Review

The Interplay Between Depression, Anxiety, Fatigue, and Pain in the Neurorehabilitation of Post-Stroke Patients: A Mapping Review

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Abstract

Introduction. Depression, anxiety, fatigue, and pain are four pathological conditions and symptoms very common in stroke patients that often occur simultaneously, affecting each other. This mutual influence seems little studied, as literature tends to study them separately.

Method. This study aims to analyze the literature on the co-presence and mutual influence of anxiety, depression, fatigue, and pain in stroke patients during neurorehabilitative hospitalization. Scopus, Pubmed, Embase, and Cinahl databases were searched from 01/2017 to 12/2023.

Results. Out of the 24 included studies, 11 investigated fatigue and depression, 10 depression and pain, 6 fatigue and anxiety, and 3 anxiety and pain. In the anxiety and fatigue domains, the observational studies reported a direct association between the two variables, while the intervention studies showed the covariation over time. In anxiety and pain, all the studies reported a direct correlation. In the depression and fatigue, the observational studies showed a positive correlation of variable degree, while the RCTs didn't indicate correlations. No clear association emerged between depression and pain.

Discussion. In conclusion, post-stroke pain and anxiety are less frequently assessed and addressed than fatigue and depression. Current assessment tools appear limited in

their adequacy for stroke patients, highlighting important methodological gaps. Further research is needed to develop more appropriate instruments and improve psychological support and pain management in this population.

Keywords: Neurorehabilitation, Nursing, Stroke, Depression, Pain, Fatigue, Anxiety

Introduction

Stroke is the neurological disease with the highest social influence, representing the second leading cause of death after cardiovascular diseases and the main cause of disability. According to the World Stroke Association in the world, there are approximately 12.5 million people with stroke every year, and it is estimated that, worldwide, 101 living people have suffered a stroke (Feigin et al., 2022).

Primarily, healthcare professionals pay attention to the neurological damages, but the neuro-psychiatric consequences of the stroke episode are just as crucial affecting the outcome of nursing care. During the rehabilitation phase, care becomes multidimensional. According to the literature, nurses should provide adequate psychosocial support to stroke survivors as well as to their families. Moreover, early depression screening among stroke survivors is recommended in order to improve patient outcomes (Babkair et al., 2023).

From a clinical perspective, these consequences can be further classified into two domains, i.e., cognitive deficit and psychiatric manifestation (Barbay et al., 2018; Mahadevan et al., 2021). The four major pathological conditions most frequently observed in this population are anxiety, depression, fatigue, and pain, all of which significantly impair the rehabilitation process and hinder functional recovery.

Neuropsychiatric disorders occur in approximately 30% of stroke survivors, with depression, anxiety, and apathy among the most prevalent conditions. These disabling psychiatric outcomes are associated with a significant reduction in quality of life and contribute substantially to caregiver burden, stress, and emotional exhaustion (Ferro et al., 2016). In addition to these core affective disturbances, pain and fatigue are also commonly reported after stroke and are often closely related to depressive symptoms (Appelros et al., 2006).

Upon close examination psychological conditions, such as anxiety and depression can be experienced by nearly 40% of stroke patients (MacKevitt et al., 2011; Murray et al., 2003; Zhang et al., 2020). Self-recorded psychological complaints are even more frequent, with about 60% of the patients with stroke experiencing depression and 67% anxiety (Murray et al., 2003). Psychological symptoms can be present in the first weeks after stroke and can negatively impact daily life (Lincoln et al., 2011), and have been associated with poorer functional recovery after 52 weeks (R. West et al., 2010).

Post-stroke depression is characterized by common somatic features, like weight loss consequent to appetite decrease, lethargy, and suicidal ideation (Beblo & Driessen, 2002; Chun et al., 2022). These behaviors may occur in both early and late post-stroke phases and may be associated with fatigue and psychomotor deficits in stroke patients (Spalletta et al., 2005).

The prevalence of post-stroke fatigue (PSF) has been estimated between 25% and 85% (Cumming et al., 2016). However, a clear and consistent definition of PSF is still lacking. PSF is recognized as a subjective deficit of mental and physical energy that interferes with daily activities (Paudel et al., 2023), often associated with older age and higher severity of neurological and medical impairments, such as diabetes, hypertension, heart failure, kidney disorder, pain, anxiety, depression, sleep problems, and cognitive deficits (Cumming et al., 2016).

Another common sequela of stroke is post-stroke pain (PSP), which can occur in 19-74% of patients (J. S. Kim, 2009). However, PSP is often underreported as it may not be disclosed directly by the patient and is described only on specific inquiries (Harrison & Field, 2015). Previous studies found that PSP may be associated with poor cognitive functioning (O'Donnell et al., 2013), lower quality of life (Naess et al., 2010), fatigue (Hoang et al., 2012), and depression (Lundström et al., 2009).

PSF and PSP can negatively impact rehabilitation outcomes, as patients may experience a lack of

motivation and difficulty adhering to treatments (Chapman & Bogle, 2014; Payton & Soundy, 2020; Urimubenshi et al., 2017). Nurses often face obstacles in coping with the shifting mood and noncompliant conduct of patients with stroke (Mackenzie & Greenwood, 2012), which could lead to problems in interpersonal relationships in both clinicians and patients. Therefore, psychological care is needed to improve nursing care (van Nimwegen et al., 2023; Luker et al.2015), and to reduce healthcare costs (Gillham et al., 2012).

These four pathological conditions and symptoms, as described above, are not only very common and frequent in patients with stroke, but in rehabilitation practice, they often occur simultaneously, affecting each other. However, despite their frequency, their mutual influence and reciprocity seem little studied in the literature, tending instead to study them separately, with exception of the well documented association between depression and fatigue.

Through this review, nurses and healthcare professionals are provided with a detailed, literature-based description, of the reciprocal interactions among these symptomatic conditions

Specifically, the aim of this review is to analyze the co-presence and mutual influence between various pathological conditions and symptoms in stroke patients, i.e., anxiety, depression, fatigue, and pain, and to determine whether these measures could affect the efficacy of rehabilitation received during hospital stay.

Materials and Methods

Search strategy and selection criteria

This review was registered with PROSPERO, CRD42022345759. A comprehensive search of the SCOPUS, PubMed, Embase, and Cinahl online databases was conducted considering studies published in the last five years (from 01/2018 to 31/12/2023). The following keywords were used: 'stroke', 'rehabilitation', 'depression', 'anxiety', 'pain' and 'fatigue' (see supplementary materials for complete queries).

To be included, studies had to meet the following criteria: participants with stroke not limited to specific clinical characteristics such as lateralization, lesion site, or types of stroke; participants older than 18 and younger than 85 years old; participants treated in neurorehabilitation centers as inpatients; assessing during the hospital stay at least one of the following variable dyads: anxiety-fatigue, anxiety-pain, depression-fatigue, depression-pain; full original articles written in English.

Candidate studies were excluded if they: included participants with neurological or severe psychiatric comorbidities; included community-dwelling individuals who did not undergo a rehabilitation period as inpatients; were rated with a high risk of bias after the risk of bias assessment.

In the case of longitudinal design, candidate studies were included if baseline measurements were performed during hospitalization. However, if follow-up measures were acquired after hospital discharge, these were not considered for the purpose of this work.

Data Extraction and Risk of Bias Assessment

All authors independently screened the titles and abstracts of articles collected from the database search. Only articles that met the inclusion criteria were selected. Any doubt or disagreement was discussed and solved among all the authors. Seven authors read selected reports and extracted relevant information following a modified version of the PICO guidelines. Data relative to sample characteristics, methods, and results were also extracted. As secondary outcomes, data concerning the patients' cognitive profile, quality of life (QoL), disability/autonomy, and sleep were also extracted. Afterward, study quality was assessed using design-specific tools. The RoB2 tool (Sterne et al., 2019) was used to evaluate the risk of bias in RCT/interventional studies, while specific JBI tools of critical appraisal were used to assess risk of bias in observational studies (Barker et al., 2026; Barker et al., 2025; Barker et al., 2024).

Results

The initial search identified 2464 records. After duplicate removal, 643 articles were retained. During the abstract screening process, 172 studies were excluded, leaving 142 studies for the full-text reading, identifying 24 records as meeting the inclusion criteria (Figure 1).

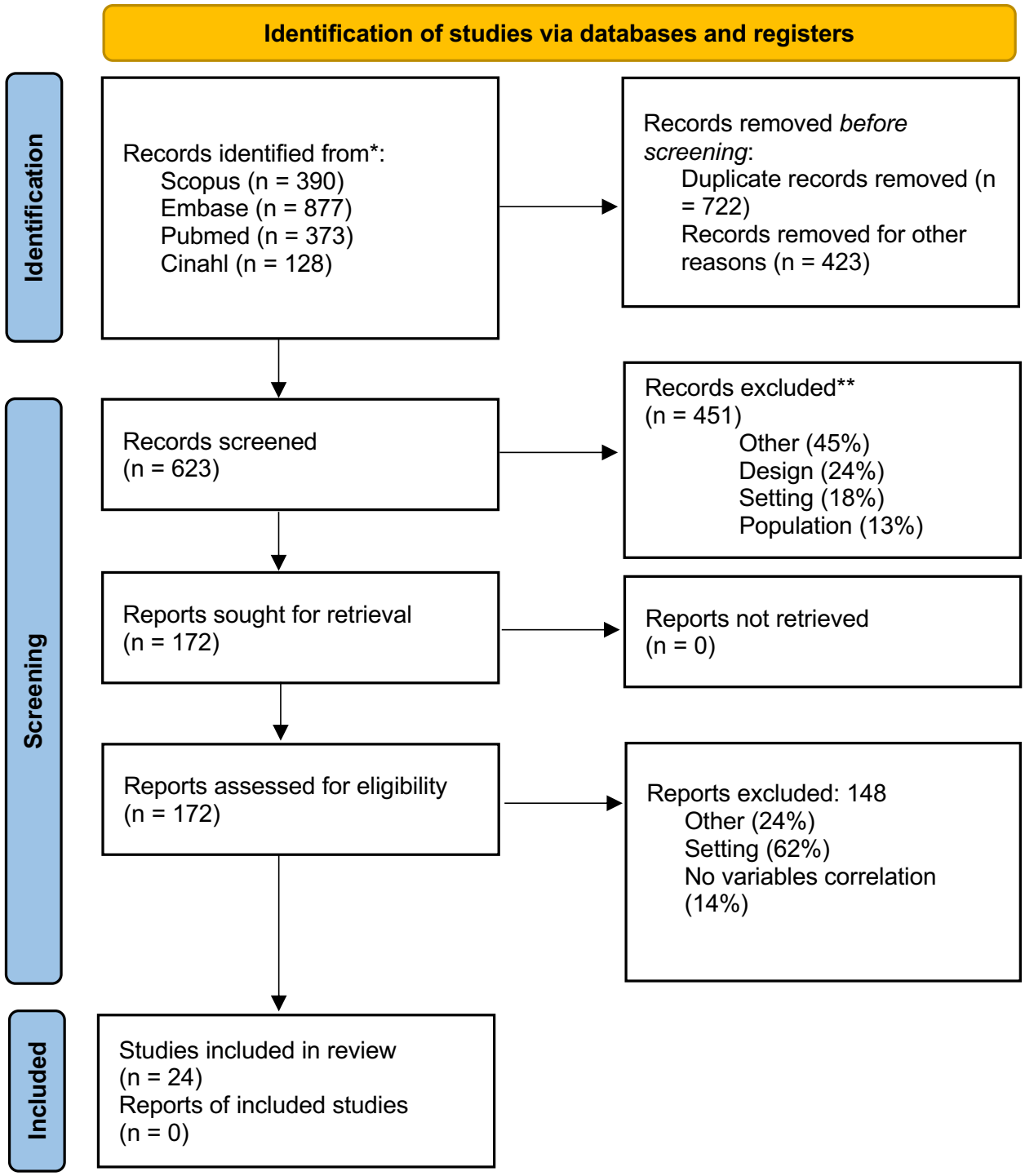

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

Results will be reported separately for each dyad of symptoms (anxiety-fatigue, anxiety-pain, depression-fatigue, depression-pain).

Overall, the studies involved 5001 patients with stroke, most of them considering both ischemic and hemorrhagic types (Chen et al., 2019; Ozyemisci-Taskiran et al., 2019; Batur et al., 2022; Kim et al.,, 2022; Hartley et al., 2022; Dornonville de la Cour et al., 2023; Kieverud et al., 2020; Rutkowski et al., 2021; Aydin et al., 2023; Chen et al., 2023; Wong et al., 2021; Zhao et al., 2021), four only ischemic patients (Chen et al., 2019; Kautzky-Willer et al., 2021; Szczepańska-Gieracha J. & Mazurek, J., 2020; Kobylańska et al.,2019), no study focused only on hemorrhagic patients. Surprisingly, 4 studies give no indications on stroke haetiology (Guidetti et al., 2020; Rivas et al., 2021; Rahamatali et al., 2021;

West et al., 2019). Furthermore, 13 studies do not mention comorbidities (Ozyemisci-Taskiran et al., 2019; Rhudy et al., 2023; Guidetti et al., 2020; Kim et al., 2022; Rivas et al., 2021; Dornonville de la Cour et al., 2023; Rahamatali et al., 2021; van Meijeren-Pont et al., 2019; Aydin et al., 2023; Baik et al., 2023; Chen et al., 2023; Zhao et al., 2021; Lin et al., 2021).

Fatigue

Thirteen of the included studies investigated fatigue and psychological concerns. Of these, six assessed both anxiety and depression levels (Ozyemisci-Taskiran et al., 2019; Batur et al., 2022; Chen et al., 2019; Guidetti et al., 2020; Kim et al., 2022; Honoré et al., 2023), one only anxiety (Rhudy et al., 2023), and six only depression (Dornonville de la Cour et al., 2023; Kjeverud, et al., 2020; Rahamatali et al., 2021, van Meijeren-Pont et al., 2019; West et al., 2019; Rutkowski et al., 2021). Notably not all the included studies explored the direct association between the variables of interest, but conversely reported their changes over time or after an intervention.

Fatigue and depression/anxiety

Studies investigating both anxiety and depression in relation to fatigue yielded inconsistent results.

In two observational studies, Ozyemisci-Taskiran et al. (2019) and Batur et al. (2022) investigated the psychometric properties of FSS and FIS in patients with stroke, respectively. Both scales showed excellent internal consistency of FSS in stroke patients. However, both studies reported that fatigue levels were only weakly (Ozyemisci-Taskiran et al., 2019) or not significantly associated with HADS scores (Batur et al).

Similar results were described also in Honoré et al. (2023), exploring changes in physical activity from the hospital to after discharge and which factors may influence the time spent in specific activities (e.g., standing, walking, etc.). The authors observed that higher levels of fatigue were associated with a reduction of active time, whereas anxiety and depression did not show any influence.

Among interventional studies, Chen et al. (2023) investigated the effect of a mind-body interactive qigong intervention on the physical and mental aspects of QoL. Qigong interactive exercise program had a beneficial effect on the physical and mental aspects of QoL. However, the concomitant presence of fatigue and depression ($p > 0.05$) in post-stroke patients was not significantly associated with a change in QoL.

Kim et al. (2022) investigated the effect of Bright Light Therapy on QoL and Sleep in patients with post-stroke insomnia. Patients received bright light therapy (10,000 lux) or placebo therapy for 30 minutes in the early morning. Anxiety was evaluated using the GAD-7, depression with the PHQ-9, and fatigue using the FSS. After bright light therapy, both anxiety, depression and fatigue scores were significantly reduced.

Conversely, Guidetti et al. (2020) reported that most patients did not experience changes in fatigue or anxiety/depression after a treatment with the F@ce ICT-based system.

Fatigue and anxiety

Only one study focused on the mutual changes of fatigue and anxiety, without assessing depression levels. Rhudy et al. (2023) investigated the feasibility of a psychosocial intervention and its effects on the quality of life and psychological symptoms in patients and caregivers. Significant improvements were observed in measures of fatigue for patients and caregivers, both immediately after the treatment and at the 6-month follow-up. Conversely, improvements in anxiety levels were found only at the follow-up evaluation.

Fatigue and depression

Overall, studies consistently described positive associations between fatigue and depression levels.

Dornonville de la Cour et al. (2023) analyzed the psychometric properties of the Dutch Multifactor Fatigue Scale (DMFS) in stroke patients. Three subscales (Impact of Fatigue, Mental Fatigue, and Signs and Direct Consequences of Fatigue) were also moderately to strongly correlated to the DASS-21 scores, measuring depression and anxiety. Stronger correlations were observed for the stress subscale of DASS-21.

Rahamatali et al. (2021) analyzed the association between modifiable factors, such as psychological ones, and fatigue in patients with chronic stroke. The authors reported that 71% of participants experienced fatigue, which was moderately correlated with depression ($r=0.63$,

p<0.001).

Other studies investigated the changes in fatigue and depression during the hospital stay. Comparing admission and discharge levels, van Meijeren-Pont et al. (2019) reported moderate to small changes in fatigue

Kjeverud et al. (40) analyzed the evolution of fatigue, assessed by FSS, from the acute phase until 18 months post-injury. In the univariate analyses, they found an association between higher fatigue levels and mild-severe depressive symptoms, investigated through BDI but this was not confirmed in the multivariate analyses.

Similarly, Rutkowski et al. (2021) found a positive correlation between fatigue and depression, which, however, impacted different outcomes related to quality of life. Moreover, higher levels of fatigue were observed also in patients not exhibiting depressive symptoms.

One interventional study (West et al., 2019) analyzed the effects of natural light on fatigue and sleep quality of patients with stroke. Fatigue and depression were evaluated with MFI-20 and MDI. Fatigue was significantly reduced in rehabilitation patients exposed to natural lighting. The author also found that depressive and fatigue scores were significantly correlated (Admission: $p = 0.0002$; Discharge: $p < 0.0001$), although both fatigue and depression could occur without each other.

Pain

Eleven of the included studies investigated pain and psychological concerns. Of note, only a limited number of studies assessed the common presence of pain and anxiety. Indeed, six studies evaluated only pain and depression (van Meijeren-Pont et al., 2019; Baik et al., 2023; Szczepańska-Gieracha J. & Mazurek J. 2020; wong et al., 2021; Zhao et al., 2021; Kobylańska et al., 2019), against 4 studies exploring pain in conjunction with depression/anxiety (Hartley et al., 2022; Kautzky-Willer et al., 2021; Rutkowski et al., 2021; Chen et al., 2023), and only one pain and anxiety (Rivas et al., 2020). Notably, as for fatigue, not all the included studies explored the direct association between the variables of interest, but conversely reported their changes over time or after an intervention.

Pain and depression

Overall, studies exploring both pain and depression currently report inconsistent results.

Among studies focusing on the pain-depression dyad, van Meijeren-Pont et al. (2019) compared the responsiveness of the USER to the BI in stroke inpatients. The USER-Pain subscale shows an improvement from admission to discharge.

Kobylanska et al. (2019) reported that depression was associated with low efficacy of rehabilitation. After three months of physiotherapy, the percentage of patients without improvement in the domains of depression and pain was 60% and 86%, respectively.

Szczepańska-Gieracha J. & Mazurek J. (2020) analyzed characteristics associated with self-efficacy levels before and after rehabilitation. Patients were divided into two subgroups: the group with improvement in self-efficacy after 3 weeks of rehabilitation ($n = 43$) had a significantly better mental and functional state at T2 with the sole exception of the level of pain.

Wong et al. (2023) assessed the profiles of HRQoL by highlighting their related dimensions among stroke survivors. On a sample of 366 subjects, a multivariable logistic regression after adjusting for confounding variables shows that stroke survivors with recurrent stroke were twice more likely to report problems and pain/discomfort. Patients with aphasia were 4 times more likely to report problems in the usual activities, yet they were less likely to report pain/discomfort. The presence of aphasia, recurrent stroke, younger age, and proxy use were significantly associated with the psychological dimensions of the HRQoL (pain/discomfort and anxiety/depression).

Two studies investigated the effects of non-invasive brain stimulation on pain and depression.

Baik et al. (2023) conducted an RCT study on tDCS for CPSP. The stimulation was applied over M1 for 2 weeks. Compared to the sham group, patients receiving tDCS showed no significant improvement in pain or depression. However, when considering changes within the tDCS group, pain and depression levels post-intervention were reduced ($p=0.049$; $p=0.008$, respectively). Moreover, when considering the site of the lesion, patients with lesions in subcortical regions (e.g., basal ganglia and thalamus) showed a reduction of pain levels compared to patients with lesions situated in the cortex.

Zhao et al. (2021) evaluated CPSP effects on QoL, mood, and social functioning by using the NRS, SF-MPQ-2, HAM-A, HAM-D, BDNF levels and MEP. Patients were randomized to receive either

rTMS on the motor cortex or a sham intervention for 3 weeks. Assessments were conducted at baseline, 3 days, 1 week, 2 weeks, and 3 weeks. Significant improvements were recorded in the NRS and SF-MPQ-2 scores on the seventh day of treatment in the rTMS group. This effect lasted until the third week. Moreover, the serum BDNF levels after 3 weeks were significantly higher in the treated group, whereas the resting motor threshold decreased. However, no significant changes were observed in anxiety or depression between groups. Results suggested that rTMS applied over the upper extremity area of the motor cortex could alleviate acute CPSP, possibly by influencing cortical excitability and serum BDNF secretion.

Pain and depression/anxiety

Concerning studies exploring both anxiety and depression in conjunction with PSP, Kautzky-Willer et al. (2021) carried out a retrospective cohort analysis of 1,437 males and 907 females suffering from cerebral infarction. During neurorehabilitation, both genders ameliorated in pain ($p < 0.001$). Pre-stroke depression was more frequent in females than men (respectively, 14.33% and 7.24%). At admission, females registered less autonomy and higher pain scores than males. At discharge, both genders experienced less pain. Overall, males had significantly less pain ($p<0.001$), anxiety ($p<0.001$) and pre-stroke depression ($p<0.001$) than women. However, the risk of post-stroke depression was comparable in both sexes.

In Hartley et al. (2022), the EQ5D-3L for self-reported HRQoL, BI for function and independence in ADL, and mRS for stroke severity were administered on admission and discharge to 41 post-stroke patients. All domains except anxiety/depression showed significant improvements in their median difference score between admission and discharge and a small improvement of patients without pain.

Chen et al. (2023) compared the effects of home-based vs hospital rehabilitation on quality of life and psychosocial variables, reporting that patients treated in the hospital showed a more significant improvement in both pain ($p=0.008$) and anxiety/depression levels ($p=0.012$).

Aydin et al. (2023) explored the effects of rTMS delivered onto the primary motor cortex (M1). After three weeks of stimulation (15 sessions), the rTMS group showed lower scores on the BPI compared to the sham group. Conversely, even though the groups differed also in depression and anxiety levels, no effect of time was observed within these variables.

Pain and anxiety

Lastly, only one study investigated the association between pain and anxiety. Rivas et al. (2020) showed how a computational model could detect the relationships of mutual exclusion between engagement and all the other states and co-occurrences between pain and anxiety.

Secondary outcomes

Almost all the studies included in the present review investigated anxiety, depression, fatigue, and pain in relation to other biopsychosocial and physical outcomes. Of note, the symptoms of our tetrad of interest were often reported as secondary outcomes in the original articles, which focused on other health parameters related to the tetrad. Given the heterogeneity of the measures investigated by each study, this section will briefly report the results on these other outcomes, focusing mainly on the following functional categories: cognition (eight studies), QoL (fifteen studies), disability/Functionality (eleven studies), Sleep, and Biopsychosocial factors (six studies). Noteworthy, out of the 24 articles in the review, only two did not investigate any outcomes besides the tetrad of interest (Ozyemisci-Taskiran et al., 2019; Dornonville de la Cour et al., 2023).

Discussion

As a main finding, we observed that anxiety, pain, depression, and fatigue, although common in stroke patients, are not all equally studied in the literature. Fatigue and depression have several studies revealing their mutual correlation, whereas consistently fewer studies focused on anxiety and pain in stroke patients. Another finding that emerged from our review is the presence of methodological issues in assessing these factors that, if not adequately addressed, could affect patients' recovery.

The lack of attention in the literature on the mutual influence of these variables in the hospital rehabilitation setting is reflected in the type of studies identified. Most had an observational design, while only 6 were RCTs (Chen et al.,

2019; Kim et al., 2022; West et al., 2019; 46, Baik et al., 2023; Zhao et al., 2021). Interestingly, the study design seemed to lead to different results in some cases, such as studies investigating the association between anxiety and fatigue. Indeed, observational studies overall described a positive correlation between the two variables, which means that when anxiety levels decrease, fatigue also decreases. Conversely, in RCT studies, the correlation between anxiety and fatigue does not appear clearly; if Guidetti et al. (2020) does not note any differences, the Qigong intervention by Chen et al. (2019) seems to act only on anxiety without an effect on fatigue, while Kim et al. (2022) reports a significant decrease in both variables.

Conversely, results from studies focusing on depression and pain were more consistent, as no clear and definitive association between the two variables emerged, and generally, their changes seem to run independently, with the exception of only one study (Zhao et al., 2021) reporting a positive correlation.

On the other hand, depression was found to be a relevant factor implicated in fatigue levels, with many studies reporting moderate to strong associations between the two variables. However, at the clinical levels, it is important to specify that these two symptoms can be present also independently, as high fatigue was observed also in patients without depression (Rutkowski et al., 2021).

Concerning available interventions for these symptoms, a promising approach is the one involving light therapy. Indeed, two RCTs described the effects of bright (Kim et al., 2022) and naturalistic light interventions (West et al., 2019), reporting positive results on fatigue, anxiety, and depressive symptoms. However, the studies presented methodological differences and are not directly comparable, with one presenting some concerns about the quality of evidence as assessed by the RoB2 tool (West et al., 2019). Given that bright light therapy may induce positive effects on depression and sleep disorders in other neurological populations (Lin et al., 2021), further larger studies are needed to explore its effects and applicability in stroke patients.

Further, in an RCT study, Zhao et al. (2021) reported the effects of rTMS applied over M1 in patients with CSPS, compared to sham stimulation. In the case group, pain intensity and anxiety showed a significant reduction after 3 weeks of treatment, while depressive symptoms showed a borderline reduction. These results are consistent with Liampas et al. (2020) that indicate the rTMS as a promising approach to managing the CSPS.

Looking at secondary outcomes, fatigue, depression, and anxiety are often detected in studies that have sleep as the primary outcome: this is the case of the RCTs by Kim et al. (2022) and West et al. (2019). Although, as shown in the Results section, the primary outcomes dedicated to mobility/independence, cognitive aspects, and QoL are represented to a greater extent, the link between sleep and its quality, with fatigue/depression/anxiety, appears very interesting. Indeed fatigue, depression, and sleep disorders belong to the so-called "sickness behavior" (Barritt, A. W., & Smithard, D. G. 2011), and the literature agrees in considering fatigue, and not necessarily depression, as clearly correlated with sleep disorders.

This issue was found in some included articles: Kim et al. (2022) found significant general effects between sleep, depression, and fatigue scores in those exposed to bright light. West et al. (2019) did not find significant differences, but the scores were still in favor of the group exposed to natural light, especially in feeling rested. We believe that this result is interesting for nursing considering its abilities in intervening and influencing patient's comfort and rest even through the ward environment.

As stated before, the considerable heterogeneity in the presence and strength of associations between our primary outcomes can be partially explained by methodological differences in using different tools not always appropriated to measure the outcomes or not right for the sample under investigation.

In our studies, nine out of fifteen used the FSS to detect fatigue. The frequency of use of this tool is consistent with what is found in the literature (Tyson, S. F., & Brown, P., 2014; Wu et al., 2015; Alghamdi et al., 2021). It is noteworthy that fatigue was often assessed using two different instruments (30,31). According to Tyson & Brown (2014), fatigue is a condition present in multiple diseases, not only neurological ones, and this may lead to methodological difficulties. Most of these derive from scales initially built for other pathological conditions. To test this problem, Batur et al. (2022) and Ozyemisci-Taskiran et al. (2019) evaluated the psychometric properties of FIS and FSS in subjects with stroke, reporting

that FIS sensitively discriminated fatigue in stroke patients from control subjects, while FSS was not sensitive against orthopedic patients.

Regarding the assessment of depression, studies predominantly used the HADS scales, which have good psychometric characteristics that enable patients with depressive symptoms to be identified, but also effectively identify anxious ones (Burton, L. J., & Tyson, S., 2015; Prismie et al., 2016). Only three studies use the BDI-II. In the studies using screening scales for depressive symptoms, no samples with clinically diagnosed depression appear, so their use is correct. Otherwise, it would have been more appropriate to use more robust scales for samples of clinical depression, such as the BDI-II (Prismie et al., 2016; Berg et al., 2009), HAM D (Carrozzino et al., 2020), or the PHQ-9 (Prismie et al., 2016; Meader et al., 2014).

Ham-A and Ham-D are considered very valid for assessing depression severity (Carrozzino et al., 2020). Zhao et al. (2021) used the 17-item version recommended by Hamilton himself, although, in the opinion of Carrozzino et al. (2020), the interviewer must be an expert clinician.

In three studies (Hartley et al., 2022; van Meijeren-Pont et al. 2019; Wong et al., 2021) QoL scales such as HRQoL or broad scales with sections dedicated to depressive symptoms. However, these tools may not be sensitive enough to detect effectively depressive symptoms in stroke patients. This could lead to a possible underestimation of the depressive and anxious condition in patients, which we have instead seen to be present and debilitating. Furthermore, the HRQoL pain/discomfort dichotomy is not always understood by the patient, who often doesn't know how to evaluate the discomfort (Kahl, C., & Cleland, J. A., 2005). Indeed, four studies (West et al., 2019; Liampas et al., 2020; Carrozzino et al., 2020; Kahl, C., & Cleland, J. A., 2005) assessed pain as part of a comprehensive assessment of QoL

Three studies evaluated VAS pain (Kautzky-Willer et al., 2021; Szczepańska-Gieracha J. & Mazurek J. 2020; Kobylańska et al., 2019). Although VAS has been validated across different pathologies, it presents strong content validity but limited reliability and criterion validity in stroke patients (Benaim et al., 2007; De Vries et al., 2017; Mandysova et al., 2022).

In Zhao's study (2021), pain was measured with two scales: the NRSs and the McGill short form, a multidimensional measure of perceived pain in adults with chronic pain. The literature indicates that both scales have good psychometric properties (Hawker et al., 2011) and are feasible to detect pain in stroke patients (Carrozzino et al., 2020), overcoming cognitive, communicative, or impairment-related problems that can significantly limit the understanding of patients. The use of the McGill short form also prevents the patient from getting tired and losing attention (Kahl, C., & Cleland, J. A., 2005).

Anxiety was mainly assessed with the Hads-A (Hartley et al., 2022; 38,40,41), the Beck Anxiety Index (Honorè et al., 2023), the GAD-7 (Rahamatali et al., 2021), the EQ5D (pain/discomfort, anxiety/depression) (West et al., 2019), HADS-A (Rutkowski et al., 2021) and by a multi-modal, multi-label machine learning system (Rivas et al., 2020).

The choice of specific and appropriate tools for evaluating our tetrad of interest is functional to a correct assessment in a neuro-rehabilitation setting, especially for nursing which has the need to use sensitive and psychometrically adequate scales. If not addressed correctly, these factors could hamper the neuromotor and functional recovery of patients. Therefore, the choice of specific scales for stroke patients and a multidimensional approach appear essential for a complete evaluation, treatment, and management of the patient's specific needs.

Given the importance of relying on sufficiently supported and well-established associations, the dyad "fatigue–pain" was not included in the present study due to insufficient evidence. These two conditions were assessed together in only one study, using the USER scale. This instrument evaluates three domains of stroke-related outcomes: physical functioning, cognitive functioning, and an additional domain encompassing pain, fatigue, and mood (Van Meijeren, 2016). However, no statistical or descriptive analyses specifically addressing the correlation between pain and fatigue were identified. In all other studies, no significant correlations were reported.

Moreover, the dyad "anxiety–depression" was not examined through correlation analysis in this study, as these conditions already constitute a well-established and robust dyad in the literature and are often assessed using the same measurement instruments (i.e. HADS, EuroQol-5, DASS-21).

A limitation of the present review lies in the heterogeneity and paucity of the included

studies, which affected the search for correlations between the outcomes of interest. This heterogeneity, together with the limited number of eligible studies, also prevented the possibility of conducting a quantitative synthesis.

Most of the studies reported our primary outcomes as secondary outcomes, further limiting the possibility of exploring robust associations between the outcomes of interest.

Another issue that affected our search was that many screened studies did not clearly report whether stroke participants were still in hospital or already community-dwelling. As our review focuses on patients hospitalized in neurorehabilitation wards, we decided to exclude those studies lacking a clear and unambiguous indication so as not to include biased results.

Conclusion

This review aimed to analyze a common phenomenon in rehabilitation settings: the co-presence and mutual influence between various pathological conditions and symptoms in stroke patients, as commonly happens in the clinical rehabilitation practice and which nursing practice deals with it every day. Despite their frequency, we observed that these factors are not often studied according to their mutual reciprocity and influence but separately. Therefore, the present review aimed to shed light on the association, its frequency and intensity, between these factors to fill the gap in the existing literature.

We observed that in literature pain and anxiety after stroke in rehabilitation hospital settings get significantly less attention compared with fatigue or depression: this can be seen from the number of studies, their quality, and the type of instruments used to evaluate the outcomes. We also noticed that the tools described in the literature for detecting these conditions are often inadequate and not validated for stroke patients. These findings, relevant to nursing practice and research, demonstrate the need for interventions targeting providing psychological support and pain management for post-stroke patients, leading to better QoL and functional recovery.

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