# Meta-Analysis: Comparison of Carpal Tunnel Syndrome Pain Degrees Between Men and Women

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**Abstract**

**Background:** Carpal tunnel syndrome (CTS) is a syndrome that occurs in the medial nerve where there is pressure on the nerve as it passes through the wrist. This syndrome has symptoms of pain in the hands, a feeling of numbness, and tingling in the area innervated by the medial nerve. The prevalence of CTS is more dominated by women than men, where in the UK General Practice Research Database in the year 2000, there were 193 incidents per 100,000 women and 88 incidents per 100,000 men. This meta-analysis was created with the aim of further evaluating the comparison of the degree of pain in CTS between men and women both from an anatomical perspective and from various other aspects so that it can become a study that can be used as a reference in the treatment and prevention of CTS.
**Objective:** Analyzing the comparison between pain level between men and women
**Methods:** Systematic review and meta-analysis were carried out using the SCOPUS, Web of Science, Science Direct, SAGE, and PUBMED databases. The research results would be screened according to the inclusion criteria. Meta-analysis would be carried out using the fixed effect method to compare the standardised mean differences between pain levels in men and women.
**Results:** The results obtained were 3464 articles, of which there were 7 articles that met eligibility. The pain scale in CTS was measured using the Boston Carpal
Tunnel Questionnaire, PainDETECT, LANSS, and NRS. There was a significant difference between the standardised mean pain levels between men and women, where women have a higher pain level than men. $I^2$ = 0% dan $Tau^2$ = 0.0029 ($p<0.0001$) (SMD -0.32; 95% CI [-0.45 – -0.19]).
**Conclusions:** Female patients were found to experience a higher degree of pain compared to men.

**Keyword:** Carpal Tunnel Syndrome; Sex; Pain

## 1. Introduction

Carpal Tunnel Syndrome (CTS) is a condition involving compression of the median nerve in the wrist, causing symptoms like pain, numbness, and tingling. Risk factors include obesity, repetitive wrist activities, hereditary factors, pregnancy, and rheumatic inflammation. The pathophysiology includes trauma, increased pressure, and ischemic damage to the median nerve within the carpal tunnel (Genova et al., 2020)

Anatomical differences between men and women, particularly in the carpal tunnel, contribute to women's higher susceptibility to CTS due to smaller palmar bowing and less elastic ligaments (Lakshminarayanan, Shah and Li, 2019). The prevalence of CTS is higher in women, and certain occupations with repetitive hand movements increase the risk for both genders (Farioli et al., 2018).

## 2. Material and Method

### 2.1 Eligibility Criteria

This study is using a quantitative method by doing a meta-analysis based on PRISMA 2020 guidelines. The inclusion criteria is the full text of the literature is accessible in both English and Indonesian languages, the population is affected by CTS and includes individuals aged over 18 years old, and derived from a randomized controlled trial (RCT) study design. The exclusion criteria is non-research study (book chapters, reports, conference papers, review article), and case-control, cross-sectional, cohort, case report, dan case series.

### 2.2 Literature Search

The literature search in this study was conducted through several electronic databases such as PubMed, SAGE Journals, Web of Science, SCOPUS, and Science Direct. The literature search utilized Mesh Terms and Boolean operators as follows: #1= ("carpal tunnel syndrome" OR "carpal tunnel" OR "CTS" OR "median neuropathy, carpal tunnel" OR "compression neuropathy, carpal tunnel" OR "entrapment neuropathy, carpal tunnel") #2= ("sex" OR "phenotypic sex" OR "genotypic sex" OR "gender") #3= ("pain" OR "ache" OR "numbness" OR "tingling") Search Strategy = #1 AND #2 AND #3

### 2.3 Literature quality assessment

This study uses PRISMA (Preferred Reporting Items for Systematic Reviews And Meta-Analyses) flowchart aims to clarify the literature search and screening process for transparency. The analysis of study quality or bias will be conducted using the Risk of Bias (ROB) version 2.0 method. The assessment, in the form of ROB version 2.0, consists of six bias domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and reporting. The evaluation of each article based on the predetermined domains will be ranked using an algorithm and based on signaling questions. The assessment will be marked as low, high risk, or some concerns and represented by the colors green (low), red (high risk), and yellow (some concerns).

### 2.4 Data extraction

Articles that meet the inclusion criteria and align with the PICO will be collected and processed using the Google Sheets application. The screening process, data extraction, and study quality analysis will be carried out independently by two individuals. In case of discrepancies, consultation with a third independent party will be sought.The extracted information will include the first author's name, year of the study, the questionnaire used to measure pain scale, the number of patients based on gender (male and female), and the Mean and SD for each gender.

### 2.5 Statistical Analysis

The collected studies will be analyzed using meta-analysis with the meta-mar version 3.5.1 program. Statistical significance will be determined if the P-value is $< 0.05$. Heterogeneity (I2) will be used to assess the degree of pain discrepancy in the studies. If heterogeneity is below 50%, the fixed-effect method will be employed, while if heterogeneity is above 50%, the random-effect method will be used. Sensitivity analysis will be performed using the leave-one-out method. The leave-one-out method in meta-analysis involves conducting meta-analysis on each subgroup of studies obtained by excluding one study at a time. This method is commonly used to evaluate the sensitivity of meta-analysis results. It is particularly useful in

situations where a study may produce exaggerated effect sizes, potentially influencing the overall outcome of the meta-analysis. The leave-one-out method is one of the most widely used approaches for sensitivity evaluation in meta-analysis.

## 3. Result

A total of 3,464 articles were obtained through the database search, and 203 articles were identified as duplicates and subsequently removed. In the first screening, 450 articles were screened, and in the second screening, 88 articles were further filtered by excluding those with titles and abstracts not relevant to this research, articles in foreign languages other than English, and articles without available full text. A total of 12 articles were then evaluated for eligibility. After evaluating variables, means and standard deviations, and PICO criteria, 7 articles were included in the meta-analysis. The selection process of the articles to be used is depicted in the PRISMA flowchart.

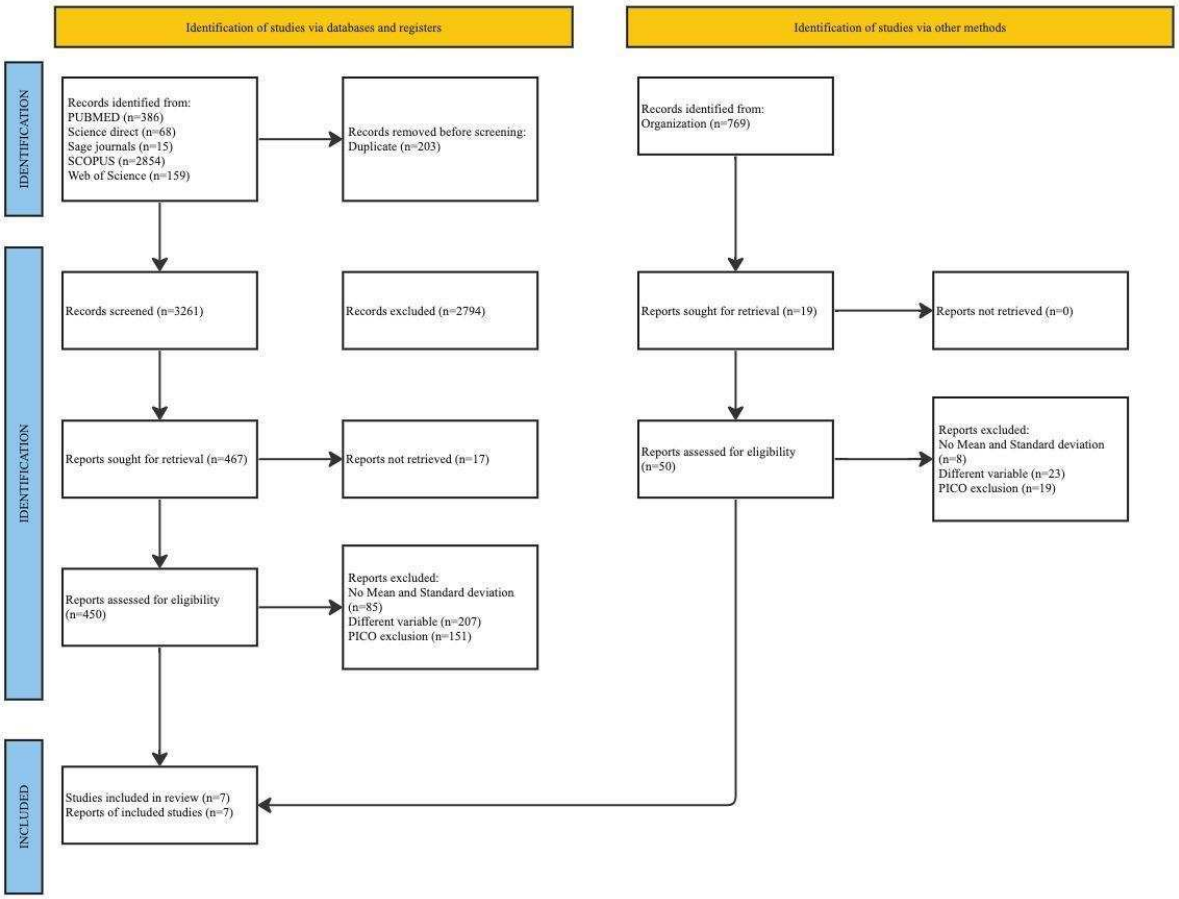


fig 1. PRISMA flow chart results

Tabel 1 Characteristics of Included Studies (N=7)

| Author, Year | Country | N | Age distribution ± SD | Gender distribution | Pain Scale |
|---|---|---|---|---|---|
| Ibrahim (2009) | United Kingdom | 479 | Mean 56 ± men 0,91;0,98; women 0,89;0,93 | 137 men; 342 women | Boston Carpal Tunnel Questionare |
| Hobby (2005) | United Kingdom | 110 | Mean 53,4 | 22 men; 75 women | Boston Carpal Tunnel Questionare |
| Motoki (2014) | Japan | 143 | Mean 66,3 ± 13,4 | 46 men; 81 women | PainDETECT |
| Azize (2013) | Turkey | 72 | Mean 47,33 | 6 men; 66 women | LANSS |
| Padua (1999) | Italy | 1123 | Mean 50,8 ±14,3 | 210 men; 913 women | Boston Carpal Tunnel Questionnaire |
| Mondelli (2005) | Italy | 172 | Mean 55,1 ±16,2 | 46 men; 126 women | Boston Carpal Tunnel Questionnaire |
| Yoshiki (2021) | Japan | 67 | Mean 66,8 ± 14,1 | 24 men; 43 women | NRS |

Table 1 illustrates the characteristics of the 7 studies included in the systematic review. Four studies originated from the European continent (Ibrahim, 2009; Hobby, 2005; Padua, 1999; Mondelli, 2005), while the remaining three studies were from Asia (Yoshiki, 2021; Azize, 2013). The total number of patients with Carpal Tunnel Syndrome (CTS) included in this research is 1994, with 491 (24.62%) being male and 1503 (75.37%) being female. Based on age distribution, most reported patients showed a median or mean falling within the older adult or elderly age group. The majority of studies utilized the Boston Carpal Tunnel Questionnaire (BCTQ) to assess pain levels in CTS patients. Other pain scales employed included PainDETECT, LANSS, and NRS.

The bias analysis was conducted using the Risk of Bias (ROB) version 2.0, which is presented in the form of an image as follows:

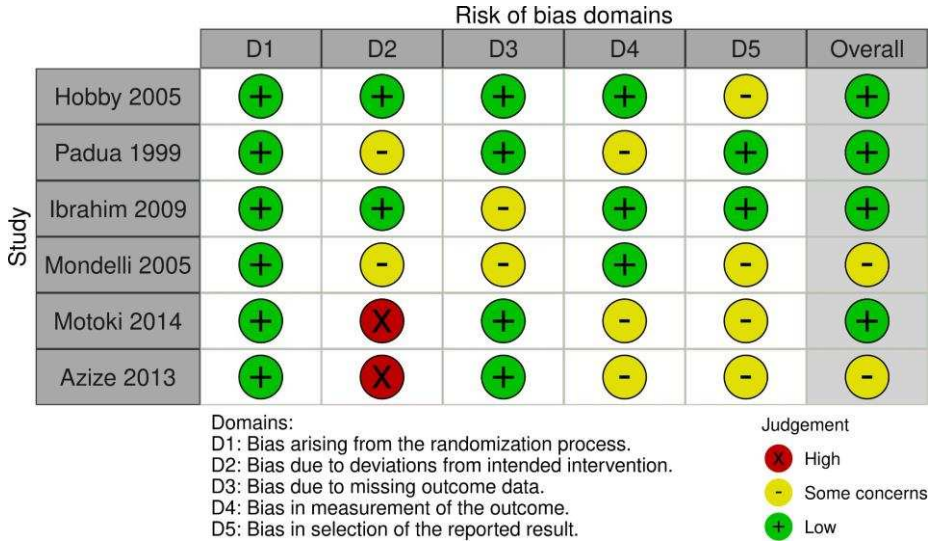


Fig 2 Risk of Bias

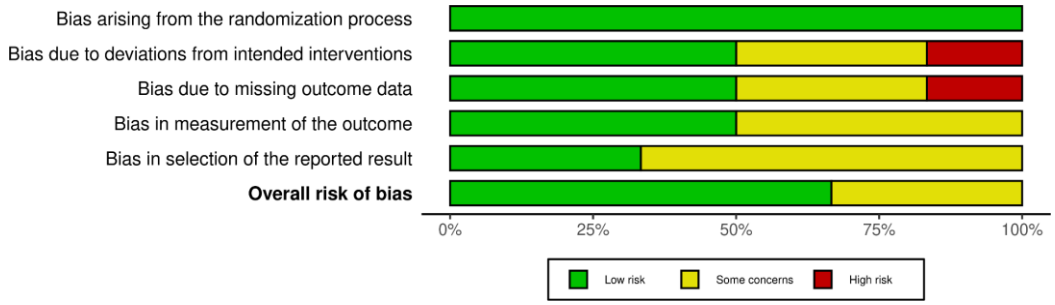


Fig 3 Risk of Bias

The ROB version 2.0 comprises 6 bias domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and reporting. The assessment of each article based on the predefined domains will be sorted using an algorithm and based on signaling questions. The assessment will be marked as low, high risk, or some concerns (Sterne et al., 2019). Bias analysis will be conducted independently by two researchers, and in case of discrepancies, consultation will be sought from a third independent party.

Table 2 Comparison of Pain Scale between Men and Women in Continuous Data

| Study | Ppain scale | Men | Mean | SD | Women | Mean | SD |
|---|---|---|---|---|---|---|---|
| Hobby (2005) | BCTQ | 22 | 2.65 | 1.23 | 75 | 3.08 | 1.57 |
| Padua (1999) | BCTQ | 210 | 2.4 | 0.8 | 913 | 2.6 | 0.9 |
| Ibrahim (2009) | BCTQ | 175 | 3 | 1.6 | 432 | 3.4 | 0.61 |
| Mondelli (2005) | BCTQ | 46 | 2.73 | 0.7 | 126 | 2.99 | 0.7 |
| Yoshiki (2021) | NRS | 24 | 0.33 | 0.57 | 43 | 0.95 | 1.33 |

Tabel 3 Comparison of Pain Levels in Men and Women in Dichotomous Data

| Study | Pain scale | Men | | Women | |
|---|---|---|---|---|---|
| | | Pain | No pain | Pain | No pain |
| Motoki (2014) | PainDETECT | 34 | 32 | 5 | 1 |
| Azize (2013) | LANSS | 133 | 64 | 67 | 36 |

Tables 2 and 3 depict the comparison of carpal tunnel syndrome pain scales between the male and female groups based on continuous and dichotomous data, respectively. In studies reporting continuous data, 4 studies used the BCTQ pain scale, and 1 study used the NRS pain scale. For studies reporting dichotomous data, 2 studies utilized the PainDETECT pain scale (Motoki, 2014), and LANSS pain scale (Azize, 2013). In the study by Motoki et al. (2014), patients were classified as having unlikely neuropathic pain if the PainDETECT score was ≤12, possible neuropathic pain if 13-18, and likely neuropathic pain if ≥19. Based on gender distribution, female patients showed a higher proportion than males in exhibiting PainDETECT scores ≥19, with a ratio of 3:1 (Motoki et al., 2019). The study by Azize et al. (2013) classified a LANSS score ≥12 to represent pain likely caused by a neuropathic mechanism and <12 to represent pain likely caused by a non-neuropathic mechanism. According to gender distribution, 34 out of 39 patients with LANSS scores ≥12 and 32 out of 33 patients with LANSS scores <12 were females (Azize et al., 2013).

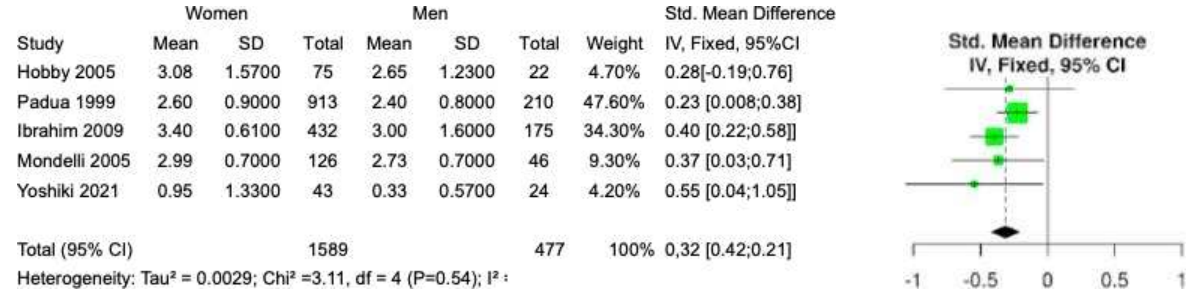


Fig 4 Forest Plot SMD Comparison of Pain Scale Between Men and Women

The meta-analysis conducted on continuous data was performed by comparing the standardized mean difference (SMD) (Figure 4). Heterogeneity in the SMD meta-analysis model is represented by an $I^2$ value of 0% and $Tau^2$ of 0.0029 ($p < 0.0001$), indicating a low proportion of variance and heterogeneity between studies. Thus, the meta-analysis was conducted using a fixed-effect model. Male patients showed a significantly lower mean pain scale compared to females (SMD 0.32; 95% CI [0.19-0.45]) P = 0.54.

## 4. Discussion

### 4.1 Basic Data

From the research articles obtained through keyword searches, totaling 3464 articles, seven research articles that met inclusion and exclusion criteria, PICO, and eligibility tests were identified. These studies originated from various ethnicities, locations, and races, with one article from Turkey and two articles each from Italy, Japan, and the United Kingdom. The total sample size from the included studies was 1994,

distributed across seven different studies. The age of the patients varied across studies but was generally above 18 years. Differences in study location, sample size, and population did not affect outcome variables. In studies by Ibrahim et al., Hobby et al., Padua et al., and Mondelli et al., the Boston Carpal Tunnel Questionnaire (BCTQ) was used to measure the severity and pain of CTS patients. In these studies, it was found that female patients had higher scores for both symptomatic and functional severity due to the high pain perceived by patients.

In Ibrahim et al.'s study, patients were categorized into two types of jobs: repetitive and non-repetitive. Repetitive jobs included construction workers, farmers, factory workers, and hairdressers, while non-repetitive jobs included accountants, managers, nurses, teachers, police officers, and couriers. There were 74 individuals in repetitive jobs and 223 individuals in non-repetitive jobs (Ibrahim et al., 2009).

For Ibrahim et al. (2009), the follow-up time in the study was six months post-patient surgery. In Motoki et al. (2014), the follow-up time ranged from 6 weeks to 6 months, with a preference for 6 months. If patients did not follow up at that time, a 6-week period was used. The follow-up time for Mondelli et al. (2005) was six months post-operation. Yoshiki et al.'s (2021) study started follow-up 4 days post-operation and was conducted three times a day. Other studies used the Numerical Rating Scale (Yoshiki et al.), LANSS (Azize et al.), and PainDETECT (Motoki et al.), each with different questions and criteria.

All these studies had a common question about gender, so the results obtained had similarities among the studies.

### 4.2 Comparison of Pain Scale in Carpal Tunnel Syndrome

Various questionnaires can be used to analyze the perceived pain level in patients with CTS, such as the Boston Carpal Tunnel Questionnaire (BCTQ), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Numerical Rating Scale (NRS), painDETECT, and others.

BCTQ is a questionnaire, also known as the Levine-Katz Questionnaire, developed to assess the functional level and severity of CTS. It consists of 19 simple questions divided into two domains. These questions assess the hand and wrist's functional level and the severity of symptoms. The severity domain includes 11 questions that assess the level of pain, paresthesia, numbness, weakness, nocturnal symptoms, and difficulties gripping. The functional status domain includes 8 questions assessing the ability to write, button clothes, hold a book when reading, grip a phone handle, open a jar, carry a shopping bag, bathe, and dress. Mean scores are generally calculated in the range of 1 to 5, with higher scores indicating worsening symptoms or function. The BCTQ questionnaire has been validated in many languages worldwide.

The Leeds Assessment of Neuropathic Symptoms and Signs Scale (LANSS) is a pain scale that analyzes sensory descriptions and examines sensory dysfunction in patients. LANSS has two parts. The first part consists of 5 questions that assess uncomfortable sensations on the skin, such as being stabbed, changes in skin color, increased skin sensitivity to touch, and sudden severe pain for no reason. In the second part, skin sensitivity is assessed by comparing the painful area with a non-painful area to review the presence of allodynia and changes in the pinprick threshold. The LANSS score is interpreted as neuropathic pain if the score is $<12$ and tends to be non-neuropathic pain if the score is $\geq 12$. The diagnostic accuracy of the LANSS questionnaire is 85% sensitivity and 80% specificity. The questionnaire has also been validated in many languages used worldwide.

The Numerical Rating Scale (NRS) is an easy and frequently used method to measure pain scale. NRS, often ranging from 0 to 10, uses 0 as no pain and 10 as severe pain for the patient. There are two forms of NRS: verbal and written, where patients mark a number on a scale of 0-10. PainDETECT is a questionnaire designed to classify the pain perceived by patients and whether the pain is neuropathic or nociceptive. It consists of several questions describing the pattern of pain perceived by patients and correlates with the diseases they have.

In these questionnaires, there is a commonality: pain is assessed by the patients themselves based on their experiences. Thus, differences in pain severity between genders are perceived by patients based on their respective genders.

4.3 Difference in Pain Scale between Men and Women

Based on the conducted meta-analysis and systematic review, there is a significant difference between male and female genders, with women having higher degrees in pain scale, severity, and functional level of carpal tunnel syndrome (CTS). The earliest evidence of this difference was found by Padua et al. (1999), who conducted a multisectoral investigation in the Italian population and found that although men were less affected by CTS than the female group, men had a higher degree of severity neurophysiologically. Furthermore, Hobby et al. (2005) showed that although women reported higher preoperative pain levels in CTS compared to men, there was no significant difference in postoperative scores between the two groups. This indicates that the post-release outcome of carpal tunnel is not influenced by gender differences. In the same year, Mondelli et al. (2005) publication indicated that there was no significant difference in the degree of CTS pain between men and women, even after considering work-related factors. These findings can be explained by how women tend to have a more sensitive perception of CTS-related symptoms than men. Additionally, men tend to ignore physical discomfort and do not emphasize CTS symptoms, resulting in a higher pain threshold than women (Mondelli et al., 2005). More recent evidence from Turkey also indicates that neuropathic pain measured by LANSS scores ≥12 does not significantly differ between male and female patients (Gursoy et al., 2013). In a clinical setting, a comprehensive assessment is required that involves not only pain report outcomes but also additional neurophysiological examinations, especially in determining more intensive therapeutic modalities.

Anatomically, a recent study by Rodriguez et al. (2022) using macroscopic dissection showed that men have a larger cross-sectional area of the carpal tunnel compared to women. Nevertheless, there was no significant difference observed between men and women in the CT size relative to its internal structures (Rodriguez et al., 2022). An MRI investigation also indicated that the mean cross-sectional area of the carpal tunnel in women was significantly smaller than in men (Sassi and Giddins, 2016). An ultrasound analysis showed that female patients with CTS symptoms had a wrist-to-arm ratio (WFR) greater than men, which was also accompanied by significant differences in clinical presentation (Gruber et al., 2016).

Changes in hormones in women, especially during menopause and pregnancy, are suspected to be one of the supporting factors that increase vulnerability to Carpal Tunnel Syndrome (CTS) pain compared to men. During pregnancy, hormonal changes leading to fluid retention often occur, causing additional pressure on the carpal tunnel and resulting in symptoms in women. However, some women may not experience symptoms until after childbirth and early breastfeeding. Meanwhile, hormonal changes during menopause can increase women's risk of developing CTS due to the enlargement of the wrist structure that can compress the median nerve at the carpal tunnel site (Hamid et al., 2020). However, a study showed that there were no differences in the expression of estrogen receptors in the transverse carpal ligament (TCL) and serum estrogen levels in menopausal women with and without idiopathic CTS (Mohammadi et al., 2016). In this study, there was also no correlation between ER expression or serum estrogen levels with electrodiagnostic parameters or the severity of CTS based on the Boston questionnaire (Mohammadi et al., 2016). A large-scale study in Taiwan reported that hormone replacement therapy in menopausal women is an independent factor associated with CTS incidence in that group (Tang et al., 2022).

## 5. Conclusion

Based on the results of the systematic review and meta-analysis, a significant difference in the degree of pain in carpal tunnel syndrome was found between men and women. Female patients were found to experience a higher degree of pain compared to men.

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