DISSERTATION SUBMITTED FOR THE MASTER'S DEGREEIN MEDICAL MICROBIOLOGY

TITLE

A SYSTEMATIC REVIEW OF CRP AND ANTI CPP MARKER IN SPESIS

SUBMITTED

BY

SAKCHAM PATEL

2022

DEPARTMENT OF MICROBIOLOGY
INTEGRAL INSTITUTE OF MEDICAL SCIENCES & RESEARCH
INTEGRAL UNIVERSITY
DASAULI, KURSI ROAD, LUCKNOW-226026, U.P.

"A SYSTEMATIC REVIEW OF CRP AND ANTI CPP MARKER IN SPESIS"

A

DISSERTATION

Submitted to

INTEGRAL UNIVERSITY

In partial fulfilment of the requirements for the award of degree of

Masters of sciences

In

Medical Microbiology

By

SAKCHAM PATEL

ENROLLMENT NO: - 1900102955

Guide:

Dr.TASNEEM SIDDIQUI

Assistant professor

Dept. of Microbiology

Co-Guide:

Dr. AUSAF AHMAD

Statistician & Associate professor

Dept. of Community Medicine

INTEGRAL INSTITUTE OF MEDICAL SCIENCE AND RESEARCH, KURSI ROAD, LUCKNOW, 226026

INTEGRAL UNIVERSITY

Established Under U.P. Act No 09 of 2004 by State Legislation
Approved by University Grants Commission
Phone No.: +91 (0552) 2890812, 2890730, 3296117, 6451039

Fax No.: 0522-2890809

Kursi Road, Lucknow-226026, Uttar Pradesh (INDIA)

DECLARATION OF CANDIDATE

I hereby declare that this dissertation entitled **" A SYSTEMATIC REVIEW OF CRP AND ANTI CPP MARKER IN SPESIS"** is bonafide and genuine research work carried out by me under the guidance of **Dr. Nasneem Siddiqui** Assistant Professor, Department of Microbiology and Co-guide **Dr. Ausaf Ahmad** Statistician & Associate Professor, Department of Community Medicine, Integral Institute of Medical Sciences and Research, Lucknow.

DATE: **SAKCHAM PATEL**

PLACE

INTEGRAL UNIVERSITY

Established Under U.P. Act No 09 of 2004 by State Legislation
Approved by University Grants Commission
Phone No.: +91 (0552) 2890812, 2890730, 3296117, 6451039

Fax No.: 0522-2890809

Kursi Road, Lucknow-226026, Uttar Pradesh (INDIA)

ENDORSEMENT BY THE HOD

This is to certify that the dissertation entitles **"A SYSTEMATIC REVIEW OF CRP AND ANTI CPP MARKER IN SPESIS "** is a bonafide and genuine research work carried out by **SAKCHAM PATEL** under the guidance of **Dr. NASNEEM SIDDIQUI** Assistant Professor, Department of Microbiology and co-guide **Dr. AUSAF AHMAD** Assistant Professor, Department of Microbiology, IIMS&R, Lucknow in partial fulfilment of requirement for the degree of Master of Science in Medical Microbiology. The research methods and procedure described have been done by the candidate and the results have been observed by the guides periodically.

DATE:

PLACE:

Dr. NOOR JAHAN

PROFESSOR AND HEAD,
DEPT.OFMICROBIOLOGY,
IIMS&R

INTEGRAL UNIVERSITY

Established Under U.P. Act No 09 of 2004 by State Legislation
Approved by University Grants Commission
Phone No.: +91 (0552) 2890812, 2890730, 3296117, 6451039

Fax No.: 0522-2890809Kursi Road, Lucknow-226026, Uttar Pradesh (INDIA)

CERTIFICATE BY THE GUIDE & CO-GUIDE

This is to certify that the dissertation entitled **"A SYSTEMATIC REVIEW OF CRP AND ANTI CPP MARKER IN SPESIS"** is a bonafide and genuine research work done by **SAKCHAM PATEL** in partial fulfilment of the necessity for the degree of Masters of Science in Medical Microbiology.

The research methods and procedures described are done by the candidate and results are observed by the guide periodically.

DATE:
PLACE:

Dr. NASNEEM SIDDIQUI
Assistant professor
Dept. of Microbiology
IIMS&R, LUCKNOW

Dr. AUSAF AHMAD
Statistician &Associate professor
Department of Community Medicine
IIMS&R, LUCKNOW

INTEGRAL UNIVERSITY

Established Under U.P. Act No 09 of 2004 by State Legislation
Approved by University Grants Commission
Phone No.: +91 (0552) 2890812, 2890730, 3296117,6451039

Fax No.: 0522-2890809

Kursi Road, Lucknow-226026, Uttar Pradesh (INDIA)

COPY RIGHT

DECLARATION BY THE CANDIDATE

I hereby declare that Integral Institute of Medical Sciences and Research, Integral University, Lucknow shall have the rights to preserve, use and disseminate this dissertation in print or electronic format for academic or research purpose.

I will publish the research paper related to my dissertation only with the consent of my guide.

DATE: **SAKCHAM PATEL**

PLACE:

ETHICAL CLEARENCE CERTIFICATE

INSTITUTIONAL ETHICS COMMITTEE (IEC)

IIMS&R INTEGRAL UNIVERSITY, LUCKNOW

IEC/IIMS&R/2022/35

CERTIFICATE

This is to certify that research work entitled **"A systemic review or CRP and CPP as master in spesis"** submitted by **Sakcham Patel Dr.Tasneem Siddiqui, Dr.Ausaf Ahmad** for ethical approval before the Institutional Ethics Committee IIMS&R.

The above mentioned research work has been approved by Institutional Ethics Committee, IIMS&R with consensus in the meeting held on **19 May 2022**.

Dr.Deepak Chopra
(Jt.Member Secretary)
IRC/IEC
IIMS &R

Dr.Q.S.Ahmed
(Member Secretary)
IRC/IEC
IIMS &R

ACKNOWLEDGEMENT

ACKNOWLEDGEMENT

I take this opportunity to extend my sincere gratitude and appreciation to all the helping hands who made my dissertation work a huge success.

Thanks to the **Almighty God** for giving me strength and energy to finish this study.

I am thankful to the **Integral University, Lucknow** for providing the opportunity, laboratory equipment, materials, and its valuable support, to complete this study.

First and foremost, I am extremely thankful to**Dr. Noor Jahan**, Professor and Head, Department of Microbiology, IIMS&R, whose benevolent guidance and constant encouragement helped me a lot doing my dissertation.

I express my heartful gratitude and regards to our esteemed teacher and my guide **Dr. Nasneem Siddiqui ,**(Assistant Professor) Department of Microbiology and co-guide**Dr. Ausaf Ahmad**, Statistician &Associate professor, IIMS&R, for providing excellent guidance, motivation and keep interest in my dissertation. It was a great opportunity and wonderful experience to work under their supervision.

I express my heartiest thanks to **Dr**. **SarverJahan** (Assistant Professor)**, Dr.Tasneem Siddiqui**

(AssistantProfessor), **Mrs.SandeepikaDubey**, **Dr.Karuna Katiyar**, Faculty members, Department of Microbiology, IIMS&R for their ready to help, support and guidance.

I am highly thankful to **Dr. Ausaf Ahmad** Statistician & Associate Professor, Department of Community Medicine for his kind interest, valuable guidance and statistical analysis in the dissertation work.

I am also thankful to **Mr. Salman**, **Mr.Dheeraj**, **Mr.Dhirendra**, **Mr.Mohsin, Mr. Vishnu** for providing laboratory facilities and guidance during the period of work.

I would also pay my special thanks to my batchmates for their continuous help and co-operation during the period of work.

Finally, Special thanks to my family also members who encouraged me to believe in hard work and not to worry about the results.

DATE: **SAKCHAM PATEL**

CONTENTS

DEDICATED TO

"TEACHERS"

FAMILY"

&

"FRIENDS

INTRODUCTION

INTRODUTION

Rheumatoid Arthritis (RA) is the maximum not unusual place systemic inflammatory, car immune Rheumatic ailment of unknown etiology four affecting almost 1% of the person populace worldwide. It is characterised via way of means of persistent and erosive polyarthritis (generally regarding small, peripheral joints in a symmetric distribution) because of ordinary boom of synovial tissue or pannus, and reasons irreversible joint deformity9 which could cause excessive disability thirteen with great morbidity6. Although the appropriate aetiology of RA stays unknown1, there is strong proof for autoimmunity, considering that numerous car antibodies are associated with the disease6.

The potential of the synovial inflammation to cause cartilage harm and bone erosions and next adjustments in joint integrity is the hallmark of the disorder. Despite its negative capability, the path of RA may be pretty variable. Some patients may also enjoy most effective a slight oligoarticular infection of short length with minimum joint damage, however maximum can have a continuing progressive poly arthritis with marked functional impairment.

The disorder happens regularly in girls than in men (2.5 – 3:1). It affects the humans of all races equally. The disorder can begin at any age, height onset generally takes place within side the fourth and 5th a long time of life.

In some families, a couple of individuals may be affected, suggesting a genetic foundation for the disorder. Genetic studies have verified that a genetic predisposition is living with inside the HLA-DR locus7,12. There is like proof that environmental factors, such as infectious agents, oral contraceptives and smoking, can also additionally play a role.

For a long time, RA is recognized usually consistent with scientific manifestations primarily based totally upon ACR criteria where in the handiest serological marker is RF check.

Rheumatoid component (RF) is an antibody directed towards the Fc area of IgG that has been used as a diagnostic marker for Rheumatoid Arthritis and is usually recommended as a screening test3. and may be detected in as much as 80% of RA sufferers .However it's far nonspecific16 and can be found in 5-10 % of healthful aged individuals or in sufferers with different autoimmune and infectious diseases .The check is finished on a recurring foundation in maximum scientific laboratories as in line with ACR standards. During the first few months of the ailment, the (1987) revised standards is hardly ever met. About one- 0.33 of the patients with chronic arthritis do now no longer satisfy the class standards, so it's far

frequently tough to diagnose RA, with inside the very early ranges of the disease6. On the opposite hand, sever research have proven that enormous irreversible joint harm happens in the first 2 years of the ailment. In many instances, irreversible harm of the joint cartilage has already passed off by the point laboratory and radiological parameters have showed the clinical analysis of RA.

So it's far therefore important to have a dependable and precise check to perceive the RA sufferers previous to the occurrence of joint harm.17The different maximum particular car antibody gadget for RA is the own circle of relatives of vehicle antibodies directed to Citrulline – containing proteins, inclusive of anti per nuclear aspect, anti keratin antibodies (AKA) in , 7 anti filaggrin antibodies (AFA) and anti-Sa3,7,11. Because of rigorous technical necessities for his or her detection, anti per nuclear component and antikeratin antibodies have in no way been broadly used as markers for Rheumatoid Arthritis, notwithstanding their excessive specificity.

Recently, a brand new serological check (biological marker) 20 the anti Cyclic Citrullinated Peptide (anti-CCP) 2,20 become developed6. Citrulline is formed via way of means of deamination of arginine residues in several proteins via way of means of the motion of enzyme peptidyl arginine deiminase (PAD) 6,7,16,21,20 that is gift abundantly in inflammatory synovium & cause near by citrullination of proteins inclusive of fibrin6,7.Citrullinated extracellular fibrin withinside the RA synovium can be one of the primary auto antigens using nearby immune reaction cautioned via way of means of the discovery of nearby manufacturing of anti – CCP antibodies in the joint.

Anti –CCP become said to have a better specificity for the analysis of RA, specially in sufferers with early ailment . Anti CCP antibodies are diagnostic & prognostic marker of early onset of RA, and predate arthritis by numerous years.

It become also located that there's an association among anti - CCP and the ailment severity in early RA6,11,23. A-CCP is the predictor of bone harm.3,7,23

The high specificity (98%) of anti-CCP in sufferers with RA can exclude different rheumatic or immune diseases,6,7,9 (like SLE & OA) in sufferers with wonderful anti- CCP. 20% of recent sufferers with RA are negative with inside the first year, whilst early analysis is vital to save you erosive joint disease7,18,24. It were beneficial to look the anti-CCP records throughout the primary, vitally crucial 12 months of ailment.

Around 40 % of RF sero negative affected person seem like anti–CCP wonderful ,which substantiates extra diagnostic potential of anti-CCP. Specificity of anti -CCP antibodies is greater than 90 %.

It has been regarded with inside the ultimate decade, RA wishes to be identified early & dealt with right away with Disease Modifying Anti Rheumatic Drugs (DMARD) so as to correctly intrude with ailment process18,19.The remaining assignment for future is to initiate therapy in early phase that the real improvement of RA is prevented, for which early diagnosis is greater critical to restriction the radiological development of the ailment (bony deformity) via way of means of starting up remedy in advance and additionally crucial for providing patients with nice outcome & first-class of life16. It is beneficial in analysis and exclusion of RA.24. Another capacity marker for improved hazard of RA can be C-reactive protein(CRP).11,18,21,22 can also be multiplied in sufferers with RA.17,22,23,25Additionally ESR is also determined in patients .

Rheumatoid arthritis (RA) is a chronic inflammatory rheumatic disease, where in autoantibodies are a part of the early disease manifestations. It is a systemic autoimmune arthritis that clinically disclosed as joint pain,stiffness and swelling. Persistent synovitis can development to cartilage and bone destruction and in the long run to long-time period disability [1]. Several mediators and factors were said to play a position in RA sufferers including cytokines [2–4], oxidative stress [5,6], angiopoietin [7] and leptin [8]. Although the hepatitis C virus (HCV) become identified in 1989, it has emerged as a main reason now no longer only of liver disease, however also of numerous extra-hepatic manifestations (EHM) [9]. The rheumatologic manifestations associated with HCV infection encompass arthralgia, myalgia, arthritis, vasculitis, and sicca syndrome. The articular manifestations of HCV patients range from polyarthralgia to mono or oligoarticular intermittent arthritis affecting large joints and symmetric chronic polyarthritis which regularly show an RA-like clinical picture [10,11]. HCV contamination need to be regarded as a systemic infectious ailment with multi organ involvement. More than 50% of HCV-positive patients develop in the course of the path of the disease as a minimum one EHM. The EHMs are regularly the primary and most effective clinical symptoms and symptoms of a chronic HCV [12]. It has been reported to be related to diverse rheumatic diseases as RA, systemic lupus erythematosus and vasculitis.

The anti-cyclic citrullinated peptide excessive sensitive (anti- CCP hs) take a look at detects auto antibodies in opposition to particular epitopes of mutated citrullinated vimentin (MCV). It is for this reason a highly touchy and a completely unique laboratory take a look at for the

diagnosis of RA especially in early disease [16]. Protein citrullination of vimentin present in hepatic stellate cells may also have a role in selling collagen synthesis with the aid of using growing the extent of collagen mRNAs which may also give an explanation for the fibrosis visible in continual HCV patients [17]. This is the first take a look at that's worried with a huge number sufferers laid low with each continual RA and HCV. In sequence, the purpose of our paintings became to take a look at anti-CCP hs in RA patients associated with continual HCV and its correlation to sickness interest and liver affection in those sufferers.

Rheumatoid arthritis (RA) is a not unusual place autoimmune disorder characterised via way of means of persistent infection of synovial joints. In maximum instances this can cause the formation of pannus tissue, in the end main to joint destruction. Early analysis, coupled with competitive use of disorder-enhancing antirheumatic drugs, has been proven to have a good impact at the direction of the disorder. Therefore, early and correct analysis has grow to be more and more essential. Several units of standards were posted to acquire such an early analysis, and they all encompass dimension of antibodies directed to citrullinated peptides or proteins. This evaluation summarizes our gift information approximately the maximum famous and set up take a look at to degree those antibodies, the anti-CCP take a look at, which measures antibodies directed to cyclic citrullinated peptides. We describe the modern-day view son how those antibodies are generated and the way genetic and environmental parameters are essential on this process. The anti-CCP take a look at is extra unique than the generally used RF take a look at (95% as opposed to much less than 90%) and has a similar sensitivity (extra than 70%). These antibodies are detectable very early with inside the disorder and are mentioned to are expecting the improvement of erosive RA. Increasing proof helps a function for those antibodies with inside the pathology of the disorder. In conclusion, trying out for anti-CCP auto antibodies is broadly familiar as an crucial device for analysis and early remedy with inside the control of rheumatoid arthritis patients.

Rheumatoid arthritis (RA) is an auto immune disease that standing the small joints and which motives pain, swelling and subcutaneous nodules throughout the joints resulting in a discounted brilliant of life. 1 RA is characterised with the useful resource of the usage of inflammation of the synovial membranes of the joints important to bone erosion. 2 RA has an widely wide-spread global prevalence of 0.5-1.0% in masses of populations with a prevalence that is instances in women than that in men and has an inclination to be greater now no longer unusual place with inside the elderly. 2, 3 However, the prevalence may additionally moreover variety in certain populations inclusive of that in Pima Indians and the Chippewa Indians that screen a immoderate prevalence (5.3% and 6. 8% respectively) in evaluation to the lower prevalence stated in China and Japan (0.2-0.3%). This shows that similarly to environmental factors, RA may additionally moreover have an underlying

genetic predisposition to immune disregulation. 3 The synovial membrane includes fibroblast-like synoviocytes (FLS) which is probably crucial with inside the pathogenesis of RA. Macrophages secrete cytokines inclusive of tumor necrosis factor alpha (TNFa), interleukin-1 (IL-1) and interleukin-6 (IL-6) which stimulate FLS important to inflammation. Activated FLS proliferate and migrate from joint to joint so usually gives as a symmetrical polyarthritis. 4 Genetic and environmental factors cause modifications of the auto antigens. 5Synovial damage or infection with inside the joint can motive cytokine release causing inflammation important to the citrullination of the auto antigens. 6 Modification of Data may be preliminary. Auto antigens together with citrullination is a cease end result of these triggers important to production of auto antibodies targeted on citrullinated peptides. Rheumatoid factor (RF) is an IgM antibody which dreams the fragment crystallisable (Fc) a part of the immunoglobulin G (IgG) forming an immune complex that promotes inflammation. 7 Anti-cyclic citrullinated peptide (Anti-CCP) aim cyclic citrullinated antibodies (CCP).Extra-articular involvement outcomes from cytokines produced with inside the joints causing the liver to deliver greater C-reactive protein (CRP) it really is an inflammatory marker. 4 14-3-3h is a protein of seven isoforms that can be advanced in RA patients and used as a very precise diagnostic biomarker for RA. 8 The multi-biomarker disease interest (MBDA) score is also crucial for the assessment of the evaluation of RA with the useful resource of the usage of presenting a disease interest score from 1-100 determined with the useful resource of the usage of the dimensions of 12 biomarkers. 9 If RA is not treated, its improvement and deterioration will bring about eternal destruction of the joints, resulting in reduced mobility and may cause excessive complications in number one organs. 8Therefore, the early evaluation and evaluation of RA severity, for set off and effective intervention, is needed to significantly decorate the scientific outcomes. The cause of this manuscript is to systematically compare the literature for role of the following biomarkers: CRP, RF, Anti-CCP, 14-3-3h and MBDA with inside the evaluation and treatment of RA and to assess whether or not or now no longer the ones must be measured routinely in scientific practice.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The name is based at the term "Rheumatic Fever" an illness which incorporates joint pain and is derived from the Greek phrase Rheumatos ("flowing"). The suffix - oid ("resembling") - joint infection that resembles rheumatic fever.

Rheumatoid Arthritis (RA) is the commonest inflammatory joint disease.1,2,3 It is characterized by chronic polyarthritis in symmetrical distribution with multiple deformities and systemic involvement.11,25,28,29 This result to irreversible joint disability.25 It is associated with large morbidity.

RA is characterized by inflammation the synovial membrane of diarthrodial joints. Early indication of RA are swelling and pain of the proximal interphalangeal and metacarpophalangeal joints. the larger then joints become affected, specially knee, elbow & ankle. Many studies show that the synovial membrane inflammation, in most cases lead to progressive destruction of cartilage and bone leading to irreversible deformity and disability1,3,8,12,13. In a study by RA severely affects the quality of life of 16 patient and also has major economic consequences for society.

Since RA is a systemic autoimmune disease, other parts or organs of the body may become affected at a later stage, example - Rheumatoid Nodule7,30,31.

Etiology

Although the precise etiology of RA remains unknown1,2,6 there is strong evidence for autoimmunity since several auto antibodies are associated with the disease.6,30,31

Family research suggest a genetic predisposition. RA is discovered at about four instances the expected charge in first-degree family of individuals with disease associated with the presence of the auto antibodyThe name is based at the term "Rheumatic Fever" an illness which incorporates joint pain and is derived from the Greek phrase Rheumatos ("flowing"). The suffix - oid ("resembling") - joint infection that resembles rheumatic fever.

Rheumatoid Arthritis (RA) is the commonest inflammatory joint disease.1,2,3 It is characterized by chronic polyarthritis in symmetrical distribution with multiple deformities

and systemic involvement.11,25,28,29This leads to irreversible joint disability.25 It is associated with large morbidity.

RA is characterized by inflammation of the synovial membrane of diarthrodial joints7. Early indication of RA are swelling and pain of the proximal interphalangeal and metacarpophalangeal joints. Later, the larger joints become affected, especially those of the knee, elbow and ankle7. Many studies show that the synovial membrane inflammation, in most cases lead to progressive destruction of cartilage and bone leading to irreversible deformity and disability1,3,8,12,13.RA severely affects the quality of life16 of a patient and also has major economic consequences for society. Since RA is a systemic autoimmune disease, other parts or organs of the body may become affected at a later stage, example - Rheumatoid Nodule7,30,31.

Risk factors:

A range of environmental and genetic variables have been evaluated as potential risk factors for RA

• Hormonal exposures

• Tobacco use33

• Dietary components

• HLA genotype, and

• Microbial exposures

But to this point no definitive danger elements for RA have been identified.

Epidemiology

RA is visible at some point of the arena and affects all races. Disease incidence is much like that of evolved countries, however better than stated from China, Indonesia, Philippines, and Rural Africa. North Indian population is genetically in the direction of Caucasians (1- 1.5%) than to different ethnic businesses. Higher incidence quotes in pima institution of Indians of Arizona & in a few Native American groups have (5-6%). And human beings from the

Caribbean region & black Africans, have lower prevalence rates . Mahajan et al, in his take a look at round Kashmir, in 2003, stated 23.9 % had Rheumatological problems, 24.9% had OA. The incidence fee is 1%.. Before the age of 45years the girl, male ratio is 6:1. Women are affected 3 to 5 instances as regularly as men. (3 - 5:1ratio) suggesting a function for intercourse hormones. (zero.5 -3.8% in girls ,1.37 % in men.) . The prevalence of RA is six instances extra in vintage girls in comparison to younger girls. The incidence will increase with age in 5 % of girls, and 2percentof guys over fifty five years, and intercourse variations decrease with inside the older age. Onset is maximum common at some point of the fourth and 5th a long time of life7. With 80% of all sufferers growing the ailment among the a while of 35 and 50 years, as proven in take a look at via way of means of Athena Linos et al. Mean a while of RA sufferers ranged from 50.zero to 52.2 yrs and % of girl sufferers from 80.9% to 89.6%.It is four instances greater not unusual lplace in people who smoke than non-people who smoke. As in step with CDC forty an predicted 1.293 million adults elderly 18 and older (zero.6%) had RA in 2005, down from the preceding 1990 estimate of 2.1 million. The incidence amongst girls in 1995 became about double that during men (1.06% as opposed to zero.61%).32 This take a look at discovered nearly a 2:1 ratio in incidence for girls to men. Prevalence is lowering now.32 Genetic concordance in monozygotic twins is about 12- 15%. First-diploma relative's incidence fee is 2-3%. Pathogenesis It is characterized via way of means of Persistent cell activation Auto immunity Presence of immune complexes at articular and further articular sites. This ends in Chronic infection Granuloma Joint destruction. Microvascular injury, thrombosis, and neovascularization with edema and infiltration via way of means of lymphocytes (CD4 Tcells), plasma cells and macrophages regularly gathered into aggregates round small blood vessels. Locally produced antibodies to tissue additives and immune complexes can set off supplement and generate anaphylatoxins and chemotactic elements. T cells produce cytokines inclusive of IFN. It stays doubtful whether or not the continual T mobile hobby represents a reaction to a continual exogenous antigen or to altered autoantigens inclusive of collagen, immunoglobulin, one of the warmth surprise proteins, or CCP. Effusion of synovial fluid into joint space, hypertrophy and congestion of synovial membrane and underlying connective tissue. Inflammatory granulation tissue-pannus, spreads over and beneathneath the articular cartilage with formation of lymphoid follicles akin to lymph node (granuloma), gradually erodes and destroys the bone. Adjacent muscle tissues get inflammed because of infiltration. Immunofluorescence confirms the Rheumatoid Factor vehiclemobile antibody synthesis via way of means of plasma cells in synovium and lymph node. Recent proof shows that antibodies can be produced in opposition to different self-antigens, inclusive of CCP, which

can be generated withinside the synovium, and this can make a contribution to RA synovitis RA-related autoantibodies (RF): Throughout the ultimate a long time numerous autoantibody structures were defined which can be related to RA. RF - the oldest and maximum well known of those autoantibodies, is directed to the Fc a part of IgG molecules. RF may be detected in as much as 80% of RA sufferers, however the research via way of means of Swedler et al, and Nehir samanchi et al shows, those antibodies are located additionally in numerous different vehiclemobile immune illnesses in addition to in healthful individuals - 5-10 % (mainly elderly) reducing its specificity for RA. The frequency of Rheumatoid Factor withinside the wellknown populace will increase with age, and 10–20% of individuals > sixty five years have a fantastic check. In addition, some of situations except RA are related to the presence of RF. These encompass Systemic Lupus Erythematosus, Sjogren's syndrome, persistent liver ailment, Sarcoidosis, Interstitial Pulmonary Fibrosis, Infectious Mononucleosis, Hepatitis B, Tuberculosis, Leprosy, Syphilis, Subacute Bacterial Endocarditis, Visceral Leishmaniasis, Schistosomiasis, and Malaria.Due to the above elements RF's diagnostic specificity has lowered. So the presence of Rheumatoid Factor does now no longer set up the analysis of RA. Therefore the RFactor check by myself isn't beneficial as a screening procedure. Both anti-CCP antibody and RF are advocated screening exams for Rheumatoid Arthritis.3 A poor RF does now no longer rule out RA, as a substitute the arthritis is referred to as seronegative. This is the case in approximately 15% of sufferers. Up to 20% of recent sufferers with RA are seronegative withinside the first year, whilst early analysis is important to save you erosive joint disease38. Previous research show, round forty% of RF-seronegative sufferers seem like anti-CCP-fantastic. This substantiates the extra diagnostic capacity of CCP. RA-Specific Autoantibodies The autoantibody structures with the finest medical capacity for RA are the antibodies directed to citrulline containing epitopes The presence of autoantibodies in opposition to citrullinated proteins in RA sufferers became first defined withinside the mid-seventies whilst the biochemical foundation of antibody reactivity in opposition to keratin and filaggrin became investigated, APF (antiperinuclear antibodies)-1964, AKA (antikeratin antibodies) -1979, aleven though particular due to technical problems now no longer extensively used. Recently Anti Cyclic citrullinated peptides (Anti CCP) detected with excessive sensitivity and specificity for RA.6 Citrulline: During infection, the enzyme peptidylarginine deiminase contains citrulline into proteins, the enzymatic conversion of peptidyl-arginine to peptidyl-citrulline.

Citrulline has been named after the Latin phrase for watermelon, Citrullus vulgaris, whichcontains massive quantities of this amino acid.

Citrulline is a non general amino acid, because it isn't always included into proteins at some stage in protein synthesis. “Cyclic citrullinated peptide" is likewise acknowledged as "CCP". It is a cyclic peptide, can comprise the amino acid citrulline and may be generated through publish translational amendment of arginine residues via way of means of peptidyl arginine deiminase (PAD) enzymes.

PAD enzymes are gift withinside the infected synovium and that their pastime is regulated on the transcriptional and translational ranges In addition, those enzymes require pretty excessive Ca2+ concentrations, approximately a hundred instances better than commonly gift withinside the cytosol of a dwelling cell.

Conversion of arginine into citrulline includes the substitute of an amine institution via way of means of an oxygen atom withinside the facet chain of this amino acid, and is related to the lack of a fantastic charge (at impartial pH). The impartial oxygen institution of the citrulline residue is the component this is identified via way of means of the autoantibodies.

Interestingly, citrullination happens typically in loss of life cells. Indeed, at some stage in inflammation, while many cells die via way of means of apoptosis or necrosis, withinside the infected synovia of RA and non-RA patients. Paradoxically, the presence of citrullinated proteins in maximum instances does now no longer result in the era of anticitrullinated protein antibodies. This phenomenon is probably associated with the genetic historical past of the patient. It has been acknowledged for a while that there's a as an alternative sturdy correlation among RA and sure HLA-DR alleles, especially HLADRB1- 0401 and HLA-DRB1- 0404)

Citrulline antibody

It is an antibody (an immune protein) directed towards a round peptide (a hoop of amino acids) containing an unusual ("non-general") amino acid referred to as citrulline that isn't always commonly found in peptides or proteins.

It is often detected in RA is patients. Recently, those antibodies have became up as effective biomarkers, which might be prevalent as a primary diagnostic device in diagnosing RA in a totally early level of disease.

Clinical Features

Complaints of ache over the affected joints, symmetrical joint involvement and morning stiffness, with feature adjustments of the hand including

• Radial deviation on the wrist with ulnar deviation of the digits, regularly with palmar subluxation of the proximal phalanges ("Z" deformity).

• Hyper extension of the proximal interphalangeal joints, with compensatory flexion of the distal interphalangeal joints (swan-neck deformity).

• Flexion contracture of the proximal interphalangeal joints and extension of the distal interphalangeal joints(boutonnière deformity).

• Hyperextension of the primary interphalangeal joint and flexion of the primary metacarpophalangeal joint with a consequent lack of thumb mobility and pinch.

Typical joint adjustments may additionally broaden withinside the feet, including

• Eversion on the hind foot (subtalar joint)

• Plantar subluxation of the metatarsal heads.

• Widening of the forefoot .

• Hallux valgus, and lateral deviation and dorsal subluxation of the toes. Later, incapacity is greater associated with structural harm to articular structures.

Disability

- Daily living activities are impaired in most individuals.

- After 5 years of disease, approximately 33% of sufferers will not be working.
- After 10 years, approximately half will have substantial functional disability.

Prognostic factors

Poor prognostic factors include

- Persistent synovitis
- Early erosive disease
- Extra-articular findings (including subcutaneous rheumatoid nodules)
- Positive serum RF findings
- Positive serum anti-CCP autoantibodies
- Carriership of HLA-DR4 "Shared Epitope" alleles
- Family history of RA
- Poor functional status
- Socioeconomic factors
- Elevated acute phase response ESR
- Elevated C-reactive protein [CRP] And increased clinical severity

Mortality

Estimates of the life-shortenin effect of RA vary. Mostsources cite a lifespan reduction of 5 to 10 years.

Laboratory diagnosis:

Currently, the classification of RA relies the criteria, originally formulated 50 years ago and last adjusted in 1987[25] are based mainly on clinical parameters and a single serological test RF. Since the damaging effects of the inflammatory process are already in progress, this set of criteria is not very suitable for the early diagnosisof RA .In the ACR criteria for RA serologic support is restricted to the determination of Rheumatoid Factor (RF).[42] RF(1937) has been widely used as a screening test for patients with arthritis[3]. However, its diagnostic specificity for RA is poor, since RF is also found in many other rheumatic and non rheumatic diseases, infectious conditions and even in a noticeable proportion of normal healthy subjects, particularly in ageing individuals .

The resulting lack of specificity for RA can lead to wrong diagnosis and unwanted treatment.

However, especially during the first few months of the disease, the 1987 revised criteria of the ACR are rarely meet .About one- third of the patients with persistent arthritis do not fulfill theclassification criteria ,so it is often difficult to diagnose RA in the very early stages of the disease [25].

On the other hand, numerous studies have shown that substantial irreversible joint damage occurs within the first 2 years .In many cases, irreversible damage of the joint cartilage has already occurred by the time laboratory and radiological parameters have confirmed the clinical diagnosis RA .So it is important to start treatment earlier. Current therapeutic strategies in RA are with increasingly aggressive regimens. Therefore, diagnostic tests with high- specificity are desirable for deciding on the optimal treatment.

Missed diagnosis of Rheumatoid Arthritis (RA) has major medical and cost implications, since this set of ACR criteria is not very suitable for the early diagnosis of RA.A specific and sensitive (serological) marker, which is present very early in the disease, is needed which should ideally be able to predict the erosive or nonerosive progression of the disease.

The shortcomings of the RF test have kept the search for more specific RA markers alive. Most autoantibody systems described during recent decades, Anti Perinuclear Factor (APF) – 1964, and Anti Keratin Antibody (AKA) tests – 1979 have failed to mature into mainstream tests for RA because of low sensitivity, and technical inconvenience .

Another group of auto antibodies have recently been detected in serum of patients with RA, in which patients develop antibodies to modified (citrullinated) arginine residues, and this has resulted in the development of the anti-cyclic citrullinated peptide antibodies (anti CCP). The only antibody system that combines good sensitivity with superior specificity for RA is that targeting citrullinated epitopes.

Antibodies to CCP (anti-CCP) can also be used to evaluate patients with RA. Although these antibodies are most commonly found in Rheumatoid Factor–positive patients, on occasion they can be detected in the absence of Rheumatoid Factor. In addition, the anti-CCP test has a similar sensitivity and a better specificity for RA than R F[34] When the citrulline antibody is detected in a patient's blood, there is 90-95% likelihood that the patient has Rheumatoid Arthritis.

The presence of anti-CCP is associated with the aggressive nature of the disease, with a tendency for developing bone erosions. It is most useful to confirm the diagnosis and establish a likely prognosis. A role in differential diagnosis comes from patients with erosive

systemic lupus erythematosus (SLE) other arthritis and excludes them. The combined presence of RF positivity and anti-CCP positivity has 99.5% specificity for RA .

The value of anti-CCP antibodies and RF for predicting the outcome of RA, clinical signs of disease activity, and the severity of radiologic joint damage has been investigated recently. The studies by van Jaarsveld et al, Kroot et al, and Meyer et al, all support the thesis that RA patients, positive for CCP, develop significanly more radiological damage than CCP-negative patients. Lately, Visser et al, assessed a clinical prediction model in early RA patients for the three forms of arthritis out come: self-limiting, persistent nonerosive and persistent erosive arthritis in which CCP was strongly associated with erosive arthritis more than RF.

- "**RA passport"** should contain
- **Serological data** (RF, OR and anti-CCP2)
- **Genetic data**(e.g. HLA-DR4) and
- **Several clinical parameters,** as suggested by Visser and coworkers [17].

Investigations

1. Neutrophils

Increase in systemic vasculitis, sepsis & decrease in rheumatoid arthritis, lupus & drugs.

Lymphocytes

Increase in infections, decrease in lupus, and in those with corticosteroid therapy

Eosinophils

Increase in systemic vasculitis, decrease in those with corticosteroid therapy.

2. Platelets

Increase in inflammation, decrease in lupus & drugs.

CRP41

CRP is also known as C - reactive protein. It is an acute phase protein present in hepatocytes and plays an important role to the body's response to inflammation.

For the below mentioned reason the protein is called as 'C'reactive protein - Gram positive, somatic portion of pneumococci contains species specific carbohydrate known as 'C' substance (antigen), which forms precitipitate with a protein (β globulin) in the blood in acute inflammatory conditions. Its production is stimulated by

a. Bacterial infection

b. Inflammation

c. Malignancy

d. Tissue destruction.

Rapid Serum assays are useful in early detection of acute inflammation. Increase of CRP denotes - onset of inflammation. Rapid decrease occurs when infection subsides. It is a close mirror of degree of inflammation.

CRP detection was done by method of latex agglutination test.It must be noted that even in known cases of inflammatory disease, such as RA and lupus, a low CRP level is possible, and is not indicative of no inflammation. CRP appears and disappears more quickly. Therefore, CRP level may drop to normal following successful treatment. CRP test is also used to assess the effectiveness of a specific arthritis treatment and monitor periods of disease flareup. Its value is as a general indicator of response to treatment and not specific to rheumatoid arthritis.

Another blood test often ordered in conjunction with CRP is known as ESR.Both CRP and ESR give similar information about non- specific inflammation.

1. **ESR** Erythrocyte Sedimentation Rate:

It is an indirect measure of the **APR –** Acute Phase Reaction.It chan ges from very low to very high levels, mirrors the degree ofinflammation, rise rapidly at onset, & fall as inflammation subsides.Soit is a direct measure of the APR. Erythrocytes donot clump normally due to their repellent electrostatic negative charge or zeta potential greater than the attractant electrical charge of the plasma constituents. In APR altered plasma protein concentrations- fibrinogen, increase indielectric constant overwhelm the zeta potential & allow erythrocytesto clump (rouleaux).So it sediment fastly, which is measured as ESR.

ESR doesn't appear and disappear more quickly and may remain elevated for a longer period. ESR increases in APR,Increased level of immunoglobulin,Myeloproliferative disorders & Autoimmune isorder.

2. RF

RF is an autoantibody directed to the Fc part of IgGmolecules.. These antibodies are found in RA, in several otherauto immune diseases and as well as in healthy individuals - 5-10 % (in elderly people). This lowers its specificity.

RF is detected by the method of latex agglutination test.

3. Anti CCP Test

Antibody to cyclic citrullinated peptide,detected by ELISA technique.

Treatment:

Chemically synthesised **DMARDs -** (disease modifying anti rheumatic drugs)

1. Azathioprine
   - Ciclosporin(cyclosporin A)
   - D- penicillamine
   - Gold salts
   - Hydroxychloroquine
   - Leflunomide
   - Methotrexate (MTX)
   - Minocycline
   - Sulphasalazine(ssz)

Low dosages of daily cortisone (e.g., prednisone)are added to a properspecific anti-rheumatic treatment.

2. Cytotoxic drug

Cyclophosphamide

3. Biological agent

- Tumor necrosi factor alpha (tnfα) blockersetanercept, infliximab, adalimumab.
- Interleukin 1 (IL-1) blockers
- Monoclonal antibodies against B cells - rituximab
- T cell costimulation blocker

- Interleukin 6 (IL-6) blockers

4. Anti inflammatory drugs

- Glucocorticoids
- Non-steroidal anti-inflammatory drug

5. Analgesics

- Paracetamol
- Opiates
- Diproqualone

Lidoquine

6. Also includes **rest and physical activity.**

Osteoarthritis

Osteoarthritis (OA) is the most common type of arthritis.

Definition

OA is joint failure, in which all structures of the joint have undergone pathologic change, often in concert. Pathologically it is defined as a condition of synovial joints characterised by focal loss of hyaline articular cartilage with proliferation of new bone and remodelling of joint contour. It involves both small and large joints.

Prevalence

OA is uncommon in adults under age 40 and highly prevalent in those over age 60. But steady rise from age 30, such that by 65, 80% will develop symptoms.Prevalence is high especially in the elderly.The Prevalence is increasing nowadays.

Risk factors:

- **Constitutional susceptibility**

  Ageing, Heredity, Gender, Hormonal status &Obesity.

- **Mechanical factors**

Trauma & Joint shape alignment usage-Occupationalor recreational.

Commonly affected joints

- Hip & Knee joints are commonly affected.
- Also cervical and lumbo sacral spine.
- In the hands, the distal and proximal interphalangeal joints and the base of the thumb are often affected.
- First metatarsal phalangeal joint (MTP).
- Usually spared are the wrist, elbow, and ankle.

Pathology & Etiology

- Metabolic
- Mechanical
- Genetic or
- Constitutional insults damage the synovial joint Panarticular involvement is present. Cartilage initially shows surface fibrillation irregularity and focal erosions develop outgrowths of new cartilage and with neurovascular invasion from the bone, this cartilage ossifies. **Osteophytes** are an important radiographic hallmark of OA. The capsule which stretches, becomes edematous, and can become fibrotic.

Clinical Features

Joint pain from OA is activity-related. Pain comes on either during or just after joint use and then gradually resolves and relievedby rest. In knees, buckling may occur. Heberden's node are present.

Diagnosis

Diagnosis based upon Structural abnormalities or on thesymptoms they evoke.

- Symptoms - usually joint pain, determine disability.
- Structural abnormalities - Cartilage loss and osteophytes.

Examination of the synovial fluidis often more helpfuldiagnostically than an x-ray.

Treatment

Nonpharmacotherapy

Since OA is a mechanically driven disease, ways of lessening focalload across the joint include

1. Avoiding activities that overload the joint,
2. Improving the strength and conditioning of muscles that bridge the joint.

Pharmacotherapy

- Acetaminophen,
- Non steroidal Anti-Inflammatory Drugs (NSAIDs), and
- COX-2 Inhibitors.
- Intra articular Injections:
- Glucocorticoids and Hyaluronic Acid, and
- Surgery.

Systemic lupus erythematosus (SLE)

Definition

SLE is an autoimmune disease in which organs and cells undergo damage mediated by tissue-binding autoantibodies and immune complexes.

Prevalence

90% of patients are women of child-bearing age group. Both sexes, all ages, and all ethnic groups are susceptible. Prevalence in the United States is 15–50 per 100,000; the highest prevalence amongethnic groups studied is in African Americans.

Etiology and Pathogenesis

Interactions between susceptibility genes and environmentalfactors result in abnormal immune responses. Cell antigens, autoantibodies, and immune complexes persist for prolonged periodsof time, allowing inflammation and disease to develop Anti nuclear antibodies, and Anti ds DNA. SLE is a multigenic disease.

Diagnostic Criteria

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Arthritis
- Renal disorder
- Haematological disorder and Anti nuclear antibodies.

Treatment

- NSAID
- Topical sunscreen
- Methotrexate
- Glucocorticoids
- Methyl prednisolone
- Cyclophosphamide
- Azathioprine
- Hydroxychloroquine.

AIM

AND

OBJECTIVES

AIMS & OBJECTIVES

Aim:

A Systematic Review of CRP and ANTI CPP Marker in Spesis

Objectives:

- To evaluate the diagnostic utility of Anti- CCP (cyclic citrullinated peptide) antibody in spesis.
- To study & compare the presence of Anti- CCP antibody in Rheumatoid arthritis (RA) with other arthritis. – Early Synovitis (ES),Connective Tissue Disorders (CTD) including SLE, and Osteo Arthritis (OA).
- To evaluate the significance of Anti- CCP antibody in Sero Negative Rheumatoid Arthritis.
- To assess the sensitivity and specificity of the Anti CCP antibody test with RF test in RA and other arthritis.

MATERIALS

AND

METHODS

METHODOLOGY

AREAOFSTUDY:- Bacteriology

TYPE OF STUDY: -Systematic- Review

RESEARCH OF DESIGN:-Qualitative and Quantitative.

DATA TYPE: - Data for this meta-analysis were collected from following sources.

a) Data from various publications in indexed journals.

b) Data from recent editions of textbooks.

c) Online data from various literature reviews.

d) Data from websites of CDC, NCDC, WHO.

TIME FRAME: - All the studies in indexed journal from year 2005 to 2021.

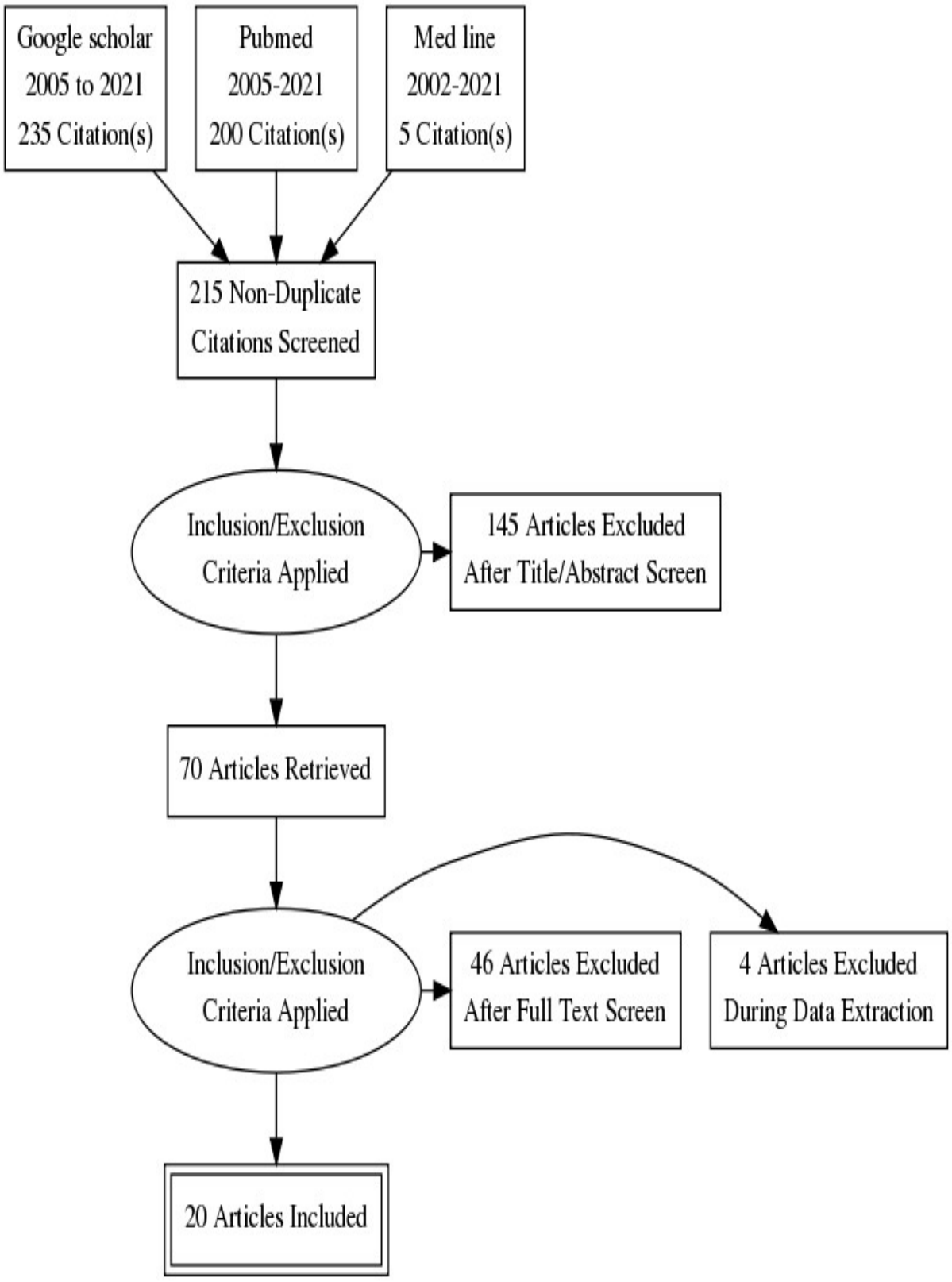
SEARCH STRATEGY: - This systematic-review followed the PRISMA guidelines. Articles were searched on PubMed, Google scholar, Web of Science, Science Direct, and Scopus using terms related to anti ccp and crp marker in sepsis where used, were used. Boolean AND, OR and NOT were used.

INCLUSION CRITERIA: - Article titles and abstracts were screened to include relevant articles.crp and anti ccp marker in sepsis infections in India, the presence of Anti- CCP antibody in Rheumatoid arthritis (RA) with other arthritis. – Early Synovitis (ES),Connective Tissue Disorders (CTD) including SLE, and Osteo Arthritis (OA).species of treatment and prevention of arthritis

EXCLUSION CRITERIA: - Article titles and abstracts were screened by researchers independently to exclude irrelevant articles.

Study Selection Process:

At the first stage of the search, 396 articles were found, and after reviewing the titles of articles, 192 duplicate and overlapping articles were deleted and 204 articles remained. In total, 192 articles were removed due to noncompliance with the criteria, the extract of 70 potentially related articles were reviewed, and 46 articles were excluded due to lack of access to the full text of the article 4 article excluded during data extraction. Finally, 28 appropriate papers were selected to enter the meta-analysis stage.


Google scholar
2005 to 2021
235 Citation(s)
Pubmed
2005-2021
200 Citation(s)
Med line
2002-2021
5 Citation(s)
215 Non-Duplicate
Citations Screened
Inclusion/Exclusion
Criteria Applied
145 Articles Excluded
After Title/Abstract Screen
70 Articles Retrieved
Inclusion/Exclusion
Criteria Applied
46 Articles Excluded
After Full Text Screen
4 Articles Excluded
During Data Extraction
20 Articles Included

OBSERVATION

AND

RESULTS

The prevalence of anti-CCP in different rheumatic diseases.

Disease	**Prevalence (%) of anti-CCP**	**Author**
1. Psoriatic arthritis Control	17.7% (11/62) 4.1% (9/98)	Bockelmann R (Ref. 33)
2. Psoriatic arthritis Control	5.6% (7/126) 0% (0/97)	Korendowych E (Ref. 27)
3. Sjogren's syndrome	7.5% (10/149)	Gottenberg JE (Ref. 30)
4. Sjogren's syndrome	0% (0/7)	Sene D (Ref. 34)
5. HCV (+) with arthragia	5.7% (2/35)	Sene D (Ref. 34)
6. Polymyalgia rheumatica	0% (0/49)	Lopez-Hoyos M (Ref. 49)
7. Palidromic rheumatism (pure form)	56.3% (18/32)	Salvador G (Ref. 44)

Studies of anti-CCP and RF levels following treatment for RA.

Study	Subjects	Serum Test	Results
Alessandri et al., 2004 [124]	Prospective cohort study of 43 patients with RA not responding to DMARDs treated with infliximab in combination with methotrexate	Serum samples collected and tested for anti-CCP antibodies and RF at baseline and after 24 weeks	(i) Serum titres of anti-CCP and RF decreased significantly after 24 weeks of treatment (anti-CCP −14%; RF −20%) (ii) Significant decreases in serum anti-CCP antibodies and RF observed only in patients with clinical improvement
Atzeni et al., 2006[128]	57 patients with RA not responsive to methotrexate treated with adalimumab as part of the ReAct open-label phase IIIb study	Serum samples collected and tested for anti-CCP antibodies and RF at baseline and after 24 and 48 weeks of followup	(i) Treatment resulted in significant decreases in anti-CCP serum levels at 24 weeks (−14%) and 48 weeks (−33%) (ii) Treatment resulted in significant decreases in RF serum levels at 24 weeks (−33%) and 48 weeks (−42%) (iii) The decrease in anti-CCP and RF antibody titers correlated with the clinical response to the therapy
Bobbio- Pallavicini et al., 2004 [131]	Prospective study of 30 consecutive patients with RA; patients were followed during 78 weeks of infliximab and methotrexate therapy for refractory rheumatoid arthritis	Serum samples collected and tested for anti-CCP antibodies and RF at baseline and after 30, 54 and 78 weeks	(i) % patients positive for RF, Anti-CCP approximately same at baseline and 78 weeks (ii) Median RF titre underwent progressive reduction from 128 IU/mL to 53 IU/mL (iii) Anti-CCP antibody titre significantly decreased at 30 weeks but returned to baselinev
Chen et al., 2006 [130]	90 patients with RA who failed treatment with DMARDs;	Serum samples collected and tested for anti-CCP and	(i) Serum anti-CCP levels decreased 31.3% in patients positive for anti-CCP at

	randomized clinical protocol in which all 90 patients continued DMARD treatment and 52 patients were assigned for additional treatment with etanercept	RFat baseline and one month intervals for three months during the treatment course	baseline treated with etanercept (ii) Serum RF levels decreased 36% in patients positive for RF at baseline treated with etanercept (iii) Decreases in serum anti-CCP and RF levels were progressive throughout the three-month treatment course (iv) Changes in anti-CCP levels was positively correlated with changes in various clinical measures of RA
De Rycke et al., 2005 [132]	Prospective cohort study of 62 patients with refractory RA treated with infliximab combined with methotrexate	Serum samples collected and tested for anti-CCP antibodies, IgM RF, CRP and ESR at baseline and after 30 weeks	(i) RF titres significantly reduced at baseline and week 30 during infliximab treatment (ii) Anti-CCP antibodies unchanged by infliximab treatment (iii) IgM RF titres correlated inversely with changes in CRP and ESR; Anti-CCP antibodies did not correlate inversely with these biomarkers
Mikuls et al., 2004 [126]	Retrospective study of serum samples from 66 RA patients who completed double-blind, randomized clinical protocols (2) methotrexate, hydroxychloroquine, and sulfasalazine, (2) minocycline versus placebo, and (3) minocycline versus hydroxychloroquine	Serum samples collected at baseline and at a followup averaging 13.7 months ± 8.6 months; Samples were stored at −80° and later and tested for anti-CCP antibodies and RF	(i) 52% of patients positive for anti-CCP antibodies at baseline had >25% reduction in anti-CCP antibody levels during treatment course (ii) 55% of patients positive for RF at baseline had >25% reduction in RF levels during treatment course (iii) Significant reductions in anti-CCP levels was only seen in patients with disease duration <12 months (iv) No association was seen between reductions in anti-CCP levels and treatment response (v) Significant reductions in RF levels were determined by treatment response

DISCUSSION

DISCUSSION

RA is associated with only a few specific auto antibodies, including APF, AKA and anti-CCP and several less specific auto antibodies including RF[4]. Despite a well-documented lack of specificity, RF continues to be a serological test for RA because of its inclusion in ACR criteria. However to date no single autoantibody has demonstrated adequate positive diagnostic value to form the basis of clinical decisions. So auto antibodies present in RA, Early Synovitis, connective tissue disorders including SLE and OA have been evaluated in the present study, mainly for their diagnostic value.

The modern trend in management of RA is to start the treatment as early as possible, based on the concept that early control of inflammation results in reduced joint damage. If undiagnosed the patients will not get treatment at an early date or if wrongly diagnosed as RA , will be unnecessarily treated with Anti Rheumatic drugs. It is therefore important to differentiate between RA and other forms of arthritis early, before the onset of symptoms. In recent research by Schellekens GA,[17] he has observed the diagnostic significance of a novel RA specific autoantibody, determined by ELISA using synthetic peptides containing citrulline. The present study was done to determine the sensitivity and specificity of the RF and anti CCP antibodies, alone or in combination in relation to RA & other arthritis.

In the present study which was carried out on patients having different Arthritic diseases, Anti CCP test results suggest the significance of anti CCP positivity in diagnosis of RA and differentiating RA from other arthritis. To minimize the errors patients were selected according to the inclusion criteria's.

For specificity calculation of RA, other arthritis and control groups were included, but ES was not included because it is in an undifferentiated form (not confined to any single entity, which maylater convert into RA or other form of arthritis).

Of all the above different Rheumatological diseases, Anti CCP was more sensitive and more specific for RA, whereas RF was almost equally sensitive but less specific than Anti CCP for RA, because it is positive in other arthritic diseases and healthy persons also.

The results were in agreement with other studies in which the Anti CCP was positive in RA, ES and CTD including SLE, but the RF was non specific and present in all groups including control.

Age/Sex distribution of various Arthritic diseases:Age :

In RA age group 51-60 years were more affected than other groups.
In age group31-40yrs and 41-50yrs ES & CTD were more common. OA was very common in age group 41-50yrs .The incidence of alltypes of arthritis is very low in age group of 20-30 years.

Other Arthritis (OA) and HBD:

The present study results showed none of the OA and Healthy Blood Donors had positive Anti-CCP values which is in positive correlation with the study by **Sibel Altun et al**[5] who also observed that none of the OA and Healthy Blood Donors had positive anti-CCP values.

Another study by **Nehir Samanci et al** [11] showed only one as (1.2%) anti-CCP positive in the control group which is not in consistent with the present study. Absence of anti CCP antibodies inOA and HBD signifies its specificity in RA and will help in excluding them from RA.

In the present study **RF** was positive in 6 of 50 (12%) OA patients (all the 6 were anti CCP –ve) and in 4of 50 (8%) HBD, which goes in agreement with the study by **Sibel Altun et al** [5] showing (10%) RF positivity in OA patients and 10% in HBD. The results denotesthe non specificity of RF because of its presence in healthy personsand other arthritic cases.

Another study by **Nehir Samanci et al** [11] shows 44.8% RF positivity in OA cases and 4.8% in controls which is higher than the present study. This disparity of the results could be due to age mis- matched controls and small sample size (due to categorization of subjects into many groups). An ideal control population would have been an age-matched normal control population.

RF –ve (sero negative):

In the present study 6 of 12 (50%) sero negative patients were positive for anti CCP, this goes in parallel with **Eric-Jan J. A. et al** [14] study which showed 43%anti CCP positivity. Similarly in a study by **Kroot EJ, and a Vallbracht et aI,**[16] 40% of seronegative patients wereanti-CCP-positive which substantiates the additional diagnostic potential of Anti CCP in seronegative patients also.In another study **by Quinn et al** [18] sensitivity was 60%, which is higher rate than thepresent study.

Gerard A. Schellekens et al [8] study shows 35% specificityand in a **multicentre** study [18] &a study by **Munevver Serdaroflu et al**

The specificity was 20%.Even though the % is less, it also showedthe anti CCP positivity in seronegative patients, signifies the diagnostic potential of anti CCP which will be helpful in treating the undiagnosed or missed diagnosis (seronegative) cases of RA and can prevent the post sequlae.

If positive, the anti-CCP test is an important surrogate marker especially for RF-negative RA.

CONCLUSION

CONCLUSION

The ACPA era has just begun, and is creating a revolution in Rheumatology. As per the findings of the present study Anti CCP test is more sensitive and highly specific. Anti CCP antibody is a very valuable serological indicator in diagnosis of RA.Besides being a specific marker in advanced RA, the anti CCP antibody in ES is a very important predictor (diagnostic marker) of RA.

Anti CCP has the hallmark of establishing as a diagnostictool and provides additive sensitivity to RF. The presence of both RF and Anti CCP in serum is a strong indicator of RA.

Association of Anti-CCP with other Connective Tissue Disorders including SLE is very low when compared to its significant association with RA.Thus it helps in distinguishing RA from other erosive disorders.

Anti CCP is positive in 50% of Seronegative arthritis (RF negative) patients.Thus it proved to be a more sensitive diagnostic tool, which helps in detection (not missing the diagnosis) of RA,very early in course.

Absence of Anti CCP in OA and HBD makes it more specific for RA.But the presence of RF to a lesser extent in the above conditions makes (RF) it less specific.

In conclusion, based upon the higher sensitivity and specificity of the Anti CCP test in RA, the current study is of diagnostic, and public importance, because it suggests that Anti CCPtest should be included in the investigation of undifferentiated arthritis, since a considerable amount of Rheumatic disease associated workdisability starts in the first few years of the disease.

Anti-CCP antibodies have all the hallmarks of establishing themselves firmly in the diagnostic algorithm of Rheumatoid Arthritis providing additive sensitivity to Rheumatoid Factor. So it should alsobe included among the diagnostic criteria of RA along with RF.

It can also be used as a prognostic indicator in RA patients on treatment.

Anti CCP and **RF - both positive** was *moderately sensitive and equally specific* for RA (similar to anti CCP), less sensitive and more specific than RF alone,and Anti CCP/ RF. But

Anti CCP/ RF - any one test positive was *more sensitive and less specific* than the combination of both tests and Anti CCP test alone and more sensitive but equally specific when compared to RF test alone.

This shows that the anti- CCP positivity gives additive value as a diagnostic test for RA and the combination of tests are valuable as a diagnostic tool in RA and in differentiating or excluding it from other arthritis. Majority of the previous studies show greater significanceof anti CCP in RA,and ES (undifferentiated arthritis) as a diagnostic tool and early predictor in ES, also in excluding them from non RA.

In the present study, Anti CCP anti bodies in Rheumatoid Arthritis and other arthritis patients were assessed and also inhealthy blood donors as control.

The anti CCP test shows high positive rate in RA patients than other arthritic disease patients, and negative in OA and in Healthy Blood Donors .This reconfirmed the better specificity of anti CCP test in RA and thus it can be used as a diagnostic tool.

Anti-CCP antibodies determination, proved to be a powerful diagnostic tool,especially in sero negative (RF negative) patients.

Anti CCP was very sensitive in Early Synovitis also.This confims it's importantance in the discrimination of early diagnosis of RAin undifferentiated arthritis.

Since Anti CCP positivity is very low in SLE it helps in differentiating RA from other connective tissue disorders including SLE patients.

Anti CCP was negative in OA and HBD. So it will be useful in excluding these cases from RA.

Even though RF is equally sensitive as Anti CCP in RA, it is less specific when compared with Anti CCP .

BIBLIOGRAPHY

REFERENCES

1. Schellekens, G.A., B.A. De Jong, F.H. Van Den Hoogen, *et al*. 1998. Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. *J. Clin. Invest.* **101:** 273–281.

2. Girbal-Neuhauser, E., J.J. Durieux, M. Arnaud, *et al*. 1999. The epitopes targeted by the rheumatoid arthritis-associated antifilaggrin autoantibodies are posttranslationally generated on various sites of (pro)filaggrin by deimination of arginine residues. *J. Immunol.* **162:** 585–594.

3. Schellekens, G.A., H. Visser, B.A. De Jong, *et al*. 2000. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. *Arthritis Rheum.* **43:** 155–163.

4. Van Boekel, M.A., E.R. Vossenaar, F.H. Van Den Hoogen, *et al*. 2002. Autoantibody systems in rheumatoid arthritis: specificity, sensitivity and diagnostic value. *Arthritis Res.* **4:** 87–93.

5. Combe, B., R. Landewe, C. Lukas, *et al*. 2007. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann. Rheum. Dis.* **66:** 34–45.

6. Arnett, F.C., S.M. Edworthy,D.A. Bloch, *et al*. 1988. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* **31:** 315–324.

7. El Miedany, Y., S. Youssef, A.N. Mehanna, *et al*. 2008. Development of a scoring system for assessment of outcome of early undifferentiated inflammatory synovitis. *Joint Bone Spine.* **75:** 155–162.

8. Syversen, S.W., P.I. Gaarder, G.L. Goll, *et al*. 2008. High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study. *Ann. Rheum. Dis.* **67:** 212–217.

9. Wild, N., J. Karl, V.P. Grunert, *et al*. 2008. Diagnosis of rheumatoid arthritis: multivariate analysis of Biomarkers. *Biomarkers* **13:** 88–105.

10. Van Der Helm-Van Mil, A.H., S. Le Cessie, H. Van Dongen, *et al*. 2007. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. *Arthritis Rheum*. **56:** 433–440

11. Klareskog L, Rönnelid J, Lundberg K, Padyukov L, Alfredsson L. Immunity to citrullinated proteins in rheumatoid arthritis. Annu Rev Immunol 2008; 26: 651-75.

12. Engelmann R, Brandt J, Eggert M, Karberg K, Krause A, Neeck G, et al. IgG1 and IgG4 are the predominant subclasses among auto-antibodies against two citrullinated antigens in RA. Rheumatology 2008; 47: 1489-92.

13. Sauerland U, Becker H, Seidel M, Schotte H, Willeke P, Schorat A, et al. Clinical utility of the anti-CCP assay. Experiences with 700 patients. Ann NY Acad Sci 2005; 1050: 314-8.

14. Riccio A, Postiglione L, La Dogana P, Spano A, Marzocchella C, Tarantino G. Anti-cyclic citrullinated peptide antibodies in patients affected by HCV-related arthritis. J Biol Regul Homeost Agents 2008; 22: 57-61.

15. Liu FC, Chao YC, Hou TY, Chen HC, Shyu RY, Hsieh TY, et al. Usefulness of anti-CCP antibodies in patients with hepatitis C virus infection with or without arthritis, rheumatoid factor, or cryoglobulinemia. Clin Rheumatol 2008; 27: 463-7.

16. Palazzi C, D'Angelo S, Olivieri I. Hepatitis C virus-related arthritis. Autoimmunity Reviews 2008; 8: 48-51.

17. Mutlu N, Bıcakcıgil M, Tasan DA, Kaya A, Yavuz S, Ozden Al. Comparative performance analysis of 4 different anti-citrullinated protein assays in the diagnosis of rheumatoid arthritis. J Rheumatol 2009, 36: 491-500.

18. Wagner E, Skoumal M, Bayer PM, Klaushofer K. Antibody against mutated citrullinated vimentin: a new sensitive marker in the diagnosis of rheumatoid arthritis. Rheumatol Int 2009; 29: 1315-21.

19. Luime JJ, Colin EM, Hazes JM, Lubberts E. Does anti- MCV has additional value as a serological marker in the diagnostic and prognostic work-up of patients with rheumatoid arthritis? A systematic review. Ann Rheum Dis 2010; 69: 337-44.

20. Sghiri R, Bouajina E, Bargaoui D, Harzallah L, Fredj HB, Sammoud S, et al. Value of anti-mutated citrullinated vimentin antibodies in diagnosing rheumatoid arthritis. Reumatol Int 2008; 29: 59-62.

21. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315-24.

22. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008; 59: 762-84.

23. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995, 22:696-9.

24. Mathsson L, Mullazehi M, Wick MC, Sjöberg O, van Vollenhoven R, Klareskog L, et al. Higher sensitivity and extended prognostic value concerning future radiographic progression as compared with antibodies against cyclic citrullinated peptides. Arthritis Rheum 2008; 58: 36-45.

25. Nicaise Roland P, Grootenboer Mignot S, Bruns A, Hurtado M, Palazzo E, Hayem G, et al. Antibodies to mutated citrullinated vimentin for diagnosing rheumatoid arthritis in anti-CCP-negative patients and for monitoring infliximab therapy. Arthritis Res Ther 2008; 10:R142.

26. Ursum J, Nielen MM, van Schaardenburg D, van der Horst AR, van de Stadt RJ, Dijkmans BA, et al. Antibodies to mutated citrullinated vimentin and disease activity score in early arthritis: a cohort study. Arthritis Res Ther 2008; 10: R12.

27. Dejaco, C, Klotz W, Larcher H, Duftner C, Schirmer M, Herold M. Diagnostic value of antibodies against a modified citrullinated vimentin in rheumatoid arthritis. Arthritis Res Ther 2006; 8: R119.

28. Bang H, Egerer K, Gauliard A, Lüthke K, Rudolph PE, Fredenhagen G, et al Mutation and citrullination modifies vimentin to a novel autoantigen for rheumatoid arthritis. Arthritis Rheum 2007; 56: 2503-11.

29. Innala L, Kokkonen H, Eriksson C, Jidell E, Berglin E,Dahlqvst SR. Antibodies against mutated citrullinated vimentin are better predictors of disease activity at 24 months in early rheumatoid arthritis than antibodies against cyclic citrullinated peptides. J Rheumatol 2008; 35: 1002-8.

30. Poulsom H, Charles PJ. Antibodies to citrullinated vimentin are a specific and sensitive marker for the diagnosis of rheumatoid arthritis. Clinic Rev Allerg Immunol 2008; 34: 4-10.

31. G. A. Schellekens, H. Visser, B. A. W. De Jong et al., "The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide," Arthritis and Rheumatism, vol. 43, no. 1, pp. 155–163, 2000.

32. Y. Takasaki, K. Yamanaka, C. Takasaki et al., "Anticyclic citrullinated peptide antibodies in patients with mixed connective tissue disease," Modern Rheumatology, vol. 14, no. 5, pp. 367–375, 2004.

33. A. Vannini, K. Cheung, M. Fusconi et al., "Anti-cyclic citrullinated peptide positivity in non-rheumatoid arthritis disease samples: citrulline-dependent or not?," Annals of the Rheumatic Diseases, vol. 66, no. 4, pp. 511–516, 2006.

34. E. Besada, C. Nikolaisen, and H. Nossent, "Diagnostic value of antibodies against mutated citrullinated vimentin for rheumatoid arthritis," Clinical and Experimental Rheumatology, vol. 29, no. 1, pp. 85–88, 2011.

35. J. Sun, Y. Zhang, L. Liu, and G. Liu, "Diagnostic accuracy of combined tests of anti cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis: a meta-analysis," Clinical and Experimental Rheumatology, vol. 32, no. 1, pp. 11–21, 2014.

36. M. Sebbag, M. Simon, C. Vincent et al., "The antiperinuclear factor and the so-called antikeratin antibodies are the same rheumatoid arthritis-specific autoantibodies," The Journal of Clinical Investigation, vol. 95, no. 6, pp. 2672–2679, 1995.

37. M. A. van Boekel, E. R. Vossenaar, F. H. van den Hoogen, and W. J. van Venrooij, "Autoantibody systems in rheumatoid arthritis: specificity, sensitivity and diagnostic value," Arthritis Research, vol. 4, no. 2, pp. 87–93, 2002.

38. C. CORDONNIER, O. MEYER, E. PALAZZO et al., "Diagnostic value of anti-RA33 antibody, antikeratin antibody, antiperinuclear factor and antinuclear antibody in early rheumatoid arthritis: comparison with rheumatoid factor," Rheumatology, vol. 35, no. 7, pp. 620–624, 1996.

39. H.-G. Schneider and L. Q. Thanh, "Procalcitonin for the clinical laboratory: a review," Pathology, vol. 39, no. 4, pp. 383– 390, 2007.

40. C. WANG, D. ZHONG, Q. LIAO, L. KONG, A. LIU, and H. XIAO, "Procalcitonin levels in fresh serum and fresh synovial fluid for the differential diagnosis of knee septic

arthritis from rheumatoid arthritis, osteoarthritis and gouty arthritis," Experimental and Therapeutic Medicine, vol. 8, no. 4, pp. 1075–1080, 2014.

41. K. Saeed, N. Ahmad, and M. Dryden, "The value of procalcitonin measurement in localized skin and skin structure infection, diabetic foot infections, septic arthritis and osteomyelitis," Expert Review of Molecular Diagnostics, vol. 14, no. 1, pp. 47– 54, 2014.

42. M. Talebi-Taher, F. Shirani, N. Nikanjam, and M. Shekarabi, "Septic versus inflammatory arthritis: discriminating the ability of serum inflammatory markers," Rheumatology International, vol. 33, no. 2, pp. 319–324, 2013.

43. T. Hügle, P. Schuetz, B. Mueller et al., "Serum procalcitonin for discrimination between septic and non-septic arthritis," Clinical and Experimental Rheumatology, vol. 26, no. 3, pp. 453– 456, 2008.

44. A. Kuuliala, A. Takala, S. Siitonen, M. Leirisalo-Repo, and H. Repo, "Cellular and humoral markers of systemic inflammation in acute reactive arthritis and early rheumatoid arthritis," Scandinavian Journal of Rheumatology, vol. 33, no. 1, pp. 13–18, 2004.

45. M. Martinot, C. Sordet, M. Soubrier et al., "Diagnostic value of serum and synovial procalcitonin in acute arthritis: a prospective study of 42 patients," Clinical and Experimental Rheumatology, vol. 23, no. 3, pp. 303–310, 2005.

46. B. Uzzan, R. Cohen, P. Nicolas, M. Cucherat, and G.-Y. Perret, "Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis," Critical Care Medicine, vol. 34, no. 7, pp. 1996–2003, 2006.

47. O. K. Eberhard, M. Haubitz, F. M. Brunkhorst, V. Kliem, K. M. Koch, and R. Brunkhorst, "Usefulness of procalcitonin for differentiation between activity of systemic autoimmune disease (systemic lupus erythematosus/systemic antineutrophil cytoplasmic antibody-associated vasculitis) and invasive bacterial infection," Arthritis and Rheumatism, vol. 40, no. 7, pp. 1250–1256, 1997.

48. F. Moosig, E. Csernok, E. Reinhold-Keller, W. Schmitt, and W. L. Gross, "Elevated procalcitonin levels in active Wegener's granulomatosis," The Journal of Rheumatology, vol. 25, no. 8, pp. 1531–1533, 1998.

49. Y. Okada, H. Minakami, T. Tomomasa et al., "Serum procalcitonin concentration in patients with Kawasaki disease," The Journal of Infection, vol. 48, no. 2, pp. 199–205, 2004.

50. C. A. Scirè, L. Cavagna, C. Perotti, E. Bruschi, R. Caporali, and C. Montecucco, “Diagnostic value of procalcitonin measurement in febrile patients with systemic autoimmune diseases,” Clinical and Experimental Rheumatology, vol. 24, no. 2, pp. 123–128, 2006.

51. C. Morath, J. Sis, G. M. Haensch, M. Zeier, K. Andrassy, and V. Schwenger, “Procalcitonin as marker of infection in patients with Goodpasture’s syndrome ismisleading,” Nephrology, Dialysis, Transplantation, vol. 22, no. 9, pp. 2701–2704, 2007.

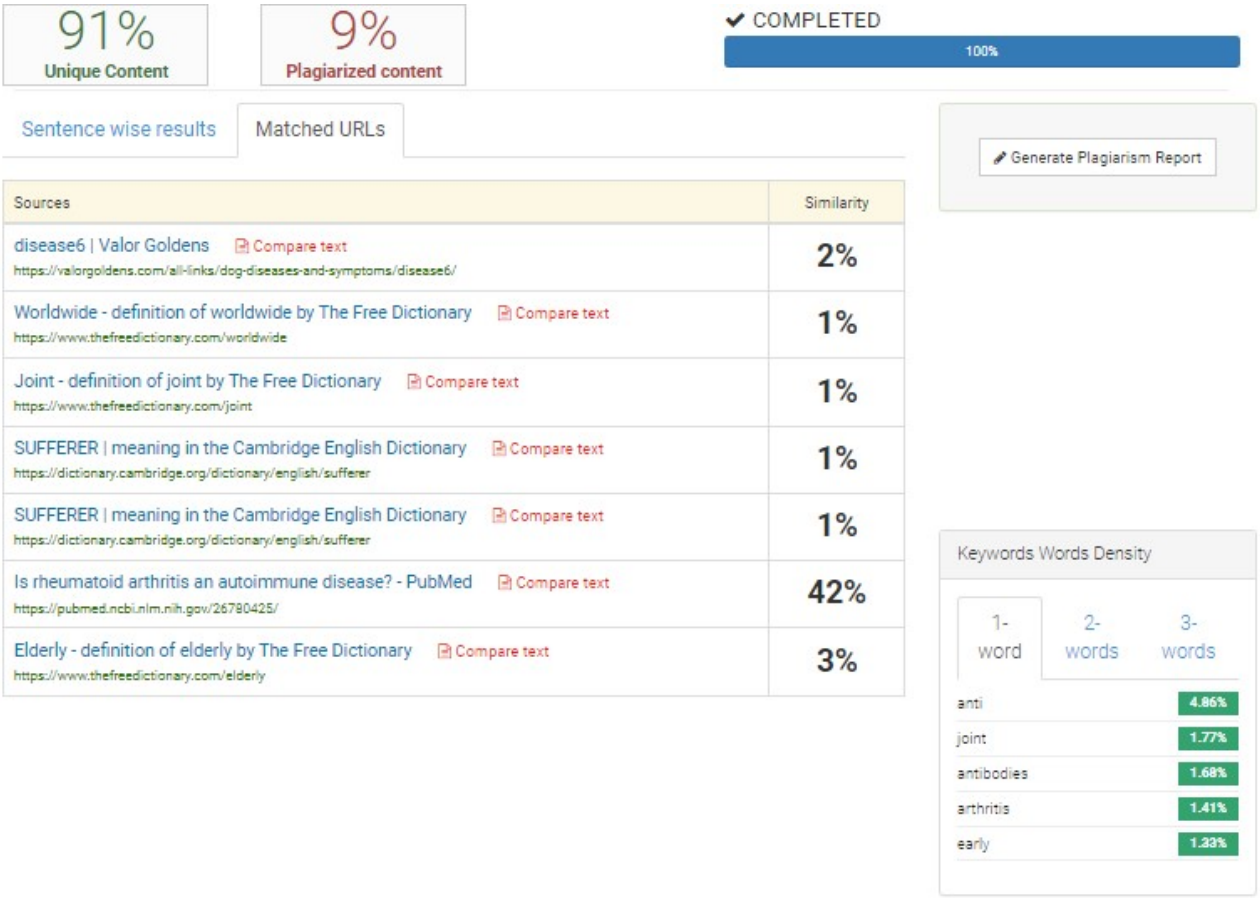
52. W. J. van Venrooij, J. J. B. C. van Beers, and G. J. M. Pruijn, “Anti-CCP antibody, a marker for the early detection of rheumatoid arthritis,” Annals of the New York Academy of Sciences, vol. 1143, no. 1, pp. 268–285, 2008.

53. K. Tsujimoto, A. Hata, M. Fujita, S. Hatachi, and M. Yagita, “Presepsin and procalcitonin as biomarkers of systemic bacterial infection in patients with rheumatoid arthritis,” International Journal of Rheumatic Diseases, vol. 21, no. 7, pp. 1406–1413, 2018.

54. P. F. Whiting, N. Smidt, J. A. C. Sterne et al., “Systematic review: accuracy of anti–citrullinated peptide antibodies for diagnosing rheumatoid arthritis,” Annals of Internal Medicine, vol. 152, no. 7, p. 456, 2010.

55. S. R. Johnson, O.-N. Goek, D. Singh-Grewal et al., “Classification criteria in rheumatic diseases: a review of methodologic properties,” Arthritis and Rheumatism, vol. 57, no. 7,

pp. 1119–1133, 2007.


91%
Unique Content
9%
Plagiarized content
COMPLETED
100%
Sentence wise results
Matched URLs
Generate Plagiarism Report
Sources
Similarity
disease6 | Valor Goldens
Compare text
https://valorgoldens.com/all-links/dog-diseases-and-symptoms/disease6/
2%
Worldwide - definition of worldwide by The Free Dictionary
Compare text
https://www.thefreedictionary.com/worldwide
1%
Joint - definition of joint by The Free Dictionary
Compare text
https://www.thefreedictionary.com/joint
1%
SUFFERER | meaning in the Cambridge English Dictionary
Compare text
https://dictionary.cambridge.org/dictionary/english/sufferer
1%
SUFFERER | meaning in the Cambridge English Dictionary
Compare text
https://dictionary.cambridge.org/dictionary/english/sufferer
1%
Is rheumatoid arthritis an autoimmune disease? - PubMed
Compare text
https://pubmed.ncbi.nlm.nih.gov/26780425/
42%
Elderly - definition of elderly by The Free Dictionary
Compare text
https://www.thefreedictionary.com/elderly
3%
Keywords Words Density
1-word
2-words
3-words
anti 4.86%
joint 1.77%
antibodies 1.68%
arthritis 1.41%
early 1.33%