes	1.44	0.95–2.18	0.081	1.75	1.14–2.70	0.010*
Diseases of the nervous system and sense organs						
Yes	1.03	0.68–1.56	0.889			
Diseases of the circulatory system						
Yes	1.42	1.02–1.99	0.039	1.058242	0.74–1.50	0.754

HR hazard ratio, *95 % CI* 95 % confidence interval, *p p* value

* $p < 0.05$

** $p < 0.01$

and middle-aged adults aged from 21 to 50 have more chances to survive. These results, in line with those reported by the Multi-Society Task Force [24], corroborate the view that adequate treatments and rehabilitation of elderly patients with DOC is a challenge for modern medicine in our ageing society.

On the other hand, a clear reduction in the mortality risk was found when time since the onset increased. The increased life expectancy of patients with DOC for more than 1 year indicates that these patients need medical and nursing care for a prolonged time. Thus, the network of services devoted to this category of chronic patients should plan long-lasting and structured intervention, both in long-term care centres and at home. Therefore, continuity of care should be firstly provided to guarantee high standards of care for patients [25] and also to prevent high levels of burden in family members and caregivers.

Our data also showed that the prognosis was worse for anoxic patients. This difference in prognosis between traumatic and anoxic aetiology may be related to differences in terms of nervous system damage. Anoxia causes diffuse cortical damage, cortical disconnection, laminar

necrosis, and severe demyelination, while trauma tends to cause diffuse axonal injury due to shearing forces, with the cerebral cortex relatively spared [16]. These results support the idea that different neurological profiles in terms of severity of aetiology are separate predictors of mortality.

Our results showed that patients' behavioural assessments were also informative of mortality risk; in particular, the absence of visual responses after severe acquired brain injury is negatively associated with chance of survival. The role of visual responses in relation to recovery of consciousness is, in fact, still debated in literature. At the moment, its presence seems to be a positive marker of partial recovery of the brainstem–cortical interaction and preserved overall brain functional organization. It is generally accepted by the scientific community that the return of tracking eye movements is one of earliest signs of recovery from VS towards MCS [26, 27], and that visual pursuit in response to salient stimuli has a crucial role in the differential diagnosis. The present study supports the view that investigation of eye behaviour is of primary importance also in predicting rate of mortality.

On the contrary, even though DOC patients performing simple tasks is another important behavioural factor that supports clinicians in the diagnostic decision process, it is not found to be significant in mortality rate prediction. Frequently, patients with DOC that perform simple tasks have a relatively high level of cognitive functioning. However, also patients who fail to perform simple tasks have sometimes spared cortical processes [28] and do not manifest severe functional consequences. This may represent a possible explanation of why this behavioural examination is not predictive in terms of mortality. Also, disability as measured by DRS proved not to be significantly associated with mortality. This is probably due to issues related to domains investigated by this scale, which capture general levels of disability in relation to activities that are usually fully compromised in patients with DOC. In fact, DRS mainly accounts for levels of disability related to communication and motor responses which identify only patients with preserved behavioural responses, as mentioned above for the performing simple tasks item.

A relation between mortality of patients with DOC and their comorbidities was also found. Endocrine, nutritional, and metabolic diseases—especially diabetes—was the most represented category of diseases reported in our sample, and it was identified as a predictor of survival. In fact, the presence of this category of diseases creates several difficulties in clinical management of patients, such as the optimization of the nutritional profile and the medical care of pressure sores, which may impact on metabolic dysfunctions and infections, respectively.

However, it must be noted that health care professionals also reported a low frequency of infections and parasitic diseases in our samples, with higher prevalence in patients with higher duration of the clinical condition. Although this figure could be influenced by sample characteristics, considering that around 75 % of patients had a duration of disease of more than 1 year, this might indicate that professionals have improved clinical management of patients with DOC, achieving a reduction of septic states and higher survival rates. Future studies are needed to better elucidate this issue; these should also consider the incidence of infections during the chronic stage of disease and the use of anti-infective drugs in patient treatments [29, 30].

This study had some limitations. Firstly, the recent publication and Italian validation of the coma recovery scale, revised (CRS-r) has partially ameliorated the behavioural assessment of patients according to standard diagnostic criteria. However, our study started before that Italian version of CRS-r, or other specific internationally accepted assessment scales for differentiating patients in MCS and VS, was commonly used in clinical practice in Italy, so the authors could use them. However, the aim of the present study is to present preliminary data on mortality rates of DOC patients, and not specifically for VS or MCS; so, the long expertise of professionals involved in the project could provide a guarantee regarding behavioural differentiation of DOC patients versus patients emerged from MCS. Considering absence of CRS-r in the protocol, the authors decided to include some features regarding functioning of patients as risk factors in order to highlight data useful for clinical practice. Visual responses and performance of simple tasks were selected as fundamental behavioral assessments of these patients. Secondly, analyses were not stratified according to place of living and care where the patient is hosted because a considerable number of participants moved form one centre to another or to their domicile during the duration of the study. Thirdly, professionals were asked to indicate only first level codes of ICD-9-CM and therefore further investigations on differences regarding types of diabetes were not carried out. Future studies should focus on differences, treatments, and functional outcomes of diabetes mellitus type I and II, also distinguishing patients with diabetes pre-injury and post-injury.

Our study results have relevant implications since both modifiable and non-modifiable risk factors have been investigated. Visual responses and comorbidities belong to the former category, and the development of treatments and techniques aimed to improve general clinical condition and visual responses should be of primary interest for professionals seeking to decrease the mortality rate. Non-modifiable risk factors found in our study are also considerably useful for clinicians who formulate a prognosis in the early stage of the disease, especially if matched with instrumental, clinical, and functional observations.

In conclusion, this work provided evidence that medical and age-related factors have a useful role in predicting mortality of patients in VS and MCS. These results are targeted to help clinicians and researchers to stratify patients for mortality risk and develop intervention and care strategies to increase survival. Knowledge of this easily available information on clinical history and behavioural assessment provides important prognostic information on negative outcomes; this has strong implications from the clinical, managerial, and ethical perspectives [31]. Improved technologies, standards of care, and therapies have been increasing the survival of patients with DOC. However, survival should not be used as a single indicator of good clinical practice, but should be complemented with other indicators related to quality of life and pathways of care and cure.

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Conflicts of interest The authors have no conflict of interest to declare.

Appendix 1

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