

# Traumatic and Non-traumatic Etiology of Complex Regional Pain Syndrome

Daifallah Mohammed Alharbi<sup>1</sup>, Abdulmalik B Albaker<sup>1,\*</sup>, Mohammed Ali Almaiyah<sup>2</sup>, Sarkhell Radha<sup>2</sup>, Ibrahim Musaad Alzahrani<sup>3</sup>, Saud Mohammed Alzahrani<sup>4</sup>, Yasmien Tawfeeq Rasheed<sup>5</sup> and Mana Ali Al Mutarid<sup>6</sup>

<sup>1</sup>Department of Orthopedics, College of Medicine, Majmaah University, 11952, Majmaah, Saudi Arabia.

<sup>2</sup>Department of Orthopedics, Croydon University Hospital, London, CR7 7YE, United Kingdom.

<sup>3</sup>General physician, King Salman Medical Complex, Medina, Saudi Arabia.

<sup>4</sup>General Physician, Prince Mishari Bin Saud Hospital, Al-Baha Health Cluster, Al-Baha, Saudi Arabia.

<sup>5</sup>General physician, Royal Commission Hospital, Yanbu City, Saudi Arabia.

<sup>6</sup>Department of Orthopedics, Najran Health Cluster, Najran, Saudi Arabia.

Corresponding author: Abdulmalik B Albaker (e-mail: [a.albaker@mu.edu.sa](mailto:a.albaker@mu.edu.sa)).

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**Abstract Background:** Complex regional pain syndrome (CRPS) is characterized by prolonged pain after an injury that persists longer than expected. Different symptoms may present, and traumatic, non-traumatic, or iatrogenic events can cause them. This systematic review aims to provide an overview of CRPS and its causes. **Objectives:** This systematic review aims to explore the different causes of CRPS and their incidence, providing valuable insights for early recognition and management of the condition. **Methods:** We conducted a comprehensive search using PubMed and Cochrane databases, utilizing keywords related to CRPS and its causes. Patients with traumatic or non-traumatic causes of CRPS or those affected by iatrogenic causes met the inclusion criteria. We excluded review articles, animal studies, and non-relevant studies. This systematic review included 50 articles that met the inclusion criteria. **Results:** There was a significant correlation between trauma and CRPS, specifically fractures and blunt injuries without fractures. The second most common cause was iatrogenic, including carpal tunnel syndrome release and open reduction of distal radius fractures. Additionally, reports included cases related to tumors, inflammatory disorders, infections, neurological diseases, and miscellaneous or idiopathic causes. Estimates indicate that CRPS affects 13.6 per 100,000 people annually, with women experiencing a higher incidence than men.

**Key Words** complex regional pain syndrome, Reflex sympathetic neuralgia, causalgia, etiology

## 1. Introduction

CRPS is a syndrome marked by persistent regional pain that appears to be more severe or long-lasting than expected, given the initial injury. The pain affects a specific area of the body rather than following the typical pattern of nerve or skin damage, often showing unusual sensory, motor, and other symptoms. Its severity and symptoms can change over time. Risk factors include conditions like fibromyalgia, rheumatoid arthritis, and psychiatric disorders, as well as trauma, fractures, crush injuries, and surgeries [1]. Three main theories suggest the origins of CRPS: dysfunction of the sympathetic nervous system, neurogenic inflammation, and maladaptive neuroplasticity [2], [3]. CRPS is categorized into two types: CRPS-I, occurring without confirmed nerve injury, and CRPS-II, which involves known nerve damage [4]. CRPS presents pain, abnormal blood flow and sweating regulation, swelling of the skin and underlying tissues, changes

in skin appearance, and movement disorders, both active and passive. Diagnosis relies on clinical evaluation due to the absence of definitive diagnostic tests, resulting in varied incidence estimates ranging from 5 to 26 cases per 100,000 per year, with a higher prevalence in women [5]. Diagnostic tools for adults, including the Veldman, International Association for the Study of Pain (IASP) criteria, Budapest Criteria, and Budapest Research Criteria, lack robust evidence and may be subject to bias [3]. Treatment options encompass pharmacotherapy, sympathetic nerve block procedures, psychological support, physiotherapy, and occupational therapy. Yet, few studies focus on mechanism-based treatments due to the condition's low prevalence and diverse clinical presentations [6]. CRPS poses challenges in treatment due to its complex biomedical and psychosocial nature [1], [7].

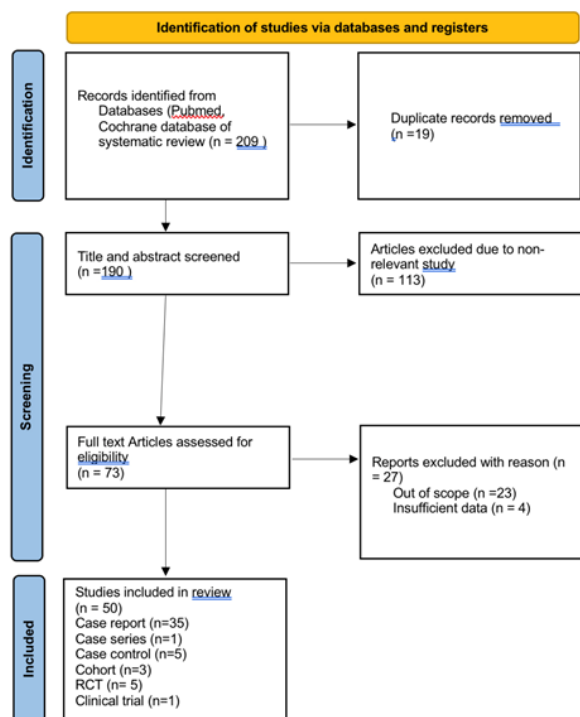


Figure 1: The PRISMA flow diagram provided the details of the screening and eligibility process

## 2. Method

We conducted this systematic review in light of the preferred reporting items for the systematic review and meta-analysis (PRISMA) checklist.

### A. Search strategy

We searched among the following search engines: Pubmed and Cochrane (central) using the following keywords: Complex regional pain syndrome OR complex regional pain syndromes OR CRPS And Cause OR causes OR caused by OR etiology OR incidence OR prevalence OR epidemiology OR epidemiological. We tried to minimize missing the related articles by reviewing the included study references.

### B. Inclusion and exclusion criteria

The inclusion criteria include all the original research that included patients with traumatic, non-traumatic, or iatrogenic causes of CRPS without restriction to date, gender, or age. The exclusion criteria include review articles or expert opinions, animal studies, non-relevant studies, and non-English studies.

### C. Data selection and extraction

Another investigator double-checked the selections made by one reviewer. Different researchers carried out the data extraction and validation independently.

## 3. Result

We retrieved a total of 209 articles. We excluded 159 articles, 19 of which were duplicates, 136 were out of scope or non-relevant studies, and 4 lacked sufficient details. Only 50 met the inclusion criteria. Thus, 50 articles formed the basis of this review. Based on the types of mechanisms, we put the causes of CRPS into eight groups: trauma-related (fracture, non-fracture, burn injury), iatrogenic, tumor-related, inflammatory, infectious, neurological disease-related, miscellaneous, or idiopathic.

### A. Incidence

The incidence of CRPS is 13.6 per 100,000 per year, according to a 2018 case-control study. The retrospective epidemiological analysis of 1043 patients with CRPS revealed that the most common cause of CRPS is trauma. The total number of traumatic cases is 706 (68.4%), which includes 441 (42%) fractures, 214 (21%), blunt trauma without fracture, 47 (5%), sharp trauma without fracture, and 4 (0.4%) burn injuries. The second most common cause of CRPS is iatrogenic causes, which include 124 (12%) cases. There are also 69 cases (7%) of carpal tunnel syndrome, 77 cases (7%) of idiopathic cases, and 52 cases (5%) of inflammatory causes. These include palmar/plantar fascial fibromatosis, Dupuytren contracture/lederhosen disease, animal bites, and local infections. The remaining cases (0.5%) include miscellaneous causes, including spinal disc herniation and venous thrombosis in the arm [5].

### B. Trauma-related causes

Trauma is considered the most common cause of CRPS [5]. Many cases report that CRPS complicates a fracture of the distal radius, scaphoid waist, ankle, or tibial [8]–[12]. Central cord syndrome and, in some cases, CRPS can be caused by injuries that don't break bones. These include blows to the knee, face, or forefoot, lumbosacral plexopathy made worse by a blast injury, brachial plexus made worse by a traction injury, and traumatic disc herniation of the neck [13]–[17]. The burn injury (esp. of the hand) may lead to CRPS [5], [18].

### C. The iatrogenic-related causes are

Iatrogenic causes are considered the second-most common cause of CRPS. A common iatrogenic cause of CRPS is the endoscopic or open release of carpal tunnel syndrome. Another example is the open reduction and internal fixation of the distal radius fracture [19]–[21]. A radial artery catheterization, nevus excision, steroid injection of the thumb in the trigger finger, surgery for a complex 5th metacarpophalangeal dislocation, radial head arthroplasty for a radial head fracture, right rotator cuff surgery, and surgery to repair a ruptured Achilli's tendon are some other known iatrogenic causes [22]–[27]. Numerous other case reports documented uncommon iatrogenic causes, including the implantation of a polytetrafluoroethylene arteriovenous graft, the administration of the COVID-19 vaccine, partial mastectomy and

sentinel lymph node biopsy for right breast cancer, the use of an artificial disc type in the L4/5 segment of the lumbar spine via a midline left-sided retroperitoneal approach, a complicated brachial artery puncture due to median nerve axonal injury, and the reduction of a planter fasciitis spur.

Dupuytren contracture can be treated in a number of known ways, including percutaneous palmar fasciotomy, collagenase injections, and open palmar fasciotomy with or without digit release. All of these procedures have been linked to CRPS [28].

#### D. Tumor-related CRPS

Tumors are not considered to be a common cause of CRPS. There are reports that CRPS can happen as a rare side effect of osteoblastoma in the talus, adenocarcinoma in the lung, and malignant peripheral nerve sheath tumors [29]–[31].

#### E. The infectious and inflammatory causes of CRPS

Many studies have concluded that CRPS can result from infection by the herpes simplex virus, the varicella-zoster virus, or the cytomegalovirus [32]–[34]. In rare cases, the infection of the cervical spine by tuberculosis, foot cellulitis, SARS-CoV-2, and leprosy neuropathy can lead to CRPS [35]–[38]. Palmar/plantar fascial fibromatosis, Lederhose disease, carpal tunnel syndrome, and Dupuytren contracture are some of the inflammatory causes [5].

#### F. Neurological-related CRPS

Possible neurological causes include stroke and a herniated intervertebral disc [5], [39]–[41]. A case report revealed a rare case of a heavy construction worker who developed dorsal scapular neuropathy and CRPS [42].

#### G. Miscellaneous and idiopathy causes of CRPS

Many other rare causes of CRPS were documented in a few studies, which include the centipede bite, venous thrombosis in the arm, Raynaud's disease, and shoulder-hand syndrome [5], [43]–[45]. CRPS can occur without a memorable traumatic or non-traumatic event, which can be considered an idiopathic cause [46].

### 4. Discussion

The results suggest that various mechanisms, such as trauma, iatrogenic, inflammation/infection, neurological, or idiopathic, could cause CRPS. This systematic review indicates that traumatic and iatrogenic causes of the extremities are considered to be more associated with CRPS than the other different causes. Similarly, a 2021 study found that the most commonly reported inciting events leading to CRPS are extremity injuries such as fractures, surgeries, sprains, and carpal tunnel syndrome.

### 5. Implications

In general, the study methodology seemed suitable and strong. The systematic review had clearly defined criteria for including or excluding studies. The study result provides an

updated and organized summary of the common and rarely documented etiology of CRPS.

### 6. Limitations and Recommendations

After reviewing the literature, it was obvious there is a lack of studies that concentrate on the causes as their main focus, which can be due to the scarcity of CRPS. As a result, the majority of the articles included in our review were case reports. Also, different studies used different criteria for diagnosis since there are articles that rely on Budapest criteria while others use IASP clinical diagnostic criteria for CRPS. In addition, some studies did not mention or explain how they reached the final diagnosis of CRPS. We recommend further studies to direct attention towards the pathophysiology of the disease and to assess the probability of getting this condition after different types of causes.

### 7. Conclusion

This systematic review concluded that multiple and different types of causes can lead to CRPS. The most prevalent etiology includes fractures, blunt trauma, and iatrogenic causes. Such information should be useful for physicians for early prevention, recognition, diagnosis, and management of patients who have one of the common or suspected causes of CRPS to improve the patient's condition and avoid missed diagnoses.

### 8. List of Abbreviations

CRPS: complex regional pain syndrome.

IASP: International association for the study of pain

### Conflict of interest

The authors declare no conflict of interests. All authors read and approved final version of the paper.

### Authors Contribution

All authors contributed equally in this paper.

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