International Survey on Diagnostic and Prognostic Procedures in Pediatric Disorders of Consciousness

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Abstract

Aims: 1. to investigate diagnostic and prognostic procedures routinely used by international professionals to assess children with disorders of consciousness (DoC); 2. to explore use and availability of internal and national guidelines for paediatric DoC; 3. to identify international differences in diagnostic/prognostic protocols.

Methods: The International Brain Injury Association DoC Special Interest Group emailed a survey link to 43,469 professionals. The survey included questions on diagnostic/prognostic procedures and guidelines for children with DoC.

Results: Data on 82 respondents [(50% physicians) primarily from Europe (43.9%) and North America (37.8%)] were analysed. Common diagnostic tools included the Glasgow Coma Scale for clinical assessment (94%), the Coma Recovery Scale-Revised for outcome measurement (57%), and cerebral MRI (94%). Clinical features used most frequently to inform prognosis varied with age. Few respondents used national (28%) admission protocols for children with DoC, and most were unaware of published national guidelines for diagnostic (72%) and prognostic (85%) procedures. Compared to North American respondents, more European respondents were physicians and used neurophysiological data for prognosis.

Conclusions: This international survey provides useful information about diagnostic and prognostic procedures currently used for children with DoC and highlights the need for guidelines to promote best practices for diagnosis/prognosis in paediatric DoC.

Keywords: Disorders of Consciousness; paediatric population; severe brain injury; diagnosis; prognosis; medical practice survey; questionnaire.

Introduction

Prolonged disorders of consciousness (DoC) following traumatic or non-traumatic severe brain injury encompass clinical conditions characterized by preserved wakefulness and a complete loss of consciousness [vegetative state/unresponsive wakefulness syndrome (VS/UWS)] (1,2) or minimal and reproducible behavioural signs of awareness of environment and self [minimally conscious state (MCS)].(3) While there is more than 25 years of research focusing on better understanding these severely disabling clinical states, diagnostic assessment and prediction of outcome of patients with DoC remains challenging.(4–6) Distinguishing patients in VS/UWS from those in MCS and predicting outcome are crucial for planning rehabilitation and apprising caregivers about ongoing recovery and life expectancy.

For children, diagnosis and prognosis are even more challenging. Accurate assessment of children with DoC is particularly difficult given the rapidly developing skills during early childhood.(7) Clinical outcomes of children with DoC are not yet well-defined, since only a few cohort studies have addressed this issue.(8–11) Studies investigating diagnosis and prognosis of children with DoC have employed measures validated in adults(9–11) or included both children and adults.(11) Given this paucity of research, there are no evidence-based guidelines for clinical assessment and prognosis of children with DoC, as reported in the recent American care recommendations for patients with prolonged DoC.(12)

The IBIA (International Brain Injury Association) DoC-Special Interest Group (DoC-SIG) developed and disseminated a survey for healthcare providers to explore which specific diagnostic protocols and prognostic indices are routinely adopted in care pathways for

children with DoC, if national or regional guidelines exist for diagnostic and prognostic procedures for children with DoC, and whether routine care or protocols differ by countries.

Methods

Survey questionnaire

The survey consisted of 34 questions. Questions focused on diagnostic tools and prognostic indices routinely used in care and management of paediatric patients with DoC by professionals within each of the respondents' facilities. Items were selected by four IBIA DoC-SIG members (E.M., B.S., A.E, C.S.) from current literature on clinical and instrumental measures for diagnosis and prognosis of patients with DoC.(4,13,14)

Questions about respondents' profession, country, institutional setting (i.e. post-acute rehabilitation, chronic facilities or nursing home), and age of admitted patients were included in the first section of the survey.

Diagnostic and outcome measures. Respondents were asked to indicate tools routinely used by professionals at their institutions by choosing among: 1. neurobehavioral assessment measures [Glasgow Coma Scale (GCS),(15) Rappaport Coma Near Coma Scale (CNCS),(16) Levels of Cognitive Functioning Scale (LCFS),(17) Coma Recovery Scale Revised (CRS-R),(18) and Western Neurosensory Stimulation Profile (WNSSP)(19)]; 2. neurobehavioral outcome measures [CNCS, LCFS, CRS-R, WNSSP, Disability Rating Scale (DRS),(20) Glasgow Outcome Scale-Extended (GOSE-E),(21,22) Glasgow Outcome Scale Extended-Paediatrics (GOS-E Peds)(23)]; 3. neurophysiological measures [electroencephalography, brain stem auditory evoked potentials, visual evoked potentials, somatosensory evoked potentials, and event related potentials](24,25); 4. neuroimaging tools [computerized axial

tomography (CT), magnetic resonance imaging (MRI), positron emission tomography, and functional MRI (*f*MRI)].(26) For each tool, respondents were asked to indicate which measure they used for individuals of various age ranges: 0-< 6 months, 6 months–<3 years, 3–7 years, 8-< 12 years, 13–<18 years.

Prognostic indicators. Questions about prognostic indicators included demographic and medical history (age, aetiology, previous brain injury and premorbid clinical conditions), clinical features (diagnosis of VS/UWS versus MCS, pupillary reflex, visual fixation, visual pursuit/tracking, spontaneous motility, and time to follow commands) and clinical phenomena (pathological postures, dysautonomias/ paroxysmal sympathetic hyperactivity, psychomotor agitation/restlessness, primitive oral automatisms), medical complications (e.g. recurrent infections/hyperthermia, assisted respiratory function, need for oxygen therapy, critical illness polyneuropathy/myopathy, heterotopic ossifications, epilepsy, severe spasticity), neurophysiological data (electroencephalography /polysomnography, brain stem auditory evoked potentials, visual evoked potentials, somatosensory evoked potentials, and event related potentials) and neuroimaging findings [CT, structural MRI, diffusion tensor imaging/tractography, *f*MRI/functional connectivity, positron emission tomography]. Respondents were asked to identify which pharmacological therapies possibly interfere with recovery of consciousness. Respondents were asked to indicate which clinical features were prognostic markers for various age ranges: 0-< 6 months, 6months-<3 years, 3-<12 years, 13-<18 years.

Guidelines. Respondents were asked about the existence of published national/regional guidelines for diagnostic and prognostic procedures in children with DoC and if they follow any national or internal protocols for patients' admission criteria. A protocol was defined as

a guideline or set of guidelines issued by a committee, technical group, or work group on behalf of a national healthcare/government system (for national protocols) or on behalf of hospital/institution (for internal protocols). The questionnaire is provided in the Supplementary Document.

Survey dissemination procedure

The survey was loaded on *SurveyMonkey* platform (https://www.surveymonkey.com). Invitation to participate were sent by e-mail to 43,469 individuals including IBIA or International Paediatric Brain Injury Society members, conference attendees, and others interested in learning about IBIA or IPBIS. Invitations were sent 3 times (initial invitation, reminders 15 days and 30 days later). A total of 9,651emails were opened and 416 emails were not deliverable. Inclusion criteria for participation were a health professional or researcher working with children (0 to <18 years) with DoC and currently working in a centre admitting paediatric patients with DoC. No minimal period of experience was required. The survey was available online from 4/12/17 to 5/20/17, took 15-20 minutes to complete, and had to be completed in one session, as respondents could not edit responses after exiting the questionnaire. It was possible to skip questions.

Data analysis

Responses and omissions were calculated for each question. Because data were not missing completely at random, missing data were dealt with by item-level Multiple Imputation (MI), a "gold standard" method in treatment of data missing at random(27–30) (Little's MCAR test, $p<0.001$). Responses towards the end of the questionnaire were most likely to be missing. For diagnostic measures and prognostic indicators, independent sample t-tests were used to compare means of those with and without missing data. Listwise deletion, pairwise

processing, and MI was applied to diagnostic and prognostic indicators. Further data normalization was performed based on respondents' report of age ranges admitted to their facilities. Missing variable were imputed and adjusted for corresponding proportions of admission for each age range. We imputed 5, 10 and 50 datasets, conducted analyses on each imputed set, and pooled results. Multiple imputation with 50 datasets was chosen for reporting results. Demographics and use of diagnostic and prognostic tools were compared between respondents in different continents through χ^2 tests.

Results

Demographics

Eighty-seven questionnaires were submitted. Five were excluded [2 respondents did not identify as health professionals or researcher (1=no response anonymous; 1=brain injury survivor), 3 did not admit children to their facilities]. Eighty-two surveys from 78 different medical centres were included (Figure 1).

Most were medical doctors (50.0%) followed by psychologists (18.3%). Most were in Europe (43.9%) and North America (37.8%), whereas few were in other continents (e.g., Asia=7.3%, Africa=2.4%). Almost all respondents worked in facilities that admitted children between 3-12 years of age (90.0%) and 13-17 years of age (92.5%). Less admitted those between 6 months-3 years of age (73.8%) and <6 months of age (56.3%). Over half worked in facilities that also admitted individuals >18 years of age. The respondents in Europe included more medical doctors (p=0.009; North America=33.3%; Europe=59.5%; for valid responses). More respondents in North America admitted 18-20 years olds (p=0.035; North America=78.8%; Europe=54.1%). (Table 1).

Over half worked in an intensive specialized rehabilitation facility for post-acute patients with DoC and one-third in a specialized rehabilitation setting for patients with chronic DoC. More than a quarter worked in community centres, private rehabilitation practices and hospitals for acute patients. A minority indicated working in more than one setting. (Table 2)

Diagnostic and outcomes measures

Neurobehavioral tools. The GCS was employed most for clinical assessment of paediatric DoC followed by the CRS-R. (Table 3)

The CRS-R was used most for outcome assessment overall and in children >3 years of age. For children <3 years of age, the GOS-E Peds was used most frequently. (Table 4)

Neuroimaging and neurophysiological tools. Of neuroimaging tools, cerebral MRI was used routinely by most; CT scans were also used by three-quarters. Of neurophysiological tools, electroencephalography was used routinely for diagnosis more than other tools. (Table 5)

Prognostic indicators

Two thirds (66.3%) reported using prognostic indicators to plan rehabilitation treatment or to provide prognostic information to family caregivers in the clinical practice.

Patient Characteristics. Aetiology of DoC was used most to inform prognosis (62.7%), followed by age (58.1%), premorbid clinical comorbidities (54.0%), and previous brain injury (52.0%). One third (33.2%) reported not using any patient characteristics to inform prognosis.

Clinical features and complications. Clinical features used to inform prognosis varied with age. Visual pursuit was reported most frequently as a prognostic marker for children <3 years, whereas clinical diagnosis (VS/UWS versus MCS) was considered most informative in older children and adolescents. (Table 6)

Clinical complications, including epilepsy, intractable severe spasticity, and neurosurgical sequelae (absence of cranioplasty or presence of hydrocephalus) were thought to be relevant for prognosis for more than three quarters of respondents, whereas need for oxygen therapy and the presence of heterotopic ossifications were used by less than half. (Table 7)

Neurophysiological and neuroimaging tools. Most respondents used structural imaging findings (82.4%), followed by diffusion tensor imaging/tractography (30.8%) and fMRI/functional connectivity (22.8%) (for prognosis. When considering neurophysiological data, 51.9% reported routinely using standard electroencephalographic background activity for prognosis. Other neurophysiological measures were reported to be used routinely less frequently [presence of N20 on somatosensory evoked potentials (29.9%), polysomnography over 24 hours/Sleep Patterns for Paediatric Unresponsive Wakefulness Syndrome (29.8%) and presence of late event related potentials (25.1%)]. A minority reported not using neuroimaging (17.1%) or neurophysiological data (36.8%) to inform prognosis.

Pharmacological therapies. Most indicated that certain medications interfered with recovery [sedatives (e.g. benzodiazepines) (85.9%), anti-epileptic (74.6%), anti-spasticity (50.9%), and GABAergic (45.3%)].

Guidelines

Few respondents endorsed following national protocols for admission criteria for children with DoC, although over half reported following institutional protocols for admission. Of those who followed national or internal protocols, many indicated that the protocols were originally developed for adults and adapted for children. Respondents who reported following national protocols for admission criteria specified several sources (e.g., Aspen workgroup on MCS, Multi-Society Task Force on PVS, document issued by Italian Ministry of Health in 2005, Proceedings of consensus conference on Rehabilitation of TBI in 2000, regional documents, etc.) Few reported knowledge of published national guidelines for diagnostic or prognostic procedures. Of those, one indicated that there were clinical practice guidelines for acute DoC for children and another noted the existence of paediatric trauma literature; none identified specific publications. (Figure 2).

Practice differences between Europe and North America

Among neurobehavioral tools routinely adopted for clinical assessment and outcome, respondents reported using the WNSSP more frequently in North America ($p=0.030$ for assessment and outcome; North America=28.6%; Europe=4.0%). Use of other neurobehavioral measures did not differ between continents. Respondents in Europe reported routinely using neurophysiological tools more than those in North America [Brainstem auditory evoked potentials ($p=0.018$; North America=7.1%; Europe=44.0%), visual evoked potentials ($p=0.038$; North America=14.3%; Europe=48.2%) and somatosensory evoked potentials ($p=0.022$; North America=14.3%; Europe=52.1%)], and cerebral MRI ($p=0.030$; North America=57.1%; Europe=88.0%). Among patients' characteristics, age ($p=0.038$; North America=85.7%; Europe=52.0%) and previous brain injury ($p=0.039$; North America=78.6%; Europe=43.8%) were more frequently considered for prognosis in North America.

Discussion

This is the first international survey exploring use of diagnostic tools and prognostic indices for routine management of children with DoC. Overall, respondents reported that commonly used diagnostic tools included GCS, CRS-R, MRI, and electroencephalography. Among clinical scales, the GCS was employed most for behavioural assessment of paediatric DoC. Frequently used neurobehavioral outcome measures varied by age, with the GOS-E Peds used for children <3 years and CRS-R for older children. Common prognostic indices included structural imaging and patient characteristics. Clinical features used most frequently to inform prognosis varied with age [visual pursuit for children <3 years, VS/UWS versus MCS for older children]. Few followed national protocols when admitting children with DoC and most were unaware of published national guidelines for diagnostic/prognostic procedures. Compared to North America, more respondents in Europe were physicians and used neurophysiological data for prognosis.

The finding that GCS was the neurobehavioral measure most frequently used for clinical assessment of children with DoC is surprising given the limitations of the GCS in detecting signs of consciousness in adults with DoC.(31,32) While CRS-R is thought to be the gold standard for detecting level of consciousness in adults,(33) no study to date has examined reliability and validity of the CRS-R in children. Additionally, some items of the CRS-R may be unsuitable for young children due to reliance on language for many items. Also, the CRS-R requires training that paediatric providers may not routinely obtain, while the GCS is a simple measure and familiar to most professionals, especially physicians.

The CRS-R was reported to be used most frequently as an outcome measure for children >3 years of age; however, the GOS-E Peds is used most frequently for children aged <3 years. While the CRS-R has not been well studied in children and may not be appropriate in young children, the GOS-E Peds, a modification of the GOS-E for adults, was developed specifically for children. There are also several studies examining the GOS-E in children with traumatic brain injury.(8,23,34)

Neuroimaging and neurophysiological tools frequently used for diagnosis included MRI and CT scans and electroencephalography. Responses are consistent with the literature showing that CT and MRI are useful to quantify structural brain disruption post-injury in children,(35) whereas electroencephalography detects factors potentially influencing clinical assessment (e.g. epileptiform abnormalities or non-convulsive epilepticus status) or complements the diagnostic process.(36,37) In adults, electroencephalography has proved useful for disentangling VS/UWS from MCS patients, since a worse background activity and lack of any electroencephalographic reactivity might characterize VS/UWS, whereas a better electroencephalographic background organization can identify patients with higher level of consciousness.(38) Recent studies have examined these methods in small cohorts of children with DoC,(25,26,39) exploring sub-tentorial diffusion tensor imaging measures as diagnostic biomarkers and electroencephalographic sleep/wake modulation as a prognostic biomarker. While advanced neuroimaging and neurophysiological techniques, such as event related potentials, visual evoked potentials and *f*MRI can supplement clinical evaluation, availability, methodological constraints and challenges in data interpretation might limit their use in clinical routine of patients with DoC.(40)

Outcome from DoC is difficult to predict in children and adults; however, similar to adults, levels of consciousness (MCS versus VS/UWS) have been associated with outcome.(10,11,41) Consistent with this literature, most respondents indicated using levels of consciousness as a prognostic marker for older children. Interestingly, for children <3 years of age, visual pursuit was thought to be most useful prognostic marker. Providers may identify visual pursuit as relevant for the youngest children because visual pursuit develops early in life and is typically present to some degree at birth. In adults in VS, prognostic utility of visual pursuit is unclear.(42,43) To date, no study has examined the prognostic utility of visual pursuit in children with DoC.

Many respondents identified aetiology of DoC and age as prognostic markers. Similar to adults,(1,38) there is strong evidence that traumatic and non-traumatic aetiologies have very different outcomes in children.(1,11) The role of age in considering prognosis after brain injury is debated. While there is growing evidence that younger children with diffuse brain injury have worse outcomes,(44–46) results are heavily biased by differences in common aetiologies of brain injury at different ages and the ongoing development of functional milestones (such as walking and talking) at young ages.(47,48)

Medical complications including neurosurgical procedures, epilepsy, and intractable severe spasticity were used to inform prognosis. Consistent with the literature, epilepsy and its treatment were thought to interfere with recovery of consciousness.(36) Spasticity is common in individuals with DoC(49) and respondents indicated that both severe spasticity and medications used to treat spasticity interfered with recovery. While oral medication may interfere with arousal and responsiveness, the use of intrathecal baclofen (instead of potentially sedating oral medications) for spasticity has been associated with improvements

in adults with disorders of consciousness(50) suggesting that treating spasticity without increasing sedation may promote recovery of consciousness (or allow for more accurate assessment of signs of consciousness).

Other prognostic markers commonly endorsed included structural MRI and diffusion tensor imaging, which is especially useful in detecting diffuse axonal injury.(26),(35) Fewer professionals employed cerebral *f*MRI, which is typically used for research purposes. Despite providing information about cerebral blood flow and oxygen use, positron emission tomography is seldom used, probably due to higher invasiveness and because paediatric normative data have been made available only recently.(51,52) Many of the less commonly used neurophysiological and neuroimaging techniques were not necessarily available in facilities, since they are expensive, experimental, and require high levels of specialized expertise.

Finally, the present study demonstrated that guidelines and recommendations for admission to institutions are lacking. A few respondents reported the existence of national guidelines for admission and specified documents created primarily for adults (such as the original position papers on PVS and MCS).(1,3) Given the paucity of national guidelines, it is not surprising that over half reported using internal guidelines for admission. None of these guidelines appeared to have been distributed outside the internal hospital system. Respondents also reported no clearly identifiable published guidelines for diagnosis and prognosis. While a few respondents indicated the existence of published guidelines for diagnosis or prognosis, no respondent identified a specific published document. The lack of reported published guidelines for diagnosis and prognosis is consistent with our review of the

literature; specifically, we found no published guidelines for diagnosis or prognosis in children with DoC.

Study limitations

Limitations include the small number of respondents out of a large number of individuals invited to participate. While the low response ratemay limit generalizability, it is likely that the survey was not relevant to many of the individuals who received the email invitation including those who do not treat patients, do not treat patients with DOC, or do not work with children. Additionally, while 80% of respondents were providing care in Europe or North America, practice differences are difficult to interpret given differences in demographics between these two regions. The preponderance of respondents from Europe/North America could highlight the lack of specialized units in for children with DoC in other regions of the world. Moreover, the survey was only available in English; we did not solicit practices and guidelines available to non-English speaking professionals. Lastly, due to missing data, we needed to apply multiple imputations, which may be imprecise.

Conclusions

This international survey provided useful information about diagnostic procedures and prognostic indices routinely used by professional working on care pathways for children with DoC. Results highlight the absence of available diagnostic tools and prognostic procedures specifically for this population. Given limited research to guide care pathways for children with DoC, a consensus conference of experts would be useful to examine extant literature, identify gaps and future directions, and develop initial guidelines of diagnosis and prognosis in children with DoC.

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Declaration of interest statement

Molteni E. reports no conflicts of interest.

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Table 1. Respondent characteristics

	Overall Sample n=82	Europe n=37	North America n=33
	% of respondents in each category		
Profession	100.0	100.0	100.0
Medical doctor	**50.0**	**59.5**	**33.3**
Researcher	**8.5**	**10.8**	**6.1**
Physical Therapist	**7.3**	**2.7**	**9.1**
Psychologist	**18.3**	**13.5**	**24.2**
Nurse	**2.4**	**0.0**	**6.1**
Speech-language therapist	**6.1**	**8.1**	**3.0**
Social worker	**0.0**	**0**	**0.0**
Occupational therapist	**2.4**	**5.4**	**6.1**
Other	**4.9**	**0**	**12.1**
Areas of the world	100.0		
Europe	**43.9**	**100**	**-**
North America	**37.8**	**-**	**100**
Asia	**7.3**	**-**	**-**
Australia	**6.1**	**-**	**-**
Africa	**2.4**	**-**	**-**
South America	**2.4**	**-**	**-**
Age of admittance*	100.0		
0 to < 6 months	**56.3**	**54.0**	**54.5**
6 months to <3 years	**73.8**	**70.3**	**69.7**
3 to <13 years	**90.0**	**81.1**	**90.9**
13 to <18 years	**92.5**	**86.5**	**90.9**
18 to 20 years	**65.0**	**54.1**	**78.8**
> 21 years	**46.3**	**45.9**	**48.5**

*multiple or null answers were allowed.

Table 2. Institutional setting selected by respondents (n=82).

Type of setting	Selected answer (n=82)					% of Respondents
Intensive specialized rehabilitative setting for post-acute DoC patients (n=45)	√		√	√		**55.6**
Specialized rehabilitative setting for chronic DoC patients (n=27)		√	√	√		**33.3**
Nursing home (n=2)				√		**2.5**
Other (n=24)					√	**28.4**
% of Respondents	**38.3**	**16.0**	**14.8**	**2.5**	**28.4**	

Note. In the questionnaire, multiple or null answers were allowed

Table 3. Neurobehavioral measures routinely adopted for clinical assessment of the individuals aged 0-17 years in DoC.

	GCS		**CNCS**		**LCFS**		**CRS-R**		**WNSSP**	
	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]
Total pediatric population	99.9	**94.1**	32.4	39.5	56.8	58.8	78.4	75.1	18.9	26.1
0 to < 6 months	47.1	**58.7**	3.6	35.8	14.6	36.5	14.6	39.9	3.6	31.0
6 months to < 3 years	63.6	**64.7**	19.4	35.2	27.6	43.5	30.4	41.8	5.6	25.0
3 to < 7 years	65.8	**64.4**	18.1	31.9	36.3	43.8	45.3	49.9	15.9	27.5
8 to < 12 years	65.8	**63.1**	20.4	31.7	38.6	46.6	49.9	52.2	13.6	25.6
13 to < 18 years	81.6	**74.3**	24.2	34.7	44.1	48.0	61.7	62.0	13.2	26.5

GCS=Glasgow Coma Scale; CNCS=Rappaport Coma / Near Coma Scale; LCFS=Levels of Cognitive Functioning Scale; CRS-R=Coma Recovery Scale – Revised; WNSSP=Western Neurosensory Stimulation Profile.

Note. Multiple or null answers were allowed, also within each age range. Results are normalized (50 imputations percent) with respect to the

percentage of institutions' admitting patients in each specific age range.

The most frequently used outcome measure in each age group are marked in bold.

Table 4. Neurobehavioral measures routinely adopted as outcome measures for individuals 0-17 years in DoC.

	DRS		**GOS-E**		**GOS-E Peds**		**CNCS**		**LCFS**		**CRS-R**		**WNSSP**	
	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]
Total pediatric population	27.0	33.9	37.8	42.8	45.9	49.5	24.3	32.6	51.3	54.3	54.0	**56.9**	18.9	26.2
0 -< 6 months	0.0	0.0	3.6	29.5	36.2	**54.1**	3.6	33.1	7.3	32.0	7.3	34.3	7.3	35.6
6 months - < 3 years	5.6	26.2	16.5	33.7	35.9	**45.8**	13.8	30.2	24.9	41.3	27.6	41.2	11.1	28.7
3 -< 7 years	9.1	24.0	15.9	29.6	31.8	41.1	13.6	27.7	31.8	40.2	34.0	**41.9**	13.6	29.1

8 -< 12 years	11.3	24.0	15.9	29.6	29.4	38.7	13.6	26.0	34.0	**42.9**	34.0	**42.0**	13.6	26.4
13 -< 18 years	22.1	32.1	28.7	37.2	35.4	41.7	19.9	29.8	42.0	**46.2**	42.0	**46.1**	15.5	27.0

Legend. Multiple or null answers were allowed, also within each age range. Results are normalized (50 imputations percent) with respect to the percentage of institutions admitting patients in each specific age range (see 'Age at admittance' at bottom of Table 1). Neonates: 0 -< 6 months; infants: 6 months -< 3 years; pre-school children: 3 -< 7 years; school children: 8 -< 12 years; adolescents: 13 -< 18 years. DRS=Disability Rating Scale; GOS-E=Glasgow Outcome Scale Extended; GOS-E Peds=paediatric adaptation of the Glasgow Outcome Scale Extended; CNCS=Rappaport Coma / Near Coma Scale; LCFS=Levels of Cognitive Functioning Scale; CRS-R=Coma Recovery Scale – Revised; WNSSP=Western Neurosensory Stimulation Profile.

The most frequently used outcome measure in each age group are marked in bold.

Table 5. Neurophysiological measures and neuroimaging tools routinely adopted in the diagnostic procedure of individuals 0-17 years in DoC.

	Neurophysiology										**Neuroimaging**							
	EEG		**BAEP**		**VEP**		**ERP**		**SEP**		**CT**		**MRI**		**PET**		**fMRI**	
	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]
Total pediatric population	81.1	**79.1**	37.8	42.1	40.5	45.4	16.2	23.6	43.2	48.3	75.7	74.8	99.9	**94.0**	18.9	26.7	24.3	32.0
0 -< 6 months	47.1	**61.0**	21.7	45.0	25.4	44.3	3.6	25.6	29.0	49.6	43.5	58.5	61.6	**69.8**	10.8	34.3	3.6	34.7
6 months -< 3 years	52.6	**57.2**	19.4	34.9	24.9	38.5	2.7	19.4	24.9	37.5	47.0	55.5	66.4	**68.9**	8.3	28.8	2.7	27.3
3 -< 7 years	49.9	**51.7**	20.4	31.3	22.7	34.3	4.6	23.0	24.9	23.1	45.3	47.8	63.4	**61.1**	9.1	24.5	6.8	22.6

8 -< 12 years	49.9	**51.1**	22.7	31.9	24.9	36.0	4.6	20.9	24.9	35.6	47.7	49.5	65.8	**64.1**	9.1	24.6	9.1	24.7
13 -< 18 years	66.2	**64.1**	30.9	37.3	30.9	39.3	13.2	27.3	35.4	44.2	61.7	60.3	81.6	**73.5**	15.5	30.3	19.9	31.4

Legend. Multiple or null answers were allowed, also within each age range. Results are normalized with respect to the percentage of institutions admitting patients in each specific age range (see 'Age at admittance' at bottom of Table 1). Neonates: 0 -< 6 months; infants: 6 months -< 3 years; pre-school children: 3 -< 7 years; school children: 8 -< 12 years; adolescents: 13 -< 18 years. EEG=electroencephalogram; BAEP=Brainstem Auditory Evoked Potential; VEP=Visual Evoked Potentials; ERP=Event Related Potentials (i.e. P300 and Mismatch Negativity); SEP=Somatosensory Evoked Potential; CT=Computerized Tomography; MRI=structural Magnetic Resonance Imaging; PET=Positron Emission Tomography; fMRI=functional Magnetic Resonance Imaging. The two most frequently used instrumental diagnostic tools in each age group are marked in bold.

Table 6. Clinical features used as prognostic markers for the individuals aged 0-17 in DoC.

	Clinical diagnosis of VS/UWS or MCS		**Pupillary reflex**		**Optical fixation ability**		**Visual pursuit**		**Presence of spontaneous motility**		**Time interval to follow commands**	
	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]	Valid percent [%]	50 imputations percent [%]
Total pediatric population	63.2	**63.6**	48.2	52.8	45.1	50.6	60.2	60.5	54.2	55.9	60.2	60.5
0 -< 6 months	16.2	43.4	36.4	57.1	28.2	51.2	40.3	**59.6**	40.3	58.5	24.2	49.1
6 months -< 3 years	27.8	43.9	30.8	46.4	30.8	42.7	43.1	**52.8**	37.0	49.5	30.8	45.2
3 -< 12 years	40.4	**46.5**	30.3	38.9	30.3	41.1	37.9	43.0	32.8	42.0	35.3	44.6

13 -< 18 years	51.6	**52.2**	39.4	45.1	34.4	43.7	44.2	47.2	39.4	45.4	49.2	50.2

Legend. Multiple or null answers were allowed, also within each age range.

Results are normalized with respect to the percentage of institutions admitting patients in each specific age range.

The most frequently used clinical prognostic markers in each age group are marked in bold.

Table 7. Clinical phenomena and clinical complications used as prognostic markers in individuals aged 0-17 in DoC.

Prognostic clinical phenomena or clinical complications.	Valid percent [%]	50 imputations percent [%]
Presence of pathological postures (decortication/ decerebration)	71.0	66.3
Presence of vegetative dysautonomia/ Paroxysmal Sympathetic Hyperactivity	61.3	59.2
Presence of psychomotor agitation/ restlessness	64.5	61.6
Presence of primitive oral automatisms (sucking, yawning, etc)	51.6	53.2
Presence of recurrent infections/ hyperthermia	67.7	63.1
Assisted respiratory function	64.5	61.2
Need of oxygen therapy	48.4	48.8
Presence of critical illness: polyneuropathy and myopathy	54.8	53.7
The presence of heterotopic ossifications	32.3	36.1

Presence of neurosurgical sequelae (absence of cranioplasty, hydrocephalus)	80.6	**73.1**
Presence of epilepsy	87.1	**79.3**
Presence of intractable (severe) spasticity	87.1	**78.7**

Note. Multiple or null answers were allowed.

Figure 1. Survey dissemination procedure and data collection

Figure 2. Use of national or institutional protocols for admission and awareness of published national guidelines or recommendations about diagnostic or prognostic procedures for children in DoC

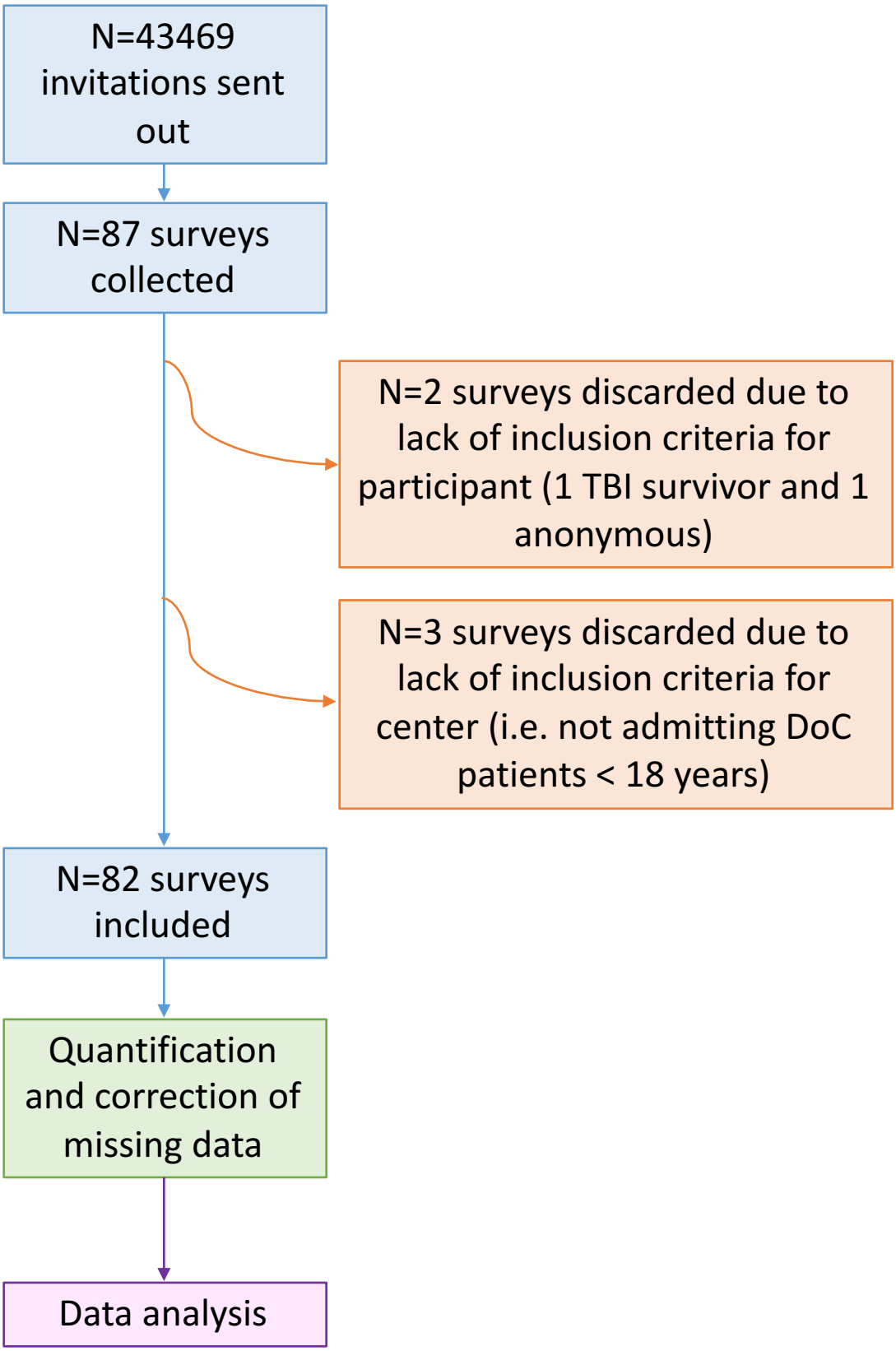
N=43469 invitations sent out
N=87 surveys collected
N=2 surveys discarded due to lack of inclusion criteria for participant (1 TBI survivor and 1 anonymous)
N=3 surveys discarded due to lack of inclusion criteria for center (i.e. not admitting DoC patients < 18 years)
N=82 surveys included
Quantification and correction of missing data
Data analysis

Figure 2. Availability of guidelines and recommended protocols