Carpal tunnel syndrome: updated evidence and new questions

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Carpal tunnel syndrome is the most common entrapment neuropathy, affecting quality of life for many people. Although it is a well recognised condition, new insights into epidemiology, diagnosis, and treatment have emerged in the past 6 years. The availability of disease-modifying treatments for rare systemic disorders associated with carpal tunnel syndrome (eg, amyloidosis) should alert clinicians to these diagnostic possibilities. Besides clinical evaluation and electrophysiology, the role of ultrasonography as a diagnostic tool has been confirmed and new ultrasound techniques have been applied, the clinical use and feasibility of which require further investigation. Surgical and non-surgical interventions are beneficial for the treatment of carpal tunnel syndrome and several treatment options are now available, giving clinicians the possibility to choose the best approach for every patient. New diagnostic and therapeutic techniques require further validation.

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Introduction

Carpal tunnel syndrome is common and affects about 10% of people in their lifetime.[1] This syndrome is due to median nerve compression within the carpal tunnel. Paraesthesias are initially nocturnal and subsequently diurnal. In advanced phases, weakness and thenar atrophy occur. Neurophysiology is a sensitive and specific tool for carpal tunnel syndrome diagnosis, and effective treatments include non-surgical and surgical therapy.

In a previous 2016 Review,[2] we covered the most recent findings in carpal tunnel syndrome, focusing on common and controversial clinical topics. We found few definite answers and concluded that "although carpal tunnel syndrome is a well studied nerve entrapment syndrome, several important questions remain unanswered".[2] Particularly, no distinct evidence existed then on the role of electrophysiology and ultrasonography in the management of carpal tunnel syndrome or the best therapeutic approach for individual patients.

We present now an updated Review on carpal tunnel syndrome as the introduction of new diagnostic and therapeutic techniques has provided added complexity to the management of the syndrome. This paper is a narrative review of evidence published since 2016 on the epidemiology, risk factors, causes, diagnosis, and non-surgical and surgical treatments. In the epidemiology section, we have focused on carpal tunnel syndrome in older adults (aged >75 years) because of the increased prevalence in this age group worldwide. We also discuss rare diseases in which carpal tunnel syndrome presents as an early sign, since such presentation could assist with the diagnosis and treatment of some rare illnesses with disease-modifying therapies at an early stage.

Epidemiology, risk factors, and causes

Prevalence of carpal tunnel syndrome is about 1–5%, depending on the diagnostic criteria used; estimates based on electrophysiological standards are lower than those based on clinical criteria.[2] Carpal tunnel syndrome is more frequent in women, although the exact male-to-female ratio varies between studies.[2–4] This syndrome occurs most often in individuals aged 50–54 years, followed by those aged 75–84 years.[5]

Carpal tunnel syndrome pathophysiology is multifactorial, but a decrease in carpal tunnel volume, with increased pressure, has a role in its development. Median nerve damage is not only caused by compression, but also by the nerve sliding in transverse and longitudinal planes, impairing dissipation of mechanical stresses. A systematic review[6] found impaired median nerve excursion in patients with carpal tunnel syndrome compared with healthy controls.

Conditions that might cause increased pressure within the carpal tunnel through mechanical, traumatic, inflammatory, or hormonal mechanisms are suspected risk factors for carpal tunnel syndrome. These conditions include diabetes, menopause, hypothyroidism, obesity, arthritis, and pregnancy.[2] However, evidence is often limited by the study design, small sample size, and differences in diagnostic criteria of carpal tunnel syndrome. A meta-analysis[7] found a two-fold increased risk of carpal tunnel syndrome in patients with rheumatoid arthritis and osteoarthritis, but the authors highlighted that confounding factors and limitations of the included studies could have influenced the results. Distal radial fractures result in acute carpal tunnel syndrome in about 4% of cases, with corrective open reduction and volar plate fixation increasing the risk.[8,9] However, a systematic review[10] did not find that prophylactic carpal tunnel release during the surgical treatment of distal radius fractures prevents carpal tunnel syndrome.

Carpal tunnel syndrome is a common condition during pregnancy, typically occurring during the third trimester, related to hormonal changes and fluid retention. A cross-sectional study[11] found a 23% prevalence of carpal tunnel syndrome during pregnancy and increased risk associated with left-handedness, older maternal age, and gestational diabetes. Pregnancy-related carpal tunnel syndrome usually resolves after delivery, but a small proportion of patients reported continued symptoms post partum. Early onset, before the third trimester of pregnancy, increased severity of carpal tunnel syndrome symptoms during pregnancy, and high depression scores post partum are predictive of persistent carpal tunnel syndrome 12 months after delivery.[12] Hormonal changes that occur after menopause increase the incidence of

carpal tunnel syndrome due to fluid retention. Hormone therapy might have a protective effect in preventing carpal tunnel syndrome among women after menopause, with a risk reduction of 22%.[13]

Environmental workplace factors could favour the development of carpal tunnel syndrome. In a meta-analysis,[14] exposure to vibrating tools increased the risk of vascular and neurological disease but the association with carpal tunnel syndrome was less clear. A cohort study[15] of 1 015 418 workers found evidence that high levels of wrist movement, expressed as angular velocity evaluated through electrogoniometric measurements, increased the risk of carpal tunnel syndrome. The association between computer use and carpal tunnel syndrome is controversial and a meta-analysis[16] did not find a link. However, a systematic review[17] found that particular workplace psychosocial factors, including high psychological work demand, high job strain, low levels of autonomy over one's work, and an absence of interpersonal relationships providing social support might be associated with carpal tunnel syndrome.

Carpal tunnel syndrome in older adults

Increasing age is a risk factor for carpal tunnel syndrome,[5] although the association has not been fully elucidated. Older individuals (aged >75 years) with carpal tunnel syndrome present with increased clinical and electrophysiological severity (probably secondary to chronic compression and mechanical stressors) and physiological factors associated with ageing, such as osteoarthritis (figure 1). Upper limb disability might persist even after surgical decompression in older individuals.[18]

Carpal tunnel syndrome in rare diseases

People affected by some genetically mediated conditions are at increased risk of carpal tunnel syndrome. A retrospective study[19] of 309 patients with hereditary motor and sensory neuropathies found that carpal tunnel syndrome was more common in individuals with hereditary neuropathy with liability to pressure palsy (75% of whom had carpal tunnel syndrome) than in individuals with other neuropathies.

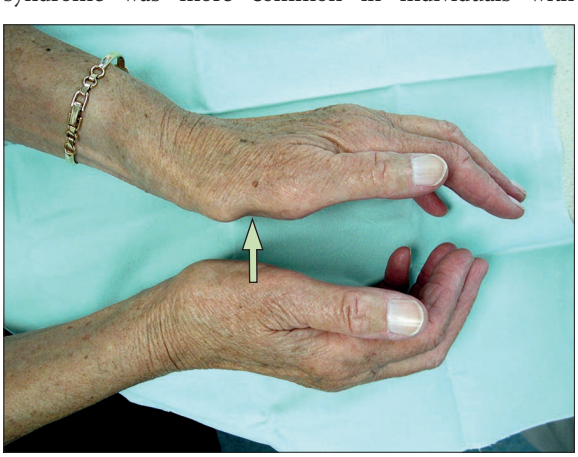

Figure 1: **Severe thenar atrophy in a patient aged 80 years with carpal tunnel syndrome**
The arrow is pointing to the area of atrophy.

In children, carpal tunnel syndrome is uncommon and usually related to lysosomal storage diseases. Mucopolysaccharidoses are the most common cause of the syndrome in children, and in mild forms of mucopolysaccharidoses 1, carpal tunnel syndrome might be the presenting manifestation.[20] Carpal tunnel syndrome diagnosis in children is often challenging because symptoms are subtle or unreported due to patient age or cognitive impairment, or both. However, a prompt diagnosis of this condition and identification of mucopolysaccharidoses 1 is crucial for early initiation of enzyme replacement therapy to achieve improved clinical outcomes.[20,21]

Carpal tunnel syndrome has also been recognised as an early manifestation of amyloidosis, especially transthyretin-related amyloidosis. Carpal tunnel syndrome might be the presenting sign and precede cardiac and other manifestations of amyloidosis by several years.[22–24] In the past decade, disease-modifying therapies have been approved for the treatment of transthyretin-related amyloidosis, including inotersen and patisiran. These therapies prevent amyloid deposition but cannot reverse existing damage caused by accumulated amyloid fibrils, so early treatment is essential.[22] Bilateral carpal tunnel syndrome in male patients, without medical or occupational risk factors and with recurrence after carpal tunnel release surgery, are considered warning signs of amyloidosis.[25] Spinal stenosis and biceps tendon rupture can be early manifestations of amyloidosis, and their presence alongside carpal tunnel syndrome should raise clinical suspicion for amyloidosis. Tenosynovial biopsy might indicate amyloid deposits. An algorithm has been proposed to identify which patients should have tenosynovial biopsy at the time of carpal tunnel release.[26] A multicentre clinical study[27] identified a morpho-functional dissociation of carpal tunnel syndrome in transthyretin-related amyloidosis as nerve cross-sectional area evaluated through ultrasonography did not correlate with carpal tunnel syndrome severity, unlike in patients with idiopathic carpal tunnel syndrome. Further studies are needed to clarify when patients with carpal tunnel syndrome require amyloidosis assessment.[28]

Acromegaly is an uncommon condition with an insidious course and diagnostic delays. Among affected patients, the prevalence of carpal tunnel syndrome ranges from 19% to 64%.[29] Carpal tunnel syndrome diagnosis often precedes acromegaly diagnosis.[29] Early initiation of treatment is necessary since untreated acromegaly leads to further complications. Clinicians should be aware of such complications when assessing patients with carpal tunnel syndrome.[29] However, screening programmes for acromegaly in patients with carpal tunnel syndrome do not exist.[30]

Carpal tunnel syndrome and COVID-19

Considering the large number of publications on the COVID-19 pandemic in the past 2 years and clinical reports of peripheral nerve involvement, we searched for an association between carpal tunnel syndrome and COVID-19, but only two studies have been reported.[31,32] In the first report, the authors described two patients who developed carpal tunnel syndrome and cubital tunnel syndrome after hospital admission for COVID-19.[31] They hypothesised that reactive arthritis, due to a hypersensitivity reaction or an autoimmune response, might have caused thickening of the synovium with subsequent nerve compression. In the second study, the authors discussed the delay of elective surgeries, including carpal tunnel release, during the early pandemic.[32] They highlighted that carpal tunnel syndrome can worsen when treatment is delayed until the damage becomes irreparable. Therefore, surgeons should consider carpal tunnel syndrome severity and chronicity in each patient when deciding whether surgical intervention can be safely postponed.[32] Hence, no definite data exist regarding the occurrence and management of carpal tunnel syndrome during the COVID-19 pandemic[32] and in patients with COVID-19.[31]

Diagnosis

Despite its prevalence and well known clinical presentation, the best diagnostic strategy for carpal tunnel syndrome remains uncertain (table 1). Clinical history and physical examination remain indispensable in screening, but their diagnostic accuracy is variable. Understanding how well clinical parameters perform is of great importance. Although a false positive diagnosis might be acceptable if non-surgical interventions are used, high diagnostic accuracy is warranted for invasive treatments. Validated questionnaires, symptom scales, and hand symptom diagrams are available (eg, Boston Carpal Tunnel Questionnaire, CTS-6) to standardise symptom reporting. Of these, the Kamath and Stothard questionnaire (sensitivity and specificity 100%) and the Katz and Stirrat hand symptom diagram with Phalen's manoeuvre or Tinel's sing (sensitivity 93%, specificity 89%) performed best.[33] Regarding physical examination, the Semmes-Weinstein 3.22 monofilament test across any radial finger as the normal threshold had the highest sensitivity across published studies (up to 98%), but tests of grip strength (94%), pinch strength (78–95%), and the presence of thenar atrophy (96–100%) have the highest specificity.[34] Clinicians are recommended to avoid reliance on any single clinical parameter when making the diagnosis.[34]

Electrophysiological evaluation (ie, nerve conduction studies and needle electromyography) complements clinical assessments by measuring slowing of nerve conduction velocities across the carpal tunnel and secondary axonal loss (appendix p 2). The tests confer additional diagnostic certainty beyond the clinical impression by providing quantitative data. However, their sensitivity and specificity depend on the exact methods chosen, test execution, and the patient population. For example, a systematic review[35] has shown that, for the median digital distal sensory latency alone, sensitivity and specificity are about 75% and 93%, whereas the median distal motor latency performed at 65% and 95%, respectively. Sensory studies have higher sensitivity than motor studies as they compare median distal sensory latencies with radial or ulnar distal sensory latencies.[35]

There are recommendations for electrophysiological testing from the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation.[37] Clinicians are advised to perform median sensory and motor nerve conduction studies across the wrist in patients with clinical signs or symptoms of carpal tunnel syndrome. If these tests are normal, clinicians should perform comparative, segmental, or comparative and segmental tests, which have high sensitivity (80–90%) and specificity (>95%). However, even in these circumstances, testing might be normal in symptomatic patients and abnormal in individuals without clinical symptoms.[37]

Over the past two decades, imaging has taken an increasingly prominent role in assessing carpal tunnel syndrome, particularly high-resolution ultrasonography (appendix p 2). High-frequency linear array transducers provide acute morphological details of the median nerve and the surrounding structures. Changes in nerve shape, size, echogenicity, and intraneural blood flow are among the alterations described. The nerve is often flattened at the site of compression, swelling proximally and distally to this point.[43] Measurement of the cross sectional area of the median nerve just proximal to or at the carpal tunnel inlet is used commonly in the sonographic diagnosis of carpal tunnel syndrome. A meta-analysis[42] assessed the diagnostic accuracy of this approach and reported a diagnostic odds ratio (OR) of 31·11 at the carpal tunnel inlet with cross-sectional area cutoffs ranging from 9·0 mm² to 12·6 mm² for inlet level measures. Furthermore, there is an association between median nerve size at the carpal tunnel inlet and electrophysiological severity, with a meta-analysis showing a mean cross-sectional area of 11·64 mm², increasing to 16·90 mm² for the most electrodiagnostically severe cases as determined by nerve conduction study-based rating scales.[41] Despite these encouraging findings, there are methodological differences between published studies, including the use of different measurement sites and differing definitions of carpal tunnel syndrome, resulting in variable diagnostic cutoff values.

Although high-resolution ultrasound B-mode imaging has dominated the scientific literature on carpal tunnel syndrome, other forms of ultrasonography are promising. Superb microvascular imaging is "a novel Doppler technique that enables detection of fine vessels and slow

See Online for appendix

	Study type	Diagnostic strategy	Comparator	Main results
Dabbagh et al (2020)[33]	Systematic review (studies of diagnostic test accuracy of at least one clinical diagnostic test)	Kamath and Stothard questionnaire; Katz and Stirrat hand symptom diagram	Any physical examination test used as a reference standard	Costly and invasive tests of carpal tunnel syndrome might be needed if diagnostic scales, questionnaires, and hand symptom diagrams are inconclusive
Dabbagh et al (2021)[34]	Systematic review (case-control, cross-sectional, and retrospective and prospective cohort studies)	Semmes-Weinstein monofilament; grip strength; pinch strength; thenar atrophy	Any reference standard	Semmes-Weinstein monofilament test sensitivity 0·49–0·96%; palmar grip strength specificity 0·94%; pinch grip strength specificity 0·78–0·95%; thenar atrophy specificity 0·96–1·00%; two-point discrimination specificity 0·81–0·98%
Demino and Fowler (2021)[35]	Systematic review (clinical studies including sensitivity or specificity cutoff value used to diagnose carpal tunnel syndrome, or both)	Median sensory and motor nerve conduction studies	Different methods in the included studies	Distal sensory latency sensitivity 73·4%; distal sensory latency specificity 93·6%; distal motor latency sensitivity 56·2%; distal motor latency specificity 95·8%
Gitto et al (2020)[36]	Systematic review (excluding narrative reviews, case reports, and case series)	Superb microvascular imaging (Doppler technique)	Variable	Improvement in vascularity detection with superb microvascular imaging
Jablecki et al (2002)[37]	Evidence-based guideline from the American Association of Electrodiagnostic Medicine, American Academy of Neurology, and American Academy of Physical Medicine and Rehabilitation*	Median sensory and motor nerve conduction studies	..	Recommendations regarding electrodiagnosis studies to confirm a clinical diagnosis of carpal tunnel syndrome
Lee et al (2021)[38]	Systematic review (primary research articles)	Sonoelastography	..	Sonoelastography is a useful noninvasive and promising modality to diagnose carpal tunnel syndrome
Liu et al (2018)[39]	Meta-analysis (clinical studies)	Magnetic resonance tractography	Clinical findings, electrophysiology, or ultrasonography, or both	Significant fractional anisotropy reduction and apparent diffusion coefficient increase in carpal tunnel syndrome
Park et al (2021)[40]	Retrospective study	Ultrasonography and sonoelastography	Clinical findings and electrophysiology	Shear wave elastography has a good diagnostic value in carpal tunnel syndrome
Roomizadeh et al (2019)[41]	Meta-analysis	Nerve ultrasound	Electrophysiology	Cross sectional area for mild carpal tunnel syndrome 11·64 mm² (95% CI 11·23–12·05; p<0·001); cross sectional area for moderate carpal tunnel syndrome 13·74 mm² (12·59–14·89; p<0·001); cross sectional area for severe carpal tunnel syndrome 16·80 mm² (14·50–19·10; p<0·001)
Torres-Costoso et al (2018)[42]	Meta-analysis (observational studies)	Nerve ultrasound	..	Inlet ultrasonography measurements, pooled diagnostic accuracy OR 31·11 (95% CI 20·42–47·40); outlet ultrasonography measurements, pooled diagnostic accuracy 16·94 (7·58–37·86)

We searched PubMed for papers published between Aug 2, 2016, and May 1, 2022. *This paper has been included despite being published before 2016 because it is the most recent guideline on electrodiagnosis in carpal tunnel syndrome.

Table 1: **Studies assessing diagnostic strategies for carpal tunnel syndrome**

blood flow".[36] Its capacity to detect slow blood flow makes superb microvascular imaging ideally suited to assessing intraneural vascularity alterations that might occur in compression neuropathies. A systematic review[36] of eight studies on superb microvascular imaging and carpal tunnel syndrome showed that this imaging technique was superior to power Doppler in measuring intraneural vascularity and had better correlation with electrophysiological measures, such as the distal motor latency (r=0·71).

In addition to novel methods of measuring intraneural blood flow, ultrasound elastography, specifically shear wave elastography imaging, has emerged as the latest means of quantifying median nerve pathology in carpal tunnel syndrome. This method and other forms of elastography measure tissue stiffness through acoustic palpation. Most published studies show that median nerve stiffness is increased in patients with carpal tunnel syndrome compared with control participants. Shear wave elastography imaging seems more sensitive at detecting increased median nerve stiffness than strain elastography.[40] This difference was reported by Park and colleagues,[40] who showed that the strain ratio could not differentiate between healthy controls and patients with carpal tunnel syndrome, but shear wave velocity and elasticity measures could. In shear wave elastography imaging, tissue stiffness

is reported in kilopascals or velocity (metres per second). Currently, too much variability exists between studies to endorse specific diagnostic cutoff values. However, some studies are reporting sensitivity of 81–83% and specificity of 82–93% for shear wave velocity measures.[38]

MRI tractography continues to be of interest in the diagnosis of carpal tunnel syndrome. Data to support routine clinical use are scarce; thus, it is rarely used outside research studies. However, a meta-analysis[39] revealed that fractional anisotropy, a radiographic scale reflecting fibre density, axonal diameter, and myelination, is reduced and the apparent diffusion coefficient, reflecting the diffusion of water and small particles, is increased in patients with carpal tunnel syndrome compared with healthy controls.

Non-surgical treatment

Corticosteroids and other drug injections

Many studies have assessed the effectiveness of local injections for the treatment of carpal tunnel syndrome, typically with corticosteroids, and have shown clinical improvement in pain and hand function. However, long-term (6-month) efficacy is unclear (table 2).[61] Local corticosteroid injections act by reducing swelling or inflammation of the median nerve and surrounding structures. In a randomised controlled trial[49] of 234 participants recruited from primary and community musculoskeletal clinics, a single injection of 20 mg methylprednisolone at the wrist improved pain and function significantly more than did nocturnal wrist splints according to the Boston Carpal Tunnel Questionnaire score. These improvements persisted at 6 weeks and 6 months.[49] Furthermore, a randomised controlled trial[52] reported that local corticosteroid injections were superior to orthosis in remission of pain and nocturnal paraesthesia as assessed clinically. Regarding the minimum effective dose for local corticosteroid injections, one randomised controlled trial[60] of 56 patients found that triamcinolone at 10 mg or 40 mg produced equivalent improvement in pain relief, electrophysiology, and Boston Carpal Tunnel Questionnaire score at 12 weeks of follow-up. Unguided injections are effective, but injections with ultrasonographic guidance are superior in terms of clinical, functional, and electrophysiological parameters, especially when performed with the in-plane approach (a long-axis approach in which the image plane is parallel to the needle course).[45,79]

Moreover, a randomised controlled trial[84] of 51 patients showed that an ultrasound-guided local corticosteroid injection through the miniscalpel needle (a medical instrument that can release transverse carpal ligament) helps to maintain significant functional improvement after 12 weeks compared with local corticosteroid injection alone. The benefit might be related to increased diffusion and absorption of the steroid when using the miniscalpel needle. Furthermore, the use of local corticosteroid injections is also related to its synergy with other treatments. In particular, the association of steroids and splinting seems better than the use of steroids alone, as shown in a randomised controlled trial of 52 patients at a tertiary care centre.[78]

Perineural injection with 5% dextrose is an alternative therapeutic approach effective in mild-to-moderate carpal tunnel syndrome that can improve neurophysiological parameters significantly and reduce the median nerve cross-sectional area.[80] Compared with local corticosteroid injection, it appears to be particularly effective at reducing pain and disability.[81] Lidocaine injection is another option and was as effective as betamethasone dipropionate in reducing carpal tunnel syndrome symptoms in a clinical trial.[54] However, to our knowledge, no randomised controlled trials, systematic reviews, or meta-analyses have studied the role of local anaesthetic injection in the treatment of carpal tunnel syndrome.

Extracorporeal shock wave therapy

Extracorporeal shock wave therapy is a non-invasive treatment using sound waves to stimulate neovascularisation and peripheral nerve regeneration by accelerating the elimination of the injured axon, increasing axonal regeneration, and Schwann cell proliferation. In a meta-analysis,[66] extracorporeal shock wave therapy and local corticosteroid injection were not significantly different in terms of pain relief and functional improvement, measured with the visual analogue scale and the Boston Carpal Tunnel Questionnaire score. Extracorporeal shock wave therapy was safer, with only mild complications reported, such as temporary pain and erythema.[66] Furthermore, patients treated with this therapy for mild-to-moderate carpal tunnel syndrome had better outcomes than did the local corticosteroid injection group at 9 weeks and 12 weeks in a randomised controlled trial of 55 patients.[82] However scientific evidence on extracorporeal shock wave therapy is scarce and unreliable; its efficacy and the best means of administration remain unclear.[44,64]

Other treatments

Studies on electroacupuncture for carpal tunnel syndrome are scarce. However, symptoms and neurophysiological parameters (median nerve sensory latency and primary somatosensory cortex somatotopy) improved in a randomised controlled trial assessing its effectiveness.[69] Similarly, data on supplement therapies are scarce. Alpha-lipoic acid was compared with placebo in a randomised controlled trial including 20 patients, showing benefits in clinical and neurophysiological outcomes (median nerve conduction studies) if administered for 1 month before surgery and for 2 months thereafter.[73] Conversely, palmitoylethanolamide use produced no significant benefits aside from improved sleep quality.[56]

Several clinical studies investigated the use of platelet-rich plasma, which is used as an alternative to surgery because of a proposed regenerative effect. Ultrasound

	Study type	Sample size (n)	Treatment	Main results
Atthakomol et al (2018)[44]	Randomised controlled trial	25	ESWT *vs* corticosteroid injection	ESWT was superior based on the Boston self-assessment questionnaire, which was the primary outcome
Babaei-Ghazani et al (2018)[45]	Meta-analysis (randomised controlled trials)	181	Corticosteroid injection (ultrasound-guided *vs* landmark-guided)	Ultrasound-guided was superior based on the Symptom Severity Scale and Functional Status Scale scores of the Boston Carpal Tunnel Questionnaire and electrodiagnostic parameters
Buentello-Volante et al (2020)[46]	Randomised controlled trial	35	Release alone *vs* release and amniotic membrane transplantation	Release and amniotic membrane transplantation were superior according to the Boston Carpal Tunnel Syndrome Questionnaire, quick DASH questionnaire, and Historical-Objective scale
Chang et al (2020)[47]	Randomised controlled trial	40	Platelet-rich plasma injection with and without ESWT	No difference according to the Boston Carpal Tunnel Syndrome Questionnaire, electrophysiological study, and cross-sectional area of the median nerve
Chen et al (2021)[48]	Randomised controlled trial	26	Ultrasound-guided platelet-rich plasma injection *vs* placebo	Ultrasound-guided platelet-rich plasma injection was superior according to the Boston Carpal Tunnel Syndrome Questionnaire, which was the primary outcome
Chesterton et al (2018)[49]	Randomised controlled trial	234	Corticosteroid injection *vs* wrist orthosis	Injection was superior according to the overall score of the Boston Carpal Tunnel Questionnaire at 6 weeks
Chiang et al (2021)[50]	Meta-analysis (original data, English language studies)	292	Release alone *vs* release and synovectomy	No difference according to grip strength, symptom severity score, functional status score, median nerve motor latency, and major complications with flexor tenosynovectomy
Chou et al (2022)[51]	Systematic review (randomised controlled trials, non-randomised cohort studies, case series)	1772	Ultrasound-guided CTR	Low-level evidence for ultrasound-guided CTR, short post-procedure recovery
de Moraes et al (2021)[52]	Randomised controlled trial	100	Corticosteroid injection *vs* wrist orthosis	Injection was superior based on the improvement in nocturnal paresthesia and Boston-Levine questionnaire score
de Roo et al (2021)[53]	Meta-analysis (clinical studies)	641	Decompression only *vs* decompression and nerve coverage	No added value for nerve coverage; no difference according to the success ratio of different surgical techniques, improvement, or pain
Dernek et al (2017)[54]	Clinical trial	67	Lidocaine *vs* betamethasone dipropionate	No difference based on the quick DASH questionnaire and Visual Analog Scale scores
Dong et al (2020)[55]	Meta-analysis (randomised controlled trials)	434	Platelet-rich plasma injection *vs* corticosteroid injection or saline injection or splint	Platelet-rich plasma injection was superior according to the visual analogue scores and the Boston Carpal Tunnel Questionnaire
Evangelista et al (2018)[56]	Randomised controlled trial	42	Palmitoylethanolamide *vs* surgery	Palmitoylethanolamide was superior in people with sleep disorders; the study was conducted on patients with carpal tunnel syndrome, with sleep disorders and painful symptoms; the primary outcome was sleep quality assessment by the Pittsburgh Sleep Quality Index
Faucher et al (2017)[57]	Systematic review (clinical studies)	Not available	Open surgery *vs* endoscopic surgery	Complications were more frequent with endoscopic surgery
Gaspar et al (2019)[58]	Randomised controlled trial	60	Open surgery *vs* endoscopic surgery	Endoscopic surgery was better for sleep disturbances; sleep disturbances were the outcome measure
Gutiérrez-Monclus et al (2018)[59]	Randomised controlled trial	117	Release alone *vs* release and transverse ligament reconstruction	Release and transverse ligament reconstruction was superior according to grip strength at 6 months
Hsu et al (2020)[60]	Randomised controlled trial	56	Corticosteroid injection (different dosages)	10 mg was equal to 40 mg according to the visual analog scale, the Boston Carpal Tunnel Questionnaire, and nerve conduction studies
Huisstede et al (2018)[61]	Systematic review (systematic reviews and randomised controlled trials)	Three Cochrane reviews, one other systematic review, and nine randomised controlled trials	Oral drug *vs* corticosteroid injection	Benefits of oral medications and corticosteroid injections were measured by different outcomes and clinical heterogeneity, the benefits were not maintained for more than 6 months; oral steroids were effective for 0–3 months, but no evidence existed for their effectiveness for more than 6 months; corticosteroid injections were effective for 0–3 months, the benefits were not maintained for more than 6 months
Huisstede et al (2018)[62]	Systematic review	9566	Various surgical techniques	No evidence of superiority because of the heterogeneity of the outcome measures used in the included studies
Jiménez del Barrio et al (2018)[63]	Systematic review (randomised controlled clinical trials)	1818	Various	No evidence of superiority according to symptoms and functional ability evaluated through heterogeneous measures
Ke et al (2016)[64]	Randomised controlled trial	69	Three sessions of ESWT *vs* one session of ESWT *vs* sham ESWT	Three sessions of ESWT were superior based on the Boston Carpal Tunnel Syndrome Questionnaire, which was the primary outcome

(Table 2 continues on next page)

	Study type	Sample size (n)	Treatment	Main results
(Continued from previous page)				
Li et al (2019)[65]	Meta-analysis (randomised controlled trials)	1020	Limited incision *vs* standard incision	Limited incision was superior in the short term (6 months) according to strength, interval to return to activities, the rate of adverse events, effectiveness, and operative time
Li et al (2020)[66]	Meta-analysis (randomised controlled trials)	204	ESWT *vs* corticosteroid injection	Equal but ESWT was safer based on the visual analog scale score, the Boston Carpal Tunnel Questionnaire, sensory distal latency, and nerve conduction velocity of the sensory nerve
Li et al (2020)[67]	Meta-analysis (randomised controlled trials)	2549	Open surgery *vs* endoscopic surgery	Endoscopic surgery was superior (in better recovery of daily life functions, earlier return to work times, fewer scar-related complications) in the short term (1–3 months) according to operative time, grip strength, Boston Carpal Tunnel Questionnaire scores, digital sensation, patient satisfaction, key pinch strength, return to work time, and complications
Lin et al (2018)[68]	Systematic review (clinical studies)	5654	Not available (heterogenous treatments)	Trigger finger as a complication after intervention
Maeda et al (2017)[69]	Randomised controlled trial	80	Local electroacupuncture *vs* distal electroacupuncture *vs* sham	Electroacupuncture improved several neurophysiological parameters: median sensory nerve conduction latency and fMRI-assessed somatotopy in the primary somatosensory cortex
Malahias et al (2018)[70]	Randomised controlled trial	50	Ultrasound-guided platelet-rich plasma injection *vs* placebo	Ultrasound-guided platelet-rich plasma injection was superior according to the quick DASH questionnaire, and visual analog scale
Mansiz Kaplan et al (2019)[71]	Randomised controlled trial	169	Orthosis *vs* kinesiology taping *vs* paraffin	Orthosis and kinesiology taping were superior according to clinical, electrophysiological, and ultrasonographic parameters
Michelotti et al (2020)[72]	Randomised controlled trial	30	Open surgery *vs* endoscopic surgery	No difference based on pain score, 2-point discrimination, Semmes-Weinstein monofilament testing, thenar strength testing, grip strength, carpal tunnel syndrome functional status score, carpal tunnel syndrome symptom severity score, and overall satisfaction
Monroy Guízar et al (2018)[73]	Randomised controlled trial	20	Alpha-lipoic acid *vs* placebo	Alpha-lipoic acid was superior based on the Boston Questionnaire score, presence or absence of Tinel's sign, Phalen's test findings, and median nerve conduction studies
Rojo-Manaute et al (2016)[74]	Randomised controlled trial	92	Ultrasound-guided CTR *vs* open limited CTR	Ultrasound-guided CTR had lesser post-operative morbidity and earlier functional return
Sayegh et al (2015)[75]	Meta-analysis (randomised controlled trials)	1859	Open surgery *vs* endoscopic surgery	Endoscopic surgery was superior in the short term (6 months) based on the outcome measures of symptom relief, Boston Carpal Tunnel Questionnaire scores, strength, digital sensibility, complications, reoperation, interval to return to work, and operative time
Shi et al (2020)[76]	Meta-analysis (clinical studies)	1028	Surgical *vs* non-surgical	Surgery was superior at 6 months based on patient self-reported functional and symptom changes, and electrophysiological studies
Vasiliadis et al (2015)[77]	Meta-analysis (randomised, quasi-randomised controlled trials)	Not available	Open surgery *vs* endoscopic surgery	Scar-related complications were more frequent with endoscopic surgery
Wang et al (2017)[78]	Randomised controlled trial	52	Corticosteroid and orthosis *vs* corticosteroid alone	Corticosteroid and orthosis were superior according to the Boston Carpal Tunnel Questionnaire score, which was the primary outcome
Wang et al (2021)[79]	Meta-analysis (randomised controlled trials)	596	Corticosteroid injection (ultrasound-guided *vs* landmark-guided)	Ultrasound-guided injection was superior according to the Boston Carpal Tunnel Questionnaire and electrophysiological indexes
Wu et al (2017)[80]	Randomised controlled trial	49	5% dextrose injection *vs* placebo	Dextrose was superior based on the visual analog scale
Wu et al (2018)[81]	Randomised controlled trial	54	5% dextrose injection *vs* triamcinolone injection	Dextrose was superior in reduction of pain and disability based on the visual analog scale
Xu et al (2020)[82]	Randomised controlled trial	55	ESWT *vs* corticosteroid injection	ESWT was superior according to the visual analog scale, the Boston Carpal Tunnel Questionnaire, and nerve conduction study
Zhang et al (2016)[83]	Randomised controlled trial	207	Double small *vs* standard *vs* endoscopic surgery	Double small incisions were minimally invasive, there was good appearance of scars, and endoscopic surgery and limited incision were superior in the short term; outcome measures were Semmes–Weinstein monofilament test, 2-point discrimination test, Levine-Kats Questionnaire, pinch grip strength, time to return to work, scar pain, and satisfaction
Zhang et al (2019)[84]	Randomised controlled trial	51	Corticosteroid injection with miniscalpel-needle release *vs* corticosteroid injection alone	Injection with miniscalpel-needle release was superior according to the Boston Carpal Tunnel Questionnaire, cross-sectional area of the median nerve, and electrophysiological parameters

We searched PubMed for papers published between Aug 2, 2016, and May 1, 2022. We included other papers outside the temporal limit of the literature search on the basis of their relevance to the topics of the Review. CTR=carpal tunnel release. DASH=Disabilities of the Arm, Shoulder, and Hand. ESWT=extracorporeal shock wave therapy.

Table 2: **Studies of treatments for carpal tunnel syndrome**

Panel: **A patient with carpal tunnel syndrome**

A right-handed woman aged 48 years noted 1 year of paraesthesia and numbness in her left hand, sparing the little finger, along with discomfort in her left forearm. Her symptoms were prominent during the night and worsened with repetitive hand movement, such as protracted computer use. She was overweight, but no other risk factors for carpal tunnel syndrome were identified.

No motor or sensory deficits were found on neurological examination, but Phalen's manoeuvre was positive in the left hand. Deep tendon reflexes were present and symmetrical in the four limbs.

We suspected carpal tunnel syndrome and performed nerve conduction studies. Sensory and motor nerve conduction studies of the left median nerve across the wrist were normal. Additionally, motor nerve conduction study of the median nerve in the segment between the wrist and elbow revealed normal motor conduction velocity.

Ultrasonography of the left median nerve in the transverse plane, done with a high-frequency probe of 18 MHz, documented a focal enlargement of the left median nerve at the carpal tunnel inlet with a cross-sectional area of 13 mm^2. The nerve was hypoechoic in appearance. The cross-sectional area and appearance of the median nerve at the distal forearm were normal.

Ultrasonography confirmed the suspected diagnosis of carpal tunnel syndrome, and the patient was treated with nocturnal splinting. At follow-up evaluation 3 months later, she reported relief of her symptoms.

guidance of platelet-rich plasma injections also improved symptoms of carpal tunnel syndrome.[70] A single ultrasound-guided perineural platelet-rich plasma injection can provide therapeutic benefit 1 year after injection, as shown in an randomised controlled trial in 24 patients.[48] Benefits included reduced median nerve cross-sectional area[48] and pain and improved function.[55] No additive effect was documented when platelet-rich plasma injection was combined with one session of extracorporeal shock wave therapy.[47]

Splinting and physical therapy

In clinical practice, splinting is a well known way to treat carpal tunnel syndrome. A randomised controlled trial[71] of 110 patients showed its efficacy in reducing nocturnal symptoms. In the panel, we present a case study of a patient with carpal tunnel syndrome treated with nocturnal splinting. Another non-surgical approach showing potential positive effects is physical therapy. Different types of physiotherapy have been compared, but not enough data exist to formulate definitive conclusions. A systematic review[63] showed that the available data do not assist with determining the best choice among different physical therapy approaches for carpal tunnel syndrome.

Surgical treatment

Surgery is a suitable and effective treatment for carpal tunnel syndrome that addresses the underlying cause by releasing pressure on the median nerve through the transection of the transverse carpal ligament. This method can be achieved with the traditional open approach (longitudinal wrist incision directly over the transverse carpal ligament; figure 2), open limited-incision (smaller incision than in the standard approach; single or double, small and mini-open), or the endoscopic technique (one or two portals).

No consensus exists on the optimal surgical approach. The guidelines of the American Academy of Orthopaedic Surgeons state that there is limited evidence that, if surgery is chosen, a practitioner might consider using endoscopic carpal tunnel release based on short-term benefits,[85] such as faster recovery of motor function, earlier return to work, and lower rates of wound and scar-related complications. Conversely, the guidelines from the European HANDGUIDE state that the preferred surgical approach is open surgery using a longitudinal, not extended incision.[86] A systematic review[62] found no unequivocal evidence for superiority of any one surgical technique over another. Similarly, a randomised controlled trial[72] of 30 patients with portal endoscopic release performed on one hand and open release contralaterally showed no significant differences at any of the post-operative timepoints in functional outcomes. Both techniques were well tolerated, although most patients stated that they preferred the endoscopic technique.[72]

Other meta-analyses have shown no significant differences in symptom improvement (pain relief measured by the Visual Analogue Scale, digital sensation with Semmes-Weinstein monofilament testing, or two-point discrimination) or functional status indices (Boston Carpal Tunnel Questionnaire, Functional Status Scale scores) between the different techniques 6 months after the operation. However, short-term outcomes were variable: the endoscopic and limited-incision techniques resulted in greater pinch strength and hand dexterity than open release,[65,67,75,83] and endoscopic release was superior to open release in improving sleep symptoms.[58] In one review, patient satisfaction (subjective rating scale of 0–100 points) was higher for endoscopic release.[67] Return to work was at least 1 week faster with endoscopic release and 1 week faster with the limited-incision than the open standard release.[67,87,88] Although the immediate procedural cost of endoscopic release exceeds that of open release, the overall estimate should also include the cost to society for missed work and complications.[88,89]

There was moderate evidence (methodological quality assessment criteria are specified in the review)[62] that corticosteroid irrigation of the median nerve before skin closure, as an adjunct to carpal tunnel release, was more effective than standard open carpal tunnel release in the short term on symptom severity scores. Direct visualisation plus the tunnelling technique was more effective than

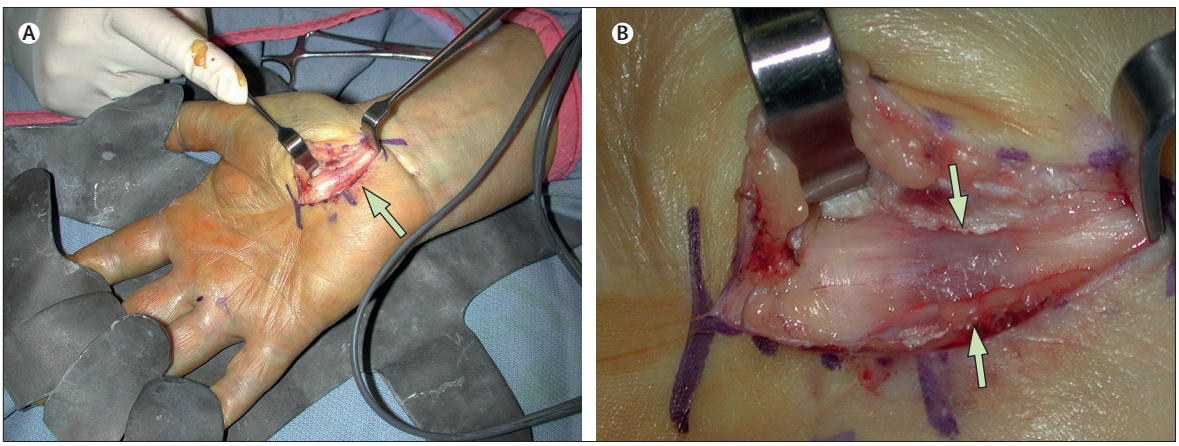

Figure 2: **Open carpal tunnel release in a patient with carpal tunnel syndrome**
(A) Open carpal tunnel release with full transection of the transverse carpal ligament. (B) The median nerve is exposed and appears constricted and erythematous (arrows).

standard open carpal tunnel release in the short term on grip strength.[62] Tunnelling is a tissue-sparing approach that allows the surgeon to limit the incision length and to respect the palmar fascia and subcutaneous tissue.[90] Carpal tunnel release with amniotic membrane transplantation was more effective at improving function severity scores than carpal tunnel release alone at 1-year follow-up.[46] There is moderate evidence[85] that the routine inclusion of adjunctive techniques, such as epineurotomy, neurolysis, flexor tenosynovectomy, and lengthening or reconstruction of the transverse carpal ligament in primary carpal tunnel release, have no benefit.[50,85] In a randomised controlled trial[59] of 117 patients with severe unilateral idiopathic carpal tunnel syndrome, reconstruction of the transverse carpal ligament in carpal tunnel release surgery significantly improved grip strength and symptom severity at 6 months compared with release only.

The main concern with the endoscopic approach is the potential damage to neurovascular structures and incomplete release of the transverse carpal ligament due to limited visualisation of the surgical field. The endoscopic approach could miss anatomic variations, an aberrant superficial palmar arch, tenosynovitis, or a mass in the surgical field.[89] Randomised controlled trials and meta-analyses have shown that the proportion of patients with short-term complications is higher with the endoscopic approach than the open release approach[57,75,88] (1·63% *vs* 0·79%);[88] complications are predominantly transient median neurapraxia (occurring in 1·45% of patients after the endoscopic technique *vs* 0·25% after open release).[88] However, more wound and scar-related complications occur with standard open release procedures than with the endoscopic approach (15 [1·3%] of 1180 open procedures *vs* one [0·1%] of 1140 endoscopic procedures; OR 0·20 [95% CI 0·07–0·59]; p=0·004).[65] Major complications, such as permanent structural injuries and moderate or severe pain more than 12 months after surgery, including complex regional pain syndrome, are infrequent (occurring in 0·9% of patients) with no significant differences observed between the open and endoscopic approaches.[88] Additionally, no significant differences exist between the two techniques in the re-operation rate.[57,77]

Ultrasound-guided carpal tunnel release emerged in 2018 as a novel, minimally invasive percutaneous treatment for carpal tunnel syndrome, performed under local anaesthesia. Ultrasound monitoring increases safety and permits the identification of anatomic variants of the median nerve. The incision size is smaller than in the open and endoscopic techniques, with quicker recovery and a better aesthetic result.[91] In a randomised controlled trial[74] of 92 patients recruited in an ambulatory office-based setting at a third-level referral hospital, equivalent neurological recovery was achieved with ultrasound-guided carpal tunnel release or mini-open carpal tunnel release, but the ultrasound-guided method provided earlier functional return and less postoperative morbidity. Based on a systematic review, ultrasound-guided carpal tunnel release might be an effective treatment for carpal tunnel syndrome, but large randomised controlled trials are needed to define the safety and effectiveness of this procedure.[51]

Symptoms of carpal tunnel syndrome can persist or recur in 3–20% of patients, leading to revision surgery in up to 12%.[92] Persistent symptoms with no temporary relief can result from incomplete decompression (with a similar incidence in endoscopic and open release), a secondary site of median nerve compression (anatomical variations accounting for about 37% of these cases), irreversible nerve pathology associated with chronic compression neuropathy, or inaccurate preoperative diagnosis. Recurrent symptoms, usually after a 6-month symptom-free interval after the operation, can occur with perineural adhesions (in about 88% of patients), excessive scarring, reconstitution of the transverse carpal ligament, or development of secondary conditions, such as tenosynovial proliferation, postoperative wound infection, or haematoma.[92] New postoperative

symptoms most commonly involve iatrogenic complications, of which nerve injuries represent up to 53%.[92] These injuries include complete or partial injury to the median nerve, palmar cutaneous branch, or recurrent motor branch. The majority are transient neurapraxia, mainly occurring with the endoscopic technique,[75] and resolve without the need for surgical intervention. Vascular complications (of the ulnar artery or superficial palmar arch) and tendon-related complications, such as trigger finger,[68] bowstringing of the flexor tendons, and flexor tendon adhesions, can also occur. Scar tenderness and pain surrounding the incision site are usually transient, and can also be included in this category.

Although no guidelines exist on surgical intervention in persistent or recurring carpal tunnel syndrome, surgical management with revision neuroplasty, nerve reconstruction, neurolysis, or local soft-tissue flap coverage, as appropriate for the individual patient's condition, is considered generally effective.[92] However, a review and meta-analysis[53] found no added value for additional coverage of the nerve, although the included studies were of low quality with moderate risk of bias.

Surgical versus non-surgical treatment

The guidelines of the American Academy of Orthopaedic Surgeons state that surgical treatment of carpal tunnel syndrome should have a greater treatment benefit at months 6 and 12 than splinting, non-steroidal anti-inflammatory drugs, and a single steroid injection.[85] A subsequent review and meta-analysis[62] found that surgical treatment was more effective than splinting or non-steroidal anti-inflammatory drugs with hand therapy at months 6 and 12, but steroid injection was more effective than surgery at 3 months and manual therapy was more effective than surgery at months 3 and 6. A review and meta-analysis[76] reported that surgery was superior to splinting or steroid injection at 6 months, but not at months 3 or 12. The outcome measures were patient-reported functional and symptom changes, and improvement of electrophysiological studies. The authors concluded that further studies on long-term outcomes are needed.[76]

A multidisciplinary group of experts from the European HANDGUIDE study identified disease severity, disease duration, and previous treatments as the main factors when selecting a suitable treatment for carpal tunnel syndrome.[86] They provided guidelines based on the association between carpal tunnel syndrome severity or duration and choice of therapy. Although no consensus could be achieved on therapeutic preferences or hierarchy, the authors suggested that the first step in the treatment of carpal tunnel syndrome is non-surgical, beginning with informing and educating the patient, followed by splinting and corticosteroids. Surgery should be reserved for more advanced compressions.[86]

Conclusions and future directions

Carpal tunnel syndrome remains the most common entrapment neuropathy and affects quality of life in 1–5% of people. However, many questions remain regarding its cause and optimal treatment. Age and sex are contributing factors, but probably play a role because of hormonal changes and chronic prolonged mechanical stressors. Similarly, clear evidence on the best therapies in specific patient populations is scarce.

In some systemic disorders, carpal tunnel syndrome might be the presenting sign. For this reason, atypical carpal tunnel syndrome (eg, paediatric carpal tunnel syndrome or bilateral presentation in men without risk factors) should raise concern for an underlying systemic cause, including lysosomal storage disorders or amyloidosis. Early diagnosis of carpal tunnel syndrome and suspicion for rare diseases could be essential for early treatment and improved outcomes. Therefore, further studies are needed to clarify when patients with carpal tunnel syndrome warrant evaluation for rare diseases.

Although diagnostic testing was studied extensively over the past 30 years and high sensitivity and specificity were reached, diagnosis remains a topic of debate and research. Patient-centred and symptom-oriented tools are becoming accepted practises. In addition to traditional neurophysiological testing, nerve ultrasonography has strengthened its role in carpal tunnel syndrome diagnosis. Moreover, new imaging methods are emerging. Surgical and non-surgical treatments are beneficial in carpal tunnel syndrome and the treatment should be tailored to the patient. Although clinical assessment, neurophysiology, and imaging have supporting evidence, selecting the best approach for diagnosis and therapeutic decision making relies on the clinician's expertise and opinion. Moreover,

Search strategy and selection criteria

We searched PubMed for publications between Aug 2, 2016, and May 1, 2022, using "carpal tunnel syndrome" as a MeSH term. We filtered the search for "randomized controlled trial", "meta-analysis", and "systematic review". No language restrictions were applied. The search provided 213 articles. After excluding redundant, duplicate papers, and those in which the topics of the Review were only marginally addressed, we identified 56 articles: 18 meta-analyses (appendix p 1), 24 randomised controlled trials, and 14 systematic reviews. Additional unfiltered literature searches were performed for pregnancy, older adults, rare disease, and COVID-19. On the basis of the relevance to the topics of the Review, we selected one editorial, two letters with data, three reviews, and 12 non-randomised clinical studies. We avoided referencing review articles when possible. We cite also other types of papers (eg, reviews, guidelines) or papers outside the temporal limit of the literature search on the basis of their relevance to the topics of the Review.

despite the extensive literature on carpal tunnel syndrome and the introduction of new methods for diagnosis and treatment, further studies are needed to validate new approaches and verify their feasibility in clinical and research settings. Therefore, a consensus protocol for carpal tunnel syndrome diagnosis and management remains elusive.

Contributors

LPa and RB conceptualised the Review. LPa designed the methods. LPa, CC, and CL were project administrators. CC, SG, DC, LPe, and LDH-W drafted the manuscript. LPa, CC, SG, DC, LPe, and LDH-W wrote the manuscript. LP, CC, CL, and LDH-W reviewed and edited the manuscript. CL provided study resources. RB supervised and validated the study.

Declaration of interests

We declare no competing interests.

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