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ORIGINAL ARTICLE

Care pathways for individuals with post-anoxic disorder of consciousness (CaPIADoC): an inter-society Consensus Conference

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Abstract

Background Accurate recognition of consciousness level and detection of neurological complications since the intensive care unit are crucial for an appropriate prognostication and tailored treatment in patients with post-anoxic disorder of consciousness (DoC).

Objective The present inter-society Consensus Conference aimed at addressing current debates on diagnostic and prognostic procedures.

Methods Twelve working groups involving 22 multidisciplinary professionals (membership of 9 Scientific Societies and 2 patients' family Associations) conducted a systematic literature review focused on 12 questions addressing diagnosis ($n=5$) and prognosis ($n=7$). The quality of evidence of the included studies was evaluated using the Oxford Centre for Evidence-Based Medicine Levels of Evidence. A Jury involving Scientific Societies and patients' family Associations provided recommendations based on the evidence levels and expert opinion.

Results An overall number of 1,219 papers was screened, and 21 were included in the review. Working groups produced a report on strengths and limits of evidence for each question. The overall suggestion was to use a multimodal assessment combining validated clinical scales, neurophysiological exams, and neuroimaging in diagnostic and prognostic procedure, to guide personalized treatment. A strong recommendation was to use standardized terminologies and diagnostic criteria for ensuring homogeneity and appropriateness in patients management.

Conclusion This multidisciplinary Consensus Conference provided the first operational recommendations for a good clinical practice procedure for patients with post-anoxic DoC. A periodic review will be necessary based on future evidence from the literature and implementation of the present recommendations.

Keywords Consciousness disorders · Diagnosis · Prognosis · Rehabilitation · Anoxia · Vegetative state

Introduction

Disorders of Consciousness (DoC) due to traumatic or non-traumatic (such as post-anoxic) severe Acquired Brain Injury (sABI) encompasses three clinical entities, based on the patient's level of consciousness: i) coma, defined by a complete absence of both arousal and awareness; ii) the Vegetative State/Unresponsive Wakefulness Syndrome (VS/UWS), defined as arousal without awareness; and iii) the Minimally Conscious State (MCS), defined as minimal, reproducible but inconsistent awareness [1]. As possible clinical evolution from the acute stage of DoC, survivors may persist in VS/UWS or in MCS more than 28 days after the injury (i.e., prolonged Disorder of Consciousness, pDoC) [2]. The pDoC may constitute a transient phase towards complete consciousness

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recovery or evolve to chronic DoC when persisting more than 3 and 12 months after post-anoxic and traumatic brain injury, respectively [2].

Although the clinical evolution of post-anoxic patients is poor since the acute stage [3, 4], advances in treatment from the acute to the long-term phase have led to an increase in the number of post-anoxic DoC, as reported in the Emilia Romagna Registry for sABI over 10 years (https://gracer.it/). The care of such patients requires qualified multidisciplinary expertise in the entire care pathway starting from the Intensive Care Unit (ICU) to chronic stage [2, 5, 6], because of high clinical complexity and high risk of complications [7] that can negatively impact clinical outcome [8]. Additionally, an accurate diagnosis of clinical status and of neurological complications and an appropriate prognostication are crucial to plan a tailored care pathway [2]. However, the diagnostic and prognostic value and feasibility of advanced electrophysiological and neuroimaging techniques for unmasking "covert cognition" [9] or the protocols for recognizing neurological complications are still debated. Also, despite the availability of solid bedside predictors of poor outcome in post-anoxic patients (i.e., the absence of bilateral somatosensory evoked potentials, SEP, as recommended by the European and American guidelines) [2, 6] and validated diagnostic tools (as recommended by the European guidelines [6, 10], the management and care of patients with DoC (especially for those with post-anoxic encephalopathy) vary significantly between different countries [11] and regions [12]. In this context, the present Italian inter-society Consensus Conference aimed at: i) identifying clinical and instrumental tools that can be reliable and widely accessible in different care settings (ICU and rehabilitation), for an accurate diagnosis of clinical status and prognosis of post-anoxic DoC people; ii) defining diagnostic procedures for most frequent neurological complications; iii) promoting evidence-based communication of diagnostic and prognostic information to patients' family.

Materials and methods

This Consensus Conference was promoted by Italian Society of Neurorehabilitation (SIRN) and Italian Society of Clinical Neurophysiology (SINC), and involved 9 Scientific Societies (Italian Society of Neurological Rehabilitation—SIRN, Italian Society of Clinical Neurophysiology—SINC, Italian Society of Physical and Rehabilitative Medicine—SIMFER, Italian Society of Neurology—SIN, Italian League Against Epilepsy—LICE, Italian Association of Neuroradiology—AINR, Italian Association of Neurophysiopathology Technicians—AITN, Italian Society of Anaesthesia, Analgesia, Resuscitation and Intensive Care—SIAARTI, Italian Society of High Specialty Rehabilitation—SIRAS), and 2 patients' family Associations (National Federation of Cranial Trauma Associations—FNATC, and the Social Cooperative "LA RETE"). The methodology followed the National Institutes of Health and the Italian Istituto Superiore di Sanità [13] guidelines (see details in the Online Resource). All Scientific Societies and family Associations involved have approved this manuscript. The Consensus Conference was developed from May 2019 to March 2023, and included the following stages:

1. **Preparation and development of questions.** The Steering and Technical-Scientific Committees identified relevant research topics and phrased the research questions using the Patient, Intervention, Comparator, Outcome (PICO) approach [14]. Twelve PICO questions were defined addressing both diagnostic ($n = 5$) and prognostic ($n = 7$) issues in patients with DoC within 28 days and pDoC (i.e., ≥ 28 days and < 3 months after brain injury).
2. **Systematic literature review and rating of the evidence.** Each PICO question was assigned to one of the 12 working groups, each constituted by two members of the 9 participating Scientific Societies. On March 16th 2022, a systematic literature search was conducted on MEDLINE (PubMed), Scopus and Web of Science online databases, using different strings of keywords selected for each PICO question (see the Online Resource for the detailed keywords). The selected keywords were searched in Title/Abstract. To be eligible, studies had to be: i) in English language; ii) published in peer-reviewed journals; iii) available in full text. We decided to restrict the field of investigation to the adult population (age ≥ 18 years) and to papers published after 2002, to ensure that the diagnosis of DoC was based on standardised international criteria [1]. Members of each working group blindly reviewed the literature to select eligible studies; thereafter, they worked together to summarise the relevant findings. Using the CEBM Levels of Evidence [15], working groups rated the Quality of the Evidence of the studies from Level 1 (best quality) to Level 5 (lowest quality), and assigned to each PICO question a grade of evidence from A (highest) to D (lowest).
3. **Celebration of the Consensus Conference and drafting of the recommendations**. The public Consensus Conference has been held on-line over two days: 23th February 2023 and 9th March 2023, during which working groups presented their findings for public discussion. Thereafter, a Jury panel met behind closed doors for producing, together with a writing panel, a preliminary Consensus paper containing the provisional recommendations for each PICO question. In the absence of clear evidence on the available literature, the Jury provided good practice recommendations based on expert opinion and/or on latest international guidelines.

4. **Peer-review and final Consensus paper**. The preliminary Consensus paper has been submitted to the members of the 9 Scientific Societies and the 2 patients' family Associations for a public peer review process from June 27th to July 17th 2023. The writing panel finalised the final version of the Consensus paper according to relevant comments from the peer review process. Detailed information about methodological procedures can be found in the Online Resource.

Results

The overall flow-chart of the included studies is depicted in Fig. 1. Flow-charts of included studies for each PICO question can be found in the Online Resource. The final agreement for each recommendation derived by the peer review process is summarised in Fig. 2. PICO questions addressing diagnosis and prognosis are reported below and, together with relative recommendations, in Tables 1 and 2. Below a brief

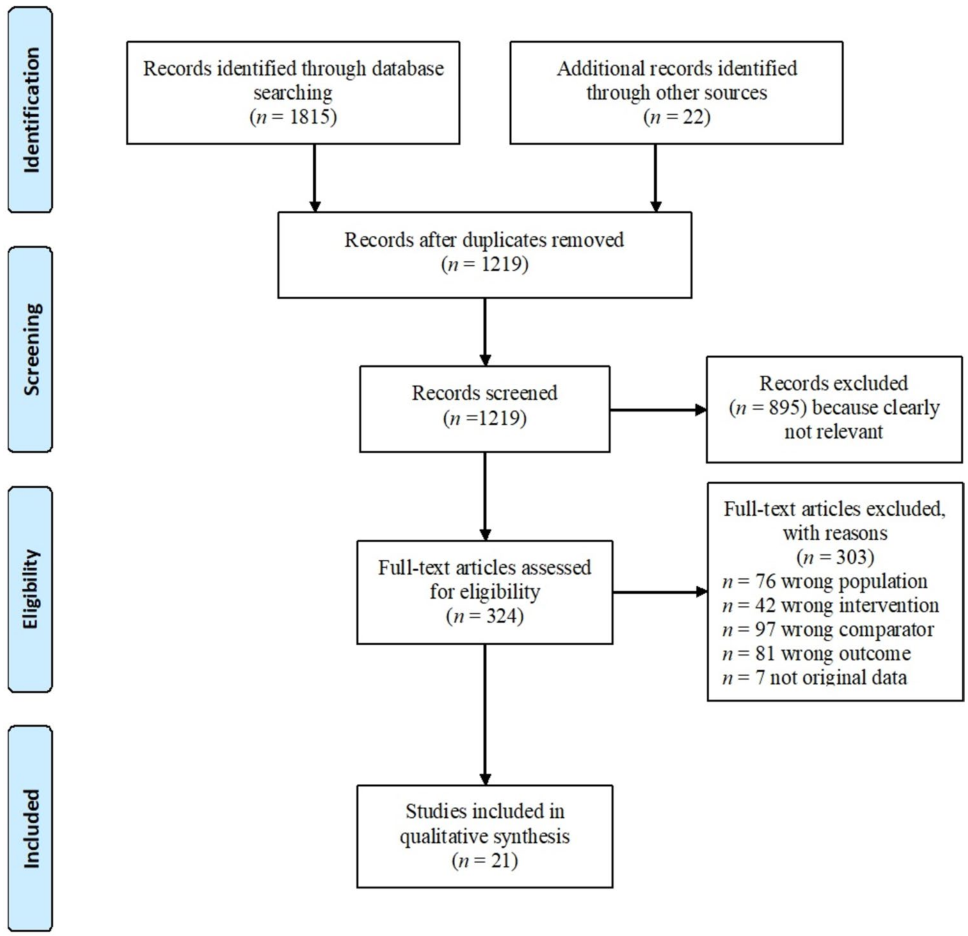

Fig. 1 Overall flow chart of the included studies

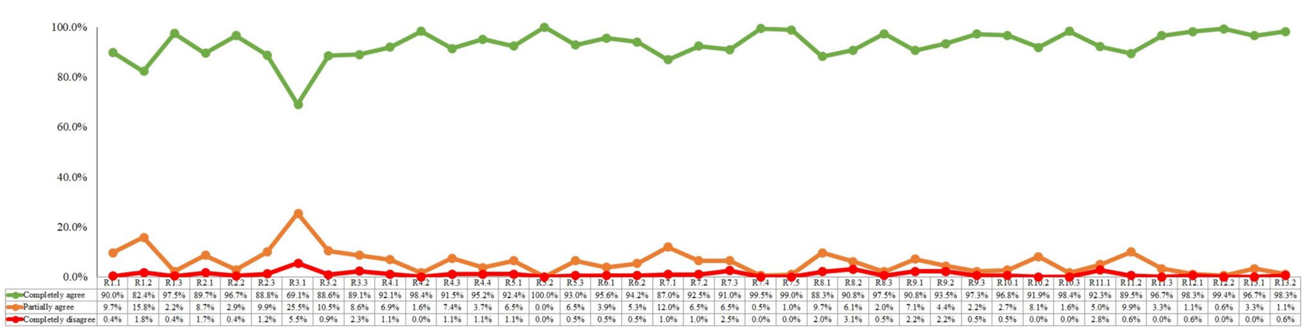

Fig. 2 Distribution of the agreement rate referred to the consensus statements by participants in the peer review

Table 1 PICO questions and recommendations [grade of evidence, eligible studies] for diagnosis of patients with DoC and pDoC

PICO 1: In patients with DoC, does behavioral assessment by means of the CRS-R, compared to assessment by GCS or FOUR, improve the diagnostic accuracy of level of consciousness in the ICU?
Good practice recommendations [based on European guidelines [10], and on expert opinion]:
1.1. It is recommended the widespread use of CRS-R in intensive/sub-intensive care units, together with GCS and/or FOUR, as it is the gold standard for differential diagnosis between coma, VS/UWS and MCS;
1.2. It is recommended the validation in the Italian language of a simplified form of CRS-R with faster administration (e.g., SECONDs, CRS-R-FAST);
1.3. It is recommended greater integration between resuscitators and neurologists/neurophysiologists in order to make professionals better trained in the use of CRS-R and who can be involved in consciousness assessments of patients in the acute phase
PICO 2: In comatose patients, does the structural MRI, compared to structural CT, improve the assessment accuracy of the extent of post-anoxic brain injury?
Good practice recommendations [based on expert opinion]:
2.1. Brain CT scan is the first choice for the initial evaluation of brain injury, as it can detect early signs of cerebral oedema and tissue ischemia;
2.2. The gray and white matter ratio measured by early brain CT (i.e., within the first 72 h after the event) is recommended for prognosis;
2.3. Where available and in the absence of contraindications, the MRI (with diffusion sequences) is recommended, especially if brain CT is unable to detect the post-anoxic damage
PICO 3: In patients with DoC and pDoC, does the use of EMG and ENG, compared to neurological objective examination, improve the diagnostic accuracy of CRIMYNE?
Good practice recommendations [based on expert opinion]:
3.1. It is recommended assessing the limb motor response to nociceptive stimuli to identify patients with suspected CRIMYNE;
3.2. It is recommended performing a neurophysiological examination (i.e., EMG/ENG) to confirm the diagnosis of CRIMYNE, because of the difficulty to clinically recognize peripheral motor impairments in such non-collaborative patients
PICO 4: In patients with pDoC, does neurophysiological assessment (EEG, ERP) combined with behavioral assessment (by means of the CRS-R), compared to the behavioral assessment alone, improve the diagnostic accuracy of level of consciousness?
Good practice recommendations [based on expert opinion]:
4.1. It is recommended recording conventional EEG combined with behavioral assessment (by the CRS-R) to provide clues for a diagnosis of the level of consciousness (i.e., VS/UWS, MCS *minus* and *plus*, locked-in syndrome or covert cognition/covert awareness/cognitive-motor dissociation) and also to rule-out a non-convulsive status epilepticus;
4.2. It is recommended classifying EEG activity according to a standardized terminology;
4.3. It is recommended considering with caution the use of ERP, as to record and analyse them in patients with pDoC could be challenging, because of issues related to the clinical condition (e.g., frequent vigilance fluctuation);
4.4. It is recommended implementing further large-sample multicentre studies to evaluate the diagnostic value of ERP by ensuring homogeneous protocols and use of salient stimuli, such as the patient's own name
PICO 5: In patients with pDoC, does advanced neuroimaging (fMRI, PET, DTI) combined with behavioral assessment (by means of CRS-R), compared to the behavioral assessment alone, improve the diagnostic accuracy of the level of consciousness?
Good practice recommendations [based on expert opinion]:
5.1. There is insufficient evidence to recommend the routine use of advanced neuroimaging for diagnostic assessment in clinical practice;
5.2. It is recommended defining criteria for identifying candidate patients, the most suitable techniques and most suitable protocols for complementing the diagnosis in case of suspected covert cognition/covert awareness/cognitive-motor dissociation;
5.3. It is recommended implementing further diagnostic studies with techniques such as PET and fMRI in resting conditions, as they can provide indices of consciousness level and are easier to perform in patients with DoC than active paradigms based fMRI exams

CRIMYNE CRitical Illness MYopathy and Neuropathy, *CRS-R* Coma Recovery Scale-Revised, *CRS-R-FAST* CRS-R For Accelerated Standardized Assessment, *CT* Computerized Tomography, *DoC* Disorders of Consciousness, *DTI* Diffusion Tensor Imaging, *EEG* Electroencephalography, *EMG* Electromyography, *ENG* Electroneurography, *ERP* Event-Related Potentials, *fMRI* functional Magnetic Resonance Imaging, *FOUR* Full Outline of UnResponsiveness, *GCS* Glasgow Coma Scale, *ICU* Intensive Care Unit, *MCS* Minimally Conscious State, *MRI* Magnetic Resonance Imaging, *pDoC* prolonged DoC, *PET* Positron-Emission Tomography, *SECONDs* Simplified Evaluation of CONsciousness Disorders, *UWS* Unresponsive Wakefulness Syndrome, *VS* Vegetative State

commentary related to each PICO question is reported. A more detailed commentary can be found in the Online Resource.

Diagnosis

PICO 1 In patients with DoC, does behavioural assessment by means of the Coma Recovery Scale-Revised (CRS-R), compared to assessment by Glasgow Coma Scale (GCS) or Full Outline of UnResponsiveness (FOUR), improve the diagnostic accuracy of level of consciousness in the ICU?

The first signs of re-emergence of consciousness in patients with DoC are typically visual fixation and visual pursuit. Based on this evidence, the European Academy of

Table 2 PICO questions and recommendations [grade of evidence, eligible studies] for prognosis of patients with DoC and pDoC

PICO 6: In comatose patients, does neurophysiological assessment (EEG, SEP, ERP) combined with behavioral assessment (by means of the GCS or FOUR), compared to the behavioral assessment alone, improve the prediction accuracy of outcome in terms of recovery of consciousness within 1 year from the event?

Good practice recommendations [based on the Canadian [16] and European [6] guidelines, and on expert opinion]:

6.1. It is recommended ensuring that the multimodal approach includes early EEG assessment (within 72 h) classified according to a widely shared standardized terminology, along with recording of upper limb SEP;

6.2. It is recommended implementing a multimodal prognostic approach that combines accurate clinical evaluation (using GCS or FOUR, or, when applicable in the intensive care setting, CRS-R), neuroradiological assessment (with CT and, when possible, MRI), neurophysiological evaluation (with EEG and SEP), and, when available, analysis of neuron-specific serum enolase

PICO 7: In patients with DoC and pDoC, is the occurrence of SE, compared to its absence, associated with a negative prognosis in terms of a lack of recovery of consciousness within 1 year from the event?

Recommendations [grade B, based on observational studies ($n = 17$, evidence level 2–3), systematic literature reviews ($n = 1$, evidence level 1), the Canadian guidelines [16], and expert opinions]:

7.1. An early diagnosis of SE is recommended in the acute phase through serial EEGs and, where available, continuous EEG monitoring;

7.2. It is recommended considering the SE as an indicator of an unfavourable prognosis when associated with other multimodal predictors of poor outcome;

7.3. A multimodal prognostic approach (e.g., neuroimaging and SEP) is recommended, alongside the clinical and EEG monitoring of SE, to guide the aggressiveness and duration of anti-seizure medication treatment;

7.4. It is recommended using shared criteria and terminology for the diagnosis of SE both in clinical and research settings;

7.5. It is suggested implementing multicentre prognostic studies that assess the impact of therapeutic strategies on convulsive and non-convulsive SE, as well as on short-term and long-term clinical outcomes

PICO 8: In patients with DoC and pDoC, does the use of advanced neuroimaging (fMRI, PET, DTI) combined with structural neuroimaging (MRI, CT), compared with structural neuroimaging alone, improve the prediction accuracy of outcome in terms of recovery of consciousness within 1 year after the event?

Good practice recommendations [based on expert opinion]:

8.1. There is currently insufficient evidence to recommend the routine use in clinical practice of advanced neuroimaging, in addition to structural neuroimaging, for prognostication;

8.2. The predictive value of techniques such as 18F-FDG-PET and fMRI in resting state should be assessed in large cohort of patients, as they provide indices of the level of consciousness and are easier to implement in patients with DoC than other fMRI methods using active paradigms;

8.3. It is suggested that further studies are implemented to identify patients who are candidates for the use of these investigative methods

PICO 9: In patients with pDoC, does advanced neuroimaging (fMRI, PET, DTI) combined with the behavioral assessment (by means of the CRS-R), compared to the behavioral assessment alone, improve the prediction accuracy of outcome in terms of recovery of consciousness at 6 months or longer after the event?

Good practice recommendations [based on expert opinion]:

9.1. There is insufficient evidence to recommend the routine use in clinical practice of advanced neuroimaging for prognostic purposes

9.2. It is suggested implementing further studies especially on techniques such as resting PET and fMRI, as they are informative for prognosis and easier to implement than other advanced methods (e.g., fMRI with active paradigms)

9.3. It is suggested implementing further studies, possibly multicentric and on a large sample size, in order to define the inclusion criteria of patients eligible for the use of these investigation methods

PICO 10: In patients with pDoC, does the neurophysiological assessment (EEG, SEP, ERP) combined with the behavioral assessment (by means of the CRS-R), compared to the behavioral assessment alone, improve prediction accuracy of outcome in terms of recovery of consciousness at 6 months or longer after the event?

Recommendations [grade B, based on observational studies ($n = 3$, level of evidence 2–3) and expert opinion]:

10.1. It is recommended using of neurophysiological tests (EEG, SEP) for prognostic purposes in association with behavioral evaluation (e.g., CRS-R assessment), when they have not been performed in the acute phase;

10.2. It is recommended using of serial EEG evaluations, in association with behavioral assessment, for prognostic purposes and for monitoring clinical evolution;

10.3. It is recommended defining homogeneous recording protocols and classification criteria for EEG and SEP by referring to a shared terminology;

10.4. It is suggested implementing multicentre studies on a large sample, to evaluate the diagnostic value of ERP with homogeneous protocols, and use of salient stimuli, such as the patient's own name

PICO 11: In patients with pDoC, does the use of prolonged EEG (24 h of conventional EEG recording and PSG), compared to conventional 30-min EEG recording, improve the prediction accuracy of outcome in terms of recovery of consciousness at 6 months or longer after the event?

Table 2 (continued)

Good practice recommendations [based on expert opinion]:
11.1. It is recommended recording a conventional EEG (associated with standardized behavioral assessment and SEP) for prognostic purposes;
11.2. It is recommended considering the use of serial or, where possible, continuous EEG or PSG to search for critical and interictal epileptiform abnormalities, and evaluate the macrostructure of sleep, as potential predictive feature;
11.3. It is suggested implementing further multicentre and large-sample studies to define the prognostic value of specific polysomnography patterns
PICO 12: Is the persistence of a pDoC at 3 months after post-anoxic brain injury, compared to a diagnosis of eMCS, a prognostic index for poor cognitive outcome, in terms of LCF score from 2 to 6, at 12 months after the event?
Good practice recommendations [based on expert opinion]:
12.1. It is recommended performing a standardized neuropsychological cognitive and behavioral evaluation in patients emerging from MCS;
12.2. It is suggested implementing longitudinal multicentre studies on individuals who recover consciousness after a post-anoxic event, to evaluate: i) the occurrence of cognitive and behavioral disorders, and ii) to identify possible risk factors for cognitive-behavioral disorders

CRS-R Coma Recovery Scale-Revised, *CT* Computerized Tomography, *DoC* Disorders of Consciousness, *DTI* Diffusion Tensor Imaging, *EEG* Electroencephalography, *eMCS* emergence from the MCS, *ERP* Event-Related Potentials, *fMRI* functional Magnetic Resonance Imaging, *FOUR* Full Outline of UnResponsiveness, *GCS* Glasgow Coma Scale, *LCF* Levels of Cognitive Functioning, *MCS* Minimally Conscious State, *MRI* Magnetic Resonance Imaging, *pDoC* prolonged DoC, *PET* Positron-Emission Tomography, *PSG* Polysomnography, *SE* Status Epilepticus, *SEP* Somatosensory Evoked Potentials

Neurology (EAN) guidelines strongly recommended the use of the FOUR [17] instead of GCS for diagnosing the level of consciousness of patients in the ICU. Indeed, the FOUR can evaluate the patient's eye movements, thus reducing the risk of misdiagnosis of locked-in syndrome and MCS [10]. Additionally, the CRS-R has been recommended for disentangling patients in VS/UWS from those in MCS since their care in the ICU, as this behavioural tool is based on diagnostic criteria of MCS [10]. However, although the CRS-R is more sensitive than the GCS and FOUR, it is time consuming and more difficult to be repetitively administered in the ICU. More recently, two scales derived from the CRS-R have been proposed for use in the ICU: the Simplified Evaluation of CONsciousness Disorders (SECONDs) and the CRS-R For Accelerated Standardised Assessment (CRS-R-FAST). Both clinical tools showed shorter administration time and sufficient concurrent validity with respect to the CRS-R. Unfortunately, the literature search did not identify any eligible papers that directly compared the diagnostic accuracy of the CRS-R and the FOUR or GCS in post-anoxic DoC. Following these literature gaps, the Jury provided good practice recommendations based on EAN guidelines and on expert opinion.

PICO 2 In comatose patients, does the structural Magnetic Resonance Imaging (MRI), compared to structural Computed Tomography (CT), improve the assessment accuracy of the extent of post-anoxic brain injury?

Neuroimaging can identify and measure the cytotoxic oedema that frequently occurs in the acute phase of post-anoxic brain injury. Brain CT can quantify the extent of cytotoxic oedema by assessing signs such as flattening of the grooves, and reduction in the densitometric Gray-White matter Ratio (GWR) in several areas of interest (such as semioval centres and basal ganglia). A low value (< 1.15–1.20) of the GWR at the level of the basal ganglia is considered a prognostic index of unfavourable outcome with a low rate of false positives. Recent systematic reviews agreed that CT-derived GWR and MRI-derived diffusivity measures (i.e., Apparent Diffusion Coefficient, ADC) may be considered prognostic indicators, even though they lack evidence at individual-patients level [18] and several studies fail for homogeneity of the GWR measurement [19]. In conclusion, there is no direct evidence of superiority of MRI over brain CT. Accordingly, a CT scan within the first 72 h after the event has been recommended for prognostication by the recent European and Canadian guidelines on coma due to cardiac arrest [6, 16], but only in association with other prognostic factors. The literature search did not identify any eligible papers that directly compared MRI with CT in post-anoxic DoC. Following these literature gaps, the Jury provided good practice recommendations based on expert opinion.

PICO 3 In patients with DoC and pDoC, does the use of electromyography (EMG) and electroneurography (ENG), compared to neurological objective examination, improve the diagnostic accuracy of critical illness myopathy and neuropathy (CRIMYNE)?

CRIMYNE is a common cause of acquired weakness in critically ill patients admitted to ICU [20]. The coexistence of the CRIMYNE with brain injury can prolong the rehabilitation stay and worsen the final outcome of patients with sABI [21]. The CRIMYNE may be underestimated in patients with DoC and pDoC because of difficulties in detection of motor deficits [20]. Patients with DoC and pDoC are unable to cooperate adequately on clinical motility examination and the frequent co-presence of pyramidal signs are confounding factors for an accurate clinical diagnosis of CRIMYNE. Therefore, the neurophysiological examination (i.e., ENG-EMG) is crucial for confirming the diagnosis of CRIMYNE. Due to this difficulty in recognising motor deficits clinically and the lack of expertise in neurophysiology, the occurrence of CRIMYNE may be underestimated. The limited evidence in DoC and pDoC patients reported neurophysiological findings suggestive for CRIMYNE diagnosis in about 60% of both traumatic and non-traumatic patients with pDoC [21, 22]. However, sub-analysis on the prevalence of CRIMYNE in post-anoxic DoC patients was not performed. The literature search did not identify any eligible papers that directly compared the accuracy of the EMG/ENG and the neurological objective examination for the diagnosis of CRIMYNE in post-anoxic DoC and pDoC. Following these literature gaps, the Jury provided good practice recommendations based on expert opinion.

PICO 4 In patients with pDoC, does neurophysiological assessment (electroencephalography, EEG; event-related potentials, ERP) combined with behavioural assessment (by means of the CRS-R), compared to the behavioural assessment alone, improve the diagnostic accuracy of level of consciousness?

In about 30% of patients in VS/UWS, active paradigms on functional neuroimaging or quantitative electrophysiology reveal cortical activation suggestive of preserved cognitive processing [9]. Additionally, recognizing the so-called patients with covert cognition (or covert awareness or cognitive motor-dissociation) is relevant for identifying patients with possible potential for recovery. However, advanced neuroimaging or electrophysiological techniques, recommended by the American Academy of Neurology (AAN) and EAN guidelines [2, 10], are not widely available in routine care due to technical problems (e.g., patient's agitation), logistical problems or lack of expertise. Conventional EEG is an easily repeatable at bedside and not invasive exam that can improve the diagnostic accuracy of patients with pDoC, as background activity and reactivity significantly differ in VS/UWS and MCS patients [23], and can recognize patients with covert cognition [24] or locked-in syndrome [25], who show normal or near-normal EEG features. Additionally, conventional EEG can rule out non-convulsive status epilepticus, which could hamper the detection of consciousness. The presence of P300 cortical component evoked by an auditory oddball paradigm can identify VS/UWS patients who recover responsiveness/consciousness [26]. However, the sensitivity of ERP is low in such a population, as in healthy subjects [27]. The literature search did not identify any eligible papers that directly compared the diagnostic accuracy of neurophysiology plus behavioural assessment with behavioural assessment alone in post-anoxic pDoC. Following these literature gaps, the Jury provided good practice recommendations based on expert opinion.

PICO 5 In patients with pDoC, does advanced neuroimaging (functional MRI, fMRI; positron-emission tomography, PET; diffusion tensor imaging, DTI) combined with behavioural assessment (by means of CRS-R), compared to the behavioural assessment alone, improve the diagnostic accuracy of the level of consciousness?

Functional neuroimaging can reveal residual cortical activation in response to passive (e.g., listening of a familiar voice) or active (e.g., motor imagery) paradigms [10]. These cortical features in patients who appear unresponsive on behavioural evaluation are suggestive of conscious content [9]. However, the absence of cortical activation is not a proof of absence of consciousness, as several confounding factors (e.g., co-existence of auditory or language comprehension deficits, or arousal fluctuations) can hamper an appropriate cognitive processing of administered task/stimuli [10]. Additionally, technical (e.g., patient agitation) and logistic (e.g., poor availability of instrumental devices and expertise in post-acute settings) problems can negatively affect neuroimaging acquisition and analysis [10]. Based on this evidence, the EAN guidelines recommended "*whenever feasible, consider PET, resting-state fMRI, active fMRI or EEG paradigms and quantitative analysis of high-density EEG to complement behavioural assessment for detecting patients with covert cognition or with high probability to recover.*" The literature search did not identify any eligible papers that directly compared advanced neuroimaging plus behavioural assessment with behavioural assessment alone in post-anoxic pDoC. Following these literature gaps, the Jury provided good practice recommendations based on expert opinion.

Prognosis

PICO 6 In comatose patients, does neurophysiological assessment (EEG, SEP, ERP) combined with behavioural assessment (by means of the GCS or FOUR), compared to the behavioural assessment alone, improve the prediction accuracy of outcome in terms of recovery of consciousness within 1 year from the event?

The prognosis of post-anoxic coma has been extensively studied through meta-analyses and systematic reviews with the aim of defining prognostic tools to guide pharmacological and rehabilitative therapies and avoid inappropriate discontinuation of care. Recent guidelines recommended a multimodal prognostic approach because no single test alone achieves an acceptable false-positive rate [6, 16]. Accordingly, the multimodal assessment should include clinical examination, neurophysiological tests (i.e., EEG, SEP), biomarker neuron-specific enolase, and neuroimaging (i.e., CT, MRI). When a patient has at least two unfavourable prognostic predictors on the multimodal evaluation, clinicians can communicate the prognosis to family members to agree on the more appropriate acute therapeutic strategies and post-hospitalization rehabilitation. The literature search did not identify any eligible papers that directly compared the prognostic accuracy of neurophysiology plus behavioural assessment with behavioural assessment alone in post-anoxic comatose patients. The Jury provided good practice recommendations based on expert opinion and on the aforementioned international guidelines, published after literature search.

PICO 7 In patients with DoC and pDoC, is the occurrence of status epilepticus (SE), compared to its absence, associated with a negative prognosis in terms of a lack of recovery of consciousness within 1 year from the event?

The SE occurred in 12.2% of post-anoxic comatose patients enrolled in 17 [28–44] out of 18 eligible studies. No data were available in patients with pDoC. The SE negatively impacts the patients' outcome, as most post-anoxic comatose patients with SE (87.6%) had a poor outcome (i.e., dead, or in VS/UWS, or conscious with severe disability), and only a few cases regained consciousness. However, the majority of studies showed several pitfalls (e.g., the impact of therapeutic hypothermia or of life-sustaining therapy withdrawal on clinical outcome has not been investigated, or standardised diagnostic criteria for SE or non-convulsive SE had not been appropriately adopted in all studies) that did not ensure the generalizability of results. Additionally, there is ongoing debate as to whether SE simply represents a marker of the severity of the initial brain insult or if it can further worsen the primary damage in the following days [41]. Notably, some studies have described that patients with SE associated to benign EEG patterns (e.g., EEG continuous background activity) and presence of N20 on SEP show favourable prognosis [28, 43]. Accordingly, the presence of these specific EEG/SEP patterns could prompt clinicians to treat SE aggressively [30]. Highly malignant EEG patterns (such as suppressed background activity) and/or absence of SEP are associated with worse outcomes that might advise against aggressive treatment [16]. Based on the 18 eligible papers gathered from the literature research [28–45], the Jury provided recommendations with a grade of evidence B.

PICO 8 In patients with DoC and pDoC, does the use of advanced neuroimaging (fMRI, PET, DTI) combined with structural neuroimaging (MRI, CT), compared with structural neuroimaging alone, improve the prediction accuracy of outcome in terms of recovery of consciousness within 1 year after the event?

Structural neuroimaging provides information on extension and localization of the anoxic brain damage in the acute phase with potential predictive value (see also PICO 2). However, there is no conclusive data on predictive value of structural neuroimaging in patients with post-anoxic injury, likely because of heterogeneity of studies (e.g., different CT-GWR and MRI-ADC measurements) [19]. Thus, the recent European guidelines on post-anoxic coma recommended structural neuroimaging evaluation for neuroprognostication only in combination with other predictors [6]. Furthermore, a prospective study on a cohort of 29 post-anoxic coma patients revealed that the combination of structural and functional assessment of connectivity between the prefrontal and postero-medial cortices can predict outcome at 3 months [46]. Among functional neuroimaging techniques, the PET with fluorodeoxyglucose tracer (18F-FDG-PET) appears to be informative on prognosis especially in pDoC, as a higher metabolic index in the better-preserved hemisphere correlates with a higher state of consciousness and thus could identify patients with covert cognition with higher potential for recovery at 6 months [47]. However, the literature search did not identify any eligible papers that directly compared the prognostic accuracy of advanced plus structural neuroimaging with structural neuroimaging alone in post-anoxic DoC or pDoC [46, 47], or data on post-anoxic patients were not available [47]. Following these literature gaps, the Jury provided good practice recommendations based on expert opinion.

PICO 9 In patients with pDoC, does advanced neuroimaging (fMRI, PET, DTI) combined with the behavioural assessment (by means of the CRS-R), compared to the behavioural assessment alone, improve the prediction accuracy of outcome in terms of recovery of consciousness at 6 months or longer after the event?

The level of consciousness, as measured by the CRS-R total score [3] or its machine-learning-based index [48], can help clinicians in the neuroprognostication of patients with pDoC at 6 months after severe traumatic and non-traumatic brain injury. However, no separated data on post-anoxic pDoC are available. A longitudinal study on 10 post-anoxic patients in VS/UWS [49] evaluated possible predictive value of an intentional behaviour (i.e., visual fixation) as assessed by CRS-R on recovery of command following at 12 months after brain injury. Both subgroups of patients (i.e., with and without visual fixation) showed hypometabolism on thalami and fronto-temporal-occipital cortex compared to healthy subjects on 18F-FDG-PET. No predictive value has been found for visual fixation. The literature search did not identify any eligible papers that directly compared the prognostic accuracy of advanced neuroimaging plus behavioural assessment with behavioural assessment alone in post-anoxic pDoC. Following these literature gaps, the Jury provided good practice recommendations based on expert opinion.

PICO 10 In patients with pDoC, does the neurophysiological assessment (EEG, SEP, ERP) combined with the behavioural assessment (by means of the CRS-R), compared to the behavioural assessment alone, improve prediction accuracy of outcome in terms of recovery of consciousness at 6 months or longer after the event?

The prognostic value of neurophysiological exams in patients with DoC is well established. The bilateral absence of the N20 cortical component on SEP and a highly malignant EEG pattern (such as suppressed EEG background activity) recorded in the ICU indicate a poor prognosis [50]. There is little evidence on the prognostic accuracy of neurophysiological examination recorded in the rehabilitation setting. In recent studies, the presence of the cortical component on SEP [51, 52] and EEG reactivity to eye opening [3] showed a positive predictive value on the recovery of consciousness at the 6-month follow-up. Indeed, patients who presented EEG reactivity to eye opening were about 5 times more likely to recover consciousness, compared to patients with absent EEG reactivity, whereas patients with higher level of responsiveness as measured by CRS-R total score were only about 3 times more likely to recover consciousness, compared to patients with lower CRS-R scores [3]. Additionally, the latest AAN guidelines [2] recommended combining SEP recorded in the sub- or post-acute phase with CRS-R in the outcome prediction of anoxic patients with pDoC. Based on the 3 eligible papers gathered from the literature search [3, 51, 52], the Jury provided recommendations with a grade of evidence B.

PICO 11 In patients with pDoC, does the use of prolonged EEG (24 h of conventional EEG recording and polysomnography, PSG), compared to conventional 30-min EEG recording, improve the prediction accuracy of outcome in terms of recovery of consciousness at 6 months or longer after the event?

The predictive value of reactivity on conventional EEG has been found in a large cohort of patients with pDoC due to both traumatic and non-traumatic aetiology [3]. To date, there are few studies on the prognostic value of continuous EEG in patients with pDoC, likely due to technical issues (e.g., presence of movement artefacts or lack of human resources for performing long exams). Most of the available studies aimed to analyse the architecture of the sleep, based on the hypothesis that a better organisation is related to the integrity of cortico-subcortical structures, which are fundamental for vigilance and higher cognitive functions [53, 54], and therefore may be a marker of favourable evolution. The absence of physiological sleep patterns is associated with negative evolution, while the presence of slow wave sleep is a useful marker for diagnosis of different levels of consciousness [54]. A single longitudinal study, conducted on a cohort of pDoC due to different aetiologies, and without separate data on post-anoxic patients, has highlighted that the recording of serial standard EEG is able to identify a greater percentage of interictal epileptiform abnormalities with an impact on the clinic evolution, as they identify patients with high risk to develop epileptic seizures [55]. The literature search did not identify any eligible papers that directly compared the prognostic accuracy of prolonged EEG with conventional 30-min EEG recording in post-anoxic pDoC. Following these literature gaps, the Jury provided good practice recommendations based on expert opinion.

PICO 12 Is the persistence of a pDoC at 3 months after post-anoxic brain injury, compared to a diagnosis of emergence from MCS (eMCS), a prognostic index for poor cognitive outcome, in terms of Level of Cognitive Functioning (LCF) score from 2 to 6, at 12 months after the event?

Most prognostic studies on patients with pDoC considered two clinical outcomes (i.e., survival and/or recovery of consciousness) and rarely investigated the recovery of cognitive and behavioural functions. However, patients with severe traumatic and non-traumatic brain injury can develop cognitive [56] and behavioural [57] disorders that negatively impact on family, social and vocational reintegration, and on patient and family's quality of life. However, the persistence of cognitive-behavioural disorders after recovery of consciousness in post-anoxic patients has not been fully investigated [58] and evidence-based conclusions on prognostic elements for late cognitive-behavioural disability are not available. The Jury provided good practice recommendations based on expert opinion.

General recommendations on family involvement in clinical management

The family caregivers should be actively involved in the entire care pathway to strengthen the therapeutic alliance with rehabilitation teams, as recommended by the national and international guidelines [2, 5, 58]. Indeed, they are highly informative in the diagnostic process, as they are the most salient stimulus for eliciting conscious behaviours [59]. Additionally, if appropriately trained in the assessment and patient's care [60], they can help clinicians in long-term monitoring of patients' clinical evolution [58]. In this context, the communication of the patient's diagnosis and prognosis by health professional team should be respectful of the dignity and wishes of the patients and their family, trying as much as possible to avoid peremptory terms in the case of an unfavourable prognosis, in order to help the family members to process the negative event. On the basis of this evidence, the two Jury members affiliated with the patients' family Associations (FNATC and La RETE) suggested to address issues related to the involvement of patients' family caregivers in the care pathway of persons with DoC, which might be of interest for the different areas explored by the CaPIADoC Consensus Conference. The procedure used for these 'out-of-topic' recommendations was different from that adopted for the recommendations on diagnosis and prognosis (i.e., the critical literature review based on specific PICO questions). The following additional good practice recommendations were formulated in a multidisciplinary and multi-professional context, since they were the result of an open discussion between all participating Scientific Societies and the two patients' family Associations:

- To encourage the active and collaborative participation of family members, starting from the acute phase after training, in gathering valuable information for diagnostic evaluation, monitoring the patient's progress, and participating in rehabilitative treatment.
- To implement accessible communication modes for patients' family members/caregivers related to diagnostic/prognostic information, ensuring homogeneity of approaches and terminology, clear and easy-to-understand messages, along the entire pathway in all care settings.
- Psychologists and clinicians should integrate their relational mode with patients' families for providing psychological support and an appropriate communication of patients' diagnosis and prognosis.

Discussion

This paper represents a first inter-society Consensus Conference on the care pathway of post-anoxic patients with DoC and pDoC, addressing issues that clinicians may routinely face in daily clinical practice since the management in the ICU. A great value of this Consensus Conference was the involvement of a broad multidisciplinary and multi-professional expertise, as they are required in the management of such complex patients from the ICU to rehabilitation setting [2, 6, 10, 16]. The overall recommendation of the present Consensus Conference is to adopt a multimodal assessment combining validated clinical scales, targeted neurophysiological testing and neuroimaging in diagnostic and prognostic procedures to guide personalised treatment. The multimodal assessment must be implemented along different care settings both in patients with DoC and pDoC, to ensure continuity of the care pathway [5]. Although each setting keeps its own specificity in the management of post-anoxic patients, because of different issues in acute and prolonged phases of this clinical condition, it is desirable to foster a bridge between the available international guidelines addressed to patients with DoC [6, 10, 16] and patients with pDoC [2, 10], to implement some recommendations both in ICU and in rehabilitation settings. An additional strong recommendation is to use standardised and validated terminologies and criteria for reporting the clinical and instrumental evaluations. Accordingly, the accuracy, appropriateness and homogeneity of diagnostic and prognostic procedures should be ensured in clinical practice and in all settings. A large consensus on these procedures can enable clinicians to provide evidence-based diagnostic and prognostic information to a patient's family, as specifically requested by the two patients' family Association involved in the CaPIADoC Jury.

The CaPIADoC systematic literature review revealed many challenges in the care pathway of patients with post-anoxic severe brain injury. First, only few studies on this specific population are available, especially in patients with pDoC. Eligible studies were identified for only 2 out of the 12 PICO questions on prognosis (PICO 7 = 18 eligible studies on comatose patients, and PICO 10 = 3 eligible studies on patients with pDoC). Most studies identified by the literature search were excluded because of a lack of a direct comparison between Intervention and Comparator or because of difficulty to extract data at single patient level. Additionally, the paucity of eligible studies, especially in pDoC, could be ascribed to the difficulty to enrol post-anoxic patients with pDoC, because of largely common attitude to life-sustaining therapy withdrawal in post-anoxic comatose patients with solid predictors of poor outcome (e.g., bilateral absence of N20 on SEP) [6, 16]. Accordingly, the only 3 eligible studies on patients with pDoC (see PICO 10) were conducted in Italian centres in which the life-sustaining therapy withdrawal is not usual. However, a recent meta-analysis reported a high percentage of patients who survive long-term in a prolonged/chronic DoC, and also a rare late recovery even with severe cognitive-motor impairment [4]. Further diagnostic and prognostic studies are warranted for gathering more specific information on post-anoxic patients with pDoC. Secondly, as far as research is concerned, the Consensus Conference revealed the need for a better understanding on the diagnostic and prognostic contribution and feasibility of advanced tools (e.g., functional neuroimaging) in the clinical setting of this specific population of DoC, as already recommended in the general population of DoC by the EAN and AAN guidelines [2, 10].

This work showed however some limitations. The literature search was restricted to MEDLINE (PubMed), Scopus and Web of Science databases, and did not involve other databases like EMBASE, Cochrane Central, or Google Scholar. However, although in some cases EMBASE provides a supplement to the search in MEDLINE, the difference is often negligible [61], and EMBASE is not freely available. For a similar reason, we did not include Cochrane Central since it has been demonstrated that it does not provide additional unique references to searches in MEDLINE or EMBASE [62]. Instead, Google Scholar was not included as it has been shown that it does not provide consistent results [63]. Secondly, the paucity of eligible literature for the majority of PICO questions could be a criticism for the recommendations and could be related to the high specificity of the PICO questions. However, the PICO questions arose from diagnostic and prognostic problems that clinicians faced in daily clinical practice and for which there were no conclusive literature indications. Consequently, many recommendations were also formulated based on the multidisciplinary shared opinion of the working group members.

The Consensus Conference did not evaluate the possible value of emerging diagnostic and prognostic markers (e.g., blood biomarkers or brain complexity indices assessed by transcranial magnetic stimulation coupled with high-density EEG) [10]. However, the CaPIADoC Steering Committee resolved to assess only tools and methods that are widely available in clinical practice, in order to ensure homogeneity of care pathways in all clinical settings most often lacking specific research expertise. Further prospective studies including both conventional and emerging markers [64] are warranted to support the adoption of a multimodal assessment in post-anoxic patients with DoC and pDoC. Besides, no treatment issues have been addressed in the CaPIADoC Consensus Conference. Further works on this topic are needed to standardise the therapeutic procedures in individuals with post-anoxic DoC and pDoC.

Conclusions

Notwithstanding these limitations, we suggest that the CaPIADoC recommendations could guide clinicians in the management of post-anoxic DoC and pDoC, and prompt an international consensus on diagnostic and prognostic procedures for such complex patients.

Most importantly, the dissemination of the results of the CaPIADoC Consensus Conference at national and international conferences, as well as through the websites of Scientific Societies and patients' family Associations, is expected to have the following future impacts: i) stimulating collaboration and dialogue among different professionals in various settings (ICU and rehabilitation wards) in order to ensure the continuum of care; ii) encouraging the development of shared protocols among professionals in different settings; iii) promoting the training of clinicians in using accurate procedures; iv) stimulating proposals for multicentre studies involving several Scientific Societies; v) enhancing communication effectiveness with families/caregivers and their active involvement in different settings.

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