



Morfeo Study II: Clinical Course and Complications in Patients With Long-Term Disorders of Consciousness



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ABSTRACT

Background: The life expectancy of patients with disorders of consciousness (DOCs) is ever-increasing, but little is known about their clinical course over late stages. Several issues (premorbid conditions, complications and pressure sores) are to be considered for their effect on clinical outcome, risk of death and recovery of functional performance. Unfortunately, in late stages of long-term rehabilitation, these aspects are still more neglected than in acute and postacute stages. The aim of this study was to investigate the clinical course and the complications of patients in the late stages of DOCs and to explore the relationship between mortality and specific biomarkers.

Materials and Methods: A total of 112 patients, admitted over 10 years in a dedicated ward, were retrospectively studied. Sociodemographic data, preadmission and inpatient clinical features were collected. Disability Rating Scale scores, complications including pressure sores and blood markers were assessed monthly. Data were analyzed through descriptive statistics and correlations using SPSS.

Results: Most patients were men older than 50 years with a nontraumatic etiology and a history of hypertension (42.86%). The most common complication was pneumonia (76.79%). No association was found between sex and mortality or between etiology and mortality ($P > 0.05$). Mortality correlated significantly with sepsis ($\rho = 0.253$), albumin ($\rho = -0.558$), hemoglobin ($\rho = -0.354$) and white blood cells ($\rho = 0.243$). Only 42% of patients remained unchanged at Disability Rating Scale evaluation.

Conclusions: These data confirmed that DOCs are not static conditions and they require ongoing monitoring and assessment of clinical status, level of consciousness and laboratory biomarkers.

Key Indexing Terms: Pressure sores; Albumin; Hemoglobin; Etiology; Complications. [*Am J Med Sci* 2016;351(6):563–569.]

INTRODUCTION

The advances in emergency services and intensive care unit practices are reported to contribute to the increasing incidence and prevalence of the vegetative state (VS) and minimally conscious state (MCS).¹ These diagnoses can be included among disorders of consciousness (DOCs) and represent possible outcomes of an acquired brain injury.

Managing and caring for and rehabilitating patients with DOCs is challenging and requires a specialized comprehensive approach, especially since the life expectancy of these patients is ever-increasing.^{2,3}

For this reason, in the last decades more attention has been paid to the care pathways for them.⁴ The continuum of care for patients with acquired brain injury is usually organized into the following 3 phases: (1) acute phase (from few hours to some weeks, that is from the injury until the stabilization of vital functions); (2) postacute or rehabilitative phase (from some weeks to several months, that is from the stabilization of vital functions to the stabilization of residual disabilities) and (3) phase of sequelae (from several months to several

years, that is from the stabilization of residual disabilities to the maintenance of achieved residual autonomies and to prevention of worsening).⁵

The duration of each phase is variable depending on the clinical evolution of the patient. Indeed, a stabilization of medical condition is not obvious with the passing of time. Patients discharged from intensive rehabilitation because of an unlikely chance to improve may still have an unstable medical condition. For them, hospitalization in a long-term hospital could be necessary to stabilize their clinical picture. Generally, this late phase received less attention than early ones, as showed by the scarce literature about it.

Due to their effect on clinical outcome, several issues to address in patients with DOCs include premorbid conditions, complications and, among them, pressure sores.

Pre-existing medical disorders reportedly influence the treatment and rehabilitation of patients with DOCs⁶; however, to the best of our knowledge, no specific study has been done on this topic. On the contrary, the issue of medical complications during the acute and postacute

stages of DOCs has been largely investigated,⁷ but it remains understudied in the chronic phase.^{8,9}

Both infectious and noninfectious complications (e.g., pneumonias, sepsis, urinary tract infections, post-traumatic seizures and hydrocephalus) are reported frequently among patients in VS and MCS early after injury¹⁰ and in the late stages of DOC.¹¹ Assessing and managing them is essential, because clinical complications can increase the risk of death and negatively affect the recovery of functional performance⁹ as well as the recovery of consciousness.²

In DOCs, pressure sores are very common¹² and managing them represents an important challenge that requires optimal levels of personal care and nutritional support. A recent review¹³ reported that impaired mobility, fever, insufficient caloric intake and low body weight were significant factors in the appearance of pressure ulcers, which cause significant morbidity and mortality and can lead to sepsis.¹⁴ As well, low levels of hemoglobin and albumin were found to play a role in their development¹⁵ and worsening.¹⁶

Most studies about the clinical course of patients in VS and MCS have been focused on the acute or postacute phases, but this topic over the chronic phase remains understudied.

MORFEO Study II is an observational longitudinal retrospective study and it represents a continuation of MORFEO study carried out by Fabbri et al,¹⁷ which focused on late complications in patients in VS. The aim of the present study is 3-fold: (1) to investigate the long-term complications in patients in VS and MCS; (2) to describe the long-term functional and clinical status of patients in VS and MCS and (3) to explore the relationships between mortality and specific biomarkers in patients in VS and MCS.

MATERIALS AND METHODS

Patients

Patients who are not eligible for intensive rehabilitative treatment are admitted to Santa Viola Hospital in Bologna, Italy after discharge from acute and postacute care wards to prevent or to minimize secondary and tertiary complications that may have deleterious effects on recovery and make therapeutic efforts useless. Caring for patients with DOCs is challenging because of complexity of their medical condition. In line with clinical praxis built over years and the Guidelines of the Italian Ministry of Health¹⁸ about the care of patients in VS and MCS, a specific care pathway has been formulated as follows:

- (1) Daily medical visits and periodic blood testing.
- (2) A dedicated staff composed of nurses, physical therapists and healthcare assistants.
- (3) A fixed multidisciplinary team composed of an internist, a neurologist and a physiatrist. In addition, psychiatrist and psychologist are included to provide

dialog with caregivers and to promote their coping attitudes. These professionals are coordinated by the chief physician of the ward.

This study, approved by local ethics committee, retrospectively considered 112 patients admitted to the 25-bed dedicated ward in S. Viola Hospital over a 10-year period between March 2003 and February 2013.

The main inclusion criterion of this study was the diagnosis of VS or MCS. The diagnosis of VS was based on the definition issued by Multi-Society Task Force¹⁹ and the diagnosis of MCS was made in accordance with Aspen Consensus Group's criteria.²⁰ Patients with locked-in syndrome, DOCs due to neurodegenerative and genetic diseases and patients admitted for respite care were excluded from this study to minimize bias.

Measures

Sociodemographic and clinical data were collected for each patient. Among these, pre-existing and inpatient characteristics were gathered from the case history that also included documents from the referring ward. The pre-existing data are:

- (1) *etiology*: traumatic, anoxic, metabolic, infectious, toxic and cerebrovascular;
- (2) *preadmission medical features and devices*: ventriculoperitoneal derivation, percutaneous endoscopic gastrostomy, tracheostomy, baclofen pump and cranioplasty;
- (3) *pre-existing morbidities clinically relevant to the medical condition, because of their effect on cardiovascular, respiratory and metabolic systems*: drug addiction, brain trauma, epilepsy, psychiatric diseases, cardiac diseases, hypertension, diabetes and respiratory diseases;
- (4) *provenance* and
- (5) *preadmission complications*: comitial crises (also known as epileptic crises), cardiac complications, pneumonias, urinary tract infections, sepsis and deep vein thrombosis.

Among inpatient features, are included:

- (1) the number of days elapsed between disease onset and admission to S. Viola Hospital (onset-admission-interval [OAI]);
- (2) the length of stay (LOS) in S. Viola Hospital, expressed in days;
- (3) for patients deceased in S. Viola Hospital, the number of days elapsed between disease onset and death;
- (4) discharge destination from S. Viola Hospital and
- (5) death as dichotomous variable (yes or no).

To monitor clinical evolution, the following data were recorded every 30 days until discharge or death:

- (1) *Number of secondary complications incurred during the hospitalization*: comitial crises, cardiac

complications, pneumonias, urinary tract infections, sepsis and deep vein thrombosis. The diagnosis of each complication was formulated according to the criteria described in the previous MORFEO study (for details Fabbri et al¹⁷).

- (2) Number and degree of severity of pressure sores, according to U.S. National Pressure Ulcer Advisory Panel.²¹
- (3) *Pressure ulcer improvement as dichotomous variable (yes or no)*: both decrease of number and decrease of degree, detected between the first and last evaluation, are considered improvement. The time between these assessments is variable and depends on the LOS of each patient.
- (4) *Biomarkers*: albumin and hemoglobin expressed in g/dL and white blood cells expressed in $10^3/\mu\text{L}$.
- (5) Outcome scales administered by trained physicians.

Disability Rating Scale (DRS)²² is a measure of general functional changes over the course of recovery from coma.

Total score ranges from 0-30 with a lower score reflecting higher functioning.

Level of cognitive functioning (LCF)²³ provides a description of 8 stages of cognitive function through which patients with brain injury typically progress during rehabilitative care. This scale permits monitoring of recovery and classification of outcome in patients with brain injury.

Statistical Analysis

Descriptive analyses were performed to outline sociodemographic and clinical features of the patients. Categorical variables are described as frequencies and percentages, and quantitative variables as means and SDs.

The Kolmogorov-Smirnov test was used to determine if the variables are normally distributed. A Spearman correlation was performed to analyze the relationships between not normally distributed continuous variables. A Chi-square test was performed for dichotomous variables. A Fisher test was used for dichotomous variables with $n < 20$.²⁴ A point-biserial correlation was performed to test the relationship between a dichotomous variable and a continuous one. All analyses were performed with SPSS V.19 (SPSS Inc., Chicago, IL). All tests were 2-tailed and statistical significance was set at $P < 0.05$.

RESULTS

The sample comprised 112 patients admitted between March 2003 and February 2013. As shown in Table 1, most of them were men (61.61%) and were married (55.36%), and on average, the age at the acute event was 59.09 (standard deviation [SD] = 16.46) years. The OAI was 338.08 (SD = 627.72) days, which indicates that the patients are admitted approximately 11 months after brain injury. On the average, the LOS

was 629.24 (SD = 828.57) days. A percentage of patients with LOS greater than 3 years was present (22.32%). Table 1 also refers to pre-existing medical characteristics.

Most patients had an anoxic (37.50%) or a cerebrovascular (35.72%) etiology, and a history of arterial hypertension was frequent (42.86%). Most patients had a percutaneous endoscopic gastrostomy (93.75%) and tracheostomy (78.57%) and almost the entire sample (98.21%) incurred some complication during the acute and postacute phase before admission to the long-term facility.

Table 2 refers to inpatient features. Most in the sample have died (56.25%), 20.54% are still hospitalized and the rest of the sample was discharged to other facilities or to home. On average, the time elapsed between the acute event and death of patients was 602.75 (SD = 862.92) days. Any association was found

TABLE 1. Sociodemographic features and pre-existing medical characteristics.

	Frequency	%
Sex		
Male	69	61.61
Female	43	38.39
Marital status		
Married	62	55.36
Unmarried	28	25.00
Widow	18	16.07
Separated	4	3.57
Etiology		
Traumatic	25	22.32
Anoxic	42	37.50
Metabolic	1	0.89
Infectious	1	0.89
Toxic	3	2.68
Cerebrovascular	40	35.72
Preadmission clinical features		
Ventriculoperitoneal derivation	20	17.86
PEG	105	93.75
Tracheostomy	88	78.57
Baclofen pump	5	4.46
Cranioplasty	8	7.14
Acute complications	110	98.21
Pre-existing morbidities		
Drug addiction	1	0.89
Brain trauma	2	1.79
Epilepsy	10	8.93
Psychiatric diseases	7	6.25
Cardiac diseases	24	21.43
Hypertension	48	42.86
Diabetes	18	16.07
Respiratory diseases	12	10.71
Provenance		
Emergency department	26	23.21
Intensive rehabilitation	60	53.57
Internal medicine wards	24	21.43
Home	2	1.79

TABLE 2. Inpatient features.

	Frequency	%
Discharge destination		
Died	63	56.25
Emergency Room	11	9.82
Nursing home	12	10.71
Home	3	2.68
Still hospitalized	23	20.54
Complications		
Comitial crises	49	43.75
Cardiac complications	22	19.64
Pneumonias	86	76.79
Urinary tract infections	64	57.14
Sepsis	49	43.75
Deep vein thrombosis	5	4.46
No complications	5	4.46

neither between sex and death ($P = 0.870$), or etiology and death ($P = 0.300$). No relationship was found between etiology and LOS ($P = 0.540$).

Nevertheless, a negative correlation was found between LOS and age at the DOC onset ($\rho = -0.275$, $P = 0.003$).

As shown in Table 2, the most common complication recorded in this sample was pneumonia (76.79%), followed by urinary tract infections (57.14%) and comitial crises (43.75%).

In the Figure, the percentages of patients with complications occurring for the first time during hospitalization in the long-term facility are compared with the percentages of patients having already incurred complications in previous hospitalizations. Exploring the association between pre-existing and inpatient complications, only a significant association was found for comitial crises ($P = 0.003$), in terms of high risk of recurrence, but not for any other kind of complication. Further analyses revealed no different

probability of comitial crises arising among etiologies ($P = 0.89$).

Concerning the relationship between complications and death, only the inpatient number of sepsis resulted significantly related with death ($\rho = 0.253$; $P = 0.009$).

Of 112 patients, all had a first pressure sore assessment, 23 patients died or were discharged before the second visit and 89 patients underwent at least a second evaluation. According to the comparison between the first and the last evaluation, most patients (56.20%) remained unchanged; 28.10% of patients showed an improvement and 15.70% of patients showed a worsening. The presence of any improvement of pressure sores correlated with LOS ($\rho = 0.341$; $P = 0.001$).

Disability Rating Scale

Of 115 patients, 94 patients had the first evaluation and 52 patients had a second evaluation. Comparing the first and the last DRS score, 42.32% of patients remained stable, 28.84% showed a score increase and 28.84% showed a score decrease of DRS in the second evaluation. In respect to the first assessment with DRS, 5 patients showed improving status and 6 patients showed a worsening one.

Level of Cognitive Functioning

Of 115 patients, 93 patients had a first evaluation and 49 patients had a second evaluation. Comparing the first and the last LCF score, 91.84% of patients remained stable, 6.12% of patients showed a score increase in the second assessment and 2.04% of patients exhibited a decrease of LCF score in the second assessment.

To facilitate correlative analyses, the median value between the first and the last entries for albumin,

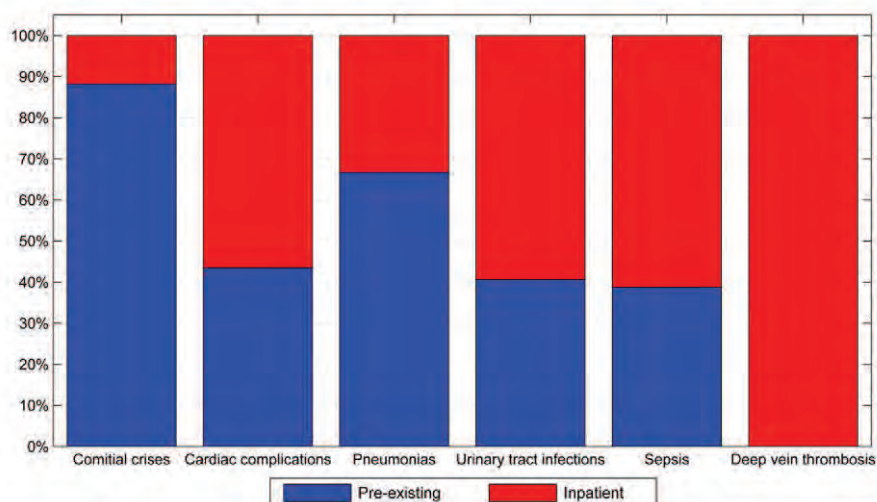


FIGURE. Comparison between prehospitalization and inpatient complications. The percentages of patients with complications occurring for the first time during hospitalization are compared with the percentages of patients having already incurred the same complication before.

hemoglobin and white blood cells for each patient were used. Albumin level was found to correlate positively with hemoglobin ($\rho = 0.607$; $P = 0.000$) and with LOS ($\rho = 0.343$; $P = 0.001$), and to correlate negatively with death ($\rho = -0.558$; $P = 0.000$), number of episodes of sepsis ($\rho = -0.367$; $P = 0.000$) and white blood cells ($\rho = -0.313$; $P = 0.002$).

Hemoglobin was correlated negatively with white blood cells ($\rho = -0.510$; $P = 0.000$), death ($\rho = -0.354$; $P = 0.000$) and number of sepsis episodes ($\rho = -0.454$; $P = 0.000$). The number of white blood cells correlated positively with death ($\rho = 0.243$; $P = 0.012$), number of sepsis episodes ($\rho = 0.302$; $P = 0.001$) and negatively with LOS ($\rho = -0.438$; $P = 0.000$).

DISCUSSION

This retrospective study was carried out to analyze the clinical course of patients in VS and MCS in a facility for long-term rehabilitation.

On average, patients were admitted 11 months after the brain injury and remained hospitalized for about 2 years, because long-term facilities generally manage patients with DOCs in more advanced stages with longer OAI.

A history of arterial hypertension was recorded in many of them, confirming its role as risk factor for cerebrovascular and cardiac disease.²⁵ Indeed in the present study, the main aetiologies were anoxic and cerebrovascular ones.

Consistent with Leonardi et al.,³ most of our patients were men older than 50 years. In respect to a previous study,²⁶ a higher average age (59.09 years) of patients was noted in this study, probably because of the prevalence of nontraumatic etiology, more common in elderly patients.²⁷

The lack of significant associations of death with sex and etiology seemed in line with a previous study,²⁸ although data from literature are not univocal (e.g., Harrison-Felix et al.²⁹). Unfortunately, no comparisons could be made because of the differences between our sample and those cited above.

The negative correlation between age at acute event and LOS may appear contradictory, because a young age at the acute event was found to be a positive prognostic factor in patients in VS²⁷ and in MCS³⁰ and this may result in a shorter LOS. In long-term rehabilitation, a longer LOS may be interpreted as a positive parameter, because frailty and late complications could lead more frequently to death, especially in elderly patients. In this respect, young age could be considered a positive prognostic factor also in the present study.

With regard to medical complications, most of the patients incurred pneumonias and urinary tract infections, as found by Sazbon and Groswasser¹¹ in a sample of patients with traumatic brain injury. This result may be explained by risk factors for the development of infections to which patients with DOCs are exposed of

impaired mobility, previous administration of antibiotics,³¹ bedside airway toilette,³² tracheostomies³³ and urinary catheters.⁹ Prevention and specific training of professional staff seems crucial to minimize their effect.

Nevertheless, a lower frequency of comitial crises was found in comparison with the study of Krimchansky et al.³³ Our results pointed out an association between the first seizure and the frequency of subsequent ones, as showed by Hauser et al.³⁴ In the authors' opinion, these data highlights the need for antiepileptic prophylaxis after a first relapse of seizure, especially because neurologic insults were reported to increase the risk of recurrence.³⁴

According to Beghi,³⁵ an antiepileptic therapy is recommended when the risk of recurrence is thought to be high or when prevention is considered worthwhile or both. In the present case, the antiepileptic prophylaxis was administered to each patient after the first seizure relapse, together with a monitoring of serum concentrations of antiepileptic drug to optimize the dose. According to our descriptive results, after the administration of antiepileptic prophylaxis 59% of patients showed no more crises over the whole hospitalization, 12% showed 1 more crisis, 8% showed 2 more crises, 2% showed 3 more crises and 16% showed more than 4 crises. The issue of antiepileptic prophylaxis is largely debated,³⁶ but no specific study was done about traumatic and nontraumatic DOCs, in the authors' knowledge. Further studies should be done to clarify this important issue in this kind of patients.

Results from DRS confirmed that a low percentage of patients exhibited recovery of consciousness; patient age, the prevalence of nontraumatic etiology and the long OAI were usually associated with a worse outcome in recovery of consciousness.³⁷

Nevertheless, VS and MCS cannot be considered as static conditions because 57.68% of our patients exhibited a change of DRS scores in the second evaluation without necessarily reflecting a diagnosis shift. These changes in functional outcomes, although small, need to be monitored because they could hypothetically be the first sign of late recovery or a clue indicating the need to consider additional diagnostic analyses or therapeutic interventions (i.e., multisensorial stimulation).

As in this study only sepsis was found to correlate with death, controlling for risk factors thus may be helpful. The literature reported the key role of abnormal albumin,³⁸ hemoglobin³⁹ and the presence of pressure sores¹⁴ in sepsis. The found correlations seem to corroborate the link of albumin and hemoglobin with sepsis and mortality as well.

Contrarily, sepsis and death were positively associated with the number of white blood cells. These data probably reflect the extreme effort of the immune system to fight infection.

In regard to pressure sores, most remained stable over time; the improvement of pressure sores was found to correlate with LOS. This finding may indicate that:

- (1) Improvement of pressure sores may be linked to an increase of life expectancy.
- (2) Their management may require time because of challenging nutritional status.

A similar relationship was found between albumin and LOS, confirming the link between low levels of albumin and pressure sores¹³ or, in general, to adverse outcomes.

CONCLUSIONS

This study described the clinical course and complications in a sample of patients in VS and MCS in the late phase of long-term rehabilitation, which generally receives less attention in the literature than acute and postacute phases, even though the life expectancy of these patients is ever-increasing.

Our preliminary results highlighted the importance of monitoring clinical trends, preventing complications and improving outcomes in these patients, who are far from being in a static condition from both medical and functional point of view. To this end, a complete periodic medical examination and assessment of blood biomarkers in patients in advanced stages of DOCs was suggested.

A number of limitations need to be mentioned. First, the high variability of LOS of patients and missing data did not allow performing an analysis over time with an adequate number of subjects. Moreover, the 10-year timespan fatally introduced nonhomogeneous elements in terms of modifications in techniques and protocols, as well as experience and growing sensitivity to quality of life of both patients and caregivers.

Second, our correlation analyses were exploratory. Further studies are needed to test focused hypotheses. Third, because the Italian validation⁴⁰ of the Coma Recovery Scale became available only in 2011, few data could be gathered to include in the analyses.

ACKNOWLEDGMENTS

Authors would like to thank Dr. Stephen Williams (Santa Viola Hospital, Bologna, Italy) for providing English revisions and helpful comments.

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Submitted September 21, 2015; accepted January 19, 2016.

The authors have no financial or other conflicts of interest to disclose.

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