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SYSTEMATIC REVIEW

The efficacy of hybrid neuroprostheses in the rehabilitation of upper limb impairment after stroke, a narrative and systematic review with a meta-analysis

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Abstract

Background: Paresis of the upper limb (UL) is the most frequent impairment after a stroke. Hybrid neuroprostheses, i.e., the combination of robots and electrical stimulation, have emerged as an option to treat these impairments.

Methods: To give an overview of existing devices, their features, and how they are linked to clinical metrics, four different databases were systematically searched for studies on hybrid neuroprostheses for UL rehabilitation after stroke. The evidence on the efficacy of hybrid therapies was synthesized.

Results: Seventy-three studies were identified, introducing 32 hybrid systems. Among the most recent devices ($n = 20$), most actively reinforce movement (3 passively) and are typical exoskeletons (3 end-effectors). If classified according to the International Classification of Functioning, Disability and Health, systems for proximal support are expected to affect body structures and functions, while the activity and participation level are targeted when applying Functional Electrical Stimulation distally plus the robotic component proximally. The meta-analysis reveals a significant positive effect on UL functions ($p < 0.001$), evident in a 7.8-point M_{diff} between groups in the Fugl–Meyer assessment. This positive effect remains at the 3-month follow-up ($M_{diff} = 8.4$, $p < 0.001$).

Conclusions: Hybrid neuroprostheses have a positive effect on UL recovery after stroke, with effects persisting at least three months after the intervention. Non-significant studies were those with the shortest intervention periods and the oldest patients. Improvements in UL functions are not only present in the subacute phase after stroke but also in long-term chronic stages. In addition to further technical development, more RCTs are needed to make assumptions about the determinants of successful therapy.

KEYWORDS

electrical stimulation, exoskeleton, hybrid neuroprosthesis, rehabilitation, review, robotics, stroke, treatment efficacy, upper limb

1 | BACKGROUND

Paresis of the upper limb (UL) is the most frequent impairment after stroke, with a prevalence of 80%.[1,2] In the more severe cases, the UL cannot be used in a functional way, and the level of independence is reduced, resulting in a need for support during Activities of Daily Living (ADL). This acquired disability is persistent in 50% of cases for >1.5 years.[3]

Neurorehabilitative protocols for the UL often include robotic therapy as well as Functional Electrical Stimulation (FES).[4] Over the last few years, the combination of both approaches (for the same joint or for different joints of the same limb) has been used increasingly in neurorehabilitation, implemented as so-called hybrid neuroprostheses or hybrid exoskeletons.[5] There are different application scenarios for these systems: therapeutic (with the objective to restore UL function) and assistive (with the objective of permanently substitute UL functions, serving as an orthosis). The robotic component of a hybrid neuroprosthesis is actuated in two ways: (1) motorized robots support the movement *actively*, with no residual function of the patient required; and (2) robots support the movement *passively* (i.e., without motorized actuators), whereby some motor control by the patient is required but reinforced by the robotic device, e.g., via spring-loaded mechanisms. Hybrid neuroprostheses typically feature different sensors (e.g., torque/position sensors, electromyography [EMG], and electroencephalography [EEG] sensors). These sensors provide either feedback on the performance of the patient or collect information for the real-time control algorithm in order to adapt the support of the device *as needed* depending on the patient's performance. Thus, hybrid devices incorporate different aspects to potentially facilitate motor learning, such as (real-time) feedback and individualized, constantly challenging therapy[6] according to the assist-as-needed concept. Systems that feature an assist-as-needed algorithm adapt the level of assistance depending on the patient's capabilities. Ideally, the patient's effort is thus neither too high nor too low.

Both scenarios of applying hybrid neuroprostheses (therapeutically and assistively) present arguments for being superior to the use of one of its components (FES or robotic) alone. The uncombined use of robotic or FES for UL recovery contributes to an asynchronous recovery of UL function (e.g., robotic-induced proximal and FES-induced distal improvements[7]). This might lead to an improvement in motor functions but not to a restoration of functional abilities (e.g., grasping and transferring an object).[8,9] The therapy with a hybrid device combining both approaches aims to overcome this limitation by improving distal and proximal functions simultaneously. Besides the therapeutic application of hybrid devices, the fact that many patients have to deal with long-term disabilities even after therapy highlights the need for assistive devices. However, the isolated use of robotic- or FES-based therapies is limited in assisting patients during daily life, since the heavy weight of some robots (especially those supporting proximal joints) restricts the use of the system during ambulation,[10] and the potentially FES-induced muscle fatigue (due to 1) nonphysiological recruitment of muscle fibers,[11] (2) synchronous recruitment of motor units,[11] and (3) a declined amplitude of the muscle action potential[12] reduces the length of use in daily life. Greater portability could be achieved by reducing the device's weight through simultaneous electrical stimulation with the potential to lower the force that must be delivered by the robot and, thus, allows for smaller and less heavy engines. In addition, combining FES with external force generation in a hybrid system could reduce muscle fatigue compared with isolated stimulation[13] by reducing FES intensity and frequency or by reducing the time of stimulation.

1.1 | Rationale

A hybrid neuroprosthesis is likely to overcome the drawbacks of each individual technology. The simultaneous use of robotic therapy and FES on the same limb is a new approach to treating UL impairments. Current guidelines for UL rehabilitation after stroke suggest that such a combination would be useful, but emphasize that there is yet not enough evidence.[4]

1.2 | Objectives

This systematic review aims to provide up-to-date evidence by investigating the efficacy of hybrid interventions for UL neurorehabilitation, also considering determinants of successful hybrid therapy. The objective is further to provide an overview of existing devices and their features, together with indications of use for individual patient impairments. The structure of this article, therefore, is twofold. The first part includes a general overview of existing hybrid neuroprostheses. In the years 2016–2017, two published reviews[14,15] described hybrid devices from a rather technical point of view, focusing on their usability. Since none of these existing reviews is devoted to the clinical efficacy of hybrid neuroprostheses, the second part of this article addresses the potential benefit of hybrid therapy for motor and functional improvements of the UL in patients after stroke.

2 | METHODS

2.1 | Eligibility criteria

This review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and follows the criteria of the Cochrane Handbook for Systematic Reviews of Interventions (version 6.2). To systematically search for literature on the implementation of hybrid neuroprostheses in stroke rehabilitation, the following inclusion criteria were defined according to PICO(S): *P*opulation: patients after stroke; *I*ntervention: simultaneous use of robot plus FES at the UL; *C*ontrol: no simultaneous use of robot plus FES, *O*utcome: UL function. For the meta-analysis, the *S*tudy design was defined to be a randomized controlled trial (RCT). With the aim to keep the search as broad as possible to find any relevant research items, no additional filters were pre-set.

2.2 | Information sources and search strategy

Literature was searched in four different databases from clinical and engineering disciplines, namely PubMed, Cochrane Library, WebofScience, and IEEExplore, with a search string that combines all aspects of the PICO criteria using the following keywords: robot OR end-effector OR exoskeleton AND electrical stimulation AND UL AND stroke. The full search string is provided in the supplementary material.

In addition, relevant studies were identified by a manual search of the reference lists of identified items. The last search was conducted on January 3, 2023. If the full text was not accessible, authors were contacted directly.

2.3 | Selection process

All the identified items were imported into the software Covidence (Melbourne, Australia). After duplicates were removed, two reviewers (CH, CK) independently screened the titles and abstracts as well as the full texts according to pre-defined inclusion and exclusion criteria. Among the eligible studies, RCTs were tagged to be included in the meta-analysis. The reviewers discussed any discrepancies that occurred during the screening phases and came to a consensus regarding whether the study was eligible for inclusion. For technical descriptions of devices, included studies on the same device were merged, as well as those references belonging to the same study.

2.4 | Data collection process

Following the screening, data extraction of each included research item was done by two independent reviewers using a previously designed data extraction template. CH acted as the first reviewer; ET, DA, and CK shared the role of the second reviewer. As technical experts, ET and DA extracted information related to the device, while CK, as a clinical expert, extracted general study data and patient-related data. Again, potential discrepancies between the first and second reviewers were resolved before exporting the data.

2.5 | Data items

The main outcome of the review's first objective (i.e., an overview of implemented hybrid neuroprostheses) was the description of the devices' characteristics. All used devices were categorized according to the robotic architecture (exoskeleton or end-effector robot), type of support (active or passive), and the supported joints (1) same joint distally (≙ wrist or fingers), (2) same joint proximally (≙ shoulder or elbow), (3) different joints. Furthermore, the implemented sensors and the kind of sensor feedback were extracted.

For the second objective of calculating the pooled effect of hybrid therapy on UL functions, the main outcomes were the patients' baseline characteristics (e.g., age, side of paresis, time since the event) and the change in clinical scores (e.g., upper extremity the Fugl–Meyer [FM] assessment) after the intervention and at potential follow-up measurements. In the case of several baseline measurements of the same measure of functional status, these scores were averaged. Whenever given, clinical scores were extracted as mean (*M*) and standard deviation (*SD*). Otherwise, the reviewer either contacted the authors to provide the raw data for self-calculation of *M* and *SD*, or the reported data was transformed accordingly, following the instructions of the Cochrane Handbook for Systematic Reviews (version 6.2[16]).

2.6 | Study risk of bias assessment

The quality of studies which are included in the second part of the paper (i.e., the synthesis of results in the meta-analysis) was assessed by two reviewers (CH and CK) using the Cochrane Risk of Bias Tool for randomized trials (RoB2[17]). Studies were categorized as high, unclear, or low risk of bias, based on five different aspects: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the

outcome, and (5) selection of reported results. Potential discrepancies in the rating were resolved by consensus between two reviewers.

2.7 | Data synthesis

In the second part of the article, a random-effect model was applied to calculate the pooled effect of hybrid interventions using the Review Manager software (version RevMan 5.4). Authors were contacted for additional data information to calculate pre-post changes for each study; however, complete data was received for only three out of six studies. To not further reduce the number of studies that are included in the meta-analyses, post, and follow-up comparisons of the mean difference between the intervention and control groups were pooled. The effect of hybrid therapy on UL functions was also calculated in the subgroups of moderately and severely impaired patients. To further answer the second objective of the article, the characteristics of the intervention, including its application intensity and the performed movements, were extracted and compared with the significance of individual studies.

3 | RESULTS

3.1 | Study selection

Following the literature search, $n=538$ studies were identified (Figure 1). Four additional studies were added after manually searching the citations. After duplicates were removed ($n=133$), 297 studies were excluded during abstract and title screening. Further, 112 full texts were sought for retrieval, of which five were not retrieved because they were only abstract publications ($n=3$), the study was retracted ($n=1$), or withdrawn ($n=1$). Of the resulting 107 full texts, 34 did not meet the inclusion criteria (i.e., no hybrid intervention [$n=26$] or no original article [$n=8$]). More specifically, in those studies which are labeled as no hybrid intervention, (1) the FES and the robotic component were either applied at different times or not at the same limb ($n=12$); (2) the robotic component was used for static weight-support or with a lockable mechanism only and thus does not provide movement assistance ($n=10$); (3) the intervention consisted of FES only ($n=3$); or (4) robot only ($n=1$). Finally, 73 studies were included in the review, 42 of which were merged due to identical hybrid systems. The resulting 32 different hybrid systems are included in the narrative review. Seven of these studies are RCTs and conclusively included in the systematic review, where their results are pooled in the meta-analysis.

3.2 | Part 1—Narrative description of the hybrid neuroprostheses

Within the 73 identified studies for the narrative review, 32 hybrid systems are published (Table 1; we refer to the primary reference, which was used for data extraction; further references are listed in the Table S1).

The first research involving hybrid neuroprostheses was published about a decade ago. Identified devices are at different levels of research, with only a description of five devices, while six devices are already validated in healthy subjects. The majority of devices ($n=21$) are already evaluated in patients after stroke, either concerning the feasibility of the system ($n=7$) or evaluating the effect on UL functions within the scope of controlled ($n=9$) and non-controlled ($n=5$) studies.

Table 1 summarizes the hybrid systems that are included in this work, with the individual items that were considered. Given recent technological advancements, a specific focus is dedicated to the description of the most recent devices published after 2014, which are not included in the previously mentioned works,[14,15] i.e., 20 out of the 32 listed in Table 1. Differentiating the devices in terms of robotic architecture (exoskeleton vs. end-effector robot) and type of actuation, three studies describe passively actuated devices, two end-effector systems, nine active exoskeletons with distal actuation, and six exoskeletons with proximal actuation.

The three *passively actuated devices* are all exoskeletons. Grimm et al. and Resquin et al. adopt a commercial spring-loaded exoskeleton, the Armeo Spring (Hocoma, Switzerland), the former exploiting the FES for distal actuation at the wrist,[27] and the latter stimulating proximal (triceps and anterior deltoid) muscles.[49] Both systems integrate a brain–machine interface (BMI) to trigger FES. While Grimm et al. combine both EEG and EMG to detect the user's intention,[27] stimulating up to two muscles with constant parameters, Resquin et al. use an EEG classifier to detect user intention, and a feedback loop based on the trajectory tracking error is combined with a neural network-based feedforward loop to adapt the FES stimuli.[49] Another passive exoskeleton prototype assisting shoulder and elbow joints is presented in Ambrosini et al., endowed with electromagnetic brakes to provide arm anti-gravity support, and a commercial FES system activated by volitionally induced EMG activity, for up to two arm muscle groups (including triceps, biceps, anterior, posterior, median deltoid), with constant stimulation parameters.[21]

Two *end-effectors* are identified. In Amano et al., a motorized cable-suspended robot attached to the user's forearm for anti-gravity support is adopted.[20] They explore a combination of shoulder FES and vibratory stimulation to provide stronger proprioceptive feedback. In Miyasaka

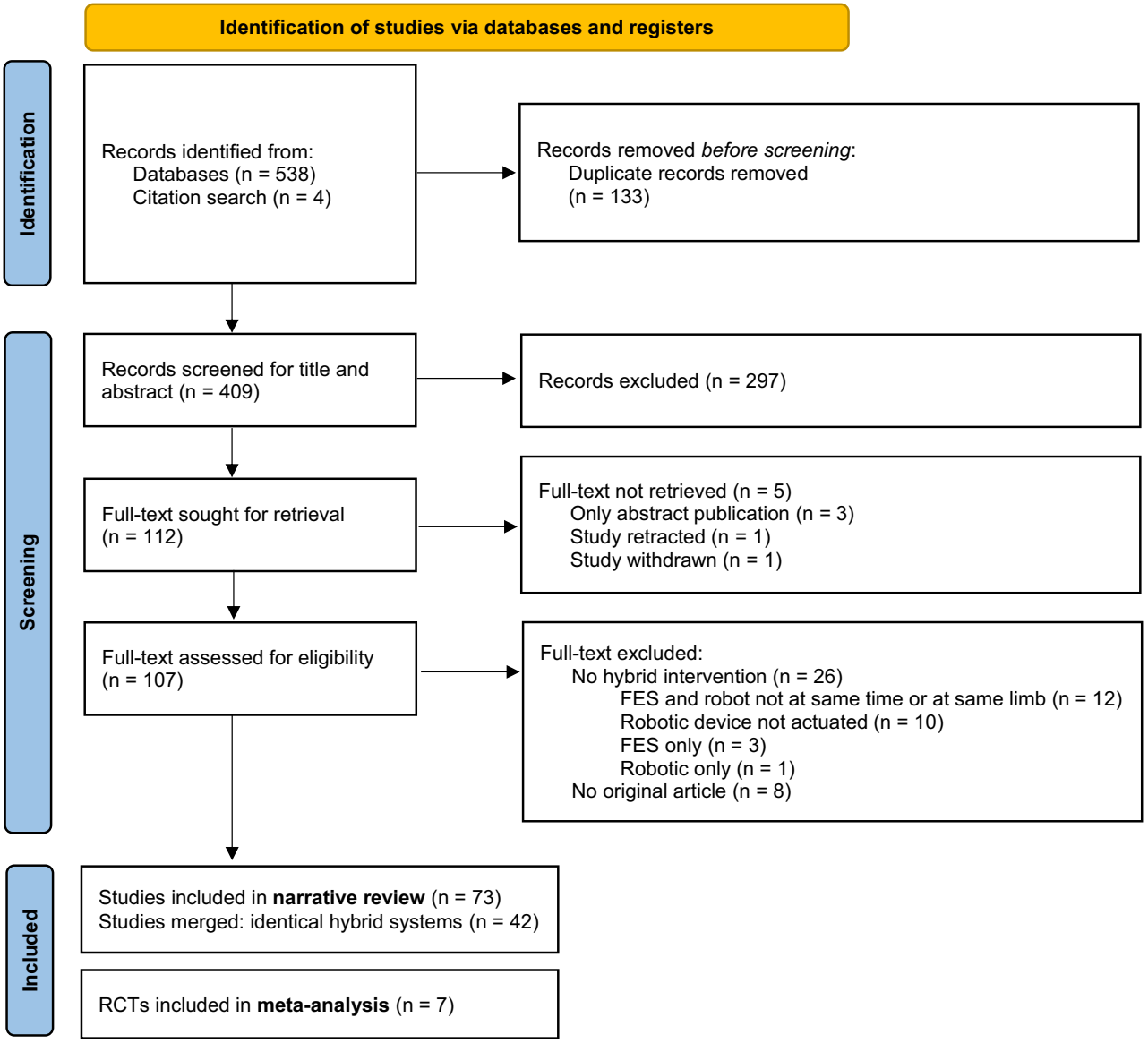

FIGURE 1 The PRISMA flow chart of the selection process (adapted from Page et al.[18]).

et al., the commercial InMotion ARM Robot (Bionik Laboratories, MA, USA) is used in combination with FES on the anterior deltoid and the triceps muscles during reaching tasks.[35] Both studies set a constant stimulation to elicit muscle contraction, without automatic decoding of the user's intentions, meaning activation is done manually.

Considering *active exoskeletons for distal actuation*, two studies describe an EEG-based BMI to trigger hand opening and closing movement assisted by a hybrid neuroprosthesis (a soft glove[41] and a rigid exoskeleton[36]) without any adaptation of the assistance level. Nam et al., Huang et al., and Neto et al. rely on EMG for activation of the assistance level,[29,37,38] with the latter also modulating the robotic assistance based on the muscle activation. Kinematic variables for the stimulation parameters are exploited in Agnanto et al.[19] A commercial device for wrist pronation/supination and flexion/extension, the Bi-Manu-Track (BMT; Reha-Stim Co., Berlin, Germany), is presented in Lee et al.[31]; FES was applied with constant parameters on extensor muscles and it was turned on/off by magnetic switches placed at the end range of the BMT handles. A hybrid FES-hand robot, in which non-adaptive assistance is delivered when EMG volitional activity is detected, is described by Qian et al. (2019); in this study,[43] they compare hybrid distal actuation with proximal actuation delivered by a hybrid wrist and elbow exoskeleton, which was introduced in Qian et al.[42]

Regarding *exoskeletons for proximal actuation*, elbow devices investigating algorithms for online adaptation of assistance are developed by Qian et al. and by Stewart et al.; the former[42] applies a switched control to determine motor and FES actuation, with the motor taking over FES only

TABLE 1 Overview of hybrid systems.

Primary reference	State of research, *n* of patients or HS	Type of robotic device (name)	Actuation	Supported joints
Agnanto et al.[19]	System testing in HS, $n=6$	Exoskeleton (HEXaFES)	Active	Distal
Amano et al.[20]	Not-controlled study, $n=6$	End-effector (prototype of CoCoroe AR2®, Yaskawa Electric Co., Japan)	Active	Proximal
Ambrosini et al.[21] +	RCT, $n=72$	Exoskeleton (RETRAINER)	Passive	Proximal
Bouteraa et al.[22]	System testing in HS, $n=1$	Exoskeleton	Active	Distal (FES), Proximal (Robot)
Crema et al.[23]	System testing in HS, $n=1$	Exoskeleton (ALEx)	Active	Distal (FES), Proximal (Robot)
Elnady et al.[24]	Feasibility, $n=9$	Exoskeleton	Active	Distal (FES), Proximal (Robot)
Exell et al.[25]	Feasibility, $n=3$	Exoskeleton (SaeboMAS, Saebo, NC, USA)	Passive	Distal (FES), Proximal (FES and robot)
Grigoras et al.[26] +	RCT, $n=25$	Exoskeleton (IHRG)	Active	Distal
Grimm et al.[27] +	Feasibility, $n=7$	Exoskeleton (Armeo®Spring, Hocoma, Switzerland)	Passive	Distal (FES), Proximal (Robot)
Hu et al.[28] +	RCT, $n=26$	End-effector	Active	Distal
Huang et al.[29] +	RCT, $n=30$	Exoskeleton	Active	Distal
Hughes et al.[30] +	Not- controlled study, $n=5$	End-effector	Active	Proximal
Lee et al.[31] +	RCT, $n=39$	End-effector (Bi-Manu-Track Reha-Stim Co., Germany)	Active	Distal
Looned et al.[32]	System testing in HS, $n=5$	Exoskeleton (RAO)	Active	Distal (FES), proximal (Robot)
Meadmore et al.[33] +	Not-controlled study, $n=5$	Exoskeleton (Armeo®Spring, Hocoma, Switzerland)	Passive	Proximal
Medina et al.[34]	Descriptive	Exoskeleton (AOD)	Active	Proximal
Miyasaka et al.[35]	RCT, $n=30$	End-Effector (InMotion®ARM, Bionik Laboratories, MA, USA)	Active	Proximal
Mizuno et al.[36] +	Protocol for RCT	Exoskeleton	Active	Distal
Nam et al.[37]	Not-controlled study, $n=15$	Exoskeleton	Active	Distal and proximal
Neto et al.[38]	System testing in HS, $n=1$	Exoskeleton (glove)	Active	Distal
O'Connor et al.[39]	Not-controlled study, $n=7$	End-effector (iPAM Mk2)	Active	Distal (FES), Proximal (Robot)
Pedrocchi et al.[40]	Descriptive	Exoskeleton (MUNDUS)	Active	Proximal and distal
Poboroniuc et al.[41] +	Descriptive	(1) Exoskeleton (EXOSLIM) (2) Exoskeleton (MANUTEX)	(1) Active (2) Active	(1) Distal and proximal (2) Distal
Qian et al.[42] +	RCT, $n=24$	Exoskeleton	Active	Distal
Qian et al.[43] +	RCT (distal vs. proximal), $n=30$	Exoskeleton	Active	Proximal and distal
Resquin et al.[44] +	Feasibility, $n=1$	Exoskeleton (Armeo®Spring, Hocoma, Switzerland)	Passive	Proximal
Rouse et al.[45]	Feasibility, $n=2$	Exoskeleton	Active	Proximal
Stewart et al.[13]	System testing in HS, $n=1$	Exoskeleton	Active	Proximal
Tu et al.[46] +	System testing in HS, $n=1$	Exoskeleton (RUPERT)	Active	Distal (FES), Proximal (FES and Robot)
Wang et al.[47]	System testing in HS, $n=1$	Exoskeleton	Active	Distal and proximal
Westerveld et al.[48]	Feasibility, $n=2$	End-effector (ATD)	Active	Distal (FES), proximal (Robot)

Note: + marks devices with further references (see Table S1). EEG: electroencephalography; EMG: electromyography; FES: Functional Electrical Stimulation; FMG: force myography; RCT: Randomized Controlled Trial—Patients were randomly assigned to intervention or control group, Not-controlled study: Pre-post assessment in patients without control, Feasibility study: Usability/feasibility test or verification of system functionality in patients, System testing in HS: Usability/feasibility test or verification in healthy subjects, Descriptive article: no data collection.

Movement supported	Sensing	Adaptation of assistance	Intention decoding
Grasping	Joint angle	FES (joint angle)	No
Reaching, pushing button	Joint angle	No	No
Reaching, grasping and moving objects, lateral arm elevation	EMG, joint angle	No	Yes (EMG)
Elbow flex./ext.	EMG, joint angle	Robot (joint angle)	Yes (EMG)
Reaching and grasping of objects	Joint angle, joint torque	No	No
Elbow flex./ext., finger flex./ext., grasping	Joint angle, motor angle, EEG	No	Yes (EEG)
Reaching, grasping, pushing button	Joint angle	FES (joint angle)	No
Finger flex./ext.	Joint angle	No	No
Wrist flex./ext.	EMG, Joint angle, EEG, grip force	No	Yes (EEG, EMG)
Wrist flex./ext.	EMG, joint torque, motor angle	FES and robot (EMG)	No
Reaching, grasping and moving soft object	EMG, joint angle	No	Yes (EMG)
Planar reaching	Joint angle, force/torque at handle	FES (joint angle)	No
Wrist flex./ext. and forearm pronation/supination	Contact event (magnetic switches)	No	No
Drinking task	Joint angle, EEG	No	Yes (EEG)
Reaching movement	Joint angle	FES (joint angle)	No
Radial ulnar deviation, wrist, elbow and shoulder flex./ext., shoulder elevation	Joint angle, EMG	No	Yes (EMG)
Shoulder and elbow movements, reaching	Force/torque at handle, motor angle	Robot (motor angle)	No
Finger flex./ext.	EEG	No	Yes (EEG)
Reaching, elbow and wrist flex./ext., hand opening/closing	EMG, actuator pressure	No	Yes (EMG)
Hand opening/closing, grasping	EMG, grip force, FMG	Robot (EMG)	Yes (EMG)
Reaching and hand opening	Joint angle, force/torque at attachments	No	Yes (joint angle)
Drinking, eating, interacting with objects	EMG, joint angle, EEG, Gaze tracking	FES (EMG)	Yes (EEG, gaze tracking, EMG)
(1) Interacting with objects (e.g., picking up a cup) (2) Finger flex./ext.	(1) Joint angle (2) Joint angle of unimpaired hand; motor angle	(1) No (2) No	(1) No (2) Yes, FES and robot (sensors of unimpaired hand)
Hand opening	EMG	No	Yes (EMG)
Elbow and wrist flex./ext., hand opening	EMG, Joint angle	No	Yes (EMG)
Reaching	EEG, joint angle	FES (joint angle)	Yes (EEG)
Biceps curls	Joint angle	FES (joint angle)	No
Elbow flex.	Joint angle, force at attachments	FES and robot (joint angle)	No
Reaching	Joint angle, actuator force sensor	FES (joint angle)	Yes (EMG)
Reaching, grasping and moving object	EMG, joint angle	No	No
Reaching, grasping and moving object	Joint angle (fingers), arm/hand position, force/torque at attachment	Joint angle	No

above a certain threshold, and only during the extension phase (flexor muscles were stimulated); the latter[13] designs an adaptive algorithm for both FES and robot, based on the trajectory tracking error. Wang et al. developed a system for the whole UL, actuating shoulder and hand with a robotic device while using FES for assisting elbow and wrist movements.[47] In Medina et al., Tu et al., and Bouteraa et al., robotic systems assisting the UL from the shoulder to the wrist are presented. In Medina et al., a controller based on tracking errors drives the robotic joints, and the FES is activated when the tracking error increases[34]; an artificial neural network classifies the movement, hence deciding which muscle to stimulate. Tu et al. employ a pneumatically driven exoskeleton, in which an iterative learning control strategy for both robot and FES is used to deal with the non-linearities of both actuation systems.[46] Bouteraa et al. present a UL exoskeleton in which an impedance controller assists the user's movement toward desired trajectories, while the type of electrical stimulation is chosen based on the detection of muscle fatigue via EMG signals.[22]

3.3 | Narrative description of individual studies

After providing an overview of existing hybrid neuroprostheses and their features, all studies ($n = 15$) that additionally provide clinical data were selected to link the systems' properties with clinical metrics. Using the data of $n = 188$ patients after a stroke, this section of the review aims to guide clinicians in the prescription of the appropriate device for the patients' needs.

First, the patients' UL function was categorized as mildly, moderately, or severely impaired. Since the FM assessment was performed in the majority of studies, the patients' results in this test are used to categorize the severity of UL impairment (mild: $FM > 40$, moderate: $25 \leq FM \leq 40$, severe: $FM < 25$[50]). For those studies in which the FM was not assessed ($n = 3$), the score in the Action Research Arm Test (ARAT) is the metric used for severity categorization (mild: $ARAT > 28$, severe: $ARAT \leq 27$[51]). Following this categorization, existing hybrid systems are tested in moderately ($n = 8$) and severely affected ($n = 7$) patient populations (Figure 2).

In addition to the FM and ARAT, a variety of measures were assessed at baseline, covering the structures and functions of the UL (e.g., Motricity Index [MI], Modified Ashworth Scale [MAS]) as well as aspects of the activity and participation level (e.g., Box and Block Test [BBT], Stroke Impact Scale [SIS]) of the International Classification of Functioning, Disability and Health (ICF). All the baseline data that indicate the degree of cognitive deficits and motor impairment of the UL is provided in the Table S2.

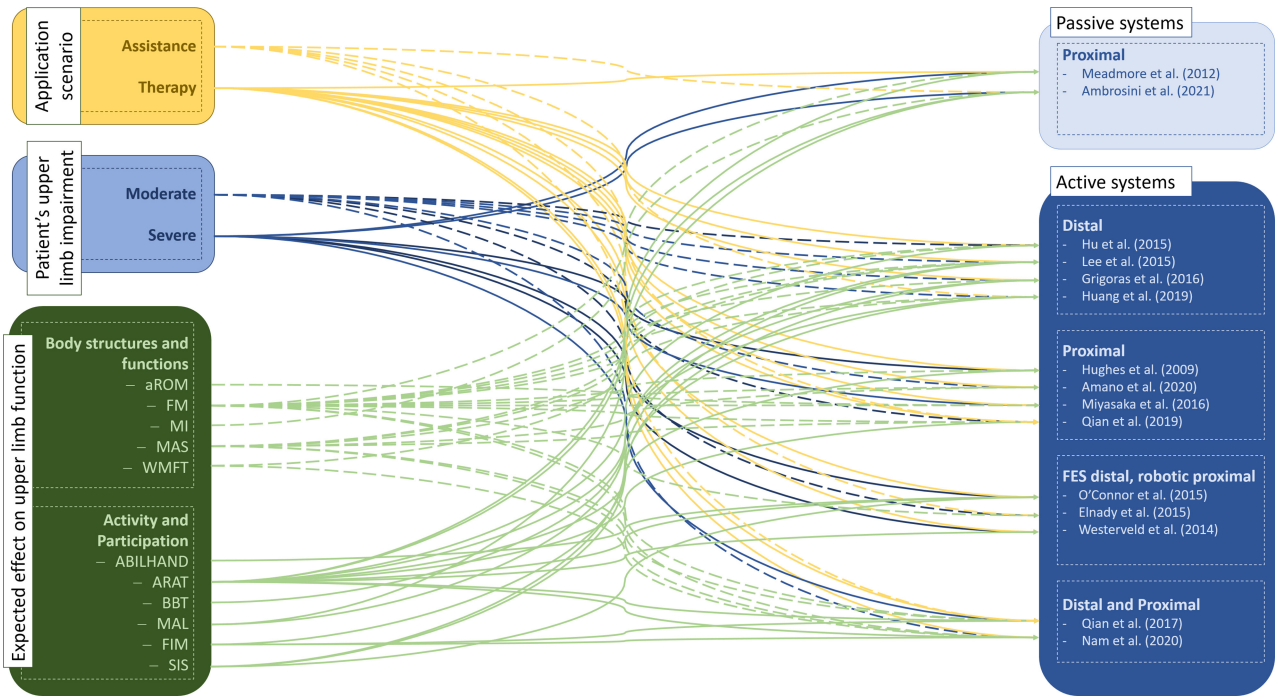

FIGURE 2 The connection between the system properties and clinical requirements. Visualization adapted from Cardoso et al.[52] Checking the color and the line type of lines ending at the grouped references, gives an impression of which device type is mainly used (1) in which application scenario, (2) in which patient group, and (3) in order to improve which level of functioning.

In Figure 2, these clinical reports are linked with the technical properties of the hybrid systems: (1) Existing devices were categorized into their type of actuation (active/passive) and the assistance they provide (proximal/distal), (2) it was indicated whether the device is suitable for rehabilitative therapy or assistance during the performance of movements (the portability of the system is seen as a decisive factor to potentially use the device in the assistive application scenario). (3) Which device is meant to be used with which degree of severity in UL impairment is visualized? (4) The level of UL function is shown on which the original authors expected an effect of the hybrid system, based on the performed assessments (assuming that the original authors have chosen assessments of UL functions for which they have expected an effect of the hybrid therapy).

The results show that there are currently no passively actuated devices to support the movement of distal joints, but only for the proximal joints ($n=2$). The vast majority of hybrid systems are motorized ($n=13$) and support either the distal joints only ($n=4$), the proximal joints only ($n=4$), distal and proximal joints simultaneously ($n=2$), or each of the hybrid components supports a different joint (FES distal, robotic proximal; $n=3$).

Ten of the existing systems might be purely used in the therapeutic application scenario, as they are limited to stationary usage in their current version. Five hybrid devices are portable systems, which theoretically enable the user to wear the device during ambulation and to receive assistive UL support throughout the day. Two of these systems can be used in combination with a static weight-support of the UL for the therapy of the lost functions, but also as a portable stand-alone for assisting and compensating the lost functions.

Surprisingly, both passively actuated systems, i.e., those with less support, were tested in severely affected patients. Interestingly, actively actuated devices for the support of distal joints were exclusively tested in patients with moderate UL impairment. All the other active systems seem to be eligible for both moderately and severely affected patients.

The results show that when applying passive systems, one might expect an effect on both the structures and functions of the UL as well as on activity and participation. The same applies to actively actuated devices that support the distal joints or actuate the distal and proximal joints simultaneously. Those systems which actively support the proximal part of the UL are rather expected to have an effect on body structures and functions. Recovery of the UL on the activity and participation level is targeted when applying FES distally and the robotic component proximally.

3.4 | Part 2—Study characteristics of RCTs with patients, included in the systematic review and meta-analyses

As stated previously, seven RCTs, published between 2015 and 2021, are eligible for the systematic part of this article (Table 2). Following the *Template for Intervention Description and Replication (TIDieR)*,[53] a detailed description of each intervention (e.g., the materials, the procedures, and the intensity) is provided in Table 3.

3.5 | Risk of bias in RCTs

The results of the risk of bias analysis of studies included in the meta-analysis are shown in Figure 3.

3.5.1 | Randomization process

Four of the studies[21,29,31,42] provide all relevant information on the sequence of randomization. Two studies[26,35]

TABLE 2 Patient and intervention characteristics of randomized controlled trials.

Reference	*n*	Mean age (y)	Etiology (i/h)	Time since stroke (m)	Comparison	Intervention duration	UL impairment
Ambrosini et al.	72	64.4	53/19	2	Conventional	9 weeks	Severe
Grigoras et al.	25	63.8	23/2	23–56	Conventional	2 weeks	Moderate
Hu et al.	26	47.4	17/9	21–108	Robotic	7 weeks	Moderate
Huang et al.	30	58.7	18/12	38–133	Robotic	7 weeks	Moderate
Lee et al.	39	54.0	21/18	10–43	Robotic+sham	4 weeks	Moderate
Miyasaka et al.	30	60.9	14/16	2–3	Robotic	2 weeks	Severe
Qian et al.	24	59.6	9/15	1–5	Conventional	4 weeks	Severe
Overall	246	58.4	155/91	1–133		5 weeks	

Abbreviations: h, hemorrhagic; i, ischemic; *n*, number of patients; UL, upper limb; y, years.

TABLE 3 Intervention characteristics of RCTs following the TIDieR criteria.

Reference	Group	Intervention	Rationale/aim	Materials	Procedures	Expertise of health prof.	Modality
[21]	HT	Task-oriented exercises + ACT	Task-oriented and high-intensity training to facilitate cortical reorganizations and UL motor recovery	EMG + FES on either two of the following muscles: biceps/triceps/anterior/medial/posterior deltoid + passive exoskeleton + daily life objects + screen	HT: EMG-triggered HT to support 7 exercises: anterior reaching, moving objects, lateral elevation of the extended arm, and hand to mouth movements with or without grasping an object + ACT: UL passive and/or active motion, arm cycle-ergometer without FES, FES of forearm muscles, VR arm exercises, repetitive task training, mirror therapy	HT: 1-week training of 4 PT on the use of the system; ACT: 4 different PTs, specifically trained on UL stroke rehab.	Individual
	CT	ACT	Test superiority of HT in the recovery of arm function, dexterity, strength, ADLs and QoL	Not specified	ACT: UL passive and/or active motion, arm cycle-ergometer without FES, FES of forearm muscles, VR arm exercises, repetitive task training, mirror therapy	ACT: 4 PTs, specifically trained on UL stroke rehab.	Individual
[26]	HT	Hybrid assisted finger flex./ext.	n.r.	Hybrid system: FES pads on left finger and wrist ext. + left hand robotic glove + right hand sensorized glove	Finger flex./ext. of left hand actuated by hybrid system which replicates the movement of the right hand; within one cycle of 15–20 sec, the fingers were opened for a duration of 7 sec	Profession and expertise of supervisor unknown	individual
	CT	Conventional	improving the patient's motor control of the paretic arm	n.r.	Standard therapy including passive and active mobilization of the UL	n.r.	n.r.
[28]	HT	Hybrid assisted wrist flex./ext. tracking	Compare motor improvements on the UL	EMG at triceps, biceps, ECR and FCR + NMES + wrist robot + screen + forearm fixor + palm supporter	Following a moving cursor on the screen with a constant angular velocity of 10°/s at the wrist joint, with a target to minimize the difference between the target and the actual wrist positions indicated by cursors as much as possible. 70 cycles of wrist flexion and extension were performed in one session	n.r.	Individual
	CT	Robot assisted wrist flex./ext. tracking	Compare motor improvements on the UL	EMG at triceps, biceps, ECR and FCR + NMES pads turned off + wrist robot + screen + forearm fixor + palm supporter	Following a moving cursor on the screen with a constant angular velocity of 10°/s at the wrist joint, with a target to minimize the difference between the target and the actual wrist positions indicated by cursors as much as possible. 70 cycles of wrist flexion and extension were performed in one session	n.r.	Individual

Location	Intensity	Adaption	Modification	Plan for compliance	Actual compliance
Within the stay in either a German or Italian rehab. clinic. Position: seated in front of a table, wearing the hybrid exoskeleton	22–27 × 30 min of HT + 22–27 × 60 min of ACT within 9 weeks Total: min of 11 h HT + min of 22 h ACT	Training parameters: type of exercises, number of repetitions, target position, gravity compensation level, duration of pauses, stimulated muscles, EMG threshold and current amplitude; selection of content of ACT based on decision of the therapist	Training para-meters could change through-out the inter-vention	None	Very high: patients received on average 26 ± 2 sessions, with a min of 22
Within a stay in either a German or Italian rehab. clinic	21–27 × 90 min of ACT within 9 weeks Total: min of 31.5 h of ACT	Selection of ACT content based on decision of therapist	None	None	Very high: patients received on average 26 ± 2 sessions, with a min of 21
Neurology Clinic within Rehab. Hospital from Iasi. Position: seated in front of a work desk, wearing the glove	12 × 30 min sessions within 2 weeks; total: 6 h	Different amount of repetitions; 90 repetitions per session on average	None	None	No dropouts
Neurology Clinic within Rehab. Hospital from Iasi	10 × 30 min sessions within 2 weeks; total: 5 h	n.r.	None	None	No dropouts
n.r. Position: in front of computer screen; paretic arm attached to system, shoulder abducted at 80° and extended 0°, elbow flexed at 90°	20 × 30 min or longer sessions over a period of max. 7 weeks; total: min. 10 h	Assistance from hybrid system as needed	None	Planning a feasible number of sessions	No dropouts
Same as HR group	20 × 30 min or longer sessions over a period of max. 7 weeks; total: min. 10 h	Assistance from robotic system as needed	None	Planning a feasible number of sessions	No dropouts

(Continues)

TABLE 3 (Continued)

Reference	Group	Intervention	Rationale/aim	Materials	Procedures	Expertise of health prof.	Modality
[29]	HT	EMG-driven NMES robotic hand training	To assist PT to provide effective long-term rehab.; to compare the rehab. effects on motor recovery	EMG-driven NMES robotic hand (EMG electrodes, NMES electrodes, robotic hand, battery, control box) + table	Robot supported hand opening and closing exercises, NMES-support for extension Performance of repetitive lateral and vertical UL movements (30 min duration each with a 10 min break in between)	n.r.	Individual
	CT	EMG-driven robotic hand training	n.r.	EMG-driven robotic hand (EMG electrodes, robotic hand, battery, control box) + table	Robot supported hand opening and closing exercises	n.r.	Individual
[31]	HT	Hybrid assisted wrist ext./flex. and pronation/supination	Effect on motor impairment, motor and daily function, and QoL	Robot + NMES on wrist extensors and either supinator or pronator (depending on the task)	HT: wrist flex./ext. and forearm pronation/supination with 3 different bimanual training modes (stimulation in mode 2 and 3): passive–passive (mode 1), active–passive (mode 2), and active–active (mode 3) Functional task training: forearm pronation/supination or wrist flex./ext. (such as twisting a towel or bouncing a ball)	Clinical occupational therapist, expertise unknown	Individual
	CT	Robot assisted wrist ext./flex. and pronation/supination with sham stimulation	Augment the effects of therapists' training and facilitate motor recovery	Robot + NMES pads on wrist extensors and supinator or pronator turned off	Bimanual training modes (no stimulation): passive-passive (mode 1), active–passive (mode 2), and active–active (mode 3) Functional task training as in HT group	Clinical occupational therapist, expertise unknown	Individual
[35]	HT	NMES + robotic training	To investigate if untriggered NMES can increase the efficacy of shoulder and elbow robotic training	Robot + NMES	Robotic + NMES (on anterior deltoid and triceps) training, reaching movements in a horizontal plane at least 1000 times in ~1 h	n.r.	Individual
	CT	Robotic training	n.r.	Robot	Robotic training, reaching movements in a horizontal plane at least 1000 times in ~1 h	n.r.	Individual

Location	Intensity	Adaption	Modification	Plan for compliance	Actual compliance
The Hong Kong Polytechnic University. Position: seated in front of a work desk, wearing the device	20-session UL training with the device with an intensity of 3–5 sessions/week, completed within 7 consecutive weeks; duration: 60 min	Before training, the pulse width of NMES was set at the min. intensity, which achieved a fully extended position of the fingers in each patient	n.r.	n.r.	No dropout
Same as HR group	20-session UL training with the device with an intensity of 3–5 sessions/week, completed within 7 consecutive weeks, duration: 60 min	n.r.	n.r.	n.r.	No dropout
Five hospitals in Taiwan. Position: in front of a height-adjustable table, elbow flexed at 90°, forearms in neutral position	20 × 60-70 min HT + 20 × 20–30 min functional task training over a period of 4 weeks; total: min. of 20 h HT + min. of 6.6 h functional task training	# of repetitions and time point of assistance trigger depending on patient's capacity, stimulation intensity adjusted to patient's max. tolerance level, 70% of patients performed supination and 30% performed pronation movements depending of the primary movement limitation	None	None	No dropouts
Same as HR group	20 × 60-70 min robotic therapy + 20 × 20–30 min functional task training over a period of 4 weeks; total: in as HT group	# of repetitions and time point of assistance trigger depending on patient's capacity	None	None	No dropouts
Fujita Health University Nanakuri Sanatorium. Position: n.r.	~1 h/day, 5 days/week for 2 weeks in addition to regular rehab.	Stimulation intensity at sub-motor threshold	n.r.	n.r.	No dropout
Same as HR group	~1 h/day, 5 days/week for 2 weeks in addition to regular rehab.	n.r.	n.r.	n.r.	No dropout

(Continues)

TABLE 3 (Continued)

Reference	Group	Intervention	Rationale/aim	Materials	Procedures	Expertise of health prof.	Modality
[42]	HT	2/3 HT: elbow, wrist and finger flex./ext. (no support for finger flex.) + 1/3 traditional therapy (see CT)	To investigate the training effects of the device-assisted approach on subacute stroke patients	Wrist robot + NMES elbow robot + hanging system + screen for visual feedback	20 min of repetitive and supported elbow ext., wrist ext., finger ext. followed by finger flex. (not supported), wrist flex. and elbow flex + 10 min break + 20 min of described supported movements + up to 20 min traditional therapy	Therapist (not further specified)	Individual
	CT	Traditional therapy: muscle stretching, passive/active ROM and occupational treatments such as feeding/eating, grooming	To compare the effects with those achieved by the traditional physical treatments	No technical support	1 h of different components of traditional therapy (such as muscle stretching, passive/active ROM and feeding/eating, grooming practices)	Therapist (not further specified)	Individual

Abbreviations: ACT, advanced conventional therapy; ADLs, activities of daily living; CT, control therapy; ECR, extensor carpi radialis; EMG, electromyography; FCR, flexor carpi radialis; FES, Functional Electrical Stimulation; HT, hybrid therapy; n.r., not reported; NMES, neuromuscular electrical stimulation; PT, physical therapist; QoL, Quality of Life; ROM, range of motion; UL, upper limb; VR, virtual reality.

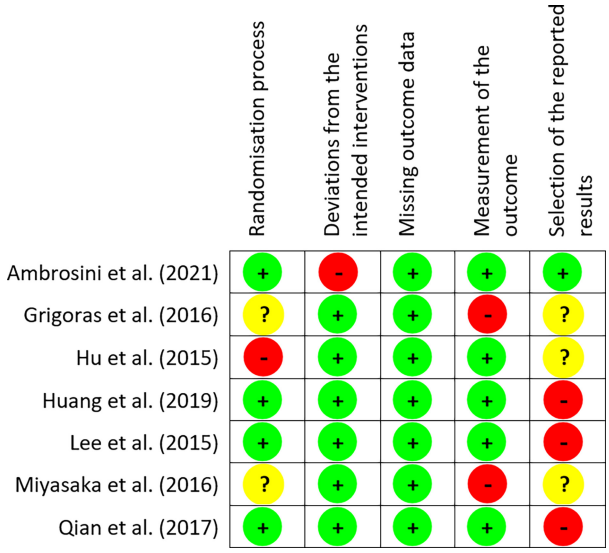

FIGURE 3 Results of the risk of bias analysis for each RCT. Green indicates low risk of bias, yellow indicates unclear risk of bias, red indicates high risk of bias.

are rated with an unclear risk of bias because there was no information given on the allocation sequence concealment. One study[28] is considered at high risk of bias due to doubts in the randomization process leading to an equal distribution of the patients' baseline characteristics for age and time since stroke. Taking into account the rather uncommon values (mean age < 50 years; mean time since injury > 4 years) in both groups without prespecified patient inclusion criteria, it is questionable whether such an equal distribution of characteristics between groups can occur after a randomization without stratification. In addition, the number of recruited patients is higher than the result of the sample size calculation.

3.5.2 | Deviations from the intended interventions

Six studies are at low risk of bias regarding deviations from the intended interventions. The assessors were either blinded, or appropriate methods were chosen to counteract this risk of bias. In Ambrosini et al., assessors were blinded to the treatment allocation, whereas physiotherapists delivering the intervention were not.[21] As reported in the paper, there were imbalances between groups in the content of additional conventional therapy. In the experimental group, a higher proportion of patients received FES of the forearm muscles during additional conventional therapy, while more patients in the control group trained with the arm cycle-ergometer. Since FES therapy

Location	Intensity	Adaption	Modification	Plan for compliance	Actual compliance
Teaching hospital of the University in Hong Kong. Position: seated in front of a monitor with the UL in a hanging system, wearing the device	20 × 40 min of HT (+20 min traditional therapy) each weekday for a duration of 4 weeks	Hanging system was needed by one subacute patient, type of traditional therapy was selected by therapists and its duration varied depending on muscle fatigue (mostly between 10 and 15 min)	None	None	No dropout
Teaching hospital of the University in Hong Kong	20 × 60 min of traditional therapy each weekday for a duration of 4 weeks	Type of traditional therapy was selected by the therapists	None	None	No dropout

involves one component of the hybrid intervention, these imbalances are rated at a high risk of bias.

3.5.3 | Missing outcome data

In the majority of studies, no drop-outs occurred. Solely in Ambrosini et al., the drop-out rate was 11% at post-assessment and 14% at follow-up.[21] Due to a large *SD*, we do not think that the results were biased by missing data.

3.5.4 | Measurement of the outcome

The selected outcome measures are appropriate in all studies. However, in two studies,[26,35] the assessors were not blinded and, therefore, considered to be at high risk of bias.

3.5.5 | Selection of the reported results

A trial protocol is available for four studies.[21,29,31,42] In Lee et al., not all registered outcome assessments were performed or reported.[31] The outcome variables in three studies[29,31,42] are on an ordinal scale but were analyzed with parametric tests.

3.5.6 | Other risks of bias

Unfortunately, the pre-post difference in UL functions of intervention and control groups is not consistently available for all studies. Therefore, in the following syntheses, only post-measurements of UL functions are compared between intervention and control groups. Since values after the intervention are compared without relation to baseline values, studies in which the groups differ significantly in UL functions at baseline bias the results of the syntheses. In Grigoras et al., the intervention group had a significantly lower baseline FM value than the control group (95% *CI* −6.54; −1.46[26]). The results of this study are thus not included in the syntheses of the FM total score to reduce the risk of bias.

3.6 | Results of the syntheses

In six of the seven RCTs, patients' UL functions were tested by means of the FM, which is, on average 21.5 ± 5.0 points at baseline (for a better interpretation of post-values, baseline measures of each individual study are included in the Table S2). In Ambrosini et al., the FM was not assessed.[21] In addition, the device in this study is the only one that is passively actuated. For the sake of

homogeneity, this study is not included in the synthesis but reported separately.

The meta-analysis of differences in the FM between the intervention and control groups after the intervention, reveals a significant positive effect of the therapy with hybrid neuroprostheses ($p < 0.001$, Figure 4). The intervention and control groups show a M_{diff} of 7.84 points on the FM scale (95% *CI* 4.26–11.42). Moderately impaired patients profit significantly more from the hybrid therapy (by 6.18 points on the FM, 95% *CI* 1.84–10.58) than from the control therapy ($p = 0.005$). An even stronger effect on UL function is seen in severely impaired patients who show an 11.05 point difference between groups in favor of the hybrid therapy (95% *CI* 3.82–18.28; $p = 0.003$).

More specifically, the effect of the therapy with a hybrid neuroprosthesis is separated for proximal and distal UL functions. The intervention significantly favors the recovery of impairments at the shoulder and elbow level ($p = 0.001$; Figure 5). Patients in the intervention group have a 4.58 point (95% *CI* 1.79–7.36) higher score in the FM shoulder–elbow assessment than the control group. This positive effect on shoulder and elbow functions applies to moderately impaired patients ($p = 0.040$) as well as to severely impaired patients after stroke ($p = 0.002$). There is no significant effect of the hybrid therapy on the recovery at the wrist and hand level ($p = 0.190$; Figure 6). While the intervention and control group of moderately impaired patients show no significant difference in the

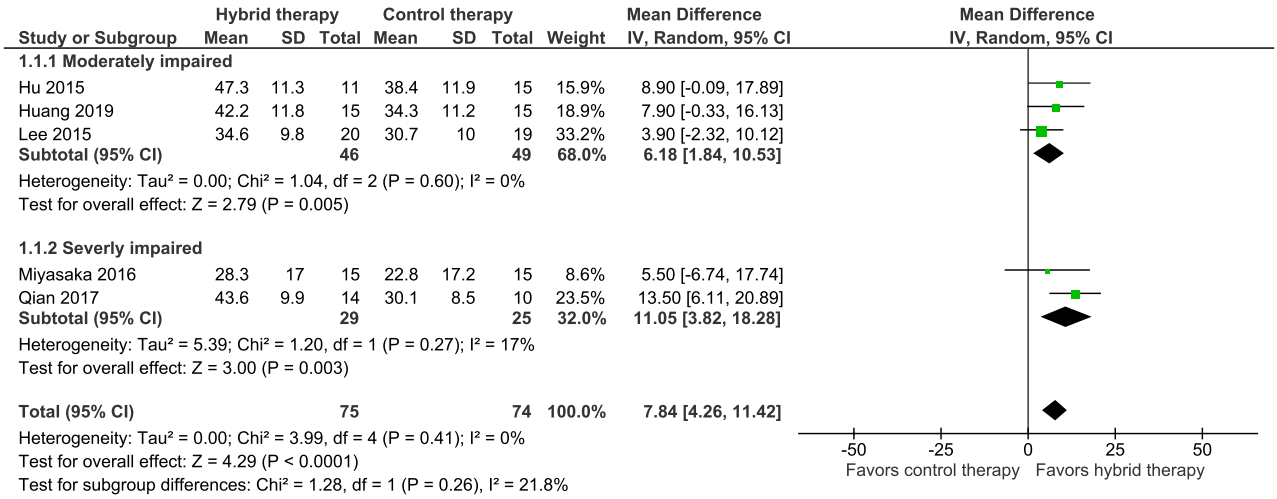

FIGURE 4 Differences between intervention and control groups in the upper extremity part of the FM after the intervention. Mean differences for individual studies are represented by squares, and pooled differences across studies are represented by the diamonds.

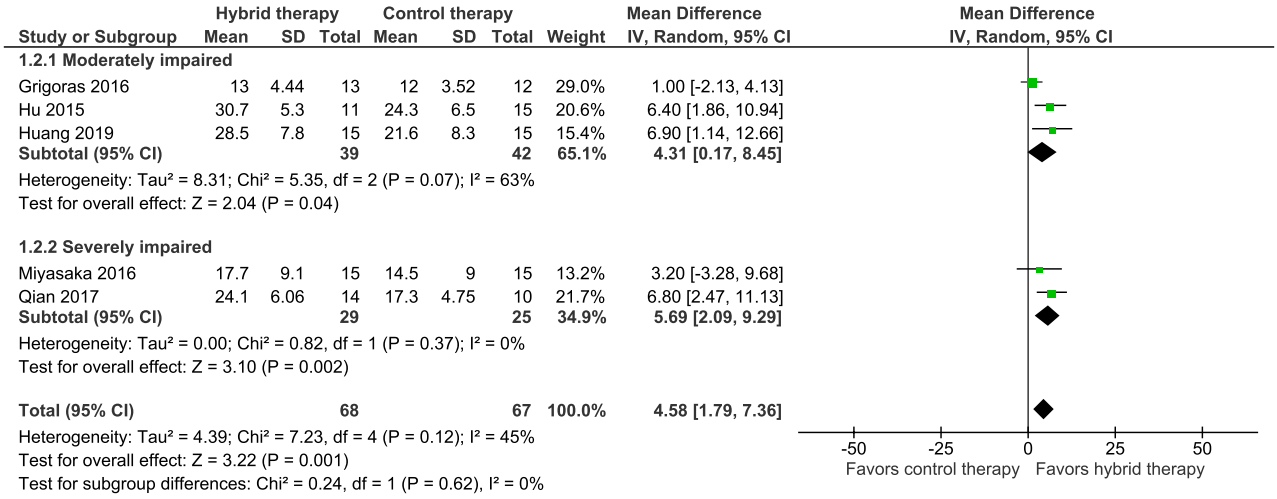

FIGURE 5 Differences between intervention and control groups in the shoulder-elbow part of the FM after the intervention. Mean differences for individual studies are represented by squares, and pooled differences across studies are represented by diamonds.

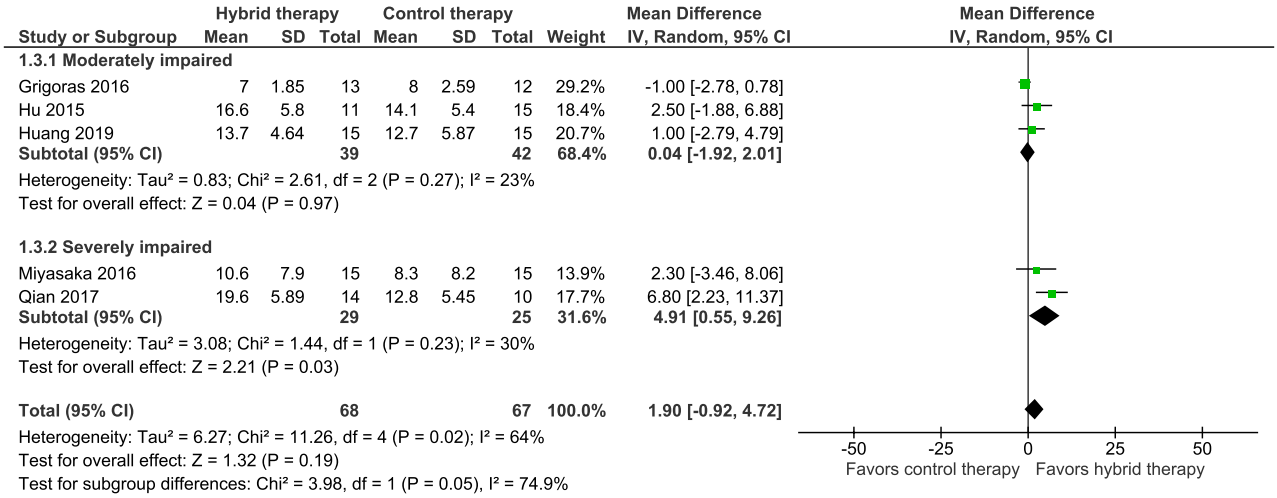

FIGURE 6 Differences between intervention and control groups in the wrist-hand part of the FM after the intervention. Mean differences for individual studies are represented by squares, and pooled differences across studies are represented by diamonds.

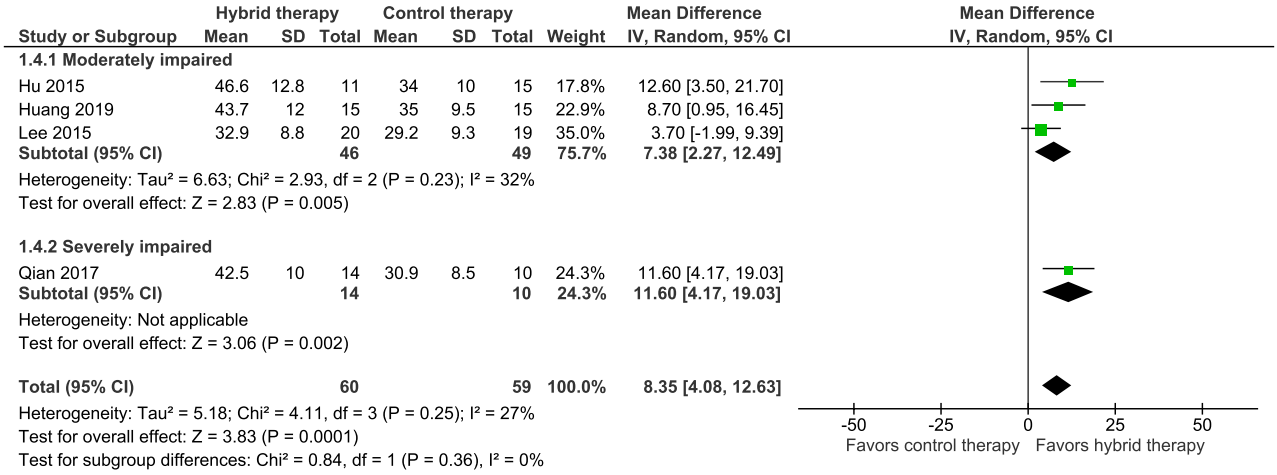

FIGURE 7 Differences between intervention and control groups in the upper extremity part of the FM at 3-month follow-up. Mean differences for individual studies are represented by squares, and pooled differences across studies are represented by diamonds.

FM wrist–hand assessment ($p = 0.970$), patients with a severe UL hemiparesis have a 4.91 point (95% *CI* 0.55–9.26) higher score when participating in the hybrid therapy compared to the control therapy ($p = 0.030$).

At 3-month follow-up, there is still a significant positive effect of the therapy with hybrid neuroprostheses on UL functions ($p < 0.001$, Figure 7). The FM score of patients in the intervention group is, on average 8.35 points higher than in the control group. The positive effect is present at follow-up for moderately impaired patients ($M_{diff} = 7.38$ points, 95% *CI* 2.27–12.49, $p = 0.005$) and even stronger for severely impaired patients after stroke ($M_{diff} = 11.60$ points, 95% *CI* 4.17–19.03, $p = 0.002$). The results of Miyasaka et al. are not included in the follow-up analysis, since they did not conduct another assessment three months post-intervention.[35]

As explained earlier, the results of Ambrosini et al. are reported outside the meta-analysis.[21] Patients who used the passively actuated neuroprosthesis improved on average by 18.4 (*SE* 3.0) points in the ARAT while patients in the control group improved by 7.4 (*SE* 2.0) points. As reported in the publication, this *group* × *time* interaction in favor of the hybrid therapy is statistically significant ($p = 0.002$). Similarly, the performance in the BBT is significantly affected by the hybrid intervention compared to the control therapy ($p = 0.048$). Patients in the intervention group improved in the BBT on average by 58 (*SE* 3) points, while patients in the control group improved on average by 53 (*SE* 3) points.

4 | CONCLUSION

4.1 | Existing devices and their indication for use

Aiming to provide an overview of existing devices and their features revealed that active end-effector devices mostly provide proximal anti-gravity support, while FES is used either on the proximal or distal joints; because they do not address the human joints individually, they might need to rely on external devices, like motion tracking systems, for monitoring and assessment of the patients' kinematics.[20,48] End-effectors' reduced technical complexity and the easier mechanical coupling with the user compared to exoskeletons (e.g., lower donning/doffing time, few to no regulations needed) make them relatively easy to be introduced in clinical settings; hence, the proportion of structured clinical studies is high for these devices (86% of studies with end-effectors vs. 28% of studies with exoskeletons). In contrast to end-effectors, robotic exoskeletons can monitor and drive individual joints, enabling more individualized rehabilitation strategies and the possibility to address functional movements while promoting physiological inter-joint coordination. Nevertheless, although they potentially allow for wider possibilities of automatic adaptation of assistance (e.g., by monitoring the user's kinematic and kinetic information in addition to the EMG signals widely explored for FES adaptive control), assist-as-needed strategies were poorly explored in the hybrid systems reviewed in this study. Indeed, in most of the works, the two components are operated independently and with constant stimulation parameters or assistance parameters. This is likely due to technological barriers for the wide adoption of wearable robots in terms of human-robot interfacing, actuation, sensing, and control, which further complicate the integration of FES in hybrid neuroprostheses and a synergic action between the two components. We hypothesize that with wearable technologies becoming more mature in the next few years, advanced, integrated hybrid FES-robotic systems will be developed, paving the way for investigating novel strategies for intuitive and cooperative FES-robot control. Such developments hold great promise for making a substantial translational impact, extending from clinical environments to daily-life assistance.

In order to answer the second part of the objective (provide indications of use to select the appropriate system according to the patient's individual impairment), the following guideline for the prescription of hybrid devices is generated based on the results of this review. Severely impaired patients are eligible for actively actuated devices, but also for passively actuated devices where the user is required to initiate the movement. However, training with distally supporting active systems is advised for patients with moderate hemiparesis. Active, proximal support can be recommended for moderately and severely impaired patients alike. Whenever clinicians target improvements on the ICF level of body structures and functions of the UL (e.g., muscle tone, muscle strength), either a passively actuated system or an active system for distal support or an active system for proximal support should be chosen. Passively actuated systems and active systems for distal support could also be described when targeting the recovery on the activity and participation level, such as the application of distal stimulation plus proximal robotic support.

4.2 | Efficacy in rehabilitating UL functions after stroke—Determinants of successful recovery

With the aim to provide up-to-date evidence for the efficacy of using hybrid neuroprostheses for UL neurorehabilitation, the body of evidence was comprehensively reviewed. The pooled results show a positive effect on the recovery of UL functions after a stroke which remains at least three months after the intervention is terminated. This positive effect applies to patients with both moderate and severe paresis. However, immediate improvements are found at the proximal joints, while the functionality of distal joints improved only in severely affected patients. Thus, moderately impaired patients showed less benefit from the hybrid therapy. Since most of the systems did not assist-as-needed, the support of active systems potentially did not appropriately challenge patients with higher functions to reveal their full recovery potential. Therefore, future systems should try to implement adaptive assistance based on the patient's capabilities.

Considering the second part of this objective (considering determinants of successful hybrid therapy) by having a closer look at the results of individual studies, it becomes apparent that the simultaneous hybrid support of distal and proximal joints in Qian et al. is the only therapy that consistently induces UL recovery of distal and proximal functions, right after the intervention period and at 3-month follow-up.[42] Interestingly, the devices of Huang et al. and Hu et al. for distal support reveal improvements exclusively in proximal functions right after the intervention,[28,29] but distal functions catch up by the follow-up assessment (as the total FM becomes significant). This finding indicates that proximal functions recover first, and distal improvements become obvious after a certain time has passed. The delay in the recovery of distal functions might be due to proximal compensatory movements while performing distal limb tasks.[28] Regarding hybrid robotics

that is passively actuated, it cannot be stated whether they drive distal or proximal UL improvements more, as these functions were not assessed individually but combined. In conclusion, the previously stated hope to counteract the asynchronous recovery of distal and proximal functions using hybrid devices might hold true for devices giving hybrid support to distal and proximal joints at the same time.

In addition to the location of hybrid support, other determinants are identified which might favor the effectivity of hybrid neuroprostheses: longer intervention duration, younger age of the study population, and more severe initial impairment level. In Grigoras et al. and Qian et al., for example, only two weeks of intervention were performed, which is the shortest intervention duration. Since robotic therapy shows a dose–response relationship when the aim is to recover motor functions,[54] this might be one reason, why there is no significant effect of the intervention in these two studies.[26,42] In terms of the age of the study population of all pooled studies, Miyasaka et al. recruited the oldest patients.[35] Since age is one factor influencing the recovery potential after stroke,[55] this might be one explanation for why this study did not reveal a significant effect on UL functions. In Lee et al., the patient population reaches a mean FM value of 30 points at baseline, which means that the included participants show less UL impairment compared to the other studies.[31] Since there is no significant effect of the treatment in this study, this might imply that the hybrid approach is beneficial for patients with more severe UL impairment.

Surprisingly, the effect of the therapy does not seem to be influenced by the time since the stroke. Both studies with subacute patients[21,42] and studies including chronic patients up to eleven years after stroke[28,29] reveal a significant treatment effect.

4.3 | Clinical relevance

The pooled results of this review show a significant positive effect on UL functions. Regarding the clinical relevance of this result, the pooled M_{Diff} in the FM score between groups is compared to its minimally important change (MIC). The MIC of the FM assessment is set at 10% of the maximum score,[56] which is 6.6 points for the UL section. The M_{Diff} in the FM score is 7.8 points and is thus clinically relevant. In moderately impaired patients, the threshold for being clinically relevant is almost but not fully reached, with a between-group difference of 6.2 points. The FM score of patients with severe hemiparesis is 11.1 points higher in the intervention group than in the control group, which is considered a clinically meaningful difference.

In addition to the meta-analysis, the hybrid therapy in Ambrosini et al. significantly enhanced UL recovery.[21] Patients in the hybrid group improved in the ARAT by 18.4 points, and patients in the control group by 7.4 points. According to a previous analysis, the MIC in the ARAT is 12 points if the dominant limb is affected and 17 points if the non-dominant limb is affected.[57] As the patients' dominant side was not assessed in Ambrosini et al., we consider the middle of 14.5 points as MIC.[21] Based on this reference, the change in UL function of patients who performed the hybrid therapy is clinically relevant, which does not apply to the control group.

The clinical relevance of the results of this meta-analysis have to be evaluated under consideration of the novelty of such systems. The used devices are still in the research stage and not yet on the market. Thus, they are not yet included in standard care, and in only four cases were evaluated in a clinical environment, while the testing environment was at a university in two cases. In three of the RCTs, therapists administered the therapy. Conclusively, even though the reviewed hybrid interventions lead to a clinically meaningful change in UL functions, there is a need for further development, therapist involvement, and implementation of devices in clinics.

4.4 | Strengths and limitations

To the best of our knowledge, this is the only review including a complete, systematic search plus a meta-analysis on the use of hybrid neuroprostheses for UL recovery after a stroke. The peculiarity of this paper is that it incorporates both a narrative description of all published hybrid systems and an analysis of their efficacy.

One strength of the meta-analysis is the uniformity in the UL assessment. In the majority of studies, the FM was assessed, which enables the results to be synthesized on a continuous scale. However, the restricted availability of data for the meta-analysis (even after contacting the primary authors) required self-calculation of metrics (i.e., the FM shoulder-elbow score based on the FM and FM wrist-hand score; and *SD* based on *IQR* or 95% *CI*). By following the instructions of the Cochrane Handbook for Systematic Reviews (version 62[16]), we expect to reduce any potential risk of bias induced by self-calculation. Still, it was not possible to perform a synthesis of pre-post gains in the FM score, which might have been an even more valid analysis.

The heterogeneity of the studies in terms of population and intervention characteristics is seen as an advantage in terms of generalizability. Determinants of a successful

therapy could be defined, and the results of the meta-analysis are highly generalizable (e.g., varying time since stroke, age, and stroke severity). Nevertheless, the overall number of RCTs is low. Consequently, the sample sizes for sub-group analysis are small. Further RCTs are needed for a better understanding of the role of hybrid neuroprostheses in stroke rehabilitation, especially when making assumptions about determinants of successful therapy. Additionally, published RCTs focus on the effect on body functions and activity, but do not investigate the impact of hybrid therapy on the participation level.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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