Prognostic factors for persistent pain after a distal radius fracture: a systematic review

Abstract

Introduction: This systematic review summarises the evidence regarding prognostic factors for persistent pain, including Complex Regional Pain Syndrome, after a distal radius fracture, a common condition after which persistent pain can develop.

Methods: Medline, Pubmed, Embase, Psychinfo, CINAHL, BNI, AMED and the Cochrane Register of Clinical Trials were searched from inception to May 2021 for prospective longitudinal prognostic factor studies investigating persistent pain in adults who had sustained a distal radius fracture. The Quality in Prognostic Studies tool and Grading of Recommendations, Assessment, Development and Evaluation framework were used to assess the strength of evidence.

Results: A search yielded 440 studies of which 7 studies met full eligibility criteria. From 5 studies we found low evidence for high baseline pain or an ulnar styloid fracture as prognostic factors for persistent pain, and very low evidence for diabetes or older age. From 2 studies, investigating an outcome of Complex Regional Pain Syndrome, there was low evidence for high baseline pain, slow reaction time, dysynchiria, swelling and catastrophising as prognostic factors, and very low evidence for depression. Sex was found not to be a prognostic factor for CRPS or persistent pain.

Discussion: The associations between prognostic factors and persistent pain following a distal radius fracture are unclear. The small number of factors investigated in more than one study, along with poor reporting and methodological

limitations contributed to an assessment of low to very low strength of evidence. Further prospective studies, investigating psychosocial factors as candidate predictors of multidimensional pain outcomes are recommended.

Keywords

Prognosis, wrist fracture, chronic pain

INTRODUCTION

Distal radius fractures (DRF) account for 17- 21% of all extremity fractures in adults in the UK[1] and the reported worldwide incidence of DRF is increasing.[2] Once a distal radius fracture has been acutely managed, either by cast immobilisation or surgery, the pain experienced by the patient should subside, typically within a 2-month period.[3] In a proportion of patients, pain to the wrist and hand does not improve but persists long after the acute management of the fracture; Friesgard et al[4] reported that 18.9% of patients still have pain at 1-year post wrist surgery.

The International Classification of Disease's (ICD-11) defines chronic pain as a pain that lasts or recurs for longer than 3 months. This classification has more recently been further subdivided into chronic primary pain, where the pain is a disease in itself, and chronic secondary pain, where the pain is a result of another pathological process.[5] On-going pain following a distal radius fracture can result from both primary and secondary pain. Proposed mechanisms of chronic secondary pain following a fracture include mechanical factors such as mal or non-union of the fracture and neuropathic pain such as carpal tunnel syndrome. The debilitating primary chronic pain condition Complex Regional Pain Syndrome (CRPS) has been

found to occur in 3.7-14% of patients within 12 weeks of a wrist fracture[6], and can persist for at least 2 years from time of onset.[7] Chronic hand and wrist pain can impact on the patient's quality of life, return to work and resumption of usual activities. For those with CRPS the days lost to work have been found to be 20 times higher following DRF, and treatment costs 13 times higher, than for someone who did not develop CRPS.[8]

It is well established that being older than 65 and a female puts you at a greater risk of sustaining a distal radius fracture,[2] and that both of these may contribute to poor outcomes following a distal radius fracture[9]. However the link between sex, age and both persistent pain and CRPS is less clear.[10,11]

A number of candidate prognostic factors for persistent pain after a wrist fracture including fracture severity and reduction[12], and high baseline pain[13,14] have been mentioned in the literature previously, and it is recognised that psychosocial factors may play a key role in mediating the transition from acute to chronic pain,[15] but there have been no systematic reviews that have looked specifically at prognostic factors for persistent pain after a distal radius fracture.

Due to being a high incidence condition, early identification of those individuals with a DRF who are most likely to develop chronic hand and wrist pain could enable timely targeted treatment approaches and improve outcomes for patients.

The aim of this review was to establish the level of evidence for prognostic factors for persistent pain, including CRPS, following a distal radius fracture in adults.

METHODS

Protocol and registration

The research question falls within the PROGRESS (PROGnosis RESearch Strategy) framework 2, “to identify prognostic factors associated with changes in health outcomes”.[16]

Our systematic review is registered with PROSPERO and can be found at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=184114

It is reported according to the PRISMA guidelines for reporting of systematic reviews.

We defined our review question using the CHARMS framework (checklist for critical appraisal and data extraction of systematic reviews of prediction modelling studies).[17] While primarily used for prognostic modelling studies, CHARMS has also been recommended for *‘defining and framing’* questions for reviews of prognostic factor studies.[18]

Search Strategy and study selection

A comprehensive search strategy generated from keywords and MESH terms relating to distal radius fracture, prognosis and chronic pain was used (supplementary file FigureS1). One reviewer (CR) conducted electronic searches in Medline, Pubmed, Embase, Psychinfo, CINAHL, BNI, AMED and the Cochrane Register of Clinical Trials from inception to May 2020, with an updated search in June 2021. Further hand searching included the personal databases of the reviewers, as well as searching the bibliographies of the full text articles included for data extraction. No language limits were applied. All results were uploaded to the COVIDENCE platform for better systematic review management, and duplicates were removed.

All the abstracts and full texts identified by the search were screened against the inclusions and exclusions criteria (Table 1) by two independent reviewers (CR and

EB), and disagreements arising from this initial screening process were resolved by a process of consensus. Full text articles were screened against the eligibility criteria (Table 1) as well as for '*applicability*' to the review question.[19] Discrepancies were discussed and if consensus could not be met a third independent reviewer (DvdW) was available for consultation.

Data extraction and quality assessment

A data extraction form was developed to collate study data (supplementary data file Table S1, as well as facilitate assessment of bias and study applicability. A single reviewer (CR) conducted the data extraction, with reviewers (EB and DvdW) cross checking a sample of the results for extraction errors. Data extraction related to statistical analysis and data presentation was reviewed by reviewer DvdW for all included studies.

For assessment of methodological quality, the Quality In Prognostic Studies (QUIPS) risk of bias tool[20] was used, as recommended by the Cochrane Prognosis Methods Group. Prior to review, decisions were made on important factors to consider in the scoring of each of the six bias domains defined in the QUIPS tool (supplementary data Table S2). Each study is considered through a series of prompting questions as to whether it has low, moderate, or high risk of bias per domain. Due to the highly subjective nature of risk of bias scoring, three reviewers (CR, EB and DvdW) independently scored the QUIPS, and any discrepancies were discussed to reach a consensus.

Evidence synthesis

Synthesising prognostic research through systematic reviews is notoriously difficult. We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework[21,22] to assess the overall strength of evidence for each of the prognostic factors investigated. Downgrading effects were applied under the following headings: 1. Study limitations (as assessed by QUIPS); 2. Inconsistency between the direction of study results; 3. Imprecision of results. We considered that it would need 3 small studies or 2 large studies to see precision. We modified the original GRADE system by dropping the fourth and fifth section on indirectness of population and publication bias, as we felt these had already been accounted for in our eligibility criteria and the QUIPS evaluation respectively. We included no upgrading effects as we were unable to assess and weigh dose response and large effect size due to the variation in outcome measures used. An overall judgement of high, moderate, low, or very low certainty in the prognostic factor was then made

RESULTS

The PRISMA flow diagram for this systematic review is presented in Figure 1. The search of seven databases and the Cochrane Register of Clinical Trials identified 482 studies. After removal of duplicates (n=42), title and abstract screening were conducted on the remaining 440 studies, 389 were found to be irrelevant and the remaining 51 had full text screening against the eligibility criteria. Seventeen studies were subsequently excluded for failing to meet the inclusion criteria for outcomes, 13 for wrong study design, 9 had too small a sample size, 3 were previously unidentified

duplicates, and 2 had poor applicability to the study question. Seven studies were included in this review.

Study characteristics

Table 2 documents the key characteristics of the included studies. Three of the studies were prospective cohort studies,[23–25] and four conducted retrospective analyses of randomised control trial cohort data.[26–29] Five of the studies investigated an outcome of persistent pain,[23,26–29] while two looked explicitly at the occurrence of the primary pain condition CRPS.[24,25] Four of the studies reported on a cohort of surgical and conservatively managed DRFs, [23,25,27,28] one on conservatively managed fractures,[24] one on surgically managed fractures,[26] and one did not stipulate what management approach was taken.[29]

There were a total of 3591 participants recruited across the studies, with a median sample size of 349 per study (range 100-1549) and chronic pain outcomes were recorded at a minimum of 3 months post fracture[23 23,24,28,29] to a maximum of 24 months.[26] All studies reporting on CRPS used the 1999 modified IASP research criteria.[30] One multi-site study looking at an outcome of CRPS (n=1506) following DRF contributed 45% of the total participants in this review.[24]

Risk of bias

The results of the QUIPS risk of bias assessment for the seven included studies are included in the supplementary information (Table S3). After a consensus approach one study was assessed as having a low risk of bias,[24] two studies to have a moderate risk of bias[25,28] and four studies to have a high risk of bias.[23,26,27,29]

Poor reporting of study participation, attrition, confounding, and statistical analysis made it difficult to assess risk of bias and confounding.

For prognostic factor measurement, five of the seven studies were assessed as having low-moderate risk.[24–28] Studies were assed to have a higher risk of bias where there was evidence of dichotomisation of a continuous variable,[29] or the prognostic factor was measured by self-report.[23] All but two of the studies were assessed as having low risk of bias for outcome measurement. Belloti et al[26] scored moderate risk for their selection of the VAS as opposed to the NRS, as it is recognised as being less reliable in assessment of pain post DRF.[31] Cashin et al[28] used an arbitrary dichotomisation of 3/10 to record if persistent pain had occurred.

A meta-analysis of results was not possible due to a high degree of heterogeneity in the prognostic factors investigated, the time of outcome measurement, and pain outcomes used. The summary results from all included studies are presented in Table 3. A narrative synthesis of prognostic factors relating to persistent pain and CRPS after a distal radius fracture is then presented.

Study findings: Prognostic factors for Persistent Pain

Five of the seven studies investigated prognostic factors for persistent pain[23,26–29]. Table 4 shows the factors identified along with the assessment of the strength of evidence using modified GRADE scores.

Two studies identified high baseline pain as a prognostic factor for persistent pain: Cashin et al[28] showed that high baseline pain of 3/10 or higher was predictive of persistent pain (Odds Ratio (OR) 1.16). Mehta et al[29] used a forward stepwise

regression to show that baseline pain intensity was predictive of chronic pain at one year, with baseline pain accounting for 22% of the variance in the final model (R^2 0.222). Mehta et al[29] reported a baseline pain score of 35/50 to have the highest sensitivity and specificity for predicting chronic pain (AUC 87%). The strength of evidence for baseline levels of pain was found to be low. Downgrading effects were applied for study limitations (both studies had at least one domain with moderate/high risk of bias); and imprecision of results.

Belloti et al[26] and Daneshvar et al[27] both studied the effect of an ulnar styloid fracture in combination with a distal radius fracture. Daneshvar et al[27] report that an ulnar styloid fracture increases risk of increased pain in the first year following DRF in a cohort of under 65-year-olds, but that this relationship was no longer present at 5 years. Belloti et al[26] also found a small but statistically significant difference (P=0.03) in pain at 1 year, with an associated ulnar styloid fracture leading to a pain score of 1.9 (+/-2.0) out of 10, and those without an ulnar styloid fracture scoring 1.2 (+/- 1.0). The strength of evidence was assessed as low, with the evidence downgraded based on study limitations, and imprecision.

We found there to be very low evidence for diabetes as a prognostic factor. Alsubheen et al[23] report a significant interaction between time and diabetes (P<.01) with most diabetic patients recovering more slowly than non-diabetics. The strength of evidence was downgraded for all three GRADE domains.

There were conflicting results across studies regarding the importance of age and sex as predictors of persistent pain. Mehta et al[29] found age over 65 years and being of female sex increased risk (R^2 0.012), and Cashin et al[28] also found that older age was associated with increased pain (OR 1.02). Alsubheen et al[23] report the opposite direction of effect, finding that older age was associated with lower pain. Cashin et al[28] found there to be no effect of sex in their development sample.

We found very low certainty of evidence for diabetes and age as prognostic factors for persistent pain, and for no association between sex and pain, with evidence downgraded because of study limitations, inconsistency, and imprecision.

Study findings: Prognostic Factors for CRPS

Only two of the seven studies looked at prognostic factors for the development of CRPS[24,25] (Table 5). In a single large (n=1,661) prospective cohort study Moseley et al[24] identified high levels of baseline pain, dysynchiria, swelling, and slow reaction time as predictive of CRPS when combined in a multivariable logistic prediction model (ROC of 0.99). Further to this it was found that baseline pain alone provided almost identical discriminative ability with an odds ratio of 3.299 and ROC of 0.98. To facilitate risk stratification Moseley et al[24] divided pain scores arbitrarily into 5 categories 0, 1-2, 3-4, 5-6, 7-8 (no one scored above an 8). They determined that a score of 5 or more was associated with a high risk of developing CRPS (likelihood ratio 15.1 (95% CI = 10.6-21.4).

There was very low evidence for psychosocial prognostic factors. Moseley et al[24] identified a significant univariable relationship of catastrophizing with an outcome of CRPS (OR 1.097) but dropped it from their final model. In a study investigating the

role of depression as a prognostic factor for CRPS, Yeoh et al[25] found that a Centre of Epidemiological Study for Depression (CES-D) score of greater than or equal to 16 at baseline had a statistically significant correlation to higher rates of CRPS at 3 months post-injury.

Moseley et al[24] found there to be no relationship between either age or sex and an outcome of CRPS when assessed in univariate analysis.

From the GRADE evaluation we determined that there was low evidence for baseline pain, dysynchiria, swelling, reaction time and catastrophizing, and an outcome of CRPS, and low evidence that age and sex are not associated with an outcome of CRPS with evidence downgraded for inconsistency and imprecision. We assessed there to be very low certainty of evidence for depression, additionally downgraded based on study limitations.

DISCUSSION

In this review we set out to establish the prognostic factors for persistent pain (including CRPS) following a distal radius fracture. High baseline pain, an associated ulnar styloid fracture, diabetes, age, and sex were identified as predictors of persistent pain. High baseline pain, slow reaction time, dysynchiria, swelling, catastrophising and depression were identified as risk factors for CRPS, with high baseline pain alone found to have high discriminative ability. Age and sex were not found to be prognostic factors of CRPS. The small number of factors investigated in more than one study, along with methodological limitations and poor study reporting resulted in no factor being assessed as having more than low to very low strength of evidence.

Two studies in this review found there to be a statistically significant positive association between high baseline pain and persistent pain,[28,29] and one with an outcome of CRPS.[24] This finding is consistent with the broader literature on persistent pain after trauma.[32,33] Injury severity may account for high baseline pain, however the mechanisms by which this acute pain becomes chronic are less well understood with conflicting results in the literature as to the importance of injury severity on chronicity.[34]

The importance of different biopsychosocial factors is recognised as contributing to chronicity in conditions such as chronic low back pain, but also as targets for intervention after musculoskeletal trauma.[35] In The Lower Extremity Assessment Project (LEAP) Castillo et al[36] found that early high pain intensity was associated with poor outcomes at 6 to 12 months, and that clustering pain with multiple sociodemographic factors provided better stratification for a range of outcomes. Recent work examining psychosocial factors and recovery trajectory after DRF [37] demonstrated that modifiable factors such as pain catastrophizing, opioid use, and use of antidepressants were related to worse patient reported outcomes at 6-9 months. In this review, no psychosocial prognostic factors were found for persistent pain.

Previous research has found that psychological factors are not a risk factor for the development of CRPS, but may have a role in predicting poor outcome.[38] In this review we found low to very low certainty of evidence for depression[25] or catastrophising[24] as predictors of CRPS.

Four of the five studies in this review looking at an outcome of persistent pain were retrospective analyses of data from RCTs and as such prognostic factor and pain outcome measurement was limited to those selected for the primary purpose of the RCT. In this systematic review we found that age, sex, fracture classification and co-morbidities were often recorded, but there was less evidence of the use of validated measures for depression, anxiety, coping, or of multidimensional pain assessment. It is worth noting that with regards to CRPS, a requirement of the Budapest diagnostic criteria[30] is that the patient reports 'Higher than expected pain'. Baseline presentation of high pain may be an early manifestation of the condition, rather than a prognostic factor.

Previous research looking at a broader group of all types of orthopaedic trauma has found moderate evidence that female sex and older age are prognostic factors for persistent pain[13]. Fragility fractures, including distal radius fractures, are commonly sustained by older women but it is not clear by what mechanism older age and female sex mediate the development of chronic pain. It may be that age and sex are simply proxies for menopausal stage and oestrogen levels, but this is an area that has been poorly researched and requires an approach that considers age, sex, menopausal stage and oestrogen levels separately in order to recognise confounding variables.

In this systematic review we found inconsistent results with very low evidence for older age and female sex as predictors of persistent pain. Studies included report relatively young mean age of women at baseline (Table 2), with four of the five studies reporting a mean age in the menopausal, rather than post-menopausal

range. This may account for the discrepancy between our result and previous research on the predictive value of age.

In this systematic review we found low evidence that an ulnar styloid fracture is predictive of higher pain levels in the first year following a DRF,[26,27] but agree with a previous systematic review that found no long term relationship.[39]

Limitations of studies in this review

The scope of this review was to evaluate an outcome of persistent pain or CRPS after a distal radius fracture. We found that persistent pain was assessed using either the Numerical Rating Scale (NRS)[28], Visual Analogue Scale (VAS)[26] or the pain subscale of the Patient Rated Wrist Evaluation.[23,27,29] These measures record pain intensity and frequency but do not help us understand pain interference, emotional wellbeing, or a patient's impression of change. To establish strong predictors of persistent pain we need to first make sure we are using appropriate chronic pain outcome measures. In a study comparing the Numerical Rating Scale (NRS) to the multidimensional Brief Pain Inventory (BPI),[40] it was found that a cut-off score of 1/10 on the NRS missed a third of all patients who were assessed as having clinically relevant pain on the BPI.

The authors acknowledge that the time pressures in trauma clinics can make it difficult to administer lengthy pain assessment tools. However, we support the recommendations from the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT),[41] which advocates the use of a variety of

core outcome domains, such as emotional functioning, physical functioning and participant rating of improvement, in pain research.

The ICD-11 subgroupings of chronic primary and chronic secondary pain are still relatively new and have not yet widely filtered into clinical practice. We found that none of the five studies reporting on an outcome of persistent pain specified whether they had excluded subjects with Complex Regional Pain Syndrome (CRPS). CRPS has been found to have an incidence of between 3.7% and 14% after a wrist fracture.[6] It is therefore possible that some of the patients identified in the papers reporting on persistent pain had CRPS, and as such it is unsurprising that there may be some crossover between the risk factors reported for persistent pain and CRPS in this review.

Strengths and Limitations of the review

A strength of this review was that the methodology conformed to that recommended in the checklist for critical appraisal and data extraction of systematic reviews of prediction modelling studies (CHARMS)[17] and the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA).[42] We rigorously examined the literature on prognostic factors for chronic pain after a distal radius fracture; however, using this approach resulted in only a small number of studies qualifying for full data extraction. Such strict criteria, in particular the exclusion criteria of sample size less than 100, may mean that some potential candidate factors were overlooked. We conducted a brief review of the 9 studies [43–51]with n<100 (Supplementary data Table S4) but did not feel that these studies would have altered the overall findings of the

review. Six of the nine studies would also have been excluded as they used a study design or outcome not relevant to our review question. The three remaining studies looked at an outcome of CRPS [43,46,47] with sample sizes ranging from 60-88, but the number of CRPS cases reported ranged from 1-15. Such small sample sizes in combination with a rare outcome event present a high risk of overfitting of the data and highlight the need for statistical rigor in prognostic studies. Although sample size for prognostic factor studies will depend on several parameters and there is no fixed threshold, a sample size smaller than 100 is unlikely to be sufficient,[19] especially in relatively rare conditions such as CRPS.

Implications for practice

- High baseline pain was identified as a potential prognostic factor for both an outcome of persistent pain and CRPS. Clinicians should consider pain of 5/10 or above as a red flag and consider multidisciplinary management.
- To evaluate long term recovery from distal radius fracture, clinicians should consider multidimensional pain assessment over pain intensity scales to better understand pain interference, psychosocial factors and perception of recovery, and guide treatment.
- This review highlights a lack of rigorous research into the development of pain after distal radius fracture, in particular the role that age and sex play in mediating chronic pain. With an aging population we feel this is an area that demands further research.

Conclusions

Due to methodological limitations and poor reporting standards, there remains limited evidence to support the association of individual prognostic factors and an outcome of persistent pain or CRPS.

There was a notable lack of studies investigating modifiable psychosocial factors. Due to the growing body of evidence indicating the likely role they play in predicting chronic pain, we would recommend these are incorporated into future high-quality prospective prognostic factor studies in people who have experienced a distal radius fracture, using appropriate outcome measures for the assessment of chronic pain.

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Figure 1: PRISMA flow diagram

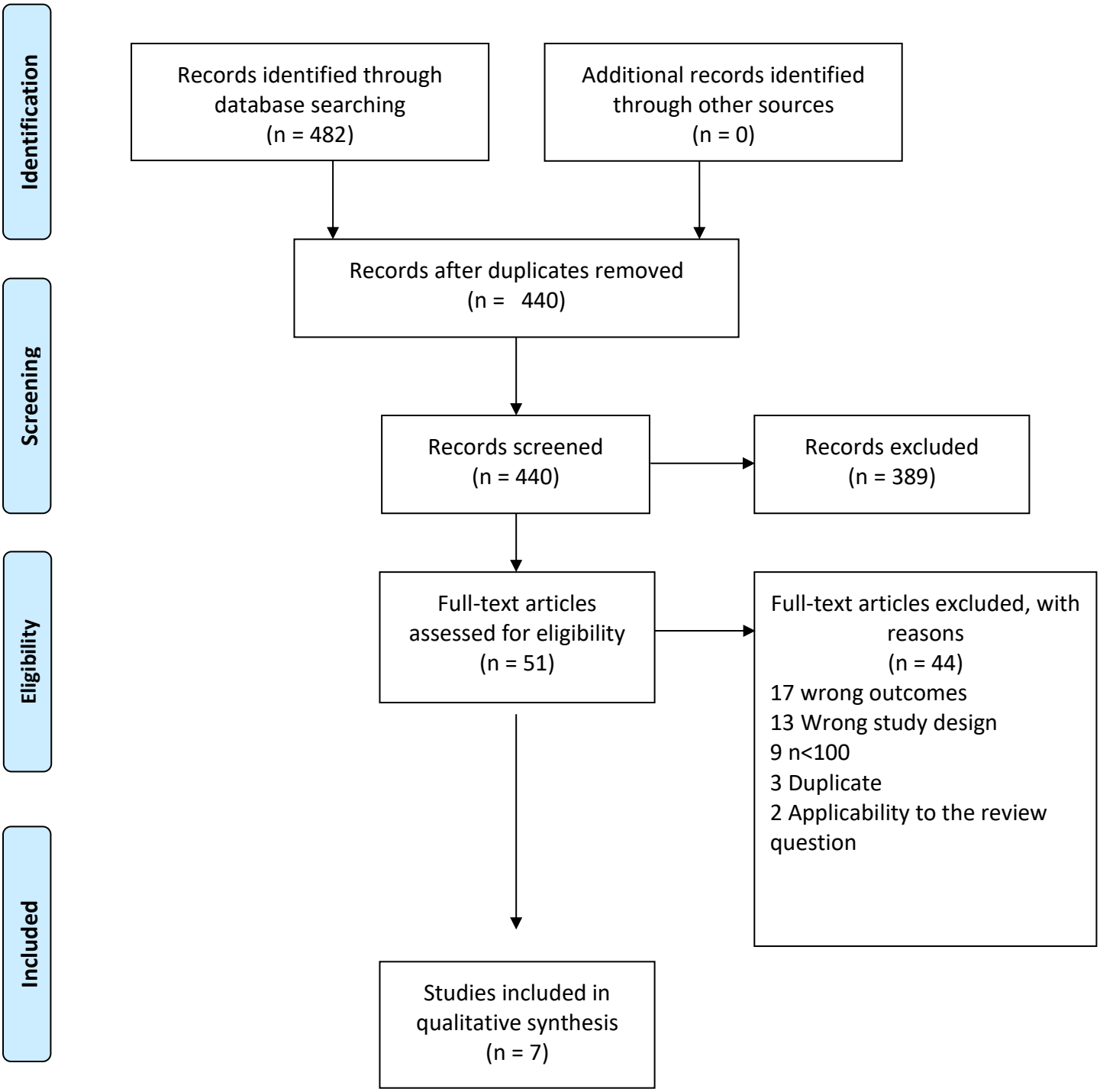

Table 1: Inclusion/Exclusion Criteria

	Inclusion Criteria	**Exclusion Criteria**
Study design	Prospective longitudinal prognostic factor studies looking specifically at risk factors for persistent pain following a distal radius fracture. Sample size greater than 100	* Note to exclude all RCTs unless it concerns a cohort analysis of trial participants. * Qualitative studies, retrospective studies, case studies or case series, case control and abstract-only reports * Study size 100 or less
Participants and conditions of interest	Population: Adults, 18 years and older who have suffered a fracture of the distal radius, regardless of treatment and are followed up from the time of experiencing / receiving first treatment of the fracture.	* Studies among populations with 'red flag' diagnoses (e.g., suspected cancer) * Studies on scaphoid outcomes * Studies on specific disease groups i.e., fibromyalgia or medication groups e.g., vitamin C * Studies focusing only on people with mal union / poorly healed fractures * Studies on subgroups with very specific types of complex (and or rare) fractures
Interventions or exposures	Studies should reflect usual care so should include a mix of conservative and surgical treatment.	Excluded are cohorts or trials where all individuals have been selected based on treatment with a specific surgical technique, as this would be selective and does not reflect usual care.
Comparisons or control groups	Any: Placebo/ Usual care / Active treatment comparison groups – if this appears to reflect usual care for wrist fracture.	Please note that treatments will usually not constitute exclusion except in above where study population has been selected based on treatment given/received
Outcomes of interest	Persistent Pain: A new pain that started at the time of the fracture and is recorded as persisting for over 12 weeks. Note: this SLR isn't specifically looking at risk factors for Complex Regional Pain Syndrome (CRPS) but CRPS will be a cause of persistent pain. Prognostic studies for CRPS can be included if they fulfil all the other criteria.	Studies that have only focussed on non-patient-oriented outcomes such as: dexterity/ Range of Movement (ROM)/grip strength/radiological outcomes. Studies only focussing on prognosis in a different pain population such as fibromyalgia are to be excluded. For studies that includes any of the non-patient-oriented outcomes above and any of our systematic review primary and secondary outcomes will be included BUT non-relevant outcomes listed above (dexterity/ ROM//grip strength/radiological) can be disregarded for data extraction purposes. NB studies which only report a combined (multidimensional) score (based on non-patient-oriented outcomes such as ROM, surgical evaluations etc), and which will usually be scored by surgeons, & Health Care Professionals rather than patients and are given as (final score often: poor, moderate, good, excellent outcome) are to be excluded.

Table 2: Study characteristics of included studies into prognostic factors for persistent pain (including Complex Regional Pain Syndrome) after a distal radius fracture

Study	Design	Setting	Sample size	Sample Characteristics	Description of fracture cohort	Follow Up
Belloti et al.2010[26]	Secondary analysis of prospective RCT cohort	Brazil 1 x Orthopaedic Unit	N = 100 at baseline N=91 at 6 months N=91 at 24 months	% Female NR Age without US fracture 56 (± 11) Age with US fracture 59 (± 13)	DRF in age ≥40 Surgical mx 49% Ex-fix 51% pinning	1 week 6 months 24 months
Mehta et al. 2015[29]	Secondary analysis of prospective RCT cohort	Canada 1 x Upper limb centre	N= 386[a]	72% Female Age M 44.8 (± 14) Age W 55.3 (± 15.5)	DRF (management NR)	≤ 1-2 week of fracture 1 year
Cashin et al. 2019[28]	Secondary analysis of prospective RCT cohort	Australia 2 x Upper limb centre	N=408 at baseline N = 384 at 4 months	28.1% Female Age 35.4±14.7	Fracture to distal third radius, ulna, carpal bone, or metacarpal bone 65% conservative mx 35% surgical mx	Within the last 28 days 4 months
Alsubheen et al.2019[23]	Prospective cohort	Canada 1 x Upper limb centre	N= 479[b]	74.50% Female Age 55±14	DRF 65% conservative mx 10.6% orthotic device 26.8% surgical mx	2-7 days from fracture 3 months 1 year
Daneshvar et al 2014[27]	Secondary analysis of prospective RCT cohort	Canada 1 x Tertiary care centre	N =312 at baseline N at subsequent timepoints not specified	70% Female Age Without US fracture 49±11 Age With US fracture 48±14	DRF in 18-64 year olds 67.7% conservative mx 32.3% surgical mx	Baseline (time NR) 3 months 6 months 12 month
Moseley et al. 2014[24]	Prospective cohort	Australia 3 x fracture clinic	N =1549 at baseline N= 1506 at 4 months	50.50% Female Age 43.3 (± 14.8)	DRF or carpal fracture conservative mx	≤ 1week of fracture 4 months
Yeoh et al 2016[25]	Prospective cohort	Canada 1 x Orthopaedic unit	N = 228 at baseline No drop out recorded	89% Female Age 67±0.59	DRF in over 55's 53% conservative mx 47% surgical mx	7-10 days from injury 3 months 1 year

[a] *complete case analysis,* [b] *data carried forward, RCT* Randomised Controlled Trial*, PRWE* Patient Rated Wrist Evaluation, *NRS* Numerical Rating Scale, *DRF* Distal Radius Fracture, *US* ulnar styloid, *N* number, m*x* management, *NR* not recorded

Table 3: Prognostic factors for persistent pain (including Complex Regional Pain Syndrome) after a distal radius fracture

Study	**QUIPS ROB**	**Pain measurement**	**Analysis**	**Prognostic factors for chronic pain**	**Authors Summary Findings**
Belloti et al 2010[26]	High (N=100)	VAS	Prognostic Factor Study, Difference in outcome at follow up, not adjusted for baseline value or confounding	**Ulnar styloid Fracture (USF)** 6 months: USF VAS 3.4 (SD2), no USF VAS 3.2 (SD 2.0) p=0.77 24 months: USF VAS 1.9 (SD2), No USF VAS 1.2 (SD 2.0)	*The results suggest patients with a distal radius fracture and an USF have worse wrist pain scores. Mean pain score was 1.2 in patients without USF and 1.9 with USF, and while the difference is small it was statistically significant.*
Mehta et al 2015[29]	High (N=386)	PRWE Pain subscale	Multivariate regression	Model 1: **Baseline pain** Adjusted R^2 0.220 Model 2: **Women over 65** Adjusted R^2 0.009 Predictive ability of baseline pain of 35 or greater all ages AUC =87%, age subgroup (65 or over) 91%	*Baseline pain intensity was found to be a strong predictor of chronic pain, explaining 22% of the variance. A baseline score of 35 out of 50 on the pain subscale had the best sensitivity and specificity cut off values for predicting chronic pain at 1 year after DRF.*
Cashin et al 2019[28]	Moderate (N=408)	NRS Persistent pain 3/10 or greater	Multivariate Regression	**Age and baseline pain.** Development sample AUC 0.63 (CI 0.56, 0.69) External validation sample AUC 0.61(CI 0.51,0.70). $R^2$2.4%	*The final model contained 2 prognostic factors: patient age and pain intensity reported at initial presentation. The model's discrimination ability is low and may not meet what many would consider to be the benchmark for clinical relevance.*
Alsubheen et al 2019[23]	High (N=479)	PRWE Pain subscale	Prognostic Factor study, Linear model to look for association between Diabetes and recovery	Interaction between time and **diabetes** for the PRWE pain subscale (P<.01)	*There was a significant interaction between time and diabetes for the pain and other subscales, indicating that patients with diabetes recovered more slowly than most of the non-diabetic cohort.*
Daneshvar et al 2014[27]	High (N=312)	PREWE pain subscale	Prognostic Factors study	Narrative report: trend towards increased pain on the PRWE subscale in patients with **USF**	*Adults under 65 years of old with DRFs and associated USFs initially have greater pain and disability that those with isolated DRFs; however, this difference dissipated over time and was not significant at 1 year.*

Moseley et al 2014[24]	Low (N=1549)	Modified IASP criteria	Multivariate Regression	Prediction model including Prognostic factors of Baseline pain, Reaction time, Dysynchiria, Swelling had discrimination ability of c index =.99. Neary comparable predictive performance was found from **Baseline pain** alone c index = .98. Pain categorised as 0,1-2, 3-4, 5-6 or 7-8. Likelihood ratio of developing CRPS with pain 3-4 was .89 (95% CI = 10.6-21.4), pain of 7-8 was 78.9 (95% CI 35-178) **Age** and **Gender** were not found to have a statistically significant univariate relationship with CRPS.	*Excessive baseline pain in the week after wrist fracture greatly elevates the risk of developing CRPS*
Yeo et al 2016[25]	Moderate (N =228)	Modified IASP research criteria	Student t-test	10% of patients overall had symptoms consistent with CRPS. CES-D >16 baseline = 17% CRPS vs CES-D <16 baseline = 8% CRPS (P=0.073) CES-D >16 3/12 = 20% CRPS vs CES-D<16 = 6% (P=0.0017)	*This study demonstrated an association of CRPS with baseline depression, suggesting that baseline depression may contribute to the development of CRPS.*

QUIPS ROB Quality in prognostic studies risk of bias*, N* number *NR* not recorded, *DRF*= distal radius fracture, *PRWE* Patient Rated Wrist Evaluation, *USF* ulnar styloid (Fracture), *VAS* Visual Analogue Scale, *NRS* Numerical Rating Scale, *R2* The coefficient of determination, *AUC* Area Under the Curve, *SD* Standard Deviation

Table 4 Strength of evidence for prognostic factors for persistent pain after a distal radius fracture using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework

					Down grading effects				
					1	2	3		
Prognostic Factor	**N**	**Number of studies**	**Phase of study**	**QUIPS ROB**	**Study limitations**	**Inconsistency**	**Imprecision**	**Score**	**Strength of Evidence**
Association with outcome									
Baseline Pain	770	2	Exploratory	serious	-1	-	-1	++	Low
Ulnar styloid Fracture	412	2	Exploratory	very serious	-1	-	-1	++	Low
Diabetes	479	1	Exploratory	very serious	-1	-1	-1	+	Very Low
Older age	1249	3	Exploratory	serious	-1	-1	-1	+	Very low
No association with outcome									
Sex	386	1	Exploratory	very serious	-1	-1	-1	+	Very low

N number of participants across studies, *QUIPS* Quality in Prognostic Studies, *ROB* risk of bias

High = ++++ Moderate = +++ Low = ++ Very low = +

Table 5 Strength of evidence for prognostic factors for Complex Regional Pain Syndrome after a distal radius fracture using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework

					Down grading effects				
					1	2	3		
Prognostic Factor	**N**	**Number of studies**	**Phase of study**	**QUIPS ROB**	**Study limitations**	**Inconsistency**	**Imprecision**	**Score**	**Strength of Evidence**
Association with outcome									
Baseline Pain	1506	1	Exploratory	Low	-	-1	-1	++	Low
Reaction Time	1506	1	Exploratory	Low	-	-1	-1	++	Low
Dysynchiria	1506	1	Exploratory	Low	-	-1	-1	++	Low
Swelling	1506	1	Exploratory	Low	-	-1	-1	++	Low
Catastrophizing	1506	1	Exploratory	Low	-	-1	-1	++	Low
Depression	228	1	Exploratory	Moderate	-1	-1	-1	+	Very low
No association with outcome									
Age	1506	1	Exploratory	Low	-	-1	-1	++	Low
Sex	1506	1	Exploratory	Low	-	-1	-1	++	Low

N number of participants across studies*, QUIPS* Quality in Prognostic Studies, *ROB* risk of bias

High = ++++ Moderate = +++ Low = ++ Very low = +