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Authors	Amber Hinsberg, Renata Loureiro-Chaves, Jonas Schröder, Steven Truijen, Wim Saeys, Laetitia Yperzeele

rehabilitation, leading up to her research on changes in balance control and integrity of descending motor pathways in poststroke recovery. She is currently improving her skills in biomechanical analysis of steady-state balance outcome variables to investigate asymmetries and interlimb coordination as growing her coding skillset to analyze diffusion MRI images.

Dra. Renata Loureiro-Chaves

Dra. Loureiro-Chaves (ORCID 0000-0002-9913-2163) is a PhD researcher in rehabilitation sciences and physiotherapy in neurological diseases at the University of Antwerp. She is a physiotherapist who graduated in Brazil with research and clinical experience and has a master's in biomedical sciences with a focus on neuroscience from the University of Antwerp. Her main research focuses on understanding the neural and anatomical substrates for motor recovery after stroke. She is furthering her skills in diffusion MRI analysis and tractography along with biomechanical analysis of walking after stroke.

Dr. Jonas Schröder

Dr. Schröder (ORCID 0000-0003-0290-9923) is a physiotherapist and clinical researcher in the field of neurorehabilitation. He focuses on improving balance in people who suffer a stroke to prevent falls and promote an active lifestyle. During his PhD at the University of Antwerp, Jonas Schröder studied specifically adaptive balance strategies after stroke with biomechanical analysis. His goal is to aid the development of a new generation of technology-assisted, intensive rehabilitation therapies, as he is also involved in the development and validation of portable measurement technologies to introduce biomechanical movement assessments as clinical routines. He is currently employed as a teaching assistant and post-doctoral researcher at Hasselt University, Belgium. He

supports various projects related to balance control and walking function in neurological conditions, including stroke, cerebral palsy, and progressive MS.

Prof. Dr. Steven Truijen

Prof. Dr. Steven Truijen (ORCID 0000-0002-0604-1431) is appointed as a professor at the University of Antwerp, and founded the research group Movement Antwerpen, MOVANT. His research focuses on biomechanical movement analysis with statistical analysis and interpretation. The goal of his research is to add value in health care through multidisciplinary cooperation, which he has achieved as: (1) President of Centre for Health and Technology of the University of Antwerp, CHaT, (2) Co-founder of the Multidisciplinary Motor Centre Antwerp, M²OCEAN lab, Hercules Grant, located at the University Hospital Antwerp (4) founder of the research group Movement Antwerpen, MOVANT and (4) promotor of 4D4A lab, 4D scanner for Accelerating Advanced motion Analysis and Application (FWO grant: medium-scale research infrastructure, 2020). He supervises 7 PhD students and has supervised 19 PhDs to completion (H-index 39; WoS 168 publications; 4749 citations; author impact citation percentile 69%). Over the past five years, he has obtained more than 2 million euros of research funding as (co)promotor.

Prof. Dr. Wim Saeys

Prof. Dr. Wim Saeys (ORCID 0000-0001-8193-5016) is appointed as 70% tenure track assistant professor at MOVANT, University of Antwerp. He combines this position with a 30% clinical position as a neurological rehabilitation specialist (Physiotherapy) at the rehabilitation hospital RevArte. He has almost 20 years of clinical and scientific experience in stroke and spinal cord rehabilitation, mainly in the field of balance and gait recovery. His research focuses on stroke rehabilitation, looking at biomarkers of (early) recovery and optimization of treatment strategies by using technology-supported

rehabilitation. As co-promotor, he obtained the FWO 2020 Medium-sized Research Infrastructure grant (I002020N) to set up a full operational 4D analysis lab (4D4All) within the Rehabilitation Hospital RevArte. He supervised 8 PhD students and has supervised 5 PhDs to completion (H-index 15; 65 publications; 870 citations; author impact citation percentile 61%). His expertise has been recognized internationally, as shown by winning different awards (Belfius Smart Award (April 2019), ISPGR conference award (March 2021), YSPR ESO award (November 2020), De Luca Foundation Award (November 2020). As vice-chair of the interfaculty institute CHaT (Center of Health and Technology), he aims to stimulate and facilitating the uptake of health care technology in rehabilitation.

Prof. Dr. Laetitia Yperzeele

Prof. Dr. Yperzeele (ORCID 0000-0002-5503-5724) is a senior vascular neurologist at the Antwerp University Hospital (UZA) in Belgium and coordinator of the hospitals' stroke program. She obtained her PhD in Medical Sciences in 2016 at the Vrije Universiteit Brussel. She is an Associate Professor (20%) at the Faculty of Medicine and Health Sciences at the University of Antwerp. She has been the Leading investigator in academic clinical trials on prehospital stroke care (e.g. FACT, AP-19 IATS), and Site Principal Investigator for national and international academic research projects (e.g. Communicare), registries (eg. BEL-FMD, NOAC-ISP) and national leader for industry-led clinical trials (AXIOMATIC SSP, LIBREXIA stroke trial). She has authored 60+ PubMed registered papers, cited 900+ times (WoS H-index 17), supervised 2 successfully defended PhD theses, and 2 ongoing PhDs.

Are standing balance and walking ability deficits poststroke related to the integrity of the corticospinal and non-corticospinal tracts? A meta-analysis.

Abstract

Background: The importance of corticospinal tract (CST) integrity in upper limb recovery poststroke is well established, but its association with standing balance and walking remains unclear. This meta-analysis aimed to establish the relationship between CST and non-CST motor tract integrity, and clinical scores of standing balance and walking poststroke.

Methods: In July 2024, five databases were searched for studies, focusing on diffusion MRI metrics and clinical scores of standing balance and/or walking independence poststroke. Meta-analyses were conducted to pool correlation coefficients (r) and group differences (d) based on CST integrity.

Results: Twenty-two studies were included. Cross-sectional analysis showed no correlation ($r<.25$) between CST metrics and the functional ambulation category (FAC) in the sub-acute phase. Weak prognostic associations were found for CST-FA and CST-FN with FAC. Significant FAC score differences were found between preserved- and disrupted CST groups in the sub-acute ($d=.79$) and chronic ($d=1.07$) phase and for prognostic analysis ($d=1.40$). Non-CST metrics showed no cross-sectional associations and mixed prognostic associations.

Conclusions: CST integrity was not significantly associated with standing balance or walking independence in the sub-acute phase. Early CST integrity showed weak prognostic value for walking at 6 months. Multimodal longitudinal research is needed to improve lower limb recovery prognostics.

Keywords: dependent ambulation, diffusion magnetic resonance imaging, postural balance, stroke, walking

Introduction

Performing functional tasks such as standing balance and walking depends on the coordinated activation of trunk and lower limb muscles. Traditionally, it has been suggested that subcortical and spinal regions govern such muscle coordination (1–4). However, recent literature has opposed this view, as both cortical brain regions and their descending motor projections appear to be involved in orchestrating muscle activity for maintaining standing balance and walking (5,6). This is evident in clinical observations of patients who experience balance and walking deficits after a stroke (7).

Given the high prevalence and impact of balance and walking deficits on community participation and quality of life, achieving independent standing balance and walking is a prioritized rehabilitation goal after stroke (8–11). Current literature suggests a significant association between muscle strength of the hemiparetic leg and sitting balance in the early sub-acute phase, and with improved walking ability and degree of ambulation in the chronic phase (12). However, improvement of patient-tailored rehabilitation services requires further investigation of lower limb motor severity poststroke and predictors of recovery, as the current literature examined limited sample sizes, and an overall consensus is lacking (12,13). Therefore, the literature could gain greater insights into the neural correlates of balance and walking ability, which may improve clinical predictions.

To date, the most investigated descending pathway in relation to poststroke recovery is the corticospinal tract (CST)(5). Previous studies (14–25) have investigated associations between reduced CST integrity and upper limb motor recovery. This contributed to more accurate prediction models of upper limb recovery poststroke, when

used in addition to clinical scores, particularly in more affected patients (26,27). However, limited literature is available on the relationship between tract integrity and the severity at different timepoints, as well as the recovery of lower-limb motor skills in daily activities (28), hindering the development and testing of precise prediction models in this area. It is important to acknowledge the differences in motor control, as balance control and walking involve bilateral limb activation that is more "automated" than unilateral arm-hand movements (29,30). Other non-CST tracts could also be considered due to their role in trunk and proximal limb muscle activation e.g., corticoreticulospinal pathway (CRP)(15,31–34), vestibulospinal tract,(35) and tectospinal tract (36). In addition, research has suggested a role for the cortico-cortical pathways in controlling balance and walking, including the corticopontocerebellar and nigrostriatal tracts (37,38).

How damage or degeneration in the aforementioned tracts contributes to balance and walking deficiencies post-stroke remains largely unknown and has not yet been systematically investigated. Therefore, our primary objective was to examine the existing literature on how CST integrity is associated with the severity of standing balance and walking ability in the sub-acute (<6 months) and chronic phases (>6 months) poststroke by investigating cross-sectional correlations. Additionally, we want to examine possible differences between associations when measured in the sub-acute and chronic phase, as poststroke recovery mostly occurs within the first 6 months poststroke. We hypothesized, in line with research regarding upper limb measurements, that CST integrity was significantly positively associated with the ability to maintain standing balance and achieve walking independence in the chronic phase, such that patients with CST damage had worse clinical scores than those with a preserved CST (20,23,39). For our second objective, we aimed to examine the prognostic associations of CST integrity, measured within the first month, and balance and walking ability measured after 6 months

poststroke. Our third objective was to examine longitudinal changes in CST integrity and recovery of balance and walking ability poststroke. We hypothesize to identify associations, but with less powerful correlation coefficients, as for upper limb recovery, between prognostic associations and longitudinal changes in CST integrity and recovery of lower limb balance and walking ability. Acknowledging the suggested greater redundancy of bilateral and non-CST tracts innervating the lower limbs relative to the upper limb (20,40).

Furthermore, we examined all three objectives for non-CST tracts and how they are associated with standing balance and walking ability. We hypothesize that these tracts will also show significant associations with standing balance and walking independence for the cross-sectional correlations in the chronic phase as well as the prognostic and longitudinal associations, specifically the CRP due to its importance in trunk and proximal limb muscle activation.

Methods

Protocol and Registration

This systematic review was registered on PROSPERO (registration No. 289161) and adheres to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA) (Supplemental material: Table S2) (41). The research project was approved by the Medical Ethics Committee of the University Hospital Antwerp (EDGE-2251).

Definitions

A stroke is defined as a blockage of blood flow toward the brain that causes restriction of oxygen. Both ischemic (blocked arteries) and hemorrhagic (intraparenchymal bleeding) are included (42). Walking independence is defined as the

degree to which a person can ambulate safely, with or without an aid (including the use of non-motorized orthoses or assistive devices such as a cane), to conduct mobility-related activities of daily living (37,43). For this review, the term walking independence was used to encompass the varying degrees of walking ability in which a person can achieve the goal of independent walking poststroke. Clinical scales were used to represent walking independence (e.g., functional ambulation category (FAC), Functional independence measure (FIM)). Standing balance refers to the ability to regulate muscular involvement to maintain an upright position by maintaining the center of mass within the base of support (44–46). Standing balance was also measured using clinical scales on the activity level of the ICF (e.g., Berg Balance Scale (BBS), mini Balance Evaluation System test (mini BEStest), and Brunel Balance Assessment (BBA)). Clinical scores were interpreted as continuous scales for correlation analyses and as dichotomized scales to determine group categories.

Diffusion Magnetic Resonance Imaging (dMRI) is a specialized MRI technique used to visualize the movement (diffusion) of H-protons within biological tissue, particularly in the brain. White matter fibers can be observed using water diffusion anisotropy and evaluated by integrity metrics (47). The integrity of the neural structure was consequently defined as the state and quality of white matter in the brain, such as the CST and non-CST tracts and brain regions (e.g., CRP, dorsolateral prefrontal cortex, corticopontocerebellar tract, Vestibulospinal tract, parieto-insular vestibular cortex, and nigrostriatal tract) (31,32,34,48–50).

Integrity is reflected in the following MRI metrics: Fractional anisotropy (FA): measure of water diffusion direction; Mean diffusivity (MD): multidirectional water diffusion; Apparent diffusion coefficient (ADC): overall water diffusion; Fiber number (FN): synonym to terms referring to the number of neuronal fibers within the region of

interest; Fiber volume (FV): synonym to terms referring to the volume of the region of interest (47). The status of tract integrity is presented by values of diffusion metrics or the quality of tract preservation. The delineation of a tract was performed based on an FA threshold of 0.2 and an angle change of >45° (51–53). The following definitions are used to define the quality of the tract: "+" refers to a preserved tract and can be defined as a tract originating from the affected hemisphere's cortex and passing around the lesion to the medulla. Additionally, "-" stands for a disrupted tract, indicating tracts that were interrupted by the lesion at any location between their origination at the cortex until the medulla e.g., CST+: preserved CST; CST-; disrupted CST (38,50,54). Phases of stroke were defined as follows: hyperacute: 0-24 hours; acute: 1-7 days; early sub-acute: 7 days to 3 months; late sub-acute: 3-6 months; and chronic phase: after 6 months (55).

Studies were pooled according to phases containing spontaneous neurobiological recovery, including metabolic and neuroplastic changes, (all phases within the first 6 months poststroke) and the chronic phase in which neurobiological changes stabilize (55–57). Our research question defined three groups for examination. First, we considered studies that examined cross-sectional associations between dMRI and balance or walking independence. These studies were further divided into two subgroups: those within the sub-acute phase and those within the chronic phase (more than six months post-stroke)(58). Second, prognostic associations were investigated by assessing dMRI in the acute to early sub-acute phase and standing balance and/or walking independence in the chronic phase. Prognostic refers to the estimation of future risk of outcome based on specific characteristics (59). Lastly, longitudinal associations were examined, which encompassed studies that performed both dMRI and standing balance and/or walking independence assessments at multiple time points during stroke recovery (60).

Search Strategy and Study Selection

In July 2024, a systematic search was conducted using the databases of Pubmed, Web of Science, Scopus, Cochrane, and PEDro. The research queries were composed following a PICO strategy and included a combination of free-text terms and Medical Subject Headings (MeSH) terms. This information can be found in supplemental material: Table S1.

The following inclusion criteria were applied: 1) study designs such as cohort studies, cross-sectional observational studies, and randomized controlled trials; 2) adult population (≥18 years of age) diagnosed with infra- or supratentorial stroke (infarction or hemorrhage); 3) use of dMRI to assess the integrity of motor tracts and cortical regions 4) including clinical tests for walking independence or standing balance. Studies were excluded based on the following criteria: 1) study designs, such as meta-analyses, systematic reviews, case reports, and expert opinions; 2) studies reporting only lesion lateralization or location.

Two blinded independent reviewers (AvH and RL-C) screened the studies according to the title, abstract, and full text. The reference lists of the included studies were screened during full-text screening for secondary literature. Disagreements were successfully resolved through discussion among the raters.

Data Extraction and Analysis

Data from the included studies were independently extracted by two reviewers (AvH and RL-C), and disagreements were successfully resolved by discussion. A third reviewer (J.S.) was available for consultation if necessary. Parameters regarding the study and sample characteristics were collected and are presented in Table 1. The outcome characteristics and a summary of the imaging and clinical assessment results are presented in Table 2.

The strength of the relationship between diffusion metrics and standing balance, and walking independence scores was defined based on the correlation coefficient. Pearson's and Spearman's coefficient r values between 0 and .25 indicated no to very weak correlations. Weak correlations are defined as r values ranging between .25 and .50, whereas values ranging from .50 to .70 indicate a moderate correlation. Finally, r values between .70 and 1 are considered very strong to excellent correlations (61,62).

Differences between groups based on the state of CST integrity were pooled and presented as Cohen's d value. Benchmark suggestions by Cohen were used to interpret effect sizes. Effect sizes between .20 and .50 indicate small effect sizes. Moderate effect sizes range from .50 to .80 and d values >.80 indicate large effect sizes (63).

Quality Assessment

The risk of bias was independently assessed by two reviewers (AvH and RL-C) using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cross-sectional- and longitudinal cohort studies. The criteria of the scales were adjusted to be consistent with the research questions: Populations were specified as ischemic and hemorrhagic stroke patients, minimum sample size was set at N=15 as recommended (64), and validated tools were adapted to the quality of the description of MRI technique and analysis (supplemental material: Appendix 1). Cross-sectional studies were assessed using the NOS version adapted by Herzorg et al. (supplemental material: Appendix 2).

If all criteria were met, a maximum score of nine was given for longitudinal cohort studies, and a maximum score of ten was given for cross-sectional studies (65). The standard cut-off values of McPheeters et al. were used to determine the risk of bias and methodological quality (<5: poor, 5-6: moderate, ≥ 7: good). (66) Scores per study and criteria can be found separately for cross-sectional studies in Table S3 and longitudinal cohort studies in Table S4 in the supplemental material.

Descriptive Analysis and Statistics

Descriptive data were collected and categorized according to study and sample characteristics (study design, sample size, lesion type, lesion side, sex, age) and outcome characteristics (imaging type, imaging analysis, clinical tool, results on 1) associations and 2) differences).

A meta-analysis was performed of correlation coefficients when the results of two or more independent studies could be pooled either within the first 6 months or after 6 months. In addition, clusters are formed based on non-CST tracts and different diffusion parameters. Effect sizes were collected from the results section of the articles. A random-effects model with restricted maximum likelihood (REML) was used to calculate pooled effect sizes using IBM SPSS Statistics 28.0.0.0®. Heterogeneity among studies was assessed using Cochrane's Q tau-squared test, and I-squared (I^2), presented as a p-value. The degree of heterogeneity can be defined as low (I^2=.25-.50), moderate (I^2=.50-.75), and high (I^2>.75). (67)

Statistical Analysis

The study results were clustered according to the investigated tract (CST and non-CST) and the method of association. All cross-sectional results analyzed within the first 6 months and after 6 months post-stroke, were clustered together. Furthermore, all studies examining prognostic associations between dMRI findings obtained within the first month and standing balance of walking ability measured obtained during the chronic phase were pooled.

Results

Study Selection

We identified 8,465 studies in the databases and by hand search. After eliminating duplicates, 5,532 unique studies were screened, and 105 studies were included after screening the titles and abstracts. The following study designs were eligible for inclusion: cohort studies, cross-sectional studies, and RCTs. The main reason (n =17.9%) for exclusion was an incorrect outcome, specifically different imaging types than diffusion MRI. In total, twenty-two studies were included in the analysis (supplemental material: Fig 1. Flow diagram) (14,30,37,38,50,52,54,68–82).

Quality and Risk of Bias

Of the included studies, nine had a cross-sectional design (30,50,68–74), and thirteen studies had a longitudinal design (14,37,38,52,54,75–82). Eight studies with a longitudinal design investigated both cross-sectional correlations in the acute or early sub-acute phase as a prognostic factor, whereby early dMRI results were associated with clinical scores in the chronic phase (14,37,52,54,75,76,78,79). Disagreements regarding quality assessment between reviewers were resolved successfully during the discussion.

CST and non-CST Structures

The CST is the most investigated region of interest as nineteen studies investigated its integrity in relation to standing balance and walking independence, as measured using the FAC (30,37,50,52,54,68–81). Other white matter pathways and cortical regions that were included in the meta-analyses or descriptively included were the corticoreticulospinal pathway (CRP) (30,37,38,73), corticopontocerebellar tract/system (37,70,74), nigrostriatal tract (38), and parieto-insular vestibular cortex (14). The following pathways and regions were not included in the meta-analysis, but were

included in the descriptive results: dorsolateral prefrontal cortex; transcallosal fibers; primary motor cortex; red nucleus; cerebral peduncle; and middle cerebral peduncle.

Walking Independence and CST Integrity

CST integrity was cross-sectionally associated with the FAC in seven studies (N=309)(30,37,50,69,76,79,80). Results were graphed separately for the sub-acute phase (Fig 2) and chronic phase poststroke (Fig 3). Pooling of the cross-sectional correlations yielded no correlation between the CST integrity metrics separately - Fractional anisotropy (FA); Fiber number (FN), Fiber volume (FV), and Mean diffusivity (MD) - and FAC in the sub-acute phase (CST-FA: r=.18, 95%CI[.01;.35], random effects, N=3 studies, N=116 participants (30,37,50); CST-FN: r=.00, 95%IC=[-.37;.38], N=27 participants (37); CST-FV: r=.02, 95%IC=[-.19;.23], N=2 studies, N=89 participants (30,50); CST-MD: r=-.06, 95%IC=[-.39;.27], N=35 participants)(50). Jang et al. (69) found a moderate correlation between CST-FA (CST-FA: r=.50, 95%IC=[.34;.66], N=35 participants) and FAC and a weak correlation between CST-FN and FAC in the chronic phase poststroke (CST-FN: r=.47, 95%IC=[.30;.64], N=54 participants). A significant subgroup difference was found between the sub-acute cross-sectional correlations and the chronic cross-sectional correlations of CST-FA and FAC (p=0.01)(69)(Fig. 4). No correlation (r<.25, p>.05, N=53)(80) was found for the unaffected CST-FN and -FA with walking independence in both the sub-acute and chronic phases.

Pooling of prognostic correlations yielded weak correlations between CST-FA and FAC (CST-FA: r=.41, 95%CI[.21;.61], random effects, N=3 studies, N=116 participants) (37,76,79) and between CST-FN and FAC (CST-FN: r=.33, 95%IC=[-.23;.83], N=63 participants) (37,76) (Fig. 5).

Sub-analysis of between-group differences based on the state of CST integrity yielded a medium difference in sub-acute stroke (d=.79, IC=[.44-1.14], random effects,

N=5 studies, N= 176 participants)(50,68,77–79) (Fig. S1) and large group differences were found in cross-sectional analysis in the chronic phase (d=1.07, 95%CI=[.04;2.10], N=2 studies, N=61 participants)(Fig. S2)(69,72), and prognostic analysis (d=1.40, 95%CI=[1.01;1.79], N=7 studies, N=265 participants) (52,54,75–79) (Fig. S3).

Balance Performance and CST Integrity

The association between CST integrity and balance performance was investigated in four studies. In these studies, the CST-FA laterality index yielded no correlation with BBS in three studies investigating cross-sectional correlations in the sub-acute (r=-.18, 95%CI=[-.70;.35], random effects, N= 3 studies, N=200 participants)(Fig. S4)(71,74,81). Prognostic analysis yielded no correlation between CST-FA laterality index stroke (r<.25, N=79 participants)(81) and CST-FA (r<.25, N=27 participants) with BBS (37).

Walking Independence and non-CST Integrity.

Descriptive synthesis yielded mixed results for correlation strength in the sub-acute phase (Fig. S5). Regarding the CRP-FA, one study found no correlation (r<.25, 95%CI=[-.11;.41], N=54)(30) and another study found a weak correlation (r=-.33, 95%CI=[-.67;.01], N=27)(37). When looking into other non-CST tracts and regions in the sub-acute phase, a weak correlation was reported between the corticopontocerebellar tract-FA with FAC (r=-.38, 95%CI=[-.70;.05], N=27)(37). Another study found no correlation between parieto-insular vestibular cortex-FA and FAC (r<.25, N=28)(14).

Regarding other integrity values, no correlation was found for CRP-FN (r<.25, 95%CI=[-.32;.43}, N=27)(37) and corticopontocerebellar tract-FN (r<.25, 95%CI=[-.55;.18], N=27)(37) with FAC in sub-acute stroke. CRP-FV and FAC showed a weak correlation in sub-acute stroke (r=.46, 95%CI=[.24;.67], N=54)(30), and parieto-insular

vestibular cortex -FV showed no correlation with FAC (r<.25, 95%CI=[-.25;.48], N=27)(37). No cross-correlation analysis was performed in the chronic phase poststroke.

Minimal prognostic correlations were found (Fig. S6) between sub-acute CRP-FA and chronic measures of the FAC. One study found no correlation (r<.25, 95%CI=[-.03;.62], N=27)(37), and another study found a weak correlation (r=.29, 95%CI=[-.03;.62], N=30)(38). No prognostic correlations were observed between corticopontocerebellar tract-FA (r<.25, 95%CI=[-.23;.51], N=27)(37), parieto-insular vestibular cortex-FA (r<.25, 95%CI=[-.52;.20], N=28)(14), and nigrostriatal tract-FA (r<.25, 95%CI=[-.11;.57], N=30)(38) with FAC.

Regarding other integrity values examining prognostic correlations, no correlation was found for CRP-FN (r<.25, 95%CI=[-.39;.35], N=27)(37) and corticopontocerebellar tract-FN with FAC (r<.25, 95%CI=[-.12;.59], N=27)(37). The nigrostriatal tract-FV (r=.79, 95%CI=[.65;.92], N=54)(38) and CRP-FV (r=.82, 95%CI=[.70;.94], N=54)(38) yielded very strong correlations. No correlation was found for parieto-insular vestibular cortex-FV (r<.25, 95%CI=[-.31;.43], N=27)(14).

Balance Performance and non-CST Integrity

A moderate correlation was found for the cross-correlation between the inferior cerebral peduncle-FA and the BBS in sub-acute stroke (r=.63, N=27)(71). Prognostic correlations yielded moderate correlations for the cerebral peduncle-FA (r=.581, N=44)(82) and the middle cerebral peduncle-FA (r=.547, N=44)(82), and the laterality index of the cerebral peduncle (=(CP-FA affected side − CP-FA unaffected side)/(CP-FA affected side + CP-FA unaffected side)) (r=.573, N=44)(82). A weak prognostic correlation (r=<.50, N=44)(82) was found between the laterality index of the middle cerebral peduncle and the BBA.

Discussion

This literature study systematically reviewed the reported associations of the integrity parameters of the CST and non-CST pathways with clinical outcomes of standing balance and walking independence. Twenty-two medium-to-high quality studies, including 1011 stroke participants, could be included. This led to the following main findings: Regarding objective 1, our hypothesis was rejected because CST integrity was not found to be significantly associated with FAC or BBS scores in the sub-acute phase in a cross-sectional manner. Pooling of cross-sectional associations in the chronic phase was not possible because only one study was found (69). Regarding the second objective, our hypothesis was partially confirmed by a significant, but weak correlation between CST integrity measures obtained <1 month poststroke and the FAC at 6 months. However, no correlation was found regarding BBS. Regarding the third objective, no studies have been identified, thus creating a gap in the literature. Regarding the associations of the integrity of the CRP (i.e., FA, FV) and other non-CST tracts (corticopontocerebellar tract, nigrostriatal, parieto-insular vestibular cortex) with FAC, negligible to no correlations were found for cross-sectional associations and mixed results regarding prognostic associations, corroborating our expectations.

Our results regarding the primary objective indicate that despite significant associations between CST integrity and upper limb outcome after stroke, which led to the identification of prediction biomarkers (20,26), results regarding balance and walking are more ambiguous. In some reports (83,84), it has been reported that independent walking can be regained even after complete disruption of the lateral CST due to stroke. Cho et al. (83) therefore assumed that the CST is less critical for recovery from walking than upper limb recovery, arguing that walking relies less on distal muscle coordination, for which the CST is mainly responsible. Moreover, compensatory movement strategies, for

example, reliance on the less affected leg to maintain stability (85), could also explain task-related results. Our findings show that simple classification tools, such as the FAC, are insufficient to determine recovery phenotypes (e.g.; dependency on compensation and aids) based on neural damage profiles (86). Furthermore, clinical tests do not adequately distinguish recovery achieved through behavioral restitution or compensations during their evaluation (85). Although improvements in balance performance and walking independence are noticeable during the first 3 to 6 months poststroke, these improvements are closely associated with learning to use compensatory strategies as they solely measure task accomplishment (13,87–89). Therefore, a variety of mechanisms can be responsible for improvements in walking and standing balance. In other words, activities can be restored in the more-affected subjects with greater neural damage by relying on less impaired body segments, such as the less affected limb (88,90). Specific outcomes such as between-limb synchronization and dynamic control asymmetry are recommended to reflect changes due to "true neurological recovery".(91) Therefore, it represents the level of behavioral restitution, which can be categorized on the anatomy and body function of the ICF, like diffusion MRI. Nonetheless, erecting against gravity remains challenging, making walking independence difficult to achieve (92,93). This difficulty was suggested to be more common in individuals with disrupted CST. This could explain our subsequent finding of significant between-group differences based on the state of CST integrity (CST+; CST-), with patients possessing a preserved CST generally showing higher levels of walking independence.

Our results regarding our secondary objective suggest the potential of using CST integrity metrics to improve the prediction of recovery outcomes when obtained < 1 month poststroke. DMRI was conducted within 7 days and 1 month in most studies, and avoided early acute, due to the effect of Wallerian degeneration, which has been

associated with worse motor outcomes at 2, 3, and 4 weeks poststroke (94–96). Better patient selection methods, with sufficient statistical power based on the stratification of biological capacity to recover, such as for the upper limb, are still non-existent. Biomarkers could be used to prognostically determine a patient's potential to show recovery and regain safety in basic activities of daily living, such as walking, to inform treatment strategies (26,87,97,98). However, we should be cautious about the promise of MRI-related biomarkers, as the added value of imaging markers is still unknown compared with existing clinical markers, such as sitting balance (12,99), due to the lack of multimodal prognostic models in this field. Therefore, you could wonder whether CST integrity is necessary to adequately predict standing balance and walking ability outcomes to improve or overrule currently available clinical prediction models (12,99). No scientific literature was found to examine our third objective.

Regarding the results of the correlation between the integrity of non-CST tracts and standing balance and walking independence, no associations were identified. However, there is evidence in scientific literature for a higher redundancy of bilateral and alternative descending pathways that are important for postural balance and walking, relative to the upper limb (30),(27)) Because of this, a one-on-one relationship between a single tract's integrity and walking independence or standing balance after stroke, as investigated in most included studies, is unlikely to yield strong associations by explaining residual functioning (12,29).

Our findings suggest the need for further research into the relevance of CST and non-CST integrity in relation to standing balance and walking independence. Future research should investigate longitudinal changes, starting in the acute phase poststroke, of both white matter integrity and lower limb motor function. Due to the evident high

redundancy of descending and horizontal tracts, future research should also include the analysis of multiple tracts, such as the CST and CRP combined (15,100,101).

Furthermore, to assess the quality of movement, we recommend incorporating biomechanical analyses of standing balance and walking (90,102). Based on this, we hypothesize that there will be a significant association between the combined fiber density of the corticospinal tract (CST) and cortico-reticular pathway (CRP) and biomechanical measures of standing balance, which would reflect movement quality rather than mere task completion.

Limitations

First, only a limited number of studies, most including a small sample size, were found eligible. This may have affected the power of significant associations in this review. Furthermore, the included studies showed heterogeneity in the measurement time points of both dMRI and the clinical assessments, and in the brain regions of interest and diffusion metrics. This hindered the pooling of results. For this reason, studies were grouped within two timeframes (sub-acute and chronic) because most measurements were performed within these phases. Second, the total group effect size was not calculated for the different analyses because multiple correlation coefficients coming from the same article and population belonged within the same pool of meta-analyses, leading to bias. A third limitation is that our results are restricted to clinical assessments that allow for compensation strategies.

Therefore, recommendations are provided to include kinetics and kinematics to measure the extent of recovery of daily activities achieved through restitution. Finally, motor-evoked potentials detected by TMS could have been beneficial to include as a functional integrity measurement because they have been associated with the walking ability and structural damage to CST integrity (12,103). However, TMS does not capture

the broader neural network involved in walking and balance because it primarily assesses CST function (104). Moreover, patient discomfort during TMS procedures and the requirement for specialized expertise for accurate interpretation further complicate its routine use in clinical settings for predicting lower limb outcomes (105,106). While motor-evoked potentials by TMS remain a strong biomarker, our review prioritized dMRI for its ability to provide a comprehensive assessment of multiple motor tracts.

Conclusion

This review found that contrary to the hypothesis for our first objective, CST integrity was not significantly associated with standing balance or walking independence in the sub-acute phase, indicating that CST disruption does not necessarily preclude the ability to walk. For our second objective, we identified a weak but significant correlation between early CST integrity and walking independence at 6 months poststroke, suggesting some prognostic value. However, studies on non-CST are lacking, limiting our understanding of their potential role in recovery. These findings underscore the complexity of using CST and non-CST integrity as prognostic indicators. Future research should prioritize multimodal, longitudinal studies with integrated biomechanical analyses to more accurately predict and understand lower limb recovery poststroke.

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Declaration of interest

The authors declare that the research was conducted in the absence of any potential conflict of interest.

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Tables

Table 1. Summary of sample characteristics

Table 1 | Summary of sample characteristics

Reference	Design	Sample	Lesion type	Lesion side	Sex	Age
Cho et al. 2007	C-P	n=40 CST+=10 CST+/-M1=12 CST-=10 CSTd=8	H=40	R = 13, L = 27	M=21; F=19	53 (10)
Choi et al. 2021	C-R	n=110 CST+/DLPFC- CST+/DLPFC+ CST-/DLPFC- CST-/DLPFC+	I=110	R=23; L=29	NA	65 (11)
Jang et al. 2008	C-P	n=25 CST+=13 CST-=12	I=25	R=15; L=10	M=11; F=14	62 (43–80)
Jang et al. 2009	CS	n=40 A>U U>A TCF-=30	I=40	R= 17 L=23	M=20; F=20	59 (23-77)

		TCF-=19				
		TCFd-U=3				
		TCFd-U=7			HC:M=17; F=9	HC= 46 (19-79)
		TCFd=7				
		TCFd=14				
		HC=26				
Jang et al. 2013 (NS)	C-R	n=21	H=21	R=12; L=9	M=6; F=15	66 ± 9 (47-80)
		CST+=11				
		CST-=10				
Jang et al. 2013 (S)	CS	n=54	H=39; I=15	/	M=39; F=16	54 (32–75)
		FAC<3=20				
		FAC≥3=34				HC= 53 (33-72)
		HC=20				
Jang et al. 2014	CS	n=82	H=49; I=33	R=46; L=36	M=54; F=28	53 (12)
		CST+=23				
		CST-=17				
		CSTd=42				
Jang et al. 2015	CS	n=35	H= 35	R=14; L=21	M=22; F=13	53 (12)
		CST+=13				
		CST-=22				
Jang et al. 2022 (HC)	C-R	n=31	I=31	R=15; L=16	M=14; F=7	
		CST+=24				CST+= 59 (12)
		CST-=7				CST-= 48 (16)

Jang et al. 2022 (M)	C-R	n=30	I=30	NA	M=15; F=15	57 (11)
Jun et al. 2021	C-R	n=27 High=6 Mod=8 Low=13	H=5; I=22	R=12; L=15	M=16; F=11	high=61 (56-67) mod=76 (63-81) low=64 (34-74)
Kim et al. 2013	C-R	n=37 CST+=16 CST-=9; C CSTd=12	I=37	R=16; L=21	M=28; F=9	57 (27–81)
Kim et al. 2018 (NSA)	CS	n=33 HC=17	H=9; I=24	R=15; L=18	M=16; F=17 HC: M=9; F=8	64 (14) HC= 63 (12)
Kim et al. 2018 (NR)	C-P	n=48 CST+=16 CST+/-M1=15 CST-=17	H=8; I=40	R=29; L=19	M=34; F=14	63
Kim et al. 2021	CS	n=27 HC=27	H=27	/	M=15; F=12	61 (17) HC= 61 (15)
Kwak et al. 2010	C-P	n=53 HC=40	H=53	NA	M=27; F=26; HC: M=20; F=20	56 (10) HC= 59 (11)
Lee et al. 2021	CS	n=94	H=47; I=47	R=40; L=54	M=45; F=49	61 ± 14

Lee et al. 2023	C-P	n=79	H=32;	R=31; L=48	M=37; F=42	61 (51-73)
			I=47			
Park et al. 2021	C-P	n=28	/	R=12; L=16	M=14; F=14	
		PIVC-=16				PIVC-=61
		PIVC+=12				PIVC+=64
Seo et al. 2014	CS	n=16	H=8;	R=10; L=6	M=12; F=4	54 (7)
		CST+=8	I=8		HC: M = 12	
		CST-=8				HC=27 (3)
		HC=12				
Wang et al. 2023	C-P	n=44	H=20;	R=44; L=0	M=36; F=8	59 (9)
			I=24			
		HC=19			HC=M=11; F=8	HC= 56 (7)
Yoo, 2014	CS	n=57	H=57	R=31; L=26	M=37; F=20	55 (34-74)
		CST+/CRP+=3				
		CST-/CRP+=4				
		CST+/CRP-=13				
					HC: M=36; F=21	HC= 53 (33-67)
		CST-/CRP-=37				
		HC=57				

Abbreviations: CS: cross-sectional; C-P: cohort-prospective; C-R: cohort-retrospective; HC: healthy control; CST: corticospinal tract; CRP: corticoreticulospinal tract; DLPFC: dorsolateral prefrontal cortex; TFC: Transcallosal fibers; PIVC: parieto-insular Vestibular cortex; M1: primary motor cortex; "+": preserved; "-": disrupted; "d": degenerated; H: hemorrhage; I: ischemic; M: male; F: female; R: Right; L: Left.

Values are means (SD). Demographics and stroke information were collected from all included studies (total: 22)

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816 Table 2. Summary of Results about Imaging and Clinical Tools

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Table 2 | Summary of results about imaging and clinical tools

CST structural connectivity

Ref.	D	Imaging type	Imaging analysis	clinical tool	Results	Conclusion
Cho et al. 2007	C-P	dMRI	CST structural connectivity	FAC	Onset: no differences in the FAC score between CST conditions 6m: difference in FAC score between CST conditions (P=.0003) CST+> CST+/-M1 > CST- > CSTd	Onset: No difference in walking independence between CST conditions. 6m: More CST+ patients have full walking independence, followed by CST+/-M1, CST- and CSTd.
Jang et al. 2008	C-P	dMRI	CST structural connectivity	FAC	Onset: no differences in the FAC score between CST conditions. (p = .103). 6m: all patients walked independently. 77% of CST+ patients and 8% of CST- had a FAC score of 5. Onset-6m: FAC score improvement of CST+ patients were higher than CST- (P=.001) 6m outcome prediction: CST condition showed good accuracy. (FAC: AUC=.843; SE=.09, P=.004).	Onset: no difference in walking independence between CST conditions 6m: More CST+ patients achieved the highest score on walking independence compared to CST-. Onset-6m: CST+ showed better walking independence recovery than CST-. 6m outcome prediction: CST condition at the early stage of a pontine infarct can help predict the FAC score.
Jang et al. 2013 (NS)	C-R	dMRI	CST structural connectivity	FAC	Onset: no differences in the FAC score between CST conditions 6m: CST+ had better FAC scores than CST- (P=.025). 6m: positive correlation between FAC and FA ratio, FN, and FL of CST (FA-FAC: r=.455, P=.038; FN-FAC: r=.602, P=.004; TL - FAC: r=.600, P=.004).	Onset: no difference in walking independence between CST conditions 6m: CST+ patients walked more independently. 6m: integrity of structural connectivity of the CST (FA, FN, and FL) was correlated to walking independence.

Jang et al. 2014	CS	dMRI	CST structural connectivity	FAC	6m: positive correlation between FAC and FA and FN ratios of CST (P<.05; r =.50, .47). 6m: CST+ > CSTd on FAC scores CST- > CSTd on FAC scores CST+ = CST- on FAC scores	6m: integrity of structural connectivity of the CST (FA and FN) was correlated to walking independence. 6m: CST+ patients had higher walking independence than CSTd. CST- patients had higher walking independence than CSTd. CST+ and CST- patients were not different
Jang et al. 2013 (S)	CS	dMRI	CST and CRP structural connectivity	FAC	>3m: FAC<3 < HC on FA values of CST-U No difference between FAC<3, FAC≥3, and HC on ADC, FV values of CST-U	FAC<3 showed lower FA values of the CST-U than HC.
Jang et al. 2015	CS	dMRI	CST structural connectivity	FAC	>2m: CST+ > CST- on FAC scores (P<.05) No correlation between FAC scores and FA, MD, and FV of the RN (P>.05).	>2m: CST+ patients had higher walking independence than CST- The integrity of structural connectivity of the RN (FA, MD, FV) was not correlated to walking independence.
Jang et al. 2009	CS	dMRI	CST structural connectivity	FAC	≤3m: no difference between TFC conditions on FAC from -U to -A and -A to -U. U -> A: TFC- = TFCd = TFCd-U on FAC (P=.157) A-> U TFC- = TFCd = TFCd-U on FAC (P=.887)	<3m: no difference in walking independence between the TFC condition of the CST.
Jang et al. 2022 (HC)	C-R	dMRI	CST integrity	FAC	Onset (12.58-4.34d): CST+ > CST- (P<.005) Onset – chronic: CST+ improved on FAC (P<.005) CST- improved on FAC (P<.005) Chronic: CST+ > CST- (P<.005)	Onset: CST+ patients had higher walking independence than CST- Onset – Chronic: Mean FAC score improved significantly in all CST conditions. Chronic: CST+ patients had higher walking independence than CST-

Jun et al. 2021	C-R	dMRI	CST, CRP, and CPCT structural connectivity	FAC, BBS	1m: No significant association between the FAC FN and FA of CST 6m: No significant association between the FAC FN and FA of CST	1m: Integrity of the CST (FA and FN) was not correlated to walking independence. 6m: Integrity of the CST (FA and FN) was not correlated to walking independence.
Kim et al. 2018 (NSA)	CS	dMRI	CST and CPCT structural connectivity	FAC	<2m: no correlation between FAC and volume CST-A. No correlation between FAC and volume CST-U No correlation between FAC and TV_AI CST	<2m: integrity of the CST (TV_AI, V-U, V-A) was not correlated to walking independence.
Kim et al. 2018 (NR)	C-P	dMRI	CST structural connectivity	FAC	Baseline: CST+ = CST- = CSTd on FAC 2y: CST+ = CST- on FAC Baseline-2year: FAC score improved but CST+ = CST- = CSTd.	Baseline: no difference in walking independence between CST conditions. 2y: CST+ and CST- had higher walking independence than CSTd but not significant. Baseline-2y: CST+, CST- and CSTd showed similar independent walking recovery.
Kim et al. 2013	C-R	dMRI	CST structural connectivity	FAC	Onset: CST+ = CST- = CSTd on FAC Onset – 6m: CST+ > CST- on FAC CST+ > CSTd on FAC CST- = CSTd on FAC 6m: CST+ > CST- on FAC CST+ > CSTd on FAC CST- = CSTd on FAC Positive correlation between FAC scores and FA ratio (P=.002, r=.500).	Onset: no difference in walking independence between CST conditions. Onset – 6m: CST+ patients had higher independent walking recovery than CST- and CSTd. The mean FAC score improved significantly in all CST conditions. 6m: CST+ had higher walking independence than CST- and CSTd. The integrity of structural connectivity of the CST (FA ratio) was positively correlated to walking independence. Infarct volume was negatively correlated to walking independence.

Kwak et al. 2010	C-P	dMRI	CST structural connectivity	FAC	Onset: no correlation between FAC scores and FN CST-U (P=.081) No correlation between FAC scores and the FA value of CST-U (P=.109) Time of DTT: no correlation between FAC scores and FN CST-U (P=.467). No correlation between FAC scores and FA value CST-U (P=.396).	Onset: The integrity of structural connectivity of the CST-U (FN and FA value) was not correlated to walking independence. Time of DTT: integrity of structural connectivity of the CST-U (FN and FA value) was not correlated to walking independence.
Lee et al. 2023	C-P		CST	BBS	1m: FA_LI of the CST was correlated with BBS scores at 3 (r=-.468) and 6 months (r=-.462) poststroke	1m: integrity of the CST (FA_LI) was correlated with standing balance performance.
Seo et al. 2014	CS	dMRI	CST structural connectivity	FAC	Chronic: CST+= CST- on FAC (P=.334)	Chronic: no difference in walking independence between CST conditions

CST/Non-CST & non-CST structural Connectivity

Reference	Design	Imaging type	Imaging analysis	clinical tool	Results	Conclusion
choi et al. 2021	C-R	dMRI	CST, thalamus-DLPFC structural connectivity	FAC	Initial: CST+ group: CST+/DLPFC+ = CST+/DLPFC- on FAC. CST- group: CST-/DLPFC+ = CST-/DPLFC- on FAC CST+ = CST- on FAC Initial-6m: CST+ group (CST+/DLPFC+ = CST+/DLPFC-) improved on FAC CST- group (CST-/DLPFC+ = CST-/DPLFC- improved on FAC 6m: CST+ group: CST+/DLPFC+ = CST+/DLPFC- on FAC. CST+/DLPFC- > CST-/DPLFC- on FAC CST+ > CST- on FAC	All CST+ showed similar results on walking independence regardless of DPLFC condition. CST-/DLPFC+ showed better walking independence recovery than CST-/DLPFC-, resulting in a higher walking independence score at 6m.

Jang et al. 2013 (S)	CS	dMRI	CST and CRP structural connectivity	FAC	>3m: No difference between FAC<3 and FAC≥3 on incidence of CRP injury FAC≥3 CRP+ > FAC≥3 CRP- on FAC No difference between FAC<3 and FAC≥3 on FA, ADC, and FV values of CRP-A FAC≥3 > FAC<3 and HC on FV values of CRP-U No correlation between FAC scores and the FV of the CRP-A, but a moderate positive correlation to the FV of the CRP-U (P=0.006)	No difference between walking independence groups on the incidence of CRP injury The group with better walking independence scores (FAC3-5) with an intact CRP shows higher walking independence scores than with injured CRP. FAC≥3 showed higher FV volumes of the CRP-U than FAC<3 and HC. Walking independence only showed a correlation with the FV of the CRP-U. No correlations were shown between FAC and CST parameters or FA and ADC of the CRP.
Jang et al. 2022 (M)	C-R	dMRI	NST, CRP	FAC	Initial (dMRI) – chronic (FAC): no correlation between FAC and FA of NST (r=.288; P=.23) and CRP (r=.295; P=.11) Significant correlation between FAC and FV of NST (r=.786; P=.00) and CRP (r=.821; P=.00) Association between FAC and FV of NST (β = .362)and CRP (β = .532) (Adjusted R2=.70, F=34.91, P< .05)	Initial (dMRI) – chronic (FAC): Walking independence did not correlate with FA values of the NST or CRP. Walking independence did correlate and associate with FV values of the NST and CRP.
Jun et al. 2021	C-R	dMRI	CST, CRP, and CPCT structural connectivity	FAC, BBS	1m: No significant association between the FAC and FN and FA of CRP and CPCT 6m: No significant association between the FAC and FN and FA of CRP and CPCT	1m: Integrity of the CST, CRP, and CPCT (FA and FN) were not correlated to walking independence. 6m: Integrity of the CST, CRP, and CPCT (FA and FN) were not correlated to walking independence.
Kim et al. 2018 (NSA)	CS	dMRI	CST and CPCT structural connectivity	FAC	<2m: no correlation between FAC and volume CPCT-A. No correlation between FAC and TV_AI CPCT	<2m: integrity of the CPCT (AITV, V-U, V-A) was not correlated to walking independence.

Kim et al. 2021	CS	dMRI	ICP/dSCP and CST structural connectivity	BBS	<2m: Correlation between FA_LI ICP and all severities of BBS (moderate: p=.002; severe: p=.039; mean p=.002) No correlation between FA_LI CST and all severities of BBS (moderate: p=.317; severe: p=1.000; mean r=.389, p=.082)	Integrity of the ICP (FA laterality index) correlated with both the moderate and severe scores of BBS and the mean BBS score. The laterality index for integrity of the CST (FA) did not correlate with the balance performance.
Lee et al. 2021	CS	dMRI	whole brain (CPCS, CST) structural connectivity	FAC	Acute: association between FAC score and FA of the CPCS at the lesioned midbrain and non-lesioned middle CP Association between FAC score and FA of the non-lesioned CST at medial lemniscus at the bilateral midbrain Association between FAC scores and MO values of the lesioned posterior corpus callosum BBS was negatively associated with FA_LI of the CST (r=-.406, p<.001)	A positive correlation has been found between FA-values in theCPCS and corona radiata of the -A hemisphere, the CST, bilateral medial lemniscus in the brainstem, and the corpus callosum of the -U hemisphere, and walking independence. A positive correlation has been found between the MO values of the posterior corpus callosum and walking independence. Balance performance was negatively associated with laterality index for integrity of the CST (FA)
Park et al. 2021	C-P	dMRI	PIVC structural connectivity	FAC	Early sub-acute: no correlation between FAC and FA, MD, and tract volume of the PIVC-A. Correlation between FAC and MI scores early sub-acute, late sub-acute, and at 6 months. Late sub-acute: correlation between FAC and FA of PIVC-A. No correlation between FAC and MD, TV of the PIVC-A 6m: no correlation between FAC and FA, MD, TV of PIVC-A Correlation between FAC early sub-acute, late sub-acute, and at 6 months.	Early sub-acute: walking independence was not correlated with DTI parameters of the PIVC-A. Walking independence was correlated with MI scores during the whole recovery process. Late sub-acute: walking independence was correlated with the FA value of the PIVC-A but not with the MD and tract volume of the PIVC-A. 6m: walking independence was not correlated with DTI parameters of PIVC-A. Walking independence was correlated with MI scores during the whole recovery process.

Wang et al. 2023	C-P	dMRI	CP and MCP	BBA	Chronic: Correlation between BBA and rFA of the CP (r=.581; p=.00) and MCP (r=.547; p=.004) Correlation between BBA and FA_LI of the CP (r=.573; p=.00) and MCP (r=.452; p=.022)	The rFA of the CP was more significantly positively correlated with the 1-year BBA score. The LI of the CP was significantly positively correlated with the 1-year BBA score. the LI of the CP had a more significant association with 1-year BBA as compared to the LI of the MCP
Yoo et al. 2014	CS	dMRI	CST and CRP structural connectivity	FAC	8-30d: CST+/CST- = CST-/CRP+ = CST+/CRP- > CRP-/CST- on FAC No correlation between FAC scores and mV	patients with injury of the CST and CRP showed worse independent walking scores than patients with injury of either the CST or CRP or no injury at all in the early sub-acute phase. These results suggest the necessity for evaluation of both the CRP and the CST in patients with putaminal hemorrhage.

CS: cross-sectional; C-R: cohort-retrospective; C-P: cohort-prospective; dMRI: diffusion magnetic resonance imaging; HC: healthy control; CST: corticospinal tract; CRP: corticoreticulospinal tract; DLPFC: dorsolateral prefrontal cortex; TFC: Transcallosal fibers; PIVC: parieto-insular Vestibular cortex; M1: primary motor cortex; RN: Red nucleus; CP; cerebral peduncle; MCP: middle cerebral peduncle; "+": preserved; "-": disrupted; "d": degenerated; H: hemorrhage; I: ischemic; FA: Fractional Anisotropy; rFA: ratio FA; ADC: Apparent Diffusion Coefficient; FL: fiber length; FN: fiber number; MD: mean diffusivity; FV: fiber volume; LI: laterality index; MO: mode of anisotropy; mV: milliliter volume; AITV: asymmetry index based on tract volume; FAC: functional ambulation category; BSS: Berg balance scale; BBA: Brunel Balance Assessment; -U: unaffected; -A: affected; peduncle >: Significantly higher; ≥; higher, not significant; <: significantly lower; =: no significant difference.

Tables caption

Table 1. Summary of sample characteristics

Table 2. Summary of Results about Imaging and Clinical Tools

Figures

Fig. 1.

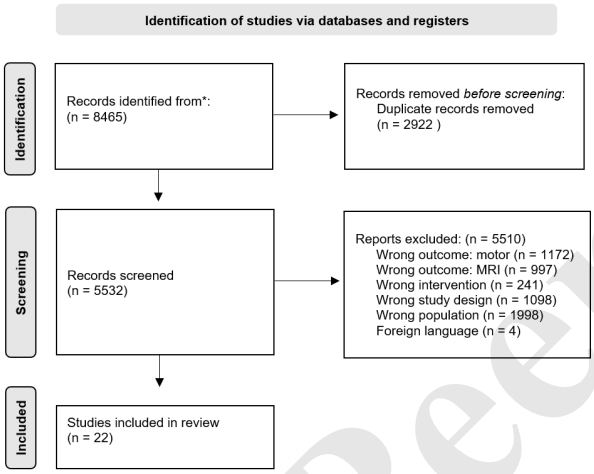
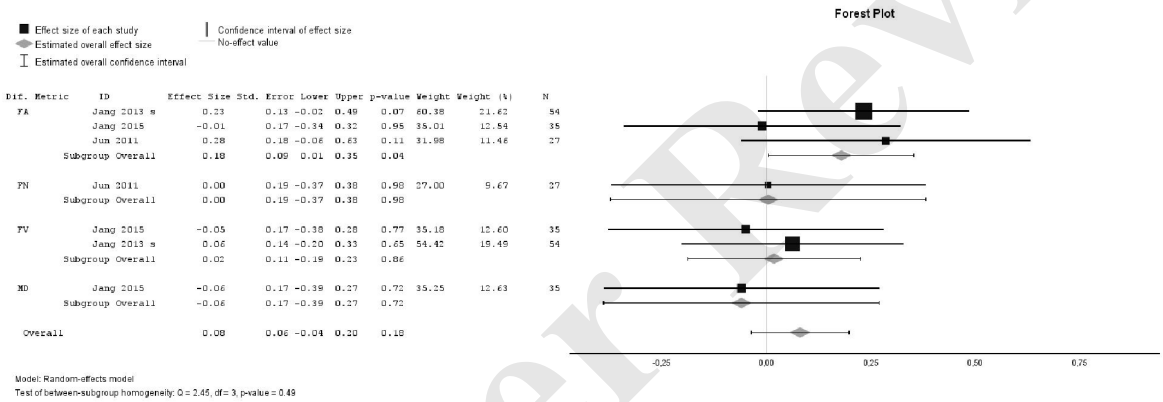


Fig. 2.



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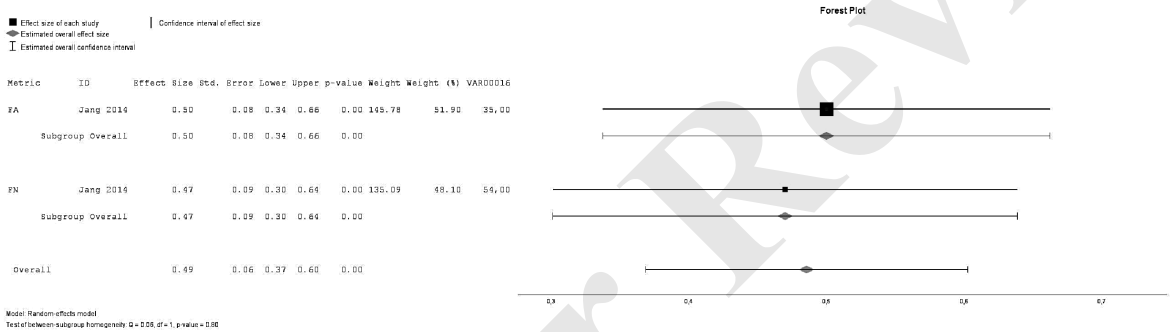

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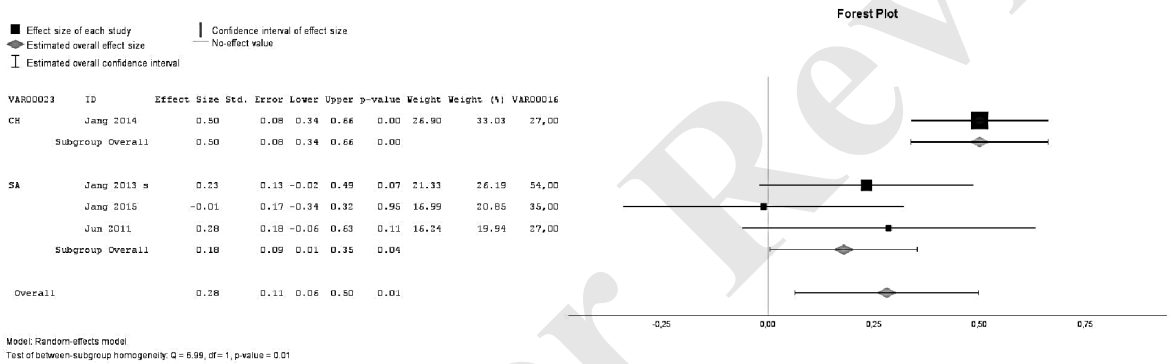
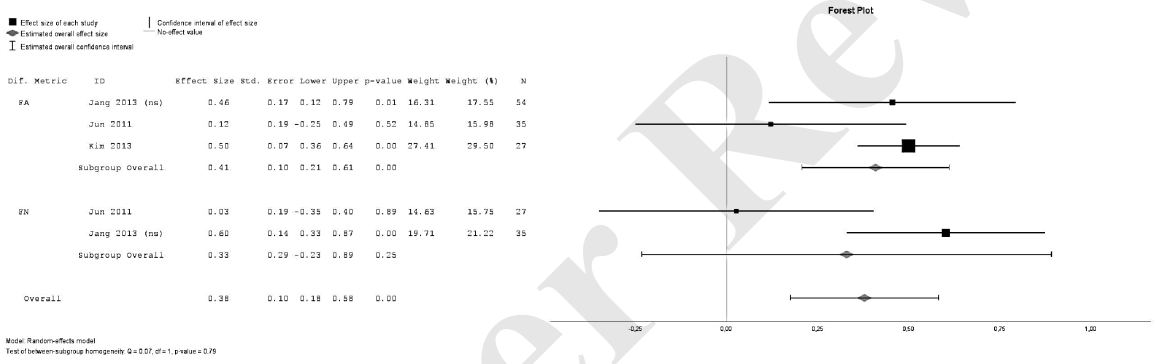


867

868 Fig. 5.



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Figures captions

Fig. 1. Flow diagram

Fig. 2. Cross-sectional associations between CST integrity metrics and FAC in the sub-acute phase.

Fig. 3. Cross-sectional associations between CST integrity metrics and FAC in the chronic phase.

Fig. 4. Differences between the sub-acute cross-sectional associations between CST-FA and FAC, and the chronic cross-sectional association.

Fig. 5. Prognostic associations between CST integrity metrics measured within the first months poststroke, and FAC, measured in the chronic phase poststroke.

Supplemental Material

Tables.

Table S1. Search strategy terms

Table S1 | Search strategy terms

Database	Search strategy
Pubmed	((("stroke"[MeSH Terms] OR "stroke"[All Fields] OR "brain ischemia"[All Fields] OR "brain Infarct"[All Fields] OR "cerebral infarction"[All Fields] OR "cerebral infarct"[All Fields] OR "cerebral haemorrhage"[All Fields] OR "cerebral hemorrhage"[All Fields] OR "cerebrovascular events"[All Fields]) AND "motor function"[All Fields] OR "walking independence"[All Fields] OR "FAC"[All Fields] OR "functional ambulation category"[All Fields] OR "gait"[MeSH Terms] OR "locomotion"[MeSH Terms] OR "dependent ambulation"[MeSH Terms] OR "postural balance"[MeSH Terms] OR "balance scale"[All Fields] OR "postural control" [All Fields] OR "balance assessment"[All Fields] OR "balance test"[All Fields] AND ("Magnetic Resonance Imaging"[Mesh] OR "diffusion Magnetic Resonance Imaging"[All Fields] OR ("diffusion" [All fields] AND "magnetic" [All Fields] AND "resonance" [All Fields] AND "imaging"[All Fields]) OR "dmri"[All Fields] OR "diffusion mri"[All Fields] OR "diffusion weighted imaging"[All Fields] OR "DWI"[All Fields] OR "diffusion tensor imaging"[All Fields] OR "DTI"[All Fields] OR "diffusion tensor tractography"[All Fields] OR "diffusion tractography"[All Fields])
Web of Science	(TS=("Stroke" OR "Brain Ischemia" OR "Brain Infarct" OR "Cerebral Infarction" OR "Cerebral Infarct" OR "Cerebral Haemorrhage" OR "Cerebral Hemorrhage" OR "Cerebrovascular Events") AND TS=("Motor Function" OR "Walking Independence" OR "FAC" OR "Functional Ambulation Category" OR "Gait" OR "Locomotion" OR "ambulation" OR "Postural Balance" OR "Balance Scale" OR "Postural Control" OR "Balance Assessment" OR "Balance Test") AND TS=("Magnetic Resonance Imaging" OR "Diffusion Magnetic Resonance Imaging" OR "Diffusion MRI" OR "Diffusion Weighted Imaging" OR "DWI" OR "Diffusion Tensor Imaging" OR "DTI" OR "Diffusion Tensor Tractography" OR "Diffusion Tractography"))
Cochrane Library	((("Stroke" OR "Brain Ischemia" OR "Brain Infarct" OR "Cerebral Infarction" OR "Cerebral Infarct" OR "Cerebral Haemorrhage" OR "Cerebral Hemorrhage" OR "Cerebrovascular Events") AND "Motor Function" OR "Walking Independence" OR "FAC" OR "Functional Ambulation Category" OR "Gait" OR "Locomotion" OR "ambulation" OR "Postural Balance" OR "Balance Scale" OR "Postural Control" OR "Balance Assessment" OR "Balance Test") AND ("Magnetic Resonance Imaging" OR "Diffusion Magnetic Resonance Imaging" OR "Diffusion MRI" OR "Diffusion Weighted Imaging" OR "DWI" OR "Diffusion Tensor Imaging" OR "DTI" OR "Diffusion Tensor Tractography" OR "Diffusion Tractography"))
PEDro	Stroke, muscle weakness, magnetic resonance imaging
SCOPUS	TITLE-ABS-KEY (("Stroke" OR "Brain Ischemia" OR "Brain Infarct" OR "Cerebral Infarction" OR "Cerebral Infarct" OR "Cerebral Haemorrhage" OR "Cerebral Hemorrhage" OR "Cerebrovascular Events") AND ("Motor Function" OR "Walking Independence" OR "Gait" OR "Locomotion" OR "ambulation" OR "Postural Balance" OR "Balance Scale" OR "Postural Control" OR "Balance Assessment" OR "Balance Test") AND ("Magnetic Resonance Imaging" OR "Diffusion Magnetic Resonance Imaging" OR "Diffusion MRI" OR "Diffusion Weighted Imaging" OR "DWI" OR "Diffusion Tensor Imaging" OR "DTI" OR "Diffusion Tensor Tractography" OR "Diffusion Tractography"))

Table S2. PRISMA 2020 Checklist

Table S2 | PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	P1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P3-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P3-5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Figurs
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Figures
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P7-8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Tables
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Tables
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	P8 & tables
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	P11-14
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	P5-6; 10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	P9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Tables
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	P9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	P9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	P9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	P8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	P8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Tables
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Tables
Study characteristics	17	Cite each included study and present its characteristics.	Tables

Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Tables
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	P11-14 & figures
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	P11-14
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P11-14 & figures
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	P11-14 & figures
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	P11-14 & figures
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	P11-14 & tables
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	P11-14 & tables
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P14-15
	23b	Discuss any limitations of the evidence included in the review.	P16
	23c	Discuss any limitations of the review processes used.	P16
	23d	Discuss implications of the results for practice, policy, and future research.	P15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	P5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	P5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P17
Competing interests	26	Declare any competing interests of review authors.	Cover letter
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Table S3: Risk of Bias Cross-sectional Associations

Table S3: Risk of Bias of cross-sectional studies

Reference	D	S1	S2	S3	S4	C1	O1	O2	Total	Score
Jang 2009	CS	−	+	−	+	−	+	+	4	POOR
Jang 2013 (s)	CS	+	+	−	⊕	−	⊕	+	7	GOOD
Jang 2014	CS	+	+	−	⊕	⊕	⊕	+	9	GOOD
Jang 2015	CS	−	+	−	⊕	⊕	+	+	7	GOOD
Kim 2018 (nsa)	CS	−	+	−	⊕	+	−	+	6	MOD
Kim 2021	CS	−	+	+	⊕	+	+	+	7	GOOD
Lee 2021	CS	+	+	−	+	−	+	+	5	MOD
Seo 2014	CS	+	+	+	+	⊕	+	+	8	GOOD
Yoo 2014	CS	−	+	+	⊕	+	+	+	7	GOOD

D: Design; CS: cross-sectional

S1	Selection; Representativeness of the sample	⊕	Two stars
S2	Selection; sample size	+	One star
S3	selection; phase of recovery	−	No star
S4	selection; MRI record ascertainment		
C1	Comparability; factors of confounders		
O1	Outcome; assessment		
O2	Outcome; statistical test		

Table 4. Risk of Bias of Cohort studies

Table S4: Risk of Bias of Longitudinal studies

Reference	D	S1	S2	S3	S4	C1	O1	O2	O3	Total	Score
Cho 2007	C-P	−	+	−	+	+	+	+	−	6	MOD
Choi 2021	C-R	−	+	+	+	+	+	+	−	7	GOOD
Jang 2008	C-P	−	−	+	+	+	+	+	−	6	MOD
Jang 2013 (NS)	C-R	−	−	+	+	+	+	+	−	6	MOD
Jang 2022 (M)	C-R	−	+	+	−	+	+	+	+	7	GOOD
Jang 2022 (HC)	C-R	−	+	+	+	+	+	−	+	7	GOOD
Jun 2021	C-R	+	−	+	−	+	+	−	+	6	MOD
Kim 2013	C-R	−	+	+	+	+	+	+	−	7	GOOD
Kim 2018 (NR)	C-P	+	−	+	+	+	+	+	−	7	GOOD
Kwak 2010	C-P	−	+	+	+	+	−	−	−	4	POOR
Lee 2023	C-P	+	+	+	+	+	+	+	+	8	GOOD
Park 2021	C-P	+	+	+	−	+	+	+	+	8	GOOD
Wang 2023	C-R	+	+	+	−	+	+	+	+	3	GOOD

D: design; C-R: cohort-retrospective; C-P: cohort-prospective

S1 Selection; Representativeness of the sample

S2 Selection; sample size

S3 selection; phase of recovery

S4 selection; MRI record ascertainment

C1 Comparability; factors of confounders

+ Two stars

+ One star

− No star

O1	Outcome; assessment
O2	Outcome; statistical test
O3	Outcome; drop-outs

Figures

Fig. S1.

Study	Cohen's d	Std. Error	Lower	Upper	p-value	Weight	Weight (%)
Jang et al. 2008	0.68	0.41	-0.13	1.48	0.10	5.90	18.83
Jang et al. 2015	1.20	0.38	0.46	1.94	0.00	7.00	22.32
Jang et al. 2022 HC	1.01	0.45	0.13	1.89	0.02	4.98	15.87
Kim et al. 2013	0.44	0.42	-0.39	1.27	0.30	5.63	17.97
Kim et al. 2018 NR	0.64	0.36	-0.06	1.34	0.07	7.84	25.01
Overall	0.79	0.18	0.44	1.14	0.00		

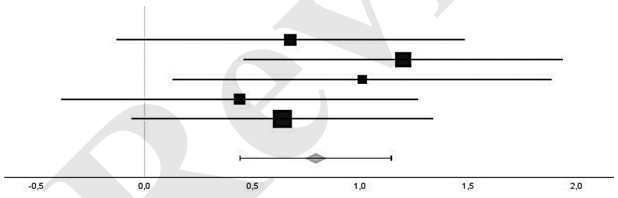


Fig. S2.

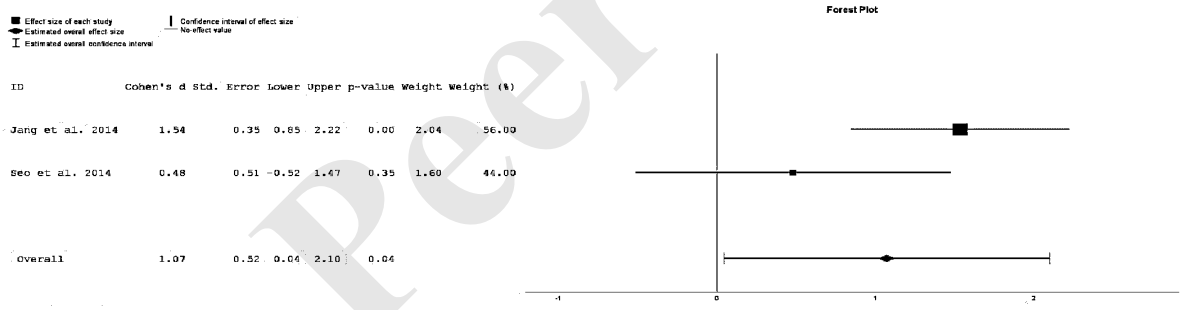


Fig. S3.

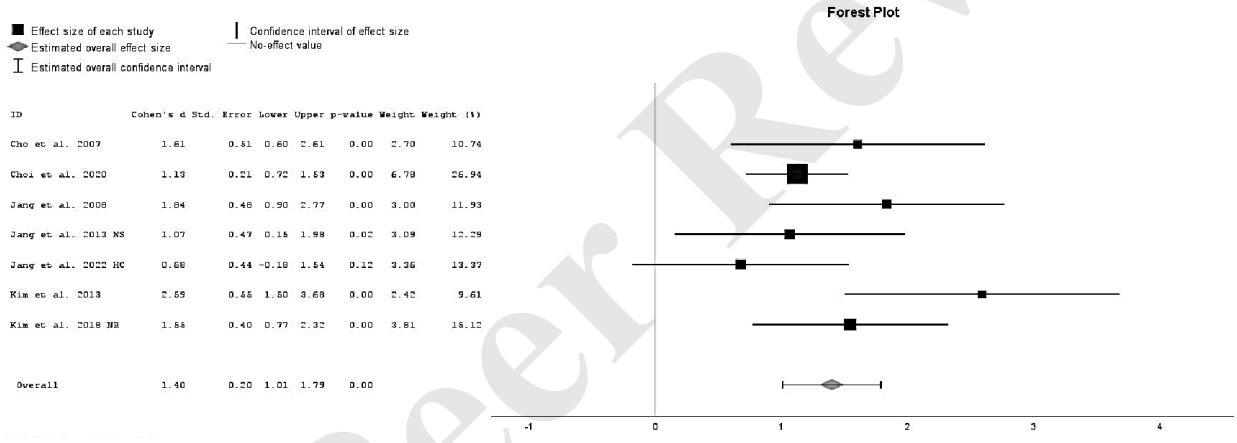
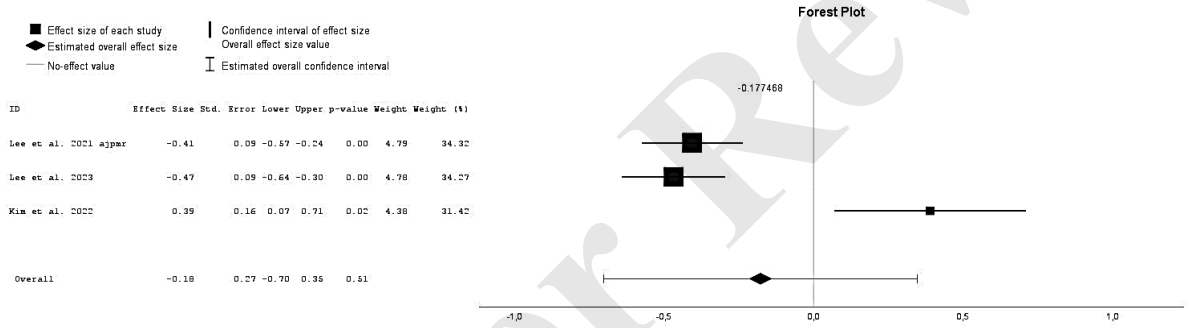
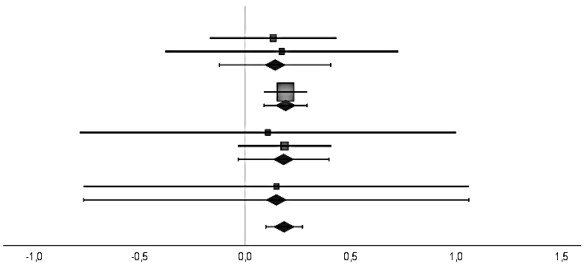


Fig. S4.



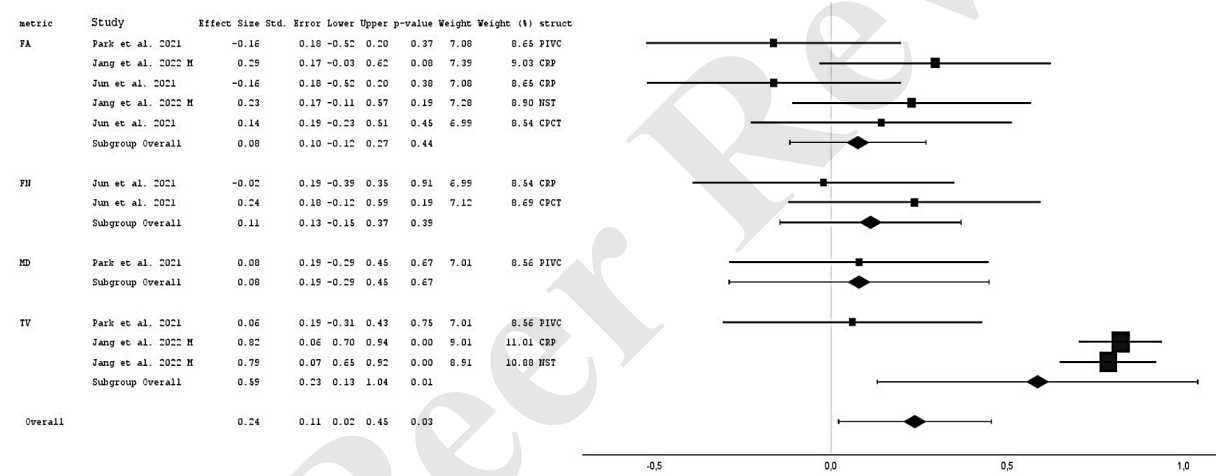
ID	Effect Size	Std. Error	Lower	Upper	p-value	Weight	Weight (%)
Lee et al. 2021 ajpmr	-0.41	0.09	-0.57	-0.24	0.00	4.79	34.32
Lee et al. 2023	-0.47	0.09	-0.64	-0.30	0.00	4.78	34.27
Kim et al. 2022	0.39	0.16	0.07	0.71	0.02	4.38	31.42
Overall	-0.18	0.27	-0.70	0.35	0.51		

Fig. S5.



metric	Study	Effect Size	Std. Error	Lower	Upper	p-value	Weight	Weight (%)	struct
FA	Jang et al. 2013 s	0.13	0.15	-0.17	0.43	0.38	42.72	8.33	CRP
	Park et al. 2021	0.17	0.28	-0.38	0.73	0.54	12.57	2.45	PIVC
	Subgroup Overall	0.14	0.13	-0.12	0.41	0.29			
FN	Jun et al. 2021	0.19	0.05	0.09	0.29	0.00	369.82	72.11	CRP
	Subgroup Overall	0.19	0.05	0.09	0.29	0.00			
FV	Jang et al. 2013 s	0.11	0.46	-0.78	1.00	0.81	4.83	0.94	CRP
	Park et al. 2021	0.19	0.11	-0.03	0.41	0.10	78.31	15.27	PIVC
	Subgroup Overall	0.18	0.11	-0.03	0.40	0.10			
MD	Park et al. 2021	0.15	0.47	-0.77	1.06	0.75	4.60	0.90	PIVC
	Subgroup Overall	0.15	0.47	-0.77	1.06	0.75			
Overall		0.18	0.04	0.10	0.27	0.00			

Fig. S6.



Figures captions

Fig. S1: CST group differences in the sub-acute phase

Fig. S2: CST group differences in the chronic phase

Fig. S3: CST group differences with prognostic analyses

Fig. S4: Cross-sectional association between CST and BBS in the sub-acute phase

Fig. S5: Cross-sectional association between non-CST tracts and FAC in the sub-acute phase

Fig. S6: Prognostic association between non-CST tracts and FAC

APPENDICES

Title: Appendix 1 Newcastle-Ottawa Quality Assessment Form for Cross-sectional Studies

Newcastle-Ottawa Scale adapted for cross-sectional studies

Selection: (Maximum 5 stars)
1) Representativeness of the sample:
a) Truly representative of the average in the target population. * Study included equally ischemic and haemorrhagic stroke
b) Somewhat representative of the average in the target population. * Study included ischemic and haemorrhagic stroke, but not equally (non-random sampling)
c) Selected group of users: only ischemic OR haemorrhagic stroke.
d) No description of the sampling strategy.
2) Sample size:
a) Justified and satisfactory. * Sample size calculation performed: always yes; if not: at least 15 participants in each group or in total.
b) Not justified OR less than 15
3) Selection of the non-exposed cohort:
a) Comparability between exposed and non-exposed characteristics is established, and the response rate is satisfactory. * Patients were all included when they were in the same phase of recovery/ hyperacute <24h, acute: 24h-7d, early subacute: 7d-3m, late sub-acute:3m-6m, chronic: >6m.
b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
c) No description of the response rate or the characteristics of the responders and the non-responders.
4) Ascertainment of the exposure (risk factor):
a) Validated measurement tool. ** MRI technique well explained (acquisition sequence, device, data analysis…) If analysis is well explained, two stars
b) Non-validated measurement tool, but the tool is available or described.* MRI technique well explained (acquisition sequence, device) data analysis not explained
c) No description of the measurement tool.
Comparability: (Maximum 2 stars)
1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
a) The study controls for… * the most important factor: time post-stroke/ for studies with one stroke group and one control group/ groups differences (cut-off: difference of >3m)
b) The study control for… * at least two others: age (difference of >20y), sex, lesion side, stroke type, gait independence at inclusion time, sensory level, handedness, education level, compared between groups, of regression analysis.
c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders. no analysis saying if differences are significant or insufficient data regarding cofounders.

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
a) Independent blind assessment. ** Assessment tools used for balance, FAC and ADL are validated scales or were fully explained as well as data analysis when needed. Clinical data blinded from imaging data. * if well explained but not blinded.
b) Record linkage. ** Assessment tools used for balance, FAC, ADL are validated scales or were fully explained as well as data analysis when needed. Clinical data blinded from imaging data. * if well explained but not blinded.
c) Self report.
d) No description.

2) Statistical test:
a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *
b) The statistical test is not appropriate, not described or incompletely given.

Title: Appendix 2 Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Newcastle-Ottawa Quality Assessment Form for Cohort Studies
Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection
1) Representativeness of the exposed cohort
- a) Truly representative * Study included equally ischemic and haemorrhagic stroke
- b) Somewhat representative * Study included ischemic and haemorrhagic stroke, but not equally (non-random sampling)
- c) Selected group
- d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort
- a) Drawn from the same community as the exposed cohort * Patients were all included when they were in the same phase of recovery and longitudinal evaluated in the same phases
- b) Drawn from a different source
- c) No description of the derivation of the non exposed cohort

3) Ascertainment of exposure
- a) Secure record (e.g., surgical record) * MRI technique well explained (acquisition sequence, device, data analysis…)
- b) Structured interview MRI not well explained
- c) Written self report
- d) No description
- e) Other

4) Demonstration that outcome of interest was not present at start of study
- a) Yes * Clear description of baseline characteristics of the patient if time point of MRI does not match with time point of motor function tests. For example: if the MRI was taken in the acute phase, but motor function was only evaluated in the chronic phase, information on the motor condition of the patient in the acute phase should also be given.
- b) No or Not mentioned

Comparability
Comparability of cohorts on the basis of the design or analysis controlled for confounders
- a) The study controls ** the most important factor: time post-stroke/ for studies with one stroke group and one control group/ groups differences (cut-off: difference of >3m)
- b) Study controls for other factors (list) * at least two others: age (difference of >20y), sex, lesion side, stroke type, gait independence at inclusion time, sensory level, handedness, education level, compared between groups, of regression analysis.
- c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders. If the data is given but there's no analysis saying if the differences are significant or not.

Outcome
1) Assessment of outcome
- a) Independent blind assessment * Assessment tools used for paresis/gait are validated scales or were fully explained as well as data analysis when needed
- b) Record linkage * Assessment tools used for paresis/gait are validated scales or were fully explained as well as data analysis when needed
- c) Self report
- d) No description
- e) Other

2) Was follow-up long enough for outcomes to occur
- a) Yes * (at least 3 months)
- b) No (<3 months)

3) Adequacy of follow-up of cohorts
- a) Complete follow up- all subject accounted for *
- b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. *
- c) Follow up rate less than 80% and no description of those lost
- d) No statement