An Update on Curing Coma Campaign

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Abstract

The Curing Coma Campaign (CCC) and its contributing collaborators identified multiple key areas of knowledge and research gaps in coma and disorders of consciousness (DoC). This step was a crucial effort and essential to prioritize future educational and research efforts. These key areas include defining categories of DoC, assessing DoC using multimodal approach (e.g., behavioral assessment tools, advanced neuroimaging studies), discussing optimal clinical trials' design and exploring computational models to conduct clinical trials in patients with DoC, and establishing common data elements to standardize data collection. Other key areas focused on creating coma care registry and educating clinicians and patients and promoting awareness of DoC to improve care in patients with DoC. The ongoing efforts in these key areas are discussed.

Keywords
- coma
- disorders of consciousness
- curing coma campaign
- research
- education

In 2018, the Neurocritical Care Research Network of the Neurocritical Care Society identified gaps in knowledge about coma and disorders of consciousness (DoC) necessitating prioritization for neurocritical care research prompting initiation of the Curing Coma Campaign (CCC), the first global public health initiative to tackle the unifying concept of coma as a treatable medical entity.[1] The CCC was officially launched in 2019 to address these knowledge gaps and improve care standards for patients with DoC.[2] The National Institute of Neurological Disorders and Stroke (NINDS) collaborated with the CCC to organize two virtual symposia in 2020 and 2021, involving various stakeholders and experts in coma science. These symposia resulted in the formation of multiple workgroups, each focused on specific domains related to research in coma and DoC. The discussions and proceedings of these workgroups have been published, providing valuable insights and action items to advance the CCC's mission.[3,4] Since its inception, the CCC platform now includes 1,685 members across 85 countries worldwide, with 15% of members directly working on various specific task-based modules and workgroups (►**Fig. 1**). The CCC leadership designed an organizational structure and 10-year roadmap, both of which are instrumental in aligning priorities among experts in the field (►**Fig. 2**).[5] The CCC recognizes the dedication of its members and their collaboration, which has facilitated harmonization of research efforts. This article serves as an update on the CCC, focusing on the identification of key knowledge gaps and the campaign's ongoing efforts in various areas pertaining to coma and DoC. These efforts are fundamental components of the 10-year strategic roadmap of the CCC, with the goal of improving the lives of patients with coma and DoC.

Key Areas of Focus

Advanced neurological assessment tools can offer vital insights into the pathophysiology of various stages of DoC which could help tailor treatment approaches. However, the

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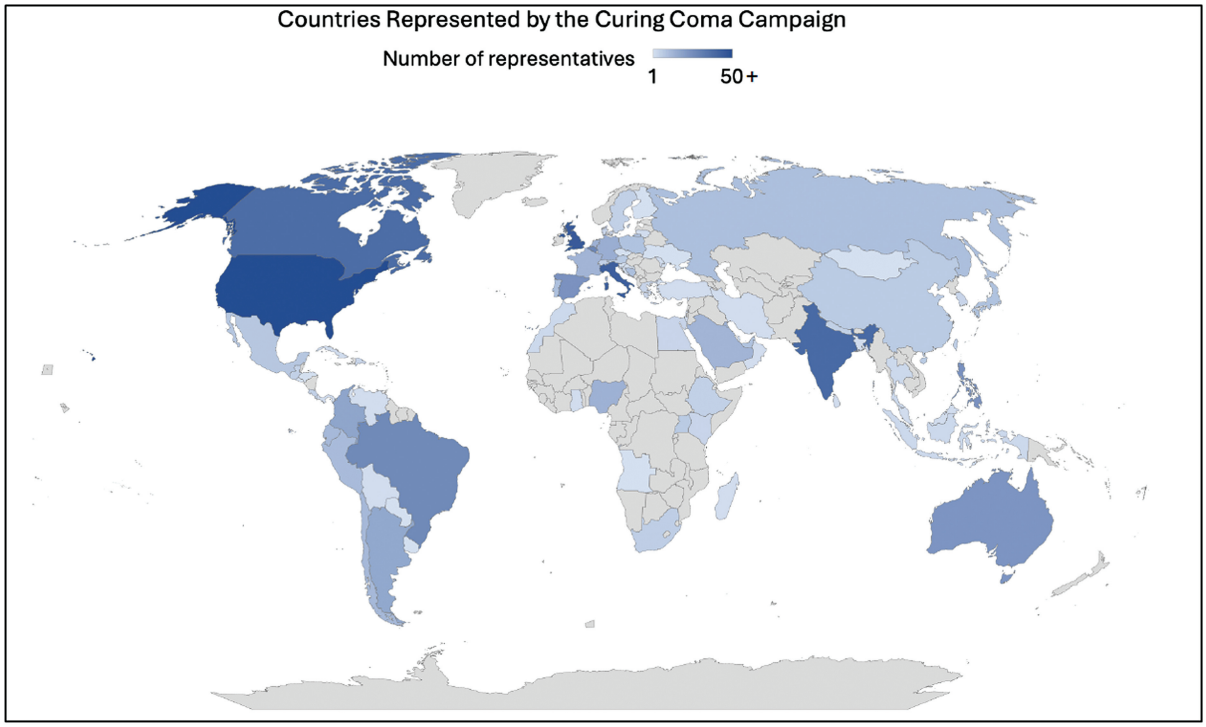

Fig. 1 A world map representing Curing Coma Campaign members. Curing Coma Campaign members across 85 countries; darker shade represents higher number of participants compared with lighter shade.

use of these advanced tools (e.g., quantitative electroencephalography (EEG)/connectivity analysis, functional magnetic resonance imaging, single-photon emission computerized tomography, positron emission tomography, invasive EEG, and cerebral microdialysis) remains limited globally, often constrained to a small number of health care systems. Currently, the diagnoses of persistent coma and DoC primarily rely on clinical assessments, which do not provide insight into the underlying dynamic pathobiological mechanisms. The absence of detailed understanding

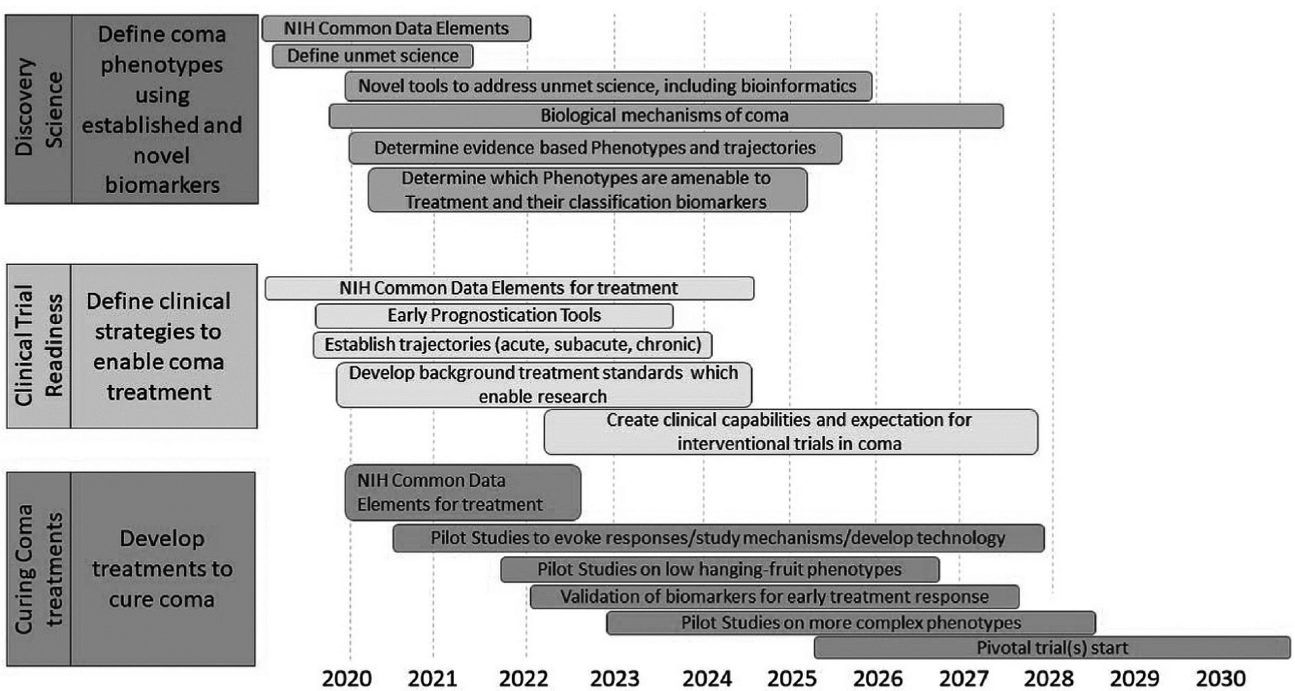

Fig. 2 Curing Coma Campaign: 10-year roadmap. An initial plan developed by Curing Coma Campaign that established three main pillars to conduct future research. Source: Olson et al.[5]

of the underlying pathology has led to a broad, yet non-targeted, application of therapeutic strategies, notably the use of neurostimulants. This generalized approach, not tailored to individual pathophysiology, results in varied and unpredictable treatment outcomes.[6] An imprecise diagnosis and inaccurate prognostication can not only result in ineffective therapeutic approaches but can also potentially lead to premature withdrawal of life-sustaining interventions. Recognizing these challenges, the CCC members have delineated critical areas of focus. This deliberate outlining of priorities is intended to guide and shape the direction of ongoing and future research in the fields of coma and DoC. A summary of research priorities is listed in ►**Table 1**.[7]

Table 1 Summary of research priorities in coma and disorders of consciousness

- Understand neurochemical substrates and biology associated with consciousness
- Differentiate clinical subtypes of DoC
- Develop comprehensive brain map using neuroimaging, behavioral assessment tools, electrophysiology, and computational models to identify structural-functional relationship
- Develop DoC specific common data elements
- Develop a comprehensive database to include imaging and text
- Build a network of organization to readily execute clinical trials
- Identify resources to institute novel statistical, analytical, and methodological approach to clinical trials design
- Develop prognostic indicators for patients with DoC
- Design an observational coma registry including pediatric population

Abbreviation: DOC, Disorders of Consciousness.
Source: Mainali et al.[7]

Current and Emerging Behavioral Assessment Tools

Of the various behavioral assessment tools, three tools are most commonly used in clinical settings, namely, Glasgow Coma Scale, Full Outline of UnResponsiveness Score, and Coma Recovery Scale-Revised (CRS-R).[8] Despite the CRS-R being the most comprehensive behavioral assessment tool for coma at the bedside, the use of advanced techniques such as stimulus-based functional MRI (fMRI) and EEG have uncovered evidence of covert command following and higher-order cortical responses (►**Fig. 3**).[9] Furthermore, although the CRS-R is endorsed by multiple clinical guidelines and is a part of the NINDS common data elements (CDE), its use is somewhat limited due to the lengthy administration time. Addressing this, the Coma Recovery Scale Revised For Accelerated Standardized Testing, an abbreviated version suitable for ICU settings, was developed; it has shorter

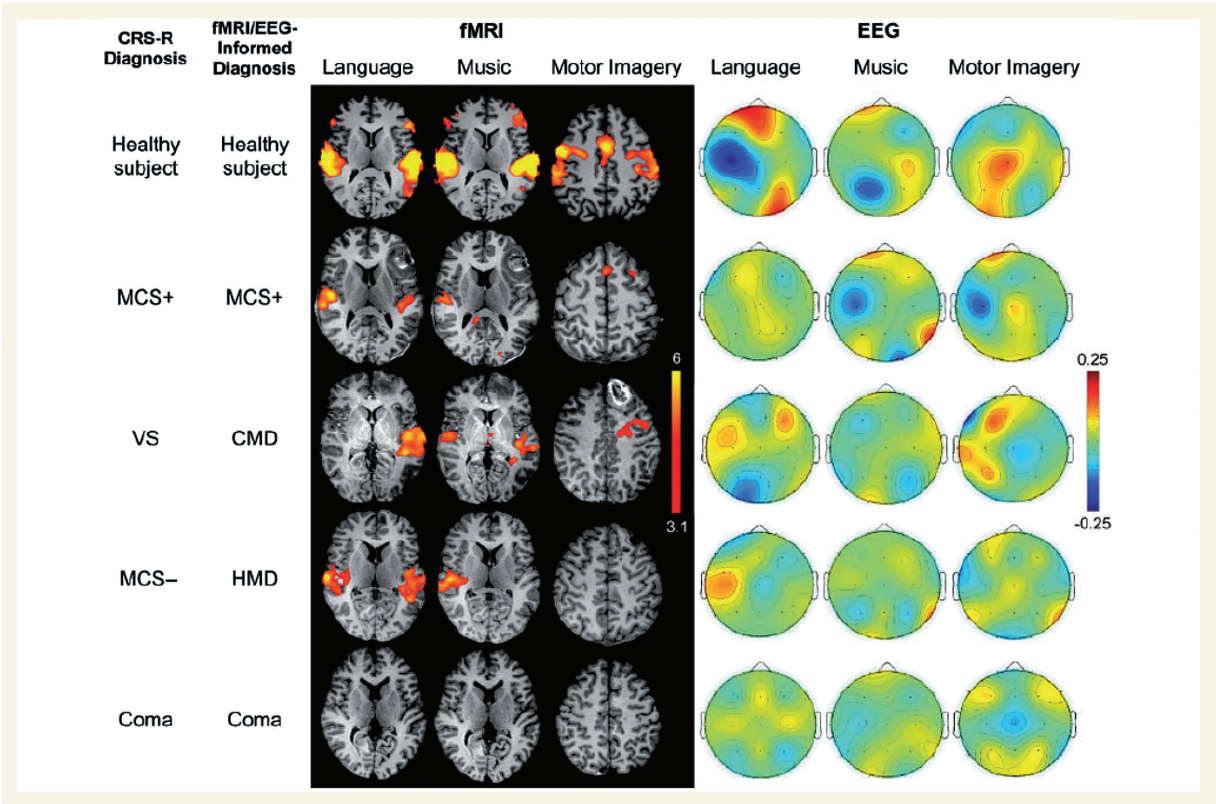

Fig. 3 Categorization of disorders of consciousness using behavioral and diagnostic tools. Abbreviations: CMD, cognitive motor dissociation; fMRI, functional MRI; EEG, electroencephalography; HMD, Higher-order cortex motor dissociation, MCS, Minimally conscious state; VS, vegetative state. fMRI and EEG results for a healthy patient and patients with different diagnosis of disorders of consciousness. Source: Edlow et al.[9]

administration time (approximately 6 minutes), potentially enabling its widespread use for early assessments following acute brain injuries.[10] Forthcoming initiatives of the CCC are actively incorporating this practical and efficient tool to enhance its utilization at a global scale.

Advancing Imaging Modalities and Electrophysiology in Practice

Incorporating various imaging modalities alongside clinical tools (such as clinical biomarkers, patient characteristics, and behavioral assessments) can provide a more comprehensive approach and potentially enhance the accuracy of prognostication. They include fMRI, quantitative EEG, transcranial magnetic stimulation EEG (TMS-EEG), and fluorodeoxyglucose positron emission tomography.[11] Presently, the correlation between clinical assessment and neuroimaging findings remains imperfect, highlighting an area ripe for further investigation. This knowledge could not only refine prognostic precision but also play a crucial role in selecting patients for acute interventions and possibly optimizing the allocation of health care resources. Ongoing efforts are being made to increase the sensitivity and specificity of imaging studies to yield more accurate prognoses. For instance, the measurement of quantitative whole-brain white matter fractional anisotropy in postcardiac arrest patients has shown promise with normal values linked to favorable outcomes at 6 months, suggesting its potential utility in guiding decisions regarding continuation of care.[12] Similarly, recent findings suggest that in patients affected by coronavirus disease 2019, quantitative diffusion tensor imaging could be effective in identification of cortical and hippocampal abnormalities that account for the altered mental states observed in many individuals.[13] The ongoing research in advanced neuroimaging is crucial, not only for enhancing its value in prognostication, but also as a vital tool for unraveling the complexities of structural and functional brain networks. This understanding is expected to significantly aid in the development and advancement of future therapeutic interventions.

EEG is increasingly utilized for assessing consciousness in intensive care units (ICUs). In ICU settings, EEG can differentiate between the unresponsive wakeful state and the minimally conscious state (MCS) with high predictive accuracy, albeit with limited sensitivity.[14] However, at times, EEG or fMRI alone may not be sufficient to evaluate for MCS. A combination of EEG with TMS may enhance diagnostic sensitivity and mitigate common confounders in ICU environments.[15] This approach, which involves directly exciting neurons using TMS and measuring the brain's response via EEG, allows for quantifiable interpretation. TMS-EEG appears to offer several advantages: it neither rely on the integrity of the sensory or motor systems nor on the cognitive function of the patient, and it provides insights into overall brain dynamics. Presently, the application of TMS-EEG is constrained by a lack of standardized procedures and interpretation methods. However, future clinical trials aimed at testing its reliability in ICU patients, along with advancements in device refinement for clinical use, could broaden its adoption among health care providers.

Assessment of Cognitive Motor Dissociation in Neuroprognostication

Cognitive motor dissociation (CMD) is characterized by a distinctive state of consciousness in which cognitive responses are evident in advanced monitoring tools like fMRI or task-based EEG, while no motor responses are observed during clinical bedside examinations. One important feature of CMD is the engagement of the associated cortex which is detected by fMRI or EEG.[16] This was first reported in a patient with traumatic brain injury who was unresponsive behaviorally but evidently showed appropriate neuronal response on fMRI. Diagnosing CMD presents substantial challenges, primarily stemming from significant gaps in current scientific knowledge and the limited availability of advanced diagnostic tools, which are accessible in only a few specialized centers globally. However, recognition of CMD is crucial, as timely detection has been linked to better functional outcomes following brain injuries. Despite this, CMD often remains underdiagnosed, underscoring the urgent need for enhanced scientific understanding, development of refined diagnostic criteria and future development of simplified and scalable tools. A summary of major gaps reported by Coma Science Working Group of the CCC is listed in ►**Table 2**. The initial steps toward addressing this gap involve in-depth exploration of the key brain networks that govern consciousness, along with an evaluation and potential repurposing of existing tools to efficiently diagnose CMD. Accurate prognostication based on improved understanding of CMD can lead to better resource allocation, individualized treatment plans, and setting realistic expectations for recovery. Furthermore, these advancements are crucial in promoting enhanced involvement and informed decision-making among caregivers, ensuring that they are more actively engaged in the care process. Thus, advancement in CMD research holds great potential for significantly impacting patient care and remains one of the CCC's areas of focus.

Harnessing Computational Modeling in Brain Injury Research

Utilizing data and algorithms through mathematical and computer science methods is a powerful tool for researchers studying brain injuries. These techniques enable the creation of diverse simulations, providing a comprehensive understanding of brain injury from the cellular to the clinical level. Recently, Luppi et al described two approaches to modeling: statistical and biophysical models. Descriptive statistical modeling, a traditional approach, focuses on identifying relationships between disease predictors.[17] It operates either by analyzing individual data points (supervised model) or by examining data point aggregations (unsupervised model). Generative statistical modeling, in contrast, infers patterns within data, thus enabling the generation of new data points. Biophysical models take a different approach, applying biological knowledge to understand the intricacies of brain injury mechanisms and effects. These models are subject to rigorous validation to ensure their reliability and

Table 2 Major Research Gaps for Patient with Cognitive Motor Dissociation (CMD)

1. Lack of consensus on a term and definition that fully encapsulates the concept of Cognitive Motor Dissociation (CMD).
2. The lack of comprehensive, multicenter studies investigating the prevalence of CMD across diverse brain injury populations.
3. Lack of firsthand accounts from patients experiencing CMD to enhance understanding and care approaches.
4. Insufficient understanding of the perspectives of caregivers, including families and healthcare professionals, who support CMD patients.
5. Uncertainty surrounding the mechanisms of CMD, necessitating comprehensive, multimodal analyses of brain structure and function at both the network and cellular levels.
6. Lack of a standardized approach/protocol to identify CMD, considering individual (age, sex), contextual (injury type, sedation level), and logistical (ICU vs. nursing home setting) variables.
7. Lack of educational programs and training for healthcare professionals regarding the implementation of existing methods for detecting CMD.
8. Lack of comprehensive understanding related to the detection of CMD and its implication on patient-focused outcomes, including quality of life and long-term recovery.
9. Lack of advanced technology such as the brain-computer interface (BCI) to establish communication with CMD patients.
10. Lack of understanding related to the variability in neural recovery pathways in CMD patients and implications for rehabilitation to optimize outcomes.

Adapted from Classen et al.[16]

reproducibility. They are instrumental in producing simulations that facilitate the testing of specific treatments, potentially influencing clinical outcomes.

Integration of clinical, biological, and imaging data can lead to the development of a neuro-recovery process model, considering various outcomes at different time points. This computational modeling approach is promising for deepening our understanding of DoC and enhancing treatment methodologies and remains a ripe area of growth for the CCC.

Study Design Considerations in Disorders of Consciousness Research

Studies focusing on DoC face several challenges, including their observational nature, limited generalizability, methodological heterogeneity, and a dearth of long-term outcome data. These limitations were thoughtfully reviewed and discussed by Cho et al, who also provided insights into the optimal design of clinical trials for DoC.[18] Clinical trials involving patients with DoC present unique challenges, particularly in terms of definitively defining endotypes, often necessitating a reliance on phenotypic characteristics. Additionally, there is a substantial challenge concerning resource allocation in both inpatient and outpatient settings, including the provision of expert DoC care and ensuring continuity of care, which may influence the overall study design. Traditional comparative effectiveness study designs may not be the most efficient approach in DoC research due to the potential presence of numerous confounders, such as patient and treatment heterogeneity, limited sample sizes, and protracted study durations. Alternatively, platform trials emerge as an appealing design choice, as they allow for the evaluation of multiple interventions within shorter timeframes and across various settings, provided that there are no significant interactions among the interventions. This innovative approach may help address some of the complexities associated with studying DoC and expedite advancements in our understanding and treatment of these conditions.

The importance of standardization through the utilization of CDEs has been widely acknowledged by research funding agencies as a crucial support mechanism for research endeavors. These efforts facilitate sharing and consolidation of datasets, particularly those generated from clinical trials. As a testament to this commitment, the CCC has commenced the publication of manuscripts describing CDEs for coma and DoC, including case report forms.[19–27] The development of these CDEs followed a meticulous process, commencing with a comprehensive review of existing CDEs from the NINDS CDE catalog. These were then supplemented with newly crafted CDEs tailored specifically to enable standardized data collection for DoC. The final selection of CDEs resulted from a consensus-driven approach, which involved evaluating and discussing factors such as availability, feasibility, reliability, and the strength of supporting evidence. On average, the timeline for the final development of these CDEs spanned approximately 2 years. The overarching goal of this initiative is to establish a standardized approach to data collection and reporting while fostering collaborations on a global scale. Notably, this effort represents one of the inaugural undertakings by the CCC, making it the first organization in this field to achieve this pivotal milestone. The CDE recommendations offer standardization for data collected on various fronts, including behavioral phenotyping, goals-of-care, family/surrogate decision-making, neuroimaging, electrophysiology, physiology, big data, hospital course/confounders, biospecimens, outcomes and endpoints, and therapeutic interventions. For researchers' convenience, case report forms are accessible on the Zenodo website (https://zenodo.org/records/8172359) and can be readily downloaded.[28]

Current Research Initiatives Endorsed by the Curing Coma Campaign

Six research studies, endorsed by the CCC, have received funding and are currently in progress. These studies include:

1. Curing Coma Campaign Acute Coma Prospective Pilot Observational Study (COMPOSE): Supported by the NeuroCritical Care Foundation, COMPOSE is a prospective, multicenter study designed to characterize the natural history of coma recovery across various etiologies in a diverse population. The ultimate goal is to identify biomarkers that define coma endotypes for targeted intervention.
2. Covert Volitional Eye Response Test (COVERT): Funded by the National Institute of Health (NIH), this multicenter study investigates whether covert tracking during ICU stays can predict recovery in brain injury patients.

3. Pilot Trial of a Web/Mobile/Tablet-Based Communication and Goals-of-Care Decision Aid: Supported by the NIH, this study focuses on a digital aid and communication (DA + C) tool for clinicians and families of patients with moderate to severe traumatic brain injury, large hemispheric acute ischemic stroke, and intracerebral hemorrhage, aiming to facilitate informed, shared decision-making.
4. Precision Care in Cardiac Arrest- Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients (ICECAP): Also funded by the NIH, this study is part of the ICECAP trial, applying machine learning to identify biomarkers predicting responses to therapeutic hypothermia and functional recovery.[29]
5. Electroencephalographic Biomarkers of Covert Conscious Processing During Pediatric Coma: This research assesses covert consciousness in pediatric acute brain injury using event-related potentials in EEG.
6. Knowledge Translation Strategies for Provider Adoption of American Academy of Neurology -American Congress of Rehabilitation Medicine-National Institute on Disability, Independent Living and Rehabilitation Research Guidelines: Targeting clinicians across various care settings, this survey-based study evaluates the understanding and implementation of DoC guidelines set by the American Academy of Neurology, American Congress of Rehabilitation Medicine, and the National Institute on Disability, Independent Living, and Rehabilitation Research.

Establishment of a Coma Care Registry

The CCC is also working on developing a coma care registry, modeled off other disease-specific registries like the American Heart Association's Get With the Guidelines—Stroke registry. The primary objective of this registry is to offer real-time feedback to participating entities and enhance the quality of care provided. Presently, the registry is in a pilot phase, concentrating on the prospective collection of data, thorough analysis, and sharing of data among participating institutions. The aggregated data from this registry will serve as an invaluable asset for monitoring, comparing current medical practices, and analyzing patient outcomes. This initiative is expected to empower clinicians and scientists with actionable insights, thereby facilitating more informed decision-making and overall enhancement of patient care. The registry will include comprehensive patient-level information, encompassing demographics, treatments, and outcomes.

Efforts Related to Coma and Disorders of Consciousness Education

In addition to ongoing efforts to promote DoC research, the CCC is working on promoting knowledge about the care of individuals with DoC. The Curing Coma Campaign International Survey on Coma Epidemiology, Evaluation, and Therapy study, an international epidemiological endeavor by the CCC, provided crucial insights into the care of patients with DoC.[6] Although the survey found significant agreement among health care professionals on the definition of coma, there was poor consensus on its cardinal features (►**Table 3**). It also highlighted the limited use of advanced neurological assessment tools (►**Fig. 4**) and the need for more definitive neuroprognostication determinants. Additionally, 86% of respondents demonstrated interest in future collaborative research. Recognizing the outcomes of the COMETOGETHER survey, which highlighted the lack of consensus among health care professionals and inconsistent practices in coma care worldwide, the CCC launched an Education Module. This module is designed for health care professionals involved in patient care across various stages, spanning from prehospital to hospital and posthospital rehabilitation care. It aims to cover an extensive range of topics crucial for a multidisciplinary care team, including the diagnosis, treatment, and prognosis of coma and DoC across all age groups. It also sheds light on the future prospects of the field, particularly focusing on ongoing research and advancements not yet integrated into routine clinical practice. This module ensures that global health care professionals receive standardized training and ongoing education. It aims to establish a consistent comprehension of coma and DoC management strategies, encourage the adoption of evidence-based guidelines, promote the utilization of advanced coma and DoC assessment techniques, and facilitate interdisciplinary collaboration and coordinated follow-up care. By educating the health care workforce on coma and DoC care, the module contributes to the efficiency of health care systems and may reduce costs associated with ineffective or inconsistent care. Furthermore, the CCC's Education Module will work collaboratively with the Community of Collaborators Module and together play a vital role in enhancing communication with patients and families, thereby improving public awareness and understanding of coma and DoC and related conditions and helping to dispel misconceptions and reduce stigma. Community of Collaborators Module serves as a communication channel between CCC and patients, families, and advocacy groups. Overall, this initiative will hopefully benefit patients by improving outcomes and quality of life and positively

Table 3 Definition of coma developed by expert consensus

Coma is defined by the absence of sustained spontaneous or stimulus-induced arousal/wakefulness. The following criteria must be met on clinical examination to establish the diagnosis of coma: 1. No command following, and, 2. No intelligible speech or recognizable gesture, and 3. No volitional movement (reflexive movement such as extensor or flexor posturing, withdrawal from pain, triple flexion may occur), and 4. No visual pursuit, fixation, saccade to stimuli, or eye opening or closing to command, and 5. The above criteria are not due to use of paralytic agent, active use of sedatives, another neurologic or psychiatric disorder (e.g., locked-in syndrome, neuromuscular disorder, catatonia, akinetic mute, abulia, conversion disorder), and 6. The patient does not have evidence of cognitive motor dissociation (i.e., the covert ability to follow commands) based on electrophysiological or functional imaging, if such testing is available.

Source: Helbok et al.[6]

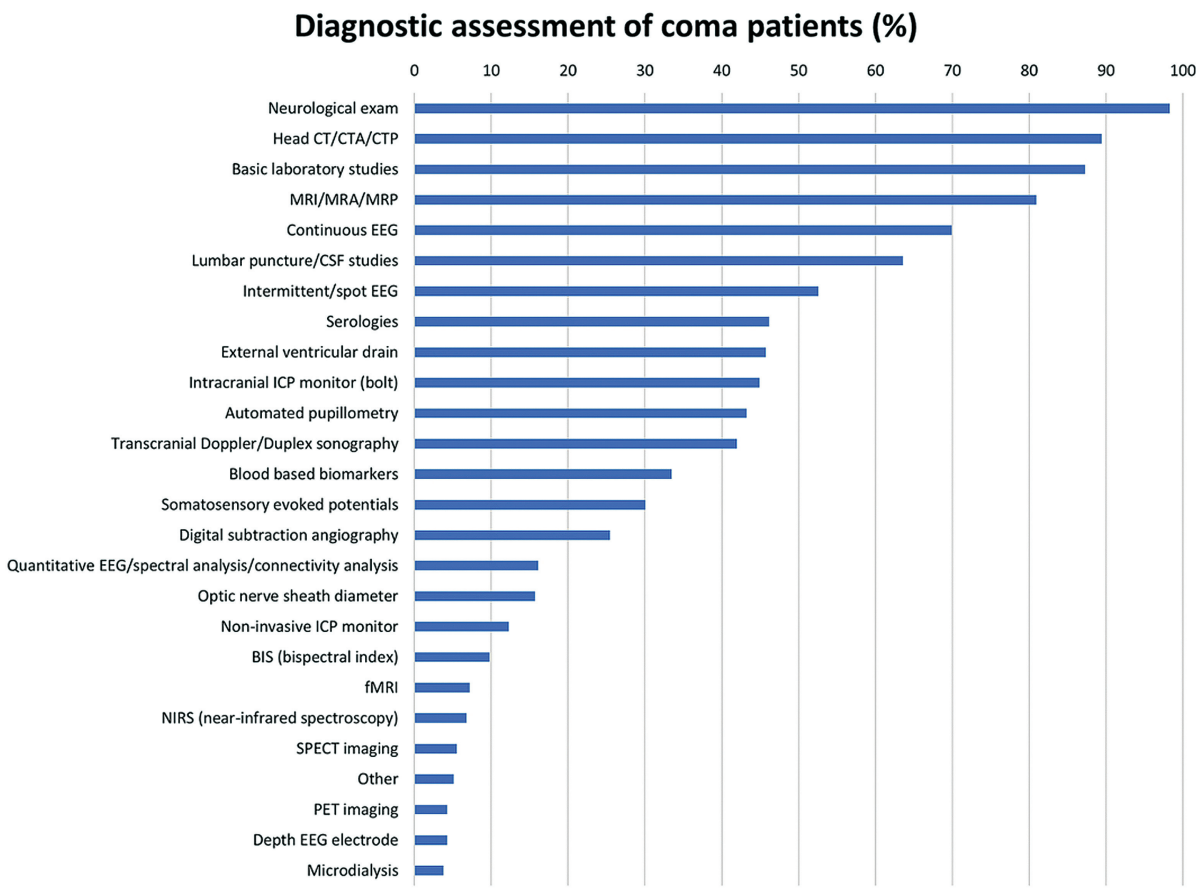

Fig. 4 Diagnostic tools used for the evaluation of disorders of consciousness. Source: Helbok et al.[6]

influence society by fostering understanding, reducing stigma, and optimizing health care resource allocation. The education efforts of the CCC mark a substantial step forward in enhancing the medical community's comprehension of coma and DoC care and equipping clinicians and scientists with essential knowledge for effective patient care coordination and the development of practical clinical trials.

World Coma Day: Raising Awareness and Fostering Global Collaboration

World Coma Day, organized under the auspices of the CCC, has emerged as an effective platform for raising awareness about coma and DoC research and facilitating networking opportunities. Celebrated annually on March 22nd since 2021, World Coma Day brings together a diverse group of stakeholders, including clinicians, scientists, patients, caregivers, and the general public. The day is dedicated to celebrating patient recovery milestones, acknowledging the perseverance of families, and highlighting the efforts of medical professionals in advancing the field of coma and DoC.

Since its inception, World Coma Day has seen remarkable growth and participation, attracting over 1,000 participants from more than 80 countries in 2023. The event features a range of activities, including presentations, discussion sessions, educational material showcases, scientific updates, inspirational recovery stories, and support messages from advocates dedicated to coma and DoC research. A particularly moving segment is the "Stories of Hope," where patients and their families share their journeys, which is subsequently archived on the curing coma webpage (www.curingomca.org) for public viewing. These narratives are powerful reminders of the importance of continuing research and treatment in the field of DoC.

Looking forward, plans are underway to restructure the event to reach an even broader audience by expanding online video access and featuring contributions from various stakeholders. Information about past and upcoming World Coma Day events is available on the Curing Coma website (https://www.curingcoma.org/), providing a comprehensive view of the initiatives and progress in this vital area of medical research and patient care.

Future of the Curing Coma Campaign

In summary, the quest to deepen our understanding and improve care for those with coma and DoC is ongoing and marked by considerable knowledge gaps. The CCC plays a crucial role in this journey, establishing key infrastructure and encouraging collaboration among medical professionals

worldwide. The CCC focuses on identifying vital research areas and educational opportunities, supporting ongoing studies and initiatives, striving for standardization in data collection and management strategies, and fostering necessary clinical collaborations. These efforts are instrumental in gathering timely, patient-centered data and creating a platform for gaining valuable insights into coma and DoC care. The field of coma and DoC research holds immense potential, and the CCC is committed to exploring this domain. The goal of the CCC is to enhance the recovery process through early and continuous interventions. As the CCC mission moves forward, its global collaborative and dedicated approach offers hope for advancements in understanding and treating coma and DoC, benefiting affected individuals and their families. More information and updates on the CCC's efforts and research initiatives are available on the CCC's official website (https://www.curingcoma.org/).

Authors' Contributions

K.K. drafted initial manuscript, provided substantial intellectual contribution, integrated feedback from co-authors, and brought the document to its final form. L.P., J.S., D.O. and C.H. contributed in critical review of the manuscript and provided essential intellectual content.

S.M. Drafted and revised portions of the manuscript, substantial intellectual insights on the overall manuscript, critical review and finalization of the manuscript.

Conflict of Interest

None declared.

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