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Risk factors for post-stroke shoulder pain: a systematic review and meta-analysis

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Title Page (with ALL author details included (including names, email addresses, degrees, and phone numbers)

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Running head:

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Conflicts of interest:

Funding received from Health Education Kent, Surrey and Sussex was to support backfill costs only and the organisation had no input into the research topic, content or design. We have no other conflicts of interest to declare.

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Prof. Biller
Editor
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February 11th, 2020

Dear Prof Biller:

Thank you for the opportunity to resubmit our manuscript entitled "**Risk Factors for Post-Stroke Shoulder Pain: A Systematic Review and Meta-analysis**" for consideration. We are again grateful to the reviewers for taking the time to reconsider our revisions.

We appreciate the reviewer's comments regarding the improved clarity the revisions have made. There was a further revision recommended:

Please add that correlates of PSSP were beyond the scope of this paper and include as a limitation in the Discussion.

We are grateful for the reviewer's comment and have added the recommended statement 'consequently correlates of PSSP were beyond the scope of this study' on line 105. However, given that we have made a number of references in the text as to why correlates were not included in the current study, we feel it would confuse the reader to say we then considered this lack of inclusion a limitation of the study. As our aim in the study was 'to identify the potential risk factors measured within the first month after stroke that predicted the onset of shoulder pain within the first year after stroke' we feel the inclusion of correlates would confound the results. We have therefore not added this to the limitation section.

We hope that the amendment is sufficient and that our justification for not including in the limitations section is clear. The revised manuscript has been appended and we have highlighted the revision on line 105 in yellow.

Thank you for your reconsideration of this manuscript.

Sincerely,

Rich Holmes, MSc MCSP
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Risk Factors for Post-Stroke Shoulder Pain: A Systematic Review and Meta-analysis

Abstract

Objective: To identify the risk factors identified within one month post-stroke that predict the onset of post-stroke shoulder pain (PSSP) within the first year after stroke.

Methods: Five databases, (AMED, CINAHL, EMBASE, Medline, PubMed) were searched from inception to April 2019. Prospective cohort studies that measured a potential risk factor for post-stroke shoulder pain within the first month after stroke were included. Two authors independently reviewed and selected articles for inclusion. Risk of bias was assessed using the Quality in Prognosis Studies tool. Data extracted included raw data for odds ratio (OR) calculations, definition and measurement of pain, study limitations and baseline characteristics of participants. The review was conducted following PRISMA guidelines.

Results: Nine articles were retrieved that met the inclusion criteria, and six presented data to use in meta-analysis. Fifty-four different factors were identified as potential risk factors. Meta-analysis was possible for four factors; sex (OR 0.93, CI 0.75-1.15), laterality (OR 0.78, CI 0.59-1.05), diabetes (OR 2.09, CI 1.16-3.78), and history of shoulder pain (OR 2.78, CI 1.29-5.97). Reduced motor function in the upper limb was also identified as a significant risk factor through qualitative synthesis.

Conclusions: Reduced motor function in the upper limb, diabetes, and a history of shoulder pain were identified as significant risk factors for the development of PSSP within the first year after stroke. Recommendations to standardise future studies in this area have been made and it is suggested that defining subtypes of PSSP may aid future interventional studies.

Introduction

Post-stroke shoulder pain (PSSP) is a common and often debilitating consequence of stroke. Wide variations of incidence have been reported in the literature dependent on the patient cohort and methodology used. Most recent studies have found an incidence rate of between 18-22% at 3-4 months after stroke onset[1-3] with a slight reduction at 1 year post-stroke to between 6-21%.[3,4] Lindgren et al[2] reported that 73% of patients with PSSP reported they had pain daily whilst a further 11% reported constant pain, and 45% required some form of analgesic medication.

PSSP is known to negatively impact on a person's ability to carry out activities of daily living, such as walking and dressing,[2] and limit their ability to participate in leisure activities.[5] Furthermore it has been shown to be associated with reduced quality of life[6,7] as well as having a direct impact on mood.[5] Barlak et al[8] also reported a significantly longer stay in rehabilitation for patients with PSSP.

There is therefore a need to limit the impact of this common consequence of stroke through robust prevention strategies and effective treatment modalities. However, difficulties arise due to the complex and multifactorial nature of PSSP.[9] A large variety of possible aetiologies are described in the literature including musculoskeletal disorders such as rotator cuff dysfunction, bursitis, adhesive capsulitis, and impingement, as well as neurogenic problems such as spasticity, central hypersensitivity and complex regional pain syndrome.[10] Unsurprisingly this multitude of aetiologies has led to multiple interventions been suggested in the

literature. However, there seems to be little consensus on the implementation of some of these interventions[11-13] making assessment of their effectiveness difficult. A review by Li and Alexander[14] supported this when they found the evidence for treatments of PSSP to be lacking, though this should not be misinterpreted as evidence that treatments are ineffective.

The lack of consensus on best management makes prevention all the more important. However, to prevent PSSP we must first understand which patients are most at risk so that strategies can be put in place and regular assessments can be done to monitor any early developments of PSSP and limit the impact in the chronic stages. To answer this question, a number of often cited studies have explored factors that are correlated with PSSP such as subluxation,[15] spasticity,[16] and abnormal joint examination.[17] But due to the lack of repeated temporal measures these correlations do not show causation and the factors explored should not be interpreted as risk factors.

To date, reviews exploring PSSP have either been narrative in nature[18] or have focussed on factors that are correlated with PSSP.[19] Whilst these give an indication of factors closely linked to PSSP, they are limited by the variations in methodologies included and do not give a satisfactory answer to the matter of risk.

There is, therefore, a need to collate those studies investigating specifically risk and predictive factors that are effectively assessed and quantified using robust

prospective studies to see if there is agreement within the literature. The aim of this systematic review was to identify the potential risk factors measured within the first month after stroke that predicted the onset of shoulder pain within the first year after stroke.

Methods

To complete and report this review the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[20] was used.

Search Strategy

The search strategy was designed with the aid of a clinical librarian with input from the two lead authors (RH/KM). The databases AMED (1985 – April 2019), CINAHL (1937 – April 2019), EMBASE (1974 – April 2019), Medline (1946 – April 2019), and PubMed were used with no limitations applied. Variants of 'stroke', 'shoulder pain', and 'risk factors' were used as keywords and combined in the search strategy. The full search strategy can be viewed on the International Prospective Register of Systematic Reviews (PROSPERO: CRD42018110406) where this systematic review was registered. Further articles were sourced by hand-searching through the reference lists of key articles. The websites www.clinicaltrials.gov and www.ukctg.nihr.ac.uk were regularly reviewed to check for any ongoing trials that may be relevant; however no articles were sourced using this method.

Study Selection

Studies were eligible for inclusion only if the following three criteria were present: a) they were prospective cohort studies, b) they measured any potential risk factor within the first month after stroke and c) they measured pain as a key outcome within one year after stroke. Any definition and measure of pain used by study authors was deemed acceptable for inclusion. Studies in languages other than English were included only if a full-text English version could be sourced. To answer the specific question of risk it was felt essential that there was an element of temporality between the measurement of the risk factor and the measurement of pain, consequently correlates of PSSP were beyond the scope of this study. Studies were therefore excluded if they were cross-sectional studies in which all measures were taken at a single time-point (thereby assessing correlation rather than risk). Case reports, conference abstracts, poster presentations or other studies where the full report was not available were also excluded.

Two reviewers (RH and KM) screened the titles and abstracts independently. Full-text versions of the selected papers were obtained and were assessed against the inclusion and exclusion criteria by the same reviewers, again independently. Where there was disagreement a consensus was made through discussion along with the third reviewer (CK).

Authors were contacted when articles were lacking sufficient detail to assess the inclusion criteria. In all cases clarity was sought to understand if baseline measures were recorded within the first month after stroke. Authors were asked at what point baseline measures were taken and, to avoid bias, were not given information of the research question or the inclusion criteria.

Data extraction & risk of bias assessment

The main data extracted included all factors that were identified and analysed as potential risks or where sufficient data were supplied for factors where an odds ratio (OR) could be calculated. Other data extracted included the aims and methodology of each study, the period of observation, baseline characteristics of the cohort, inclusion/exclusion criteria, how pain was defined and measured, the temporal aspect of baseline and repeated measures, and limitations of the study in relation to the research question.

The risk of bias of included studies was independently assessed by two reviewers (RH and KM) using the Quality in Prognosis Studies (QUIPS) tool.[21] This tool considers six domains (Study Participation, Study Attrition, Prognostic Factor Measurement, Outcome Measurement, Study Confounding, and Statistical Analysis and Reporting) and rates these as having low, moderate or high risk of bias. Any disagreement between reviewers related to these assessments was resolved through discussion until a consensus was reached.

The overall risk of bias was determined *a priori* and judged as: *low* if 4 or more of the domains were rated low and no domains rated as high, *moderate* if 4 or less domains were rated low with one domain rated as high or 3 or less domains rated as low with no high risk domains, and *high* if 2 or more domains were rated as high or if 1 domain was rated as high with no low risk domains.

Data Synthesis

The articles were described and summarised in a narrative form. Where possible, raw data were extracted from the original papers to calculate ORs and 95% confidence intervals (CI) with the intention of pooling these outcomes in meta-analysis. Where raw data were not available the ORs presented in the original articles were used.

Attempts were made to perform meta-analysis when data for a dichotomous variable were presented in three or more studies. Between-study heterogeneity was evaluated at face value based on methodological characteristics such as inclusion criteria and the method of outcome measurement. If there was substantial variation in the methods used then data were interpreted narratively. When it was possible to combine data, heterogeneity was assessed using the I^2 statistic, although it is acknowledged that detecting true heterogeneity with a very small number of studies is thought to be very difficult.[22]

All analyses were performed using random effects models to account for the varied approaches within the studies. Funnel plots to assess for publication bias were not presented as it was felt that the small number of studies included would limit their usefulness of this analysis. All analyses were undertaken using the software package Comprehensive Meta Analysis (V3.3.070) (www.Meta-Analysis.com).

Results

Literature Search

The search from the selected databases returned a total of 1,077 articles (**figure 1**). An additional 31 articles were sourced through hand-searching reference lists from key articles (n=3) and through search alerts following the initial search (n=28). During screening 593 were excluded as they clearly did not meet the necessary inclusion criteria. A further 11 abstracts were discarded as they were found to be poster presentations or conference abstracts, and one final paper published in Spanish[23] was excluded as it was not possible to access in English.

The full text of the remaining 30 articles were assessed in more detail. A further 21 were excluded due to (a) risk factors not been measured within the first month after stroke,[8,17,24-30] (b) exploring factors correlated with PSSP rather than risk,[15,16,31-36] (c) retrospective methodologies,[37,38] and (d) studies' aims not exploring risk of PSSP.[39,40] Authors of four articles were contacted to seek further clarification regarding the timing of baseline measures. For two of these studies[41,42] the authors

were able to confirm that the baseline measures were recorded within the first month and were included in the review. Of the other two, one author was unable to recall[17] and one author did not respond.[8] These were therefore excluded.

Figure 1. PRISMA Flow diagram of study selection

<insert Figure 1>

The remaining nine[2,3,41-47] articles were included in the systematic review. Of these, seven provided sufficient data to calculate ORs on the four risk factors that had sufficient data to conduct meta-analyses. However, the study by Isaksson et al[43] was excluded from all meta-analyses as it was thought to be too heterogeneous due to only including patients with pronounced UL weakness. It was felt that this was a significant difference from the populations of the other studies and was likely to significantly skew the analysis.

Characteristics of included studies

The nine papers included consisted of eight prospective cohort studies from seven different countries published between 2003[44] and 2018.[41] A summary of the characteristics of the included studies is presented in **table 1**. The mean sample size of the studies was 309 (range: 31-1474). In total 2474 patients were included in the data synthesis consisting of 1237 (50%) males and 1237 (50%) females. It was not possible to calculate a combined description of participants' age due to the variation

in descriptive statistics provided across studies. Three studies[2,3,45] reported types of stroke and found that 87% (n=566) patients had an ischaemic stroke. Side of stroke was reported in four studies[3,45-47]; 54% (n=247) of participants having a left hemispheric stroke and 46% (n=211) having a right hemispheric stroke.

Table 1. Characteristics of included studies

<insert Table 1>

Three papers[2,3,44] included all stroke patients and took steps to ensure that participants with communication or cognitive impairments were included by involving carers or next-of-kin. One paper[43] restricted participants to only those with pronounced arm weakness limiting the comparability with other studies. Another[47] explored only patients who had persistent PSSP leading to the loss of two patients who had pain but were excluded from the final analysis.

Five studies[2,3,44,46,47] presented prevalence rates or provided sufficient data to calculate a rate for PSSP at specific time points. Two studies did not present clear enough data to calculate a true prevalence, and one study looked at a specific subsection of patients. At baseline (within the first week), data was available on 1672 patients[3,44] and gave a prevalence rate of 16%. This prevalence increased to 21% (103/483) at four months,[2,3] 24% (293/1235) at 6 months[44,47] and 23% (105/453) at one year post-stroke.[2,3]

The nine papers presented data on a total of 54 different factors that were measured temporally to allow the calculation of risk. Within these, seven were categorised as *Demographic factors*, 13 as *Co-morbidities*, and 34 as *Clinical assessments and measures* (**table 1**).

Pain Measurement

There were large variations in how pain was defined and measured. Four papers defined pain as either at rest or during passive or active movement[43,45-47] but none of these reported how the data was handled when conflicting results between 'at rest' and 'on movement' were found. Four papers did not specify how they defined PSSP,[2,41,42,44] and a final paper defined PSSP as any subjective complaint in the hemiplegic shoulder.[3] Six papers used either the Visual Analogue Scale[2,3,41,42] or the Numeric Rating Scale[45,47] but only two[42,45] reported a cut-off value to signify who had and did not have pain. The other three studies[43,44,46] simply reported whether pain was 'present' or 'absent' to group their cohorts. Four studies assessed for pain using only subjective reports,[2,43-45] whilst the others combined clinical examination and history-taking to determine if pain was present.

Risk of Bias

The risk of bias was assessed using the QUIPS tool and the ratings for each individual domain can be seen in **figure 2**. The level of agreement between the two

252 assessors (RH and KM) was calculated using the weighted Cohen's kappa statistic
253 (weighted κ = 0.68) which corresponded to a substantial degree of agreement.[48]

254

255 Using these domains and *a priori* determined criteria, two studies[2,3] were judged to
256 have an overall low risk of bias, five studies to be moderate risk of bias,[42-45,47] and
257 two studies[41,46] to have a high risk of bias overall.

258

259 **Figure 2.** Assessment of risk of bias using the Quality in Prognosis Studies tool

260 **<insert Figure 2>**

261

262 *Meta-analysis*

263 Only four factors had sufficient data to enable meta-analysis. All analyses were
264 conducted using a random effects model to account for variations in the approaches
265 used and samples taken.

266

267 Five studies were included in the analysis of sex. Meta-analysis showed that there
268 was no difference in the odds for men and women developing PSSP (OR 0.93, CI
269 95% 0.75-1.15, p=0.501) (**figure 3**). The I^2 statistic was very low (0.13%) suggesting
270 heterogeneity was not present. However, Kontopantelis et al[22] suggest caution when
271 I^2 is so low as it is likely that heterogeneity is present but undetected. Indeed the
272 wide 95% CI for Roosink et al[47] suggests poor precision and could potentially mask
273 heterogeneity.

Four studies were included in the analysis of stroke laterality. Again no statistical difference was found in relation to whether the stroke was in the right or left hemisphere (OR 0.78, CI 95% 0.59-1.05, p=0.097, I^2=9.52%) (**figure 4**). Interestingly, although not statistically significant, there is a shift of the 95% CI towards patients with right hemisphere strokes having a slightly increased risk of PSSP. Further studies would be needed to explore this.

Figure 3. Forest plot displaying the pooled OR analysis for sex

<insert Figure 3>

Figure 4. Forest plot displaying the pooled OR analysis for laterality

<insert Figure 4>

The analysis for diabetes included six studies. Meta-analysis showed that diabetic patients were twice as likely to develop PSSP as patients without diabetes (OR 2.09, 95% CI 1.16-3.78) and that this finding was statistically significant (p=0.015). However, there was a high degree of statistical heterogeneity (I^2=74.15%) as can be seen by the large spread of ORs and 95% CIs seen in **figure 5**.

Only three studies were available to conduct a meta-analysis for history of shoulder pain thereby limiting the acceptability of the results. The analysis identified that a history of shoulder pain increased the risk of developing PSSP (OR 2.78, 95% CI 1.29-5.97) which was significant (p=0.009). Again, as can be seen in **figure 6**, there was a high level of heterogeneity between studies although an I^2 statistic was not calculated as it was felt displaying this with the small number of included studies would provide misleading or inaccurate information. It is also worth noting that two studies with data were excluded from analysis due to significant variations in their inclusion criteria. Isaksson et al[43] only included patients with pronounced weakness, and Roosink et al[47] excluded patients with severe pre-morbid pain. Notably both of these studies showed non-significant results (**table 3**).

All other factors were not appropriate for combining in meta-analysis and are summarised in narrative synthesis below.

Figure 5. Forest plot displaying the pooled OR analysis for diabetes

<insert Figure 5>

Figure 6. Forest plot displaying the pooled OR analysis for history of shoulder pain

<insert Figure 6>

Demographics

The data for demographic data can be viewed in **table 2**. Analyses for age as a risk factor were inconclusive due the variations in measurement used. One study[45] reported an increased risk for younger patients (<70 years). However, two other studies[3,44] found age to be nonsignificant as a predictor of PSSP when used as a factor in multivariate analysis.

Four papers reported data on the type of stroke. Isaksson et al[43] reported data that showed patients with haemorrhagic strokes were more likely to develop PSSP, however only patients with pronounced weakness were included which could bias the result. The other three studies[2,3,45] showed no significant difference between types of stroke as a predictor.

It was possible to calculate ORs for the subtype of stroke (Oxfordshire classification) in two papers.[2,3] Only the total anterior circulation stroke was shown to be a significant risk for developing PSSP at four months when compared with lacunar stokes.

One paper[42] considered smoking habits as a potential risk factor but data was not available to calculate an OR.

Table 2. Demographics - Factors with sufficient data to calculate OR

<insert Table 2>

Co-morbidities

Diabetes and a history of shoulder pain has been discussed in the meta-analysis. Of the other co-morbidities with data available for ORs none showed a statistically significant increased odds of developing PSSP (**table 3**). Temporary unconsciousness at onset was considered as a risk factor in one paper[42] but data was not available to calculate an OR.

Table 3. Comorbidities - Factors with sufficient data to calculate OR

<insert Table 3>

Clinical assessments and measures

The full list of measures and ORs for clinical assessment and measures can be seen in **table 4**. Severity of upper limb (UL) motor function was concluded to be a major risk factor in four papers.[2,3,44,45] Unfortunately a variety of outcome measures was used making comparisons unfeasible. Significant results were found for the odds ratio of a poor score on item 5 on the National Institutes of Health Stroke Scale (≥3) for the development of pain within 6 months[45] and within 1 year.[3] This measure was also shown to be significant (p=0.03) in a logistic regression analysis by Lind et al[2] but no data was supplied to calculate an OR.

Kim et al[45] also measured motor function using the Fugl-Meyer arm score and found those patients with lower motor function (a score of 20 or less) were statistically more likely to develop PSSP at 6 months post-stroke than those with higher scores.

Ratnasabapathy et al[44] reported an increasing risk of PSSP as UL motor deficit increased from mild to moderate to severe, suggesting a potential trend. However it is worth noting that these categories were subjective reports from study participants and not based on standardised measures.

It was deemed inappropriate to combine the findings for UL motor function in a meta-analysis due to the substantial heterogeneity in the method of measurement. However, an impairment in UL motor function at baseline consistently produced a significantly increased chance of developing PSSP leading to the conclusion that it was an important risk factor to be aware of.

Adey-Wakeling et al[3] considered a specific set of shoulder tests (namely the modified Neer's test, passive hand-behind-neck, and passive external rotation compared with the unaffected limb) as originally described by Rajaratnam et al.[36] Despite finding that these tests were able to identify a higher frequency of PSSP than by patient-report, when included in a multivariate analysis the odds ratio was not significant. This was supported by 2 other studies[45,47] who explored early reduced range of movement as a predictor for PSSP and found non-significant results.

Table 4. Clinical assessments and measures - Factors with sufficient data to calculate OR

<insert Table 4>

Aspects of somatosensory function including sensation to light touch, sensation to temperature, sharpness, proprioception, tactile inattention and tactile extinction were also explored. Only tactile extinction and proprioception were found to significantly increase the risk of developing PSSP.

Kim et al[45] presented data on various baseline radiological and sonographic findings (**table 1**). Readers are directed to the original article to see the full list of ORs for the factors explored as they are too extensive to be repeated here. Only tendinosis or tear of the supraspinatus tendon at baseline sonography was associated with PSSP onset within the first 6 months (OR 4.21, 95% CI 1.37-12.93).

Data was available to calculate ORs for PSSP at baseline in 2 studies,[3,44] and found conflicting results. Paci et al[46] did not provide data to calculate an OR but did find pain at baseline to be significantly associated with pain at follow-up in their multiple regression analysis ($p<0.001$), though this was approximately 2 to 3 months after stroke.

Across the included studies, it was possible to calculate ORs for a number of other baseline measures including motor impairment, stroke severity, spasticity in the UL, subluxation of the glenohumeral joint, dependency during gait, cognition, visual problems, and autonomic function (**table 4**). These factors were each reported in only one study and the majority showed no significant relationship to the onset of PSSP. Only motor impairment (measured using the Motricity Index) and subluxation showed significant results though the wide 95% CIs for these results would bring into question the precision of this result.

Anxiety, depression, communication disorders, and motivation for rehabilitation were factors considered in one paper[42] but data was not supplied to calculate an OR.

Discussion

This systematic review has identified reduced motor function in the UL, diabetes, and a history of shoulder pain as risk factors for the development of PSSP within the first year after stroke. It has also identified a number of clinical assessments made in the acute stages of stroke that were statistically significant but were only measured in single studies and lack the benefit of confirmatory evidence. These factors were reduced motor function, presence of subluxation, tactile extinction and impaired proprioception.

The results presented should be interpreted with caution. Care was taken to limit bias as much as possible by only including prospective studies and by undertaking a complete and thorough literature search. However, meta-analyses of observational studies are prone to the biases inherent in the original studies,[49] and unfortunately, the majority of studies included in this review were rated as a moderate or high risk of bias. Because of this potential bias, as much of the raw data as was feasible was included to increase transparency. This was also done so that the reader could make their own conclusions regarding the weighting each study had on the level of risk for each factor.

The likelihood that reduced motor function in the UL leads to an increased risk of PSSP is unsurprising. The loss of motor function will undoubtedly alter the kinetics and kinematics around the shoulder complex. This suboptimal performance of scapula kinesis and the reduced control of forces around the humeral head on the glenoid has the potential to lead to deleterious effects on anatomical structures around the shoulder.[50] Indeed, Idowu et al[51] found a significantly higher frequency of shoulder pathologies in hemiplegic shoulders when compared with unaffected shoulders and control subjects, whilst Yi et al[52] found a trend towards a higher prevalence of rotator cuff tears with worsening hemiplegia. Unfortunately, neither of these studies correlated these sonographic findings with the incidence of pain.

A more recent prospective study[53] of 121 participants further confirmed the association of reduced motor function of the UL as a risk factor for PSSP. They also concluded, in support of Paci et al,[46] that subluxation was an important risk factor

and reported a significant proportional difference between those with subluxation who did and did not have PSSP at the 8-10 week follow up (p=0.026). However, when the data are used to calculate an OR in the same method as this review the outcome is non-significant (OR 1.68, 95% CI 0.49-5.70). It would seem logical that subluxation of the glenohumeral joint would lead to similar pathobiomechanics as previously discussed and thereby also be a risk factor for PSSP. However, further confirmatory studies with a temporal element to the measurement of risk factors and pain are required to clarify this.

The identification of diabetes as a risk factor for PSSP is also unsurprising given the increased prevalence of shoulder pain in diabetic patients in the general population.[50] Both tendinopathy[51] and adhesive capsulitis[52] were found to be more prevalent in patients with diabetes and both of these conditions are a potential source of PSSP. The increased risk of shoulder pain in diabetic patients is thought to be due to advanced glycation end-products causing stiffness and weakness in connective tissues,[53] this, coupled with the reduced function following a stroke, may further enhance the damaging effects of structures in the shoulder complex.

This exploratory review has identified a number of factors from the best available evidence that may aid clinicians in the early identification of patients who may develop PSSP. Based on these results it is advised that clinicians ensure they routinely enquire about diabetes and any history of shoulder pain when taking a patient's medical history. It is not recommended that these findings should be construed as definitive due to the limitations mentioned hereinafter, however they

should be used as a guide to aid clinical reasoning and decision-making when deciding on which patients to focus preventative strategies. Knowledge of these risk factors may aid in the understanding of causation and thereby lead to more targeted prevention strategies. They will also provide clinicians with prognostic information to better inform patients, carers and relatives.

Study Limitations

There were a number of limitations within this systematic review that will impact on the validity of these results. These limitations were to be expected given the complex nature of PSSP observed in a clinical setting. Firstly, there were large variations in the included studies with regards to how pain was defined, how and when risk factors were measured, and how data were analysed. This has made comparability between studies very challenging and whilst some data have been combined in meta-analysis the results should be viewed as informative rather than definitive due to the heterogeneous nature of the studies included.

Secondly, due to the large number of potential factors measured, the included studies may have been limited in what could feasibly be reported, potentially causing under-reporting or selective reporting of certain variables. Attempts were made to overcome this potential bias by calculating ORs for all factors where possible, thereby allowing the recognition of certain risk factors not reported or considered in the original studies. Whilst calculating crude ORs in this way allowed a larger pool of data it is recognised that univariate analysis of this type does not take into account the impact these different factors have on each other thereby potentially leading to an oversimplification of which factors are associated with PSSP.

Recommendations

The current categorisation of PSSP within the literature presents a potential problem. Whilst it is well documented that PSSP is complex and multifactorial in nature it is often referred to as a single entity rather than as an umbrella-term for a number of different aetiologies. This broad definition of PSSP is potentially limiting the specificity of research trials leading to conflicting results. It is recommended that future studies should explore improved classification of PSSP subtypes to allow more accurate links to be made between risk factors and PSSP presentation.

It is also recommended that future studies exploring risk have a standardised and comparable approach to the measurement of pain. Whilst it is acknowledged that the measurement of pain in stroke patients presents some difficulties with regards to validity and reliability,[58] a vertical numeric rating scale would be the preferred option. It is also recommended that data for pain at rest and on passive or active movement is analysed and reported separately to improve comparability. Studies exploring factors associated with PSSP should also give consideration to, and report on, any qualitative differences in the nature and pattern of pain between subjects, as well as factors such as whether the pain was at night or on clinical assessment only. Observational studies of this nature may help to better understand PSSP subtypes and improve specificity. Where possible, efforts should be made to ensure the inclusion of patients with communication or cognitive difficulties by using carers as proxies when needed to more accurately represent the target population.

Motor impairment of the upper limb was repeatedly shown to increase the risk of PSSP, however it was not possible to combine in meta-analysis due to variation in measurement. This important factor warrants further investigation. In this review the Fugl-Meyer Assessment was the most credible of the outcome measures used and would be the authors recommendation for future studies to allow comparative analysis.

Conclusions

This review has identified motor deficits in the UL, diabetes and a history of shoulder pain to be significant predictors of the development of PSSP within the first year after stroke. Whilst it is acknowledged that the lack of robust studies included prevent definitive conclusions to be made, it is hoped that the results presented will provide clinicians with a potential 'at risk' group of patients in the acute stage of stroke on whom to focus preventative strategies. A number of recommendations to standardise future studies in this area have been made. Future observational studies defining and categorising the subtypes of PSSP would be beneficial to aid research into the specificity of treatments for this complex and frequent problem.

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Legends of Figures and Tables

Figure 1. PRISMA Flow diagram of study selection

Figure 2. Assessment of risk of bias using the Quality in Prognosis Studies tool

Figure 3. Forest plot displaying the pooled OR analysis for sex

Figure 4. Forest plot displaying the pooled OR analysis for laterality of stroke

Figure 5. Forest plot displaying the pooled OR analysis for diabetes

Risk Factors for Post-Stroke Shoulder Pain: A Systematic Review and Meta-analysis

Abstract

Objective: To identify the risk factors identified within one month post-stroke that predict the onset of post-stroke shoulder pain (PSSP) within the first year after stroke.

Methods: Five databases, (AMED, CINAHL, EMBASE, Medline, PubMed) were searched from inception to April 2019. Prospective cohort studies that measured a potential risk factor for post-stroke shoulder pain within the first month after stroke were included. Two authors independently reviewed and selected articles for inclusion. Risk of bias was assessed using the Quality in Prognosis Studies tool. Data extracted included raw data for odds ratio (OR) calculations, definition and measurement of pain, study limitations and baseline characteristics of participants. The review was conducted following PRISMA guidelines.

Results: Nine articles were retrieved that met the inclusion criteria, and six presented data to use in meta-analysis. Fifty-four different factors were identified as potential risk factors. Meta-analysis was possible for four factors; sex (OR 0.93, CI 0.75-1.15), laterality (OR 0.78, CI 0.59-1.05), diabetes (OR 2.09, CI 1.16-3.78), and history of shoulder pain (OR 2.78, CI 1.29-5.97). Reduced motor function in the upper limb was also identified as a significant risk factor through qualitative synthesis.

Conclusions: Reduced motor function in the upper limb, diabetes, and a history of shoulder pain were identified as significant risk factors for the development of PSSP within the first year after stroke. Recommendations to standardise future studies in this area have been made and it is suggested that defining subtypes of PSSP may aid future interventional studies.

Introduction

Post-stroke shoulder pain (PSSP) is a common and often debilitating consequence of stroke. Wide variations of incidence have been reported in the literature dependent on the patient cohort and methodology used. Most recent studies have found an incidence rate of between 18-22% at 3-4 months after stroke onset[1-3] with a slight reduction at 1 year post-stroke to between 6-21%.[3,4] Lindgren et al[2] reported that 73% of patients with PSSP reported they had pain daily whilst a further 11% reported constant pain, and 45% required some form of analgesic medication.

PSSP is known to negatively impact on a person's ability to carry out activities of daily living, such as walking and dressing,[2] and limit their ability to participate in leisure activities.[5] Furthermore it has been shown to be associated with reduced quality of life[6,7] as well as having a direct impact on mood.[5] Barlak et al[8] also reported a significantly longer stay in rehabilitation for patients with PSSP.

There is therefore a need to limit the impact of this common consequence of stroke through robust prevention strategies and effective treatment modalities. However, difficulties arise due to the complex and multifactorial nature of PSSP.[9] A large variety of possible aetiologies are described in the literature including musculoskeletal disorders such as rotator cuff dysfunction, bursitis, adhesive capsulitis, and impingement, as well as neurogenic problems such as spasticity, central hypersensitivity and complex regional pain syndrome.[10] Unsurprisingly this multitude of aetiologies has led to multiple interventions been suggested in the

literature. However, there seems to be little consensus on the implementation of some of these interventions[11-13] making assessment of their effectiveness difficult. A review by Li and Alexander[14] supported this when they found the evidence for treatments of PSSP to be lacking, though this should not be misinterpreted as evidence that treatments are ineffective.

The lack of consensus on best management makes prevention all the more important. However, to prevent PSSP we must first understand which patients are most at risk so that strategies can be put in place and regular assessments can be done to monitor any early developments of PSSP and limit the impact in the chronic stages. To answer this question, a number of often cited studies have explored factors that are correlated with PSSP such as subluxation,[15] spasticity,[16] and abnormal joint examination.[17] But due to the lack of repeated temporal measures these correlations do not show causation and the factors explored should not be interpreted as risk factors.

To date, reviews exploring PSSP have either been narrative in nature[18] or have focussed on factors that are correlated with PSSP.[19] Whilst these give an indication of factors closely linked to PSSP, they are limited by the variations in methodologies included and do not give a satisfactory answer to the matter of risk.

There is, therefore, a need to collate those studies investigating specifically risk and predictive factors that are effectively assessed and quantified using robust

prospective studies to see if there is agreement within the literature. The aim of this systematic review was to identify the potential risk factors measured within the first month after stroke that predicted the onset of shoulder pain within the first year after stroke.

Methods

To complete and report this review the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[20] was used.

Search Strategy

The search strategy was designed with the aid of a clinical librarian with input from the two lead authors (RH/KM). The databases AMED (1985 – April 2019), CINAHL (1937 – April 2019), EMBASE (1974 – April 2019), Medline (1946 – April 2019), and PubMed were used with no limitations applied. Variants of 'stroke', 'shoulder pain', and 'risk factors' were used as keywords and combined in the search strategy. The full search strategy can be viewed on the International Prospective Register of Systematic Reviews (PROSPERO: CRD42018110406) where this systematic review was registered. Further articles were sourced by hand-searching through the reference lists of key articles. The websites www.clinicaltrials.gov and www.ukctg.nihr.ac.uk were regularly reviewed to check for any ongoing trials that may be relevant; however no articles were sourced using this method.

Study Selection

Studies were eligible for inclusion only if the following three criteria were present: a) they were prospective cohort studies, b) they measured any potential risk factor within the first month after stroke and c) they measured pain as a key outcome within one year after stroke. Any definition and measure of pain used by study authors was deemed acceptable for inclusion. Studies in languages other than English were included only if a full-text English version could be sourced. To answer the specific question of risk it was felt essential that there was an element of temporality between the measurement of the risk factor and the measurement of pain, consequently correlates of PSSP were beyond the scope of this study. Studies were therefore excluded if they were cross-sectional studies in which all measures were taken at a single time-point (thereby assessing correlation rather than risk). Case reports, conference abstracts, poster presentations or other studies where the full report was not available were also excluded.

Two reviewers (RH and KM) screened the titles and abstracts independently. Full-text versions of the selected papers were obtained and were assessed against the inclusion and exclusion criteria by the same reviewers, again independently. Where there was disagreement a consensus was made through discussion along with the third reviewer (CK).

Authors were contacted when articles were lacking sufficient detail to assess the inclusion criteria. In all cases clarity was sought to understand if baseline measures were recorded within the first month after stroke. Authors were asked at what point baseline measures were taken and, to avoid bias, were not given information of the research question or the inclusion criteria.

Data extraction & risk of bias assessment

The main data extracted included all factors that were identified and analysed as potential risks or where sufficient data were supplied for factors where an odds ratio (OR) could be calculated. Other data extracted included the aims and methodology of each study, the period of observation, baseline characteristics of the cohort, inclusion/exclusion criteria, how pain was defined and measured, the temporal aspect of baseline and repeated measures, and limitations of the study in relation to the research question.

The risk of bias of included studies was independently assessed by two reviewers (RH and KM) using the Quality in Prognosis Studies (QUIPS) tool.[21] This tool considers six domains (Study Participation, Study Attrition, Prognostic Factor Measurement, Outcome Measurement, Study Confounding, and Statistical Analysis and Reporting) and rates these as having low, moderate or high risk of bias. Any disagreement between reviewers related to these assessments was resolved through discussion until a consensus was reached.

The overall risk of bias was determined *a priori* and judged as: *low* if 4 or more of the domains were rated low and no domains rated as high, *moderate* if 4 or less domains were rated low with one domain rated as high or 3 or less domains rated as low with no high risk domains, and *high* if 2 or more domains were rated as high or if 1 domain was rated as high with no low risk domains.

Data Synthesis

The articles were described and summarised in a narrative form. Where possible, raw data were extracted from the original papers to calculate ORs and 95% confidence intervals (CI) with the intention of pooling these outcomes in meta-analysis. Where raw data were not available the ORs presented in the original articles were used.

Attempts were made to perform meta-analysis when data for a dichotomous variable were presented in three or more studies. Between-study heterogeneity was evaluated at face value based on methodological characteristics such as inclusion criteria and the method of outcome measurement. If there was substantial variation in the methods used then data were interpreted narratively. When it was possible to combine data, heterogeneity was assessed using the I^2 statistic, although it is acknowledged that detecting true heterogeneity with a very small number of studies is thought to be very difficult.[22]

All analyses were performed using random effects models to account for the varied approaches within the studies. Funnel plots to assess for publication bias were not presented as it was felt that the small number of studies included would limit their usefulness of this analysis. All analyses were undertaken using the software package Comprehensive Meta Analysis (V3.3.070) (www.Meta-Analysis.com).

Results

Literature Search

The search from the selected databases returned a total of 1,077 articles (**figure 1**). An additional 31 articles were sourced through hand-searching reference lists from key articles (n=3) and through search alerts following the initial search (n=28). During screening 593 were excluded as they clearly did not meet the necessary inclusion criteria. A further 11 abstracts were discarded as they were found to be poster presentations or conference abstracts, and one final paper published in Spanish[23] was excluded as it was not possible to access in English.

The full text of the remaining 30 articles were assessed in more detail. A further 21 were excluded due to (a) risk factors not been measured within the first month after stroke,[8,17,24-30] (b) exploring factors correlated with PSSP rather than risk,[15,16,31-36] (c) retrospective methodologies,[37,38] and (d) studies' aims not exploring risk of PSSP.[39,40] Authors of four articles were contacted to seek further clarification regarding the timing of baseline measures. For two of these studies[41,42] the authors

were able to confirm that the baseline measures were recorded within the first month and were included in the review. Of the other two, one author was unable to recall[17] and one author did not respond.[8] These were therefore excluded.

Figure 1. PRISMA Flow diagram of study selection

<insert Figure 1>

The remaining nine[2,3,41-47] articles were included in the systematic review. Of these, seven provided sufficient data to calculate ORs on the four risk factors that had sufficient data to conduct meta-analyses. However, the study by Isaksson et al[43] was excluded from all meta-analyses as it was thought to be too heterogeneous due to only including patients with pronounced UL weakness. It was felt that this was a significant difference from the populations of the other studies and was likely to significantly skew the analysis.

Characteristics of included studies

The nine papers included consisted of eight prospective cohort studies from seven different countries published between 2003[44] and 2018.[41] A summary of the characteristics of the included studies is presented in **table 1**. The mean sample size of the studies was 309 (range: 31-1474). In total 2474 patients were included in the data synthesis consisting of 1237 (50%) males and 1237 (50%) females. It was not possible to calculate a combined description of participants' age due to the variation

in descriptive statistics provided across studies. Three studies[2,3,45] reported types of stroke and found that 87% (n=566) patients had an ischaemic stroke. Side of stroke was reported in four studies[3,45-47]; 54% (n=247) of participants having a left hemispheric stroke and 46% (n=211) having a right hemispheric stroke.

Table 1. Characteristics of included studies

<insert Table 1>

Three papers[2,3,44] included all stroke patients and took steps to ensure that participants with communication or cognitive impairments were included by involving carers or next-of-kin. One paper[43] restricted participants to only those with pronounced arm weakness limiting the comparability with other studies. Another[47] explored only patients who had persistent PSSP leading to the loss of two patients who had pain but were excluded from the final analysis.

Five studies[2,3,44,46,47] presented prevalence rates or provided sufficient data to calculate a rate for PSSP at specific time points. Two studies did not present clear enough data to calculate a true prevalence, and one study looked at a specific subsection of patients. At baseline (within the first week), data was available on 1672 patients[3,44] and gave a prevalence rate of 16%. This prevalence increased to 21% (103/483) at four months,[2,3] 24% (293/1235) at 6 months[44,47] and 23% (105/453) at one year post-stroke.[2,3]

The nine papers presented data on a total of 54 different factors that were measured temporally to allow the calculation of risk. Within these, seven were categorised as *Demographic factors*, 13 as *Co-morbidities*, and 34 as *Clinical assessments and measures* (**table 1**).

Pain Measurement

There were large variations in how pain was defined and measured. Four papers defined pain as either at rest or during passive or active movement[43,45-47] but none of these reported how the data was handled when conflicting results between 'at rest' and 'on movement' were found. Four papers did not specify how they defined PSSP,[2,41,42,44] and a final paper defined PSSP as any subjective complaint in the hemiplegic shoulder.[3] Six papers used either the Visual Analogue Scale[2,3,41,42] or the Numeric Rating Scale[45,47] but only two[42,45] reported a cut-off value to signify who had and did not have pain. The other three studies[43,44,46] simply reported whether pain was 'present' or 'absent' to group their cohorts. Four studies assessed for pain using only subjective reports,[2,43-45] whilst the others combined clinical examination and history-taking to determine if pain was present.

Risk of Bias

The risk of bias was assessed using the QUIPS tool and the ratings for each individual domain can be seen in **figure 2**. The level of agreement between the two

252 assessors (RH and KM) was calculated using the weighted Cohen's kappa statistic
253 (weighted κ = 0.68) which corresponded to a substantial degree of agreement.[48]

254

255 Using these domains and *a priori* determined criteria, two studies[2,3] were judged to
256 have an overall low risk of bias, five studies to be moderate risk of bias,[42-45,47] and
257 two studies[41,46] to have a high risk of bias overall.

258

259 **Figure 2.** Assessment of risk of bias using the Quality in Prognosis Studies tool

260 **<insert Figure 2>**

261

262 *Meta-analysis*

263 Only four factors had sufficient data to enable meta-analysis. All analyses were
264 conducted using a random effects model to account for variations in the approaches
265 used and samples taken.

266

267 Five studies were included in the analysis of sex. Meta-analysis showed that there
268 was no difference in the odds for men and women developing PSSP (OR 0.93, CI
269 95% 0.75-1.15, p=0.501) (**figure 3**). The I^2 statistic was very low (0.13%) suggesting
270 heterogeneity was not present. However, Kontopantelis et al[22] suggest caution when
271 I^2 is so low as it is likely that heterogeneity is present but undetected. Indeed the
272 wide 95% CI for Roosink et al[47] suggests poor precision and could potentially mask
273 heterogeneity.

Four studies were included in the analysis of stroke laterality. Again no statistical difference was found in relation to whether the stroke was in the right or left hemisphere (OR 0.78, CI 95% 0.59-1.05, p=0.097, I^2=9.52%) (**figure 4**). Interestingly, although not statistically significant, there is a shift of the 95% CI towards patients with right hemisphere strokes having a slightly increased risk of PSSP. Further studies would be needed to explore this.

Figure 3. Forest plot displaying the pooled OR analysis for sex

<insert Figure 3>

Figure 4. Forest plot displaying the pooled OR analysis for laterality

<insert Figure 4>

The analysis for diabetes included six studies. Meta-analysis showed that diabetic patients were twice as likely to develop PSSP as patients without diabetes (OR 2.09, 95% CI 1.16-3.78) and that this finding was statistically significant (p=0.015). However, there was a high degree of statistical heterogeneity (I^2=74.15%) as can be seen by the large spread of ORs and 95% CIs seen in **figure 5**.

Only three studies were available to conduct a meta-analysis for history of shoulder pain thereby limiting the acceptability of the results. The analysis identified that a history of shoulder pain increased the risk of developing PSSP (OR 2.78, 95% CI 1.29-5.97) which was significant (p=0.009). Again, as can be seen in **figure 6**, there was a high level of heterogeneity between studies although an I^2 statistic was not calculated as it was felt displaying this with the small number of included studies would provide misleading or inaccurate information. It is also worth noting that two studies with data were excluded from analysis due to significant variations in their inclusion criteria. Isaksson et al[43] only included patients with pronounced weakness, and Roosink et al[47] excluded patients with severe pre-morbid pain. Notably both of these studies showed non-significant results (**table 3**).

All other factors were not appropriate for combining in meta-analysis and are summarised in narrative synthesis below.

Figure 5. Forest plot displaying the pooled OR analysis for diabetes

<insert Figure 5>

Figure 6. Forest plot displaying the pooled OR analysis for history of shoulder pain

<insert Figure 6>

Demographics

The data for demographic data can be viewed in **table 2**. Analyses for age as a risk factor were inconclusive due the variations in measurement used. One study[45] reported an increased risk for younger patients (<70 years). However, two other studies[3,44] found age to be nonsignificant as a predictor of PSSP when used as a factor in multivariate analysis.

Four papers reported data on the type of stroke. Isaksson et al[43] reported data that showed patients with haemorrhagic strokes were more likely to develop PSSP, however only patients with pronounced weakness were included which could bias the result. The other three studies[2,3,45] showed no significant difference between types of stroke as a predictor.

It was possible to calculate ORs for the subtype of stroke (Oxfordshire classification) in two papers.[2,3] Only the total anterior circulation stroke was shown to be a significant risk for developing PSSP at four months when compared with lacunar stokes.

One paper[42] considered smoking habits as a potential risk factor but data was not available to calculate an OR.

Table 2. Demographics - Factors with sufficient data to calculate OR

<insert Table 2>

Co-morbidities

Diabetes and a history of shoulder pain has been discussed in the meta-analysis. Of the other co-morbidities with data available for ORs none showed a statistically significant increased odds of developing PSSP (**table 3**). Temporary unconsciousness at onset was considered as a risk factor in one paper[42] but data was not available to calculate an OR.

Table 3. Comorbidities - Factors with sufficient data to calculate OR

<insert Table 3>

Clinical assessments and measures

The full list of measures and ORs for clinical assessment and measures can be seen in **table 4**. Severity of upper limb (UL) motor function was concluded to be a major risk factor in four papers.[2,3,44,45] Unfortunately a variety of outcome measures was used making comparisons unfeasible. Significant results were found for the odds ratio of a poor score on item 5 on the National Institutes of Health Stroke Scale (≥3) for the development of pain within 6 months[45] and within 1 year.[3] This measure was also shown to be significant (p=0.03) in a logistic regression analysis by Lind et al[2] but no data was supplied to calculate an OR.

Kim et al[45] also measured motor function using the Fugl-Meyer arm score and found those patients with lower motor function (a score of 20 or less) were statistically more likely to develop PSSP at 6 months post-stroke than those with higher scores.

Ratnasabapathy et al[44] reported an increasing risk of PSSP as UL motor deficit increased from mild to moderate to severe, suggesting a potential trend. However it is worth noting that these categories were subjective reports from study participants and not based on standardised measures.

It was deemed inappropriate to combine the findings for UL motor function in a meta-analysis due to the substantial heterogeneity in the method of measurement. However, an impairment in UL motor function at baseline consistently produced a significantly increased chance of developing PSSP leading to the conclusion that it was an important risk factor to be aware of.

Adey-Wakeling et al[3] considered a specific set of shoulder tests (namely the modified Neer's test, passive hand-behind-neck, and passive external rotation compared with the unaffected limb) as originally described by Rajaratnam et al.[36] Despite finding that these tests were able to identify a higher frequency of PSSP than by patient-report, when included in a multivariate analysis the odds ratio was not significant. This was supported by 2 other studies[45,47] who explored early reduced range of movement as a predictor for PSSP and found non-significant results.

Table 4. Clinical assessments and measures - Factors with sufficient data to calculate OR

<insert Table 4>

Aspects of somatosensory function including sensation to light touch, sensation to temperature, sharpness, proprioception, tactile inattention and tactile extinction were also explored. Only tactile extinction and proprioception were found to significantly increase the risk of developing PSSP.

Kim et al[45] presented data on various baseline radiological and sonographic findings (**table 1**). Readers are directed to the original article to see the full list of ORs for the factors explored as they are too extensive to be repeated here. Only tendinosis or tear of the supraspinatus tendon at baseline sonography was associated with PSSP onset within the first 6 months (OR 4.21, 95% CI 1.37-12.93).

Data was available to calculate ORs for PSSP at baseline in 2 studies,[3,44] and found conflicting results. Paci et al[46] did not provide data to calculate an OR but did find pain at baseline to be significantly associated with pain at follow-up in their multiple regression analysis ($p<0.001$), though this was approximately 2 to 3 months after stroke.

Across the included studies, it was possible to calculate ORs for a number of other baseline measures including motor impairment, stroke severity, spasticity in the UL, subluxation of the glenohumeral joint, dependency during gait, cognition, visual problems, and autonomic function (**table 4**). These factors were each reported in only one study and the majority showed no significant relationship to the onset of PSSP. Only motor impairment (measured using the Motricity Index) and subluxation showed significant results though the wide 95% CIs for these results would bring into question the precision of this result.

Anxiety, depression, communication disorders, and motivation for rehabilitation were factors considered in one paper[42] but data was not supplied to calculate an OR.

Discussion

This systematic review has identified reduced motor function in the UL, diabetes, and a history of shoulder pain as risk factors for the development of PSSP within the first year after stroke. It has also identified a number of clinical assessments made in the acute stages of stroke that were statistically significant but were only measured in single studies and lack the benefit of confirmatory evidence. These factors were reduced motor function, presence of subluxation, tactile extinction and impaired proprioception.

The results presented should be interpreted with caution. Care was taken to limit bias as much as possible by only including prospective studies and by undertaking a complete and thorough literature search. However, meta-analyses of observational studies are prone to the biases inherent in the original studies,[49] and unfortunately, the majority of studies included in this review were rated as a moderate or high risk of bias. Because of this potential bias, as much of the raw data as was feasible was included to increase transparency. This was also done so that the reader could make their own conclusions regarding the weighting each study had on the level of risk for each factor.

The likelihood that reduced motor function in the UL leads to an increased risk of PSSP is unsurprising. The loss of motor function will undoubtedly alter the kinetics and kinematics around the shoulder complex. This suboptimal performance of scapula kinesis and the reduced control of forces around the humeral head on the glenoid has the potential to lead to deleterious effects on anatomical structures around the shoulder.[50] Indeed, Idowu et al[51] found a significantly higher frequency of shoulder pathologies in hemiplegic shoulders when compared with unaffected shoulders and control subjects, whilst Yi et al[52] found a trend towards a higher prevalence of rotator cuff tears with worsening hemiplegia. Unfortunately, neither of these studies correlated these sonographic findings with the incidence of pain.

A more recent prospective study[53] of 121 participants further confirmed the association of reduced motor function of the UL as a risk factor for PSSP. They also concluded, in support of Paci et al,[46] that subluxation was an important risk factor

and reported a significant proportional difference between those with subluxation who did and did not have PSSP at the 8-10 week follow up (p=0.026). However, when the data are used to calculate an OR in the same method as this review the outcome is non-significant (OR 1.68, 95% CI 0.49-5.70). It would seem logical that subluxation of the glenohumeral joint would lead to similar pathobiomechanics as previously discussed and thereby also be a risk factor for PSSP. However, further confirmatory studies with a temporal element to the measurement of risk factors and pain are required to clarify this.

The identification of diabetes as a risk factor for PSSP is also unsurprising given the increased prevalence of shoulder pain in diabetic patients in the general population.[50] Both tendinopathy[51] and adhesive capsulitis[52] were found to be more prevalent in patients with diabetes and both of these conditions are a potential source of PSSP. The increased risk of shoulder pain in diabetic patients is thought to be due to advanced glycation end-products causing stiffness and weakness in connective tissues,[53] this, coupled with the reduced function following a stroke, may further enhance the damaging effects of structures in the shoulder complex.

This exploratory review has identified a number of factors from the best available evidence that may aid clinicians in the early identification of patients who may develop PSSP. Based on these results it is advised that clinicians ensure they routinely enquire about diabetes and any history of shoulder pain when taking a patient's medical history. It is not recommended that these findings should be construed as definitive due to the limitations mentioned hereinafter, however they

should be used as a guide to aid clinical reasoning and decision-making when deciding on which patients to focus preventative strategies. Knowledge of these risk factors may aid in the understanding of causation and thereby lead to more targeted prevention strategies. They will also provide clinicians with prognostic information to better inform patients, carers and relatives.

Study Limitations

There were a number of limitations within this systematic review that will impact on the validity of these results. These limitations were to be expected given the complex nature of PSSP observed in a clinical setting. Firstly, there were large variations in the included studies with regards to how pain was defined, how and when risk factors were measured, and how data were analysed. This has made comparability between studies very challenging and whilst some data have been combined in meta-analysis the results should be viewed as informative rather than definitive due to the heterogeneous nature of the studies included.

Secondly, due to the large number of potential factors measured, the included studies may have been limited in what could feasibly be reported, potentially causing under-reporting or selective reporting of certain variables. Attempts were made to overcome this potential bias by calculating ORs for all factors where possible, thereby allowing the recognition of certain risk factors not reported or considered in the original studies. Whilst calculating crude ORs in this way allowed a larger pool of data it is recognised that univariate analysis of this type does not take into account the impact these different factors have on each other thereby potentially leading to an oversimplification of which factors are associated with PSSP.

Recommendations

The current categorisation of PSSP within the literature presents a potential problem. Whilst it is well documented that PSSP is complex and multifactorial in nature it is often referred to as a single entity rather than as an umbrella-term for a number of different aetiologies. This broad definition of PSSP is potentially limiting the specificity of research trials leading to conflicting results. It is recommended that future studies should explore improved classification of PSSP subtypes to allow more accurate links to be made between risk factors and PSSP presentation.

It is also recommended that future studies exploring risk have a standardised and comparable approach to the measurement of pain. Whilst it is acknowledged that the measurement of pain in stroke patients presents some difficulties with regards to validity and reliability,[58] a vertical numeric rating scale would be the preferred option. It is also recommended that data for pain at rest and on passive or active movement is analysed and reported separately to improve comparability. Studies exploring factors associated with PSSP should also give consideration to, and report on, any qualitative differences in the nature and pattern of pain between subjects, as well as factors such as whether the pain was at night or on clinical assessment only. Observational studies of this nature may help to better understand PSSP subtypes and improve specificity. Where possible, efforts should be made to ensure the inclusion of patients with communication or cognitive difficulties by using carers as proxies when needed to more accurately represent the target population.

Motor impairment of the upper limb was repeatedly shown to increase the risk of PSSP, however it was not possible to combine in meta-analysis due to variation in measurement. This important factor warrants further investigation. In this review the Fugl-Meyer Assessment was the most credible of the outcome measures used and would be the authors recommendation for future studies to allow comparative analysis.

Conclusions

This review has identified motor deficits in the UL, diabetes and a history of shoulder pain to be significant predictors of the development of PSSP within the first year after stroke. Whilst it is acknowledged that the lack of robust studies included prevent definitive conclusions to be made, it is hoped that the results presented will provide clinicians with a potential 'at risk' group of patients in the acute stage of stroke on whom to focus preventative strategies. A number of recommendations to standardise future studies in this area have been made. Future observational studies defining and categorising the subtypes of PSSP would be beneficial to aid research into the specificity of treatments for this complex and frequent problem.

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Legends of Figures and Tables

Figure 1. PRISMA Flow diagram of study selection

Figure 2. Assessment of risk of bias using the Quality in Prognosis Studies tool

Figure 3. Forest plot displaying the pooled OR analysis for sex

Figure 4. Forest plot displaying the pooled OR analysis for laterality of stroke

Figure 5. Forest plot displaying the pooled OR analysis for diabetes

Figure 1. PRISMA Flow diagram of study selection

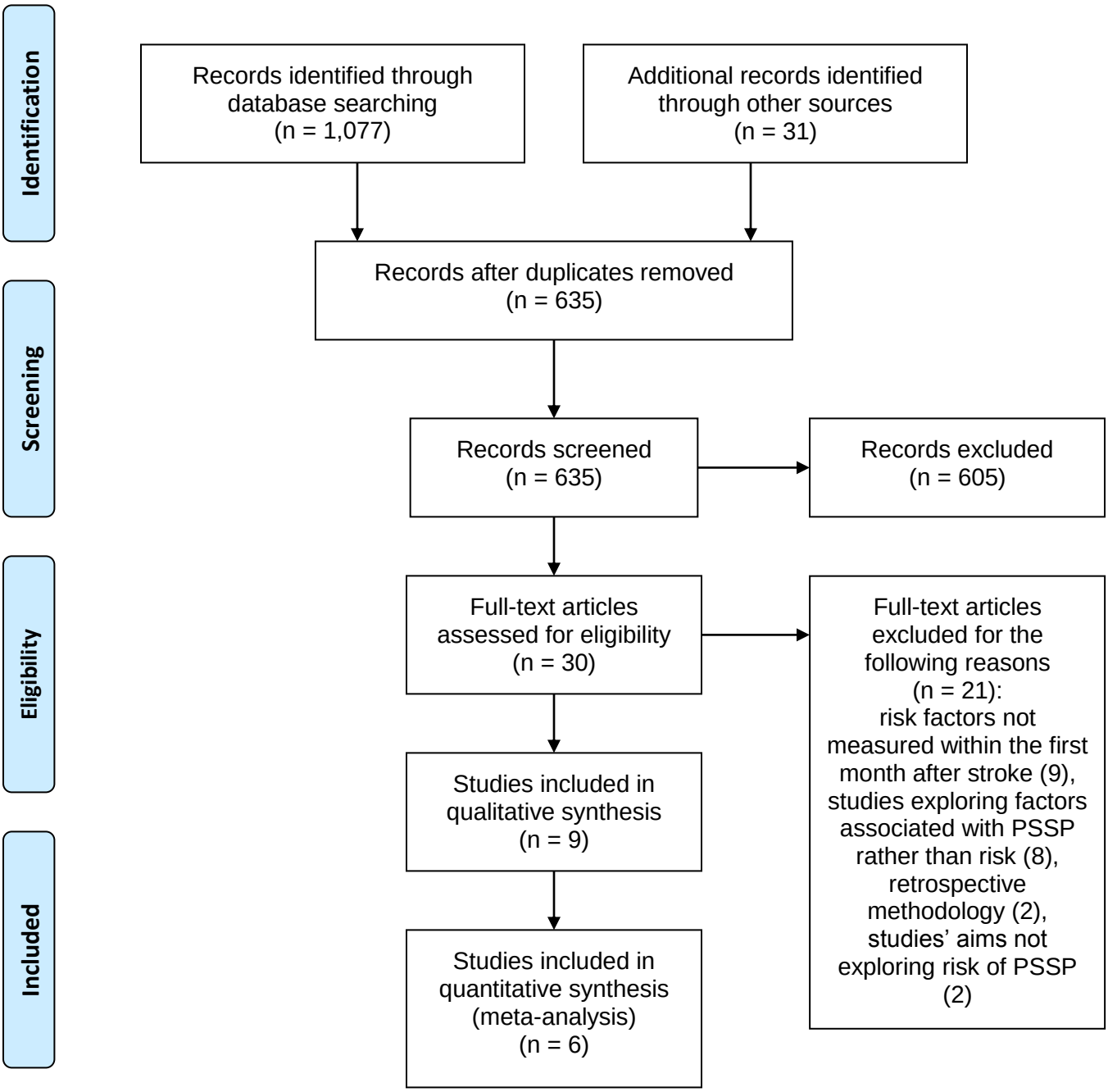

Figure 2. Risk of bias

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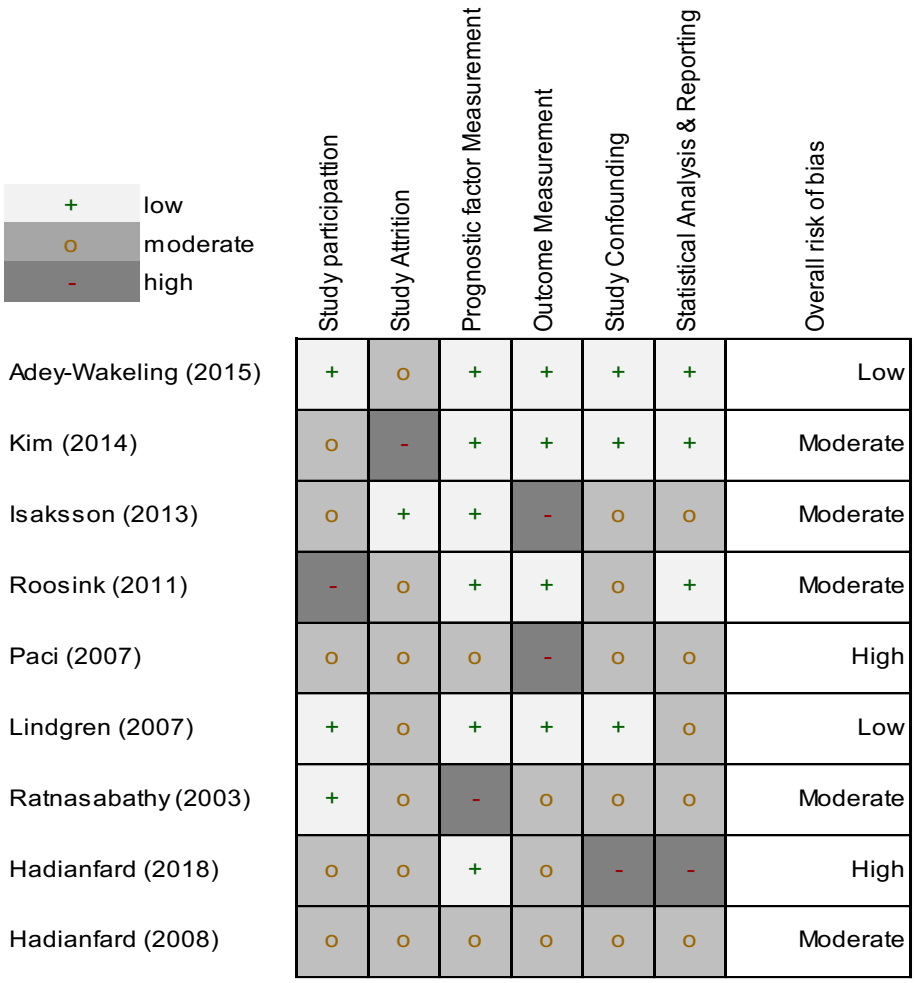

Figure 3. Meta Sex

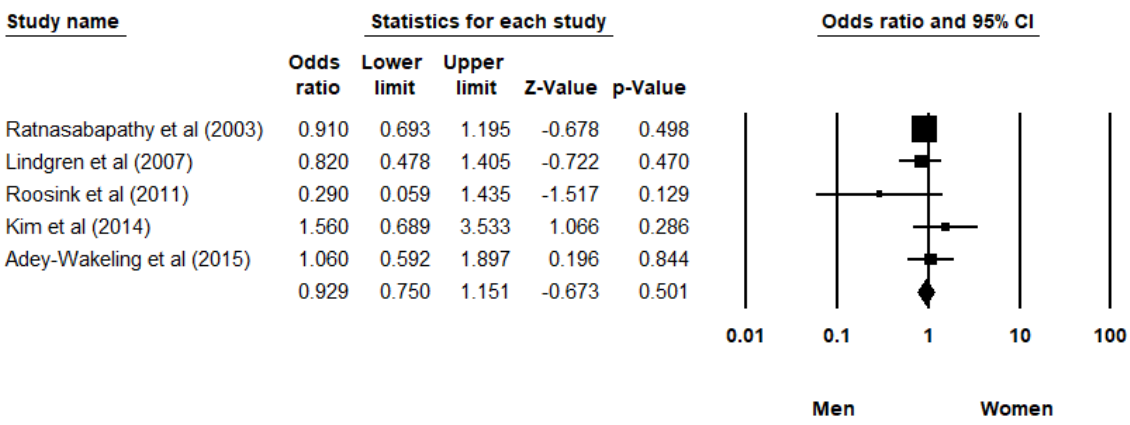

Figure 4. Meta Laterality

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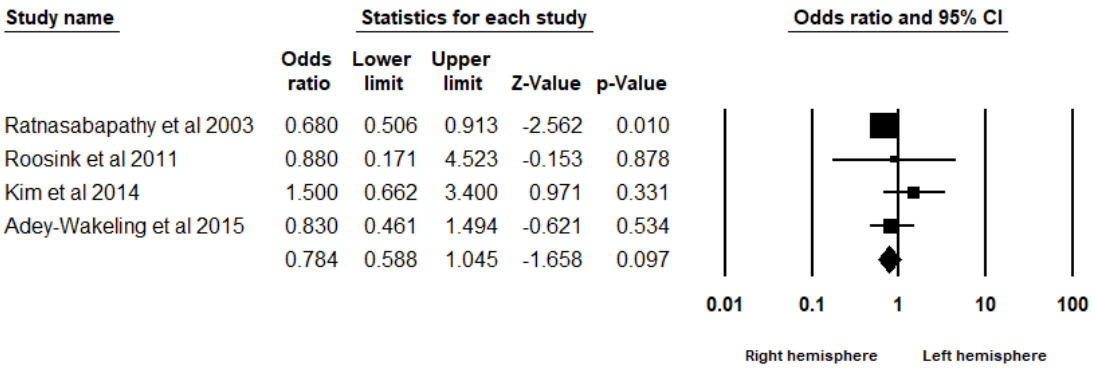

Figure 5. Meta Diabetes

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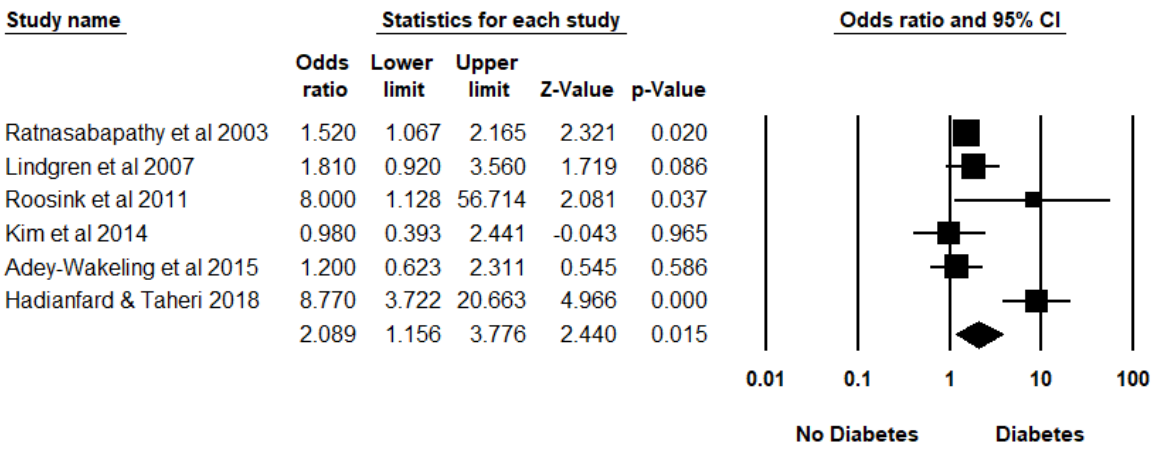

Figure 6. Meta History

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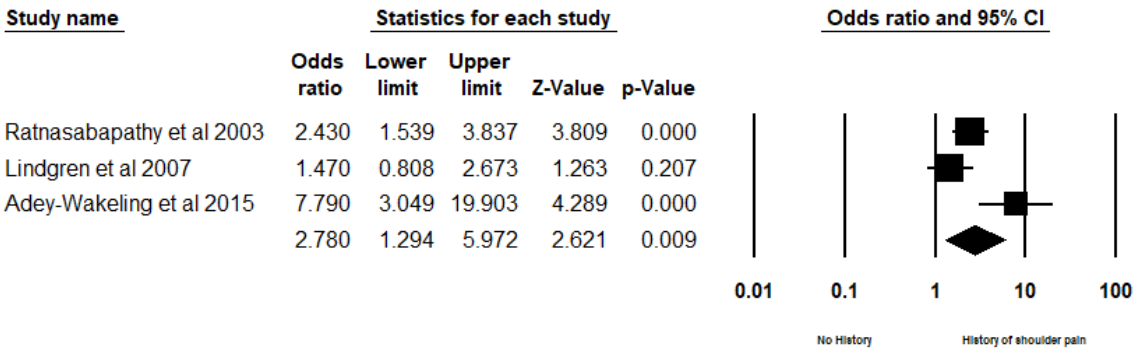

Table 1. Characteristics of included studies

Lead author (year)	Country	Study Aims	Sample size	Age	Sex	Eligibility criteria	Risk factors explored: Demographics	Comorbidities	Clinical	Time points for follow-up assessments
Adey-Wakeling (2015)	Australia	Determine frequency, characteristics and determinants of PSSP	226	Mean (SD) 73 (15) in no pain group 72 (14) in shoulder pain group	124M 102F	All patients admitted with diagnosis of stroke Excluded if subject data ascertained retrospectivey, subject denied participation, or deceased	– Age – Sex – Laterality of stroke – Type of stroke – Classification of stroke	– Diabetes mellitus – Previous stroke – Hypertension – Previous MI – History of shoulder pain	– Stroke severity – Arm motor function – Clinical shoulder tests	3 months & 12 months
Hadianfard (2008)	Iran	Explore factors that can predict PSSP	152	Mean 61.2	75M 77F	Any patients admitted with the diagnosis of a stroke Excluded other causes of hemiplegia and profound cognitive problems	– Age – Sex – Smoking habits	– Temporary unconsciousness in early phase of stroke – History of shoulder pain	– ADLs – Decreased motivation for rehabilitation – Communication disorder – Anxiety – Depression – Decreased visual field – Increased vibration threshold – Increased light touch threshold	Every 2 months upto 12 months
Hadianfard (2018)	Iran	Investigate relationship of diabetes mellitus and hyperlipidemia with PSSP	152	Mean 61.2	75M 77F	Any patients admitted with the diagnosis of a stroke Excluded other causes of hemiplegia and profound cognitive problems		– Diabetes mellitus – Hypercholesterolaemia – Hypertriglyceridaemia		Every 2 months upto 12 months
Isaksson (2013)	Sweden	Identify clinical factors associated with the development of PSSP in patients with pronounced arm weakness	63	Median 79 (70-86)	26M 37F	Stroke patients with pronounced arm paresis Excluded palliative care, denied participation, and patients developing centralised pain	– Age – Sex – Laterality of stroke – Type of stroke	– Fall at stroke onset – History of shoulder pain – Previous stroke	– Arm motor function – Gait – Stroke severity	Every 2 weeks until discharge
Kim (2014)	Republic of Korea	To determine baseline risk factors for the occurrence of PSSP during rehabilitation period	94	Mean 65.63 in shoulder pain group 65.49 in no pain group	49M 45F	Acute stroke patients within 1 month confirmed by magnetic resonance imaging Excluded history of shoulder pain/surgery, recurring or bilateral stroke, severe cognitive impairment, unstable medical condition	– Age – Sex – Laterality of stroke – Type of stroke	– Diabetes mellitus – Hypertension – Cardiovascular disease – Malignancy	– Arm motor function – Sensation to light touch – Reduced range of movement (diagnosed adhesive capsulitis) – Shoulder spasticity – ADLs – Radiological factors (subluxation, acromioclavicular arthropathy, subacromial spur, calcification) – Sonographic factors (supraspinatus, subscapularis and infraspinatus tendinosis/tear, acromioclavicular and glenohumeral degeneration, long head of biceps tendon effusion, subacromial-subdeltoid bursa effusion)	3 months & 6 months
Lindgren (2007)	Sweden	To provide detailed data about PSSP in relation to prevalence, characteristics, influence on daily life, and predictors	327	Mean 73.1	195M 132F	All first-ever strokes included	– Age – Sex – Type of stroke	– Diabetes mellitus – History of shoulder pain	– Stroke severity – Arm motor function	4 months & 12 months

Table 1. Characteristics of included studies (cont.)

Lead author (year)	Country	Study Aims	Sample size	Age	Sex	Eligibility criteria	Risk factors explored: Demographics	Comorbidities	Clinical	Time points for follow-up assessments
Paci (2007)	Italy	To study the relationship of shoulder subluxation with PSSP and functional recovery within the first 3 months after stroke	107	Mean (SD) 71.3 (10.5) in subluxed group 72 (9.6) in non-subluxed group	53M 54F	First-ever stroke patients where baseline measures taken within 30 days Excluded patients with severe, aphashia, severe cognitive impairment, history of shoulder pain/damage and where the diagnosis of subluxation was unclear	– Age – Sex – Laterality of stroke – Time since onset		– ADLs – Sensorimotor impairment – Subluxation	At discharge and 30-40 days post-discharge
Ratnasabathy (2003)	New Zealand	Examine PSSP prevalence and factors associated with its occurrence in the first 6 months after stroke	1474	Only frequency of age ranges given	701M 773F	All strokes included	– Age – Sex – Laterality of stroke	– Diabetes mellitus	– Sensorimotor impairment	1 month & 6 months
Roosink (2011)	The Netherlands	Identify factors associated with persistent PSSP in the first 6 months after stroke	31	Mean (SD) 72 (10) in persistent pain group 65 (13) in no pain group	14M 17F	All first-ever, cortical or sub-cortical unilateral strokes resulting in senory and/or motor symptoms were eligible Excluded large amount of patients with comorbidities that could influence pain, premorbid arm pain, unable to adequately respond to closed questions, discharged within first 3 days after stroke	– Age – Sex – Laterality of stroke – Handedness – Time since onset	– Diabetes mellitus – TIA – Hypertension – COPD – Obesity – History of shoulder pain	– Motor function – Reduced range of movement – Spasticity of elbow flexors – Subluxation – Impaired sensation (light touch, temperature, sharp, proprioception) – Cognition – Depression – Visual inattention/extinction – Tactile inattention/extinction – Autonomic function	3 months & 6 months

Abbreviations: MI, myocardial infarction; ADLs, activities of daily living; TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary disease.

Table 2. Demographics - Factors with sufficient data to calculate OR

Risk factor (exposure group)	Number of participants	Time of follow-up (months)	Method of measurement		OR (95% CI)
Age (older)	226	within 12	Mean age		0.96 (0.79-1.17)[3]
	1201	6	10 year increments		1.08 (0.99-1.18)[44]
	94	within 6	<70, 70 >		0.27 (0.09-0.80)[45]
Sex (female)	31	6			0.29 (0.06-1.47)[47]
	327	4			0.82 (0.48-1.41)[2]
	1201	6			0.91 (0.69-1.19)[44]
	226	within 12			1.03 (0.77-1.37)[3]
	94	within 6			1.56 (0.69-3.54)[45]
Type of stroke	327	4	Imaging		0.75 (0.30-1.89)[2]
(haemorrhagic)	94	within 6			0.80 (0.30-2.16)[45]
	226	within 12			1.07 (0.39-2.91)[3]
	63	not stated			6.25 (1.1-35.6)[43]
Stroke subtype	226	within 12	Oxfordshire	LACS	Reference
			classification	POCS	0.77 (0.41-1.42)[3]
				PACS	0.78 (0.49-1.24)[3]
				TACS	1.28 (0.74-2.24)[3]
	327	4		LACS	Reference
				POCS	0.56 (0.22-1.41)[2]
				PACS	0.64 (0.32-1.29)[2]
				TACS	5.19 (2.34-11.51)[2]
Laterality	63	not stated	Imaging		0.51 (0.17-1.48)[43]
(left hemisphere)	1008	6			0.69 (0.51-0.92)[44]
	226	within 12			0.87 (0.65-1.17)[3]
	31	6			0.88 (0.17-4.49)[47]
Handedness (right)	31	6	Subjective report		1.26 (0.11-14.05)[47]

Abbreviations: LACS, lacunar syndrome; POCS, posterior circulation syndrome; PACS, partial anterior circulation syndrome; TACS, total anterior circulation syndrome.

Table 3. Comorbidities - Factors with sufficient data to calculate OR

Risk factor (exposure group)	Number of participants	Time of follow-up (months)	OR (95% CI)
Diabetes Mellitus	226	within 12	1.2 (0.62-2.30)[3]
	1201	6	1.52 (1.07-2.17)[44]
	327	4	1.81 (0.92-3.56)[2]
	31	6	8.00 (1.13-56.79)[47]
	152	within 12	8.77 (3.72-20.65)[41]
TIA	31	6	0.29 (0.01-6.27)[47]
Previous stroke	63	not stated	0.42 (0.12-1.49)[43]
	26	within 12	0.47 (0.21-1.07)[3]
Previous MI	226	within 12	1.16 (0.53-2.54)[3]
Hypertension	31	6	0.18 (0.02-1.71)[47]
	94	within 6	0.87 (0.39-1.99)[45]
	226	within 12	0.96 (0.50-2.54)[3]
History of shoulder	327	4	1.47 (0.81-2.67)[2]
pain	31	6	1.63 (0.27-9.98)[47]
	63	not stated	1.64 (0.56-4.74)[43]
	1201	6	2.43 (1.54-3.84)[44]
	226	within 12	8.09 (3.16-20.80)[3]
Fall at onset	63	not stated	1.79 (0.61-5.21)[43]
Obesity	31	6	1.25 (0.10-15.80)[47]
COPD	31	6	0.56 (0.05-5.86)[47]
Hyperlipidaemia	152	within 12	0.80 (0.35-1.83)[41]
Hypertriglyceridaemia	152	within 12	1.39 (0.64-3.02)[41]
Malignancy	94	within 6	0.48 (0.11-2.11)[45]

Abbreviations; TIA, transient ischaemic attack; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease.

Table 4. Clinical assessments and measures - Factors with sufficient data to calculate OR

Risk factor (exposure group)	Number of participants	Time of follow-up (months)	Method of measurement		OR (95% CI)
Stroke severity	226	within 12	NIHSS		1.39 (0.78-2.49)[3]
Arm motor function (reduced)	73	3	NIHSS (Question 5)		3.08 (1.29-7.38)[45]
	58	6			3.67 (1.55-8.70)[45]
	226	within 12			2.81 (1.40-5.61)[3]
	73	3	Fugl-Meyer arm		2.72 (1.14-6.49)[45]
	58	6	score		3.59 (1.52-8.45)[45]
Motor function (reduced)	31	6	Motricity index		25.00 (2.27-275.71)[47]
Sensorimotor impairment	1201	6	Subjective report	None	Reference
				Mild	2.44 (1.73-3.45)[44]
				Moderate	3.72 (2.38-5.82)[44]
				Severe	6.25 (4.15-9.43)[44]
Motor evoked potential (no response)	73	3	EMG		4.09 (1.34-12.40)[45]
	58	6			2.20 (0.84-5.76)[45]
Sensation (abnormal light touch)	73	3	NS		1.55 (0.66-3.61)[45]
	58	6			1.18 (0.52-2.66)[45]
	31	6	Cotton wool		1.67 (0.35-8.04)[47]
Senation (abnormal cold sensation)	31	6	Metal tuning fork		2.67 (0.52-13.70)[47]
Sensation (abnormal sharp sensation)	31	6	S-W filament		6.00 (0.63-57.00)[47]
Proprioception (impaired)	31	6	Thumb JPS		6.4 (1.16-35.40)[47]
Tactile inattention (impaired)	31	6	Uni- & bilateral stimuli		2.26 (0.04-123.00)[47]
Tactile extinction (impaired)	31	6	Uni- & bilateral stimuli		7.60 (1.06-54.10)[47]
Pain at baseline (present)	226	within 12	Subjective report		1.57 (0.29-8.45)[3]
	1201	6			2.20 (1.61-3.01)[44]
Spasticity (present)	73	3	Modified Ashworth		0.86 (0.27-2.77)[45]
	58	6	Scale		2.79 (0.87-8.92)[45]
ADLs (reduced)	73	3	Barthel index		1.40 (0.59-3.34)[45]
	58	6			1.28 (0.56-2.94)[45]
Shoulder assessment tests (positive)	226	within 12	Neer's test, PHBN, PER		2.10 (0.54-8.35)[3]

ROM (reduced)	73	3	Goniometry	1.75 (0.75-4.09)[45]
	58	6		1.29 (0.57-2.92)[45]
	31	6	NS	6.00 (0.47-76.70)[47]
Subluxation (present)	107	Approx 2-3	Palpation	28.93 (10.11-82.71)[46]
Gait (immobile)	63	Approx 1-2	FAC	2.11 (0.22-20.12)[43]
Cognition (impaired)	31	6	MMSE	2.71 (0.31-23.1)[47]
Visual field (impaired)	31	6	Uni- & bilateral stimuli	2.71 (0.31-23.10)[47]
Visual extinction (impaired)	31	6	Uni- & bilateral stimuli	3.00 (0.47-19.00)[47]
Autonomic Dysfunction (present)	31	6	Trophic changes	3.40 (0.62-18.80)[47]

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; EMG, electromyography; NS, not stated; S-W, Semmes-Weinstein; JPS, joint position sense; ADLs, activities of daily living; PHBN, passive hand-behind-neck; PER, passive external rotation; ROM, range of movement; FAC, Functional Ambulation Classification; MMSE, Mini-Mental State Examination.