What Is the Incidence of Complex Regional Pain Syndrome (CRPS) Type I within four months of a wrist fracture in the adult population? A Systematic Review

Abstract:

Introduction*:* Complex Regional Pain Syndrome (CRPS) is a severe chronic pain condition, the symptoms of which may develop following trauma to a limb. Despite wrist fracture being a common antecedent, estimates of the incidence of CRPS following this injury vary widely. Our objective was to establish the incidence of CRPS in adults within four months of a wrist fracture, using a systematic review of the literature published since 2010.

Methods*:* The databases MEDLINE, PubMed, EMBASE, PsychINFO, CINAHL, BNI and AMED were searched for observational studies reporting the incidence of CRPS following a wrist fracture. Inclusion criteria were the use of a validated diagnostic tool to assess for CRPS within four months of the fracture. Randomised Control Trial's (RCT's) and Clinical Trials were excluded, as were data from patients with evidence of prior neurology. Incidence risk was then extracted or calculated. Included studies were assessed for methodological rigour using the Newcastle Ottowa Scale for assessment of bias.

Results*:* Nine studies met the inclusion criterion. There was a high degree of heterogeneity in study populations including study setting, fracture management, and diagnostic criteria. From the three studies with the most methodological rigour we determined that the incidence risk of CRPS in adults is between 3.7% and 14% using the Budapest criteria, with an observation of lower rates with conservatively managed fractures.

***Discussion**:* We found evidence that the incidence of CRPS is influenced by choice of diagnostic criteria, along with the study location and/or how the fracture is managed.

Keywords:

Complex Regional Pain Syndrome

Incidence

Wrist Fracture

Introduction

Complex Regional Pain Syndrome (CRPS) is a debilitating chronic condition that can occur after surgery or trauma and is most commonly found in the wrist, foot or ankle[1]. Historically it has been known by several names including: Sudeck's dystrophy, algodystrophy, causalgia and Reflex Sympathetic Dystrophy (RSD). It can occur in adult or paediatric populations[2]. Clinically, CRPS presents with persistent pain that is greater in severity and duration than would be expected from the inciting event. Pain is accompanied by other signs and symptoms including: allodynia, hyperalgesia, skin and temperature changes, oedema, sweating, muscle weakness, tremor, and dystonia[3]. CRPS can be defined as occurring in the absence (CRPS Type I) or the presence (CRPS Type II) of nerve injury. CRPS causes significant burden to individuals and the NHS and health related quality-of-life is worse than other long-term conditions such as diabetes[4].

Wrist fractures account for one-sixth of all emergency department visits[5]. The term wrist fracture is a broad descriptor for fractures occurring in the distal forearm including a distal radius, Colles fracture, distal ulnar fracture, or fracture of the carpal bones. Incidence of wrist fracture in the UK has a bimodal distribution, with peak

incidences in childhood and the elderly[6]. It is estimated that a 50 year old white woman, in Northern Europe or America will have a 15% lifetime risk of sustaining a distal radius fracture[6]. Common treatment options include conservative management in a cast, external fixation, Kirschner wire (K-Wire) fixation and open reduction external fixation (ORIF)[7]. The British Orthopaedic Association Standards for Trauma (BOAST) recommend that a distal radius fracture, requiring surgical fixation, should be fixed within either 72 hours of injury, or after detection that the fracture position has 'slipped' at the two-week check X-ray[8].

Historically there have been a variety of diagnostic criteria for CRPS[9], Whilst individual objective assessments are available (e.g. thermography or triple phase bone scan) these are not diagnostic tests nor considered necessary for diagnosis. Diagnostic criteria have relied on patient reported symptoms, such as disproportionate pain, along with a variety of clinically assessed signs. This subjectivity in the assessment of CRPS has impacted on sensitivity and specificity of these measures making earlier estimates of the incidence of CRPS type I highly variable, with previous estimates of incidence following a wrist fracture varying from 2-37%[10–13].

Patients who develop CRPS following a wrist fracture are typically seen by orthopaedic surgeons early on in the CRPS process, or by pain physicians once the condition is more established. Many of the early signs of CRPS such as swelling and reduced movement are observed in a patient following a wrist fracture[14,15]and this can contribute to high incidence reports in this setting. This finding led to the development of the Atkins criteria[12] specifically for use in orthopaedic clinics.

In 1994, the International Association of Pain (IASP), by a consensus process, agreed the IASP/CRPS diagnostic criteria[16]. These criteria were intentionally broad,

in an attempt to capture the spectrum of pain conditions that exhibit sudomotor and vasomotor dysfunction[17]. Subsequently, studies have demonstrated that the IASP diagnostic criteria have high sensitivity (100%) when discriminating between CRPS and non-CRPS neuropathic pain patients, rarely missing a case of CRPS, but, due to poor specificity (41%), these criteria can lead to significant overdiagnosis[18].

In 2003 a panel of experts agreed new diagnostic criteria, the 'modified IASP' or 'Budapest diagnostic criteria'[3] (Figure 1). Based on the research and recommendations of Harden and Bruehl[1719], it is scored differently for research or clinical purposes: a patient must report one symptom in all four categories for research and one in at least three categories for clinical purposes. For both clinical and research purposes, at least one sign in two or more categories must also be displayed. Research into the validity of this diagnostic tool[18], found comparable sensitivity (99%) but higher specificity (68%) than the 1994 IASP diagnostic criteria leading to recommendation in 2010 that the Budapest diagnostic criteria be universally adopted in order to better standardise diagnosis of CRPS[18]. Use of the Budapest diagnostic criteria in research and clinical practice are advocated by the IASP, the European standards for the diagnosis and management of CRPS[20], and the international CRPS diagnostic and treatment guidelines. It is also recommended in the UK within the Royal College of Physicians' (RCP) UK CRPS guidelines[21].

Despite this strong advocacy the Budapest diagnostic criteria have not been universally adopted and the impact of this on current incidence data is not known. Early identification and timely referral to interdisciplinary management has been previously shown to reduce the incidence of CRPS post wrist fracture[22]. Alongside this, the healthcare costs associated with CRPS post trauma have been found to be

13 times that for people without CRPS[23]. Improving our understanding of the incidence of CRPS in this acute post fracture period has implications for healthcare providers, and health economists in the justification of provision of care to this patient group. To our knowledge there has not been a review of the incidence of CRPS post wrist fracture since these 2010 recommendations. The primary aim of this review is to establish the incidence of CRPS type I within four months of a wrist fracture in the adult population. Previous work by Gillespie and Cowell[22] has demonstrated the potential to reduce the incidence of CRPS with restructuring of care in the acute post fracture period, a 4 month curt-off was decided on as it is the authors experience that this would be a typical fracture clinic follow-up timeframe.

We have chosen 2010 as the start point for our review as this is when the IASP formally advocated the use of the Budapest diagnostic criteria. We recognise that some papers will have collected data prior to 2010 but we have taken a pragmatic approach and set our search date from 2010 onwards. As it is not known how quickly and widely the Budapest diagnostic criteria were adopted following the 2010 recommendations, we also anticipate the use of other criteria that pre-dated this in our search.

Methods

Search Strategy

A systematic review was undertaken, the review protocol was not registered with PROSPERO but is detailed in the supplementary information. Lists of terms and MESH terms relating to Complex Regional Pain Syndrome type I, wrist fracture and incidence were generated. One reviewer (CR) conducted a literature search via the Healthcare Database Advanced Search (HDAS) platform, and the Cochrane Trials Register. An identical search was subsequently performed in MEDLINE, PubMed,

EMBASE, PsychINFO, CINAHL, BNI and AMED from 2010 until the present date (October 2019). Additional hand searching included the personal databases of the reviewers (CR, CM, AL), and the bibliographies of included studies. The search was limited to English language papers on adults (age 18+).

Study Selection

After removing duplicates and papers published prior to 2010, all remaining titles and abstracts were evaluated by the primary reviewer (CR and by two further reviewers (CM and AL) against the inclusion/exclusion criteria (Table 1). Inclusion and exclusion criteria were developed following the advice on methodological guidance for systematic reviews of observational epidemiological studies from the Joanna Briggs Institute[24]. The rationale for exclusion of any publication was recorded. Results of this primary screening were compared between reviewers and any discrepancies resolved by a process of consensus. The full text version of all shortlisted articles was re-checked against the inclusion and exclusion criteria by the primary reviewer and any ambiguity discussed with the second reviewers.

Data Extraction and Quality Assessment.

Due to time constraints only the primary reviewer (A) conducted the data extraction and quality assessment. Evaluation of methodological bias was conducted on each of the included studies using a modified version of the Newcastle-Ottowa scale (NOS)[25] for cohort studies as recommended by the Cochrane collaboration for use with non-randomised trials[26], and ambiguity in the scoring was discussed with an epidemiologist (GJ) familiar with the NOS.

There was a considerable heterogeneity between the study populations and research methodology, so results were not grouped for quantitative assessment and meta-analysis. Instead a qualitative analysis of the results was conducted (Table 2).

Results

The search of the seven databases yielded 320 papers reduced to 208 following preliminary title and abstract screening. Following full text screening, nine papers met all the inclusion/exclusion criteria. (PRISMA diagram Figure 2).

Full characteristics of the included studies are described in Table 2. All nine studies were prospective cohort studies with a median sample size of 291 (range of 36-1506). While all studies were published post 2010, five of the studies were conducted prior to 2010[9,27–29]. One study used the 1993 Veldman diagnostic criteria[30], two used the 1994 IASP diagnostic criteria [28,31] and five used the Budapest criteria[9,15,27,29,32,33]. Moseley et al used the criteria as recommended by Harden and Bruehl[17], as these became the Budapest criteria we have grouped these together. Within those using the Budapest criteria four used the research criteria [9,29,32,33] and two used the clinical criteria[15,27]. Seven of the nine studies were conducted in hospital fracture clinics/recruited from the emergency department[9,15,27–29,33,34] and two were conducted in rehabilitation units[30,32], on patients referred by orthopaedic surgeons. The studies originated from at least eight different countries with one paper not explicitly stipulating the study location[29].

Methodological quality and characteristics of the studies

The Newcastle Ottowa Scale (NOS)[35] was used, with dichotomous scoring, to assess the quality of the papers from which data were extracted in this study (Supplementary Information Appendix B). None of the studies in the current review

had a non-exposed cohort, so the instrument was modified accordingly, to omit these questions*, giving a maximum score (highest quality) of 6. Studies were considered of low risk of bias if they scored 5-6; moderate risk 3-4; and high risk <=2.

Summary results of the quality assessment are shown in Table 3. (Full scoring: Supplementary Information Appendix D).

Selection bias

Only two of the nine selected studies were conducted on both surgically and conservatively managed patients[9,15]. Studies that included only surgically managed[27], or only conservatively managed[29,30,33] patients were considered to have a selection bias as they did not encompass the whole wrist fracture population; therefore the impact of the fracture management strategy on the population incidence of CRPS was unknown. Two studies that recruited patients referred for rehabilitation post wrist fracture[30,32], were also considered to have a selection bias. It is the authors' experience that, as patients with a more complex fracture or exhibiting early signs of CRPS are more likely to be referred to physiotherapy, this would present a significant source of bias. Neither of these papers documented 'usual care' post fracture so it is possible that all patients were routinely referred to therapy.
Only one study explicitly included prior CRPS in their exclusion criteria[29]. Four others reported that previous upper extremity/limb conditions[15,33,34], 'or '*concomitant injuries of the upper limb (p488)*'[30] would be excluded. The lack of documented exclusion of pre-existing CRPS in the remaining four papers was considered a potential selection bias.

Outcome Bias

As per the NOS guidance, follow up of cohorts was considered adequate if there was less than 20% drop out of the starting cohort[25]. Two of the nine studies made no statement[31,33], and one had a high drop-out rate (41.0%)[27]. Of the remaining six studies there was minimal drop out and good explanation for loss to follow-up. All nine studies were initially considered to have conducted adequate assessment through use of a validated diagnostic tool, as per the inclusion criteria. However the paper by Jellad et al.[30] was later downgraded. The article they referenced to justify their use of the Veldman criteria in fact makes specific recommendations for the use of the Budapest diagnostic criteria[9]. Their choice of the Veldman criteria may represent an institutional bias.

Incidence of CRPS

In order to define the current incidence risk for CRPS following a wrist fracture, we used the three studies with the highest methodological quality and lowest risk of bias (see Table 3) and which were deemed to be on comparable study populations[7,20,22,]. From these three studies there is evidence that the current incidence risk of CRPS following a wrist fracture lies within the range of 3.7-14.0% when using the Budapest diagnostic criteria. Whilst some of the studies reported on both wrist and ankle fractures[9,15], it was possible to extract the data pertaining only to the incidence of wrist fracture. All studies used a calculation of incidence risk, expressed as a percentage ratio, however there was variability in how loss to follow-up was accounted for within this calculation. Only Moseley[29] reported a “naïve“ estimate of risk, as well as using a multiple imputation method to account for patients lost to follow-up to calculate a “primary estimate”. To aid comparison the authors calculated

incidence risk within four months of a wrist fracture for each of the studies (Table 4). The high sensitivity and low specificity of the 1994 IASP criteria[18] and the Veldman criteria[36] is reflected in the incidence risk of 13.3-26% found within the three studies that used these criteria[28,30,31] (Table 4). Two studies used the Budapest clinical diagnostic criteria.[15,27] We calculated an incidence of 10.83% for Zyluk et al.[27] in a population of surgically managed patients, and 14.0 % for Hall et al.[15] in a cohort of surgical and conservatively managed patients.

The final four studies used the Budapest research diagnostic criteria.[9,29,32,33] Farzad et al.[32] reported a high incidence of 25% from a cohort of surgical and conservatively managed patients. As with Jellad et al.[30], who found an almost identical incidence rate of 26%, the study was conducted by therapists in a rehabilitation unit. Moseley et al.[29], Beerthuizen et al.[9] and Roh et al.[33] reported an incidence risk of 3.7, 8.6 and 8.8% respectively.

Discussion

This review finds evidence that the incidence risk for CRPS following a wrist fracture is within the range of 3.7-14.0%. The study by Moseley et al.[29] reported the lowest incidence risk (3.7%). This study had a large sample size (n=1506), was multi-centred and demonstrated minimal bias (other than being conducted solely on conservatively managed patients). As such it is felt that the figure of 3.7% incidence risk for a conservatively managed wrist fracture is likely to be the best estimate. Along with Moseley[29], Beerthuizen et al[9] and Roh et al.[33] also used the Budapest research criteria. Their incidence figures of 8.6 and 8.8% respectively reflect incidence in both conservative[29,33] and mixed conservative and surgical cohorts[9]. The consistently low incidence is in keeping with previous work that demonstrated

that the Budapest research criteria is highly specific, but the least sensitive[18]. These predictions of risk can only be said to be applicable within the geographic context (West Europe).

Calculating an accurate incidence risk, as opposed to rate, relies on two variables: Firstly, the number of 'at risk' patients at the start of the process being present at the end. In all but two[27,28] of the nine studies reviewed, drop out was below 10%, (Table 4) an acceptable level for this calculation.

Secondly, the accuracy of the diagnostic tool. The Budapest diagnostic criteria are the recommended diagnostic tool by the International Association for the Study of Pain[20] but despite this gold standard, our results demonstrate there is still high variability of diagnostic criteria used across the nine studies. The 1994 IASP diagnostic criteria have been criticised for its inability to differentiate CRPS from other causes of neuropathic pain[18]. By comparison both the research and clinical variants of the Budapest diagnostic criteria have lower sensitivity and higher specificity than the IASP diagnostic criteria resulting in potentially a more accurate diagnosis. This review shows that while there has been uptake of the Budapest diagnostic criteria since it was published in 2010 it is not complete, with two studies collecting data post 2010 still using alternative diagnostic criteria[30,34]. There is also still variability in whether the research or clinical criteria are used, even in the research setting. These findings are in keeping with earlier work done by Bean et al[37] that demonstrated high variability in choice of diagnostic criteria in CRPS studies in general.

The high specificity of the research criteria would be of benefit in a pharmaceutical trial where it is critical to ensure only CRPS patients are receiving a treatment,

however in a clinical context, where there is merit in identifying “at risk” patients, the clinical criteria is arguably more useful.

One criticism of the Budapest criteria, in the context of fractures, is how to quantify ‘atypical’ pain. All four of the diagnostic criteria cited in this review ask about pain which is “disproportionate to the inciting event”. This assumes a prior understanding of what proportionate wrist fracture pain would be. The Atkins criteria uses dolorimeter to increase the objectivity of the assessment of hyperalgesia in CRPS and was designed specifically for use in fracture clinics[12]. It has been found to have similar validity to the 1994 IASP diagnostic criteria in the context of early CRPS[14] but has not been compared to the 2010 Budapest diagnostic criteria. It also requires the use of equipment that is not widely available in fracture clinics. Moseley et al.[29] studied the intensity of pain in the week following wrist fracture, measured on a 0–10 numerical rating scale, as a predictor of developing CRPS. They concluded that *“a pain score ≥5 in the first week after fracture should be considered to be a “red flag” for CRPS” (p20).* Further validation of this simple but potentially effective pain scale in the context of wrist fracture and CRPS could help to more accurately determine which patients are most at risk of CRPS enabling more rapid access to appropriate therapeutic or pharmaceutical treatment. This approach of stratifying patients according to their risk of developing a condition and pairing with appropriate care pathways has been successfully used in other musculoskeletal conditions such as low back pain[38]

Limitations

Other than Moseley et al.[29] the sample size of the other eight papers was modest,

ranging from n=36-477 (at baseline). In large studies calculations of incidence rate (as opposed to incidence proportion/risk) are possible. This calculation of the number of new cases of CRPS over a cumulative number of patient months/years tends to be more accurate because participant-time prior to loss to follow-up can be correctly accounted for, however on studies such as these, reporting data over a 4 month period this is less likely to have a large effect.

The use of only one reviewer in the full text screening and conducting the quality assessment is acknowledged to be a limitation. Furthermore, there has been some criticism of the NOS with regards to weighting the quality of observational studies, especially, although not relevant here, when used in meta-analysis[39]. In the context of this review, all the studies included used a screening tool for CRPS where the assessor was not blinded to the outcome. This lack of blinding may add to the potential for confirmation bias. The modification of the NOS to exclude components related to the 'non-exposed' cohort also resulted in a narrow assessment scale (0-6) on which to judge quality. All the studies in the current review are single-group cohort studies – i.e. cohort studies with a single exposure group (fracture). A cohort study would typically have an exposed and a non-exposed group, therefore the critical appraisal tools tend to follow suit. An alternative would be to use a tool designed for case-series, although these tend not to include issues relating to participant follow-up, which was important for the current research question. Thus, while there are other instruments available, we feel it is unlikely that they would have resulted in a different interpretation of study quality – i.e. studies that we've categorised as "moderate risk" that could otherwise have been "low risk", or vice versa.

Only two studies were excluded on the grounds of being non-English language, and both of these studies were also excluded for being clinical trials. We felt that in this instance, limiting the review to English language papers would not have influenced the overall findings.

Conclusion

Overall, the quality of the nine studies was adequate, but there were some studies of notably higher quality. We found evidence that the incidence risk falls within the range of 3.7% and 14% using the Budapest diagnostic criteria. One high quality study into conservatively managed wrist fractures had a lower incidence than studies into combined conservative and surgically managed fractures. However, we cannot conclude from the data that surgical management is a predictor for CRPS. Within the orthopaedic setting CRPS would be considered to be a rare but debilitating condition among patients who have experienced a wrist fracture. While the incidence may be relatively low, in comparison to the inciting fracture itself, the burden of care to therapy and pain management providers, as well as the reduced quality of life for patients would be considered to be significant. Future work to identify and diagnose those patients most at risk is still needed.

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Tables and Figures

Figure 1: 2010 Modified IASP/"Budapest" Clinical Diagnostic Criteria

(1) Continuing pain, which is disproportionate to any inciting event
(2) Must report at least one symptom in *three of the four* following categories:
    - Sensory: Reports of hyperesthesia and/or allodynia
    - Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
    - Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry
    - Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
(3) Must display at least one sign at time of evaluation in *two* or more of the following categories:
    - Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement)
    - Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry
    - Sudomotor/edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
    - Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
(4) There is no other diagnosis that better explains the signs and symptoms

Note: For the Budapest research criteria to be met the patient must report at least one symptom in *each* of the four categories under (2)

Figure 2: PRISMA flow diagram

Table 1: Inclusion/Exclusion criteria

Criteria for Inclusion:	
Study Design	Observational studies published after 2010 (including work conducted, but not published, prior to this date.)
Condition	Complex regional pain syndrome type I, or the following synonyms; Sudek's dystrophy, Algodystrophy, Reflex Sympathetic Dystrophy or Atkin's criteria. *Diagnosis:* The authors must state how the diagnosis of CRPS was made in their patient group. Either; 1. The diagnostic criteria they used or 2. clinical presentation observed + outcome measures used that enable the researcher to verify the population/participant meet the Budapest CRPS criteria
Context	CRPS to have been diagnosed within the first 4 months following a wrist fracture.
Population	Adults who have sustained a wrist fracture. To be defined as fractures involving one or more of the following: radius, carpal, ulna and scaphoid The fracture can have been conservatively managed or internally fixated. If internally fixed this must have occurred within 3 weeks of the inciting event as per BOAST guidance.
Criteria for Exclusion of Studies:	
Study Design	• Clinical Trials and RCTs • Not published in full article format • Published in language other than English • Published prior to 2010
Condition	• Patients with CRPS Type II • Patients who have a previous history of CRPS, have a pre-existing neurological or chronic pain condition affecting their upper limb, and those with CRPS type II. • No diagnostic criteria described by the author, or data collected from sources such as health insurance records where it is unclear how the diagnosis was made.
Context	• Patients with the occurrence of CRPS following secondary or corrective procedures that occurred later than 3 weeks following the injury or using an external fixation device beyond three weeks of the fracture.
Population	• Studies where reporting of CRPS is exclusively after 4 months of injury, and data prior to the 4 month cut off cannot be extracted. • Animal studies • Children, to be defined as anyone under 18 at the time of their injury. • Fractures to the upper limb above the level of the wrist, or with wrist plus an upper arm injury.

Table 2. Studies investigating the incidence of CRPS within 4 months of a wrist fracture.

FIRST AUTHOR, YEAR	SETTING, LOCATION AND PERIOD STUDY CONDUCTED IN	STUDY POPULATION	AGE AND GENDER	DIAGNOSTIC CRITERIA	TIME OF DIAGNOSTIC ASSESSMENT WITHIN FIRST 4 MONTHS	NUMBER OF ENROLLED PATIENTS WITH A WRIST FRACTURE	% OF WRIST FRACTURE LOST TO FOLLOW-UP
Farzad (2018)[32]	May 2015-Feb 2016 Hand Therapy Unit (Tehran)	Surgical and conservative management	Mean age 49.80 (+/-14.40), 53% Female, 46.7% male.	Budapest	Assessed weekly between week 2 (post fracture reduction) and week 8.	60	0
Zyluk (2013)[27]	May 2008-Dec 2010 Department of Hand Surgery (Poland)	Surgical management (k-wire)	Mean age 57 (range 28-86), 80% female, 20% male	IASP	Patients assessed at a mean of 6 weeks and 12 weeks post-op.	120	41%
Roh (2014)[33]	July 2010-April 2013 Department of Orthopaedics, Regional Trauma Centre (Korea)	Surgically treated	Mean age 50.5, 55% female, 45% male	Budapest	Assessed at 6, 12- and 24-weeks post-surgery.	477	Not known [a]
Dilek (2012)[28]	Jan 2006-May2007 Emergency Unit, University Hospital (Turkey)	Conservative management (cast for 6/52)	Mean age 57.70, 64% female, 36% male	IASP	Assessed weekly in first month (post cast removal) and bi-weekly up to 8 weeks.	57	12%
Hall (2016)[15]	May 2011 for 18 months Outpatient Fracture Clinic University Teaching Hospital (UK)	Surgical and conservative wrist and ankle fractures	Not known [b]	Budapest	week 10-12	36	Not known [a]

Beerthuizen (2012)[9]	Pre-2010 Emergency Department 1 teaching hospital and 2 general hospitals (Netherlands)	Surgically and conservatively treated wrist, scaphoid, ankle or V metatarsal fracture	Can't extrapolate wrist fractures from overall data.	Used three criteria but can only extract Budapest for wrist.	Assessed immediately after removal of plaster (at on average 6 weeks), then at 3 months	209	4.7% across the study [c]
Moseley (2014)[29]	Jan 2006-Dec 2008 Fracture clinic 3 hospitals, ? UK	Conservatively treated	Mean age 43.4 (range 18-75), 50.5% female, 49.5% male	Harden and Bruehl research diagnostic criteria and where ambiguous assessment by a pain consultant	Assessed at 4 months	1506	8.96%
Jellad (2014)[30]	Jan 2009-March 2011 Rehabilitation Unit in University Teaching Hospital (Tunisia)	Conservatively managed	Mean age 51.6, 62% female, 38% male,	Veldman	Assessed post cast removal at 6 weeks, then at around 11 weeks (1 month post cast removal)	90	none
Jesswani (2015)[34]	Jan 2013-April 2014 Department of Orthopaedic surgery Karachi (Pakistan)	Fracture management not documented.	Mean age 45.6, Female 41.3%, Male 58.7%	IASP and physical examination	Assessment at 16 weeks (4 months)	150	none

Table 3. Methodological quality out of 6 using modified Newcastle Ottowa Scale (NOS) There is a maximum score of 3 stars for selection and 3 stars for outcome giving an overall maximum of 6. Studies were considered of low risk of bias if they scored 5-6; moderate risk 3-4; and high risk <=2.

FIRST AUTHOR	NOS SCORE	SELECTION	OUTCOME
Dilek[28]	4	*	***
Moseley[29]	5	**	***
Zyluk[27]	3	*	**
.Jellad[30]	4	**	**
Beerthuizen[9]	5	**	***
Roh[33]	4	**	**
Jesswani[34]	4	**	**
Hall[15]	6	***	***
Farzad[32]	4	*	***

Table 4: Incidence risk of CRPS within 4 months of a wrist fracture.

First Author/Year	Incidence reported in paper (%)	Percentage missing data	Incidence Risk within 4 months calculated by authors (%)			
			1994 IASP	Budapest Clinical Diagnostic criteria	Budapest Research Diagnostic criteria	Veldman
Dilek (2012)[28]	26	12	22.8			
Moseley (2014)[29]	3.7	9			3.7	
Zyluk (2013)[27]	8.4[a]	41		10.83		
Jellad (2014)[30]	26	0				26
Beerthuizen (2012)[9]	NR	5			8.6	
Roh (2014)[33]	NR	0			8.8	
Jesswani (2015)[34]	13.3	0	13.3			
Hall (2016)[15]	NR	8		14.0		
Farzad (2018)[32]	25	0			25	

Data rounded to 1dp
a Incidence calculated at week 12 not within 12 weeks
NR Exact wrist data not recorded (NR)