

Original article

Post-discharge plight of patients with chronic disorders of consciousness: A systematic review of socioeconomic and health aspects

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Abstract: *Objective* — the presented study aims to systematize and structure significant information regarding the problems of patients with disorders of consciousness (DOC) and their families after discharge from the hospital, and to search for possible solutions.

Material and Methods — to identify eligible studies, we searched the Medline database (via PubMed) for studies on socioeconomic and medical issues of patients with chronic DOC at the post-hospital stage of rehabilitation for the last 20 years.

Results — we included 28 studies with 21 cohorts of patients from 7 different countries in our study. The components of informal caregiver burden and their impact on the quality of life were identified and systematized. These components include high physical load, high economic costs, vast time expenditures, strong emotional involvement, and a top level of expertise in caregiving, all of which are required from the relatives.

Conclusion — It was affirmed, that the lack of healthcare system support was a major contributing factor to the overall burden. Our research also showed that delivering care without receiving information, advice, and training is extremely painful for family caregivers.

Keywords: Disorders of consciousness (DOC), vegetative state, minimally conscious state, healthcare, ambulatory care, social problems, psychological support, medical aspects, economics, caregiver burden.

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Introduction

Epidemiological transition observed in Western countries leads to an increase in the number of patients surviving a severe acquired brain injury, caused by traumatic events, vascular lesions, global ischemia, etc. In the first days after the event, severe brain injury usually causes coma, which is a transient state, resolved in 12-14 % of cases [1] by chronic disorders of consciousness (DOC). Chronic DOC patients are characterized by the presence of arousal in line with a total or near-total absence of awareness, also known as the content of consciousness. Awareness normally manifests itself in intentional behavior, the lack of which is currently interpreted as a sign of nonperception of oneself and surroundings. Chronic DOC encompasses such conditions as vegetative state [2] or, in updated terminology, unresponsive wakefulness syndrome [3], and minimally conscious state.

Along with the absence of intentional behavior, patients with vegetative state (VS) do not exhibit any indications of purposeful response to external stimuli, speech understanding, and maintenance of attention during irregular alternating states of sleep and wakefulness [4]. They do not control functions of the pelvic organs and have partially or completely intact brainstem and spinal reflexes. A minimally conscious state (MCS) is a clinical state, accompanied by severe impairment of consciousness, in

which, nevertheless, there are distinct, albeit minimal and often unstable, signs of intentional behavior [5]. Patients in MCS can fix their gaze on a significant object and exhibit emotional responses, such as smiling or crying to stimuli that are meaningful to them in case of MCS – form, or even follow basic instructions and produce a simple answers, like yes/no with gestures in MCS+ form.

Prevalence of chronic DOC worldwide is about 0.5-5 cases per 100,000 of the population [6]; and the number of new cases constitutes 2.5 per 100,000 of the population per year [7]. In Germany, according to the data of Pichler and Fazekas [8], 1,500-5,000 people permanently live in a vegetative state; in Australia, their prevalence is 3.36 per 100,000 of the population; in the Netherlands, their occurrence is 0.2 per 100,000 people [9]. At the end of the 20th century, it constituted 1.9 cases per 100,000 residents in Japan [10] and 4-10 cases per 100,000 people in the USA [1]. For some countries, no statistical data of the kind is available. The difference between these figures may be due to different inclusion criteria, the poor methodological quality of some studies, and end-of-life problems in countries where they occur.

One can consider these numbers low enough to not raise a serious question about this category of patients before the healthcare system, still some considerations must be taken into

account. First, the state of chronic DOC, no matter how hard it is, can be medically stable. Their life expectancy was estimated at 2–5 years [11], albeit 10 years and even decades of life in this condition were observed [12, 13]. Second, extensive care they need after their discharge, its repeatability and time-consuming nature, the severity of procedures, and the overall duration of care virtually cut off the caregiver of such patient from all forms of public life. Since a primary caregiver (a primary caregiver is defined as an individual who spends most of the time with the patient, and the secondary caregiver is the one, who provides additional support or instrumental tasks (e.g., using the telephone, shopping, and taking medications) and emotional support [14]) of DOC patient is in most cases a family member or informal caregiver (ICG) (The term ‘family caregiver’ was defined as unpaid family member who takes care of a sick individual and is involved in an extended role of caregiving related to managing the patient’s physical and medical needs [15]), we have, so to speak, ‘multiple victims’ of one event and should, accordingly, multiply economic and social losses by 2 or even 3, because a secondary caregiver often endures the same devastating problems, as a primary one [16]. In some studies, a caregiver is even considered another patient [17].

Furthermore, even in developed countries, where long-term care institutions and formal caregivers are available, the entire healthcare system often relies on ICGs as an important mechanism of care for such patients [18]. It is not surprising: knowing the number of miscellaneous skills and expertise they acquire in the process of caring, experienced ICGs can be virtually considered professionals. Their financial contribution to post-discharge recuperation of patient is important. But in this case, it seems appropriate for the healthcare system to display deep concern about their condition and needs. Furthermore, special measures are direly required to effectively arrange post-discharge care for DOC patients and some possible reimbursement to their families.

It is worth noting, that DOC patient itself is unique, being fundamentally different from any other chronic patient due to the absence of consciousness. Decorticated, the patient lives a life as harshly disturbed in its course as it is only possible to imagine. This difference makes doctors and caring personnel perceive VS patients as ‘another form of life.’ Similarly, the experience of caregivers is exceptional and therefore deserves thorough investigation.

In the light of the aforementioned rationale, our study aims to systematize and structure significant information about the problems of DOC patients and their families in the post-acute stage after their discharge from the hospital, to search for possible solutions, or at least to prepare the ground for the effective and fruitful decisions. As a method to achieve the goal, the systematic review was chosen to impartially evaluate the situation worldwide based on the highest quality research. Key questions to address were as follows:

1. What discharge policy and treatment planning are typically applied to DOC patients?
2. What healthcare facilities are available for DOC patients?
3. How huge is the burden of caregiving for the relatives of DOC patients?
4. What constitutes this burden?
5. What consequences does it have for caregivers?
6. What influences the caregiver burden and how?

7. What measures could be introduced to help resolving the situation?

We consider answers to these questions seven clues to the post-discharge dilemma of DOC patients.

Material and Methods

Search strategy

To identify eligible studies, we searched the Medline database (through PubMed) for studies on socioeconomic and medical issues of patients with chronic DOC at the post-hospital stage of rehabilitation for the last 20 years. Search query included the following keywords: (‘Disorders of Consciousness’ OR ‘Vegetative State’) AND (‘Ambulatory Care’ OR ‘Nursing’ OR ‘Relatives’ OR ‘Caregiver Burden’).

Inclusion/exclusion criteria

We included full-text original studies with over 10 participants (DOC patients or their caregivers) with straightforward and reasonable methodology, written in English. Such small eligible sample size criterion (>10) is explained by the relative scarcity of such patients and, in general, by a small number of those included in the studies. We did not extract reviews and systematic reviews, letters, editorials, abstracts in the proceedings of conferences. Articles written in the form of conversation or contemplation without clear research methodology, articles in other languages, and with fewer than 10 participants were excluded as well. Also, we did not include materials regarding philosophical questions, euthanasia, and treatment/feeding withdrawal, because of grave discrepancies regarding this issue worldwide. Another restriction was imposed by the post-discharge stage of caring: we did not include research on caregivers during the hospital stay of their DOC relative, no matter how interesting and important it could be, we rather focused on what happens to them after discharge.

Data extraction

For organizing the study, we employed Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Available at www.covidence.org.

Two authors (YN and SR) independently searched the database and checked titles and abstracts of retrieved publications. Presumably relevant articles were included in our selection of full-text reading. Whenever disagreement arose, we resolved it with the help of the third author (MK). If it could not be resolved, we were switching to group discussions. In highly relevant articles, we carefully read all citations to detect other studies on the topic. We also took advices of our colleagues on finding important studies in the field under our consideration.

Full texts of all potentially eligible studies were retrieved. A sample of full-text studies was independently screened by three authors (YN, IB, and SR) until concordance was achieved. After full-text reading, inclusion and exclusion criteria were applied, and eligible articles were subsequently included in our research.

Two review authors (PP and YN) extracted data from eligible studies. Extracted data were compared, with any discrepancies being resolved through discussion. Study characteristics (first author, year of publication, country, number of patients), main findings, and relevant limitations were extracted from all included articles. All proceedings were checked by MP.

Results

Study selection and characteristics

A total of 243 results were identified through the database search. We manually removed 3 duplicates. After checking the author, title, and abstract, 202 documents were excluded. We carefully reviewed the remaining articles in terms of inclusion and exclusion criteria, and established that 10 of them had no full text available, 3 had a small number of participants, 3 were written in ineligible languages (German, Italian and Japanese), 3 did not present any methods and were considered speculative, 2 articles were reviews, and 1 explored a different category of patients. We included 12 additional studies after careful consideration of reference lists of the most important publications. As a result, a total of 28 studies were identified as relevant. PRISMA selection flow diagram is presented in *Figure 1*.

The main characteristics of selected studies are shown in *Appendix 1*. We identified studies from 7 different countries: Italy (n=16), Iran (n=6), the USA (n=1), Israel (n=1), Spain (n=1), Japan (n=1), and Canada (1 own study and 1 joint study with Italian researchers). Selected literature sources were published between 2001 and 2021. Overall, selected for our review studies encompassed 135,181 participants.

We distinguished 21 different cohorts. Three cohorts had their data reported in more than one article (Leonardi et al. 2012, Pagani et al. 2013, Giovannetti et al. 2013 and Covelli et al. 2016; Goudarzi et al. 2015, Goudarzi et al. 2018 and Goudarzi et al. 2020; Imanigohary et al. 2016 and Noohi et al. 2016).

Discharge policy, treatment planning, and healthcare facilities for DOC patients

As results of our study demonstrated, post-discharge ways for DOC patients are diverse and depend mostly on the existing healthcare system facilities; yet discharge policy, personal preferences of caregivers, their religious views and some medical and psychological contributions have an impact on the decision-making process.

In developed countries, DOC patients are usually cared for by formal caregivers with family members cooperating in providing care [19]. Though, even in these countries, some caregivers prefer to take their loved ones home, claiming that it can be better, both for the patient and the family [20]. The hospital is often considered a place that attends and gives protection and assistance to patients, but at the same time do not give patient individual care and dignity that family caregivers believe to be the only ones who can provide [21]. Some caregivers reported a lack of trust in medical personnel and a wish to supervise their work [20].

The reasons behind the choice of home care can also lie in the field of flaw or simply missing discharge policy for DOC patients in many institutions. Discharge can often be precipitous and without warning, leaving relatives scrambling in ignorance and hurrying decide about where their loved ones will be placed [22].

Furthermore, the very selection of possible facilities is limited for DOC patients. They are usually seen as patients with very low rehabilitation potential and rehabilitative institutions often deny their admission, because attempts at restoring consciousness and intensive rehabilitation programs seem inexpedient. E.g., as the Dutch study implies, more than 50% of patients in a VS/UWS (unresponsive wakefulness syndrome) did not receive rehabilitation [23]. Rehabilitation potential is assessed mostly by the degree of recovery, which is estimated by the presence of intentional behavior. But since neither timing is defined for recovery from DOC, nor intentional behavior has proven itself an absolute measure of consciousness, this issue involuntary becomes a subject for abuse, errors, and excesses. Thus, those patients who have not made a requisite amount of overt progress in the time frames, defined by hospital admission policy, will be sent to a chronic care facility with uncertain, if any, rehabilitative services. If, of course, they are not proposed to become organ donors in the first place [22]. Caregivers expectedly resent this situation and arrange a home rehabilitation environment, richer in stimulation and personalized attention. This especially happens in the case of children [24]. The overall number of caregivers from developed countries, who prefer familial care, is not presented in the studies under consideration and needs to be elaborated upon.

In developing countries, the situation is even worse. Rehabilitation institutions, such as specialized nursing facilities can either be missing or short-term and low-quality; hence, home care is often the only feasible option for families with DOC patients. Moreover, physician and even nursing support at home can be too expensive and, consequently, unavailable [25]. Often, there is no insurance support for caregiving activities at home, and caregiving services are provided by the private sector only [26]. This leaves a relative all alone with huge amount of care required for the patient special skills and knowledge to provide it. In the absence of elaborate and universally accepted discharge recommendations, it is left upon the hospital to procure information and competencies for relatives: some do, but some do not [22].

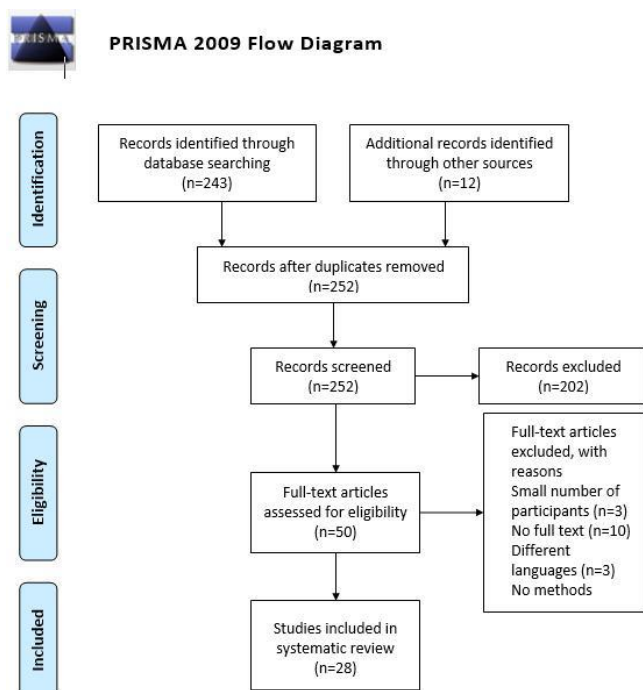


Figure 1. PRISMA selection flow chart. From: Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6(7): e1000097. <https://doi.org/10.1371/journal.pmed.1000097>. For more information: www.prisma-statement.org.

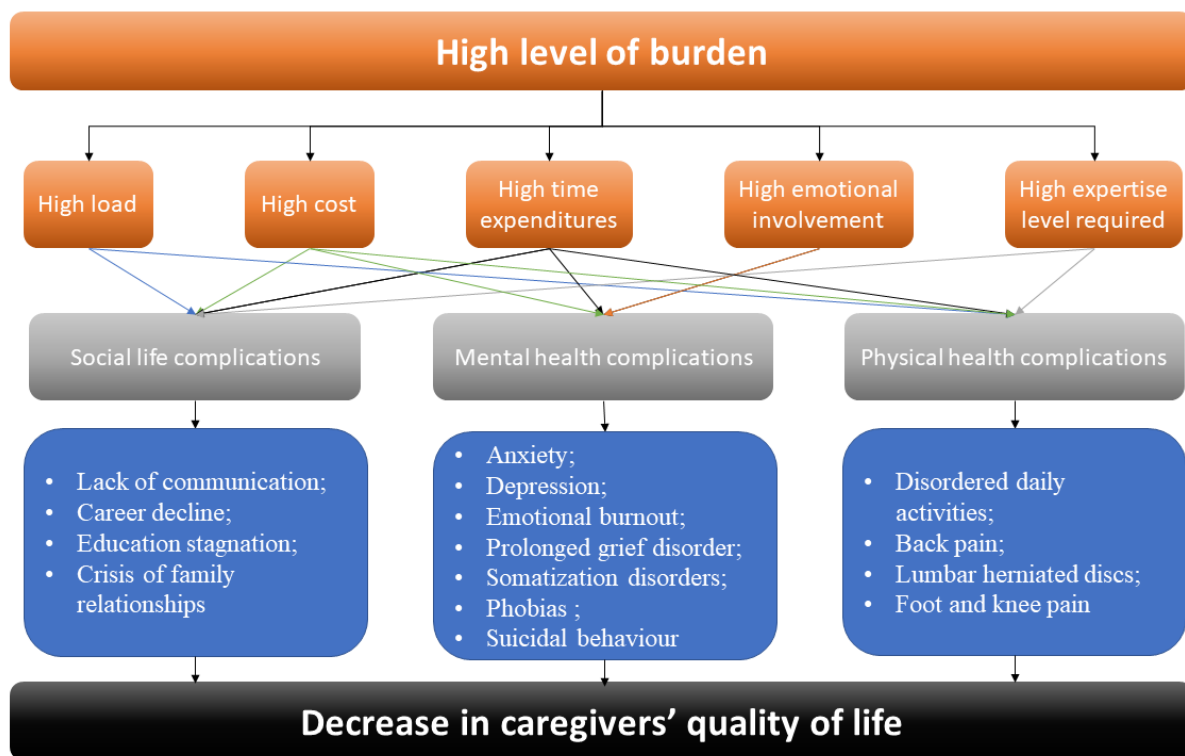


Figure 2. Structure of caregiver burden for informal caregivers of DOC patients.

Caregiver burden and its components

In order to gain a deeper understanding of the problems that relatives of DOC patients usually face, we attempted to systematize all components of the caregiver burden, link them with each other and review their consequences (Figure 2).

High load. Patients with DOC are known to be unable and dependent, and in need of comprehensive continuous care [16]. It is difficult to manage the patients in any generic residential structures because they require constant, and what is even more challenging, special medical and nursing care even when their medical condition has stabilized: almost all of them have a tracheal cannula and a pump for parenteral nutrition and need programmed mobilization every 2 h [27].

But above all, they are prone to different health complications, comorbidity, and loss of a stable condition. When they are discharged from acute care and are called 'chronic', technically, they are halfway between acute and chronic phases [22], and there is no way to know where they will be found the next morning. To prevent complications, ICGs are involved in miscellaneous activities. The Royal College of Physicians Guidance on DOC describes several fundamental steps that should be implemented:

1. adequate nutrition (usually via a percutaneous endoscopic gastrostomy tube);
2. good skin care;
3. suction to avoid inhalation pneumonia associated with nasogastric tube feeding, tracheostomy decannulation management;
4. supervision of bladder and bowel incontinence;
5. care for dental and oral hygiene [28].

Add to this some medical routines, such as pain assessment and treatment, caring for intravenous line, management of drug and fluid therapy, management of complications like intracranial pressure and aspirations, jeopardized mobility, joint contractures, spasticity, wound dressing, evaluation of vital signs and even obtaining medical specimens conducted by family caregivers [16], and one will have a number of activities enough for a small department. A high level of burden was reported by all studies, included in the review.

Care coordination, which in some cases is provided by a paid employee, also substitutes a part of the caregiver's load. An interesting example of a caregiver, who calculated how his everyday work as a coordinator would be remunerated if done by a professional was reported by Gonzalez-Lara et al. [29].

He estimated his load as a job with an annual salary of \$ 60,000.

High cost. The need for a variety of consumable and non-consumable supplies including a functional bed, anti-decubitus mattress, suction machine, oxygen capsules, etc., all types of Nelaton catheters, foley, and stomach catheters, sterile gas, serum, medications, band-aids, nappies, and extensive hygiene needs were among the causes of expensive care of vegetative patients [25]. In addition, these patients need various nutrition which costs a lot. Authors themselves faced a situation when relatives of DOC patients refused to use specialized nutrition due to its high cost and switched to homemade food, which led to quite understandable somatic deterioration due to malnutrition.

Performing care procedures by professional caregivers who came home from private centers (doctor's visits, nursing, occupational and physical therapists) imposed even additional costs on caregivers from countries, where insurance does not cover family care [25]. Moreover, being forced to leave work for at

least several hours a day to take care of the VS patient or totally losing one's main source of income, impose a big financial load on the caregiver [30]. 'Family economic collapse' was the outcome of this condition [25].

Participants of a national major study held in Italy between June 2009 and March 2010 complained of financial difficulties, declaring only a sufficient income, and resigned from their job temporarily or permanently due to patient health conditions [12], [31]. In the process of caring for children with DOC, 60% of caregivers declared financial difficulties [32]. In the study by Covelli et al. [33], caregivers also acknowledged that the costs of the needed care for their patients worsened their economic conditions. Yet, Bastianelli et al. [21] noted that the increased financial worries of caregivers might also be due to Italy's economic crisis at the time of the study, also involving the national healthcare system.

In recent studies, the exact amounts of money spent on DOC patients are rarely indicated. Goudarzi et al. [25] provided evidence of a caregiver, who declined \$25 aid from a welfare agency per month since having a DOC patient at home in Iran costs more than this sum per week. In the last decade of the XX century in the USA, caring for a VS child at home cost \$129,000±51,000 per first year after the event that caused DOC. Second-year costs decreased by an average of \$ 32,000 per patient [24]. By adjusting for inflation, it can be calculated that today this amount would be approximately \$ 236,794. Covelli et al. [33] reported a sum of €1,000 spent per month per patient. In line with this, 40.2% of caregivers reported earning a net income of fewer than 17,000 euros per year [12].

High time expenditures. The caring process for a fully dependent DOC patient consists not only of harsh activities but also frequent and repetitive [16], so that home care can take up to 20 hours a day of the caregiver's time [26]. Hence, caregivers had to reduce or interrupt their work for daily relative's assistance [33], and it had a negative impact on their income. The situation of caregivers of patients that reside in long-term care institutions is somewhat better. Nevertheless, many of them spend from 3 to 6 hours per day with the patient [12].

Reference [31] considered daily hours of caregiving the only significant factor associated with the overall level of burden perceived by caregivers. In this research, daily hours of caregiving were a significant predictor of the Family Strain Questionnaire (FSQ) total score, where those who dedicated more than three hours per day to providing informal care reported lower scores, and those who dedicated less than three hours reported higher scores.

It should be noted that a feature of care for DOC patients is not just a large amount of required time, but also its almost uniform distribution of it around the clock: nighttime care, such as changing position every two hours [16], is just as necessary for these patients as daytime care. This leads to sleep deprivation and mental health problems for caregivers.

Strong emotional involvement. Caregivers of DOC patients, since the very moment of injury, are involved in intense and often contradictory feelings. They are exposed to conflicting opinions and views related to the prognosis of the disease and the state of consciousness [25]. When the DOC state becomes undoubtedly chronic, they experience the feelings, that [34] defined as an 'emotional paradox'. Their loved one appears in some borderline condition between life and death [35], present, yet absent, alive,

yet dead [30]. They have to cope with the loss of the person as he/she usually was. But the presence of a patient near them prevents the relatives from mourning and elaborating on the loss.

To address the phenomenon of emotional paradox, the concept of ambiguous loss has been introduced. It is a newly identified type of loss that occurs when a loved one is physically present but psychologically absent. Because the lost person is here, but not here, grief is frozen, life is put on hold, and people are traumatized. This experience is so prominent and specific that the very caregiving for DOC patients can be described as the process of facing an ambiguous loss. It has to be carefully studied because features of ambiguous loss could guide clinicians' interventions to support the adjustment of caregivers of patients with DOC [36].

At the same time, there is a feeling of impending 'final' loss of a loved one. Similar phenomena are also observed in dementia, which allows transferring some of the developments obtained in the study of patients with dementia to patients with DOC. Thus a concept of anticipatory grief, studied by Rando [37], can be used to understand the emotional predicament of DOC patient's caregivers. Being already in prolonged grief and anticipating a bigger one is something that requires attention and help from medical psychologists.

The caregiver's own role is also contradictory and complicated. Many caregivers perceive their DOC patients not as husbands or parents, but mostly as their helpless children [16], [36], [22]. So, their contradictory roles exist simultaneously, such as being a partner and a child.

Several caregivers described their relative as being the same but at the same time a different person [36]. The conflict between the representation of the person as familiar and the impossibility of recognizing him/her as he/she generates, sensu Freud, a 'familiar estrangement' [38].

Complex and multifaceted emotions are often experienced about the outcome of injury in DOC patients. Some caregivers said that it would have been better if the patient had not been resuscitated at the time of the accident. Those who had been in this situation for 1 or 2 years believed that if the patients died it would be painful, but it would end their suffering. Only a few caregivers believed themselves fortunate to have the patient still with them [20].

It often happens that caring for a DOC patient changes the caregiver's world outlook: they report changes in perceptions of their life and the value of human life, gaining respect for every form of life [33]. Also, the perception of time is frequently transformed. Caregivers' life is focused on the present and the future scares them [25]. They mostly live in the present but long for the past, their future is unthinkable except for very practical issues. This difficulty can be defined as a 'time gap experience' [33]. All the above mentioned circumstances lead to consideration of the emotional experience of caregivers as a deeply personal phenomenon.

High expertise requirement. It was stated that patients with DOC are in continuous need of extensive and comprehensive care, including maintaining correct oxygenation and body fluid balance, parenteral and enteral feedings, modifying bolus consistencies, skin and corneal care, preventing tracheostomy complications, urinary and fecal elimination, and providing sensory stimulations [25], [38]. One also needs to know how to deal with septic shock, impaired cardiopulmonary status, articular alterations, and

spasticity. The above mentioned services undoubtedly require professional knowledge and skills and, if done in an unprofessional manner, can endanger DOC patients, provoke perilous complications or, in some cases, lead to refusing to take patients home from the hospital [9].

Meanwhile, an improvement in consciousness level, assessed by Kohnan Score, was observed in DOC patients with professional nursing care [39]. Thus, the quality of patient care can be considered a significant factor in the possible recovery and prevention of complications, which puts the issue of providing caregivers with all the necessary skills and knowledge at one of the first places in the organization of post-discharge care.

Caregivers per se often report problems with medical skills and take measures to find the necessary information and learn it [9]. Furthermore, expertise in neurology and nursing DOC is also necessary for making certain decisions and understanding the patient's condition and doctor's recommendations. Thus, in Italian observational multicenter cross-sectional study [12] over 75% of participants reported six perceived needs belonging to the factor of information and communication:

1. Need to be informed by physicians and health professionals about what is done to The Relative (93%);
2. Need to cooperate and be involved in decisions or choices (90.2%);
3. Need to communicate satisfactorily with all the professionals of the medical treatment team (88.3%),
4. Need to be able to easily contact the staff of the care team of their relative (87.3%),
5. Need to know what problems may arise in the course of the disease (85.6%);
6. Need to be enabled to perform all tasks related to the care of their relative (83.2%).

Some ICGs point out the need for knowledge about the psychology of caregiving, relatives' conditions, and problems regarding social involvement [12]. Some caregivers stated that their fears and anxieties decreased as a result of receiving training [9].

Consequences of caring for DOC patient

The clinical experience and scientific literature highlighted a deterioration in the perceived quality of life of different categories of chronic patients, which can be defined as a multidimensional construct comprising three domains: physical, psychological, and social functioning [40]. We decided to use this scheme as the basis for the analysis of the consequences of the burden of care concerning DOC patients (*Figure 2*).

Indeed, our research demonstrated that studies on ICGs of patients with DOC showed the impact of caregiving in terms of distress [32]. The high burden of caregiving, both physical and psychological, leads to a decrease in the caregiver's quality of life. This decrease is expressed by physical and mental health complications and deleterious changes in lifestyle that complete this vicious circle and trap the caregiver inside of it.

Physical health complications. Primary caregivers of DOC patients often describe their disordered daily activities, such as sleep, nutrition, hygiene, sexual intercourse, and in general paying attention to their health [16]. This leads to health deterioration by itself, and if we add to this the specific features of caring for a

seriously ill patient, such as transportation, washing, turning over, and other actions associated with the effect of the patient's weight on the caregiver, then it becomes clear why physical damages such as back pain and lumbar herniated discs, as well as foot and knee pain, are the most common problems that the main family caregivers experience [25].

Mental health complications. Mental health complications of caregivers of DOC patients are vast and varied. Among reported disorders are anxiety, depression, emotional burnout [31], prolonged grief disorder (PGD) [41], somatization disorders, and phobias [42]. Mild depressive symptoms were reported by more than 60% of caregivers of whom more than 30% were allocated in the severe range [31].

PGD is usually less common than a depression state, though in the Spanish cohort, the frequency of PGD was 60.40% [43]. However, it is likely that PGD warrants attention because it can become chronic and disabling and lead caregivers to substantial psychiatric morbidity such as, for example, suicidal behavior [41]. The term *PGD* was introduced by Prigerson et al. [44] as a distinct mental disorder that is different from symptoms of depression. People with PGD feel that their lives lack meaning without the deceased and are stuck in a state of persistent mourning, thereby feeling stunned, unfulfilled, and empty. For DOC patients, according to [41], three conditions of psychiatric illness emerge: PGD only, depression only, and PGD jointly with depression. Herewith, caregivers showing both conditions together were more likely to have the patient's DOC caused by a traumatic event, had less time since the event, and cared for younger patients.

It is worth noting, that that the level of mental health complications can have some gender differences. High levels of anxiety symptoms were associated with negative mental health outcomes in both genders, whereas depressive symptoms were found to impact females' mental and physical health only. Overall, men reported higher levels of mental health state, than women [45].

Social life complications. Daily engagement with caregiving procedures requiring the full commitment of time and effort precludes recreational activities, leads to education stagnation, career decline, lack of communication, and finally social isolation of caregiver [31], [25] so that caregivers' everyday lives are characterized by limited social relationships, and indoor and outdoor interests [27]. The latter is known to further endanger an individual's health [41], [32], [16] and also refers to social isolation as an intensifying factor for the emotional problems of ICGs.

Hostility and anger towards healthcare professionals [21], [12], fear of judgment, and misunderstanding from other relatives, friends, and members of the significant community [25] contribute to increasing the feeling of social isolation

In addition to physical isolation from society, so to say, 'domestic imprisonment', caregivers often experience internal isolation, imprisonment to own thoughts and complex psychological feelings, not being able to relax and enjoy anything, and continuously thinking about their relative [36].

Social problems in caregivers of DOC patients are often aggravated by apparently unsatisfactory domestic and family relationships. During the first period after the emergence of DOC, family ties loosened because everyone suffered and reacted in a personal way, independently from other family members. In some families, this distance and silence went on for years and became the prevalent relationship model [20]. However, a recent study

[46] showed good levels of cohesion and flexibility in families who already spent a long time with patients. The families included in the study were able to adapt to new events by balancing extreme behaviors and showed independence and connection between family members. Moreover, the caregiver burden negatively correlated with rigidity and disengagement in families.

Factors affecting caregiver burden

To answer the question, 'What influences caregiver burden and how?', we identified the following factors: duration of care, level of consciousness, and the facility of the patient (any kind of institution or home).

Duration of care seems to affect both the mental and physical state of caregivers: individuals who were caregivers for <2.3 years reported better physical health, but worse mental health with higher levels of state of anxiety [32]. The mental state roughly affected by the onset of DOC and often expressed in severe anxiety and mental distress tends to stabilize or even slightly improve over time when individuals gradually accept the situation by establishing new homeostasis and managing family roles and relationships [46], [32]. Similarly, in the study conducted by Covelli et al. [47], caregivers' mental health improved, whereas the emotional burden and the presence of depressive symptoms as well as the need for information about the disease, thoughts of death, and the use of avoiding coping strategy decreased with time.

Anxiety also tends to reduce with time and is significantly lower in the group of caregivers with more time from the acute event, in comparison with those who become caregivers more recently [36]. It is also reported, that caregivers of long-term patients expressed more need for social involvement [31]. PGD is shown to remain stable over time because caregivers continue to feel imprisoned by memories and regrets as they felt when the VS of their loved one began [21].

Overall assessment of the quality of life (QOL) using pre- and then-evaluation with Caregiver QOL Questionnaire showed that generally the effective QOL worse over time [21]. As the authors suppose, this observation is probably due to an uncertain condition experienced by VS caregivers that do not allow them to react to their living conditions, thus blocking possible changes in the psychological state and thus preventing mental health from improving. In the study [48], caregiver burden was not associated with the duration of caregiving at all. The discrepancy in conclusions could be attributed to different methodologies and cross-sectional designs of all the studies, included our research, and consequently, conclusions about possible temporal changes should be made with caution in anticipation of a full-scale longitudinal study that would shed light on this issue.

According to the level of consciousness, caregivers of VS and MCS patients reported similar levels of burden, including the severity of depressive symptoms. Although compared to caregivers of patients in MCS, caregivers of VS patients scored significantly higher on the Thoughts about Death scale of FSQ [31]. They also were likely to use avoidance as a coping strategy and display a marked sense of loss, whereas relatives of patients in MCS were mostly focused on problems with emotional and social support [31]. Stress reaction was different between two groups of caregivers (VS and MCS), and it may vary according to the used coping strategies [42]. Further studies on the topic are needed, especially in the field of finding the difference between

communicating and non-communicating groups of patients, i.e., between VS and MCS+ form, since the perceived difference between them lies in the very ability to communicate.

Primary caregivers are known to experience the most physical and mental pressures compared to others [16]. No significant differences in family strain patterns, coping orientations, caregiver needs, level of depression and anxiety were found between caregivers of patients hosted in long-term care facilities, where the relative was not the main caregiver, and at home, except for FSQ Problems on Social Involvement scale [31].

Discussion

The last but not least question we have to address is what can be done, to help caregivers dealing with their complex and intense role, that leads to physical, emotional, social, and economic burdens. It is already known, that the lack of healthcare system support was a major contributing factor to the overall burden and QOL decrease [29]. Thus, the very simple measure would be elaborating on discharge strategies for DOC patients, which would give relatives enough time and information to make a conscious and reasonable decision. Schools for relatives, that give future caregivers at least the minimum skills and knowledge required can be considered a commendable practice. Post-discharge support of caregivers, arranged by hospitals, is also urgently needed today until special measures are introduced, because it is nowadays undoubtedly, that delivering care, without receiving information, advice, and education is extremely painful for family caregivers [30].

Additionally, the entire system of long-term facilities for DOC patients requires reconsideration according to the singularity of DOC. DOC patients, regardless of whether they have a traumatic, anoxic, or vascular injury, are refugees between acute and chronic care, awaiting rehabilitation but still not healthy enough for that critical next step [49].

We should redraw the trajectory between active rehabilitation and palliative care to satisfy the special needs of DOC patients, adjust rehabilitation to their demands and abilities, and allow them receiving the elements of care they need irrespective of the facility. Regardless of medical expediency, however much it may define, we must remember that receiving appropriate care lies in a civil right domain.

We also cannot let ourselves forget that in defining the vector of long-term care for brain-injured patients, we are guided by incomplete forms of evidence. We have to admit that at the current stage of our scientific understanding of DOC, the more we know about them, the less hope, it seems, we leave to help these patients. Any specialist who works with this category of patients has encountered several exceptional cases, covert consciousness and cognitive and motor dissociations, neuroimaging findings that were not consonant with behavioral manifestations of progress, unpredicted time frames of recovery, and, finally, diagnostic mistakes. We are obliged to have all possibilities ready for the future expanse of our understanding of the injured brain physiology.

In this regard, we consider perspective a project of mosaic care, partly presented in Mohonk Report to the U.S. Congress, which sought to outline a seamless pathway from acute care through rehabilitation and aftercare [49]. Our version of the project involves the creation of network of facilities arranged in four tiers: homecare facilities and social services; skilled nursing

facilities (SNFs), where most patients reside; expert acute rehabilitation facilities; and research centers of excellence, around which the first three are clustered, according to territorial division. We would also add to Mohonk project special emergency teams that would be trained to provide acute medical aid to this specific category of patients, mobile rehabilitation teams hosted at research centers, psychological, telerehabilitation, and statistical departments, that would interact with home-cared patients, and special training facilities (Figure 3).

Currently, in some countries, we have every, or almost every, part of this system and only have to arrange appropriate interactions between them, but in some countries even SNFs are unavailable. An interesting decision, that can be very handy in this situation was introduced by Zylberman et al. [50]. It is an innovative model of in-house assistance, named Casa Iride, which was recently implemented in an attempt to ensure health, safety, and well-being for people with DOC and their families. The model of Casa Iride assumed the development of nonmedicalized cohousing community, which allows severely disabled people living with dignity within domestic environment. In Casa Iride, DOC patients and their families have their own living space, but share common areas, and benefit from general support services including nursing assistance, physical therapy, and periodic visits of general practitioners and specialists. ICGs can communicate with other people with similar challenges, become more aware of their situation, learn to cope with it, and maintain their productivity at work. Economic advantage is defined by the reduction in a hospital stay, which is often prolonged due to discharge difficulties and optimization of resources in the case of group home care. The ability of ICG to perform an active job could

also lower the indirect costs of caregiving. With lack of resources, duration of living in a cohousing community can be limited. Authors propose that this model is especially fit for families with underage DOC patients.

It is to be remembered, though, that to perform the above-mentioned redesigning of the healthcare system, some preliminary actions need to be taken. For example, the lack of centralized statistics for these patients prevents economic calculations of expenses and the lack of separate classification for DOC in the 10th revision of International Statistical Classification of Diseases and Related Health Problems (ICD) and International Classification of Functioning, Disability, and Health (ICF), in turn, prevents the emergence of statistics.

Possible measures are summarized in Figure 4.

In Step 1, we propose an allocation of DOC patients into a separate group (category) and statistical registration of them and their families. Step 3 involves amelioration of discharge policy, providing relatives with a real choice between affordable care facilities and decent maintenance of their loved one at home. Steps 2 and 4 can include appropriate insurance coverage, psychological support interventions in the forms of traditional counseling or telemedicine consultations, providing the required number of specialists educated in DOC, and creating recommendations on caregiving (checklists for relatives and nurses, instructions, websites, etc.), schools for relatives and, possibly, cohousing communities like Casa Iride, national and international programs for caregiver's support and other activities the need for which will be defined on site.

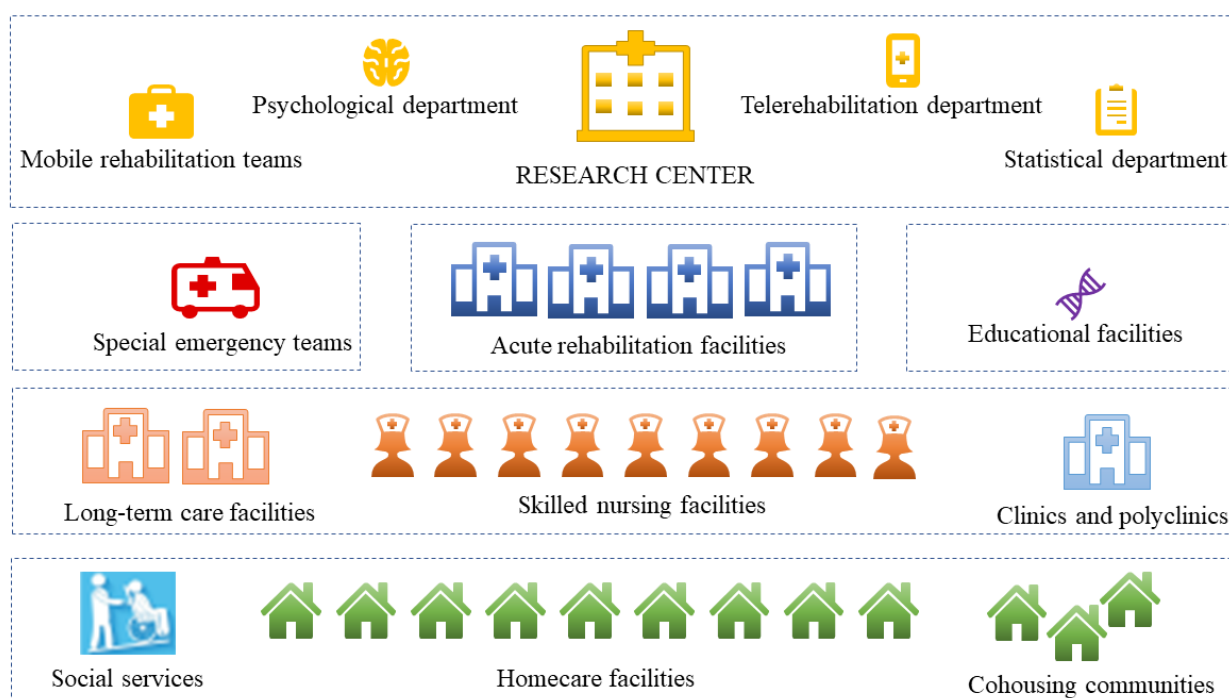


Figure 3. Proposed structure of long-term care facilities for DOC patients.

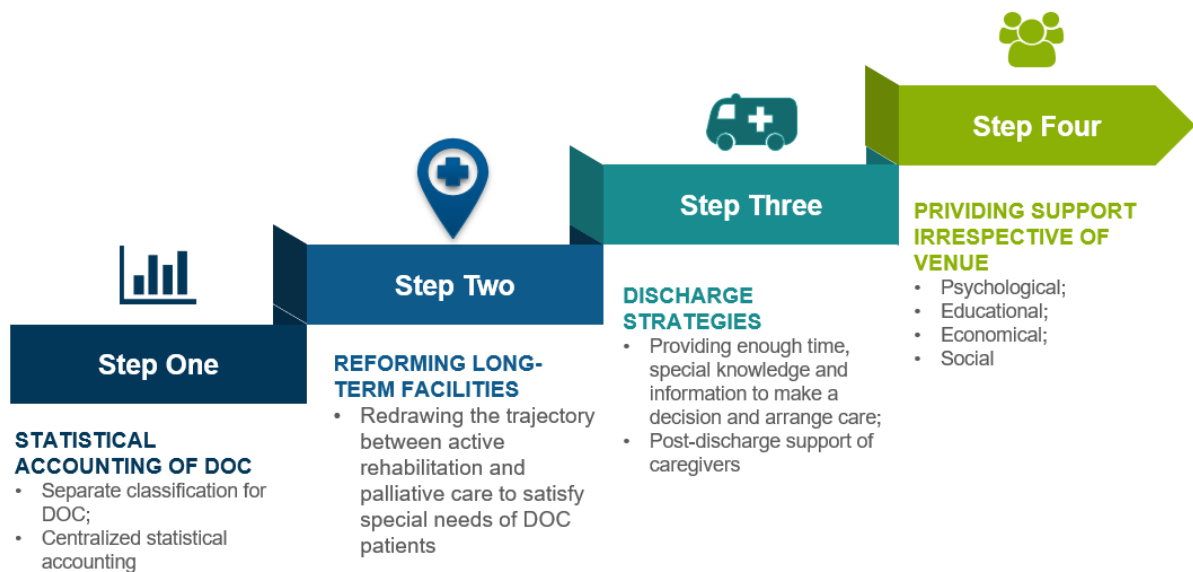


Figure 4. Summary of possible measures needed for long-term care for DOC patients.

Finally, the authors would cautiously suggest that the attention of the World Health Organization (WHO) to this problem, a worldwide analysis of the number and plight of DOC patients and their relatives, consolidated recommendations on caregiving, emerging of national and international ICG support programs would immensely help solving this problem in all its aspects.

Whatever it may be, failure to take any action cannot be a possible alternative in the face of an increase in the number of DOC patients in the modern conditions of providing emergency medical care.

Some limitations of the study must be taken into account. First, it was rather narrow coverage in relation to the variety of countries. The problem of DOC remains specific and the patients are still quite rare, so our conclusions can be used to characterize a global trend with some caution. Second, our study inherited the limitations of included sources, such as a small number of participants and mostly cross-sectional design. Future longitudinal studies can be, therefore, considered useful to gain novel insight into this field.

Conclusion

The study aimed to systematically assess the burden and needs of caregivers of patients with chronic DOC at the post-discharge stage. The performed research was based on 28 original articles with 21 cohorts of patients from 7 different countries, and it demonstrated that the burden was high and the needs were immense.

Components of a caregiver burden and their influence on the quality of life were identified and systematized. These components include high physical load, high economic cost, vast time expenditures, tight emotional involvement, and a major level of expertise in care, required from the relative. This overall level of

burden leads to physical, mental, economic, and social complications for ICGs, who are frequently left with them alone.

There are some differences in healthcare systems of different countries, but it must be stated that leaving ICGs without support leads to doubling (or tripling) the casualties of the initial injury, which increases indirect losses and does not allow the healthcare system unflinchingly relying on ICGs when organizing care for DOC patients. Research also showed that delivering care, without receiving information, advice, and education was extremely painful for family caregivers.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Appendix 1. The main characteristics of the articles, included in the study

No.	Study	Country	Methods			Main findings	Limitations
			No. of participants	Data acquisition	Data analysis		
1	Chiambretto et al. 2001 [27]	Italy	Principal caregivers of 20 persistent vegetative state (PVS) patients in long-term care facilities	Cognitive Behavioral Assessment – Primary Scale, Coping Inventory for Stressful Situations, Family Strain Questionnaire (FSQ2)	Frequency distribution, Student's t-test, Pearson's test	<ul style="list-style-type: none"> All caregivers used situation-oriented coping strategies, had unsatisfactory family relationships, and their emotional distress increased with disease duration; The thoughts of the possible death of the patient were associated with anxiety and depressive symptoms; The caregivers' everyday lives were characterized by limited social relationships and indoor and outdoor interests; The study underlines the importance of psychosocially assessing PVS patient caregivers, who are often alone in coping with an irreversible situation; It also introduces a questionnaire (FSQ2) that seems to be sufficient to assess caregiving-related problems. 	Small number of participants, the results may not be representative of the general population.
2	Chiambretto et al. 2010 [41]	Italy	45 caregivers of 41 patients in VS or MCS for long-term inpatient care	Prolonged Grief 12 (PG-12), Depression Questionnaire (DQ)	Contingency coefficient V by Cramer, Fisher's test and Mann-Whitney U test, Kruskal-Wallis test	<ul style="list-style-type: none"> Three conditions of psychiatric illness emerged: Prolonged Grief Disorder only, depression only and Prolonged Grief Disorder combined with depression; The caregiver's syndrome-level grief was associated with patients' young age and with younger age of a caregiver; Caregiver's syndrome-level depression was associated with less time from the event; Caregiver's grief symptoms are distinct from their depressive symptoms among family members and each disorder has distinct risk factors. 	A small sample of MCS subjects in comparison to the VS subjects.
3	Giovannetti et al. 2012 [32]	Italy	35 children with VS and MCS	Disability rating scale (DRS) for children and Coping Orientations to Problem Experiences, Short Form-12, Beck Depression Inventory, Spielberger State-Trait Anxiety Inventory-Y for caregivers	Descriptive statistics, within-subjects t-tests, with application of Bonferroni correction	<ul style="list-style-type: none"> 60% of caregivers declared financial difficulties, 57.2% reported depressive symptoms, poor mental health, and high level of state and trait anxiety; Rehabilitative programs for children with VS and MCS should provide interventions on surrounding systems: improving the network of psychological support and social assistance; It may decrease the burden of caregivers and, in turn, improve caring abilities and children's quality of life (QoL). 	<ul style="list-style-type: none"> Limited sample size, which restricts the possibility to extrapolate the results to the whole population of children and adolescents with VS and MCS; The intrinsic weakness of the cross-sectional study design does not allow assuming a causal relationship between variables.
4	Leonardi et al. 2012 [12]	Italy	487 caregivers	Caregiver Needs Assessment, Family Strain Questionnaire, Short Form 12, Spielberger State-Trait Anxiety Inventory-Y, Beck Depression Inventory, Prolonged Grief Disorder Questionnaire, and Coping Orientations to Problem Experiences	Descriptive statistics, one-sample t-tests	<ul style="list-style-type: none"> Family members play an important role in the caregiving of DOC patients; Caregivers exhibited lower physical and mental health scores vs. the normative Italian sample; Caregivers of patients in VS or MCS can be an important resource for both patients and institutions in which patients are admitted, but they should receive targeted support and should never be left alone; This reported sample needs to know the disease of their beloved, high needs for information and communication, several problems in social involvement, and in emotional burden; The most frequently adopted coping strategies are acceptance, turning to religion, positive reinterpretation, and planning; 40.2% of caregivers report earning a net income of fewer than 17 000 euros per year. 	<ul style="list-style-type: none"> Self-reported information, particularly concerning the evaluation of caregivers' financial condition, is partially based on self-perception and could be unreliable; The cross-sectional study design did not allow unambiguous assumption of a causal relationship.
5	Hamama-Raz et al. 2013 [22]	Israel	12 wives of husbands with PVS	Semi-structured interviews	Content analysis	<ul style="list-style-type: none"> Wives of PVS patients experienced emotional duality (the ongoing process of finding significance in the situation based on acceptance of the husband's condition and focusing on positive emotions and values such as love, commitment, and loyalty and an increase in negative emotions such as 	A small number of participants.

No.	Study	Country	Methods			Main findings	Limitations
			No. of participants	Data acquisition	Data analysis		
						sadness, pain, loneliness, loss, and grief);	
6	Fins 2013 [49]	USA	35	In-depth interviews	Observations on narratives	<ul style="list-style-type: none"> Therapists need to help women maintaining a balance without giving in to negative concepts and emotions and finding unique significance in their tragic situations. Families encounter a disinterested, if not hostile, healthcare system; We should redesign systems of care to achieve a proper mix of acute and rehabilitative services; The argument concludes that when it comes to caring for a disorder related to consciousness, its provision is not discretionary, and its receipt is not an entitlement but a civil right. 	Scholarly observations and policy recommendations on narratives of laypeople (however, bioethics reminds us, that there is an ethical saliency to illness narratives).
7	Giovannetti et al. 2013 [31]	Italy	487 participants	The Family Strain Questionnaire, Copingtest, Orientations to Problem Experiences, Caregiver Needs Assessment, Short Form-12, Beck Depression Inventory, and State-Trait Anxiety Inventory	Kruskal-Wallis UNIANOVA	<ul style="list-style-type: none"> Caregivers of post-acute patients reported low scores in mental health and higher state of anxiety, whereas caregivers of long-term patients expressed more needs for social involvement; Burden and distress were high for all caregivers of VS and MCS patients; As caregiving is a long-term commitment process, support to the caregiver should be guaranteed throughout the duration of the relative's disease despite the patient's diagnosis or the place where the patient is hosted. 	<ul style="list-style-type: none"> Some Italian regions were not included in this survey; The assessment was conducted by professionals with different backgrounds and in different centers all over Italy; Groups were not equally distributed: most of the participants were caregivers of patients in VS, and most of the patients were hosted in long-term care institutions; The intrinsic weakness of the cross-sectional study design does not allow us assuming causal relationships.
8	Elvira de la Morena and Cruzado 2013 [43]	Spain	53 caregivers	PG-12 and Brief COPE-28	Bonferroni-adjusted t-tests, Cohen's d	<ul style="list-style-type: none"> The frequency of PGD was very high (60.40%); Most common coping strategies were problem-focused; Acceptance and problem-focused strategies should be promoted, and Denial and Self-blame should be diminished. 	<ul style="list-style-type: none"> Small sample size Cross-sectional study design
9	Pagani et al. 2014 [45]	Italy	418 caregivers	State-Trait Anxiety Inventory-Y, Beck Depression Inventory, Short Form-12	Hierarchical multiple regression analyses	<ul style="list-style-type: none"> Men reported higher levels of mental health state, whereas physical health was not different across gender; High levels of anxiety symptoms were associated with negative mental health outcomes in both genders, whereas depressive symptoms were found to impact female's mental and physical health only; A comprehensive and cost-effective screening of anxiety and depressive symptoms may help identifying determinants of health worsening in order to plan, when necessary, caregivers' support. 	<ul style="list-style-type: none"> All measures were self-reported and based of self-perception and were therefore subject to reporting bias; The cross-sectional study design did not allow assuming a causal relationship.
10	Cipolletta et al. 2014 [51]	Italy	61 caregivers of VS patients	Anxiety and Depression Short Scale, Prolonged Grief 12, Family Strain Questionnaire, Coping Orientations to Problem Experiences	Descriptive statistics, hierarchical cluster Analysis using the Ward method, Mann-Whitney U test	<ul style="list-style-type: none"> The burden of providing care to a VS patient is mediated by a range of factors including the different coping strategies adopted by caregivers; Support for these caregivers should take this consideration into account and should be subsequently personalized. 	The limited number of study participants prevented this study from deriving wider considerations.
11	Covelli et al. 2014 [33]	Italy	15 female caregivers	Caregivers' narratives	Qualitative methodology	<ul style="list-style-type: none"> Caregivers experience important personal and interpersonal changes and difficulties while integrating past, present, and future, defined as a 'time gap'; Targeted interventions aiming to empower 	<ul style="list-style-type: none"> Caregivers came from one region of Italy; Some biases could occur due to the interviewer's personal interpretation.

No.	Study	Country	Methods			Main findings	Limitations
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						and support caregivers together with patient-focused interventions should be implemented.	
12	Corallo et al. 2015 [18]	Italy	48 caregivers	Psychological support for one group, no intervention for control group	Wilcoxon signed-rank test, Mann-Whitney U test	Psychological support improves caregivers' ability to process the experience of DOC illness, independent of the diagnosis type .	A small number of participants in each group.
13	Giovannetti et al. 2015a [36]	Italy	20 caregivers	In-depth interviews with a psychologist	Three-step coding scheme	<ul style="list-style-type: none"> • Experience of caregivers of patients with DOC can be described as the process of facing an ambiguous loss; • Features of ambiguous loss could guide clinicians' interventions to support the adjustment of caregivers of patients with DOC. 	All caregivers were interviewed while their relatives were hospitalized within the week service for diagnostic and prognostic evaluation
14	Giovannetti et al. 2015b [52]	Italy	129 caregivers	World Health Organization Quality of Life-BREF, State-Trait Anxiety Inventory-Y, Beck Depression Inventory, Prolonged Grief Disorder Questionnaire, Coping Orientations to Problem Experiences, State-Trait Anger Expression Inventory-2, Medical Outcome Study Social Support Survey	Descriptive statistics, one-sample t-tests	<ul style="list-style-type: none"> • Study results affirmed caregivers' poor QoL, difficulties in social support, and high levels of burden. • Time dedicated to caring is not strictly related to burden; • Social support is highly associated with caregivers' depressive symptoms that are a strong predictor of poor QoL; • Supportive intervention able to integrate psychological, social, and environmental levels is needed. 	<ul style="list-style-type: none"> • The cross-sectional design of the research does not allow concluding causal relationships between variables; • Caregivers were interviewed while their relatives were hospitalized at the center, which was a highly different moment from their daily routine.
15	Goudarzi et al. 2015 [16]	Iran	16 caregivers	Unstructured interviews and observations	Content analysis, Lincoln and Guba's criteria	<ul style="list-style-type: none"> • All family members of vegetative patients, depending on their responsibilities, were affected by physical, mental, social, and economic issues; • The main caregivers in the family experienced the most physical and mental pressures compared with the other members of the family. 	With a small number of participants, the results may not be representative of the general population
16	Romaniello et al. 2015 [48]	Italy and Canada	19 caregivers	Caregiver Burden Inventory, the Attachment Style Questionnaire (ASQ), and the Beck Hopelessness Scale	Descriptive statistics, correlations, one sample t-test, multiple regression analysis	<ul style="list-style-type: none"> • The burden was not associated with the duration of caregiving; • Gender did not affect the overall burden; • Multiple regression analysis indicated that preoccupied attachment style jointly with hopelessness predicted 49% of the total variability of burden. 	<ul style="list-style-type: none"> • Single-center design of this study yields a small sample size with specific socio-demographic features; • a single measurement (ASQ) has been used to characterize attachment style in caregivers of patients with DOC.
17	Covelli et al. 2016 [47]	Italy	216 informal caregivers of patients with DOC	Short Form-12, Family Strain Questionnaire, Beck Depression Inventory, and Coping Orientations to Problem Experiences.	Family Data collected were analyzed at two time points (mean distance was 2.7 years).	<ul style="list-style-type: none"> • Caregivers' mental health improved, whereas the emotional burden and the presence of depressive symptoms as well as the need for information about the disease, thoughts of death, and the use of avoiding coping strategy decreased with time; • The acute event and patients' health condition still have a deep impact on the economic situation of the family; • The study suggests the importance to plan strategies or targeted interventions to reduce the psychosocial and financial burden. 	<ul style="list-style-type: none"> • Large range of time between the acute event and start of survey; • Differences due to the various settings where patients are living (long-term care settings, home, etc.)
18	Bastianelli et al. 2016 [21]	Italy	52 caregivers	Anxiety and Depression Short Scale, Prolonged Grief Questionnaire, Family-Strain Questionnaire, Caregiver QOL	General Linear Model, Wilk's lambda, partial η^2	<ul style="list-style-type: none"> • The study was the first to explore the effect of response shift on VS caregivers' QoL; • Data obtained from 52 caregivers showed high levels of prolonged grief and family strain, and low quality of life; • Prolonged grief did not change during time; • Clinical intervention with the caregivers of VS patients should be differentiated on based on the duration of the caring experience. 	<ul style="list-style-type: none"> • Exiguous number of participants; • Exclusion of some variables, that could influence the changes found over time.
19	Cipolletta et al.	Italy	24 caregivers	Individual semi-	Interpretative	<ul style="list-style-type: none"> • Caregivers felt they were the only ones 	<ul style="list-style-type: none"> • The limited

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	al. 2016 [20]			structured interviews	phenomenological analysis	able to understand and give an answer to patients' needs, but neglected their own lives in their total commitment to the patient; <ul style="list-style-type: none"> The findings highlight the importance of considering new possibilities of life that go beyond the assistance of VS patients. 	geographic area where the study was conducted; <ul style="list-style-type: none"> The limited number of cases where the patient returned home; Only the main family caregiver was involved.
20	Noohi et al. 2016 [30]	Iran	12 (10 family caregivers and 2 professional caregivers)	In-depth interviews	Descriptive and qualitative method	<ul style="list-style-type: none"> Caring for VS patients is a long-term process, and it may be accompanied by physical and psychological problems for caregivers and a decline in the quality of patient care; Delivering care, without receiving information, advice and education, counseling, and emotional, financial, and practical support is extremely painful for family caregivers. 	A small number of participants, the results may not be representative of the general population.
21	Imanigoghar y et al. 2016 [17]	Iran	14 caregivers	Face-to-face in-depth interviews	Constant comparative method, MAXQDA10 software	<ul style="list-style-type: none"> Nurses can play an effective role in improving the caregivers' well-being by considering the importance of training at discharge time and during home care, helping families in providing care and supporting them during the care process; Three notions of 'nurse as a pursuer teacher', 'nurse as a compassionate caregiver', and 'nurse as a supporter' were derived from the analysis that represents various roles of a nurse in the coping process of family caregivers. 	A small number of participants, the results may not be representative of the general population.
22	Sato et al. 2017 [39]	Japan	11 PVS patients and 6 elderly bedridden subjects with consciousness	Kohnan Score, plasma cortisol and adrenaline levels, General Well-Being Schedule score, and facial expression assessments	Nonparametric tests	<ul style="list-style-type: none"> Among the multiple evaluation methods, Kohnan Scores was the most effective; A reduction in the Kohnan Score was observed, indicating an improvement in consciousness level. 	<ul style="list-style-type: none"> A small sample size; The assessment of facial expressions by nurses was subjective.
23	Goudarzi et al. 2018 [25]	Iran	22 (17 family caregivers and 5 professional caregivers)	Unstructured interviews	Strauss and Corbin approach, MAXQDA10 software; Lincoln and Guba's criteria	<ul style="list-style-type: none"> Because of the healthcare system weakness in the establishment of caring centers or providing home visits for vegetative patients, their family caregivers are forced to undertake compulsory care of their patients; they experienced physical and psychological burnouts as well as financial dissipation; Planning and policymaking of the healthcare system for the appropriate care of vegetative patients in the form of designing specific care units for them, determining the composition of visit and care at home, determining a specific support organization for these patients, and the provision of financial or educational support for the families of such patients can be very effective in preventing the damages to their family and caregivers. 	A limitation in this study was finding the patients in VS and their family caregivers due to the weakness in recording the information of the patients.
24	Corallo et al. 2018 [42]	Italy	80 caregivers	Self-administered measures of distress and coping: Symptom Check List-90-R, Coping Orientations to Problem Experiences	χ^2 test, Mann-Whitney U test, Spearman's coefficient, multiple regression analysis on the SCL-90 subscale scores	<ul style="list-style-type: none"> In DOC, the caregiver has a state of chronic, prolonged stress which often can result in the onset of psychopathological symptoms and an increase of varied physical consequences; A reaction to stress was different between two groups of caregivers (VS and MCS) and it may vary according to the coping strategies used; The results showed the importance of developing effective coping strategies aimed to reduce psychological distress and improve the caregiver's well-being. 	A limited number of participants were hospitalized in the neuro intensive care unit of one institute.
25	Goudarzi et al. 2020 [9]	Iran	22 (17 family caregivers and 5 professional caregivers)	Unstructured interviews and field notes	Content analysis based on Graneheim and Lundman's approach	<ul style="list-style-type: none"> The family caregivers did not have adequate knowledge about the methods of providing care to patients in PVS in the early days after discharge, and this made them worried and stressed and even led some families to refuse to take the patients home from the hospital, thus increasing the risks of physical and mental health problems; Family caregivers started to search for 	The main limitation of this study is related to the generalizability of findings to other environments.

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					information from diverse resources to learn the care process; <ul style="list-style-type: none"> • They received the majority of their training from professional home caregivers; • In a limited number of cases, family caregivers consulted their peers to get the needed information; • Family caregivers stated that their fears and anxieties decreased as a result of receiving education from the mentioned sources. 		
26	Imani-Goghary and Ghaljeh 2020 [26]	Iran	15 caregivers	Purposeful sampling, semi-structured, in-depth interviews at participants' homes.	Qualitative content analysis, Graneheim and Lundman's methodology	<ul style="list-style-type: none"> • Family caregivers are faced with many challenges because of the high burden of care, round-the-clock concern, taking care of an alive but unresponsive patient without receiving enough support; • They experience mental and inner turmoil because of social isolation and dealing with contradictory feelings in their daily life. 	A limited group of participants in Iran; therefore, the results may not be representative of the general population.
27	Gonzalez-Lara et al., 2021 [29]	Canada	12 caregivers	Semi-structured qualitative interviews	Constructive-grounded theory	<ul style="list-style-type: none"> • Participants described that caregiving was often the central role that they identify as their top priority; • All participants described the caregiver role as complex and intense that leads to physical, emotional, social, and economic burdens; • Lack of health system support was a major contributing factor. 	With a small number of participants, the results may not be representative of the general population.
28	Corallo et al. 2021 [46]	Italy	35 caregivers	Family Adaptability and Cohesion Evaluation Scale, Novak's Burden Inventory Caregiver Scale	Spearman's coefficient, Mann-Whitney U test, Chi-squared test	<ul style="list-style-type: none"> • Families can maintain a balanced functioning and control distress; • The traumatic event does not affect the family structure. 	<ul style="list-style-type: none"> • MCS patients only; • All correlations are weak or marginally moderate.