Behavioural Brain Research 421 (2022) 113729

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Impact of MRI on decision-making in ICU patients with disorders of consciousness

Simon S. Albrechtsen[a,f], Robert G.C. Riis[b], Moshgan Amiri[a], Gry Tanum[a], Ove Bergdal[c,1], Morten Blaabjerg[d,1], Claus Z. Simonsen[e,1], Daniel Kondziella[a,f,*]

[a] Department of Neurology, Rigshospitalet, Copenhagen University Hospital, Denmark
[b] Department of Radiology, Rigshospitalet, Copenhagen University Hospital, Denmark
[c] Department of Neurosurgery, Rigshospitalet, Copenhagen University Hospital, Denmark
[d] Department of Neurology, Odense University Hospital, Denmark
[e] Department of Neurology, Aarhus University Hospital, Denmark
[f] Department of Clinical Medicine, University of Copenhagen, Denmark

A R T I C L E I N F O

Keywords:
Cardiac arrest
Coma
Prognostication
Subarachnoid hemorrhage
Stroke
Traumatic brain injury
Unresponsive wakefulness syndrome
Vegetative state

A B S T R A C T

Background: Recovery of consciousness is the most important survival factor in patients with acute brain injury and disorders of consciousness (DoC). Since most deaths in the intensive care unit (ICU) occur after withdrawal of life-support, medical decision-making is crucial for acute DoC patients. Neuroimaging informs decision-making, yet the precise effects of MRI on decision-making in the ICU are poorly understood. We investigated the impact of brain MRI on prognostication, therapeutic decisions and physician confidence in ICU patients with DoC.
Methods: In this simulated decision-making study utilizing a prospective ICU cohort, a panel of neurocritical experts first reviewed clinical information (without MRI) from 75 acute DoC patients and made decisions about diagnosis, prognosis and treatment. Following review of the MRI, the panel then decided if the initial decisions needed revision. In parallel, a blinded neuroradiologist reassessed all neuroimaging.
Results: MRI led to changes in clinical management of 57 (76%) of patients (Number-Needed-to-Test for any change: 1.32), including revised diagnoses (20%), levels of care (21%), diagnostic confidence (43%) and prognostications (33%). Decisions were revised more often with stroke than with other brain injuries ($p = 0.02$). However, although MRI revealed additional pathology in 81%, this did not predict revised clinical decision-making (p-values $\geq$0.08).
Conclusion: MRI results changed decision-making in 3 of 4 ICU patients, but radiological findings were not predictive of clinical decision-making. This highlights the need to better understand the effects of neuroimaging on management decisions. How MRI influences decision-making in the ICU is an important avenue for research to improve acute DoC management.

1. Introduction

Every year, traumatic brain injury alone results in 1.5 million hospital admissions and 57,000 deaths in the European Union [1]. Of all comatose patients with traumatic brain injury, 40% die in the intensive care unit (ICU) and 20% enter a prolonged disorder of consciousness (DoC) with varying degrees of awareness (or lack thereof) of themselves and their environments [2].

Recovery of consciousness is the most important prognostic factor for survival after severe traumatic and non-traumatic brain injuries [3], but physicians underestimate the level of consciousness in 40% of unresponsive patients with brain injury [4], and they may have difficulties recognizing unusual coma presentations [5]. Moreover, 15–20% of patients without clinical evidence of consciousness have paraclinical evidence of consciousness when assessed with advanced EEG and functional imaging methods [6]. As the majority of deaths in the ICU occur because of withdrawal of life-sustaining therapy (e.g., 7 out of 10 ICU death following traumatic brain injury [7]), medical

* Correspondence to: Rigshospitalet, Afdeling for Hjerneog Nervesygdomme, Blegdamsvej 9, 2100 København Ø, Denmark.
E-mail address: daniel.kondziella@regionh.dk (D. Kondziella).
1 Equal contribution.

https://doi.org/10.1016/j.bbr.2021.113729
Received 7 September 2021; Received in revised form 2 December 2021; Accepted 21 December 2021
Available online 31 December 2021
0166-4328/

decision-making is of immediate importance to DoC patients with acute brain injury [7].

Neuroimaging is essential for the diagnosis, management and prognostication of acute brain injury, and hence medical decision-making in ICU patients with DoC. Owing to its higher resolution, brain MRI is often regarded as superior to CT, but CT is more available, and the exact contribution of MRI to medical decision-making in patients with brain injury and DoC remains unknown: Compared to CT, does an additional MRI scan lead to revision of clinical decisions in the ICU, and if so, how often and in what direction?

To address this, we took advantage of the CONNECT-ME project (NCT02644265) which is a prospective cohort study of patients with DoC and severe traumatic or non-traumatic brain injury admitted to the ICUs of a tertiary care center [8].

An independent panel of neurocritical care physicians reviewed clinical details of CONNECT-ME patients, including CT scans, and made judgements about diagnosis, therapy, prognostication and continuation or withdrawal of life-sustaining therapy. Then, the panel was shown the MRI scans and decided, for each patient, if its decisions needed revision. In parallel, a blinded neuroradiologist reviewed all neuroimaging and assessed if the MRI had revealed novel information, in order to disentangle the objective radiological data from the more complex effects of MRI on clinical decision-making.

We hypothesized that, compared with brain CT, the more detailed imaging information of MRI translated into greater diagnostic precision, improved confidence, and new therapeutic interventions in many ICU patients but that in a subset of them MRI would lead to diagnostic uncertainty by adding a layer of detail that is challenging for clinicians to apply to decision-making.

In summary, the overall objective was to study how brain MRI influences decision-making in the management of ICU patients with brain injury and DoC, including decisions about continuation or withdrawal of life-sustaining therapy.

2. Methods

We conducted a simulated decision-making study based on clinical data from a prospective cohort study of ICU patients with severe brain injury and DoC [8]. The objective was to determine the impact of MRI on clinical decision-making, including diagnosis, management, and prognostication, in DoC patients with brain injury in the ICU.

2.1. Patient population, inclusion and exclusion criteria, and definition of DoC

The Consciousness in neurocritical care cohort study using fMRI and EEG (CONNECT-ME; ClinicalTrials.gov Identifier: NCT02644265) is an ongoing project with a database that encompasses prospectively enrolled patients with DoC and acute traumatic or non-traumatic brain injury admitted to the ICUs of a tertiary care center (Rigshospitalet, Copenhagen University Hospital), investigated with CT, structural and functional MRI, EEG and automated pupillometry. ICUs comprise neurocritical, cardiological and general ICUs. Enrollment started in April 2017. In the first three years of the CONNECT-ME study patients were prospectively enrolled on a convenience basis and since then based on a daily screening procedure (using identical inclusion criteria). Details have been published elsewhere [8]. For the present work, functional MRI and automated (but not manual) pupillometry results were omitted.

Briefly, patients admitted to the ICU with DoC and acute or subacute ($\leq$31 days from injury) traumatic or non-traumatic brain injury, are enrolled into CONNECT-ME when they have functional MRI performed during acquisition of a structural MRI of the brain for clinical reasons while being in the ICU [9]. Levels of consciousness are determined by a board-certified neurologist experienced in neurocritical care (DK), or neurology residents supervised by DK, following detailed neurological examination, including the Full Outline of UnResponsiveness (FOUR) scale [10], and categorized into coma, vegetative state/unresponsive wakefulness syndrome, minimally conscious state (MCS) minus, MCS plus, "emerged from MCS" (eMCS), or locked-in syndrome as described earlier [3,11]. Patients with locked-in syndrome are included because their phenotype exists on a clinical continuum with cognitive motor dissociation (CMD) with comparable challenges related to diagnostics and clinical decision-making in the ICU [12].

More precisely, we define coma as a state of profound unawareness from which patients cannot be aroused, while eyes are closed, and a normal sleep–wake cycle is absent [13]. VS/UWS is diagnosed when patients open their eyes but exhibit only reflex behaviors and are considered unaware of themselves and their surroundings [14]. Furthermore, patients are considered MCS, when they show unequivocal signs of non-reflex behaviors occurring inconsistently, yet reproducibly, in response to environmental stimuli [15]. MCS patients are further classified into MCS plus (i.e., if they are able to obey commands) or MCS minus (i.e., if they localize pain, exhibit visual pursuit, or show appropriate emotional expressions) [16]. Patients who recover functional communication or functional object use are classified as eMCS [15]. Hence, rather than the total FOUR score, classification of consciousness levels into coma, VS/UWS, MCS minus/plus, and eMCS is based on visual and motor FOUR subscales, as well as evidence of command following, appropriate emotional expressions, communication, and functional object use [11]. In the locked-in syndrome, a patient is fully aware and, despite being anarthric and tetraplegic, able to communicate by partially preserved eye movements [12].

Exclusion criteria were severe cardiorespiratory compromise and other acutely life-threatening conditions, evidence of severe pre-morbid neurological deficits such as aphasia or deafness and age $<$ 15 years, as well as intracranial devices incompatible with MRI acquisition [8].

We reviewed the first 75 patients from the CONNECT-ME cohort with an MRI of sufficient quality performed during ICU-admission (1.5T or 3T Siemens MRI scanners). If a patient had multiple MRIs, the first MRI after admission to the ICU was the index MRI. (MRIs preceding the admission to the ICU such as MRIs done at referring hospitals or hyperacute stroke MRI protocols were included in the summarized clinical details; see below.).

2.2. Independent clinical and radiological expert reviews

SA, GT, and MA summarized all salient clinical details, including temporal development of neurological deficits and the disease course, preceding the index MRI, from all 75 patients in a standardized manner under the supervision of DK. These details included a detailed neurological examination (as described earlier [11]), Glasgow Coma Scale and Full Outline of UnResponsiveness [10] scores, sedation, level of ventilatory support, time from admission, and if applicable, do-not-resuscitate and similar orders. Furthermore, we summarized age, sex, previous medical history, symptom onset and development (including any changes in the neurological status over time), non-neurological complications (e.g., infections, kidney failure), neurological and neurosurgical treatments up to the index MRI, and results of laboratory investigations such as CT, EEG, biochemistry, and cerebrospinal fluid analysis.

An independent expert panel was appointed, consisting of one consultant neurosurgeon (OB) and two consultant neurologists (CZS, MB), who are affiliated with external institutions and not involved in the care of the patients, all with $>$ 10 years of experience in neurocritical care at academic tertiary centers in Denmark. This panel of experts convened in two sessions spread over two days, 14 days apart.

In the first step, the clinicians reviewed the anonymized case report forms along with the raw CT images of the brain (including CT angiography and CT perfusion, if present) and made decisions concerning diagnosis, prognosis, and treatment, including continuation or withdrawal of life-sustaining therapy, first independently and then by consensus.

In the second step, they were shown the MRI images and decided a) if their decisions needed revisions and b) how knowing the MRI results altered their confidence in the decisions made. If a patient had multiple MRIs, the index MRI was the first MRI after admission to the ICU. As stated earlier, MRIs preceding the admission to the ICU (e.g., MRIs done at the referring hospital or hyperacute stroke MRI protocols) were included in the summarized clinical details. All the typical clinical MRI sequences (e.g. DWI, ADC, FLAIR, SWI, contrast enhanced T1) were available, but some sequences were more frequently reviewed by the expert panel than others (see Results). Diagnostic confidence and prognostication were rated on a 5-step Likert-Scale, ranging from "not at all" to "complete" for diagnostic confidence, respectively, from "highly unlikely" to "highly likely" for prognostication regarding the likelihoods of recovering any degree of consciousness (e.g., from MCS minus to MCS plus) including functional 2-way communication, within three years. This extended time span was chosen to reflect emerging evidence for late recovery of consciousness more than two years post-injury [17,18]**.** The primary outcome was the number of patients for whom decision-making was revised after the index MRI. Details are available from the online supplemental files.

In addition, a neuroradiologist (RGCR) who was not involved in the management of the patients first reviewed all neuroimaging performed during the admission (mainly CT scans) preceding the index MRI. RGCR was blinded for all information except the patients' age and sex and systematically scored anatomical and pathological details. He then repeated this for the index MRI and recorded whether he had found additional radiological pathology and how much the MRI had contributed to his final radiological interpretation. Outcomes were the number of patients in whom the index MRI uncovered additional pathology compared to the preceding neuroimaging, as well as the neuroradiologist's assessment of how much the information from the index MRI had changed the initial radiological interpretation, using a visual analog scale from 0 to 100 (0 = "no change in the final radiological interpretation after index MRI"; 100 = "completely different radiological interpretation after index MRI"). Furthermore, we examined whether the presence of additional pathology and/or the evaluated contribution by MRI predicted changes in clinical decision-making by the expert panel.

2.3. Statistics, data availability and ethics

All data were captured in standardized surveys and recorded in a REDCap database [19]. Descriptive statistics were performed using RStudio (version 1.4), including Welch's two-sample t-tests and Fisher's exact tests, where appropriate. Numbers Needed to Test were calculated as N/n, where N is the total number of patients and n is the number of patients in whom decision-making was changed after MRI [20]. Data can be accessed from the online supplemental files. Approval for the CONNECT-ME study was obtained from the Ethics Committee of the Capital Region of Denmark (journal nr: H-16040845) and the Danish Data Protection Agency (RH-2016–191, I-Suite nr: 04760). Individual patient (re-)consent was waived for the present study.

3. Results

3.1. Patient characteristics

Seventy-five patients were included between April 2017 and October 2020 (mean age 49.3 ± 18.4 years; 39% women), including 54 (72%) with non-traumatic brain injuries (13 anoxic brain injuries, 25 hemorrhagic or ischemic cerebrovascular injuries, 16 other injuries: Fig. 1). Index MRI was performed after a median of 11 days (range 0–88 days), with an average of 3 preceding CT scans (median, range 0–12). Forty-five patients (60%) were investigated with 3 T MRI, the remainder with 1.5 T MRI. At the time of the index MRI, 28 (37%) patients were in a coma, 23 (31%) in vegetative state/unresponsive wakefulness, 14 (19%) patients in MCS minus, 4 (5%) in MCS plus, 2 (3%) in eMCS (confused or better), and 4 (5%) patients were locked-in after a cerebrovascular event. The median FOUR Score was 7 (range 0–14). Details are shown in Table 1, Fig. 1, and the online supplemental files.

3.2. Clinical decision-making

The clinicians adjusted their initial diagnosis in 15 (20%) of the patients after having seen the index MRI. Reasons to update the clinical diagnosis included the identification of secondary brain damage (e.g., ischemic infarcts), recognition of the underlying etiology (e.g., autoimmune encephalitis), elimination of differential diagnoses or documentation of previous pathologies in remission (e.g., hydrocephalus; Fig. 1, Fig. 2b, and online supplemental files). The diagnostic confidence of the clinicians was affected by the index MRI in roughly half of the cases: Most of the time they felt more confident (n = 32, 43%), but occasionally MRI increased diagnostic uncertainty (n = 6, 8%, Fig. 2b). Adjustments to the level of care were made in 16 (21%) of the patients, almost always towards lesser care, including recommending withdrawal of life-sustaining therapy in 13 patients (Fig. 1 and Fig. 3). Yet in one patient a previous do-not-resuscitate order was revoked after the MRI (case 16, Fig. 1). In addition, the panel suggested new therapeutic or diagnostic interventions (e.g., placement of an extra ventricular drainage or prescription of anticoagulation therapy; online supplemental files) in 6 (8%) of the patients (Fig. 2b). The most often reviewed MRI sequences by the expert panel were diffusion-weighted imaging (DWI; 77.3%) and fluid-attenuated inversion recovery (FLAIR; 58.7%).

Knowing the MRI results, the expert clinicians changed the prognostication for 24 (32%) of the patients, being less (n = 14) or more optimistic (n = 10) than before in terms of a patient's potential to recover consciousness (Fig. 1 and Fig. 2b). The panel recommended withdrawal of life-sustaining therapy in 13 of the 14 cases with a poorer prognosis. However, the panel also recommended withdrawal of life-sustaining therapy in 5 patients before seeing the MRI, indicating that MRI in these cases was not necessary to reach a withdrawal of life-sustaining therapy decision, (although it increased diagnostic confidence in 3 of the 5 patients). All the 18 patients, for whom the panel recommended withdrawal of life-sustaining therapy were in a coma, UWS or MCS minus, and none were sedated (Fig. 3).

The etiology of brain injury (i.e. TBI, stroke, anoxia, and other; Fig. 1) influenced the frequency with which clinical decisions after MRI were revised ($p = 0.02$; two-sided Fisher's Exact Test). Comparing the four etiological groups revealed a significant difference between "stroke" and "other", with revised decisions in 23/25 stroke patients and 8/16 "other" patients ($p = 0.007$; Bonferroni-corrected for multiple comparisons), indicating a higher impact of MRI in stroke patients and a lower impact in "other" patients.

In sum, the Number Needed to Test for *any* change in clinical management was 1.32, for a change of diagnosis 5, for a change in diagnostic confidence (either way) 1.97, for recommendation of a new therapeutic intervention or a change in the level of care 3.41, and for a change of prognostication 3.13.

3.3. Radiological evaluation and its relation to clinical decision-making

According to the blinded neuroradiologist, MRI detected additional pathology (previously unrecognized pathology or another degree of a previously CT-visualized pathology) in most cases (n = 61, 81%), including in 12 of the 13 patients in whom a decision to withdraw life-sustaining therapy was made. The contribution of the MRI to the final radiological interpretation of the individual case varied widely (Fig. 2a). Neither the contribution of the MRI to the overall radiological evaluation nor the presence of additional pathology identified by MRI was correlated to changes in clinical decision-making by the expert panel (Fig. 4).

Case	Clinical details				MRI		Decision-making after MRI					
											Prognostication	
	Diagnosis	ICU days[1]	DoC		Additional pathology[2]	VAS[3]	Treatment level	Interven-tion[4]	Etiology diagnosis	Confidence (etiology)[5]	2-way comm[6]	Better DoC[7]
1	ANOX(CA), ANOX(other)	4	UWS			63	Full → WLST					
2	TBI	12	Coma			80	DNR → WLST					
3	iSTROKE, Metab ketoacidosis	4	Coma			64	DNR → WLST					
4	TUMOR, EPILEPSY	10	Coma			21	DNR → WLST					
5	TBI	20	Coma			17	DNR → WLST					
6	iSTROKE, SAH, Hydrocephalus	14	UWS			63	DNR → WLST					
7	TBI	30	UWS			63	DNR → WLST					
8	EPILEPSY, ANOX(CA)	3	Coma			3	DNR → WLST					
9	iSTROKE	3	UWS			12	DNR → WLST					
10	iSTROKE	4	Coma			79	DNR → WLST					
11	TBI	15	Coma			70	DNR → WLST					
12	ANOX(CA), mENCEPH(other)	13	UWS			21	DNR → WLST					
13	ANOX(CA), Bacterial meningitis	48	MCS -			43	DNR → WLST					
14	iSTROKE	1	Coma			82	DNR → (WLST)*					
15	TBI, ANOX(other)	29	MCS -			58	Full → DNR					
16	iSTROKE	11	LIS			86	DNR → Full					
17	iSTROKE	6	Coma			13	WLST pre-MRI					
18	ANOX(CA)	5	Coma			3	WLST pre-MRI					
19	iSTROKE	13	Coma			75	WLST pre-MRI					
20	TBI	12	Coma			30	WLST pre-MRI					
21	ICH, IVH	22	UWS			78	WLST pre-MRI					
22	EPILEPSY	88	MCS -			15						
23	iSTROKE, Stroke due to fat emboli	5	MCS -			2						
24	TUMOR, Hydrocephalus	11	MCS -			4						
25	mENCEPH(other), Global brain edema	25	MCS +			27						
26	ANOX(CA)	11	Coma			49						
27	Metabolic encephalopathy	8	Coma			57						
28	mENCEPH(other)	0	UWS			3						
29	TBI, ANOX(other)	12	MCS -			91						
30	iSTROKE, TBI	14	UWS			32						
31	iSTROKE, SAH	30	MCS -			50						
32	ICH, Hydrocephalus	18	MCS +			3						
33	TUMOR, EPILEPSY	6	Conscious			17						
34	iSTROKE	1	Coma			39						
35	NM, Metabolic (nephro)	18	MCS -			47						
36	iSTROKE	3	Coma			58						
37	SAH	19	Coma			3						
38	iSTROKE	9	MCS +			9						
39	iSTROKE	5	LIS			32						
40	SAH, Vasculitis	22	MCS -			31						
41	TBI	10	MCS -			97						
42	ICH	15	LIS			29						
43	TBI	16	Coma(Sed)			12						
44	ANOX(CA)	7	Coma			100						
45	TBI	8	MCS -			81						
46	TBI	6	Coma(Sed)			100						
47	TBI	10	UWS			76						
48	ANOX(other)	23	MCS +			21						
49	TBI	40	MCS -			3						
50	iSTROKE, Stroke due to fat emboli	2	Coma(Sed)			93						
51	iSTROKE	1	MCS -			89						
52	iSTROKE, SAH	16	LIS			20						
53	SAH	16	UWS			34						
54	TBI	6	Coma(Sed)			11						
55	ANOX(other), Metab encephalopathy	12	UWS			64						
56	ANOX(other), Intoxication	13	Coma			3						
57	ICH	5	UWS			50						
58	ANOX(CA)	22	UWS			71						
59	ANOX(CA)	5	UWS			99						
60	EPILEPSY	14	MCS -			34						
61	mENCEPH(other)	29	UWS			0						
62	TBI	13	Coma			61						
63	TBI	26	UWS			50						
64	NM, mENCEPH(other)	0	Coma			2						
65	TBI, ANOX(other)	3	UWS			66						
66	AIE, Global brain edema	17	UWS			1						
67	Autoimmune encephalitis	29	Confusional			30						
68	EPILEPSY	10	Coma			0						
69	ANOX(CA), IVH after PE-treatment	10	UWS			78						
70	CVST, Hydrocephalus	0	Coma(Sed)			50						
71	TBI	28	Coma			23						
72	TBI, EPILEPSY	2	UWS			63						
73	TBI, ANOX(CA), ANOX(other)	17	UWS			99						
74	EPILEPSY, Hypoglycemia	6	UWS			97						
75	ANOX(other), Intoxication	4	UWS			68						

(caption on next page)

Fig. 1. Overview of the clinical characteristics, timeline, and MRI results, including the impact of MRI on clinical decision-making in individual patients (n = 75). This figure provides an overview of the clinical details at the time of index MRI, including the levels of consciousness and length of stay in the intensive care unit prior to the index MRI. Furthermore, the figure shows whether index MRI revealed additional pathology compared to previous CT scans (including CT angiography) and how this changed radiological interpretations, as well as the impact of the additional information gained from MRI on clinical decision-making. The latter included possible adjustments to the level of care, revised diagnoses (including changes in diagnostic confidence), and prognostication of the patients' potential to recover consciousness, including the ability to perform 2-way communication. In total, MRI lead to revised clinical decision-making in 76% of the patients (cases 1–57). *Abbreviations*: ANOX(CA) - anoxic-ischemic brain damage (cardiac arrest); ANOX(other) - anoxic-ischemic brain damage (other); coma(sed) – high dose IV sedatives; CVST - cerebral venous sinus thrombosis; DNR – do-not-resuscitate order; DoC - disorder of consciousness; eMCS - emerged from MCS; EPILEPSY - epileptic seizures (including status epilepticus); ICH - intracerebral hemorrhage; iSTROKE - ischemic stroke; LIS - locked-in syndrome; MCS (-/+) - minimally conscious state minus/plus; mENCEPH(other) - meningoencephalitis (other); Metab – metabolic; NM - neuromuscular weakness; PE - pulmonary embolism; SAH - subarachnoid hemorrhage; TBI - traumatic brain injury; TUMOR - brain tumor (including metastases); UWS - unresponsive wakefulness syndrome; VAS - visual analogue scale; WLST - withdrawal of life-sustaining therapy; (WLST)* - withdrawal of life-sustaining therapy "if no improvement is seen within 2 days". *Colors*: Orange - additional pathology detected by MRI; blue - any change; green - more/better, red - less/worse; white - no/no change. [1]Days between ICU admission and index-MRI. [2]Any additional pathology identified on the index-MRI compared to previous CT scans. [3]Contribution of index-MRI to the radiological interpretation (0 = no change in radiological interpretation, 100 = completely different radiological interpretation). [4]Change in recommended treatment or diagnostic procedures. [5]Relative change on a 5-step scale (from "no confidence" to "complete confidence"). [6]Likelihood of regaining clinical 2-way communication within three years. [7]Likelihood of regaining some consciousness (e.g., from MCS- to MCS+) within three years. [C]No CT-scan available. [L]Relative change on 5-step scale (from "highly unlikely" to "highly likely"). [M]Early non-index MRI available from before admission to intensive care unit.

Table 1
Baseline data and rates of changes to decision-making after MRI.

A. **BASELINE DATA**		
	Non-TBI n = 54	TBI n = 21
ICU days (median [IQR])	10.00 [4.25, 16.75]	13.00 [10.00, 20.00]
DoC (%)		
Coma	17 (31.5)	6 (28.6)
Coma (Sedation)	2 (3.7)	3 (14.3)
Confusional state	1 (1.9)	0 (0.0)
Conscious	1 (1.9)	0 (0.0)
LIS	4 (7.4)	0 (0.0)
MCS -	9 (16.7)	5 (23.8)
MCS +	4 (7.4)	0 (0.0)
VS/UWS	16 (29.6)	7 (33.3)
Additional pathology found on MRI (%)	42 (77.8)	19 (90.5)
Rated contribution of MRI to the radiological interpretation of the patient [VAS] (mean (SD))	40.46 (31.59)	56.33 (31.13)
B. **DECISION-MAKING AFTER MRI**		
Change of treatment level n (%)		
Full treatment → WLST	1 (1.9)	0 (0.0)
DNR → WLST	8 (14.8)	4 (19.0)
DNR → WLST if no further improvement within 48 h	1 (1.9)	0 (0.0)
WLST pre-MRI	4 (7.4)	1 (4.8)
Full treatment → DNR	0 (0.0)	1 (4.8)
DNR → Full treatment	1 (1.9)	0 (0.0)
Unchanged	39 (72.2)	15 (71.4)
Change of intervention (%)	6 (11.1)	0 (0.0)
Change of diagnosis (%)	11 (20.4)	4 (19.0)
Diagnostic confidence (%)		
Higher	22 (40.7)	10 (47.6)
Lower	3 (5.6)	3 (14.3)
Unchanged	29 (53.7)	8 (38.1)
Prognostication (%)		
Better	9 (16.7)	1 (4.8)
Worse	10 (18.5)	4 (19.0)
Unchanged	35 (64.8)	16 (76.2)

Abbreviations: DNR – do-not-resuscitate order; DoC – disorders of consciousness; ICU – intensive care unit; IQR – interquartile range; LIS – locked-in syndrome; MCS- - minimal conscious state minus; MCS+ - minimal conscious state plus; MRI – magnetic resonance imaging; SD – standard deviation; TBI – traumatic brain injury; VAS – visual analog scale; VS/UWS – vegetative state/unresponsive wakefulness syndrome; WLST – withdrawal of life-supporting therapy.

4. Discussion

Of 75 ICU patients with acute brain injury and a disorder of consciousness, MRI led to a revision of the clinical diagnosis in 20%. Furthermore, it increased the diagnostic confidence in 43% and decreased the confidence in 8% of the cases. MRI also led to revision of the level of care in 21% of the patients, most of whom had life-sustaining therapy withdrawn. The panel recommended new therapeutic or diagnostic interventions in 8% and changed their prognostication for 32% of the patients. Overall, MRI led to a revision of decision-making in 3 of 4 patients. MRI revealed additional radiological pathology in 81% of the patients, but the contribution of MRI to the overall radiological interpretation varied from insignificant to critical. Neither MRI-identified additional pathology nor the contribution of MRI to the final radiological interpretation predicted the frequency of clinical revisions.

MRI discovers lesions such as cytotoxic edema, diffuse axonal injury, hypoxic encephalopathy, and cortical laminar necrosis that are not visible by CT [21,22]. Algethamy et al. found that brain MRI detected additional abnormalities compared to CT in 129 of 136 ICU patients (95%), including additional findings for 55.6% of hemorrhagic lesions, 92% of ischemic strokes, 70% of traumatic lesions, 57% of infections, 62.5% of metabolic abnormalities and 100% of neoplasms [23]. Like Algethamy and co-workers, we found that MRI scans revealed additional pathology in most patients (81%), but we further showed that the radiological findings were not predictive of clinical decision-making. This is in line with our hypothesis that the contribution of MRI to clinical decision-making is more complex than simply detecting brain lesions, which perhaps is best exemplified by the fact that diagnostic confidence in a subset of patients was lower after MRI than before. Similarly, following the MRI results, the panel changed their prognostication for the potential to regain consciousness in every third patient.

We suggest the mismatch between radiological findings (or lack thereof) and clinical impact has multiple causes. For instance, in many patients the MRI was ordered to rule out a reversible cause for impaired consciousness. If no such cause was found, suggesting a poor prognosis, a higher confidence prompted clinicians to consider withdrawal of life-sustaining therapy. Conversely, in one patient in whom the MRI showed less severe pathology than expected, the panel revoked a do-not-resuscitate order. In all these cases the MRI did not contribute novel radiological pathology, yet its impact on clinical management was significant. In addition, MRI may reveal new pathology that does not influence clinical decision-making when, for instance, previously suspected lesions are not visible on CT but can be seen on MRI (e.g., diffuse axonal injury).

In the present study, we attempted to minimize confirmation bias due to retrospective analysis. Even though we collected clinical information from a database, this information was based on results from a prospectively enrolled cohort with highly granular clinical information, including temporal development of the disease course and neurological exam, and the final data we collected were from a simulated, prospective clinical setting. In contrast to previous studies, which examined the impact of MRI on prognostication in the ICU by reviewing historical clinical decisions and correlating them to radiological findings [24], we

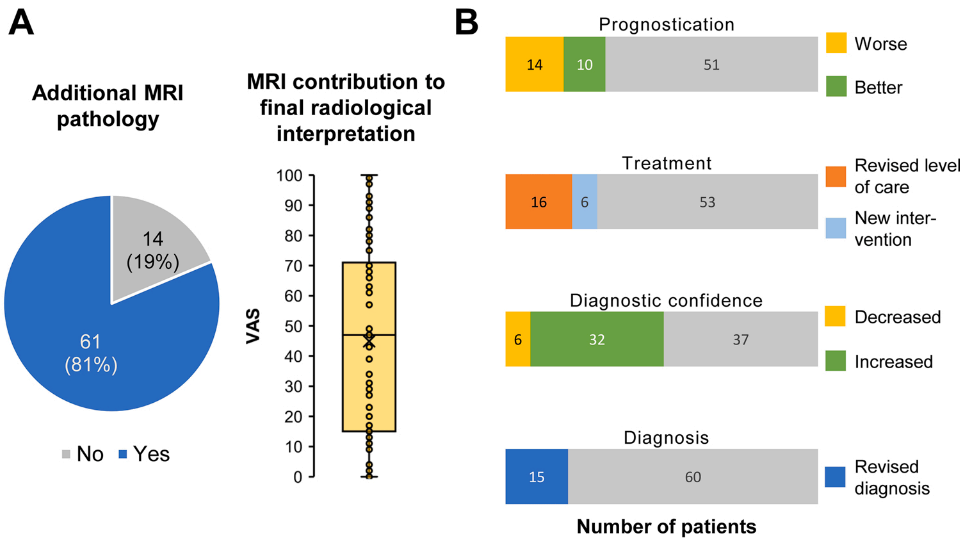

Fig. 2. Impact of MRI on clinical decision-making I. (A) MRI revealed additional pathology in 81% of the patients (pie chart, left). But the contribution of MRI to the final radiological interpretation varied widely (rated by neuroradiologist on a visual analog scale: 0 = no change in radiological interpretation, 100 = completely different radiological interpretation, box plot, right). (B) After seeing the MRI, the panel of clinicians changed the prognostication for 32% of the patients, more often towards a worse prognosis. They decided to revise the level of care in 21% of the patients and suggested a new therapeutic or diagnostic intervention in 8%. They rated their diagnostic confidence as higher in 43% and lower in 8%; and revised the diagnosis in 20% of patients. *Abbreviations*: VAS - Visual Analogue Scale. Gray color: no change.

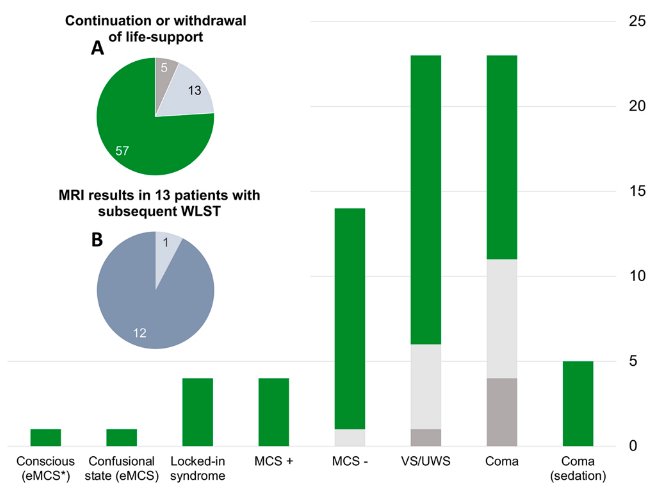

Fig. 3. Continuation and withdrawal of life support. This figure shows decisions about continuation (green) or withdrawal of life-sustaining therapy (gray, blue), in relation to patients' levels of consciousness (n = 75). A decision to withdraw life-sustaining therapy was never made for patients in MCS plus or better and never in those with a coma owing to sedation. Light gray denotes the number of patients for whom a decision to withdraw life-sustaining therapy was made after reviewing the MRI (n = 13), and dark gray denotes patients for whom such a decision had been made before the MRI was reviewed (n = 5), suggesting the MRI was not necessary to reach this decision. Insert (A) shows the absolute number of patients and insert (B) the number of patients who had life-sustaining therapy withdrawn according to MRI results (additional pathology on MRI, dark blue; no such pathology, light blue). *Abbreviations*: eMCS - emerged from MCS; MCS (+/-) - minimally conscious state (+/-); UWS - unresponsive wakefulness syndrome; WLST - withdrawal of life-sustaining therapy. * this patient recovered consciousness immediately prior to the MRI scan.

used a more direct approach with an expert panel making prognostications before and after the index MRI. We also avoided a previously observed high inter-rater variance [24] by using a consensus-based approach, mimicking a real-life clinical setting. We systematically reassessed the neuroimaging data to separate the objective radiological information from the clinical decision-making process, and we performed limited statistical analyses and refrained from subgroup analyses, focusing instead on a real-life, diagnostically heterogeneous patient population, which increases generalizability to ICU patients with acute brain injury and DoC. A similar expert panel approach has been used to investigate the effects of other diagnostic modalities on decision-making in clinical neurological practice such as the added diagnostic value of 11C-PiB-PET imaging [25] and neuropsychological tests and CT-/MRI-based neuroimaging [20] in patients with dementia.

Further investigation is warranted to determine when precisely MRI findings become clinically relevant for decision-making in acute brain injury and DoC. First, future studies should delineate the effects of MRI in patients in MCS plus or better and in those who are heavily sedated, as we did not observe a large effect on clinical decision-making in these two patient groups. Importantly, clinicians need to better understand how MRI results can be used to prevent therapeutic nihilism and self-fulfilling prophecies, which are known to contribute to withdrawal of life-sustaining therapy in ICU patients [26,27]. Second, it would be instructive to systematically investigate whether serial MRI leads to a higher diagnostic precision in the ICU than just one or two MRIs and, if so, what the optimal time interval between MRI scans is. We found that clinicians generally rely on a limited number of MRI sequences, and it might be worthwhile to investigate what the optimal number and characteristics of MRI sequences is in terms of cost-benefit for decision-making. Third, although it is a widely held clinical notion that transportation to the MRI scanner involves a risk to systemically unstable patients, recent studies have shown remarkably high safety when patients are screened for cardiovascular and respiratory contraindications [22,28]. Systematic evaluation of patient transfers from the ICU to MRI scanners and back again including analysis of any adverse events is needed to know how this risk should be factored into the clinical decision-making process, and how clinical decision-making may evolve with technological developments such as portable low-field MRI [29]. Finally, studies should investigate the specific referral questions related to MRI in the ICU, and how these questions are best phrased to maximize the yield of MRI for decision-making, as well as the effects of reimbursement practices, resource allocation and psychological factors for caregivers.

4.1. Limitations

This study has limitations which need consideration. The CONNECT-ME database includes ICU patients with a DoC and a clinical indication for MRI, thereby excluding conscious ICU patients, ICU patients in whom MRI is contraindicated owing to e.g., intracranial devices or cardiopulmonary compromise, and unresponsive patients with brain injury in whom MRI is deemed unnecessary. The latter includes patients at the extremes of the clinical spectrum, i.e., those whose neurological condition is either particularly poor or particularly good. Therefore, results from this study cannot be extrapolated to all ICU patients with

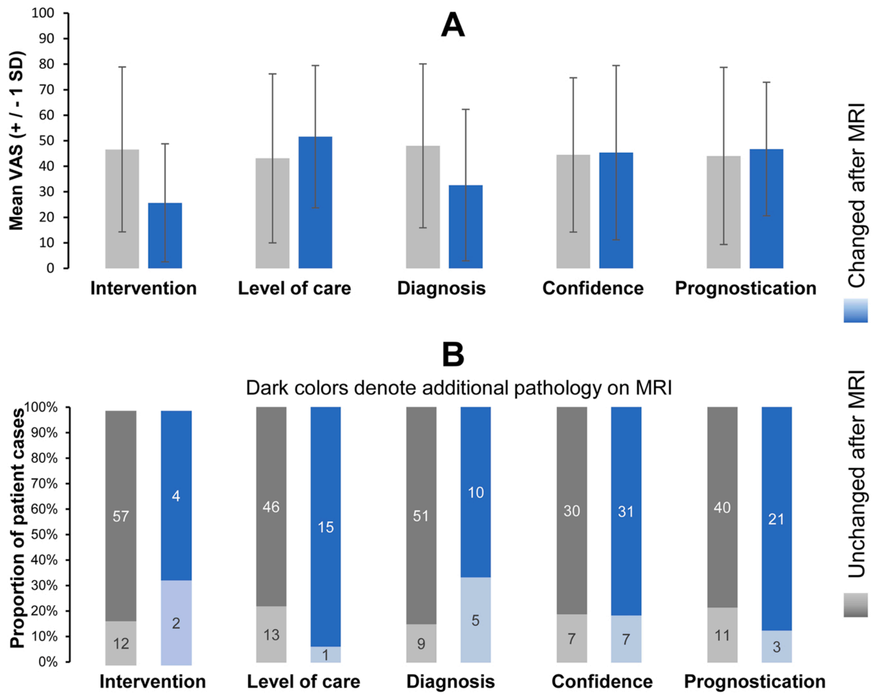

Fig. 4. Impact of MRI on clinical decision-making II. Changes in clinical decision-making (blue) or lack thereof (gray) were not predicted by the contribution of MRI to the final radiological interpretation (A; all p-values $\geq$0.08) or the presence of additional pathology on MRI compared to previous scans (B; all p-values $\geq$0.14). Data labels in (B) denote the number of cases. *Abbreviations*: VAS - visual analogue scale; SD - standard deviation.

brain damage. Also, it should be noted that our expert panel consisted of three clinicians experienced in neurocritical clinicians, but future studies will need to involve a larger number of clinicians with different backgrounds to increase generalizability. Similarly, the CONNECT-ME cohort represents a Scandinavian tertiary care setting and the generalizability to other geographic and socio-economic settings and different levels of care is limited. Specifically, differences in MRI reimbursement can have a big impact on the frequency with which MRI is ordered compared to CT [30]. Furthermore, the cohort is heterogenous including various traumatic and non-traumatic brain injuries. Although this reflects a real-life clinical setting, studies with larger numbers are needed to investigate if the influence of neuroimaging on decision-making differs between diagnostic categories. In addition, loss of clinical information from abstracting medical records is unavoidable and review of patient charts conveys a different clinical impression than seeing a patient at the bedside. Yet we did not aim to compare the expert panel's decisions to the actual historical outcomes but rather wanted to identify the impact of MRI on clinical decision-making, so we believe the bias is limited. Finally, for most patients there was a time gap between the latest CT scan and the index MRI during which further brain pathology could have progressed. New MRI pathology does not necessarily indicate these lesions would have been missed by simultaneously performed CT. As such, our results should not be understood as a head-to-head comparison between CT and MRI but rather as revealing the impact on the clinical care pathway once a decision is made in the ICU to order an MRI in a patient with brain injury and DoC.

4.2. Conclusions and future directions

In this first-of-its-kind study simulating a real-life setting with neurocritical care practitioners, we found MRI led to revised clinical management decisions by the expert-panel in 3 of 4 ICU patients with acute DoC, particularly in patients who were MCS minus or worse. Although MRI lead to more frequent revisions of clinical decisions in stroke patients compared to patients with other brain injuries, the radiological findings as evaluated by a blinded neuroradiologist did not predict changes in clinical decision-making. This paper thus highlights the need for coordinated research into the effects of neuroimaging in the ICU and DoC. We here focused on structural MRI, but this need obviously extends to other diagnostic modalities that are clinical routine such as EEG and also to more advanced measures such as functional MRI which might become important for the future. In sum, we propose decision-making is a neglected area of low-cost research that might readily improve clinical practice. Multicenter studies involving international ICU practitioners, various socio-economic backgrounds and large numbers of patients are required for an improved understanding of the impact of MRI and other imaging modalities in various clinical settings, with the ultimate aim to improve clinical decision-making in ICU patients with DoC.

Funding

The CONNECT-ME project (ClinicalTrials.gov Identifier: NCT02644265) is supported by: Offerfonden, F-23101-04, Region Hovedstadens Forskningsfond til Sundhedsforskning, 2019 – A6597, Rigshospitalet Forskningspulje, Skolarstipendier 2020, Jascha Fonden, 2021-0067 2020, and Offerfonden, F-21-610-00119 (2021).

CRediT authorship contribution statement

Simon S. Albrechtsen: Investigation, Formal analysis, Data Curation, Writing – original draft, Writing – review & editing, Visualization. **Robert G.C. Riis:** Investigation. **Moshgan Amiri:** Investigation. **Gry Tanum:** Investigation. **Ove Bergdal:** Investigation. **Morten Blaabjerg:** Investigation. **Claus Z. Simonsen:** Investigation. **Daniel Kondziella:** Investigation, Conceptualization, Methodology, Formal analysis, Resources, Data Curation, Writing – original draft, Writing – review & editing, Visualization, Supervision.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbr.2021.113729.

References

[1] M. Majdan, D. Plancikova, A. Brazinova, M. Rusnak, D. Nieboer, V. Feigin, A. Maas, Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis, Lancet Public Health 1 (2016) e76–e83, https://doi.org/10.1016/S2468-2667(16)30017-2.

[2] J.V. Rosenfeld, A.I. Maas, P. Bragge, M.C. Morganti-Kossmann, G.T. Manley, R. L. Gruen, Early management of severe traumatic brain injury, Lancet 380 (2012) 1088–1098, https://doi.org/10.1016/S0140-6736(12)60864-2.

[3] D. Kondziella, A. Bender, K. Diserens, W. van Erp, A. Estraneo, R. Formisano, S. Laureys, L. Naccache, S. Ozturk, B. Rohaut, J.D. Sitt, J. Stender, M. Tiainen, A. O. Rossetti, O. Gosseries, C. Chatelle, European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness, Eur. J. Neurol. 27 (2020) 741–756, https://doi.org/10.1111/ene.14151.

[4] C. Schnakers, A. Vanhaudenhuyse, J. Giacino, M. Ventura, M. Boly, S. Majerus, G. Moonen, S. Laureys, Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment, BMC Neurol. 9 (2009) 35, https://doi.org/10.1186/1471-2377-9-35.

[5] D. Kondziella, J.A. Frontera, Pearls & Oy-sters: eyes-open coma, Neurology 96 (2021) 864–867, https://doi.org/10.1212/WNL.0000000000011715.

[6] D. Kondziella, C.K. Friberg, V.G. Frokjaer, M. Fabricius, K. Møller, Preserved consciousness in vegetative and minimal conscious states: systematic review and meta-analysis, J. Neurol. Neurosurg. Psychiatry 87 (2016) 485–492, https://doi.org/10.1136/jnnp-2015-310958.

[7] A.F. Turgeon, F. Lauzier, J.-F. Simard, D.C. Scales, K.E.A. Burns, L. Moore, D. A. Zygun, F. Bernard, M.O. Meade, T.C. Dung, M. Ratnapalan, S. Todd, J. Harlock, D.A. Fergusson, Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: a Canadian multicentre cohort study, CMAJ Can. Med. Assoc. J. J. l′Assoc. Med. Can. 183 (2011) 1581–1588, https://doi.org/10.1503/cmaj.101786.

[8] A.P. Skibsted, M. Amiri, P.M. Fisher, A. Sidaros, M.C. Hribljan, V.A. Larsen, J.L. S. Højgaard, M. Nikolic, J. Hauerberg, M.E. Fabricius, G.M. Knudsen, K. Møller, D. Kondziella, Consciousness in neurocritical care cohort study using fMRI and EEG (CONNECT-ME): protocol for a longitudinal prospective study and a tertiary clinical care service, Front. Neurol. 9 (2018) 1012, https://doi.org/10.3389/fneur.2018.01012.

[9] D. Kondziella, P.M. Fisher, V.A. Larsen, J. Hauerberg, M. Fabricius, K. Møller, G. M. Knudsen, Functional MRI for assessment of the default mode network in acute brain injury, Neurocrit. Care 27 (2017) 401–406, https://doi.org/10.1007/s12028-017-0407-6.

[10] E.F.M. Wijdicks, W.R. Bamlet, B.V. Maramattom, E.M. Manno, R.L. McClelland, Validation of a new coma scale: the four score, Ann. Neurol. 58 (2005) 585–593, https://doi.org/10.1002/ana.20611.

[11] M.H. Othman, M. Bhattacharya, K. Møller, S. Kjeldsen, J. Grand, J. Kjaergaard, A. Dutta, D. Kondziella, Resting-State NIRS–EEG in unresponsive patients with acute brain injury: a proof-of-concept study, Neurocrit. Care (2020), https://doi.org/10.1007/s12028-020-00971-x.

[12] E. Smith, M. Delargy, Locked-in syndrome, BMJ 330 (2005) 406–409, https://doi.org/10.1136/bmj.330.7488.406.

[13] J.B. Posner, C.B. Saper, N.D. Schiff, F. Plum. Plum and Posner's Diagnosis of Stupor and Coma, fourth ed., Oxford University Press, Inc, New York, 2007.

[14] S. Laureys, G.G. Celesia, F. Cohadon, J. Lavrijsen, J. León-Carrión, W.G. Sannita, L. Sazbon, E. Schmutzhard, K.R. von Wild, A. Zeman, G. Dolce, European task force on disorders of consciousness, unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome, BMC Med. 8 (2010) 68, https://doi.org/10.1186/1741-7015-8-68.

[15] J.T. Giacino, S. Ashwal, N. Childs, R. Cranford, B. Jennett, D.I. Katz, J.P. Kelly, J. H. Rosenberg, J. Whyte, R.D. Zafonte, N.D. Zasler, The minimally conscious state: definition and diagnostic criteria, Neurology 58 (2002) 349–353.

[16] M.-A. Bruno, A. Vanhaudenhuyse, A. Thibaut, G. Moonen, S. Laureys, From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness, J. Neurol. 258 (2011) 1373–1384, https://doi.org/10.1007/s00415-011-6114-x.

[17] J.T. Giacino, D.I. Katz, N.D. Schiff, J. Whyte, E.J. Ashman, S. Ashwal, R. Barbano, F.M. Hammond, S. Laureys, G.S.F. Ling, R. Nakase-Richardson, R.T. Seel, S. Yablon, T.S.D. Getchius, G.S. Gronseth, M.J. Armstrong, Practice guideline update recommendations summary: disorders of consciousness, Neurology 91 (2018) 450–460, https://doi.org/10.1212/WNL.0000000000005926.

[18] C.A. Bareham, J. Allanson, N. Roberts, P.J.A. Hutchinson, J.D. Pickard, D. K. Menon, S. Chennu, Longitudinal assessments highlight long-term behavioural recovery in disorders of consciousness, Brain Commun. 1 (2019) 017, https://doi.org/10.1093/BRAINCOMMS/FCZ017.

[19] M. Klipin, I. Mare, S. Hazelhurst, B. Kramer, The process of installing REDCap, a web based database supporting biomedical research, Appl. Clin. Inform. 5 (2014) 916–929, https://doi.org/10.4338/ACI-2014-06-CR-0054.

[20] C. Geroldi, E. Canu, A.C. Bruni, G. Dal Forno, R. Ferri, C. Gabelli, R. Perri, D. Iapaolo, O. Scarpino, E. Sinforiani, O. Zanetti, G.B. Frisoni, The added value of neuropsychologic tests and structural imaging for the etiologic diagnosis of dementia in Italian expert centers, Alzheimer Dis. Assoc. Disord. 22 (2008) 309–320, https://doi.org/10.1097/WAD.0b013e3181871a47.

[21] N. Weiss, D. Galanaud, A. Carpentier, L. Naccache, L. Puybasset, Clinical review: prognostic value of magnetic resonance imaging in acute brain injury and coma, Crit. Care 11 (2007) 1–12, https://doi.org/10.1186/cc6107.

[22] C. Williamson, L. Morgan, J.P. Klein, Imaging in neurocritical care practice, Semin. Respir. Crit. Care Med. 38 (2017) 840–852, https://doi.org/10.1055/s-0037-1608770.

[23] H.M. Algethamy, M. Alzawahmah, G.B. Young, S.M. Mirsattari, Added value of MRI over CT of the brain in intensive care unit patients, Can. J. Neurol. Sci. 42 (2015) 324–332, https://doi.org/10.1017/cjn.2015.52.

[24] G. Mortamet, M. Kossorotoff, A. Baptiste, N. Boddaert, M. Castelle, P. Hubert, F. Lesage, S. Renolleau, M. Oualha, Description and contribution of brain magnetic resonance imaging in nontraumatic critically Ill children, J. Child Neurol. 31 (2016) 1584–1590, https://doi.org/10.1177/0883073816666737.

[25] K.S. Frederiksen, S.G. Hasselbalch, A.-M. Hejl, I. Law, L. Højgaard, G. Waldemar, Added diagnostic value of 11C-PiB-PET in memory clinic patients with uncertain diagnosis, Dement. Geriatr. Cogn. Disord. Extra 2 (2012) 610–621, https://doi.org/10.1159/000345783.

[26] C.J. Ong, A. Dhand, M.N. Diringer, Early withdrawal decision-making in patients with coma after cardiac arrest: a qualitative study of intensive care clinicians, Neurocrit. Care 25 (2016) 258–265, https://doi.org/10.1007/s12028-016-0275-5.

[27] J.M. Weimer, A.S. Nowacki, J.A. Frontera, Withdrawal of life-sustaining therapy in patients with intracranial hemorrhage: self-fulfilling prophecy or accurate prediction of outcome? Crit. Care Med. 44 (2016) 1161–1172, https://doi.org/10.1097/CCM.0000000000001570.

[28] D. Pinggera, M. Luger, I. Bürgler, M. Bauer, C. Thomé, O. Petr, Safety of early MRI examinations in severe TBI: a test battery for proper patient selection, Front. Neurol. 11 (2020) 1–6, https://doi.org/10.3389/fneur.2020.00219.

[29] K.N. Sheth, M.H. Mazurek, M.M. Yuen, B.A. Cahn, J.T. Shah, A. Ward, J.A. Kim, E. J. Gilmore, G.J. Falcone, N. Petersen, K.T. Gobeske, F. Kaddouh, D.Y. Hwang, J. Schindler, L. Sansing, C. Matouk, J. Rothberg, G. Sze, J. Siner, M.S. Rosen, S. Spudich, W.T. Kimberly, Assessment of brain injury using portable, low-field magnetic resonance imaging at the bedside of critically Ill patients, JAMA Neurol. 78 (2021) 41–47, https://doi.org/10.1001/jamaneurol.2020.3263.

[30] I.K. Ip, A.S. Raja, S.E. Seltzer, A.A. Gawande, K.E. Joynt, R. Khorasani, Use of public data to target variation in providers' use of CT and MR imaging among medicare beneficiaries, Radiology 275 (2015) 718–724, https://doi.org/10.1148/radiol.15141964.