"ROLE OF ELASTOGRAPHY IN ASSESSING MEDIAN NERVE CHANGES IN RHEUMATOID ARTHRITIS PATIENTS WITHOUT SYMPTOMS OF CARPAL TUNNEL SYNDROME"

By

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DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, KOLAR, KARNATAKA

In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE
IN
RADIODIAGNOSIS

Under the Guidance of

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The Institutional Ethics Committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has examined and unanimously approved the Synopsis entitled **"Role of Sonoelastography in Assessing Median Nerve Changes in Rheumatoid Arthritis Patients without Symptoms of Carpal Tunnel Syndrome"** being investigated by Dr.YASHAS ULLAS.L, Dr. N Rache Gowda & Dr. Hari Prasad S[1] in the Departments of Radio Diagnosis & Orthopaedics[1] at Sri Devaraj Urs Medical College, Tamaka, Kolar. **Permission is granted by the Ethics Committee to start the study.**

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GLOSSARY	ABBREVIATIONS
1D-TE	1dimesnion transient elastography
ACPA	Anti-citrullinated protein antibodies
ACR-EULAR	American college of Rheumatology-European League Against Rheumatism
CNS	Central nervous system
CSA	Cross-sectional area
CT	Connective tissue
CTS	Carpal tunnel syndrome
DMARD	Disease modifying anti-rheumatic drugs
EMG	Electromyography
ESR	Erythrocyte sedimentation rate
FGF	Fibroblast growth factor
FLS	Fibroblast-like synoviocytes
GAGs	Glycosaminoglycans
IQR	Interquartile range
MMPS	Matrix metalloproteases
NCS	Nerve conduction studies
PAD	Peptidyl-arginine-deiminase
PDGF	Platelet-derived growth factor
pSWE	Point shear wave elastography
RA	Rheumatoid arthritis

RANKL	Receptor activator of nuclear factor kappa-b ligand
SD	Standard deviation
SE	Strain elastography
SNAP	Sensory nerve action potential
SR	Strain ratio
SWI	Shear wave imaging
TGF	Transforming growth factor
TIMPs	Tissue inhibitors of metalloproteinases
TLC	Transverse carpal ligament
TNF	Tumor necrosis factor
US	Ultrasonography
USE	Ultrasound elastography

ABSTRACT

Introduction: Rheumatoid arthritis (RA) is autoimmune disorder with increased prevalence in the female population especially in older age. The association of carpal tunnel syndrome (CTS) in RA is well-known and the median nerve involvement is extensively studied in RA and CTS. However, the elastography measurements in RA without CTS are least studied. Hence the present assessed the role of sonoelastography in detecting the median nerve changes before development to CTS in subjects with rheumatoid arthritis.

Material and methods: This were a prospective study involving subjects with RA without any symptoms of CTS as cases and healthy individuals as controls. Sonoelastography was performed in all study participants and the cross-sectional area and strain ratio were evaluated by sonoelastography in all subjects. Chi-square used to test significance for qualitative data and an independent *t*-test was used as a test of significance for quantitative data. *p* value < 0.001 was considered statistically significant.

Results: This study involved 112 subjects with equal subjects (56 each) in cases and control group. The mean age in the cases group was 48.5 ± 13.31years and in the control group was 48.02 ± 13.41 years. There was significant difference among the cases and controls in right and left side cross-sectional area (Cm^2) (P< 0.001). There was statistically significant difference between controls and cases in right and left side strain ratio (P< 0.001).

Conclusion: The use of sonoelastography in evaluating the median nerve changes in RA subjects without CTS was useful as changes in the CSA and strain ratio was significant in

cases compared to controls. Early diagnosis of median nerve changes can be made before developing to carpal tunnel syndrome in Rheumatoid arthritis patients using sonoelastography.

Key words: Rheumatoid arthritis, carpal tunnel syndrome, median nerve, cross-sectional area, strain ratio, sonoelastography.

INTRODUCTION

INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic inflammatory multisystem disorder which has symmetrical involvement of large and small joints. Prevalence of clinical neuropathy varies from 0.5% to 85% in patients with RA.[1] Presence of peripheral neuropathy exacerbates to functional disability in patients with RA.[2] A previous study by Goldin and Hart was first case series of patients with peripheral neuropathy and RA.[2] Patients with peripheral neuropathy present with diverse signs and symptoms such as numbness, pain, pins and needle sensation and muscle weakness.[3] The etiology of peripheral neuropathy is poorly understood. Previous studies show causative agent as drug toxicity, nerve entrapment, vasculitis, autoimmune phenomenon and amyloidosis as possible causes of peripheral neuropathy in patients with RA.[4] It is responsible for deteriorating quality of life and life expectancy rates.[5]

RA is associated with various neurological extra-articular manifestations including nerve compression by sensory or sensorimotor neuropathies, synovial proliferation and impingent on central nervous system (CNS) causing neurologic symptoms. The most frequent occurring neuropathy is CTS in RA and least occurring is tarsal tunnel syndrome and ulnar nerve entrapment.[6]

Normally wrist joint is most affected in RA along with CTS as a sequela.[7] The RA wrist leads to joint erosions, ligamentous laxity and synovial expansion resulting in the loss of height and increasing the pressure in the carpal tunnel. This pathology leads to diminished axonal conveyance, compression of the median nerve and vessels in the perineurium initiating median nerve ischemia.[8] The other plausible culprit mechanisms that have been implicated in rheumatoid neuropathy are drug toxicity, vasculitis and amyloidosis. CTS is by and large a clinical diagnosis, while electrophysiological tests (nerve conduction studies [NCS],

electromyography [EMG]) and sonographic assessment of the median nerve may be useful to support the diagnosis, detect subclinical CTS and rule out other abnormalities.[9] Unfortunately, the neuropathic pain in RA is often overlooked and mistaken for arthritic pain.[10] Several electrophysiological and sonographic studies have examined the median nerve in RA with variable findings.

Ultrasonography (US) has shown increased cross-sectional areas of median nerves in patients with "carpal tunnel syndrome" (CTS).[11] Various US measurements may be used to measure pathology in median nerve. The CSA (cross-sectional area) at entrance of carpal tunnel seems to have highest diagnostic sensitivity and specificity for CTS.[12,13] In healthy controls, the mean (SD) cross-sectional area of median nerve at this level has been found to be between 7.0 (1.0) mm^2 - 10.2 (2.5) mm^2.[14] Areas of 10.0–13.0 mm^2 have been stated in subjects with mild symptoms due to idiopathic CTS, 13.0–15.0 mm^2 signified symptoms of moderate CTS and areas >15.0 mm^2 were seen in subjects with severe idiopathic CTS.[15] It was observed that subjects with arthritis and CTS have an increase of similar magnitude in cross-sectional areas of median nerve as observed in idiopathic CTS.[16]

NEED FOR STUDY:

CTS is a frequent condition in subjects with RA, but normal cross-sectional area of median nerve in subjects with RA without any signs and symptoms of CTS has not been evaluated. RA is a systemic disease and inflammatory activity may affect area of nerves. Present study aimed to explore the distribution of cross-sectional areas of median nerve in subjects with RA who have no signs or symptoms of CTS.

AIMS & OBJECTIVES

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OBJECTIVES OF STUDY:

1. To evaluate morphological changes in median nerve by routine ultrasonography and sonoelastography of median nerve in subjects with and without RA.
2. To assess role of sonoelastography in detecting median nerve changes before progression to carpal tunnel syndrome in subjects with rheumatoid arthritis.

REVIEW OF LITERATURE

REVIEW OF LITERATURE:

Median nerve (Embryology and Anatomy)

Fetal development occurs in 3 distinct stages. The initial phase is the pre-differentiation period in 1 and 2 weeks, the 2nd phase is the developing period that happens during the 3rd till the 8th week and the final is the gestation period from the 9th week onwards. During the emergent period, the differentiation of the upper limb starts in the 5th week.

The gathering of cells situated at the distal ridge of the limb bud is identified as the apical ectodermal ridge and it facilitates the maturation and differentiation process for the upper extremity. The condensation of the mesenchyme leads to the initiation of cartilaginous reporters of the shoulder, the forearm, the arm and finally the hand. These cartilaginous

correspondents ossify into bones in about the 6th week of pregnancy.[17] The ossification of the primary centres begin at the early 12th week to form long bones.

The chronological development of the hollows in the joints, muscle differentiation and ligament condensation start at the start in the shoulder girdle and gradually go to distally to the hand during the 6 to 8 weeks of pregnancy. Post 9 weeks, joints, bones and ligaments further undergo maturation.[18]

The formation of the median nerve is in the axilla by the union of two roots, the lateral and medial roots. The medial root of the median nerve arises from the medial cord (C8, T1) of the brachial plexus. The lateral cord (C5, C6 and C7) gives rise to the lateral root of the median nerve. The two roots unite either anterior or lateral to the third part of the axillary artery.[19]

Median nerve then enters the arm lateral to the brachial artery. At the side by side of insertion of the coracobrachialis muscle, it crosses the artery in front of it and then descends medial to it up to the cubital fossa. It passes in the forearm between the two heads of the pronator teres muscle. A high percentage of disparities in the formation of the median nerve have been reported. It includes the presence of additional roots, formation of the nerve in the arm and formation medial to the axillary artery.[20]

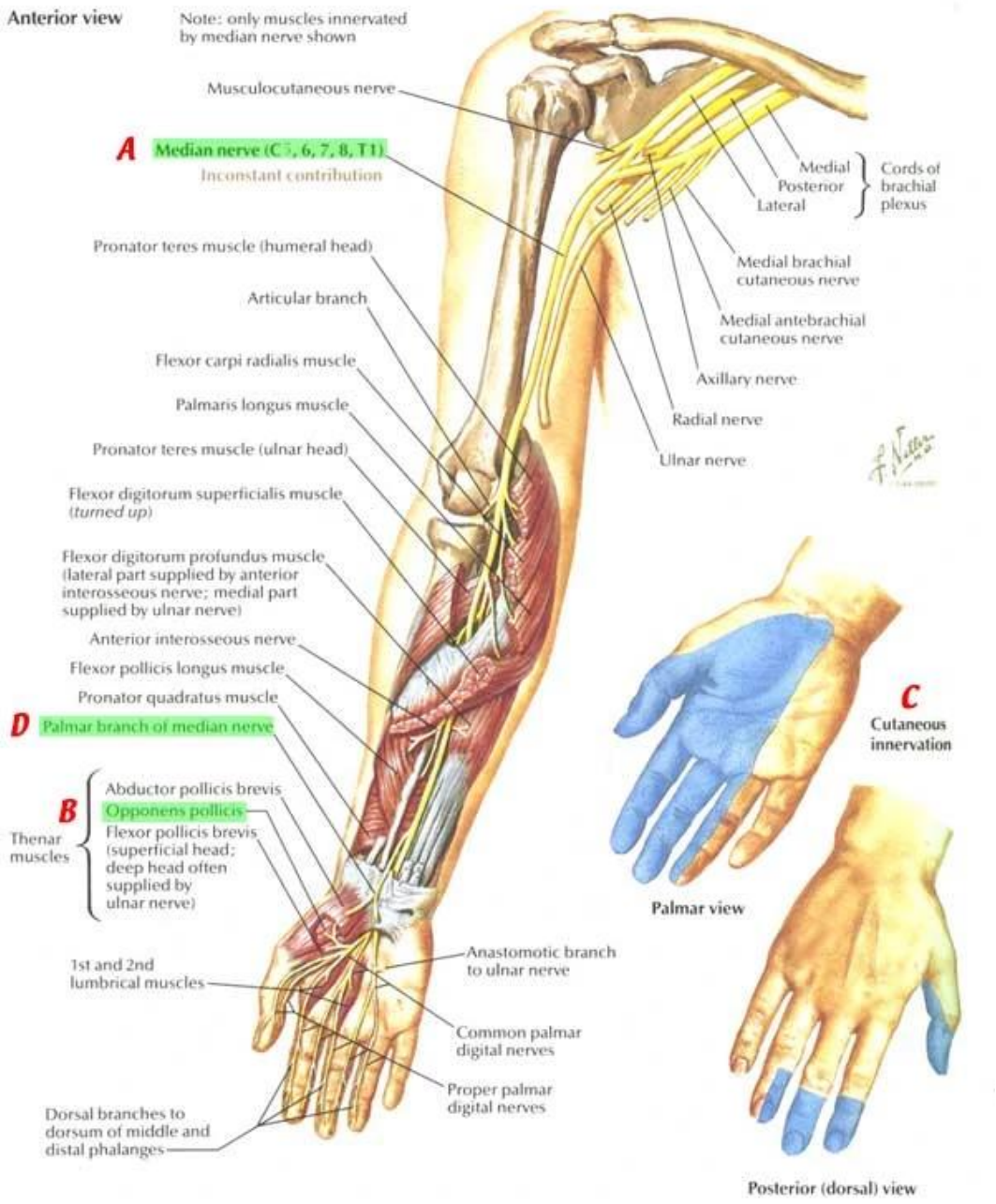


Figure 1: Showing the anatomy of the median nerve.

1. Rheumatoid arthritis

a) Definition, criteria

Rheumatoid arthritis (RA) is a longstanding disease which has an auto immune mechanism predominantly found in females compared to males and most frequent in the elder population.[21] The synovial joints are lining are the primary site affected in RA. The disease course can cause disability, increase the socioeconomic burden and premature death.

Clinical manifestations

- There is proportioned joint involvement, swelling, arthralgia, even limiting the range of motion and redness.
- In severe and poorly controlled illness, there is a risk that extra-articular indicators such as pulmonary granulomas (rheumatoid nodules), keratitis, pericarditis/pleuritis, small vessel vasculitis and further non-specific extra-articular symptoms can develop.[22]

Early diagnosis is measured as the key development index for the most necessary outcomes (i.e., compact joint destruction, fewer radiologic progression, not any functional disability and disease-modifying anti-rheumatic drugs {DMARD}-free lessening) as well as cost-efficiency as the initial 12 weeks after early symptoms arise is viewed as the optimal therapeutic window.[23,24] The initial estimate of RA is a challenge as it is purely based on clinical information from the subject and also should have laboratory tests and physical examination. There has been a difference in the reportage of RA in developing and underdeveloped countries due to reduced healthcare facilities in these countries.[25]

b) Epidemiology – Global, Indian – prevalence, incidence

Global Epidemiology of RA:

The prevalence of RA globally has been increasing over the years.[26] In the year 2017, 19,965,115 RA cases were globally prevalent 17,990,489-21,995,673 cases, with an age-standardized incidence rate of 246.6 cases/100,000 population, which augmented by 7.4% between 1990 and 2017. The age-standardized DALY (Disability-adjusted life years) rate reduced by 3.6% (95% UI, -9.7% to 0.3%) from 1990 to 2017. From the regional analysis, it was found the RA was most prevalent in developed countries and lowest in the developing and under developed countries.[26]

Indian epidemiology of RA:

Prior reports have shown a prevalence of RA in India ranged from 0.28% to 0.7%.[27] They reported a prevalence of 0.51% for RA diagnosed with ACR criteria and a frequency of 0.6% (95% CI: 0.4, 0.9) for RA diagnosed clinically among nearly 6000 men and women 16 years or elder (2998 men; 3000 women).[27] Using the COPCORD surveys within urban and rural localities of Jammu, a prevalence of 0.7% was found by Mahajan et al.[28] In a third COPCORD study, Joshi et al.[29] measured over 8000 adults, 16 years or elder (4010 men and 4135 women) living in the Pune city in Maharashtra. They recorded a crude incidence of 0.28% (95% CI: 0.18, 0.42) for RA diagnosed with ACR criteria and a crude incidence of 0.45 (95% CI: 0.32, 0.63) for RA diagnosed clinically. In a fourth study, Malaviya et al.[30] surveyed 5 villages in the Ballabhgarh township (Haryana) and reported an incidence of 0.7% among nearly 40 000 men and women over 15 years of age.

Among all the epidemiological studies one study studied the seropositivity among RA where they found 62% of the RA cases identified clinically were seropositive for RF factor while 100% were seropositive for anti-cyclic citrullinated peptide (anti-CCP) antibody.[29]

a) Aetiology and Pathophysiology

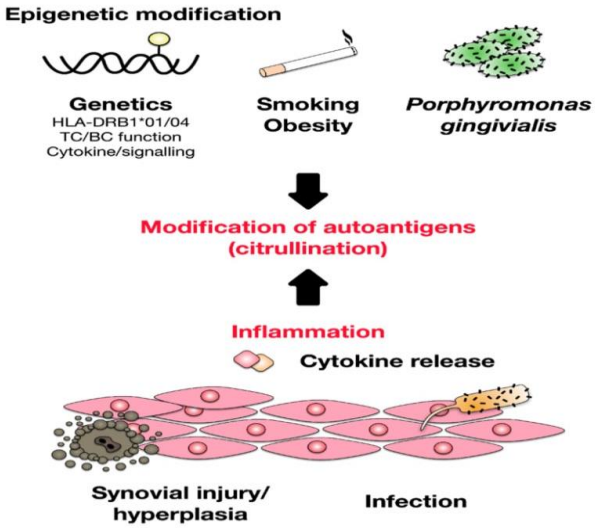


Figure 2: Contributing Factors contributing to RA development. Environmental factors such as obesity, smoking, infections Porphyromonas gingivitis and genetic factors, cytokine production, T- and B cell function and signal transduction succeeding immune cell activation subsidize the progress of RA. Furthermore, also synovial injury and hyperplasia of synovial fibroblasts can contribute to the founding of RA via the activating of inflammatory conditions. In general, these procedures lead to the alteration of autoantigens which produces neoepitopes by a loss of surface charge and an increased susceptibility to proteolytic degradation.[31]

Pathophysiology of RA:

There are 2 major subtypes of RA based on the existence or nonappearance of ACPAs (anti-citrullinated protein antibodies). Citrullination is catalyzed by the calcium-dependent enzyme peptidyl-arginine-deiminase (PAD). ACPAs can be spotted in about 67% of RA subjects and serve as a useful diagnostic reference for subjects with undifferentiated arthritis and early deliver a sign of likely ailment development through to RA. The ACPA +ve subset of RA has a more violent clinical phenotype compared to ACPA -ve subset of RA.[32] It is described that ACPA-ve RA has unlike genetic patterns[33] and discrepancy retorts of immune cells to

citrullinated antigens from those of ACPA +ve subset. In relation of treatment, not as much of active treatment response of rituximab or methotrexate (MTX) was detected in the ACPA-ve subset. This suggests a prerequisite for an upcoming study on possible pathophysiology differences between these 2 subsets. It is remarkable to mention, nevertheless, that these phases may occur serially or instantaneously.[22]

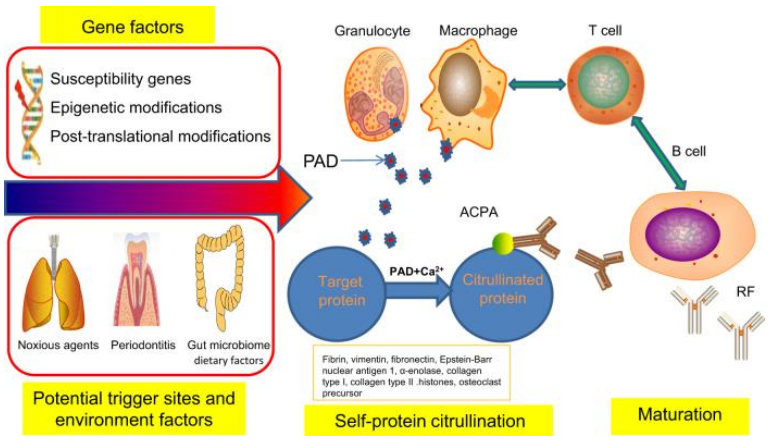


Figure 3: Triggering stage.

RA can be activated in the possible trigger sites (oral, lung, gut) by the interface between the environmental factors and genes, which is considered by the onset of self-protein citrullination subsequent in the creation of autoantibodies contrary to citrullinated peptides. Lung exposure to, infectious agents (Porphyromonas gingival is, Aggregatibacter actinomycetemcomitans and Epstein-Barr virus), noxious agents, dietary factor and gut microbiome may encourage the self-protein citrullination and maturation of ACPA. The calcium-dependent enzyme PAD catalyzes the Citrullination and this leads to changing a positively charged arginine to polar but neutral citrulline as the result of a post-translational alteration. In RA, PAD can be veiled by the granulocyte and macrophage. ACPA happens as a result of an atypical antibody response to a range of citrullinated proteins, including vimentin, fibrin, fibronectin, α-enolase, type II collagen, Epstein-Barr Nuclear Antigen1 and histones, all of which are dispersed throughout the entire body.[22]

Maturation stage:

The maturation stage is triggered at the areas of bone marrow or secondary lymphoid tissues. Epitope dispersion refers to the advance of immune retorts to endogenous epitopes consequential from the issue of self-antigens. The immune retort to autoantigens may be present from many years prior to disease onset and may present exterior to the joints. At this stage when there is epitope widespread there is a marked increase in the ACPA which can last for many years prior to the onset of symptoms of joint. Hence ACPA is of good importance at can predict the onset of the disease.[22]

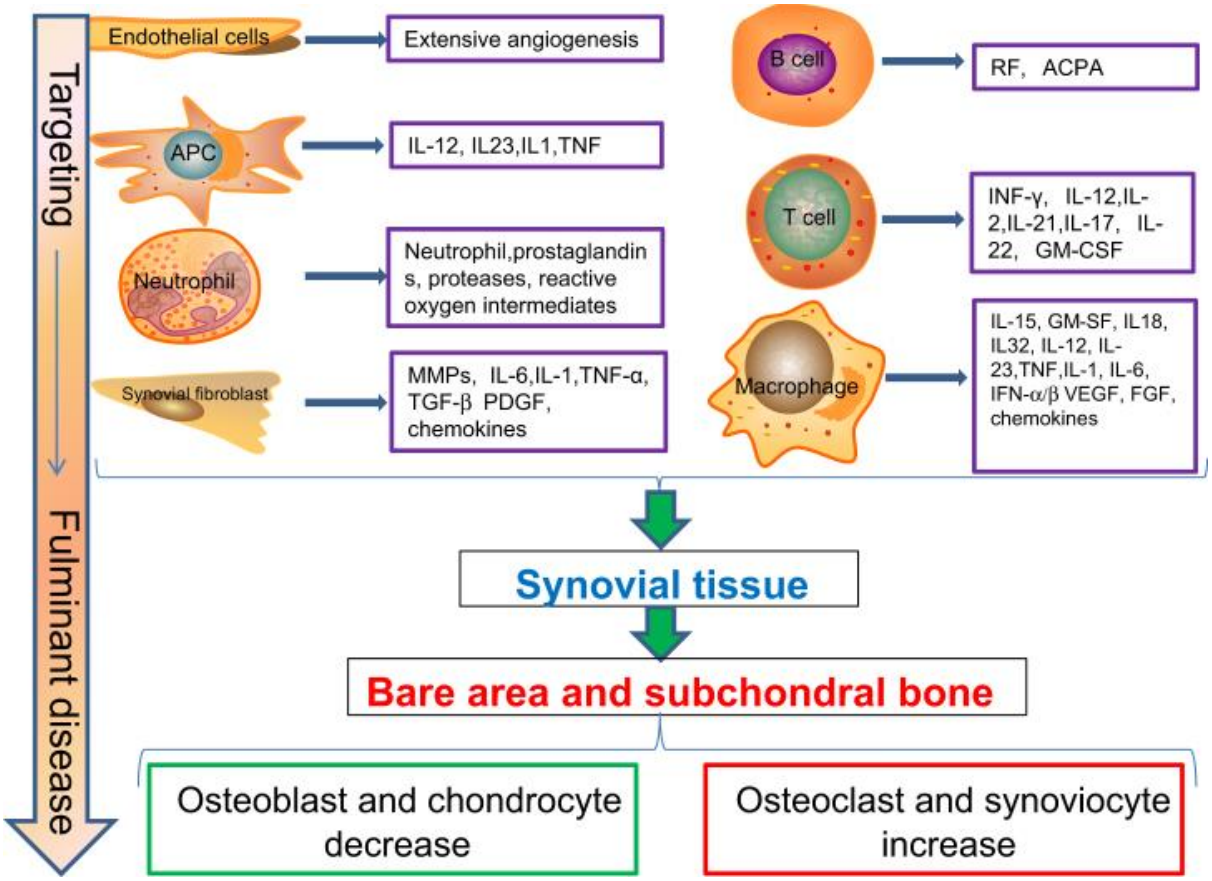


Figure 4: Targeting stage.

Several cells and their cytokines show vital role in progression of RA. Synovial compartment is penetrated by leukocytes and synovial fluid is flooded with pro-inflammatory mediators

that are formed to persuade an inflammatory force, which is categorized by communications of fibroblast-like synoviocytes (FLS) with the cells of the distinctive immune system, with monocytes, macrophages, mast cells and so on, as well as cells of adaptive immune system such as B cells and T cells. Endothelial cells help in widespread angiogenesis. Fulminant stage comprises bone erosion, cartilage damage, hyperplastic synovium. Resorption of Bone nearly makes bone erosions, which are typically found at spots where synovial membrane enclosures into periosteum. Obliteration of subchondral bone can ultimately result in deterioration of articular cartilage as result of a reduction in osteoblasts and increase in osteoclasts and synoviocytes. TNF (tumor necrosis factor), IL interleukin, MMP, TGF (transforming growth factor), PDGF (platelet-derived growth factor), macrophage colony-stimulating factor, IFN interferon, FGF (fibroblast growth factor), GM-CSF (granulocyte–VEGF vascular endothelial growth factor).[22]

Fulminant stage:

Hyperplastic synovium:

Synovium is made up by a combination of FLS and macrophages.[34] Synovial cells uphold the stable state of the joint by concealing hyaluronic acid and lubricin for joint lubrication. It also helps in dispensation waste products. Especially in RA, there were a dysfunction of FLS leading to hyperplastic synovium.

The irregular propagation of FLS outcomes from a loss of connection inhibition plays a serious role in RA by creating proteinases and MMPs and "tissue inhibitors of metalloproteinases" (TIMPs) that disseminate joint obliteration. They create a microenvironment that permits for the existence of B cell and T cell and neutrophil buildup.[35] Other hypothesis, shows that the cause for hyperplastic synovium was due to confrontation to apoptosis-related with characteristic pathways.[36]

Cartilage damage:

Cartilage acts as an important factor of synovial joints, involving ECM extracellular matrix and chondrocytes and type II collagen and glycosaminoglycans (GAGs). The hyperplastic synovium leads to the foremost injury to the cartilage in RA over adhesion and invasion. In contrast, the inflammatory signals, with those free from the ECM, can further rise FLS activity. Factors such as matrix metalloproteases (MMPS), thrombospondin type 1 motifs 4 and 5 and cathepsins and a disintegrin-like metalloprotease act as the mediators of cartilage.[37]

Bone erosion:

Bone loss is a pathological symbol of RA and displays as periarticular, localized and systemic bone loss. The bone loss is due to the initiation of osteoclastic activity and suppression of osteoblasts. The loss of periarticular bone denotes to cellular variations of subchondral bone marrow, such as differentiation of osteoclast and the establishment of inflammatory infiltrates. It remains debatable as to whether autoimmunity or inflammation is the crucial factor for bone loss. As known inflammatory theory: tumor necrosis factor-alpha (TNF-α), IL-6, IL-1β, IL-17 and other inflammatory cytokines elaborate in RA, it could employ pro-osteoclastogenic effects and defeat bone formation in suitable environment via satisfactory signals, such as M-CSF and receptor activator of nuclear factor kappa-B ligand (RANKL).[38] They encourage differentiation and influx of the monocytes into osteoclasts in background of inflammation, whereas anti-inflammation treatments for RA grab hold of advance of bone mutilation and vice versa.[39,40]

The second likely trail for bone loss in RA includes 2 mechanisms for autoimmunity that turn as an activating factor for structural bone damage. The 2nd is the establishment of anti-citrullinated vimentin antibodies contrary to the most citrullinated protein, creating osteoclasts the ideal antigenic targets for anti-citrullinated protein antibodies (ACPA). It is stated that

ACPA binding to osteoclast precursors encourages osteoclast genesis, bone loss and resorption.[40] Bone resorption practically produces a shack, which is typically seen at spots where synovial membrane enclosures into periosteum, which is known as a bare area. Subchondral bone plays an important role in sustaining the homeostasis of bulk-bearing joints and the devastation of the subchondral bone can in due course result in the disintegration of the articular cartilage.[41,42]

b) Clinical presentation

With RA, there are times when symptoms get worse, known as flares and times when symptoms get better, known as remission.[43]

Signs and symptoms of RA include:

- Pain or throbbing in more than one joint.
- Swelling and tenderness of more than one joint.
- Similar symptoms persist on both limbs as both knees and both the hands.
- Loss of Weight.
- Fever.
- Exhaustion or tiredness.
- Weakness.

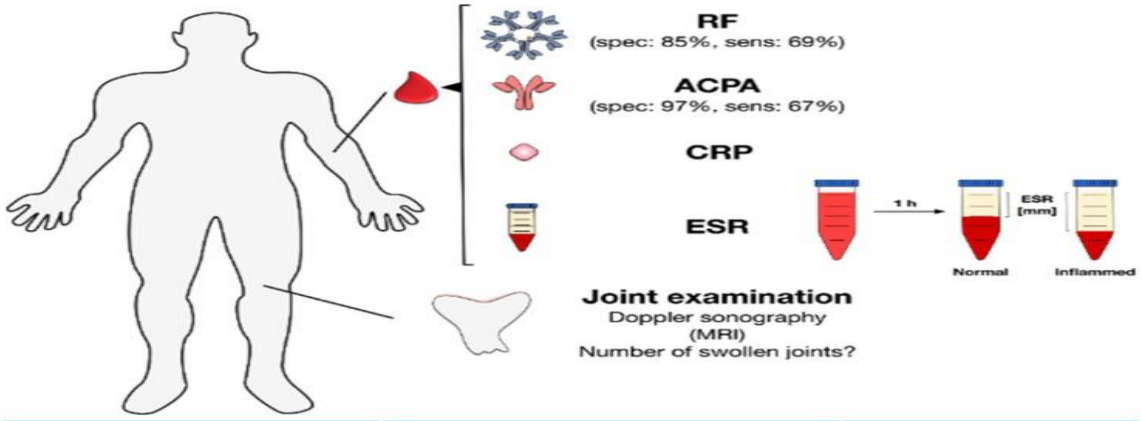
c) Diagnosis

EULAR (European League Against Rheumatism) Criteria for the Diagnosis of RA:

Depending on the size and number of joints involved, 2010 EULAR graded with 0–5 points (requiring the attendance of at least 1 clinically swollen joint), up to 3 points are given reliant on the incidence and concentration of RF and ACPAs autoantibodies and 1 point each for the existence of atypical levels of CRP and amplified ESR along with the overall duration of

disease symptoms. This classification permits for an all-out disease score of 10 points. Further RA diagnosis is made if

1) The complete score of the patient is >6.
2) Further causes for synovitis (e.g., infections, other inflammatory arthritic conditions, or trauma) can be excluded. Overall, the sensitivity of the 2010 EULAR criteria was reported to be 82% with a specificity of 61%.[44]



Criteria		Points
Joint involvement:	1 large 2 – 10 large 1 – 3 small 4 – 10 small > 10 (at least 1 small)	**0** **1** **2** **3** **5**
Serology:	Negative RF and ACPA Low positive RF/ACPA High positive RF/ACPA	**0** **2** **3**
Acute phase reactants:	Normal CRP/ESR Abnormal CRP/ESR	**0** **1**
Symptom duration:	< 6 weeks > 6 weeks	**0** **1**
		∑ = overall score

Figure 5: Clinical parameters commonly used in the finding of RA and their quantification using the 2010 ACR-EULAR (American College of Rheumatology-European League against Rheumatism) classification criteria. Clinical diagnosis (left) of RA depends on joint examination (chiefly via sonography, but also by MRI) and the serological purpose of RA-specific autoantibodies (Rheumatoid factor (RF) and ACPAs) and recognition of elevated levels of C-reactive protein (CRP) and an increased erythrocyte sedimentation rate (ESR). The 2010 ACR-EULAR RA classification criteria (right). Scoring parameters are the number

and size of the affected joints, the occurrence and concentration of RA-specific ACPAs and RF autoantibodies, the existence of atypical levels of CRP and augmented ESR and complete duration of disease symptoms. According to the 2010 ACR-EULAR RA classification criteria, a RA diagnosis is made if the overall score is >6 than six and other reasons for synovitis (see above) can be omitted.

d) Complications

- The peril of cardiovascular events. An increase in cytokines and activation of endothelial factors and unstable atheromatous plaques are the potential risking key elements in RA.
- In untreated RA presenting in an active state can have a risk of developing increased lipid, reduced total low-density and high-density cholesterol.[45]
- In lungs there can be fibrotic changes, further can affect exocrine glands leading to secondary Sjogren's syndrome;
- RA in skeletal muscles may lead to sarcopenia and the bones leading to osteoporosis.
- Lastly, RA subjects may pose danger for developing cancer especially kidney and hematologic cancers.[46]

e) Management

In a subject with otherwise unsolved new-onset polyarthritis, an imperative referral to a rheumatologist is thus compulsory to confirm RA diagnosis. Early initiation of a DMARDs-based treatment plan should be aimed to remit the disease and prevent deformity due to disease. Anti-inflammatory drugs and oral corticosteroids are of great use in patients with RA as it can contribute to the modification of disease. Additionally, RA patients should be subjected to symptomatic treatment.

1. Carpal Tunnel Syndrome -CTS

a) Definition

b) Anatomy of carpal tunnel with focus on median nerve, Epidemiology, Etiology, pathophysiology,

ANATOMY:

Carpal Tunnel (CT) is composed of bony canal, which contains carpal bones, roof of which is fibrous but rigid transverse carpal ligament. CT contains median nerve and nine flexor tendons, which enters tunnel. Sensory branches of the median nerve supply 3 radial digits and radial half of the fourth digit - hence this is the reason why carpal tunnel syndrome (CTS) symptoms are felt in these fingers. The palmar sensory cutaneous branch of median nerve supplies cutaneous skin of palm and arises on average, 6 cm proximal to the transverse carpal ligament (TLC).[47]

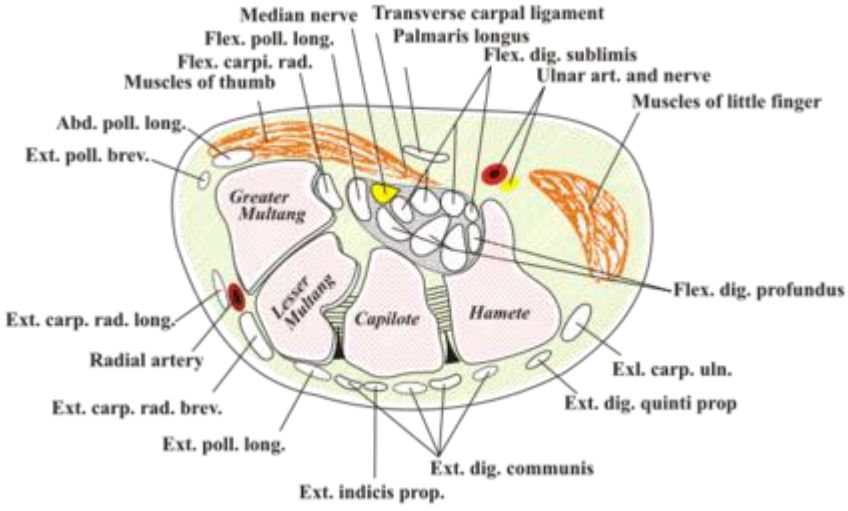


Figure 6: Showing anatomy of carpal tunnel.

Epidemiology:

From a systematic analysis, in majority of the studies, the diagnosis of CTS is based on a combination of symptoms (tingling sensation, paranesthesia, pain at the site of innervation of

median nerve), signs (+ve Tinel's or Phalen test) and electrophysiological findings.[48] The precise diagnostic criteria and definition of CTS used across the studies were quite diverse. Hammer et al. demarcated CTS grounded on a palm-to-wrist median sensory nerve action potential (SNAP) onset latency of >2.0 ms or absence of SNAP and median distal motor latency of >4.9 ms whereas Sim et al.[49] defined CTS "as a palm to wrist median nerve latency of less than 50%. The occurrence of CTS in RA extended from 3.5% to 22.8%.[50,51] Pooled data from the systematic analysis with an arbitrary selection of RA patients exposed that 86/1561 (5.5%) subjects had CTS. Subclinical CTS, on other hand, had a pooled occurrence of 14.0% (30/215).[52]

Pathophysiology of CTS:

Traction and compression are the 2 main mechanisms involved in entrapment neuropathy. This mechanism can lead to various disorders in the intraneural microcirculation, alterations in the connective tissue and lesion in the axon and myelin sheath. Entrapment of nerve can be caused by the narrowing of the compartment from which it passes through leading to deformation within the nerve and its function within the site and far beyond the site compression.[53] CTS is the classic example for this, as median nerve gets entrapped due to compression in the tunnel. There are several mechanisms which contribute to an increase in pressure within tunnel.

Increased carpal tunnel pressure:

From an anatomy point of view there exist two sites of nerve compression:

1) At proximal edge of carpal tunnel, instigated by wrist flexion as well due to the alteration in thickness and rigidity between the antebrachial fascia and the proximal portion of flexor retinaculum.

2) At the slenderest portion at the hook of the hamate. The carpal tunnel has recorded a

normal range of pressure which is 2 to 10 mm Hg. Few variation in the pressure is noticed with wrist movement, its extension lead to 8 fold rise and extension lead to increasing in 10 fold.[54] the fluid pressure of carpal tunnel when the wrist is at rest is 32 mm Hg. Wrist flexion can cause the pressure to reach 94 mm Hg. Any abnormality in the surrounding tissues of the nerve can affect the flexibility of CT (connective tissue) which form the basis for the increase in pressure. Experimental studies have recommended a dose-response association between median nerve dysfunction and the extent and volume of carpal tunnel compression.[55] From the experimental studies it is learnt that increased pressure of carpal tunnel could be due to ischemia caused by the firmness of the median nerve and vice versa.[56] Seiler et al. used laser Doppler to demonstrate the refurbishment of normal pulsatile blood flow within the median nerve in one minute of transverse carpal ligament release.[57] In cases of idiopathic CTS the increase in pressure in the tunnels could be attributed to many factors such as redeployment of the upper limb fluids in a flat position; absence of muscle pump mechanism that backs to the drainage of interstitial fluid in the tunnel; propensity to place the wrist in flexion thereby growing intracanalicular pressure; amplified blood pressure in the 2nd half of the night; and decrease of cortisol level.[58]

Median nerve microcirculation injury:

Ischemic vascular injury and the cessation in the blood-nerve barrier have also been recognized as a component in CTS. The blood-nerve barrier is shaped by the inner cells of the endothelium cells of endoneurial capillaries and perineurium that escort the median nerve over the carpal tunnel. These endoneurial microvessels are moulded from nutrient branches that arise from the ulnar and radial arteries, proximal to flexor retinaculum.[59] A rise in pressure inside the tunnel can lead to a collapse of vasculature within this barrier, causing an accretion of proteins and inflammatory cells. This may encourage a minute closed section syndrome by growing the absorbency, contributing to augmented pressure in the endoneurium

and advance of intra-fascicular edema. Subjects with vascular problems or protracted exposure to motionless loading are mainly are prone to a collapse in the blood-nerve-barrier.[60]

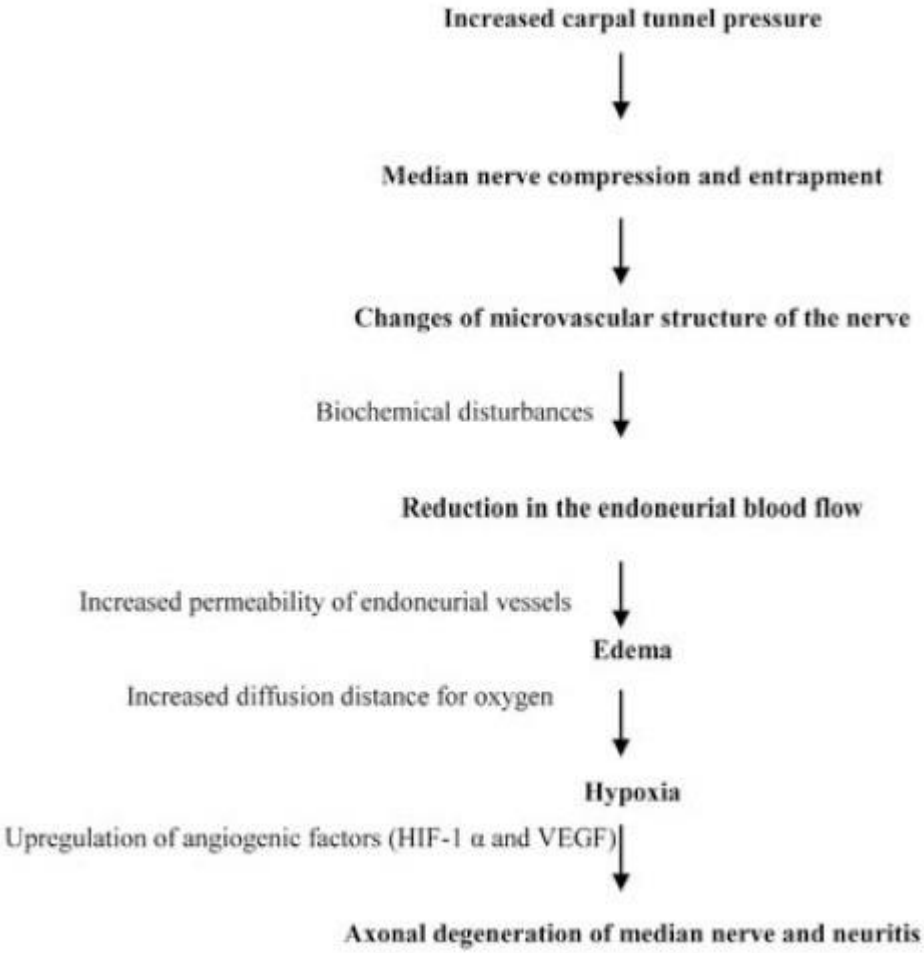


Figure 7: Represents diagram demonstration for the vascular mechanism of CTS and median nerve injury. VEGF - vascular endothelial grown factor, HIF-1α - hypoxia-inducible factor 1α.

Median nerve connective tissue alterations:

Nerve fibres have sheets of connective tissue neighboring it. These sheets are the mesomerism (excluding the peripheral nerve sheath), perineurium, epineurium and endoneurium. The extensibility of these layers is critical to nerve gliding (nerve gliding properties are due to the

integrity of epineurium only), which is necessary to accommodate joint motion; otherwise, nerves are stretched and become injured.[61] It is projected that in usual subjects, median nerve at wrist can move up to 9.6 mm between full flexion and extension of this joint but in presence of stiff surrounding connective tissue, this is limited and disclosures nerve to shearing forces that could lead to injury.[62]

The longitudinal drive of the median nerve in the carpal tunnel in flexion was 9.6 mm and in wrist extension, it was 0.7-1.4 cm. It can differ from 2.5 to 19.6 mm depending on the position of the shoulder, elbow, wrist and fingers. The median nerve tension fluctuates from 8% dependent on the site of the shoulder and 19% liable on the position of the digits. In total transverse movement and longitudinal movement of the median nerve ensures with wrist position or during finger flexion counter to resistance. In firmness and epineural adhesions, there is a hindrance in the mobility, generating lesions due to frequent traction on the nerve through wrist movements.

Lundborg and Dahlin, explained the mechanism and complexity involved in nerve traction and compression.[63] They also explained as to how a series of events set a rancorous cycle causing nerve injury. A long-standing increase in the pressure in the trunk of the nerve leads to a pressure gradient which reorganizes apparatuses of trampled tissue in the direction of the side not compressed, with the succeeding elongating of the vascular structures and epineurium. A quick advance of edema, chiefly in the epineurium causing nerve swelling, would more limit the movement of the nerve inside the previously narrowed anatomical section. This situation limits nerve sliding during actions of the extremes, further imperiling the nerve to extra irritation, amplified pressure on the nerve trunk and edema, opening a vicious cycle.[63]

Synovial tissue hypertrophy:

Hypertrophy of the synovial tissue of the flexor tendons can also upsurge the pressure in the carpal tunnel and result in the progress of CTS.[64] Several histological and biochemical studies have reported tenosynovitis as a closely related risk factor to the advance of idiopathic CTS.[65,66] This has been established by the presence of increased expression of prostaglandin E2 and VEGF in synovial biopsy tissue from patients with symptomatic CTS.[67] In retort to this injury, there is a rise in fibroblast density, collagen fiber size, vascular proliferation and type III collagen in the synovial connective tissue.[68]

Constrictive tissue scar would be formed around the median nerve, which in turn can result in tethering of the nerve.[69] The inflammatory thickening of synovial tissue rises volume of tissue which in turn increases fluid pressure within carpal tunnel. The most reflective thickening of synovial tissue has been stated to be at the entering and departure regions of the canal where the tendons slide over a fulcrum of the flexor retinaculum. Strain and micro-damage to synovial tissue as well as median nerve can happen due to the diverse degrees of excursion between flexor tendons and median nerve.[70] These structural changes are aggravated by diabetes mellitus. As non-enzymatic glycosylation of collagen is increased in diabetes, resulting in the alteration of packing, cross-linkage and turnover of collagen. Augmented glycosylation unfavorably affects collagen degradation, resulting in the accumulation of less compliant connective tissue and ultimately fibrosis.[71] An upsurge in lysyl oxidase activity, an enzyme involved in collagen cross-link creation that adds to the fibrosis and stiffness, has also been recommended to play a role.[72] This may lead to an upsurge in the intra-compartmental pressure and restrict the peripheral nerve gliding movement between tissues.

Also, dual crush syndrome was described by Upton and McComas, who primarily proposed that focal compression of an axon often occurs at more than one level. They assumed that

nonsymptomatic impairment of axoplasmic flow at more than one site along a nerve might summate to cause symptomatic neuropathy. This was proposed by clinical observation that the majority of patients had a median neuropathy associated with evidence of cervicothoracic root lesions. Other researchers have since reported a series of patients supporting the frequent association of a proximal and distal nerve compression syndrome, including CTS associated with cervical radiculopathy, brachial plexus compression and diabetic neuropathy.[73] MacKinnon and Dellon have also expanded the description of this syndrome to include a) Multiple anatomic regions along a peripheral nerve, b) Multiple anatomic structures across a peripheral nerve within an anatomic region, c) Superimposed on a neuropathy and d) Combinations of the above.[74]

2. Ultrasound elastography (USE)

It is an imaging technology related to tissue stiffness that was first introduced in the 1990s. It has been more developed and sophisticated in recent years to permit quantitative valuations of tissue stiffness. Elastography methods take benefit of altered elasticity of soft tissues ensuing from specific physiological or pathological processes. For example, many solid tumors are known to fluctuate automatically from neighboring healthy tissues. Likewise, fibrosis-related with chronic liver diseases leads the liver to become firmer than normal tissues. Hence Elastography methods help in discriminating pathology from normal tissue and can aid in diagnostic purpose.[75]

B-mode ultrasound (US) has benefit of being low-priced, adaptable and can be easily accessible at the bedside and also seen in USE. In recent years USE is seen to be explored in many clinical conditions and also used as a routine screening aid especially in liver fibrosis and assessing breast lesions. The utilization of elasticity in USE gives corresponding evidence to the conventional US by totaling stiffness as another quantifiable property to existing US

imaging techniques.[76]

Elastography and Real-Time Elastography (Principles and Techniques of Ultrasound Elastography)

Historic background:

Assessing the stiffness of tissues using ultrasound evolved from tissue motion studies which were performed in the 1980s in England. Around 1988, a system that utilized colour Doppler to track the movement of the tissue and produce tissue stiffness-based images was created by the researchers at the University of Rochester. Elastography was introduced after 1990 and came into the clinical setting in 1997. Sono-elasticity had the ability to determine the stiffness of lesions present in various organs as dark areas with a green background of moving tissue. In vibrational Doppler imaging, the lesion is seen dark against a background of tissue that's vibrating. However, with this technique, the image that is obtained is of relatively low resolution and required an inconvenient external vibratory device that induces motion within the tissue.[77]

Local shear wave velocity and stiffness of the tissues can be assessed by using a newer application of a second vibration that operates at a different frequency and is seen producing a shifting interference pattern.[78]

Elastography is the first successful method of imaging the elasticity of tissue. It is known as strain elastography reported in 1991 by Cespedes and Ophir. This is an imaging modality where the local tissue strains are calculated directly in strain ratio/Young Modulus or indirectly in shear wave velocity following the application of external stress either static or dynamic used to compress or perturb the tissue.[77]

The following explains the USE physics and existing techniques.

Ultrasound elastography physics:

Elastography evaluates tissue elasticity that is the propensity of tissue to battle distortion with a functional force, or to recommence its novel shape after elimination of the force. Pretentious that material is completely elastic and its distortion has not any time dependence (i.e., viscosity), elasticity can be labelled by Hooke's Law.

$$\sigma=\Gamma\cdot\varepsilon \quad \text{(eqn.1)}$$

where strain (ε) is expansion per unit length which is dimensionless(second row), stress (σ) is force per unit area with units kilopascals (i.e. N/m^2) (top row), and elastic modulus (Γ) relates stress to strain with units kilopascal.[79]

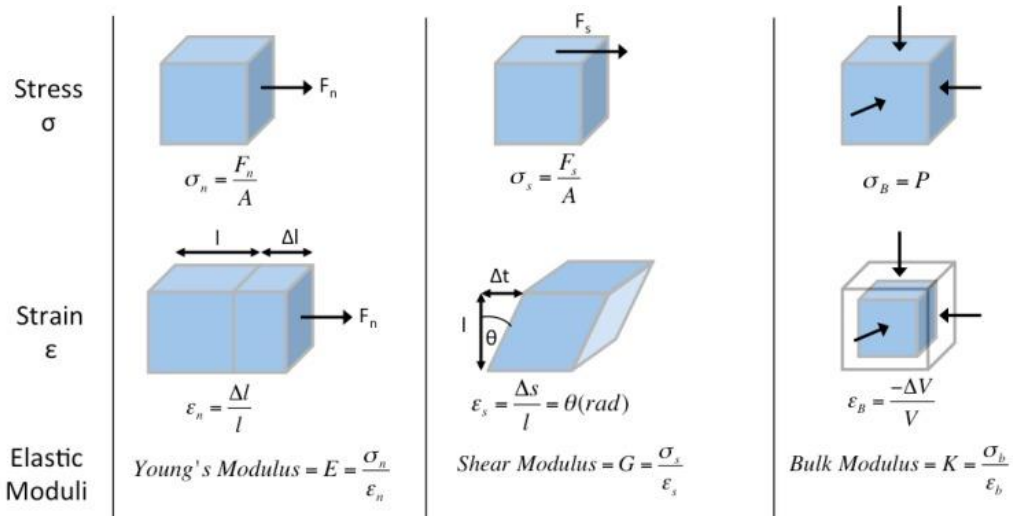


Figure 8: Ultrasound elastography physics, deformation models. Static distortions of entirely elastic materials can be described by stress σ (force per unit area, top row), strain ε (expansion per unit length, middle row) and elastic modulus Γ (stress divided by strain, bottom row). This is applied to regular (upright to the surface, first column), shear (tangential to surface, second column) and bulk (normal inward or pressure, third column) forces used in ultrasound elastography.

1) Strain imaging: In this method, a normal stress σ_n is applied to normal strain and tissue ε_n is measured; Equation 2 is used to deliver a qualitative appraisal of Young's modulus *E*.

Strain imaging:

Strain imaging was the first familiarized by USE technique and there are 2 methods for strain imaging using US: ARFI (acoustic radiation force impulse) and Strain imaging and Strain elastography (SE).[79, 80]

Technical Limitations of Ultrasound Elastography:

- Many procedural confounders are known to distress USE.
- Most of these confounders can be outlined back to all-purpose sonography limits such as reverberation, shadowing and clutter artefacts or the operative-reliant on nature of free-hand ultrasound systems.
- Likewise, tissue weakening declines ultrasound signal as a function of depth, limiting precise valuation of deeper tissue or organs.
- In subjects with obesity, the fluid and fat at subcutaneous can impede the spread of external stimuli from the surface of the skin, this can lead to improper measurement in such subjects.
- Parameters such as US frequency, gains and sampling rate can lead to the biased outcome if they are not standardized across subjects and time points in longitudinal applications. To add, the lack of regularity of viable system design and settings makes equating measurements from one manufacturer system to another a problematic task.[81]

Recent studies:

A prospective study by Smerilli, G et al. 2021 aimed to assess the sonographic spectrum of carpal tunnel syndrome (CTS) in subjects with rheumatoid arthritis (RA) and in subjects with idiopathic CTS. The study included 50 subjects with RA and 25 patients with idiopathic CTS. The prevalence of CTS among RA subjects was 26.3%. They found significant difference in CSA of median nerve in idiopathic CTS than in RA subjects +CTS (17.7 mm2 vs 10.6 mm2, $p < 0.01$). The study results found that mean CSA of the median nerve to be dominant in idiopathic CTS and median swelling in RA subjects with CTS.

A prospective study by Anno S et al. 2020 compared the CSA and strain ratio of median nerve in subjects with RA and without RA.[82] They involved 402 subjects, grouped in as RA and non- RA groups. This study results found an insignificant difference among the groups in CSA of median nerve but found a significant difference in strain ratio between the group.

A systematic review by Zakrzewski, J et al. 2019 aimed to evaluate the use of shear wave elastography (SWE) and strain elastography (SE) of peripheral nerves in subjects with neuropathy of several aetiologies.[83] This analysis found US elastography to be extremely useful and precise in the diagnosis of several types of peripheral neuropathies especially CTS and even helped in the staging of the disease.

A study by Roghani R. et al. 2018 aimed to assess the diagnostic accuracy of US in subjects with CTS among the older population.[84] They involved 103 subjects. The study results suggested the use of the US as an effective tool in diagnosing CTS as the US has good sensitivity and specificity.

A study by Cingoz M. et al. 2018 aimed to assess the use of diffusion tensor imaging and

shear wave elastography in subjects with CTS.[85] They involved 77 wrists in which normal were 18, mild was 35, moderate to severe were 9 and severe CTS was in 15 wrists. RTE measurements were performed for the median nerve at 3 levels: carpal tunnel inlet, carpal tunnel outlet and mid carpal tunnel. They found that subjects with CTS had greater elasticity of median nerve compared to the controls. Further, the moderate to severe CTS found to have greater elasticity values compared to mild CTS. Subjects with CTS had lesser fractional anisotropy at the mid- carpal than the controls. Subjects with moderate to severe CTS also found lesser fractional anisotropy and greater apparent diffusion values compared to the mild cases of CTS.

A systematic analysis by Sakthiswary R. et al. 2017 assessed the incidence of CTS among RA subjects and further analyzed the median nerve in RA through sonoelastography. They analyzed 13 studies where they found an incidence of CTS to be 5.5%, subclinical CTS in 14%. From the cross-sectional studies, they found that the mean CSA in RA patients without RA be similar between the cases and controls. However, 8 studies found no such association.

A case-control study by Okano T et al. 2016 aimed to see the difference in the elasticity of median nerve among RA subjects without CTS and with CTS.[86] They involved 340 hands in 177 subjects with RA and 158 hands in 81 as controls. There no significant results in the CSA of the median nerve at the entrance of the carpal tunnel and near the tunnel in either group. However, the strain ratio was significantly greater in RA subjects with CTS compared to controls. These results recommend that inflammation of the flexor tendon and wrist joint may generate fibrotic change for the median nerve.

A study by Miyamoto H, et al. 2013 aimed to see any difference in the stiffness of TCL (transverse carpal ligament) among the healthy population and CTS subjects using sonoelastography.[87] They involved 17 controls (healthy) and 13 subjects with CTS. The

strain ratio had a positive association with symptoms (duration) among the CTS subjects. The results also recommended that greater stiffness of the TCL may be one of the reasons for CTS.

A case control study by Sulaiman, M et al. 2012 aimed to evaluate the electromyographic function aberrations and peripheral nerve conduction and in subjects with rheumatoid arthritis. Hundred normal subjects as controls and 100 subjects with RA were included in this study. They found 54% with peripheral neuropathy and mononeuritis simplex to be the most frequent lesion (66.6%). Among the patients with entrapment neuropathy 46.74%, the median nerve was the most common (24.07%), to be effected followed by 14.81% in posterior tibial and 7.40% in the ulnar nerve. The results concluded with the presence of myogenic lesions with none of them present in the RA subjects.

A study by Hammer, H et al. 2007 demonstrated, Ultrasonography (US) showed augmented CSA of the median nerve in CTS.[88] The authors further aimed to study the distribution of cross- sectional areas of the median nerve in subjects with RA. They involved 154 subjects with RA. The mean CSA of the median nerve in subjects with RA was the same as to those of healthy controls. But, yet 10% of the subjects had values that overlay with areas commonly reported in patients with mild idiopathic CTS.

LACUNAE IN LITERATURE:

RA is an autoimmune disease and causes inflammatory synovial propagation of the joint and tenosynovitis. Though inflammation of the wrist joint and synovial tissue of the flexor tendons can cause augmented compression in the carpal tunnel, there is a likelihood that even RA patients lacking symptoms of CTS can also have median nerve involvement because of the synovial proliferation and inflammation.[90] The majority of the studies have extensively

studied the sonoelastography of the median nerve in RA subjects who already have had established CTS. However, early changes of the median nerve before progressing into the CTS are what a concern is. Hence early changes which can be noticed and appreciated in advanced sonoelastographic methods can help the clinician to diagnose and prevent the severity of the disease course.

MATERIAL & METHODS

MATERIAL AND METHODS:

Study setting: The study was conducted in the Department of Radio-Diagnosis at" R.L. Jalappa Hospital and Research Center attached to Sri Devaraj Urs Medical College, Tamaka Kolar.

Study population: Patients were grouped into 2 groups Cohort A and Cohort B.

Cohort A(Cases): Patients with RA without CTS.

Cohort B(Controls): Age and gender-matched patients without RA undergoing ultrasound for causes unrelated to RA or CTS.

Study design: Hospital-based prospective study was conducted over a period of eighteen months from January 2020 to July 2021.

Study duration: The data collection for the study was done between to over an 18 months period.

Sample size:

Sample size estimated by using the proportion of subjects with RA without symptoms CTS and patients without rheumatoid arthritis assessed by sonoelastography from the study by Anno S, et al.[82]

Required sample size per group = 51

In our study, 56 study subjects per group were included.

Inclusion criteria for cohort A:

All patients diagnosed with rheumatoid arthritis.

Exclusion criteria for Cohort A:

Subjects with RA and exhibited symptoms of carpal tunnel syndrome.

Patients with CTS symptoms are excluded by clinical evaluation that included Phalen's test, a manual muscle test of the abductor pollicis brevis muscle and a search for Tinel-like signs and thenar muscle atrophy.

Inclusion criteria for Cohort B:

Age and gender-matched subjects without rheumatoid arthritis undergoing ultrasound for causes unrelated to rheumatoid arthritis or carpal tunnel syndrome.

Exclusion criteria for Cohort B:

Subjects with RA or carpal tunnel syndrome.

Sampling method: All the study subjects were recruited consecutively till the sample size was reached.

Methodology:

A study was conducted on individuals who are diagnosed with RA without symptoms of carpal tunnel syndrome and also on individuals who are referred for ultrasonography other than RA or CTS to the Department of Radio Diagnosis at R.L. Jalappa Hospital attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

A total of 112 patients were included in the study. Baseline data was collected from the patient with pertinent clinical history and relevant lab investigation reports and were included in the study if they met inclusion criteria.

Each subject was asked to lie on the examination bed with his or her elbow extended and the hand supinated. Fingers were kept relaxed and slight flexion of the wrist was kept during the measurements.

B mode ultrasonography was done first and CSA of the nerve is noted, trailed by elastography of median nerve is done by using a 5–12 MHz linear array transducer (PHILIPS EPIQ 5G Ultrasound Machine).

Elastography values were calculated between any two areas as the index of elasticity. The region of interest box is placed over the whole cross-sectional area of the median nerve (average strain represented as B), with the adjacent tissue at the acoustic coupler (average strain represented as A) used as the reference. The elasticity of the median nerve is assessed as the B/A strain ratio in a transverse plane at the identical point with B-mode imaging.

Comparison of strain ratio of the median nerve in a transverse plane at the carpal tunnel inlet in the rheumatoid arthritis group without symptoms of CTS and the non-RA group.

Real time elastography (RTE) was performed and the color code, which ranged from red (soft) to blue (hard), indicates the relative stiffness of the tissues within the region of interest (green and yellow indicates medium elasticity) in noted down.

Figure 9: PHILIPS EPIQ 5G Ultrasound Machine

ETHICAL CONSIDERATIONS: The study was started after obtaining ethical clearance from institutional ethical committee meeting. Informed written consent was obtained from all the participants after providing detailed information on the objectives of the study, risks and benefits involved and the voluntary nature of participation. The confidentiality of the study participants was maintained throughout the study.

STATISTICAL METHODS:

Rheumatoid arthritis factor was considered as the primary outcome variable. Study group (cases/control group) considered as Primary explanatory variable. Age, gender, right side and left side were considered as other study relevant variables. Descriptive statistics were used to analyze data in accordance with the study's objectives. Data was also represented using appropriate diagrams like Error bar diagram, bar diagram, staked bar diagram and box plots. All Quantitative variables were checked for normal distribution. Continuous variables were analyzed by independent-sample T-tests and expressed as the mean and standard deviation. The count variables were analyzed by the Chi-square expressing as a number. For non-normally-distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Mann Whitney u test (2 groups). P value < 0.05 was considered statistically significant. CoGuide was used for statistical analysis**.**

Note: Elastography color code is blue in all cases and controls, as the nerve is generally stiff as compared to surrounding soft tissue.

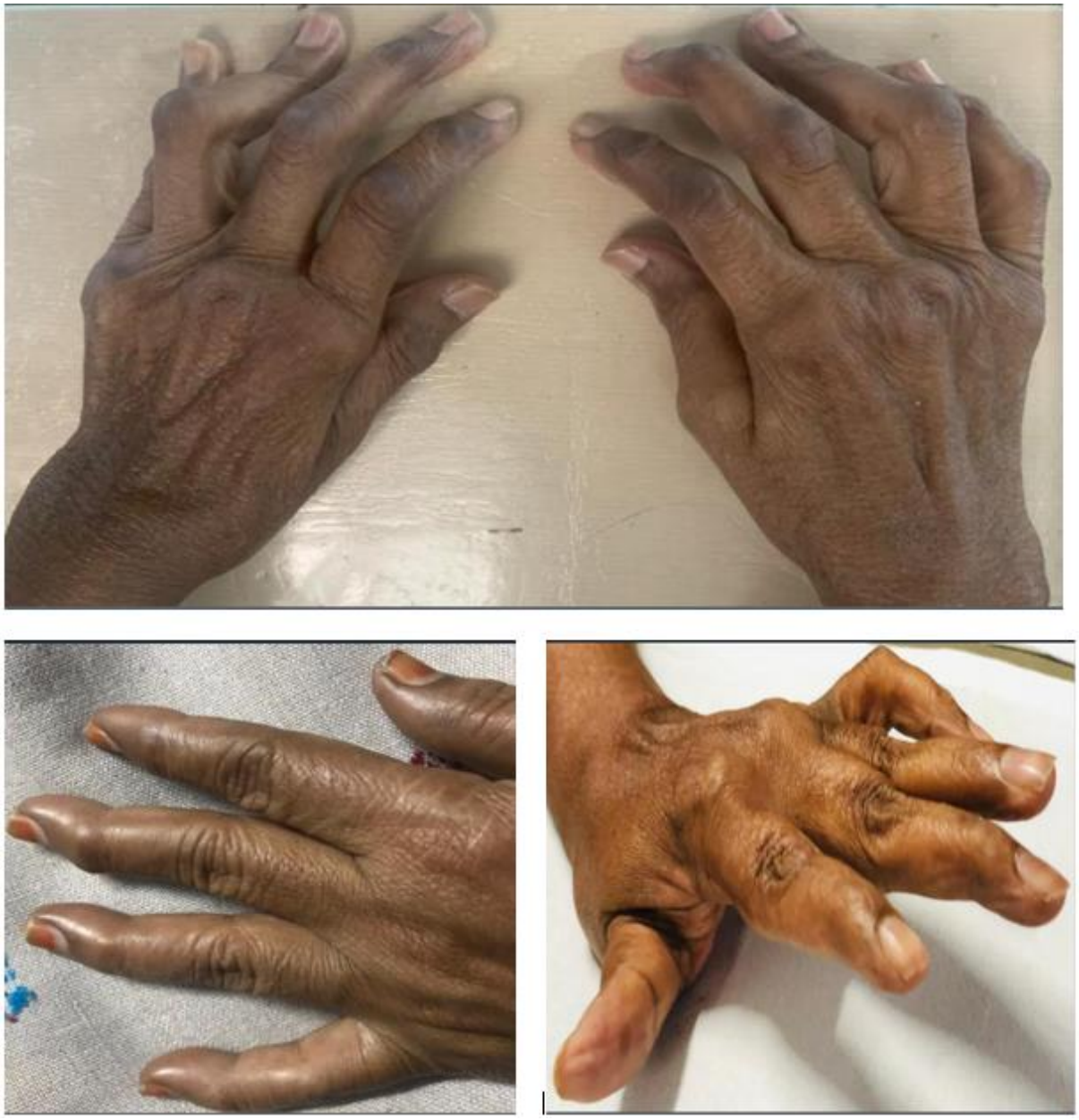


Figure 10: Images showing various deformities associated with rheumatoid arthritis – Swan neck deformity, boutonniere's deformity & Hitchhiker's thumb.

RESULTS

OBSERVATIONALS & RESULTS

A total of 112 subjects were include in the final analysis, 56 (50%) were cases group and 56 (50%) were control groups.

Table 1: Comparison of mean age between study group (N=112)

Parameter	Study group		P value
	Cases (N=56)	Controls (N=56)	
Age	48.5 ± 13.31	48.02 ± 13.41	0.849

Out of the study population, the mean age was 48.5 ± 13.31 years in the cases group and it was 48.02 ± 13.41 years in the control group. The difference in mean age between the cases and controls was statistically not significant (P Value 0.849). (Table 1 & Figure 11)

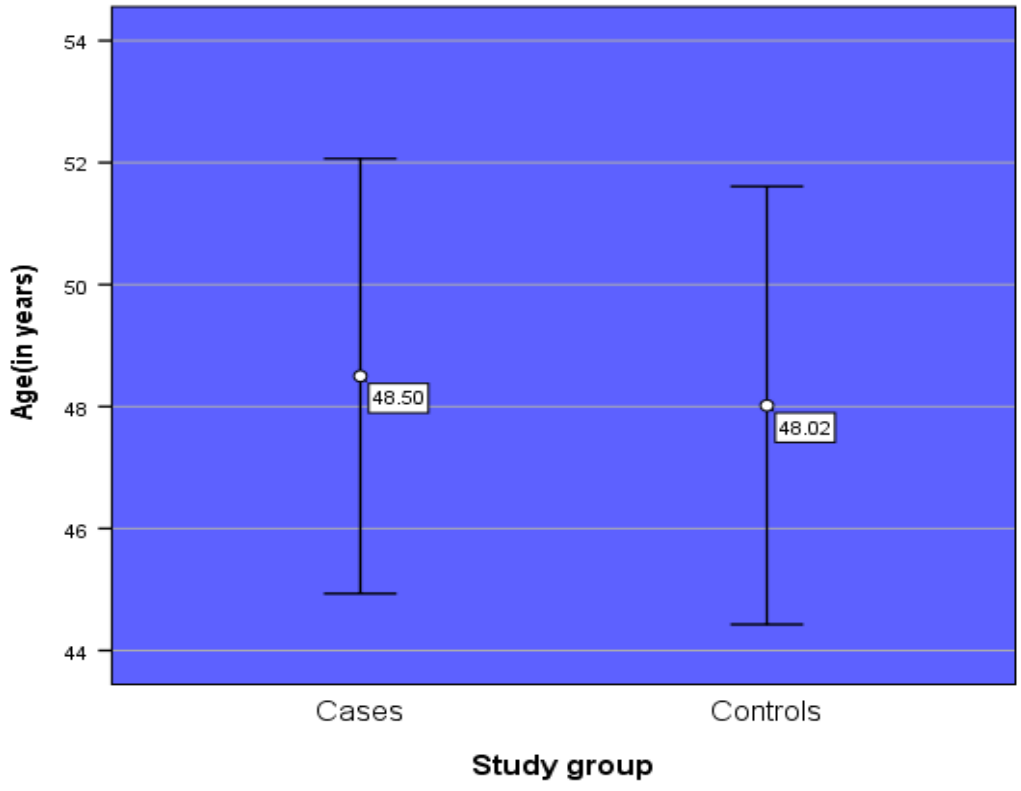


Figure 11: Error bar chart of comparison of mean age (in years) between study group (N=112)

Table 2: Comparison of gender between study group (N=112)

Gender	Study group		P value
	Cases (N=56)	Controls (N=56)	
Male	20 (35.71%)	20 (35.71%)	1.000
Female	36 (64.29%)	36 (64.29%)	

Out of 56 participants in the cases group, 20 (35.71%) participants were male and 36 (64.29%) participants were female. Out of 56 participants in the control group, 20 (35.71%) participants were male and 36 (64.29%) participants were female. The difference in the proportion of gender among the cases and controls was statistically insignificant (P Value 1.000). (Table 2 & Figure 12)

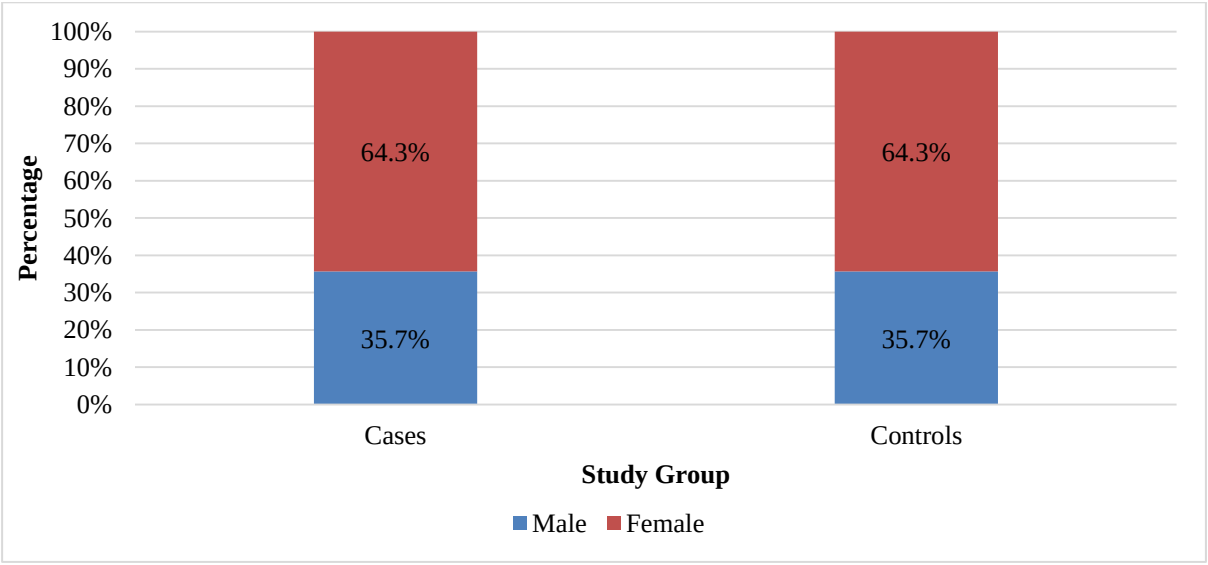


Figure 12: Staked bar chart of comparison of gender between study group (N=112)

Table 3: Comparison of median cross-sectional area (Cm^2) in study groups (N=112)

Right side	Study group		Mann Whitney U Test P value
	Cases (N=56) Median (IQR)	Controls (N=56) Median (IQR)	
Cross-sectional Area (Cm^2)	0.110 (0.105 to 0.116)	0.090 (0.083 to 0.095)	<0.001

The median cross-sectional area was 0.110 (cm^2) (IQR 0.105 to 0.116) in the cases group and it was 0.090 (cm^2) (IQR 0.083 to 0.095) in the control group. There was a statistically significant difference between cases and controls in the right-side cross-sectional area (Cm^2) (P< 0.001). (Table 3 & Figure 13)

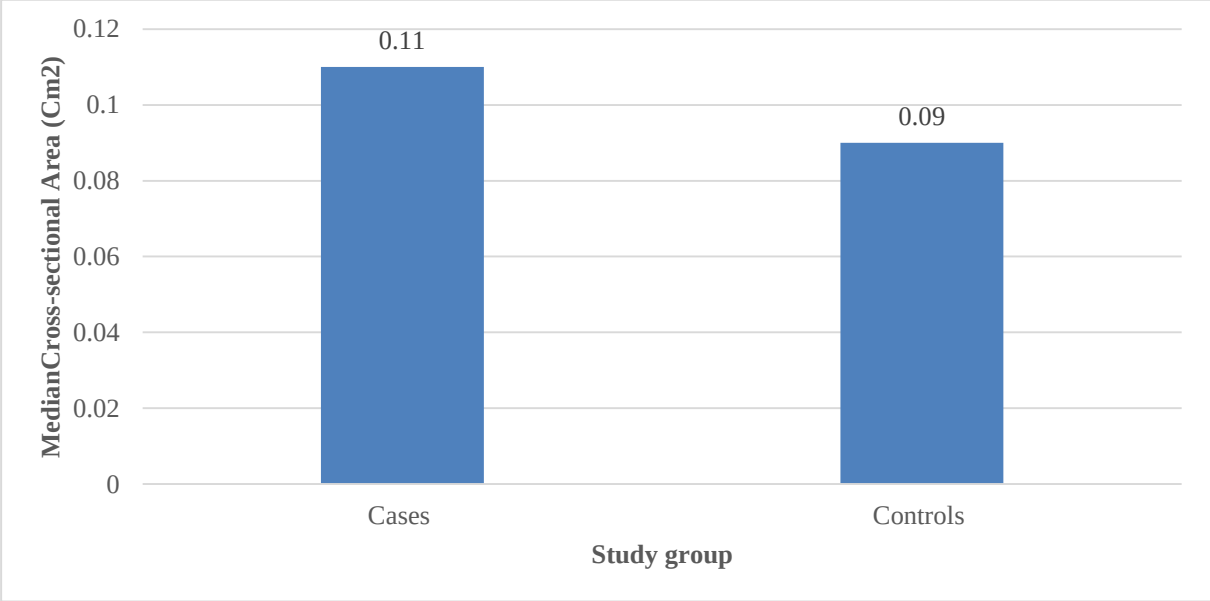
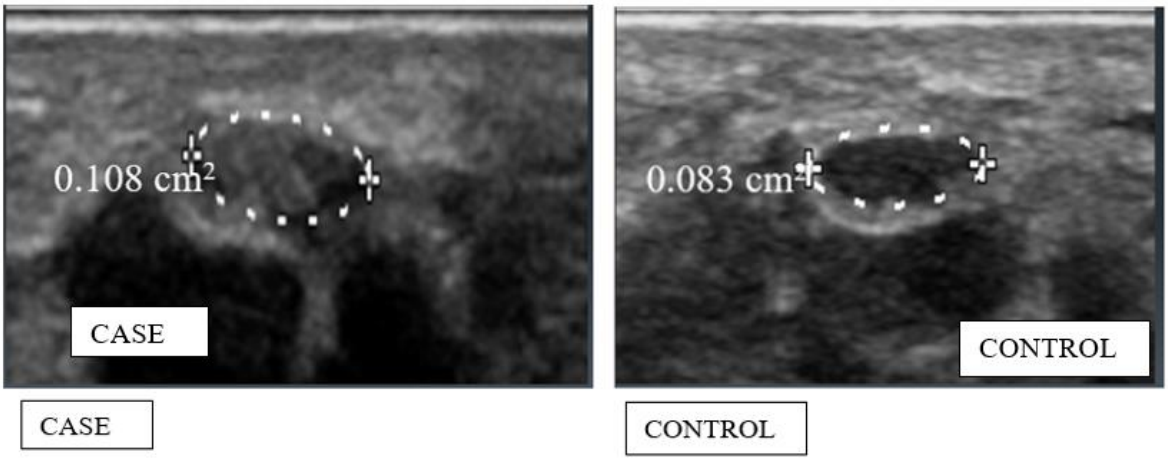


Figure 13: Bar chart of comparison of median cross-sectional area (Cm^2) between study group (N=112)



Ultrasound grey scale image showing cross-sectional area of median nerve in cases and controls at the level of carpal tunnel inlet.

Table 4: Comparison of median strain ratio in study groups (N=112)

Right side	Study group		Mann Whitney U Test P value
	Cases (N=56) Median (IQR)	Controls (N=56) Median (IQR)	
Strain Ratio	2.84 (2.41 to 2.98)	1.65 (1.41 to 1.94)	<0.001

The median right-side strain ratio was 2.84 (IQR 2.41 to 2.98) in the cases group and it was 1.65 (IQR 1.41 to 1.94) in the control group. There was significant variance between controls and cases in the right-side strain ratio (P< 0.001). (Table 4 & Figure 14)

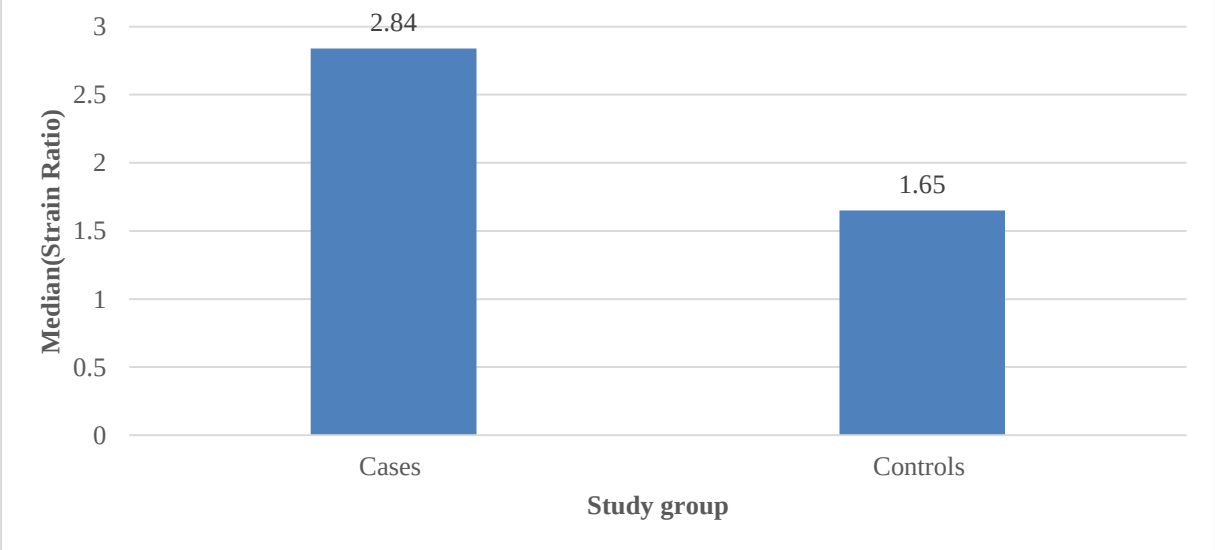


Figure 14: Bar chart of comparison of median strain ratio between study group (N=112)

Table 5: Comparison of median cross-sectional area (Cm^2) in study groups (N=112)

Left side	Study group		Mann Whitney U Test P value
	Cases (N=56) Median (IQR)	Controls (N=56) Median (IQR)	
Cross-sectional Area (Cm^2)	0.109 (0.104 to 0.116)	0.089 (0.082 to 0.093)	<0.001

The median left-side cross-sectional area was 0.109 (IQR 0.104 to 0.116) in the cases group and it was 0.089 (IQR 0.082 to 0.093) in the control group. There was a significant difference between controls and cases in the left side cross-sectional area (Cm^2) p value <0.001. (Table 5 & Figure 15)

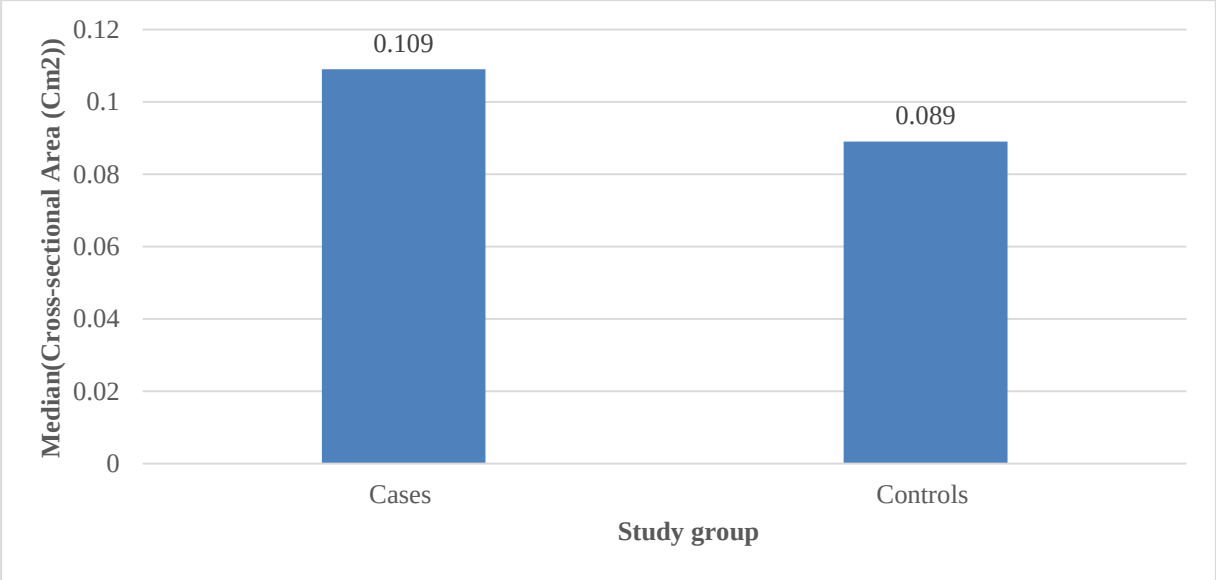
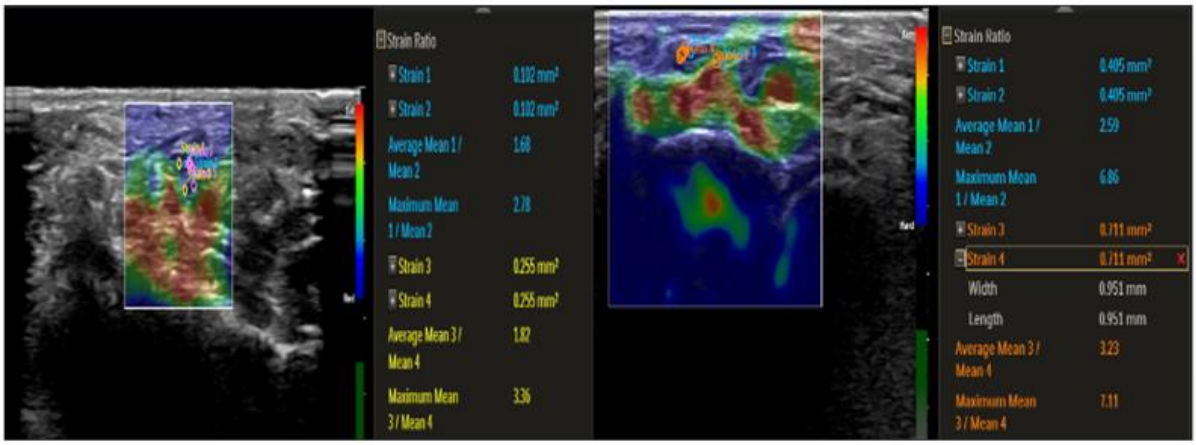


Figure 15: Bar chart of comparison of median cross-sectional area (Cm^2) between study group (N=112)

Table 6: Comparison of median strain ratio in study groups (N=112)

Left side	Study group		Mann Whitney U Test P value
	Cases (N=56)	Controls (N=56)	
Strain Ratio	2.76 (2.45 to 3.04)	1.66 (1.43 to 1.93)	<0.001

The median left-side strain ratio was 2.76 (IQR 2.45 to 3.04) in the cases group and it was 1.66 (IQR 1.43 to 1.93) in the control group. There was a significant difference between controls and cases in the left side strain ratio (P<0.001). (Table 6 & Figure 16)



Elastography image showing calculation of strain ratio in cases and controls.

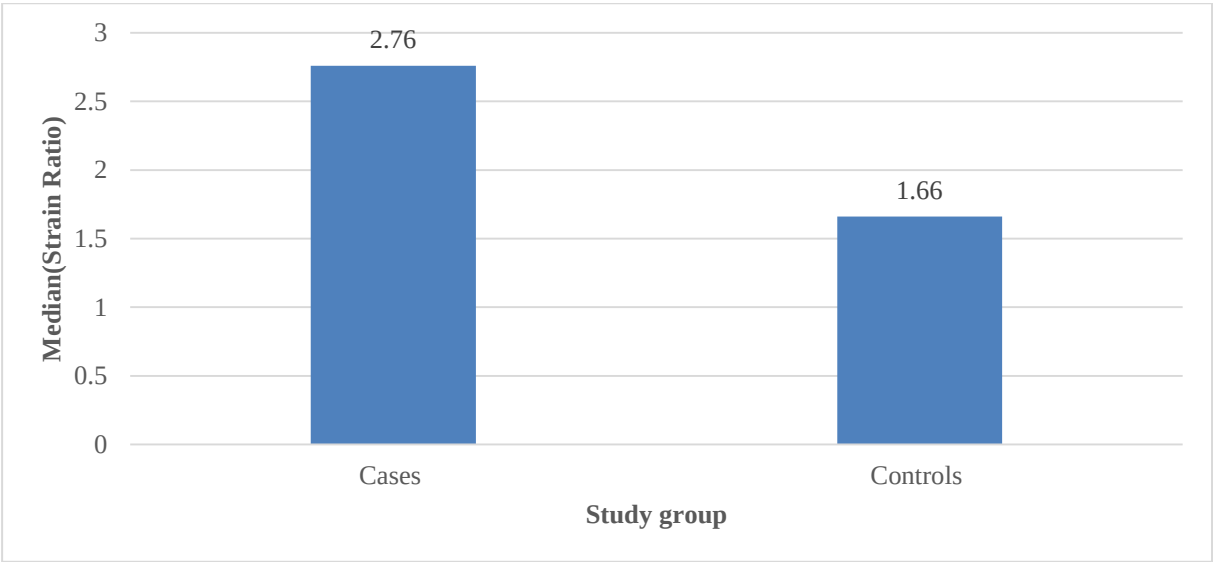


Figure 16: Bar chart of comparison of median strain ratio between study group (N=112)

Table 7: Comparison of rheumatoid arthritis factor between study group (N=112)

Rheumatoid arthritis factor	Study group		P value
	Cases (N=56)	Controls (N=56)	
Positive	56 (100%)	0 (0%)	*
Negative	0 (0%)	56 (100%)	

*No statistical test was applied- due to 0 subjects in the cells

Out of 56 participants with the cases group, 56 (100%) were reported with rheumatoid arthritis factor. Out of 56 participants with the control group, 56 (100%) were reported without rheumatoid arthritis factor. (Table 7 & Figure 17)

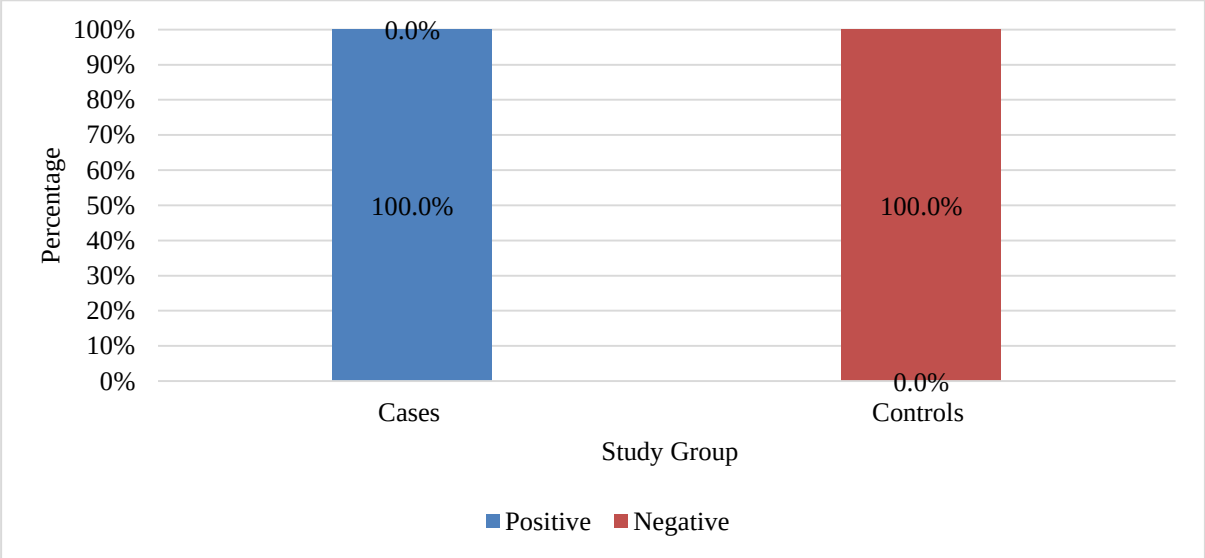


Figure 17: Staked bar chart of comparison of rheumatoid arthritis factor between study group (N=112)

Cases:

Table 8: Comparison of mean age between gender in cases (N=56)

Parameter	Gender		P value
	Male (N=20)	Female (N=36)	
Age	49.2 ± 14.82	48.11 ± 12.61	0.772

In cases, the mean age was 49.2 ± 14.82 years in male participants and it was 48.11 ± 12.61 years in female participants. There was an insignificant difference between the gender in age (years) (P value=0.772). (Table 8)

Table 9: Comparison of median right-side cross-sectional area and strain ratio between gender in cases (N=56)

Parameter	Gender		P value
	Male (N=20)	Female (N=36)	
Right side			
Cross-sectional Area (Cm2)	0.109 (0.104 to 0.119)	0.110 (0.105 to 0.116)	0.871
Strain Ratio	2.87 (2.58 to 3.07)	2.82 (2.40 to 2.98)	0.263

In cases with ride side, the median cross-sectional area was 0.109 (cm^2) (IQR 0.104 to 0.119) in male participants and it was 0.110 (cm^2) (IQR 0.105 to 0.116) in the control group and the median right-side strain ratio was 2.87 (IQR 2.58 to 3.07) in the cases group and it was 2.82 (IQR 2.40 to 2.98) in female participants. There was a statistically not significant difference between gender in right side cross-sectional area (Cm^2) (P value 0.871) and strain ratio (P value 0.263). (Table 9)

Table 10: Comparison of median left side cross-sectional area and strain ratio between gender in cases (N=56)

Parameter	Gender		P value
	Male (N=20)	Female (N=36)	
Left side			
Cross-sectional Area (Cm2)	0.109 (0.103 to 0.117)	0.109 (0.105 to 0.114)	0.851
Strain Ratio	2.63 (2.45 to 3.09)	2.80 (2.48 to 2.99)	0.784

In cases with left side, the median cross-sectional area was 0.109 (cm^2) (IQR 0.103 to 0.117) in male participants and it was 0.109 (cm^2) (IQR 0.105 to 0.114) in the control group and the median left-side strain ratio was 2.63 (IQR 2.45 to 3.09) in the cases group and it was 2.80 (IQR 2.48 to 2.99) in female participants. There was a significant difference between gender in the left side cross-sectional area (Cm^2) (p value 0.851) and strain ratio (P value 0.784). (Table 10)

Table 11: Comparison of rheumatoid arthritis factor between gender in cases (N=56)

Rheumatoid arthritis factor	Gender		P value
	Male (N=20)	Female (N=36)	
Negative	0(0%)	0(0%)	*
Positive	20(100%)	36(100%)	

*No statistical test was applied- due to 0 subjects in the cells

In cases, out of 20 males, 20 (100%) were reported with rheumatoid arthritis factor. Out of 36 females, 36 (100%) were reported with rheumatoid arthritis factor. (Table 11)

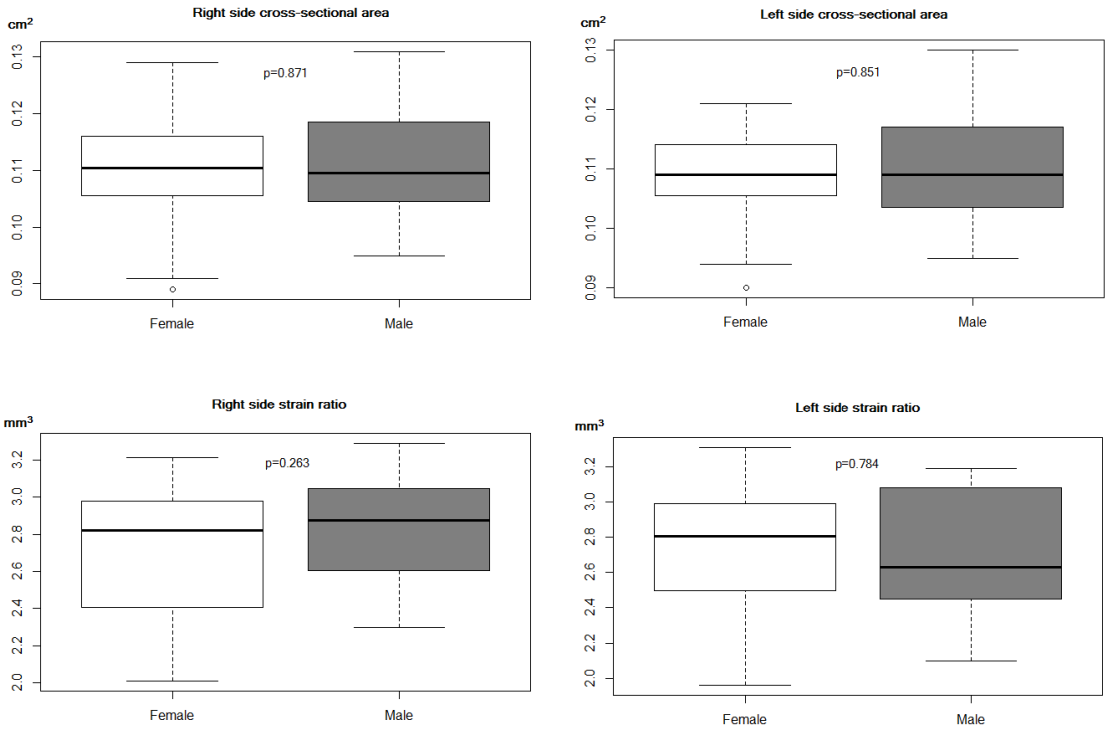


Figure 18: Box plots of comparison of right and left side cross-sectional area and strain ratio between gender in cases (N=56)

Controls:

Table 12: Comparison of mean age between gender in controls (N=56)

Parameter	Gender		P value
	Male (N=20)	Female (N=36)	
Age	48.2 ± 14.13	47.92 ± 13.2	0.940

In controls, the mean age was 48.2 ± 14.13 years in male participants and it was 47.92 ± 13.2 years in female participants. There was an insignificant difference between the gender in age (years) (P value=0.940). (Table 12)

Table 13: Comparison of median right-side cross-sectional area and strain ratio between gender in controls (N=56)

Parameter	Gender		P value
	Male (N=20)	Female (N=36)	
Right side			
Cross-sectional Area (Cm2)	0.089(0.083 to 0.095)	0.091(0.084 to 0.096)	0.493
Strain Ratio	1.61 (1.50 to 1.94)	1.69 (1.36 to 1.94)	0.681

In controls with ride side, the median cross-sectional area was 0.089 (cm^2) (IQR 0.083 to 0.095) in male participants and it was 0.091 (cm^2) (IQR 0.084 to 0.096) in the control group and the median right-side strain ratio was 1.61 (IQR 1.50 to 1.94) in the cases group and it was 1.69 (IQR 1.36 to 1.94) in female participants. There was an insignificant difference between gender in the right-side cross-sectional area (Cm2) (p value 0.493) and strain ratio (P value 0.681). (Table 13)

Table 14: Comparison of median left side cross-sectional area and strain ratio between gender in controls (N=56)

Parameter	Gender		P value
	Male (N=20)	Female (N=36)	
Left side			
Cross-sectional Area (Cm2)	0.086 (0.081 to 0.095)	0.089 (0.084 to 0.092)	0.771
Strain Ratio	1.73 (1.42 to 1.91)	1.63 (1.43 to 1.93)	0.857

In Controls with left side, the median cross-sectional area was 0.086 (cm^2) (IQR 0.081 to 0.095) in male participants and it was 0.089 (cm^2) (IQR 0.084 to 0.092) in the control group and the median right-side strain ratio was 1.73 (IQR 1.42 to 1.91) in the cases group and it was 1.63 (IQR 1.43 to 1.93) in female participants. There was an insignificant difference between gender in the left side cross-sectional area (Cm^2) (p value 0.771) and strain ratio (P value 0.857). (Table 14)

Table 15: Comparison of rheumatoid arthritis factor between gender in controls (N=56)

Rheumatoid arthritis factor	Gender		P value
	Male (N=20)	Female (N=36)	
Positive	0(0%)	0(0%)	*
Negative	20(100%)	36(100%)	

*No statistical test was applied- due to 0 subjects in the cells

Out of 20 males, 20 (100%) were reported without rheumatoid arthritis factor. Out of 36 females, 36 (100%) were reported without rheumatoid arthritis factor. (Table 15)

Controls:

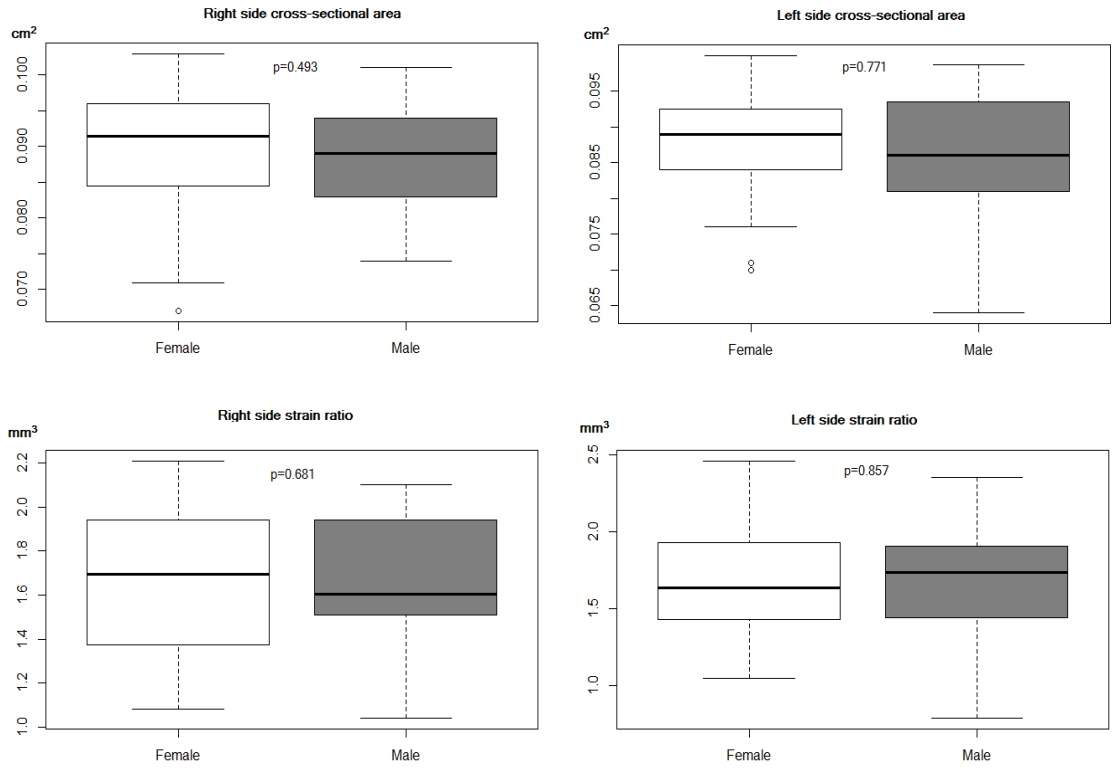


Figure 19: Box plots of comparison of right and left side cross-sectional area and strain ratio between gender in controls (N=56)

DISCUSSION

DISCUSSION:

Rheumatoid arthritis (RA) is one of most common etiology of CTS. Median nerve involvement is one of earliest signs to be detected in progression of RA to CTS. RA is an autoimmune disorder that leads to tenosynovitis and intra-articular synovitis. The inflammatory action can affect the nerves directly or indirectly. Hence there are probabilities that even RA subjects without CTS signs and can have subclinical median nerve changes due to the inflammatory process surrounding the median nerve. Real-time elastography is the best diagnostic tool in finding the early changes in the median nerve. This study aimed to assess the cross-sectional areas of the median nerve in patients with RA who have no symptoms or signs of CTS.

Our study analyzed 112 subjects with equal subjects (56 each) in cases and control group. The mean age in cases group was 48.5 ± 13.31years and in control group was 48.02 ± 13.41 years. The difference in mean age between cases and controls was statistically not significant. A case control study by Anno, S et al. involved 312 patients with 201 subjects with RA patients and 111 subjects with non-RA.[82] This study also had no significant difference in the mean age group as our study. Another similar study by Smerilli, G et al. found cases with RA patients with CTS (n=15) and controls as subjects without CTS(n=42).[52] The present study found both the groups prevalent with female gender (cases 64.29% vs controls 64.29%). The difference in proportion of gender between controls and cases was not statistically significant (P Value 1.000).

Table 16: Comparing the mean age and sample size across various studies to present study.

Studies	Cases (N)	Controls (N)	Age (mean) years	Gender prevalence %
Anno, S et al.	201	111	65.6±12.1- cases 68.7±13.2- controls	Female Cases -81.7 Controls-82.9
Smerilli, G et al.	15	42	59 ± 11- cases 55 ± 14- controls	Female – Cases 93.3 Controls-90.4
Present study	56	56	48.5 ± 13.31-cases 48.02±13.41controls	Female- 62.9% each in both groups

The cases in total were positive for the rheumatoid arthritis factor and in controls, all were negative for the rheumatoid arthritis factor. However, in a study by Smerilli, G et al. found rheumatoid factor positivity (%) in 71.4% of RA subjects with CTS and 66.6% in RA subjects without CTS.[52]

Table 17: Comparing the RA factor across the group's studies among study to present study.

Studies	Cases	Controls
Smerilli, G et al.	71.4%	66.6%
Present study	100%	0

The use of grey scale US measurement of median nerve has been studied by several studies. Several elastography parameters have been used to define the pathology of median nerve.[89] Few authors have found cross-sectional area (CSA) of median nerve at entrance of the carpal tunnel in healthy controls to be 7.0-10.2mm^2.[90] Another study reported the CSA of 10-13 mm^2 in subjects with mild symptoms due to idiopathic CTS, CSA of 13.0–15.0 mm^2 represented moderate CTS and CSA of 15.0 mm^2 was estimated in subjects with severe idiopathic CTS. However, earlier studies have observed that patients with RA without symptoms have a wide range of CSA of median nerve. It was also noticed that mean CSA of

the median nerve in subjects with RA without symptoms was same to those of controls which were healthy.[88] In our study we found mean CSA of right and left median nerve in cases to be 0.110 (0.105 to 0.116) cm^2 and 0.109 (0.104 to 0.116 cm^2 (i.e. right -11mm^2; left-10.9mm^2) which can be matched to findings for mild symptoms.[15]

The controls in our study found the mean CSA of the median nerve in right and left to be 0.090 (0.083 to 0.095) and 0.089 (0.082 to 0.093)(i.e. right- 9mm^2; left-8.9mm^2) as comparable to normal values found in the healthy individuals as previously stated.[90] Although, we observed a slight variation in the CSA of the median nerve between the cases and controls there was a significant difference noticed in both right and left sides between the groups. In contrast Anno, S et al,[82] found no significant difference between the cases (RA patients cases and control as healthy patients both without any symptoms of CTS) and control in the mean CSA of the median nerve. In a meta-analysis by Sakthiswary R. et al. also found no significant difference in the CSA of the median nerve of cases with RA without CTS and controls of healthy individuals.[7] This offers credibility to the concept that the chronic inflammatory courses in RA does not affect the size of the median nerve in spite of the adjacent immediacy between the wrist joint and the median nerve and. However, Yagci et al. had opposing results of RA subjects having greater CSA of the median nerve regardless of nonappearance of clinical and neurophysiological sign of CTS.[91] Similarly a study by Smerilli, G et al. found mean CSA greater in RA with CTS compared to RA without CTS.[52] However, study findings have found mild changes in median nerve among the RA group without any CTS (cases) compared to healthy subjects in control.

Table 18: Comparing the CSA of median nerve across between the study groups at various studies to present study.

Studies	Cases mean CSA mm2	Controls mean CSA mm2
Smerilli, G et al.[52]	10.6 ± 4.2 (RA with CTS)	8.6 ± 2.1 (RA without CTS)
Anno, S et al.[82]	10.3 ± 1.7 right hand and 7.7 ± 2.4 in the left hand	8.2 ± 2.4 mm2 right hand 8.2 ± 2.4 mm2 left hand
Present study	11.0 (10.5 to 11.6)-right hand 10.9 (10.4 to 11.6)-left hand	9.0 (8.3 to 9.5) -right hand 8.9 (8.2 to 9.3)- left hand

Our study found a significant strain ratio difference between control and cases in the right side and left side (P< 0.001). Similarly in Anno S. et al, studies found a significant difference in mean strain ratio at the inlet of the carpel tunnel in RA patients compared to non-RA.[82] These findings support that RTE is extremely sensitive for indicating median nerve degeneration. Hence RTE can suffice the criteria for distinguishing CTS subjects with mild and moderate-to-severe disease from the controls and in our study RTE could predict early changes in the median nerve before it progresses to CTS in RA subjects. Hence strain ratio evaluation by RTE can be firmly recommended as RTE does not eliminate subjects even with a milder form of the disease.[92] Few among the other authors, Miyamoto et al. found that the median nerve in subjects with CTS was firmer compared to healthy controls, signifying that RTE offers a significant enhancement in the diagnostic precision of US assessment of CTS.[93]

On a further note, Yagci et al. stated the CSA of the ulnar and median nerve was greater in RA subjects compared to healthy controls signifying that RA subjects could have subclinical neuropathy.[91] This finding further adds to the present study evidence.

A study by Tatar I. et al. evaluated that CSA and strain ratio (SR) in CTS patients and in controls and they found SR to be helpful in identifying even mild cases whereas failed to

group them based on the severity of the disease.[92] But on other hand, CSA of the median nerve found to be supportive in grouping the patients based on their severity. However, in our study we found both CSA and SR measurements to be useful in identifying early changes of median nerve before it takes its course towards CTS in RA subjects.

Table 19: Comparing the strain ratio of median nerve between the study groups at various studies to the present study.

Studies	Cases Mean strain ratio mm2	Controls mean strain ratio mm2
Anno, S et al.[82]	2.3 ± 1.2 right hand and 2.1 ± 1.0 in the left hand	2.0 ± 0.9 right hand 1.9 ± 0 left hand
Present study	2.84 (2.41 to 2.98)-right hand 2.76 (2.45 to 3.04)-left hand	1.65 (1.41 to 1.94)-right hand 1.66 (1.43 to 1.93)- left hand

CONCLUSION

CONCLUSION:

- Inflammatory condition of flexor tendon and wrist joint in patients with Rheumatoid Arthritis (RA) may generate fibrotic changes in the median nerve which later progresses to carpal tunnel syndrome.
- Use of sonoelastography in evaluating median nerve changes in RA subjects without CTS was useful as changes in CSA and strain ratio was significant in cases compared to controls.
- Early diagnosis of median nerve changes can be made before developing to carpal tunnel syndrome in Rheumatoid arthritis patients using sonoelastography.

LIMITATIONS AND RECOMMENDATIONS:

- Although our study had matched age gender in both controls and cases in our results cannot be generalized as it was conducted in a single centre.
- There could be greater chances of intra and inter observer dependability of median nerve cross sectional area (CSA) measurements.
- Large prospective studies involving multicenter should be considered to evaluate the usefulness of CSA and strain ratio in the early diagnosis of median nerve pathology.

SUMMARY

SUMMARY:

This study was a prospective study conducted in a tertiary centre to assess median nerve changes in RA and healthy individuals using ultrasonography and elastography of median nerve. The subjects were into two groups Cases: Patients with RA without CTS and controls: healthy individuals without CTS and RA. A total of 56 subjects in each group were analyzed for CSA and strain ratio.

The study results found a significant difference between left- and right-hand CSA and strain ratio of median nerve between cases and controls. We found a statistically significant difference between gender in the left side cross-sectional area and strain ratio among cases. However, an insignificant difference in the CSA and strain ratio between the genders across cases and controls was found. There were significant results found in CSA and strain ratio in cases group indicating early changes although there is no sign of median nerve pathology.

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ANNEXURE

ANNEXURES

STUDY PROFORMA

Name:

Age:

Gender:

Clinical History:

Local Examination:

Laboratory reports:

Clinical Diagnosis:

Elastography report:

Median nerve

Parameters	Cases / controls	
	Left hand	Right hand
Elastography colour code		
Cross sectional area		
Strain ratio		

Final diagnosis:

INFORMED CONSENT FORM

PG guide's name: Dr. N. RACHEGOWDA

PG co-guide's name: Dr. HARIPRASAD S.

Principal investigator: Dr. YASHAS ULLAS L.

Name of the subject:
Age :
Gender :

a. I have been informed in my own language that this study involves ultrasonography and elastography as part of procedure. I have been explained thoroughly and understand the procedure.
b. I understand that the medical information produced by this study will become part of institutional record and will be kept confidential by the said institute.
c. I understand that my participation is voluntary and may refuse to participate or may withdraw my consent and discontinue participation at any time without prejudice to my present or future care at this institution.
d. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).
e. I confirm that Dr. N. RACHEGOWDA / Dr. YASHAS ULLAS L. (chief researcher/ name of PG guide) has explained to me the purpose of research and the study procedure that I will undergo and the possible risks and discomforts that I may experience, in my own language. I hereby agree to give valid consent to participate as a subject in this research project.

Participant's signature/thumb impression
Signature of the witness: Date:
1)
2)

I have explained to _____ (subject) the purpose of the research, the possible risk and benefits to the best of my ability.

Chief Researcher/ Guide signature Date:

PATIENT INFORMATION SHEET

Principal Investigator: YASHAS ULLAS L.

I, Dr. YASHAS ULLAS L., post-graduate student in Department of Radio-Diagnosis at Sri Devaraj Urs Medical College. I will be conducting a study titled "Role of elastography in assessing median nerve changes in rheumatoid arthritis patients without symptoms of carpal tunnel syndrome." for my dissertation under the guidance of Dr. Rachegowda N., Professor & HOD, Department of Radio-Diagnosis and under co-guidance of Dr. Hariprasad S., Associate professor department of orthopaedics. In this study, we will assess the role of Elastography In this study, we will assess the diagnostic value of Conventional ultrasonography and elastography sequence in evaluation of breast mass. You would have undergone ultrasonography before entering the study. You will not be paid any financial compensation for participating in this research project. You will not be paid any financial compensation for participating in this research project.

All of your personal data will be kept confidential and will be used only for research purpose by this institution. You are free to participate in the study. You can also withdraw from the study at any point of time without giving any reasons whatsoever. Your refusal to participate will not prejudice you to any present or future care at this institution.

Name and Signature of the Principal Investigator

Date

MASTER CHART

MASTER SHEET

Sl no.	Hospital number	Study group	Age	Gender	Right-side cross-sectional area (cm2)	Right side strain ratio (mm3)	Left side cross sectional area	Left side strain ratio (mm3)	Rheumatoid arthritis factor
1	738748	Cases	67	Female	0.105	2.93	0.09	2.82	Positive
2	768392	Cases	35	Female	0.113	2.7	0.109	3.23	Positive
3	827602	Cases	30	Male	0.101	2.3	0.102	2.61	Positive
4	824091	Cases	46	Male	0.108	3.25	0.106	3.1	Positive
5	818087	Cases	38	Female	0.089	2.79	0.101	3.17	Positive
6	830212	Cases	54	Female	0.091	2.4	0.094	2.67	Positive
7	717199	Cases	42	Female	0.103	2.8	0.095	2.3	Positive
8	770115	Cases	45	Female	0.109	2.84	0.121	2.4	Positive
9	819403	Cases	48	Female	0.107	2.5	0.113	2.6	Positive
10	826380	Cases	70	Male	0.121	2.9	0.13	2.4	Positive
11	826375	Cases	40	Male	0.122	2.7	0.103	2.56	Positive
12	817965	Cases	65	Female	0.102	2.2	0.108	2.1	Positive
13	827154	Cases	65	Male	0.128	2.4	0.105	2.2	Positive
14	816819	Cases	37	Male	0.131	3.1	0.129	2.82	Positive
15	810865	Cases	52	Male	0.101	3.2	0.111	2.89	Positive
16	842441	Cases	32	Male	0.125	2.52	0.095	2.1	Positive
17	845216	Cases	47	Female	0.109	2.01	0.099	1.96	Positive
18	850273	Cases	32	Female	0.106	2.15	0.112	2.32	Positive
19	850009	Cases	60	Female	0.112	2.32	0.105	2.56	Positive
20	849316	Cases	49	Female	0.118	2.41	0.106	2.79	Positive

21	765969	Cases	25	Female	0.099	2.15	0.115	2.89	Positive
22	742631	Cases	65	Male	0.095	2.82	0.12	2.45	Positive
23	779649	Cases	38	Male	0.107	2.65	0.101	2.65	Positive
24	482503	Cases	60	Male	0.116	2.92	0.103	2.31	Positive
25	771248	Cases	45	Female	0.128	2.98	0.121	3.12	Positive
26	847444	Cases	45	Male	0.114	2.85	0.119	2.93	Positive
27	802695	Cases	65	Female	0.129	3.15	0.111	3.31	Positive
28	650922	Cases	60	Female	0.124	2.41	0.096	2.63	Positive
29	784996	Cases	32	Female	0.103	2.65	0.117	2.73	Positive
30	789498	Cases	61	Female	0.109	3.19	0.119	2.91	Positive
31	798170	Cases	60	Female	0.107	2.84	0.108	2.86	Positive
32	838418	Cases	64	Male	0.1	2.69	0.104	2.59	Positive
33	824036	Cases	72	Female	0.111	2.46	0.106	2.7	Positive
34	875398	Cases	45	Female	0.113	2.15	0.11	2.23	Positive
35	870886	Cases	42	Female	0.11	2.21	0.107	2.34	Positive
36	880066	Cases	36	Female	0.106	2.33	0.103	2.28	Positive
37	876639	Cases	45	Male	0.113	2.56	0.106	2.45	Positive
38	893432	Cases	50	Male	0.105	2.39	0.109	2.57	Positive
39	881804	Cases	28	Female	0.101	2.42	0.11	2.51	Positive
40	899246	Cases	52	Female	0.113	2.98	0.109	2.48	Positive
41	906539	Cases	65	Female	0.115	2.89	0.103	2.52	Positive
42	636829	Cases	60	Female	0.109	3.12	0.112	3.13	Positive
43	908150	Cases	28	Female	0.114	2.95	0.109	2.89	Positive
44	903622	Cases	86	Male	0.107	2.96	0.116	3.13	Positive
45	584087	Cases	45	Female	0.115	2.93	0.118	2.96	Positive

46	897618	Cases	55	Female	0.101	3.16	0.113	2.99	Positive
47	721799	Cases	40	Male	0.106	3.27	0.118	3.06	Positive
48	683331	Cases	31	Male	0.104	3.29	0.109	3.12	Positive
49	648293	Cases	45	Male	0.111	2.99	0.11	3.19	Positive
50	735183	Cases	43	Male	0.113	2.98	0.116	3.16	Positive
51	644815	Cases	40	Female	0.116	3.21	0.119	3.06	Positive
52	715698	Cases	58	Female	0.124	3.16	0.106	2.93	Positive
53	639192	Cases	55	Female	0.126	3.17	0.109	2.98	Positive
54	900473	Cases	46	Female	0.128	3.13	0.108	2.99	Positive
55	721012	Cases	30	Female	0.116	2.96	0.116	3.17	Positive
56	738748	Cases	45	Female	0.119	2.98	0.119	3.09	Positive
57	665058	Controls	56	Female	0.067	1.34	0.07	1.54	Negative
58	725260	Controls	39	Male	0.079	1.04	0.07	0.79	Negative
59	280494	Controls	38	Female	0.076	1.08	0.088	1.05	Negative
60	877279	Controls	30	Male	0.095	1.53	0.064	1.2	Negative
61	829081	Controls	45	Male	0.083	1.5	0.086	1.66	Negative
62	820149	Controls	45	Male	0.091	1.6	0.09	1.55	Negative
63	814142	Controls	50	Male	0.085	1.4	0.081	1.48	Negative
64	802558	Controls	62	Male	0.082	1.55	0.086	1.62	Negative
65	812959	Controls	82	Female	0.075	1.1	0.071	1.2	Negative
66	849812	Controls	44	Female	0.086	1.35	0.089	1.45	Negative
67	850016	Controls	33	Female	0.081	1.21	0.085	1.15	Negative
68	851309	Controls	48	Female	0.078	1.4	0.081	1.31	Negative
69	834994	Controls	50	Male	0.089	1.35	0.084	1.41	Negative
70	812968	Controls	42	Male	0.083	1.52	0.079	1.33	Negative

71	853275	Controls	62	Female	0.071	1.21	0.083	1.29	Negative
72	850366	Controls	50	Female	0.085	1.33	0.091	1.41	Negative
73	851121	Controls	44	Female	0.089	1.44	0.094	1.45	Negative
74	849650	Controls	20	Male	0.078	1.79	0.081	1.86	Negative
75	850325	Controls	47	Female	0.092	1.65	0.084	1.62	Negative
76	853172	Controls	28	Male	0.089	1.93	0.091	1.8	Negative
77	812710	Controls	48	Male	0.096	2.1	0.087	1.74	Negative
78	849713	Controls	40	Female	0.084	1.74	0.076	1.65	Negative
79	847950	Controls	65	Female	0.091	1.78	0.084	1.75	Negative
80	847786	Controls	42	Female	0.091	1.56	0.088	1.43	Negative
81	846346	Controls	85	Male	0.085	1.59	0.081	1.84	Negative
82	824150	Controls	45	Male	0.074	1.34	0.079	1.24	Negative
83	846071	Controls	60	Female	0.095	1.47	0.091	1.56	Negative
84	845206	Controls	42	Female	0.078	1.59	0.081	1.43	Negative
85	843559	Controls	42	Female	0.083	1.98	0.093	1.92	Negative
86	843267	Controls	48	Female	0.085	1.33	0.087	1.12	Negative
87	836051	Controls	30	Female	0.101	2.21	0.1	2.14	Negative
88	842951	Controls	29	Female	0.087	1.84	0.076	1.89	Negative
89	834609	Controls	55	Female	0.094	1.56	0.088	1.65	Negative
90	848207	Controls	47	Female	0.095	1.83	0.091	1.71	Negative
91	888880	Controls	40	Male	0.101	1.92	0.098	1.73	Negative
92	889264	Controls	40	Female	0.089	1.45	0.091	1.53	Negative
93	889795	Controls	47	Female	0.096	1.85	0.088	1.46	Negative
94	893823	Controls	33	Female	0.098	1.64	0.096	1.57	Negative
95	892916	Controls	35	Female	0.097	1.24	0.091	1.33	Negative

96	745557	Controls	63	Male	0.095	1.61	0.099	1.88	Negative
97	839695	Controls	80	Female	0.089	1.91	0.091	1.91	Negative
98	834633	Controls	60	Female	0.092	1.92	0.095	1.88	Negative
99	814152	Controls	50	Male	0.093	1.95	0.094	1.96	Negative
100	834994	Controls	52	Male	0.095	1.99	0.093	1.94	Negative
101	893432	Controls	58	Male	0.086	1.96	0.097	1.93	Negative
102	893655	Controls	62	Female	0.098	1.95	0.096	1.98	Negative
103	894629	Controls	45	Female	0.092	1.94	0.089	1.93	Negative
104	890203	Controls	47	Female	0.095	1.99	0.078	1.95	Negative
105	599204	Controls	60	Female	0.096	1.78	0.093	1.97	Negative
106	889346	Controls	36	Female	0.093	1.96	0.092	2.1	Negative
107	897436	Controls	68	Female	0.098	2.2	0.098	2.46	Negative
108	892037	Controls	34	Female	0.097	1.94	0.089	1.93	Negative
109	889486	Controls	34	Female	0.096	1.95	0.094	1.94	Negative
110	889264	Controls	40	Female	0.103	1.97	0.091	1.97	Negative
111	741349	Controls	60	Male	0.089	1.92	0.096	1.98	Negative
112	737209	Controls	52	Male	0.94	2.1	0.96	2.35	Negative