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Clinical course and prognostic factors in conservatively managed carpal tunnel syndrome: A systematic review

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Running Head: The Course and Prognosis of Carpal Tunnel Syndrome

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Abstract

Objective

To summarize the available evidence regarding the course of symptoms and prognostic factors in patients diagnosed with CTS and treated conservatively. Details of the protocol for this systematic review were registered on PROSPERO (CRD42013006608).

Data Sources & Study Selection

Through a systematic search we identified 16 cohort studies from hospital and clinical database settings, describing the course of CTS.

Data Extraction

Methodological bias was assessed using the Quality in Prognosis Studies (QUIPS) tool. A high risk of bias, (predominantly relating to study attrition, confounding and/or statistical analysis and reporting) was judged to be present in 8 studies. Designs showed wide variability with respect to: characteristics of the included population; definition of CTS; assessment of prognostic factors; types of interventions provided and types of outcome measures applied. This prevented pooled estimates being produced.

Data Synthesis

Negative outcome at 3 years follow-up of conservatively treated participants ranged from 23 – 89%. Four included studies observed the rate of surgical intervention following initial conservative management and found this to be 57-66%. Evidence regarding factors predicting the negative outcome of no treatment or conservative

treatment was graded taking into account the number of studies evaluating the factor, the methodological quality of these studies and the consistency of the available evidence. There was 100% agreement in at least 3 or more cohorts with a medium or high risk of bias that: symptom duration; a positive Phalen's test; and thenar wasting were associated with a negative outcome of conservative management, however not all results were statistically significant and hence the overall judgement remained inconclusive.

Conclusions

Results of this review should be treated with caution due to the heterogeneity of studies, and the risks of bias identified. However, the course of CTS appears variable and poor prognosis may be predicted by a longer symptom duration, a positive Phalen's test and thenar wasting.

Key words: carpal tunnel syndrome; disease management; prognosis

Abbreviations

CTS	carpal tunnel syndrome
NSAIDS	non-steroidal anti-inflammatory drugs
PF	prognostic factor
QUIPS	Quality in Prognostic Studies

Introduction

Carpal tunnel syndrome (CTS) is a chronic focal compressive neuropathy caused by the entrapment of the median nerve at the level of the carpal tunnel [1]. CTS is the most common of the entrapment neuropathies, accounting for 90% of presentations [2] and is characterised by numbness, tingling, hand and arm pain and muscle dysfunction [3]. Between 55–65% of CTS cases present bilaterally[4] and the condition can be associated with hypothyroidism, diabetes, and rheumatoid arthritis, amongst others. CTS may present in late pregnancy but is usually transient.

Studies in different countries have reported varying results with respect to the incidence of CTS [5]. A survey of the Skåne Health Care Register in Sweden by Atroshi et al was age-adjusted to the 2000 US standard population to allow comparison with the results of a US based survey of the Rochester Epidemiology Project [6]. The estimated incidence of CTS in Sweden was reported as 324 per 100,000 in women compared with 542 in the US, and in men, 166 in Sweden compared with 303 in the US [5, 6]. The explanation for variation between countries is unknown, however suggested possibilities include: differences in healthcare seeking behaviour and variation in aetiological factors including occupation, diabetes and inflammatory joint disease [5].

The treatment of CTS is often categorised as either surgical or conservative (non-surgical). Surgical treatment is generally recommended for those with severe CTS i.e. evidence of denervation of the median nerve, whilst conservative treatments are recommended for the initial management of those who have intermittent or mild symptoms or in whom surgery is contraindicated [7]. The US-standardised annual

incidence of carpal tunnel release surgery per 100,000 persons was 166 in Sweden compared with 171 in the US and, among men, 58 in Sweden compared with 96 in the US [5, 6]. Examples of conservative treatment include; oral steroids, steroid injections, physical therapy, electrotherapy, night splinting and workplace alterations[8]. In UK primary care, steroid injections and night splinting form the mainstay of conservative treatment options, as indicated by national care pathways (for example National Institute for Health and Care Excellence Clinical Knowledge Summaries) [9, 10]. Guidelines for the management of CTS by the American Association of Orthopaedic Surgeons [11] conclude that patients with more severe and prolonged CTS may not benefit from extended conservative treatment. However the authors were unable to recommend in which patients conservative treatments were unlikely to be effective [11].

Cochrane systematic reviews of conservative treatments for CTS [12] have included the assessment of local corticosteroid injections [13] and splinting [7]. In respect of splinting, the authors conclude that there is limited evidence that night splinting is more effective than no treatment in the short term. They do however suggest that that more research is needed on the long-term effects of this intervention [7]. With regard to steroid injections, it was concluded that robust evidence demonstrates clinical improvement up to one month compared to placebo but relief beyond this time period has not yet been shown [13].

With on-going clinical uncertainty regarding the most effective management strategy for CTS, there is a clear need for a greater understanding of the likely long term course of CTS symptoms (overall prognosis) of the condition and patient factors that may be associated with outcome (prognostic factors).

Outcomes and predictors of surgical outcome have been well reported in the literature, however few studies and no systematic reviews have been performed to summarise the evidence for prognosis and prognostic factors in conservatively managed disease, i.e. that which can be delivered in a primary care environment. An estimate of average prognosis is required by public health policy makers in order for the population burden of a condition to be assessed. Understanding the future outcomes of patients with a particular condition in relation to current practice and even in the absence of clinical care (the natural history) is crucial as it allows the potential impact of interventions to be more fully assessed [14]. Such information is not only important when considering the potential benefits of interventions, but also in order to inform patients, clinicians and policy makers of the potential harms, variations (such as underuse, overuse, misuse) and potential impact on healthcare efficiencies [14].

This systematic review and narrative synthesis initially focuses on summarising the prognosis research regarding the general course of CTS. The 'startpoint' of this review will be the point of diagnosis of CTS that is being treated conservatively or with no clinical treatment. The 'endpoint' will vary depending upon on the primary study. This synthesis therefore seeks to describe the course of CTS, being managed with either no intervention or with conservative approaches.

The second part of this systematic review aims to identify predictors of long-term outcome (prognostic factors) in CTS. A prognostic factor (PF) is *"any measure that, among people with a given health condition (startpoint), is associated with a subsequent clinical outcome (endpoint)* [15]. Prognostic factor research thus seeks to identify the predictive value of such factors.

Research of prognostic factors aims to identify features that could potentially contribute to the development of prognostic models or represent predictors of differential treatment response, which may further contribute to a stratified care approach to a condition. Prognostic factors may also represent modifiable targets for interventions and could hence lead to the development of new management strategies through an improved understanding of disease mechanisms [15].

Methods

2.1 Identification and selection of the literature

Details of the protocol for this systematic review were registered on PROSPERO (CRD42013006608) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013006608#.VYk_RflVhBc. Eligible publications had to report; the course of CTS symptoms (persistence / recovery or severity of pain or other symptoms), and / or the association between a potential prognostic factor and outcome as well as meeting the following eligibility criteria:

- The study included adults (aged 18 years or over), diagnosed with CTS in either a clinical setting or population setting. Studies in pregnant women and in populations such as specific occupational groups were excluded
- The study observed the course of CTS over at least a 6 week period in patients receiving no treatment or usual care that included conservative (non-surgical) treatments. Studies reporting risk factors for onset of CTS as opposed to predictors of outcome were excluded, as were studies investigating predictors of the effectiveness of a specific treatment (which

would ideally require a review of randomised clinical trials and is planned for the future)

- The design was of a longitudinal cohort study with either prospective or retrospective data collection
- There were no language restrictions and none of the research identified was only reported in abstract.

A systematic, computerised search of the literature was conducted in Medline, Embase, AMED, HMIC, PsychINFO, Cinahl, Cochrane, SCI-EXPANDED and CPCI-S from their inception until December 2013. The Medline search strategy can be found in Supplementary table S1. References of all included full-text articles were hand-searched and the first 15 pages of Google Scholar results for 'carpal tunnel syndrome' and 'prognosis' were screened as a further check for relevant hits. Experts were contacted to identify any further studies or publications in the grey literature that had not been identified in the search. The titles were screened by one reviewer (CB) and abstracts were screened by two reviewers (CB and LC) and full papers of potentially eligible studies retrieved. Such papers were screened by the two reviewers independently for eligibility and included in the review if they met the pre-specified criteria.

2.2 Quality assessment

All selected studies were assessed independently for quality by CB and LC using the Quality in Prognosis Studies (QUIPS) tool [16]. The QUIPS tool assesses bias in the six following domains: 1) study participation; 2) study attrition; 3) prognostic factor measurement; 4) outcome measurement 5) study confounding and 6) statistical analysis and reporting. Judgements of low, moderate or high risk of bias were made

for each applicable domain using descriptors recommended by Hayden et al [16]. Summated scores for overall study quality are not generally recommended, however assessment of the overall risk of bias is suggested to be useful when synthesising existing evidence [16]. Using suggestions from Hayden et al.,[16] studies were judged to be of low overall risk of bias if all or most of the domains were judged as low risk, and studies in which all or most of the domains were judged as high risk were considered to be of high overall risk of bias. Studies with a moderate risk of bias were those with all or most of the domains being judged as moderate risk of bias. Differences between reviewers were discussed and a decision made by agreement. Agreement between reviewers (CB and LC) regarding the judgement of overall risk of bias was presented as percentage agreement.

2.3 Data extraction

Data were extracted by CB and checked by LC. Data extraction included details of the study setting, population demographics, diagnostic criteria of CTS used, management approaches used, prognostic factors (type of factors and how measured), outcome measures (definition and instrument used), sample size, rate of attrition and length of follow up. With regard to clinical course, the percentage of patients with a negative outcome following conservative treatment or no treatment were recorded. All reported prognostic factors were listed and measures of association with their significance levels recorded.

2.4 Analysis

Results regarding the course of symptoms in patients with untreated and conservatively treated CTS were summarised narratively. Pooling of results was not possible due to heterogeneity with regard to study setting, case definition, follow-up

periods and measures of outcome. We summarised findings for the reported prognostic factors by taking into account the number of studies evaluating the factor, the risk of bias of these studies and the consistency of the available evidence (as defined as significant association with the same direction). A level of evidence was defined for each factor, based on Sackett et al. [17] and Ariens et al. [18] and adapted for use with the QUIPS tool (Table 1).

Results

3.1 Selection of studies

Figure 1 presents a flow chart of study selection. 15,572 citations were identified (6987 Medline, 6445 Embase, 197 AMED, 19 HMIC, 92 PsychINFO, 707 Cinahl, 755 Cochrane, 370 SCI-EXPANDED and CPCI-S). Following the removal of duplicates and a screen of the titles, 146 abstracts were screened and 42 full text publications retrieved for further eligibility screening. 26 papers were excluded for the following reasons: one foreign language duplicate was found, 3 studies reported conditions not specific to CTS (i.e. wrist pain or unspecified entrapment neuropathies), 6 studies reported outcomes in a specific population, 4 studies reported aetiology of CTS only, 6 studies reported on outcomes of specific treatments and 6 studies used a design other than that described in the selection criteria. 16 papers (reporting on 16 cohorts) met all eligibility criteria and were included in the review.

3.2 Study Characteristics

Table 2 summarises the characteristics of the studies including the QUIPS score, study design and setting, study population, interventions used in the study, the primary outcome measure including the definition of a negative outcome, and

duration of follow-up. The table also presents the percentage of the cohort experiencing a negative outcome (e.g. surgery) of conservative or no management.

One study was a retrospective follow-up study of cases identified in the Marshfield Epidemiologic Study Area, a population-based cohort [19]. All other studies were based in secondary or tertiary care, of which 6 were in surgical clinics and 8 in EMG (Electromyography) laboratories. No studies were based in primary care. The case definitions used to identify CTS differed: 6 studies used clinical features only whilst the remaining 10 studies required accompanying electrophysiological abnormality. The combination of clinical characteristics used and the electrophysiological criteria also varied between studies. The interventions used in the studies included; wrist splinting (7 studies), NSAIDS (non-steroidal anti-inflammatories) (3 studies), other analgesia (2 studies), oral steroids (3 studies), local steroid injections (6 studies) and paraffin treatment (1 study). Three studies provided conservative management without specifying which mode exactly. In 4 studies, the course of (clinically) untreated CTS was observed [20-23]. In some studies, parts of the cohort were treated surgically. Their specific outcomes were not included in this review. A range of outcome measures were used: 3 studies used a surgical episode as a proxy for a negative outcome; 1 study used the *Quick*dash score; 5 used measures of global improvement; 2 used a change in symptom and function severity scores; 1 used the Historic and Objective Scale [24]; 1 used work absence; 2 observed electrophysiological changes and 1 used absence of clinical contact as an indicator of recovery. The follow-up periods ranged from 12 weeks to 10 years.

3.3 Methodological quality

The results of the quality assessment are presented in Table 3. In 4 studies, investigating course of CTS symptoms only, the prognostic factor domain was not assessed. The percentage agreement between authors CB and LC, with regard to judgement of the overall risk of bias was 75% and 100% following discussion. Further adjudication was therefore not required.

Eight studies were judged to have a moderate risk of bias and 8 to have a high risk of bias. The domains that carried a particularly high risk of bias across all studies were: study attrition (12 studies); study confounding (10 studies) and statistical analysis and reporting (9 studies). Study attrition tended to be at high risk of bias as the response rates in several studies were low (see table 3), attempts to collect information on participants who dropped out was often lacking, reasons for loss to follow-up were rarely provided and differences between those lost to follow-up and those actively followed up were not frequently compared. Study confounding was also a frequent finding largely due to the fact that not all potential confounders were appropriately accounted for and hence the observed associations of the potential prognostic factors with outcome were likely to be at least partly explained by other (unmeasured) factors. This was particularly true in studies using retrospectively collected data. Statistical analysis and reporting was commonly identified as being of high risk of bias as presentation of the data was frequently insufficient and in some studies selective reporting of results was evident.

3.4 Course of carpal tunnel syndrome

For each included study, Table 2 describes results regarding the course of CTS in conservatively treated or untreated patients by describing the proportion of patients

who experience a negative outcome, the definition of which varied between studies (i.e. persisting or worsening symptoms, progression to surgery, or work absence due to CTS). Table 4 further summarises results regarding the course of CTS in terms of the percentage of patients reporting a negative outcome for different follow-up time points.

4 studies examined the course of untreated CTS [20-23]. OrizCorredor et al observed that of 132 patients with untreated CTS over a 2 year period, 23.5% showed a deterioration in the HiOb score but most cases did not show an electrophysiological deterioration (89 remained the same, 33 recovered and 10 deteriorated. Only 1 patient had both an electrophysiological and clinical deterioration[22]. Padua 1998 et al reported whether the clinical outcome was unchanged or worse in groups of patients with different electrophysiological classifications. They found the clinical outcome was worse in 50% of patients with negative electrophysiology, 27.5% with moderate studies and 50% of extreme studies [20]. Padua 2001 et al further observed the electrophysiological, symptomatic, functional, HiOb and pain changes in patients with CTS. They reported that 16%, 21%, 16%, 32% and 12% of patients in each of these outcome areas worsened [21], whilst 27%, 34%, 23%, 23% and 26% of patients improved [21]. Resende et al presented the change in electrophysiological measures and accompanying change in symptoms over a 4 to 9 year periods and found that 25% of patients had a marked improvement in electrophysiological outcome (100% of whom had improvement in terms of symptoms); 15% showed slight improvement (of whom 33% had worsening of symptoms); 50% showed no significant change (of whom 50% had worsening in terms of symptoms) and 10% had a worsening of electrophysiological measurements (of whom 50% had a worsening of clinical symptoms) [23]. In summary, 32 - 58% of participants receiving no treatment were

reported to have a negative outcome at 12 months follow-up in two studies [20, 21], both of which were of moderate risk of bias. The two further studies reporting at 3 and 10 years were at high risk of bias and reported a negative outcome in 23.4%[22] and 50% [23].

In the 9 cohorts receiving conservative treatment: 68.5% - 75% of patients were reported to have a negative outcome within 3 months follow-up [25, 26]; 82% within 6 months [27]; 23 – 89% within 3 years [19, 28-31] and 22 – 24% within 10 years [28, 32]. A wide variation in findings was noted according to risk of bias, with studies of a moderate risk of bias appearing to show lower percentages of patients with a negative outcome (e.g. 23 – 68% at 3 years [19, 28-30]), compared to studies of high risk of bias (82% at 6 months[27] and 89% at 3 years[31]). Four studies used a surgical episode as a marker of negative outcome of conservative management [27, 33-35]. A range of 57% to 66% of patients were observed to receive surgery following conservative management over a period of between 1 and 3 years [27, 33-35]. In summary, the reported course of conservatively managed CTS is highly variable but symptoms do improve over time.

3.5 Prognostic factors predicting negative outcome of carpal tunnel syndrome

Eleven of the studies presented data on the association between potential prognostic factors and a negative outcome of conservatively managed CTS.

Table 5 presents potential prognostic factors observed in the studies and reported associations. Not all studies presented estimates of associations with confidence intervals. Some presented P values only; some simply reported a finding as non-significant. Therefore, the number of studies investigating each association, the

number of studies of moderate or high risk of bias (none were of low risk) and the number showing an association (direction and significance) are summarised.

In total 39 potential prognostic factors were identified from the studies. All of these were found to have inconclusive levels of evidence of an association with a negative outcome. This was due to inconsistencies in study findings, non-significant results, low numbers of studies investigating each factor and the moderate to high risk of bias of the studies included.

Discussion

This study is the first systematic review of the prognosis of conservatively managed CTS. A substantial amount of heterogeneity exists in terms of study setting, case definition, follow-up periods and measures of outcome between the included studies, which prevented meta-analysis from being conducted. A best evidence synthesis was therefore presented.

4.1 Course of carpal tunnel syndrome

Four studies observed the course of untreated CTS [20-23], which is helpful when considering the need for or impact of treatment. These studies suggest that a proportion (28% - 62%) [20-23] of patients will recover or not deteriorate further in the absence of treatment and hence a certain period of ‘watchful waiting’ (not clearly defined by the available evidence) may be considered clinically when discussing treatment options with patients. When considering potential mechanisms for recovery (not including mechanisms of treatment) Padua et al 1998 suggest that certain undefined CTS cases are self-limiting due to a process of neural adaption,

whereby the functional relationship between the nerve and the carpal tunnel adapts over time[20].

Due to outcomes being measured at discrete time points by each study, it was not possible to provide a cumulative percentage of patients recovering in each period and so provide clearer information about what is happening to patients with CTS over time. Table 4 does however show that a proportion of patients can be observed to have deteriorated from baseline at any point between 3 months and 10 years, suggesting that the course of CTS is likely to be highly variable. It is possible that the studies with longer follow up periods may be representative of patients who improve and relapse over time, but as none of the studies were designed to observe the longitudinal course of CTS (i.e. at a week-to-week or month-to-month level), such a symptom course could not be illustrated by this review.

With regard to symptom relapse, only one study[31] specifically addressed this issue. Goodwill et al reported that 85% of patients initially responding to conservative treatment approaches relapsed within 1 to 4 years[31]. The possibility of future relapse therefore puts into question the observations of all studies conducted over a shorter time frame. A further consideration is that a recurrence of symptoms following a conservative treatment which then responds to a further episode of conservative management (if deemed clinically appropriate), may not necessarily represent treatment failure. However, longitudinal data which may describe this phenomenon was not available, again emphasising the importance of long-term studies with repeated assessment of symptoms in patients with CTS.

The observed between-study variability may be partially explained by substantial differences in study setting, study design, case definitions, interventions (the

effectiveness of which cannot be compared between studies), and outcomes used but possibly also by differences in patient or disease factors (potential prognostic factors) between studies.

4.2 Prognostic factors predicting negative outcome of conservatively managed carpal tunnel syndrome

Due to inconsistencies between study findings and the lack of studies with a low risk of bias, it was not possible to identify conclusive evidence for any of the factors reported by individual studies to predict a negative outcome of conservative management.

There was however 100% agreement in at least 3 or more cohorts with a medium or high risk of bias that: symptom duration; a positive Phalen's test; and thenar wasting were associated with a negative outcome of conservative management, however not all results were statistically significant and hence the overall judgement remained inconclusive.

Due to a lack of robustness in design and conduct of most of the included studies, the overall body of evidence identified was felt to be of moderate and high risk of bias. This limited whether the synthesised evidence could be considered as conclusive and as such evidence regarding the prognosis of untreated and conservatively treated CTS remains weak. To improve future research key recommendations would include identifying patients with CTS at baseline using a robust case definition of the condition. Patients should be followed up for a prolonged period (over 3 years), preferably at a number of time points using a clinically meaningful, valid and reliable outcome measure. This would allow a longitudinal picture of CTS to be mapped. Attempts could be made to reduce

attrition or better describe the risk of attrition bias by collecting information from non-responders and to provide a description and reason for any loss to follow up. Ideally, all potential prognostic factors should be included and measured at baseline using valid and reliable measures [16].

To capture the start point of the condition and its earliest management, it would be beneficial to set such a study in primary care, where it is likely most patients present initially with their symptoms and commence treatment.

4.3 Limitations

We searched electronic databases considered to be important and relevant to the topic. Titles were screened by one person due to the significant number; hence human error may have led to some titles being missed. Studies not included in databases and not identified through reference checking, Google Scholar and expert advice may have been overlooked, such as unpublished cohort studies. As the review did not find strong evidence for any of the prognostic factors, it is unlikely that further unpublished material would have strongly influenced our conclusions. The review focussed on studies observing the course of symptoms in patients being treated conservatively for CTS but excluded cohorts being allocated specific treatments. Predictors of differential treatment response (moderators) are best identified by randomised trials and as such a further systematic review of these studies is planned.

Results of studies presenting only descriptive results and P-values were included in the review, without any risk estimates. All evidence found could therefore be included but there is a possibility that the lack of statistical significance was due to small sample sizes and hence represent a lack of evidence for some of the

prognostic factors rather than a genuine absence of association. Future prognosis research in the area of CTS should therefore ensure that estimates of associations with outcome are adequately reported and that the study population is of adequate sample size to investigate the hypothesised associations with outcome.

The unit of analysis differed between studies i.e. some analysed outcomes at patient level (not necessarily taking into account the laterality of the condition); whilst others analysed outcomes at wrist level (i.e. patients with bilateral symptoms may be included as 2 cases, not taking dependence of outcomes within individuals into account). Issues relating to the statistical analysis of bilateral CTS has been discussed at length for clinical trials by Page et al [36]. A unit-of-analysis error, which may give rise to overly narrow confidence intervals and small P values, may occur when data is analysed on the basis of the number of wrists without adjustment for non-independence [36]. Such an error may also occur in prognosis research, including the reviewed studies, and be a further source of bias. Future prognostic studies should, where possible, take into consideration this risk of bias in their design and analysis plan.

4.4 Implications for clinical practice

Patients presenting with CTS can be informed of the possibility of recovery with no treatment or conservative treatment i.e. that they will not require surgery, however factors which help to predict their likelihood of falling into this group have not been robustly determined. Increasing symptom duration, positive Phalen's test and thenar atrophy are likely to be prognostic factors of poor outcome of conservatively managed CTS but need confirmation in further well-designed prognostic studies. The review did not identify electrophysiological severity as a significant predictor of a

negative outcome of conservative management. This may have implications for services which ration surgery to patients with more severe results and suggest other factors should be taken into consideration alongside laboratory investigations.

Conclusion

In this review we found useful descriptions of both the course of untreated CTS and that of conservatively managed CTS. Although none of the studies were of low risk of bias, studies of moderate and high risk of bias showed a widely ranging course of symptoms, with 23 – 89% of participants reporting negative outcome at 3 years follow-up. We found no consistent evidence to support factors which predict future outcome and may help to explain the wide variability in the course of symptoms.

There is likely to be an optimum time by which conservative management should be deemed to have failed and surgical intervention considered, in order to prevent long term harm, although this point has not been clearly determined nor is it clearly possible to predict which patients may be included in this group.

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Legends of Figures and Tables

Table 1 Levels of evidence for prognostic factors [17, 18]

Table 2 Summary of study characteristics and results regarding the course of symptoms of prognostic cohort studies in carpal tunnel syndrome

Table 3 Results of the methodological assessment of prognostic cohort studies on CTS

Table 4 Course of carpal tunnel syndrome in conservatively treated or untreated patients (percentages not cumulative)

Table 5 Prognostic factors and strength of association for an unfavourable outcome of carpal tunnel syndrome in patients who are **conservatively treated or untreated**

Figure 1 Study selection

Table 1 Levels of evidence for prognostic factors [17, 18]

Level of evidence	
Strong	Consistent findings (≥ 75%) in at least 2 cohorts with a low risk of bias
Moderate	Consistent findings (≥ 75%) in one cohort with a low risk of bias and at least one cohort with a moderate/high risk of bias
Weak	Findings of one cohort with a low risk of bias or consistent findings (≥ 75%) in at least 3 or more cohorts with a moderate / high risk of bias
Inconclusive	Inconsistent findings irrespective of study quality, or less than 3 cohorts with a moderate / high risk of bias
No evidence	No data presented

1 Table 2 Summary of study characteristics and results regarding the course of symptoms of prognostic cohort studies in carpal

2 tunnel syndrome

Author (Year)	Risk of bias (QUIPS score)	Study population	Interventions provided to entire cohort	Primary outcome measure / duration follow - up	Measure of negative outcome of **conservative management**	Proportion of patients **treated conservatively** experiencing negative outcome
Treated populations: prospective cohort studies						
Boyd et al. 2005[33]	High	Setting: tertiary hand and upper limb	Splint: all wrists Surgery: 27	No surgery versus surgery by 6 months	Progression to surgery	57% of wrists

Canada		centre CTS diagnosis: clinical findings and electrophysiological abnormality 68% female Mean age: 49.3 years N=25 patients	(57%) wrists	12 weeks, with an option to continue follow-up >6 months		

		(47 wrists) Drop-out = 17%				
Duckworth et al. 2013[34] **Scotland**	Moderate	Setting: hand clinic CTS diagnosis: clinical findings and electrophysiological abnormality	Splint: all patients Injection: 150 (55%) (of whom 38 had surgery) Surgery: 122	*Quick*DASH Score 1 year	Progression to surgery	58% of patients

		67% female Mean age: males 57 (s.d. 14) years; females 54 (s.d. 14) years N=275 patients Drop-out = 28%	(44%) patients No further treatment: 3 (1%) patients			
Goodwill. **1965**[31]	High	Setting: EMG laboratory	Splint: 98 (63%) wrists	Judgement made at follow- up: cured,	Evidence of symptoms	Following steroid injection: 88%

England		CTS diagnosis: paraesthesia and pain with electrophysiological abnormality 93% female Age bands: 30-39: 7 40-49: 19 50-59: 39 60-69: 18	Injection: 58 (37%) wrists Surgery: 55 (35%) wrists	temporary relief or no relief 1 - 3 years (average 14 months)		of patients Following splinting: 89% of patients Following surgery: 5% of patients

		70+: 13 patients N=96 patients (155 wrists) Drop-out = 0%				
Kaplan, Glickel & Eaton. 1990[27] **USA**	High	Setting: hand clinic CTS diagnosis: presence of pain or paraesthesia and clinical	Splint: 'most patients' Non-steroidal anti-inflammatory:	Success of therapy as defined by absence of symptoms for > 6 months	Evidence of symptoms after 6 months Progression to surgery	82% of wrists 66% of wrists

		findings (thenar atrophy, altered sensation or Phalen's sign) 75% female Mean age 55 years N = 229 patients (331 wrists) Drop-out =	149 (65.2%) patients Oral steroid: 61 (26.8%) patients Steroid injection: 38 (16.4%) patients	Minimum of 6 months or until had surgical release (average 15.4 months)		

		12%				
Katz et al. **1998 a**[30] **USA**	Moderate	Setting: surgical clinics CTS diagnosis: paraesthesia involving at least 2 digits (thumb or index, middle or ring fingers) and symptom duration of at least 1 month	Non-surgical cohort: 34 patients received surgery at less than 3 months and were not included in analyses By 30 months: Splint: 76	Change in status in symptom severity, functional limitations and health status were recorded over time. Associations were measured for patients crossing	Would not be happy to live the rest of their lives with symptoms	60% of patients

		74% female Surgical cohort: >55yr mean age 68.0 years (sd 9.1); <55yr compensation non recipient 42.0 years (sd 7.3); compensation recipient mean age 39.0 years (sd 8.1).	(94%) patients Injection: 36 (44%) patients Physical or occupational therapist: all	between non-surgical to surgical cohorts after > 3 months. Follow up took place at 6, 18 and 30 months		

		Non-surgical cohort >55yr mean age 64.0 years (sd 7.0); compensation non-recipient mean age 41.0 (sd 8.9); compensation recipient mean age 37.0 years (sd 8.8) N = 297 patients				

		Drop-out = 31%				
Kiylioglu et al. 2009[26] **Turkey**	Moderate	Setting: EMG laboratory CTS diagnosis: clinical findings, supported by electrophysiological abnormality. 90% female	Treatment methods not controlled or standardised 'Rehabilitation': patients treated with splints, paraffin treatments and / or oral non-	Symptom severity score and functional status (Boston questionnaire translated into Turkish) Patients were followed up in the early	Percentage improvement in symptom severity scale Percentage improvement in function severity scale	Rehabilitation 82 Surgery 77 Untreated 25 Rehabilitation 73

		Diabetic rehabilitation group mean age 59.3 years (sd 7.4); diabetic untreated group mean age 54.6 (sd 11.1); idiopathic rehabilitation group mean age 47.8 years (sd 9.9); idiopathic	steroidal anti-inflammatories	follow-up period (3-5 months) and late follow up period (6-12 months)		Surgery 85 Untreated 17

		surgery group mean age 49.2 (sd 9.8) N = 42 patients (80 wrists) Drop-out = 0 (assumed)				
Treated populations: retrospective cohort studies						
Kouyoumdjian et al. 2003[32]	High	Setting: EMG laboratory CTS diagnosis:	Surgery: 147 (66%) wrists	General patient satisfaction: complete relief; improved	Symptoms unchanged or worse	23.7% of wrists

Brazil		symptoms including hand paraesthesia, numbness and pain mainly at night. 95.8% female Surgical cure group mean age 46 years (range 24 – 70); unchanged / worse group 44	Non-surgical (splint, local injection, medication and others): 75 (34%) wrists	“much better”; improved “little”; unchanged; worsened Poorly recorded. Between 5-10 years, (mean 5.9 years following surgery)		

		years (range 39 – 58); non-surgical cure group mean age 61 years (range 48 – 79); worse group 50 years (range 30 – 83) N = 165 patients (222 wrists) Drop-out =				

		69%				
Lian, Urkunde & Verma. 2006[25] **Singapore**	High	Setting: EMG laboratory CTS diagnosis: clinical history and examination, confirmed using AAEM criteria and additional testing if this was normal	Conservative management: 88 (77%) patients Surgery: 27 (23%) patients	Clinician review of medical records and decision made as to category: resolved; improved; same; worse Follow up took place at 3 and	Symptoms unchanged or worse	68.5% of patients

		81.3% female Mean age 53.6 years N = 115 Drop-out 14%		6 months (limited data available)		
Miranda, Asaad & Cerovac. 2013[35]	High	Setting: plastic surgery clinic CTS diagnosis: based on clinical	Injection: 66 (49%) patients Surgery: 68	Symptom relief and / or surgery 22.5 +/- 0.5	Progression to surgery	62% of patients

UK		symptoms Gender not reported Mean age 56 years (sd 3) N = 134 Drop-out 10%	(51%) patients	months		
Muhlau, Both & Kunath.	Moderate	Setting: EMG laboratory CTS diagnosis:	Conservative management: 72 (48%) wrists	An overall categorisation was made at	No evidence of cure	68% of patients

1984[28] **Germany**		distal motor latency was >4.7ms Gender and age not reported N = 157 (214 wrists) Drop-out 38%	Surgery: 112 (52%) wrists	follow up: cured; clear improvement; slight improvement; unchanged findings; further deterioration. These were then dichotomised so that groups 1 and 2 = cured and 3,4 and 5 = not		

				cured. Follow up was at least 2 years and defined as when the patient had reached a 'steady state'		
Treated populations: Retrospective follow-up study of a population-based case series						
DeStefano, Nordstrom & Vierkant.	Moderate	Setting: patients identified from	Analgesia: 143 (34%) patients	No surgery versus surgery and resolution	Evidence of symptoms	1 month: 75% of patients

1997[19] **USA**		the Marshfield Epidemiologic Study Area CTS diagnosis: ICD-9-CM code 354.0 and evidence of a clinical and / or electrophysiological abnormality in the records. 62% female	Non-steroidal anti-inflammatories: 132 (31%) patients Injection: 6 (1%) patients Splint: 295 (69%) patients	of symptoms Median follow-up 1979 - 1983: 12.0 years (5 and 95th percentiles:10.0 and 14.8 respectively). 184-1988: 7.3 years (5.0-9.8)		2 years: 40% 8 years: 22%

		Mean age 62 years N= 425 Drop-out 0%	Surgery: 198 (47%) patients			
Treated populations: Secondary analysis of Katz et al.1998 a						
Katz et al 1998 b[29] **USA**	Moderate	Setting: surgical clinics CTS diagnosis: paraesthesia involving at least 2 digits	Surgery: 179 (71%) patients	Out of work at 18 months Questionnaires were completed at 6,	Work absence at 18 months, due to CTS	23% of patients

		(thumb or index, middle or ring fingers) and symptom duration of at least 1 month 72% female Mean age 43 years (sd 11) N= 253 patients Drop-out =		18 and 30m		

		20%				
Untreated populations: prospective cohort studies						
OrtizCorredor et al. 2008[22] **Columbia**	High	Setting: EMG laboratory CTS diagnosis: as per Rempel et al 81.1% female Mean age 48.8 years (sd 10.2)	The course of untreated CTS was observed	The Historic and Objective Scale (HiOb) was used as the clinical classification. The electrophysiological classification was according to Padua 1997	Deterioration in the Historic and Objective Scale	23.4% of patients

		N = 132 patients Not possible to determine drop-out		(mild; moderate A; moderate B; Severe; Extreme) 24.2 months (sd 4.2)		
Padua et al. 1998[20] **Italy**	Moderate	Setting: EMG laboratory CTS diagnosis: based on neurophysiological evaluation	The course of untreated CTS was observed	Patient reported global improvement scale: stable, worse, improved	Clinical outcome: unchanged	Neurophysiological classification Negative 50% Minimal 38%

		graded: negative, minimal, mild, moderate, severe and extreme (Padua et al). 78.8% female Mean age 48.8 years (sd 10.2) N = 80		Neurophysiological classification: negative, minimal, mild, moderate, severe, extreme 11.6 months (range 5-23)	Clinical outcome: worse	Mild 15% Moderate 27.5% Severe 0% Extreme 50% Negative 50% Minimal 31% Mild 58% Moderate 45% Severe 20% Extreme 0%

		Drop-out 84%				
Padua et al. **2001**[21] Italy	Moderate	Setting: EMG laboratory CTS diagnosis: based on clinical diagnostic criteria proposed by the American Academy of Neurology and the American Association of Electrodiagnost	The course of untreated CTS was observed	Electrophysiological changes, patient reported changes and clinical changes were used to describe if patients had: improved, remained stationary or worsened.	Neurophysiologic class Symptoms Function Historic and	Stationary 57% Worsening 16% Stationary 45% Worsening 21% Stationary 61%

		ic Medicine 82% female Mean age 52.0 years (sd 13.4) N = 202 (267 wrists) with a further 62 (87 wrists) re-evaluated by phone Drop-out 34%		10 - 15 months	objective scale Pain	Worsening 16% Stationary 46% Worsening 32% Stationary 62% Worsening 12%

Untreated populations: retrospective cohort studies						
Resende et al. 2003[23] **Brazil**	High	Setting: EMG laboratory CTS diagnosis: clinical findings, supported by electrophysiological abnormality Patients in an EMG lab with a	The course of untreated CTS was observed	Clinical and electrophysiological changes were observed. 4 – 9 years	Conduction studies	Marked improvement 25% (of which 100% had improvement in symptoms) Slight improvement 15% (of which 33% had worsening of clinical

		diagnosis of CTS based on. N=12 Drop-out not possible to determine				symptoms) No significant change 50% (of which 50% had worsening of clinical symptoms) Worsening 10% (of which 50% had worsening of clinical symptoms)

Table 3 Results of the methodological assessment of prognostic cohort studies on CTS

Author (year)	1. Study Participation	2. Study Attrition	3. Prognostic Factor Measurement	4. Outcome Measurement	5. Study Confounding	6. Statistical Analysis and Reporting	Overall Risk of bias
Studies including an analysis of prognostic factors							
Boyd et al. 2005[33]	High	High	Moderate	Moderate	Moderate	High	**High**
DeStefano, Nordstrom & Vierkant. 1997[19]	Low	Moderate	Moderate	Moderate	Moderate	Moderate	**Moderate**

Duckworth et al. 2013[34]	Moderate	High	Moderate	Moderate	High	Low	**Moderate**
Goodwill. 1965[31]	High	High	High	High	High	High	**High**
Kaplan, Glickel & Eaton. 1990[27]	High	High	High	High	High	High	**High**
Katz et al. 1998a[30]	Low	Moderate	Moderate	Moderate	Low	High	**Moderate**
Katz et al 1998b[29]	Low	High	Moderate	Low	High	Low	**Moderate**
Kiylioglu et al. 2009[26]	Moderate	High	Moderate	Moderate	Moderate	High	**Moderate**

Kouyoumdjian et al. 2003[32]	Moderate	High	Moderate	Moderate	High	High	**High**
Muhlau, Both & Kunath. 1984[28]	Moderate	High	Low	Moderate	Moderate	Low	**Moderate**
Padua et al. 2001[21]	Low	Moderate	Low	Moderate	Moderate	Moderate	**Moderate**
Studies observing the course of CTS only (with no analysis of prognostic factors)							
Lian, Urkunde & Verma. 2006[25]	High	High	Not applicable	High	High	High	**High**
Miranda, Asaad &	High	High	Not applicable	High	High	High	**High**

Cerovac. 2013[35]							
OrtizCorredor et al. 2008[22]	Moderate	Moderate	Not applicable	Low	High	High	**High**
Padua et al. 1998[20]	High	High	Not applicable	Low	High	Low	**Moderate**
Resende et al. 2003[23]	High	High	Not applicable	High	High	Moderate	**High**

Table 4 Course of carpal tunnel syndrome in conservatively treated or untreated patients (percentages not cumulative)

Number of studies	Sample size range	% of cases reporting deterioration within 3 months	% of cases reporting deterioration within 6 months	% of cases reporting deterioration within 12 months	% of cases reporting deterioration within 3 years	% of cases reporting deterioration within 5 years	% of cases reporting deterioration within 15 years
Untreated cases							
4 [20-23]	12 – 344			32 - 58	23.4		50
Studies observing cases receiving surgery as a consequence of conservative management failure (% of patients receiving surgery NOT outcome of surgery)							
4 [27, 33-35]	47 - 331		57	58	62 - 66		

Studies of conservatively managed patients reporting other definitions of negative outcome							
9 [19, 25-32]	80 - 425	68.5 - 75	82	*% improvement of up to 82%* *	23 - 89		22 - 23.7

The percentages shown are not cumulative as it cannot be assumed that patients reporting a change in symptoms at 6 months, would not have reported something different at an earlier or later date if the study had provided them with such opportunity

- % change provided in positive direction [26]

Table 5 Prognostic factors and strength of association for an unfavourable outcome of carpal tunnel syndrome in patients who are **conservatively treated or untreated**

Prognostic factor	**Direction of association and significance**	**Risk of bias (number of studies)**	**Number and % of studies demonstrating predictive association with a negative outcome *(statistically significant)***	**Level of evidence**
Demographic characteristics				
Female gender	+* [34] + [19] 0 [28], [30], [29] 0 [27]	Moderate (5) High (1)	2/6: 33% *(1/6: 17 %)*	Inconclusive
Increasing age (group not otherwise specified or >50 years)	+* [21], [29] 0 [30], [28] -* [34], [26], [19] +* [27] -* [33] - [32]	Moderate (7) High (3)	3/10: 30 % *(3/10: 30 %)*	Inconclusive

Obesity	+ [19] -* [26]	Moderate (2)	1/2: 50% *(0/2: 0%)*	Inconclusive
Litigation	+* [29] 0 [30], [28]	Moderate (3)	1/3: 33% *(1/3: 33%)*	Inconclusive
Deprivation quintile	- [34]	Moderate (1)	0/1: 0 %	Inconclusive
Vibration tool use	- [34]	Moderate (1)	0/1: 0 %	Inconclusive
Occupation status	+*[29]	Moderate (1)	*(1/1: 100)%*	Inconclusive
Smoking	+[34]	Moderate (1)	1/1: 100% *(0/1: 0%)*	Inconclusive
Comorbidity				
Diabetes	+* [26]	Moderate (1)	*(1/1: 100%)*	Inconclusive
Diabetes *or* hypothyroid	+[19]	Moderate (1)	1/1: 100% *(0/1: 0%)*	Inconclusive
Pregnancy *or injury associated CTS*	- [19]	Moderate (1)	0/1: 0 %	Inconclusive
Arthritis	+[19]	Moderate (1)	1/1: 100% *(0/1: 0%)*	Inconclusive
Previous fracture or sprain	0[27]	High (1)	0/1: 0 %	Inconclusive
Stenosing	+*[27]	High (1)	*(1/1: 100%)*	Inconclusive

flexor tenosynovitis				
Mental health status	+*[29]	Moderate (1)	*(1/1: 100%)*	Inconclusive
Disease characteristics				
Tinnel's sign positive	+ [34]	Moderate (1)	1/1: 100% *(0/1: 0%)*	Inconclusive
Phalen's sign positive	+*[21] + [34] +*[27]	Moderate (2) High (1)	3/3: 100 % *(2/3: 67%)*	Inconclusive
Thenar wasting	+* [28] +[34] +*[27]	Moderate (2) High (1)	3/3: 100 % *(2/3: 67%)*	Inconclusive
Paraesthesia	+*[27]	High (1)	*(1/1: 100%)*	Inconclusive
Abnormal two-point discrimination	0[30] +*[27]	Moderate (1) High (1)	1/2: 50% *(1/2: 50%)*	Inconclusive
Semmes Weinstein monofilament testing	0[30]	Moderate	0/1: 0 %	Inconclusive
Electrophysiological severity	+[34] 0[26] -*[21]	Moderate (3)	2/5: 40% *(0/5: 0%)*	Inconclusive

	+[31] -[32]	High (2)		
Symptom severity	-*[26] -*[21] +*[33]	Moderate (2) High (1)	1/3: 33% *(1/3: 33%)*	Inconclusive
Functional severity	+*[29] -*[26], [21] 0[33]	Moderate (3) High (1)	1/4: 25% *(1/4: 25%)*	Inconclusive
CTS category of severity[19]	+*[19]	Moderate (1)	*(1/1: 100%)*	
Sensory SF-MPQ	+[34]	Moderate (1)	1/1: 100% *(0/1: 0%)*	Inconclusive
Affective SF-MPQ	+[34]	Moderate 1	1/1: 100% *(0/1: 0%)*	Inconclusive
SF-36	0[33]	High (1)	0/1: 0 %	Inconclusive
DASH	0[33]	High (1)	0/1: 0 %	
Hi-Ob	-*[21]	Moderate (1)	0/1: 0 %	Inconclusive
Visual analog scale	+[34]	Moderate (1)	1/1: 100% *(0/1: 0%)*	Inconclusive
Laterality: left only	-[19]	Moderate (1)	0/1: 0 %	Inconclusive
Laterality: right only	-*[19]	Moderate (1)	0/1: 0 %	Inconclusive
Laterality: left >	-[19]	Moderate (1)	0/1: 0 %	Inconclusive

right				
Laterality: right > left	-[19]	Moderate (1)	0/1: 0 %	Inconclusive
Bilateral	+*[21] +[34] 0[27]	Moderate (2) High (1)	2/3: 67% *(1/3: 33%)*	Inconclusive
Grip strength	0[30] m - [34] m	Moderate (2)	0/2: 0%	Inconclusive
Hand stress	-*[21]	Moderate (1)	0/1: 0 %	Inconclusive
Increasing symptom duration	+* [28], [21] +[26] +*[27] +[32]	Moderate (3) High (2)	5/5: 100% *(3/5: 60%)*	Inconclusive

0 = not significant and direction not provided

+ = predictive of a negative outcome

- = not predictive of a negative outcome

* = statistically significant

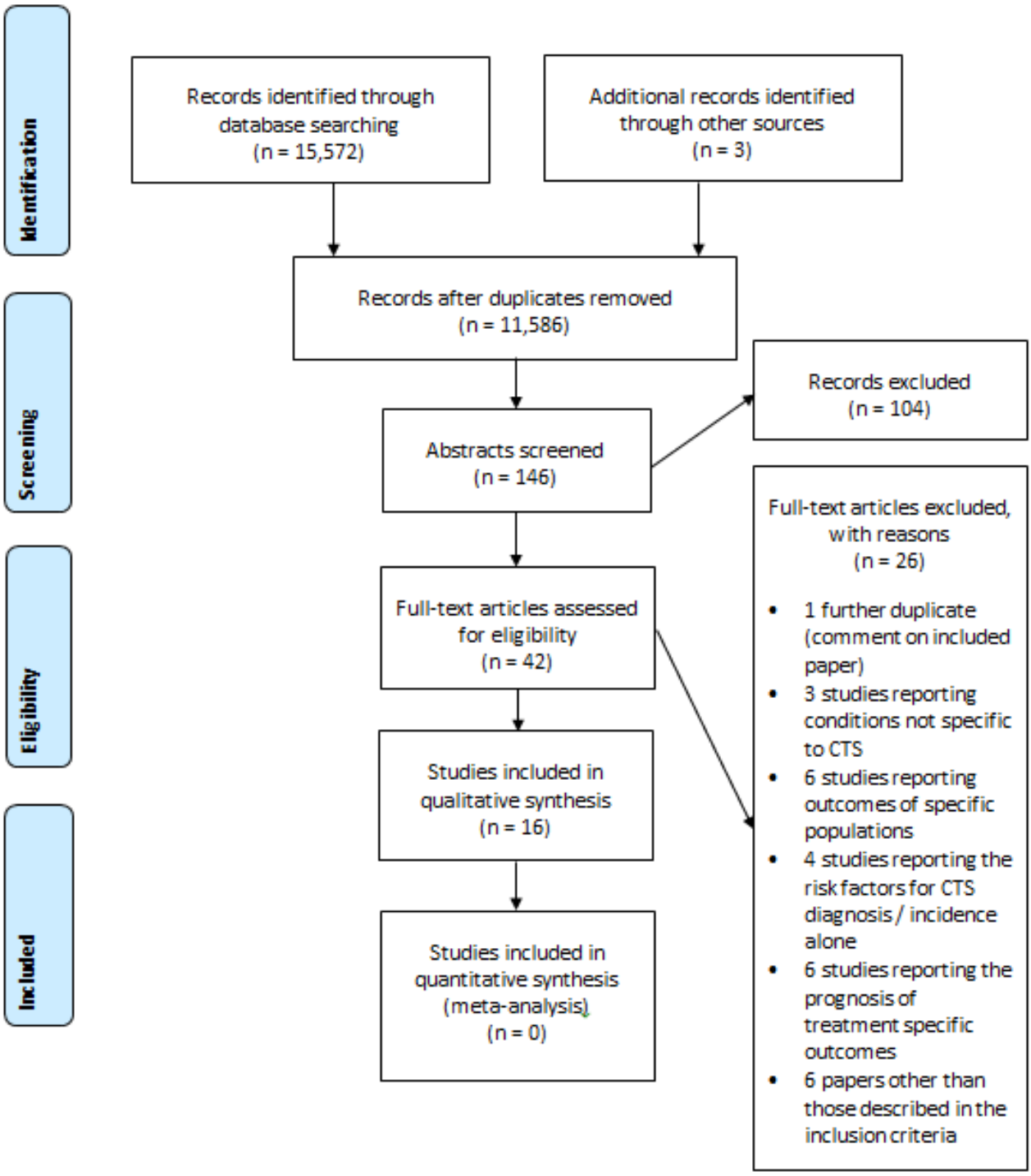
SF-MPQ – Short-Form McGill pain questionnaire

SF-36 **–** Short-Form 36

DASH – Disabilities of the arm, shoulder and hand questionnaire

Hi-Ob – Historical objective scale

Figure 1 Study Selection



Supplementary Table: Medline Search Strategy

1. median neuropathy/ or exp carpal tunnel syndrome/

2. "carpal tunnel syndrome".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

3. Nerve Compression Syndromes/

4. entrapment neuropath*.ti,ab.

5. exp Median Nerve/

6. nerve entrapment*.ti,ab.

7. Hand/ and Pain/

8. Pain/ and Wrist/

9. (carpal$ adj3 tunnel$).mp.

10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

11. exp Prognosis/

12. exp Disease Progression/

13. prognos*.mp.

14. predict*.mp.

15. factor*.mp.

16. risk*.mp.

17. model*.mp.

18. evolution.mp.

19. history.mp.

20. indicator*.mp.

21. course.mp.

22. rule*.mp.

23. transition*.mp.

24. determinant*.mp.

25. pattern*.mp.

26. subgroup*.mp.

27. sub-group*.mp.

28. screen*.mp.

29. long-term.mp.

30. progress*.mp.

31. modif*.mp.

32. mediat*.mp.

33. or/11-32

34. exp Epidemiologic Studies/

35. cohort*.mp.

36. follow-up.mp.

37. follow-up.mp.

38. ("case control" or "case controlled").mp.

39. retrospective*.mp.

40. prospective*.mp.

41. ((patient* or medical) adj3 (record* or review* or histor*)).mp.

42. longitudinal*.mp.

43. inception.mp.

44. observation*.mp.

45. time series.mp.

46. outcome*.mp.

47. or/34-46

48. 33 and 47

59. 10 and 48