Clinical Neurophysiology 144 (2022) 98–114

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

EEG-based methods for recovery prognosis of patients with disorders of consciousness: A systematic review

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HIGHLIGHTS

- Simpler experimental setups for EEG recording were preferred (i.e., 10–20 International System and reduced number of electrodes).
- *Qualitative* and *quantitative* features were equally investigated but they are rarely studied together.
- The adoption of robust, generalisable, and validated methods for DoC prognosis is lacking and great heterogeneity exists among methods.

ARTICLE INFO

Article history:
Accepted 19 September 2022
Available online

Keywords:
Disorders of Consciousness
Electroencephalography
Qualitative analysis
Prognostic biomarkers
Quantitative feature extraction
Rehabilitation

ABSTRACT

Objective: Disorders of consciousness (DoC) are acquired conditions of severely altered consciousness. Electroencephalography (EEG)-derived biomarkers have been studied as clinical predictors of consciousness recovery. Therefore, this study aimed to systematically review the methods, features, and models used to derive prognostic EEG markers in patients with DoC in a rehabilitation setting.
Methods: We conducted a systematic literature search of EEG-based strategies for consciousness recovery prognosis in five electronic databases.
Results: The search resulted in 2964 papers. After screening, 15 studies were included in the review. Our analyses revealed that simpler experimental settings and similar filtering cut-off frequencies are preferred. The results of studies were categorised by extracting qualitative and quantitative features. The quantitative features were further classified into evoked/event-related potentials, spectral measures, entropy measures, and graph-theory measures. Despite the variety of methods, features from all categories, including qualitative ones, exhibited significant correlations with DoC prognosis. Moreover, no agreement was found on the optimal set of EEG-based features for the multivariate prognosis of patients with DoC, which limits the computational methods applied for outcome prediction and correlation analysis to classical ones. Nevertheless, alpha power, reactivity, and higher complexity metrics were often found to be predictive of consciousness recovery.
Conclusions: This study's findings confirm the essential role of qualitative EEG and suggest an important role for quantitative EEG. Their joint use could compensate for their reciprocal limitations.
Significance: This study emphasises the need for further efforts toward guidelines on standardised EEG analysis pipeline, given the already proven role of EEG markers in the recovery prognosis of patients with DoC.

Abbreviations: ApEn, Approximate Entropy; BCI, Brain Computer Interface; Cross-ApEn, Cross-Approximate Entropy; CRS-R, Coma Recovery Scale – Revised; DRS, Disability Rating Scale; dwPLI, debiased weighted Phase Lag Index; E-MCS, Emergence from Minimally Conscious State; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; LZC, Lempel-Ziv Complexity; LZW, Lempel-Ziv Welch Complexity; MCS, Minimally Conscious State; NMI, Normalised Mutual Information; QPSC, Quadratic Phase Self-Coupling; SSEP, Somatosensory-Evoked Potential; SSVEP, Steady-State Visual-Evoked Potential; SWS, Slow Wave Sleep; UWS, Unresponsive Wakefulness Syndrome; vS, Vegetative State.

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https://doi.org/10.1016/j.clinph.2022.09.017
1388-2457/

1. Introduction

Patients who are comatose after severe acquired brain injuries (sABI) often develop disorders of consciousness (DoC). Specifically, the condition of sABI is defined as 'traumatic, post-anoxic, vascular, or other brain damages that cause coma for at least 24 hours' (Gazzetta Ufficiale della Repubblica Italiana, 1998). Patients who transition to a state of DoC can be classified as having unresponsive wakefulness syndrome (UWS) or being in a vegetative state (VS) or minimally conscious state (MCS); the latter can additionally be subdivided into minus (MCS −) or plus (MCS +) (Bruno et al., 2011). These diagnostic categories are defined by the presence and nature of behavioural responses (reflexive in UWS/vS and intentional in MCS) to multisensorial stimuli (Giacino et al., 2002). Lastly, some patients may emerge from their MCS and be classified as emergence from MCS (E-MCS). Clinically, the difference between MCS and EMCS can be based on responses to presented stimuli (e.g., functional object use) with a large increase in functional connectivity between anticorrelated brain networks (Perri et al., 2016; Sun et al., 2018). These clinical conditions, characterised by fluctuating but detectable conscious behaviour, could persist chronically, especially with the latest advances in life-saving medical technology significantly increasing survival rates for patients with DoC (Abeyasinghe et al., 2020).

The mechanisms underlying recovery from UWS and MCS remain unknown and have high inter-individual variability, conditioned by aetiology, severity at baseline, and medical complications (Edlow et al., 2021; Estraneo et al., 2021). In particular, patients in an MCS (compared with UWS) are associated with a superior prognosis in terms of consciousness and functional improvement (Liuzzi et al., 2022; Mannini et al., 2021; Portaccio et al., 2018b, 2018a) as well as patients with a traumatic brain injury, respectively considering the baseline stratification and the aetiology (Edlow et al., 2021; Liuzzi et al., 2022). Thus, conducting a thorough assessment of patients with DoC remains a critical challenge. Such an assessment is required to define an effective rehabilitation plan in terms of duration, intensity, and the information provided to caregivers. Moreover, a precise diagnosis is essential for ensuring a reliable prognostic prediction.

In terms of clinical diagnostic tools, the Coma Recovery Scale-Revised (CRS-R) is the reference scale currently used for the clinical assessment of consciousness level (Seel et al., 2010). The CRS-R enables a fast stratification of DoC into UWS, MCS−, MCS+, or E-MCS based on various subitems related to the auditory, visual, motor, oromotor, communication, and arousal domains. A study reported that when a diagnosis is based on non-standardised clinical scales only, up to 40 % of patients may receive an incorrect diagnosis, and using the CRS-R can partially reduce this error (Schnakers et al., 2009). Furthermore, the following suggestions for containing misdiagnosis errors have been proposed: repetition of the assessment at least five times (Wannez et al., 2017), involvement of the caregiver (Formisano et al., 2011), and mirror use (Keromnes et al., 2019). However, clinical assessment alone does not seem sufficient for achieving a high level of diagnostic accuracy (Formisano et al., 2019a). Therefore, the latest international guidelines recommended the introduction of instrumental evaluations, such as functional neuroimaging or electroencephalography (EEG) in addition to clinical evaluation for an improved consciousness diagnosis and, consequently, prognosis definition (Giacino et al., 2018; Kondziella et al., 2020). Evidence in the literature also supports this suggestion; for example, Aubinet *et al.* (Aubinet et al., 2020) demonstrated that patients in the MCS + group presented a higher metabolism mainly in the left middle temporal cortex, which is known to be crucial for semantic processing, compared with the MCS − group. Furthermore, Thibaut *et al.* (Thibaut et al., 2021) demonstrated how the use of FDG-PET improves patient assessments by enabling the identification of a specific condition called 'non-behavioural MCS' or 'MCS*'.

In the last century, EEG has been introduced into clinical practice for patients with DoC (Comanducci et al., 2020; Scarpino et al., 2020b). The aim is to increase the number of information sources related to patients' consciousness levels, reduce misclassification rates, and find new prognostic factors. Among the various instrumental evaluations suggested in the guidelines for DoC diagnosis, EEG is more economical and easier to apply directly at the bedside; moreover, it is probably the most straightforward method for obtaining neurophysiological information from the human brain in a non-invasive manner (Pastor et al., 2021). In the last decades, the crucial contributions of EEG in the diagnosis and prognosis of patients with DoC have become increasingly evident (Sondag et al., 2017).

Regarding the reporting of EEG recordings, many modalities have been used. They can be broadly distinguished as *qualitative* or *quantitative* methods, which are described as follows:

Qualitative EEG measures are features that can be detected by the neurophysiopathologist/neurologist by visually inspecting the recordings. Specifically, Doerrfuss *et al.* (Doerrfuss et al., 2020) defined *qualitative* EEG analysis as an investigation that comprises the characterisation of the frequency, amplitude, and localisation of cortical electrical activity. On the other hand, quantitative EEG has been defined as a set of computerised algorithms capable of extracting features objectively following precise numerical rules (Gudmundsson et al., 2007; Kaiser, 2007).

When first used, *qualitative* modalities were characterised by higher degrees of subjectivity in terms of the adopted nomenclature and medical reporting guidelines, which are strongly influenced by the interpreter (Grant et al., 2014). To address this issue, an attempt has been made to reduce the interrater variability among neurophysiologists by introducing a consensus for EEG interpretation through developing guidelines (Hirsch et al., 2021, 2012). The first step was to standardise the terminology (neutral from clinical connotations; e.g., ictal and epileptiform), allow multi-centre research projects, and facilitate communication. The second step was to promote more precise boundaries (e.g., in voltage, frequency, and the number of bursts per minute) to reduce interrater variability. Although the guidelines introduce some objectivity into EEG analysis, the information extracted is mostly represented by *qualitative* or binary (present/absent) variables. Noteworthily, however, examples of confirmed associations of these features with the patient outcome are available in the literature. For instance, the bilateral absence of the N20 cortical component of somatosensory evoked potentials in traumatic patients has been found to be associated with a poor outcome (Amantini et al., 2005), whereas the presence of mismatch negativity (Qin et al., 2008), and the positive component of P300 (Cavinato et al., 2009) were found to be predictors of better recovery from vascular and traumatic encephalopathy. *Qualitative* methods of EEG analysis provide simple and essential information determined through decades of clinical experience. *Qualitative* features have already demonstrated their fundamental predictive power, paving the way for EEG to be used as a prognostic tool.

On the other hand, *quantitative* EEG (qEEG) includes any type of online/offline numerical method used to obtain insights into the frequency and temporal domains, brain dynamics and synchronisation patterns, and connectivity graphs. Time-domain analysis reveals the modification of signals in time, which are often event-locked, whereas the frequency-domain analysis provides information about the contribution of the different frequency bands in a range of frequencies.

Features extracted from *quantitative* analyses are often more complex, and therefore, they are currently underused in clinical practice (Doerrfuss et al., 2020). Additional problems encountered are the lack of interpretation training and the practical complexity of assembling or synchronising complex setups. However, given the already promising results (Amantini et al., 2005; Cavinato et al., 2009; Qin et al., 2008), the possibility of introducing more complex and informative features should be explored by promoting further specialised training in interpreting such measures and guidelines for multimodal assessment setups (e.g., TMS-EEG, polygraphy, and ECG-EEG synchrony).

Findings related to the use of qEEG in patients with DoC have indicated that functional connectivity is usually impaired (Rizkallah et al., 2019; Wang et al., 2022) and the connection between cortical and subcortical structures is often damaged (Schiff et al., 2014). It is clear that a relationship exists between clinical evaluations and brain activity. Specifically, Lechinger *et al.* (Lechinger et al., 2013) reported a correlation between the peak frequency of the power spectrum and the CRS-R score. Alpha power was recognised as an indicator of consciousness, specifically in frontoparietal networks (Naro et al., 2016a). Moreover, its increase over time was positively associated with consciousness recovery (Stefan et al., 2018), while a consistent decrease was found in UWS patients compared with MCS patients (Rossi Sebastiano et al., 2015). Furthermore, Engemann *et al.* reported that such a significant difference is independent of the EEG configuration, also providing robust results for smaller configurations (Engemann et al., 2018).

Today, the new frontiers for EEG analysis are the optimisation of this information source by improving the mathematical and technical tools applied after EEG acquisition. Complex artefact rejection and feature extraction methods, connectivity measures, graph theory analysis, and machine learning (ML) models may still be far from daily clinical practice; however, parameters extracted through qEEG analysis are already finding their place as biomarkers for prognostic prediction (Wutzl et al., 2021). Furthermore, qEEG has the potential to provide additional insights when combined with other diagnostic tools. For instance, Gosseries *et al.* (Gosseries et al., 2016) demonstrated that, despite the clear potential of various neuroimaging techniques, their joint use increases the possibility of providing a precise rehabilitative assessment in patients with DoC. This was also demonstrated by Hermann *et al.* (Hermann et al., 2021). Similarly, Chennu *et al.* (Chennu et al., 2017) reported that neuroimaging tools and advanced analytics are crucial in improving outcome prediction in this population, while also recognising the prognostic utility of qEEG.

To summarise, both *qualitative* and *quantitative* techniques have their merits and pitfalls. In particular, the low sensitivity and high interrater variability of *qualitative* analysis are compensated for by the ease of reporting EEG recordings in clinical daily settings. By contrast, qEEG could improve the reliability and deepen the information extracted from raw neurophysiological data about the cerebral functional state while increasing the level of complexity. Indeed, such measures and the cut-offs derived from numerical analyses require extensive validation in different settings, with different machines and noise levels (Gudmundsson et al., 2007). Furthermore, conditioned on thorough validations, *quantitative* cut-offs allow the easier generalisation of results to a wider population as well as the use of such data for training multivariate prediction models. Such models, specifically in the case of ML models, require data to be extracted following the same rules across training and testing, rehabilitative/acute settings, and neurophysiologists. The latter indubitably calls for automated extraction pipelines to simplify the burden on doctors and promote the translatability of such solutions.

In patients with DoC, these aspects have not been fully explored due to the complexity of the mechanisms that underlie this condition. Indeed, due to the heterogeneity of aetiologies and damage severity, the neurophysiological patterns that originate from brain injuries in DoC are considered among the most complex (Aubinet et al., 2020; Bodart et al., 2017, 2013; Giacino et al., 2014). Moreover, complex computational methods require large datasets collected with a systematic instrumental approach as well as robust and noise-insensitive protocols. The availability of such data sets is often impractical in patients with DoC, particularly regarding noise. Indeed, EEG signals can intrinsically store a large amount of information, but the processing of such data is not always effortless. In these patients, the presence of artefacts can often deeply affect the quality of data, and thus, it is vital to be extremely careful in both data collection and processing. Several methods and dedicated toolboxes (e.g., EEGLab, FieldTrip, BrainVision Analyzer, Brainstorm, MNE, and sLORETA; (Huang, 2019) exist for extracting *quantitative* information from data, but different conclusions and interpretations can be drawn just by choosing different preprocessing parameters, feature extraction steps, and correlation/interpretation models (Khosla et al., 2020). For these reasons, we chose to take stock of the pipelines used to study EEG signals in DoC, focusing on prognostic purposes. Currently, reviews in the literature about the use of qEEG in patients with DoC (Bai et al., 2020; Wutzl et al., 2021) have aimed to provide an overall analysis of extracted features. However, a distinction between diagnostics and prognostics and a detailed analysis of the methodological implementation of solutions have not yet been reported. In this systematic review, given the growing interest in the prognosis of consciousness recovery, we aimed to investigate which EEG features have been found to be predictors of consciousness recovery in patients with DoC. Moreover, we extended previous literature through a systematic analysis of preferred computational methods adopted for the extraction of *qualitative* and *quantitative* EEG features, focusing on prognostic purposes. The remaining paragraphs of this paper is structured as follows: Methods, Results, Discussion, Limitations, and Conclusions. Specifically, the section of Methods is subdivided into Selection criteria, Search method, Data collection, Data synthesis and Data availability, performing a description of the chronological steps performed for the analysis of this systematic review.

Concerning the Results section, sub-paragraphs were created to report separately information regarding the included studies (Search results and selection of studies), the samples enrolled in each (Population), the analyses applied (Analysis pipeline), and the outcomes selected (Outcome measures). The Analysis pipeline section was further subdivided distinguishing the different phases of analysis of the EEG signals: EEG Signal Pre-processing, Domain Analysis, EEG Features Extracted, and Data Analysis.

2. Methods

We performed a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The protocol was registered on PROSPERO (CRD42021231435).

2.1. Selection criteria

The papers to include in this study were selected according to the Population, Intervention, Comparison, and Outcome (PICO) framework (Eriksen and Frandsen, 2018). The search string was also designed over the same framework.

We included studies that involved patients affected by sABI with prolonged DoC in the subacute or chronic phase assessed with the CRS-R. Since the CRS-R was published and validated in 2004, only papers from that year onward were selected. Due to their strong heterogeneous characteristics, we excluded papers from the search involving sABI participants with metabolic, neoplastic, and infectious aetiology. In terms of age, only adult participants (age $\geq$ 18 years) were considered. More precisely, for all criteria regarding population characteristics (i.e., time from injury, age and aetiology), we evaluated papers as follows: those for which the results of a nonconforming group of patients could be separately distinguished were included considering only the group within the criteria; by contrast, for papers with non-separable results, only those with non-conforming participants accounting for less than 5 % of the total sample size were included.

Regarding the interventions, we selected papers that used any *qualitative* or computational method to elaborate participants' EEG to gain insights into prognostic factors. This was performed independently on the presence and type of applied stimulations since we did not consider specific exclusion criteria for this aspect. We considered prognostic analysis to be any type of method that used data derived from a longitudinal assessment of the cohort, independent of the presence of model validation. Thus, we selected studies that evaluated predictors assessed at the admission of the rehabilitation unit and outcomes occurring either at discharge, upon follow-up, or in intermediate evaluations during recovery. For this reason, regarding the design of the studies, no specific criteria were applied except for the exclusion of cross-sectional studies. Otherwise, both prospective and retrospective works were included.

The outcome of interest was the recovery of consciousness defined as a full recovery, a clinical status change, or an improvement in assessment based on any measurement scale. In each paper, only analyses with an outcome of consciousness recovery were included.

Finally, in terms of the type of study, we selected all types of primary studies, excluding overviews and reviews.

2.2. Search method

We conducted a systematic search in the PubMed, Web of Science, Scopus, Embase, and CENTRAL databases. The search string was designed using the PICO framework as a guideline and the following main keywords: 'Disorders of Consciousness', 'Electroencephalography', 'Brain injury', 'Prognosis', and 'Rehabilitation' (Supplementary Material Table 1).

Once the results had been exported, three reviewers (SB, SC, and PL) screened the titles and abstracts, followed by the full texts. A fourth reviewer (AM) was involved if a disagreement occurred. During this phase, only papers in English were considered eligible for screening. The selection concerning outcomes was not applied during the search phase; it was performed in the screening phase only.

Moreover, studies included by other reviews close to our topic were analysed (Bai et al., 2020; Wutzl et al., 2021), through which three additional papers were included (Bai et al., 2019; Bareham et al., 2020; Formisano et al., 2019b).

2.3. Data collection

For the data collection, the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) was used (Moons et al., 2014). The following data were extracted from the included studies:

- Source of data (authors' names and year of publication);
- Participant characteristics (age, number, consciousness stratification, aetiology, time from event, and presence of epilepsy);
- Setting (monocentric or multicentric, number of electrodes, sampling frequency, and signal duration);
- Study design (randomised controlled trial [RCT] or non-RCT);
- Stimuli (auditory, visual, electric, tactile, transcranial direct current stimulation [tDCS], transcranial magnetic stimulation [TMS], and others);
- Methods (preprocessing filters and segmentation parameters, analysed domain, model type, model performances, and frequency band);
- Features (measures used to quantify an independent variable);
- Outcomes (measures used to evaluate a dependent variable and its timing).

2.4. Data synthesis

Only the content of papers that fulfilled the inclusion criteria was used for the analyses. The results were displayed through narrative data synthesis since, due to the heterogeneity of the methods in the extraction pipelines, a meta-analysis was not applicable. For the same reason, the use of the PROBAST tool to evaluate the methodological quality of prognostic studies was not possible (Wolff et al., 2019).

Moreover, a PICO format was generally used to display the results. First, a general description of the participants included in the studies and the experimental setting was provided. Then, the intervention types were displayed following the consecutive steps of the *analysis pipeline*, namely the *EEG signal preprocessing* methods, the *domain analysis* performed (time, frequency, or both), the *EEG features extracted,* and the *data analysis* used to identify candidate prognostic factors (Fig. 1). Lastly, a brief paragraph was dedicated to the description of the outcomes. In line with the definition of the string and selection criteria, the PICO component of 'Comparison' was not addressed in the results.

Regarding features, the results were presented distinguishing between *qualitative* and *quantitative* features. In the case of the latter, additional categorisation was conducted as follows: evoked potentials (EPs) and event-related potentials (ERPs), spectral measures, entropy measures, and graph-theory measures.

2.5. Data availability

Data were extensively included within the manuscript and Supplementary Material. However, a comprehensive version of the data set with the data extracted from the included papers can be obtained for research purposes by submitting a request to the corresponding author.

3. Results

3.1. Search results and selection of studies

Our systematic review included 12 papers out of 2964 found in the initial search (Fig. 2). Additionally, three more papers were included from external sources due to missing specifications about the subacute or chronic phase of patients (Bai et al., 2019; Bareham et al., 2020) and the use of EEG (Formisano et al., 2019b) in the abstract, title, or keywords. Thus, a total of 15 papers were included. Unsurprisingly, the two main reasons for exclusion were the absence of a baseline clinical status evaluation with the CRS-R and the absence of a prognostic aim in the study intervention.

3.2. Population

The number of participants ranged between 4 and 260 and their ages varied from a minimum of 20 ± 3.4 to a maximum of 69.9 ± 1 1.4 years. Although different DoC clinical states were considered in the search string, the studies were mainly focused on UWS and MCS patients, and the latter were further stratified into MCS – and MCS + in four studies. Three studies included E-MCS patients (Arnaldi et al., 2016; Bareham et al., 2020; Martens et al., 2020), whereas no study investigated coma patients. Regarding locked-in syndrome, one study (Pan et al., 2020) investigated the presence of cognitive motor dissociation (CMD), also known as functional locked-in syndrome, with a brain-computer interface (BCI)-based algorithm in patients initially classified as UWS or MCS. By contrast, some studies have considered this condition an exclusion criterion. The majority of patients included in the studies were in a subacute (1–3 months after non-TBI and 1–12 months after TBI) rather than chronic state (3 months after non-TBI and 12 months after TBI) (Giacino et al., 2018). Moreover, 13 studies included both traumatic and nontraumatic aetiology, comprising anoxic, ischaemic, haemorrhagic, and vascular ones, whereas the remaining two works (Bareham et al., 2018; Straudi et al., 2019) included only patients with traumatic sABI. Furthermore, two studies specified the presence of epileptiform activity in the included patients (Bagnato et al., 2016; Pascarella et al., 2016) as a potential predictor in patients with DoC. More information about the population is reported in Table 1.

3.3. Experimental setting

The number of EEG channels varied between 6 and 128, with nine studies using fewer than 20 electrodes and 11 studies applying the 10–20 International System for Electrode Placement. The sampling frequency varied between 128 and 2500 Hz (median 500 Hz [IQR = 628]). More information about the experimental setting is reported in Table 2.

Most studies did not use any stimulation, except when extracted features were strongly related to the presence of physical stimulation (e.g., to elicit EPs). We found two papers that applied tDCS to investigate whether it affected the recovery of consciousness (Martens et al., 2020; Straudi et al., 2019). Six studies used auditory, visual, tactile, or electrical stimuli, but only two studies performed intra-stimulus comparisons (Pan et al., 2020; Wu et al., 2011).

3.4. Analysis pipeline

3.4.1. EEG signal preprocessing

Thirteen studies used a band-pass filter, whereas the remaining two (Scarpino et al., 2020a, 2019) used a low-pass filter (Fig. 3a). The band-pass filter cut-off frequencies varied between 0.48 ± 0. 3 Hz and 52.69 ± 22.04 Hz. Seven studies, in which the band-pass included power line interference (50 or 60 Hz, depending on the country in which the study was conducted), also applied a

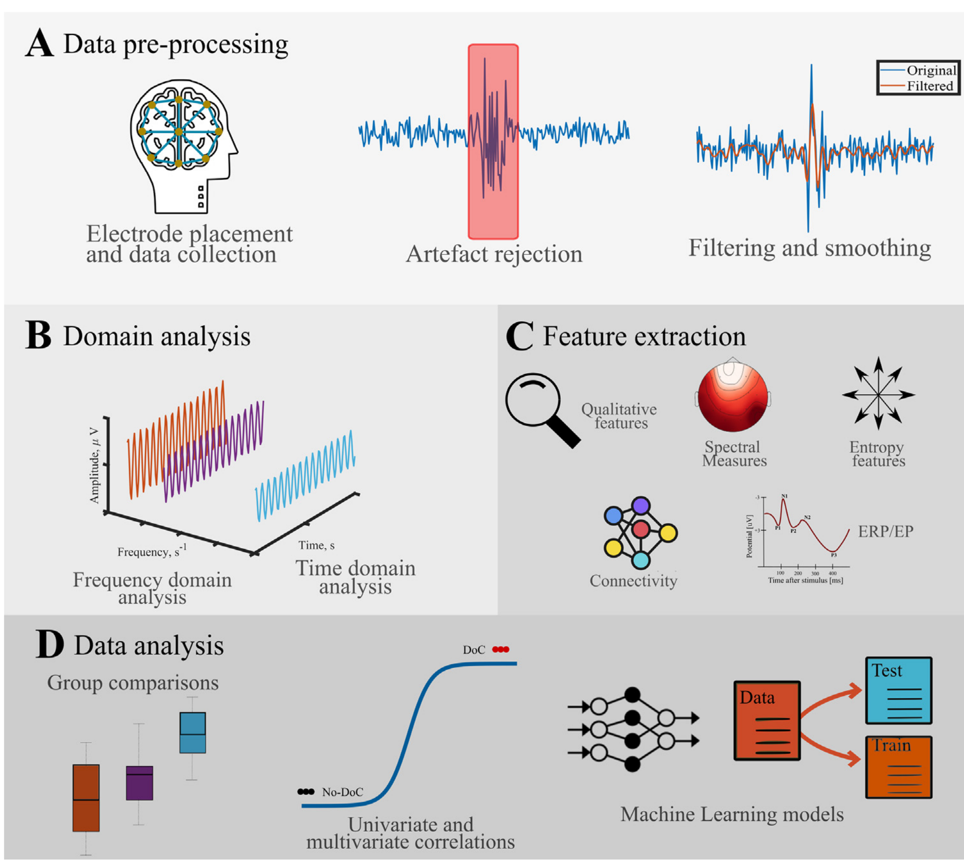

Fig. 1. Steps commonly adopted within the EEG analysis pipeline: data preprocessing, domain analysis, feature extraction, and data analysis.

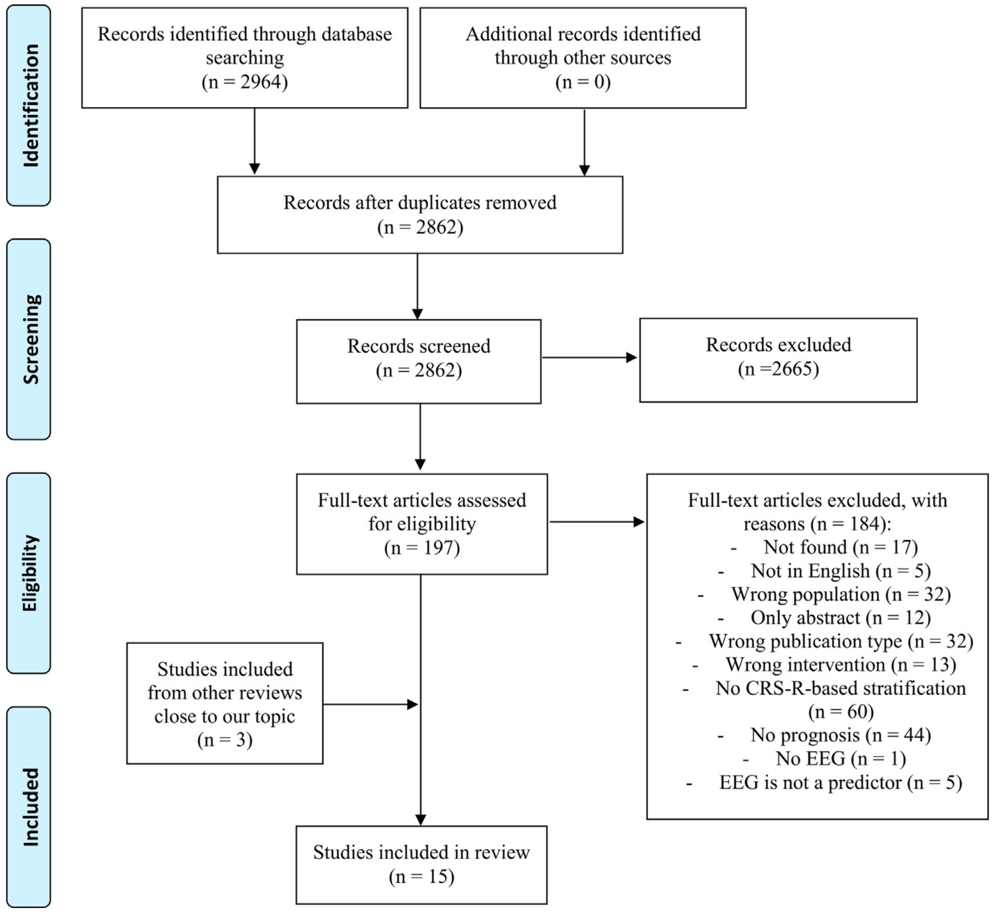

Fig. 2. Flow chart of the study.

Notch filter to remove it (Fig. 3a). Furthermore, three studies applied independent component analysis (Fig. 3a) to identify and reject noisy components (Bai et al., 2019; Bareham et al., 2020, 2018), whereas the remaining studies removed artefacts through visual inspection or automatic detection with voltage threshold-based algorithms. Moreover, nine studies divided signals into epochs (Fig. 3a); the epoch length was set in accordance with the EEG feature requirements, and this step was applied depending on the EEG features extracted. For instance, segmentation into epochs was used in studies that extracted entropy-related features (Martens et al., 2020; Wu et al., 2011).

Among the studies that involved stimulation, we did not find that different preprocessing steps or analyses had been conducted on the signals during stimulation compared with the resting state. In two studies (Formisano et al., 2019b; Pan et al., 2020), the epochs for signal segmentation were centred around stimulus presentation, whereas the other studies provided the epochs' length but not their boundaries.

3.4.2. Domain analysis

Nine studies extracted features in the temporal domain, five did so in the frequency domain, and one did so in both (Arnaldi et al., 2016) (Fig. 3b). Most temporal domain analyses were associated with studies that performed a *qualitative* extraction of features.

The oscillatory activity of the EEG, in clinical practice, is divided into five bands depending on its oscillation frequency: delta (0–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (>30 Hz). Some studies further divided these bands into subgroups or used mildly different frequency boundaries; for example, sigma (12,25–16 Hz in Arnaldi *et al.* (Arnaldi et al., 2016) is a subclassification of the beta band. Frequencies above 30 Hz, although critical in cognitive research, are not customarily used in clinical practice due to the notably lower gamma power that patients with DoC retain (Naro et al., 2016a). On the other hand, gamma waves were evaluated only when applying transcranial alternating (Naro et al., 2016b) or direct (Naro et al., 2016c) current stimulation. Ten studies focused their analysis on the delta, theta, and alpha bands, which are typical frequencies generally investigated in patients with DoC; three added beta bands (Arnaldi et al., 2016; Straudi et al., 2019; Wu et al., 2011); and only one also included sigma band (Arnaldi et al., 2016) (Fig. 3b, inner plot).

3.4.3. EEG feature extraction

We found high heterogeneity in the type and number of features extracted (Supplementary Material Table 2). Five studies focused on an analysis of a single feature, whereas Bareham *et al.* (Bareham et al., 2020) examined 42 features, 14 for each of the three frequency bands (i.e., delta, theta, and alpha).

To obtain an enhanced understanding of the differences between measures, we considered the distinction between *qualitative* and *quantitative* features. Table 3 presents a summary of the

Table 1
Information about the population in terms of number, age, baseline clinical state, aetiology, time post-onset, scales used for assessment, and presence of epileptic seizures.

Author	Participants	Age range	Clinical state	Aetiology	Time Post Onset	Assessment Scale	Epileptic patients	Stimuli
Wu et al., 2011	37 Patients 30 Controls	19–80	21 UWS 16 MCS	32 Traumatic 35 Vascular	67 Subacute	CRS-R GCS GOS	No	Electrical Auditory
Arnaldi et al., 2016	27 Patients	18–81	20 UWS 2 MCS – 4 MCS+ 1 E-MCS	13 Traumatic 8 Anoxic 6 Haemorrhagic	27 Subacute	CRS-R	No	-
Bagnato et al., 2016	112 Patients	36.6 ± 16.5	65 UWS 47 MCS+	61 Traumatic 51 Non Traumatic	-	CRS-R	Yes	-
Pascarella et al., 2016	130 Patients	55.8 ± 17.33	97 UWS 33 MCS	36 Traumatic 45 Anoxic 49 Vascular	130 Subacute	CRS-R	Yes	-
Wang et al., 2017	11 Patients 5 Controls	26–60	6 UWS 5 MCS	2 Traumatic 2 Vascular 2 Ischemic 5 Haemorrhagic	4 Subacute 7 Chronic	CRS-R	No	Auditory
Bareham et al., 2018	4 Patients	20–45	2 UWS 2 MCS-	4 Traumatic	4 Chronic	CRS-R GCS	No	-
Bai et al., 2019	51 Patients 20 Controls	17–79	31 UWS 20 MCS	10 Traumatic 18 Anoxic 14 Vascular 9 Haemorrhagic	-	CRS-R	No	-
Formisano et al., 2019a	15 Patients 10 Controls	25–73	7 UWS 3 MCS- 5 MCS+	7 Traumatic 1 Anoxic 7 Haemorrhagic	15 Subacute	CRS-R	No	Auditory
Scarpino et al., 2019	102 Patients	55.5[15.2]	61 UWS 41 MCS	30 Traumatic 31 Anoxic 41 Vascular	102 Subacute	CRS-R	Yes	Auditory
Straudi et al., 2019	10 Patients	21–63	10 MCS	10 Traumatic	10 Chronic	CRS-R	No	tDCS
Bareham et al., 2020	39 Patients	19–75	16 UWS 15 MCS- 7 MCS+ 1 E-MCS	18 Traumatic 14 Anoxic 5 Vascular 2 Other	11 Subacute 28 Chronic	CRS-R	No	-
Estraneo et al., 2020	147 Patients	49.4 ± 20.41	71 UWS 76 MCS	55 Traumatic 36 Anoxic 56 Vascular	147 Chronic	CRS-R DRS	No	Tactile Electric Visual Auditory
Martens et al., 2020	46 Patients	20–77	17 UWS 23 MCS 6 E-MCS	22 Traumatic 24 Non traumatic	16 Subacute 30 Chronic	CRS-R	No	tDCS
Pan et al., 2020	78 Patients 8 Controls	15–66	45 UWS 33 MCS	41 Traumatic 17 Anoxic 20 Vascular	72 Subacute 6 Chronic	CRS-R	No	Visual Auditory
Scarpino et al., 2020	260 Patients	67[21]	108 UWS 152 MCS	71 Traumatic 50 Anoxic 139 Vascular	260 Subacute	CRS-R	Yes	-

Abbreviations: CRS-R = Coma Recovery Scale – Revised; DRS = Disability Rating Scale; E-MCS = Emergence from Minimally Conscious State; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; MCS = Minimally Conscious State; UWS = Unresponsive Wakefulness Syndrome.

Table 2
Information about experimental settings. In particular, the number and configuration of electrodes, sampling rate, and duration of the recordings were reported together with information on rejected data.

Author, Year	Number of electrodes	10–20 International System	Signal Duration, minutes	Rejected/Retained Data	Sampling Rate (Hz)
Wu et al., 2011	16	Yes	> 5	Total of 5 epochs rejected	500
Arnaldi et al., 2016	8	Yes	1440	not reported	128
Bagnato et al., 2016	19	Yes	> 30	not reported	256
Pascarella et al., 2016	19	Yes	> 30	not reported	-
Wang et al., 2017	128	No	not reported	not reported	1024
Bareham et al., 2018	91	No	15	10.7 minutes retained on avg.	500
Bai et al., 2019	62	Yes	20	not reported	2500
Formisano et al., 2019a	27	Yes	not reported	not reported	512
Scarpino et al., 2019	19	Yes	30	not reported	128
Straudi et al., 2019	6	Yes	15	not reported	1000
Bareham et al., 2020	91	No	15	17 trials rejected on avg.	500
Estraneo et al., 2020	19	Yes	> 35	not reported	1024
Martens et al., 2020	8	Yes	20	not reported	500
Pan et al., 2020	30	No	not reported	not reported	250
Scarpino et al., 2020	19	Yes	30	not reported	128

Abbreviations: avg. = average; E-MCS = Emergence from Minimally Conscious State; MCS = Minimally Conscious State; UWS = Unresponsive Wakefulness Syndrome.

models realised in each study together with the baseline clinical status, aetiology, and numerosity of samples. Only models in which at least one feature resulted in statistical significance were reported. Colours were used to describe classes of features included in the study. In particular, the green dashed box represents *qualitative* features, red represents EPs or ERPs, orange represents spectral measures, blue represents entropy measures, and purple represents graph-theory measures.

Qualitative measures were obtained from a visual analysis of EEG patterns that informed the researchers about the characteristic frequency, amplitude, and localisation of cortico-electrical activity (Doerrfuss et al., 2020). Visual inspection of the signal provides information related to the background activity of patients as well as epileptiform activity (e.g., detecting sharp waves, spikes, and polyspikes) and sleep-related markers (e.g., observing spindles and K-complexes). This category also includes EPs, which are dependent on the stimulus type (e.g., visual or auditory), and ERPs, which are associated with the late stages of information processing (Comanducci et al., 2014). This activity could be elicited by different types of stimulation, such as auditory, somatosensory, visual, and painful, and it could be identified visually. Nine studies extracted *qualitative* features from EEG signals, four of which focused on EP/ERP, two of which focused on epileptiform activity, and another focused on sleep-related markers (Arnaldi et al., 2016;

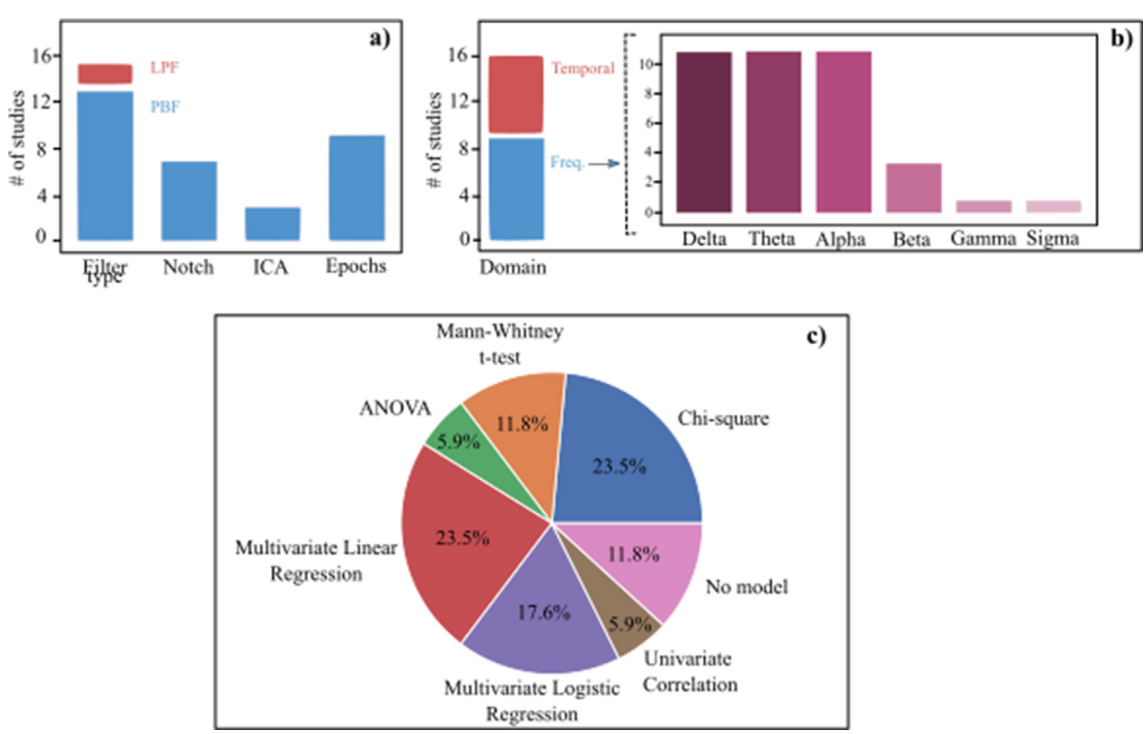

Fig. 3. Analysis pipeline details from the included studies: (**A**) EEG signal preprocessing: bar plots report information about filtering, independent component analysis, and segmentation into epochs; (**B**) domain analysis: bar plot depicting the domain in which the studies extracted features; the inner plot indicates the frequency bands analysed; and (**C**) predictive models.

Bagnato et al., 2016; Estraneo et al., 2020; Formisano et al., 2019b; Pascarella et al., 2016; Scarpino et al., 2020a, 2019; Wang et al., 2017; Wu et al., 2011).

Quantitative measures were obtained using various computational methods with the aim of maximising the amount of information extracted from EEG signals. These methods can be applied in the frequency or temporal domain, allowing for the investigation of different cerebral mechanisms. In this review, we considered the following categories:

- EPs and ERPs: In this category, only EPs and ERPs investigated in a *quantitative* manner were included (Genna et al., 2017). Only one study was included, in which the identification of EPs was automatised by employing a support vector machine (Pan et al., 2020).
- *Spectral measures*: These measures were obtained from a mathematical investigation in the frequency domain. In most cases, they consisted of an estimation of the oscillations at given frequency ranges; this is typically assessed using various types of transforms and generally expressed as either the dominant frequency or power spectral density per frequency band (Geraedts et al., 2018). Six studies reported spectral features, one of which focused on sleep-related measures (Arnaldi et al., 2016; Bai et al., 2019; Bareham et al., 2020, 2018; Martens et al., 2020; Straudi et al., 2019).
- *Entropy measures:* These measures were obtained with nonlinear analyses of patterns that provided information about the complexity of EEG signals. For instance, in a population with DoC, abnormally low entropy values are related to pathological

Table 3
Summary of results with the different features and models in each study. Only statistically significant features obtained by each model are reported together with baseline clinical status, aetiology, and number of participants. Each square represents a model, and the different colours provide information about the class of features used in the study. In particular, the green dashed box represents qualitative features, red represents evoked potentials (EPs) or event-related potentials (ERPs), orange represents spectral measures, blue represents entropy measures, and purple represents graph-theory measures.

Author, year	Significant features resulted in each model	Population	Clinical State	Aetiology	Outcome
Wu et al., 2011	LZC (Pain affected) ApEn (Pain affected) Cross-ApEn (Pain affected) LZC (Pain unaffected) ApEn (Pain unaffected) Cross-ApEn (Pain unaffected) Cross-ApEn (Auditory music)	37	MCS UWS	Traumatic Vascular	Recovered versus non-Recovered (defined with GOS scale)
Arnaldi et al., 2016	CRS+ baseline Age Index of sleep structure SWS Index of sleep structure CRS+ baseline Age SWS	27	E-MCS MCS UWS	Traumatic	Recovery of consciousness (defined with CRS +)
Bagnato et al., 2016	None of the parameters showed significant effect on prognostic prediction.	112	MCS UWS	Traumatic Vascular Anoxic Other aetiology	UWS versus MCS (defined with CRS-R)
Pascarella et al., 2016	None of the parameters showed significant effect on prognostic prediction.	130	MCS UWS	Traumatic Vascular Anoxic	Improvement versus non-improvement (defined with CRS-R)
Wang et al., 2017	The study only conducted a descriptive analysis.	11	MCS UWS	Traumatic Vascular	UWS vs MCS (defined with CRS-R)
Bareham et al., 2018	The study is a case report.	4	MCS UWS	Traumatic	Change of clinical state (defined with CRS_R)
Bai et al., 2019	QPSC Frontal Theta.	51	MCS UWS	Traumatic Vascular	CRS-R score increase or change of clinical state

Table 3 (*continued*)

Author, year	Significant features resulted in each model	Population	Clinical State	Aetiology	Outcome
				Anoxic	
Formisano et al., 2019a	N400	15	MCS UWS	Traumatic Vascular Anoxic	EMCS versus no recovery (defined with CRS-R)
Scarpino et al., 2019	Background frequency Variability Sleep transient	102	MCS UWS	Traumatic Vascular Anoxic	Change of clinical state or towards EMCS (defined with CRS-R)
	Background frequency Reactivity Variability Sleep transient	61	UWS	Traumatic Vascular Anoxic	Change of clinical state or towards EMCS (defined with CRS-R)
Straudi et al., 2019	ΔPower for upper α in parietal site (between T1 and baseline, where T1 is at 1 week from baseline)	10	MCS	Traumatic	ΔCRS-R score between one week after baseline and baseline
Estraneo et al., 2020	Reactivity Age Time from onset CRS-R at baseline (These features resulted significant in four different models)	147	MCS UWS	Traumatic Vascular Anoxic	Improvement in patients' clinical diagnosis (defined with CRS-R)
Martens et al., 2020	LZW in theta band	29	E-MCS MCS	Traumatic Vascular Anoxic Other	ΔCRS-R score between baseline and end of treatment
Pan et al., 2020	Total BCI accuracy index BCI accuracy index (obtained from P300 and SSVEP during photograph paradigm)	33	MCS	Anoxic	Change of clinical state from MCS (defined with CRS-R)
	Total BCI accuracy index BCI accuracy index (obtained from P300 during audio-visual paradigm) BCI accuracy index (obtained from P300 and SSVEP during photograph paradigm)	45	UWS	Anoxic	Change of clinical state from UWS (defined with CRS-R)
Scarpino et al., 2020	CRS at baseline Bagnato's score Estraneo's score EEG score based on ACNS terminology Background Frequency Reactivity Variability AP gradient Sporadic epileptic activity	260	MCS UWS	Traumatic Vascular Anoxic	Change of clinical state (defined with CRS-R)

(*continued on next page*)

Table 3 (*continued*)

Author, year	Significant features resulted in each model	Population	Clinical State	Aetiology	Outcome
Bareham et al., 2020	Assessment number HdEEG (δ,θ,α) Mean/ Std power Median/Std dwPLI Mean/Std clustering coefficient Path length Global efficiency Modularity Mean/Std centrality Modular span Mean/Std participation coefficient (Features significant in two models) CRS-R score HdEEG (δ,θ,α) Mean/Std power Median/Std dwPLI Mean/Std clustering coefficient Path length Global efficiency Modularity Mean/Std centrality Modular span Mean/Std participation coefficient ΔHdEEG (δ,θ,α) Mean/Std power Median/Std dwPLI Mean/Std clustering coefficient Path length Global efficiency Modularity Mean/Std centrality Modular span Mean/Std participation coefficient (Features significant in three models)	39	MCS UWS	Traumatic Vascular Anoxic Other	Normalized ΔCRS-R score between 9 and 12 months from baseline

Abbreviations: ApEn = Approximate Entropy; BCI = Brain Computer Interface; Cross-ApEn = Cross-Approximate Entropy; CRS-R = Coma Recovery Scale – Revised; dwPLI = debiased weighted Phase Lag Index; E-MCS = Emergence from Minimally Conscious State; LZC = Lempel-Ziv Complexity; LZW = Lempel-Ziv Welch Complexity; MCS = Minimally Conscious State; NMI = Normalised Mutual Information; QPSC = Quadratic Phase Self-Coupling; SSVEP = Steady-State Visual-Evoked Potential; SWS = Slow Wave Sleep; UWS = Unresponsive Wakefulness Syndrome.

states since the nervous system loses the ability to promptly respond to changes (Gosseries et al., 2011). Two studies analysed entropy measures (Martens et al., 2020; Wu et al., 2011).

- *Connectivity measures:* These measures were obtained to investigate brain connectivity and the organisation of cerebral patterns. Functional connectivity is fundamental for understanding the mutual connection of EEG patterns recorded in different brain regions (Chennu et al., 2014; Vecchio et al., 2021). Two studies reported connectivity measures (Bareham et al., 2020, 2018), but that of Bareham *et al.* (Bareham et al., 2018) was only a case report; thus, this feature was analysed only on a descriptive basis. The remaining study aimed to assess information on cluster dimensions and the strength of the network division in communication and functional modules.

Furthermore, one study compared models with *qualitative* and *quantitative* aspects as well as both together (Arnaldi et al., 2016), while five studies implemented models based on different *quantitative* feature classes (Arnaldi et al., 2016; Bareham et al., 2020, 2018; Martens et al., 2020; Wu et al., 2011). Only Bareham *et al.* (Bareham et al., 2020) included connectivity and spectral features within the same multivariate model; the remaining papers focused on a single type of measure, excluding the comparison between features belonging to different categories.

3.4.4. Data analysis

Various approaches were used to understand the predictive power of the features extracted from EEG signals on the recovery of consciousness. The algorithms were selected according to the type of variable considered for the outcome and treated either as categorical (e.g., recovered/non-recovered) or numerical variables (e.g., the CRS-R score at discharge). Among the studies that implemented group comparisons, the chi-square test was used four times (Formisano et al., 2019b; Pan et al., 2020; Pascarella et al., 2016; Wu et al., 2011), and the *t*-test was used two times (Pascarella et al., 2016; Wu et al., 2011), while the Mann–Whitney test (Bai et al., 2019) and analysis of variance (Bagnato et al., 2016) were each used one time. Regarding tests targeting the association between variables, three studies (Arnaldi et al., 2016; Bareham et al., 2020; Scarpino et al., 2019) adopted multivariate linear regressions, three studies (Estraneo et al., 2020; Scarpino et al., 2020a, 2019) adopted multivariate logistic regression, and two studies (Martens et al., 2020; Straudi et al., 2019) adopted univariate correlation (Fig. 3c). Two studies did not conduct any *quantitative* analysis because one was a case study while the other conducted a descriptive interpretation of the results (Bareham et al., 2018; Wang et al., 2017).

Moreover, 10 studies implemented predictive models only with EEG features, while the remaining five also considered other clinical variables, including age, gender, aetiology, CRS-R score, diagnosis at admission, time since brain injury, and lesion site. Martens *et al.* (Martens et al., 2020) and Bareham *et al.* (Bareham et al., 2020) compared the performances of models including EEG-based features with those including only clinical variables; however, given our focus on EEG-derived features, we did not report the models that considered clinical variables exclusively.

3.5. Outcome measures

The selected outcome for this study was the recovery of consciousness. All of the included papers used the CRS-R as the preferred measure for the definition of the outcome, except for that of Wu *et al.* (Wu et al., 2011), who used the Glasgow Outcome Scale (GOS). Even though the measure used was similar, different modalities were used for the definition of the specific outcome metric. Specifically, four studies considered a continuous score (Arnaldi et al., 2016; Bareham et al., 2020; Martens et al., 2020; Straudi et al., 2019), two studies considered both a dichotomised and a continuous metric (Estraneo et al., 2020; Pascarella et al., 2016), and the remaining nine studies considered a categorical metric. Among the studies that selected a continuous outcome, three calculated a delta version of the CRS-R score (Bareham et al., 2020; Martens et al., 2020; Straudi et al., 2019), one used the CRS-R total score weighted on the clinical state of the patients (the so-called CRS +) (Arnaldi et al., 2016), and two used the total CRS-R score (Estraneo et al., 2020; Pascarella et al., 2016). Regarding categorical metrics, the majority of the studies determined a dichotomised version of recovery of consciousness. The modalities used for these dichotomous metric calculations were based on the following:

- Emergence from the MCS (Formisano et al., 2019b);
- A change in clinical state (Bareham et al., 2018; Pan et al., 2020; Pascarella et al., 2016; Scarpino et al., 2020a; Wu et al., 2011);
- A combination of emergence from the MCS and a change in clinical state (Estraneo et al., 2020; Scarpino et al., 2019);
- The comparison of two consciousness-state groups (Bagnato et al., 2016; Wang et al., 2017);
- A combination of a change in clinical state and a minimum increase in the CRS-R total score (Bai et al., 2019).

Regarding the outcome timing, three studies (Martens et al., 2020; Scarpino et al., 2020a, 2019) selected an outcome at discharge from hospitalisation or end of treatment, three studies at the 3-month follow-up (Bagnato et al., 2016; Bai et al., 2019; Pan et al., 2020), and nine studies at a follow-up longer than 6 months after the event or admission to hospital, reaching up to 30 months (Pascarella et al., 2016). Additionally, two studies selected the outcome through multiple intra-treatment or hospitalisation assessments (Bareham et al., 2018; Straudi et al., 2019).

4. Discussion

This systematic review aimed to investigate which EEG features have been found to be predictors of consciousness recovery in patients with DoC after rehabilitation as well as which are the preferred technical pipelines for extracting these features from EEG signals.

Given the systematic reviews that already exist on this topic in the literature, we did not want to strictly focus our study on the extracted features, but rather to extend the analysis to the processes and computational methods used. The objective of this analysis was to provide a useful tool that is able to summarise the methods and information extracted for consciousness recovery prognosis. Thus, the analysis and data extraction of this study chronologically followed the analysis pipeline for feature extraction, starting from the definition of the experimental setting up to the prognostic analyses. Moreover, given our rehabilitation context, we focused on the prognostic application only. The aim was to offer useful insights for the future development of automated tools that can support clinical decisions and rehabilitation optimisation through the inclusion of instrumental assessments based on EEG.

As previously mentioned, the aspect that we studied first was the experimental setting, for which the selected number of electrodes and sampling frequency seemed to lack consensus (Table 2). Regarding the configuration of channels, the included studies mostly used a limited number, suggesting that some predictive EEG features could even be extracted from low-density EEG. However, also critical to mention is that lower-density EEGs are typically found in clinical practice; thus, this number could partially have resulted from the availability and routine preference for using lower-density EEGs in hospitals over higher-density ones. For this reason, higher-density EEG should be further investigated given the results obtained in the literature. As an example, Chennu *et al.* (Chennu et al., 2017) demonstrated that the use of 256 channels could reach high performances and correlate with other functional neuroimaging methods.

Similarly, we did not find a clear consensus on the sampling frequency, which varied over a wide range (128–2500 Hz). Considering the great advantage of having a high temporal resolution in EEG, the choice of a sampling rate that is too low could lead to a loss of information. Thus, as proposed by five of the included studies, a possible trade-off between the computational cost for parameter calculation and the temporal resolution of signals for *qualitative* analysis exists in the acquisition of recordings at high frequencies followed by down-sampling.

Regarding the extraction pipeline, the very first preprocessing steps were shared across solutions, namely the use of band-pass filtering, use of a notch filter, and selection of common frequency bands (Fig. 3). Nevertheless, the following preprocessing steps did not reach an agreement across the included studies (Fig. 3). Although the majority of *quantitative* studies segmented the signals, there was no consensus on the epoch parameters. Similarly, even though all included works applied methods for noise removal, different approaches were proposed, leading to extremely distinct effects on artefacts. It is also crucial to view these results in light of the type of stimuli applied when present. However, even if the operations applied are strictly related to the features to be extracted, the definition of general guidelines in preprocessing steps could ensure more robust and reliable analyses. Indeed, in the definition of protocols for data acquisition, the wrong preprocessing steps could affect the results (Khosla et al., 2020). For example, Robbins *et al.* (Robbins et al., 2020) found significant discrepancies in signals analysed with different processing pipelines, although the results exhibited common characteristics. These aspects are critical in patients with DoC since their complex conditions are combined with the absence of collaboration, resulting in the presence of several artefacts in signals, which are added to the common disturbances typically present (e.g., those related to muscle, ocular, and cardiac activity). For these reasons, a structured procedure for artefact detection is crucial in this population. Among the studies included, five (three of which applied independent component analysis) used automated or quasi-automated procedures based on a voltage threshold, above which all epochs/channels were completely removed. Regardless of the reliability of visual inspection for artefact detection, the use of automated algorithms based on different features could reduce the computational time as well as support clinicians. The automation process can be based on different features and parameters, allowing one to choose the final data quality. However, independent of the specific artefact-rejection technique, only a few epochs of the entire EEG recording are often retained for further analyses in patients with DoC. This is a consequence of frequent involuntary movement, hyperhidrosis, and difficulty in performing closed-eye recordings in such a case mix. In our analysis, among the included studies, only three of them explicitly reported details about the number of epochs processed (Bareham et al., 2020, 2018; Wu et al., 2011).

Thus, as previously mentioned, the formulation of shared and standardised guidelines, including automatic methods for artefact rejection, is crucial. They could promote the generation of standards according to the preprocessing steps to apply for feature extraction given the specific characteristics of the sample.

Moreover, uniformity in the characteristics of the experimental design and preprocessing methods could favour the analyses based on patient conditions, providing more insights regarding which EEG-derived biomarkers are effective predictors given the different characteristics of baseline patients. Among the included studies, three (Martens et al., 2020; Pan et al., 2020; Scarpino et al., 2019) have already attempted to differentiate the features associated with consciousness recovery in different DoC clinical statuses, obtaining both common and different significant features for each group. Similarly, as demonstrated by Estraneo *et al.* (Estraneo et al., 2020), the clinical complexity varies based on the various aetiologies.

Finally, a standardised set of guidelines as well as deeper research into characteristic-specific EEG biomarkers could also pave the way for more advanced prognostic analyses, for which the present study highlighted high heterogeneity. Indeed, this study highlighted how the prognostic analyses applied to consciousness recovery are all characterised by the absence of validation approaches, with many of the included studies not even addressing multivariable analyses. This panorama is very different from that in other pathologies, such as epilepsy (Ayodele et al., 2020; Rasheed et al., 2020), depression (Li et al., 2020), schizophrenia (Aslan and Akin, 2020) or stroke (Hosseini et al., 2020). In fact, while probably in the latter contexts the most influential prognostic factors are known and more attention is paid to model complexity or result validation, these aspects have not yet been addressed in consciousness recovery. Statistical analyses allow for the detection of correlations and associations/differences among groups (Fig. 3c); instead, more complex methods (e.g., ML algorithms) can find patterns within data and have the capability to generalise prediction results. Given these characteristics, statistical methods are typically easier in terms of interpretation and computational complexity, whereas ML requires a larger amount of data to guarantee the accuracy and reliability of findings. Reasonably, the delay in the use of more complex models could be due to the identification of EEG-based predictive features associated with consciousness recovery still being an open issue for patients with DoC, preventing a straightforward validation of the methods that start from such measures. This is also reasonable considering that the possibility of a robust clinical stratification of patients from both diagnostic and prognostic points of view is relatively recent due to the introduction of new capable and efficient clinical scales, such as the CRS-R (Seel et al., 2010).

Another aspect characterised by heterogeneity was the type of features extracted from EEG data. To enhance the interpretability of the results, we considered the typical categorisation in *qualitative* and *quantitative* measures due to the different approaches used to extract information from an EEG track. Then, we subdivided each of these categories into groups depending on the nature of the features extracted and the methods used. No specific trend was noted among the feature classes selected by the studies and the baseline characteristics of participants in terms of aetiology and clinical status (Table 3).

Moreover, the analysis revealed that *qualitative* studies are equally as common as *quantitative* ones. The ability of skilled clinicians to visually analyse recordings and easily extract a large amount of information explains this tendency. Moreover, medical personnel's expertise may help in the detection of particular neurophysiological patterns, leading to single-subject/precision medicine. On the other hand, the objectivity of *quantitative* features can help to identify small but significant variations in signals and hidden processes that would be more complex to detect without automatic algorithms, such as the identification of particular cerebral patterns or the reconstruction of brain maps (Fellinger et al., 2011; Rizkallah et al., 2019). For instance, the identification of predominant background EEG frequency, relevant for assessing the level of consciousness of patients with DoC, is qualitatively identified by counting the number of cycles per second; this method, especially in a long EEG track, is time-expensive and subject to inaccuracy. *Quantitative* EEG analysis can overcome these problems by introducing automatic methods (e.g., different types of transforms) for calculating the contribution of a given frequency band. Indeed, although the introduction of bias within analyses is sometimes unavoidable, automatic approaches could prevent the influence of possible subjective factors present in visual inspections (e.g., experience, fatigue, distractions, and misinterpretation).

In our analysis, most studies that performed a *qualitative* inspection of signals (four out of nine) included the features in predictive models with other clinical variables (e.g., age, gender, aetiology, CRS-R at admission, time since brain injury, and activating drugs). Among the clinical variables considered, age and CRS-R assessment at admission resulted to be predictors of consciousness recovery in various studies, including those of Arnaldi *et al.* (Arnaldi et al., 2016), Estraneo *et al.* (Estraneo et al., 2020), and Scarpino *et al.* (Scarpino et al., 2020a, 2019), in accordance with the literature. Among the *qualitative* features, background reactivity was found to be one of the features most significantly associated with the recovery of consciousness. This was also confirmed and investigated in another systematic review on this topic (Azabou et al., 2018). By contrast, features related to the presence of epileptiform activity did not result in high predictive power for consciousness recovery, since significant results were achieved in only one study (Scarpino et al., 2020a) out of the four that investigated them.

Among the subgroups of *qualitative measures*, EPs/ERPs were recorded with different types of stimulation. Responses elicited by auditory stimuli were the most studied, as in five of the included studies (Estraneo et al., 2020; Formisano et al., 2019b; Pan et al., 2020; Scarpino et al., 2019; Wang et al., 2017; Wu et al., 2011). These included the N400 component, mismatch negativity (MMN), and brain auditory EP (BAEP). Among these potentials, the presence or absence of N400 in the centroparietal area was found to be significantly associated with consciousness recovery (Formisano et al., 2019b). This is in agreement with and well demonstrated in other studies in the literature (Balconi, 2011; Balconi et al., 2013; Steppacher et al., 2013). Conversely, BAEP was not found to be a predictor of improvement, nor were Somatosensory-Evoked Potentials (SSEPs) elicited by somatosensory stimulation (Wu et al., 2011). Regarding the MMN component, only a descriptive analysis of how it could be related to the recovery of consciousness was conducted. The same analysis was performed on the P300 component, which obtained similar results; sudden changes in the amplitude and latency of these components may be helpful for predicting changes in consciousness (Wang et al., 2017). In Wang *et al.* (Wang et al., 2017), the two evoked responses were found to be located in the temporal area, specifically in the superior and middle areas for MCS and the inferior and middle areas for UWS. Regarding P300, other studies in the literature have confirmed its ability to predict recovery (Cavinato et al., 2009).

Noteworthily, EPs/ERPs were addressed using both *qualitative* and *quantitative* methods. Relative to the latter, no study computationally extracted event-related responses, except for that of Pan *et al.* (Pan et al., 2020), who used P300 and the steady-state visual-evoked potential (SSVEP) to define a real-time index (i.e., the BCI accuracy index) during BCI experiments. This index was employed to divide the population into CMD and non-CMD patients. The BCI index-based classification was found to be significantly associated with the outcome of patients, depending on the type of stimulation that elicited the potentials (Pan et al., 2020).

Another feature significantly associated with a positive outcome in patients with DoC was the presence of alpha frequency, for which there was again a tendency to analyse both *qualitative* and *quantitative* points of view. In particular, in terms of *qualitative* analyses, the overall background frequency was considered and found to be significantly associated with consciousness recovery in two studies (Scarpino et al., 2020a, 2019). In terms of *quantitative* analyses, spectral analysis in the alpha band was found to be a predictor of consciousness recovery Bai *et al.* (Bai et al., 2019), and Straudi *et al*. (Straudi et al., 2019). Moreover, these two studies investigated different cerebral areas, namely the frontal, and parietal areas, respectively. Considering both *qualitative* and *quantitative* analyses, an agreement seemed to exist that alpha power is a promising result. Still, no study included the shape of the spectral density function among the independent variables, instead evaluating only the spectral power through numerical integration. This information may play a crucial role for patients with DoC since it is characterised by a higher power in lower frequency bands. Hence, the evaluation of the frequency content is performed through a cumulative measure inherently lacking in case of shifts in the frequency axes of functional EEG peaks (Chandrasekaran et al., 2019; Weber et al., 2020). Features of sleep transients and sleep structure were transversally indicated by Arnaldi *et al.* (Arnaldi et al., 2016) as well as Scarpino *et al.* (Scarpino et al., 2020a, 2019) as candidate predictors of consciousness recovery.

In terms of *quantitative* analysis of the frequency domain, the most explored bands were delta, theta, and alpha, which was expected since they are typical in DoC (Rivera-Lillo et al., 2021). Various studies have demonstrated the presence of an association between the power modulation of these three frequency bands and the CRS-R score. In particular, Bareham *et al.* (Bareham et al., 2018) reported that a decrease in delta power was significantly correlated with an increase in CRS-R score. Regarding the theta band, Bai *et al.* (Bai et al., 2019) reported that the quadratic phase self-coupling in this band and frontal side is significantly associated with consciousness recovery.

Furthermore, higher frequencies (e.g., beta and gamma rhythms), typically related to sensorimotor information processing, were not generally investigated in patients with DoC due to lower spectral power (Naro et al., 2016a). These bands acquire interest when external stimulation is applied, such as tACS (Naro et al., 2016b) or tDCS (Naro et al., 2016c). This is due to the capability of the stimulation to arouse silent neurophysiological patterns, causing a possible increase in activity in the superior frequency ranges. This tendency was in agreement with various studies included in our analysis. In particular, the beta band was considered in both of the studies that used tDCS, even though Martens *et al.* (Martens et al., 2020) did not include it in their analysis that focused on the lower frequency bands, while Straudi *et al.* (Straudi et al., 2019) did not find the relative power in this frequency range to be significant. Similarly, Wu *et al.* (Wu et al., 2011) included the contribution of the beta band in the *qualitative* analysis of signals, which was not found to be significant in their analysis. Finally, Arnaldi *et al.* (Arnaldi et al., 2016) used the relative power in different frequency bands, including beta, to calculate an index of slow-wave sleep (SWS), which resulted in significance. In particular, their comparison between the relative power in SWS (delta oscillations) and fast activities (alpha and beta oscillations) allowed them to assign a score for each time interval. The index was obtained by averaging these interval scores and weighing their total duration.

Among *quantitative* methods, more elaboration is required for the extraction of features related to entropy and graph theory due to their ability to describe and represent more complex cerebral processes. Regarding *entropy*, Lempel–Ziv complexity (LZC), a useful complexity measure that describes the development of spatiotemporal patterns (Kaspar and Schuster, 1987), was the most analysed feature in two studies (Martens et al., 2020; Wu et al., 2011). Among them, one of the studies found LZC to be more predictive in the delta band. In addition, approximate entropy (ApEn) and cross-ApEn, the other two common measures for explaining the randomness of EEG signals, were investigated. Although Wu *et al.* (Wu et al., 2011) studied all three of these nonlinear indexes in the bilateral frontal area and found all to be significantly associated with prognosis, a higher predictive value was associated with ApEn and cross-ApEn. Furthermore, a comparison between DoC and controls revealed that these features were significantly lower in pathological groups than in healthy subjects. These findings are in line with the idea that lower levels of complexity are associated with DoC pathological conditions due to the reduced and slower response of the nervous system to changes (Thul et al., 2016). Moreover, Martens *et al.* (Martens et al., 2020) and Wu *et al.* (Wu et al., 2011) demonstrated that the prognostic value of these measures depended on the stimulation with which it was presented.

Different from entropy, a wide heterogeneity was found across *graph-theory measures*, although each of them explained a different aspect of cerebral connectivity. These features, such as the clustering coefficient, participation coefficient, path length, modularity, and network centrality, allowed researchers to increase the knowledge related to the transfer of cerebral dynamics information to improve the prognosis in DoC. To compensate for this variety, Bareham *et al.* (Bareham et al., 2020) merged various clinical, spectral, and graph-theory measures for each frequency band (delta, theta, and alpha) into one variable, which they subsequently used in their model. Clinical and electrophysiological variables were related to each other using canonical correlation analysis, and the combination was found to be a predictor of consciousness recovery (Bareham et al., 2020). In particular, a significantly predictive contribution was associated with high-density EEG (hd-EEG) in theta band power and alpha band connectivity. Moreover, the analysis confirmed the potential of hd-EEG-based features for improving prognosis prediction when combined with clinical measures. Despite the heterogeneity, a consensus was noted where the included studies mainly considered features calculated in the alpha band (Bareham et al., 2018).

In addition, the potential of merging *qualitative* and *quantitative* methods was not particularly deepened in the included studies. Arnaldi *et al.* (Arnaldi et al., 2016) were the only authors to test this approach, demonstrating that the joint use of the two techniques could improve the results and prognosis of consciousness recovery by compensating for their limitations. In particular, although the *qualitative* identification of specific sleep patterns significantly predicted the outcome, the addition of a *quantitative* sleep-related index further consolidated the prediction results. The *qualitative* and *quantitative* indexes were only partially correlated; thus, this implementation leads to an enrichment of the predictive model. Moreover, in this study, considering the often long duration of polysomnographic tracks, the *quantitative* analysis could help clinicians in the assessment of sleep scoring. By contrast, a *qualitative* inspection can rely on clinical experience, making the feature extraction process more straightforward in EEG clinical daily reporting and helping to detect particular patterns. This is particularly relevant in patients with DoC, who are not cooperative and might have uncontrolled spasms, resulting in EEG artefacts, frequent ocular movements or blinking, or sweating.

Regarding the outcomes, although any criteria were set on the outcome measures, the recovery of consciousness was assessed through different measures obtained from the CRS-R score in all cases except for in the study of Wu *et al.* (Wu et al., 2011), who calculated the recovery of consciousness using the GOS. This observation confirmed the preferred use, both for research and clinical purposes, of the CRS-R. Regarding the timing of outcome occurrence, five models developed by three authors considered long-term outcomes (≥12 months from onset). Among them, two identified candidate predictors of long-term recovery of consciousness (Arnaldi et al., 2016; Formisano et al., 2019b). Similarly, Bareham *et al.* (Bareham et al., 2020) performed multiple assessments up to 2 years from the onset and found models that identified significant prognostic value for predicting long-term behavioural outcomes in prolonged DoC. Among the remaining 11 studies that considered outcomes ≤ 12 months from the event, 20 out of the 55 models developed led to significant features. Given the complexity connected to the long-term hospitalisation of patients with DoC, it is reasonable that only a reduced number of the included studies considered a long-term outcome. However, given the increasing life expectancy of these patients, it could be worth deepening the research to include long-term outcomes or outcomes assessed at multiple time points.

5. Limitations

From a methodological point of view, we conducted a systematic search, but some limitations were still present. Regarding the search, some restrictions were related to the English language and the requirement for a baseline CRS-R evaluation of patients. Despite such restrictions, we considered this standardisation essential for a more robust stratification of participants, which allowed us to display and evaluate the results considering the heterogeneity of the populations.

Moreover, although other studies have successfully performed a meta-analysis (e.g., (Kotchoubey and Pavlov, 2018), we considered it unfeasible in our case. We recognise its utility for the identification of optimal methods for extracting EEG-based features and their effectiveness in terms of consciousness recovery prognosis; however, we believe that a meta-analysis would be more useful in studies that have already performed validation of prognostic models to determine the degree of evidence of the obtained results. In our case, the methods employed were highly heterogeneous and difficult to compare. For all of these reasons, we believe that more evidence should be available before considering a meta-analysis.

6. Conclusions

This systematic review investigated the combinations of preprocessing techniques, feature extraction methods, and predictive models for assessing prognostic factors in patients with DoC using EEG. The results revealed high heterogeneity among EEG-based predictors of consciousness recovery. This is mainly due to the complexity of patients with DoC, who have different clinical behaviours and aetiologies. Regardless, beyond the aforementioned limitations, the first attempts to combine clinical and instrumental data to obtain a prognosis were encountered. *Quantitative* EEG enables access to additional information, unavailable at the *qualitative* level, at the expense of more complex and difficult-to-interpret analyses. However, whether this additional level of information improves the prediction of DoC prognosis still requires further research.

We believe that to provide a large consensus on procedures and methods for extracting prognostic models from EEG in patients with DoC, more evidence is required. Future studies will need to involve even larger pools of patients, thereby enabling the implementation of models that are complex enough to cope with the heterogeneity of such a pathological condition.

Funding

This study was supported in part by the Tuscany Region through the Tuscany Network for BioElectronic Approaches in Medicine: AI-based predictive algorithms for fine-tuning of electroceutical treatments in neurological, cardiovascular and endocrinological diseases (TUNE-BEAM, n. H14I20000300002) and by the Department of Excellence in Robotics & AI, Scuola Superiore Sant'Anna, Italy. The study was also supported by the Italian neuroscience and neurorehabilitation research hospitals network (‘‘Rete IRCCS delle Neuroscienze e della Neuroriabilitazione"), the ‘‘Ricerca Corrente RC2020-2022 program", and the 5x1000 funds AF2018: ‘‘Data Science in Rehabilitation Medicine" AF2019: ‘‘Study and development of biomedical data science and machine learning methods to support the appropriateness and the decision-making process in rehabilitation medicine" by the Italian Ministry of Health.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2022.09.017.

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