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Chronic Nonbacterial Osteomyelitis (CNO) at a Single Center Large Academic Children's Hospital

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Bachelor of Science

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2022

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An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Global Health

2024

Abstract

Chronic Nonbacterial Osteomyelitis (CNO) at a Single Center Large Academic Children's Hospital
By Mara Rodriguez

Objective

One of the conditions patients are seen in pediatric rheumatology for is Chronic Nonbacterial Osteomyelitis (CNO), also referred to as Chronic Recurrent Multifocal Osteomyelitis (CRMO). Within the United States, there is a lack of literature published regarding extra osseous features present within patients that have CNO/CRMO, along with any differences in patterns of disease amongst genders, age, and having a familial history of autoimmunity. The objective of this study was to assess the patients clinical features and outcomes at their last clinical visit at this single center large academic children's hospital that have CNO/CRMO.

Methods

The study population is 111 pediatric patients that have been diagnosed with CNO/CRMO and are seen by pediatric rheumatologists at this institution from August 1st, 2013-August 1st, 2023. The inclusion criteria for this study consisted of patients with a physician designated diagnosis of CNO/CRMO on their EPIC Chart, have at least one whole body MRI, and age <21 years old at time of enrollment. The pediatric patients that do not fit all three of these inclusion criteria points were not included, along those who were diagnosed with osteomyelitis as a result of infection. The procedures that were fulfilled for data compilation began with obtaining list of pediatric subjects with rheumatology encounters who also have ICD-9 or ICD-10 codes consistent with CNO/CRMO.

Results

Within the study population, 44.1% of the study participants were male, 54.1% of the study participants were female and 1.8% of the study population chose not to disclose their gender. This study found the average age of onset of disease for both males and females was 9 years old. The average age of diagnosis for females was 10 years old and 9 years old for males. The most significant extra osseous features that were associated with CNO/CRMO were arthritis with 7.2%, psoriasis with 6.3%, and IBD with 4.5%. Additionally, we found a consistent familial history of autoimmunity present on both the maternal side with 40.5% and paternal side with 20.7% .

Conclusion

As this study was conducted at a single center large academic children's hospital in the Rheumatology Department, many patients who come in have extra osseous features such as arthritis, psoriasis, and IBD. As well, there should be an emphasis on diagnosis and standardized clinical questionnaires for physicians within pediatrics as this can aid in bridging the gap with the ramifications of delayed treatment. This study points an emphasis on the continuation of publishing literature on the various clinical features and outcomes that are present amongst those diagnosed with CNO/CRMO. This is important as a wide array of features and outcomes can present themselves amongst pediatric patients.

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Acknowledgements

First, I would like to express my wholehearted appreciation to my superb advisor Dr. Solveig Argeseanu Cunningham who has been the biggest supporter and leader for me these last two years of my masters study with my thesis. I would also like to express my earnest gratitude to Dr. Sampath Prahalad who has also supported me and guided me unconditionally throughout my two-year master study. Without both of their professional leadership, provision, and fortitude, my thesis would not have been feasible. I would like to also extend my utmost gratitude to thank Dr. Rob O'Reilly at Emory's Center for Digital Scholarship who guided me in using SAS 9.4 Software with my extensive dataset. As well, I would like to send my greatest appreciation and thankfulness to Allison Dodo at the Emory Writing Center for her guidance and support with my thesis structure. Lastly, I would like to thank my beautiful family and friends for their inspiration and empathy throughout the extent of my education.

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I. Introduction

Background

Chronic Nonbacterial Osteomyelitis (CNO) also referred to as Chronic Recurrent Multifocal Osteomyelitis (CRMO) are both classified as rheumatic autoimmune diseases that present bone lesions on a patient's body either in one distinct location (CNO) or multifocally on the patient's body (CRMO) (Cebecauerová et al., 2022). Rheumatic diseases are defined as, "an umbrella term that refers to arthritis and several other conditions that affects the joints, tendons, muscles, ligaments, bones, and muscles" (CDC, 2022). It is vital to understand that regarding juvenile rheumatologic diseases, they are noted to be, "a collection of autoimmune disorders where the body's immune system attacks the body's own cells rather than protecting the body from disease. This abnormal immune system activity is what causes pain, inflammation, and many other symptoms" (Soybilgic, 2015). CNO/CRMO affects the bones, resulting in negative alterations in ones joints, ligaments, and overall mobility. CNO/CRMO is severely underdiagnosed and has been noted have an average delay of one year from the onset of symptoms to final diagnosis (Schnabel et al., 2022). CNO is relatively less frequent among childhood rheumatic disorders, with an overall incidence of 0.4 per 1,000 people per year (Cebecauerova, 2022). Numerous studies conducted globally have reported that the consensus is that "about 1 in every 100,000 children are living with this condition" (Suo et al., 2022). Looking more broadly at rheumatic diseases in general, it is important to know that "more than one million children in the United States are affected by rheumatologic diseases each year" (The Children's Hospital at Montefiore, 2023). Two of the more common childhood rheumatic

diseases are juvenile idiopathic arthritis and childhood onset systemic lupus erythematosus, however it has been reported that “more than 500,000 children develop other rheumatic diseases” (The Childrens Hospital at Montefiore, 2023). CNO is noted to be seen more in pediatric patients, and as a rheumatic disease, these sort of diseases “are one of the chronic conditions with high risk of mortality and a long-term disability if not recognized and treated properly” (Dahman, 2017). This statistic points out the importance of how critical timing is in terms of diagnosis and treatment regarding childhood rheumatic diseases.

Challenges to Pediatric Rheumatology in the US

There are various barriers that present themselves with the intricate details and steps physicians need to take when seeing and treating pediatric patients with rheumatic diseases here in the United States. One of the first barriers is “there is no single test to diagnose rheumatologic diseases in children. Moreover, the collection of symptoms experienced by children with these conditions can often make diagnosing the disease difficult and time consuming” (Soybilgic, 2015). In regard to CNO/CRMO, this is a disease with diagnosis of exclusion. This means that in order for physicians to diagnose patients with this disease they first need to rule out all other diseases based on the symptoms being displayed. This makes it more challenging for physicians when trying to diagnose patients due to the various clinical features patients can present based on a plethora of reasons such as the patients demographics, overall health, and other underlying factors. Regarding CNO/CRMO and other rheumatic diseases, it is important to know that “the exact causes of autoimmune diseases and disorders remain unknown” (Soybiligic, 2015). Therefore, “the confusing presentation of musculoskeletal (MSK) symptoms, which are the primary features of rheumatic diseases are also present in other systemic disorders such as

metabolic, endocrine, neoplastic and infectious conditions" (Dahman, 2017). This ultimately broadens the cascade of potential disorders physicians may have to treat their patients for.

Another challenge is the relative paucity of pediatric rheumatologists across the United States (Correll et al., 2024). This can present challenges for those with rheumatic diseases that may be living in areas with shortages of pediatric rheumatologists. In return, this may prevent those from being seen and ultimately treated. Those living in these areas may resort to seeing other physicians, whom may not be experts in rheumatology and may not have the concentrated training in this realm. Data that was reported in 2020, noted that "there was only approximately 300 practicing pediatric rheumatologists in the United States " (Pine, 2023). Numerous studies have estimated that "by 2030, the number of rheumatologists was projected to drop by 25% from 2015 baseline levels, while the patient demand for rheumatologic care is projected to exceed the supply of rheumatologists by over 100%" (Nierengarten, 2022). This statistic magnifies the shortage of trained rheumatic physicians with an increased demand in care from these physicians. With a surplus of pediatric rheumatologists that is being demanded, those living with serious conditions can be effectively aided.

Challenges to Diagnosing Autoimmune Diseases in Pediatric Patients

Due to the broad presentations of autoimmune diseases, they can sometimes be mistaken for common ailments such as flu or viral illnesses. However, these symptoms could be due to underlying childhood rheumatic disorders, that may not be easily detected by a physical examination.. For example, "many of the earliest symptoms like fever and fatigue are nonspecific, meaning they're found in a variety of illnesses, and a single autoimmune disease can show up in different ways in different people or include features of other autoimmune diseases"

(Boston Children's Hospital, 2023). This points out how difficult it can be for physicians to detect certain autoimmune diseases due to the broad range of clinical symptoms the patient can be presenting that are very common in other diseases. This can be very challenging to physicians due to rheumatologist responsibility to "conduct a thorough physical exam" while researching autoimmune history in the family. Once they suspect an autoimmune disease, they must follow up this appointment with "heredity, environmental factors and hormonal factors" (Boston Children's Hospital, 2023). This entire process does take a great length of time and relies on the families to be able to consistently see physicians. This also requires the assumption that this is feasible for families and physicians to have consistent availability for these visits and are not backed up in their schedules. Many times, this is what can create delays in diagnosis for those who may have developed certain rheumatic diseases.

Research Question and Objective

The research question being posed here is what are the clinical features and outcomes of patients at their last clinical visit who are diagnosed with CNO/CRMO at this institution. The data set used is unique because it is from pediatric patients that have been seen in CAP from present day all the way back to August 1st, 2013. The purpose of this descriptive study is to expand understanding and knowledge for pediatric rheumatologists who care for patients with CNO/CRMO whom may present various clinical features and outcomes. What makes this study important and stands out from existing literature is the criterion for patients to be included; all subjects have had at least one whole body MRI. In much of the literature, it is very common to see patients only getting MRI's on certain locations of the body, which can prevent other lesions that may present on the body from being detected. Physicians may not order whole body MRI's

for various of reasons such as insurance purposes or the patient may be experiencing asymptomatic lesions, meaning they do not have any pain or inflammation notable on the body and would only be detectable from a whole-body MRI. This cohort of 111 children is large enough to display a various number of clinical features and outcomes due to the various treatment plans, locations on the body, and extra osseous features present, which ultimately will aid in answering the research question of what the clinical features and outcomes are amongst this research population. This study aims to provide the necessary groundwork for the continuation of prioritizing to learn about this condition by further spreading education on the clinical features and outcomes of the center's CNO/CRMO cases along with diagnoses and treatment plans. This can help lead to the expansion of knowledge and awareness of this rare rheumatic disease for families with young children.

II. Literature Review

Chronic Non-Bacterial Osteomyelitis / Chronic Recurrent Multifocal Osteomyelitis

Background

Chronic Non-Bacterial Osteomyelitis (CNO) is an interchangeable term used with Chronic Recurrent Multifocal Osteomyelitis (CRMO). It has been noted that CNO is the broader terminology used to describe the disease, whereas CRMO indicates the disease was multifocal, which may not always be the case (Zhao et al., 2022). CNO/CRMO is characterized as an autoinflammatory bone disease where there are bone lesions present on the patient's body (Cebecauerová et al., 2022). CNO/CRMO is a diagnosis of exclusion, which prior to final diagnosis creates barriers for patients because many times their symptoms are considered as non-specific or even "silent", meaning asymptomatic. Much literature has pointed out how the average delay from onset to diagnosis is one year for patients (Schnabel et al., 2022). The incidence of this disease is 0.4 per 1,000 people per year, exuberating the need for more awareness surrounding this disease regarding its clinical features, outcomes, diagnostic material, and treatment plans (Cebecauerová, 2022). The disease can be unifocal wherein the bone lesions are only in one location on the body, or multifocal meaning the bone lesions are in various locations on the body. Alternatively, CNO/CRMO can present with intermittent or occasional clinical symptoms and bone lesions, or the disease can be persistent, with clinical and/or radiographic lesions over long durations. CNO/CRMO follows an unpredictable waxing and waning course, however complete remission is observed in some patients. There has not been an official molecular pathway defined of what causes the etiology of this disease to arise in patients (Cebecauerová, 2022). Various systemic features have been noted in patients diagnosed with

CNO/CRMO, such as skin involvement, arthritis, fevers, and weight loss (Taddio et al., 2017). As well, there can be noticeable swelling on the body where the lesions are present, along with pain and warmth in the locations where lesions are existent. What makes it challenging for those who have not undergone MRI's, x-rays, and bone biopsies, is that many patients can also be asymptomatic. This alludes to the notion that without these diagnostic methods, the patient nor the physician would be aware of any bone lesions formed on the body. Other systemic features that have been noted are found from laboratory detection where there are elevated levels of C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) in the patient's blood test results (Schnabel et al., 2022). These elevated inflammatory markers are nonspecific and can be seen in a variety of other inflammatory conditions, but not limited to several other rheumatologic diseases. The areas on the body where CNO/CRMO has been documented to be most present are the pelvis, vertebrae, clavicles, femurs, and tibias (O'Leary et al., 2021). When comparing boys to girls, the disease is more present in young girls with a mean age of nine but was not found to be statistically significant (Cebecauerová et al., 2022). It has been found that typically patients with CNO/CRMO can be showing symptoms for up to ten years, while primarily two years is the average amount (Kumar et al., 2018).

Clinical Features of CNO/CRMO

CNO/CRMO can present various clinical features in patients. However, due to the fact that it can be a silent disease, meaning asymptomatic in patients, without any MRI, x-ray, bone biopsy, or blood test, a patient may have no indication they even have some underlying rheumatic condition. Therefore, without any clear indication of being affected, this would not direct a patient to seek a physicians aid. It has been documented that girls have a higher

prevalence of showing clinical features compared to boys, with the average age of clinical features presenting themselves is nine years old (Ursani, 2023). The clinical symptoms that often lead them to seek care are swelling, pain, redness, and possible skin alterations in the affected areas (Yousaf et al., 2021). The areas on the body most commonly impacted by CNO/CRMO are the tibia, pelvis, femur, clavicle, and spine (Ferguson, 2013). Due to the severe pain and tenderness this disease can produce, this can majorly impact the quality of life of those affected, causing them to participate in less activities or even attend school due to the immense pain and fatigue (Zhao et al., 2021). Overall, this can have a negative impact on a person's life not only physically, but also mentally. Some patients present with limping, but in active, growing pediatric patients, limping has a broad differential including childhood bumps and bruises related to routine play, growing paints, or other inflammatory etiologies. Weight loss and recurrent fevers have also been reported as clinical features of CNO/CRMO in patients, along with high frequencies of hospital admissions due to the known etiology and magnitude of these recurrent systemic features (Zhao et al., 2021). Children diagnosed with this disease may present other co-morbidities such as inflammatory bowel disease, psoriasis, and arthritis (Cebecauerová et al., 2022) CNO/CRMO also has clinical overlap with SAPHO Syndrome, which stands for "Synovitis, Acne, Pulstosis, Hyperostis, Osteitis" (Merola, 2022). Though the disease is a diagnosis of exclusion, laboratory tests are helpful to assess severity of the disease. It is common for patients to have elevated C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) (Hedrich et al., 2013). The laboratory detection can be a key insight to display if one is having severe inflammation, which is a key contributor to CNO/CRMO in children.

Many patients report that the pain is most severe at night, however due to the rarity of this condition and limited research, the reasons for this are not yet understood (Taddio et al.,

2017). In some instances, presenting features of CNO/CRMO may be asymmetries of limb length, kyphosis, chronic spondyloarthropathy, vertebral collapse and stunting for early closure of the growth-cartilages (Taddio, et al., 2017). The episodes/flare ups in children with CNO/CRMO can last as little as few weeks or as long as months at a time (Indiana University Health, 2023). It has been reported that 30% of all CNO/CRMO cases involve the adjacent joint, with the incidence of damage to the articular cartilage and/or synovial thickening (Taddio et al., 2017). Expanding on this, "CNO/CRMO often results in abnormal bone overgrowth/deformity; this in turn can result in injury to other adjacent structures" (Khanna et al., 2009). An example of where this occurs is, "osseous enlargement of the medial clavicle, which compresses the adjacent vessels/nerves supplying the neck and upper extremities, creating a condition known as thoracic outlet syndrome, where patients often present with pain/swelling of their neck and/or arm" (Khanna et al., 2009).

Epidemiology

The incidence of CNO/CRMO is reported to be four per every million children, but due to increased awareness among physicians, there has been an increase in cases overall, (Zhao et al. 2021). CNO/CRMO is mostly diagnosed in children around the age of elementary school, where few new cases are being seen diagnosed amongst full grown adults, as this is primarily a disease of childhood (Ursani, 2023). There is yet to be a confirmed documented common infectious pathogen relating to CNO/CRMO amongst all cases (Cebecauerová et al., 2022). Familial cases have been reported where parents and siblings who are affected have a higher likelihood of having the presence of other inflammatory diseases, such as inflammatory bowel disease, psoriasis, or arthritis, as well those diagnosed with CNO/CRMO and their first-degree

relatives with CNO/CRMO. These suggest the potential for genetic factors underlying susceptibility to this disease (Hedrich et al., 2013) There have been no specific genes identified which cause CNO/CRMO, however rare familial forms of CNO/CRMO that have an underlying genetic etiology have been reported such as Majeed Syndrome (Ferguson et al., 2005). Histopathological exam results in CNO/CRMO patients will display non-specific chronic or subacute osteomyelitis with the intrusion of bones with plasma cells, macrophages, histiocytes, neutrophils and plasma cells (Kopeć et al., 2021).

Due to this being a disease of exclusion, meaning physicians have to rule out all other possibilities first, it is very common for patients to be seen by a vast array of different types of physicians such as rheumatologists, pediatricians, infectious disease specialists, oral surgeons, radiologists, oncologists, and orthopedists (Zhao et al., 2021). It is critical to attempt to treat patients early before the expansion of issues or the use of ineffective or unnecessary treatment for those who are young (Zhao et al., 2021). The typical route that has been seen is that once a patient has been diagnosed with CNO/CRMO they are followed up and treated by pediatric rheumatologists (Zhao et al., 2021). The ratio that has been documented between girls to boys of CNO/CRMO cases is approximately 2:1 (Zhao et al., 2021). It has been reported in many studies that those who are younger than three with stand-alone CNO/CRMO is considered to be “rare” and in this age group, differential diagnoses, including systemic autoinflammatory diseases that include the bones needs to be well-thought-out prior to final diagnosis (Zhao et al., 2021). Though most reported cases of CNO/CRMO in published literature so far have been among Non-Hispanic White Individuals, CNO/CRMO can impact children of all ethnicities and racial groups (Zhao et al., 2021). It has been noted that the clinical pathway of CNO/CRMO is frequent, self-

limiting, and prolonged, making the prognosis quite inconsistent and unpredictable (Ferguson et al., 2013).

Projection of the disease is unpredictable; one can be affected for up to twenty-five years in their lifetime and there is no set treatment that is guaranteed to be effective (Ferguson et al., 2013). It has been noted that remission can occur randomly regardless of treatment plans, which also makes it challenging for physicians when not trying to over-treat or under-treat a patient (Ferguson et al., 2013). Due to the broad array of the clinical features that can occur in patients, this can create a delay in the diagnosis of CNO/CRMO. In a study that was conducted in the United States, it found that there is an average delay of when symptoms arise to diagnosis to be two years (Zhao et al., 2021). Two years is a lot of time for a patient to be experiencing the pain CNO/CRMO can present. As well, for those who are young and bodies are not fully developed, the impact of being untreated and undiagnosed can be detrimental on a patients overall health.

Modalities of Diagnosis

Due to the disease being a diagnosis of exclusion, this poses many challenges and barriers for physicians to diagnose those with CNO/CRMO at a timely rate. The most commonly used methods of diagnosis that physicians carry out on their patients are MRI's, x-rays, bone biopsies, and laboratory blood tests. Diagnosis is based on a vast array of blood exams and imaging results from x-rays, MRI's and bone biopsies (Swidrowska-Jaros et al., 2019). The issues that arise in the diagnosis of CNO/CRMO are the similarities of the various imaging and clinical results the patient may be presenting simultaneously (Swidrowska-Jaros et al., 2019). Unfortunately, many times the diagnosis relies on the exclusions of it being infectious arthritis or even tumors, which are both extremely serious health conditions, which just magnifies the heavy

emphasis on physicians being 100% sure the patient has CNO/CRMO when final diagnosing (Swidrowska-Jaros et al., 2019).

Whole-body MRI is currently considered the gold standard for assessing active bone lesions, detect new potentially silent lesions, or to assess the status of previously noted bone lesions (Ursani, 2023). MRI results demonstrating spine involvement has serious implications as vertebral involvement could potentially indicate neurological deficits. Hence vertebral lesions require aggressive treatment. In some children MRI results may be inconclusive for CNO and may suggest possibility of aggressive processes such as malignancies. In these instances, a bone biopsy is often necessary to enable accurate diagnosis (Zhao et al., 2023). Whole body MRI's initially often used to confirm the suspected diagnosis of CNO/CRMO, while also working up/ excluding other diseases including but not limited to multifocal infection. By doing so, this can help examine the patterns of locations of the lesions and their distribution, which can help exclude inaccurate diagnosis' in patients (Nico et al., 2022).

Bone biopsies are another common method used for diagnosis for patients with CNO/CRMO. In the published literature on this topic, it has been reported that bone biopsies are conducted in about 60-80% of those diagnosed with CNO/CRMO (Zhao et al., 2021). It has been noted that bone biopsies do not aid in reporting specific patterns seen in patients with disease, however they can help with diagnosis in terms of excluding the diagnoses of Fibrous Dysplasia, Langerhans Cell Histiocytosis, infections, and malignancy (Zhao et al., 2021).

Laboratory tests tend to help less with establishing a diagnosis but can often assists in the follow up of the patients role. Generally, those with CNO/CRMO will have inflammatory markers that are marginally raised or even within their anticipated normal parameters, which does not give any clear indication of a red flag to be raised. It has been reported that there is no

actual correlation between CNO and the HLA B27 antigen, which tends to be very common for rheumatic diseases (Kopeć et al., 2021). Additionally, another laboratory test diagnosis challenge that presents itself is that autoantibodies particular to systemic connective tissue disorders and the rheumatoid factor are all presented as stable and normal (Kopeć et al., 2021). As well, it is common to see tests done to check for viral, fungal, and bacterial infections all show up as negative (Kopeć et al., 2021).

A clinical scoring criterion that has been proposed is called the Jansson and Bristol criteria. This states that the four major criteria to diagnose CNO/CRMO is "radiologically proven osteolytic/sclerotic bone lesions, multifocal bone lesions, palmoplantar pustulosis or psoriasis (PPP), sterile bone biopsy with signs of inflammation and/or fibrosis, sclerosis" (Kopeć et al., 2021). As well, there are also six minor criteria points, being "normal blood count and good general state of health, C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) mildly-to-moderately elevated, observation time > 6 months, hyperostosis, association with other autoimmune diseases apart from PPP and Psoriasis, and grade I or II relatives with autoimmune or autoinflammatory disease" (Kopeć et al., 2021). It has been documented that CNO/CRMO is diagnosed in a patient when they fulfill "at least two major criteria or at least one major and three minor criteria" (Kopeć et al., 2021). However, this is not a criterion that every physician around the world uses, it is just an example of one of the various criteria's physicians have created.

There are no distinct scoring criteria's that are deemed as the gold standard; therefore, it solely relies on the physicians ability to detect from diagnostic imaging results, clinical findings, and the combination of microbiological and histological exams, which can pose many challenges (Ferguson, 2013). Since the disease can display a broad complex presentation, physicians have created a lengthy variable list of the various differential diagnosis' that one can consider.

Radiologist Dr. Iyer has created a systematic list to aid in making diagnosis of CNO/CRMO by exclusion of these factors he listed. These factors being, “lack of causative organism, no abscess, fistula or sequestra formation Radiographic appearance of sub-acute or chronic osteomyelitis, atypical location compared to infectious osteomyelitis, non-specific histopathologic and laboratory findings compatible with sub-acute or chronic osteomyelitis or other known disease process, prolonged (> 6 months) and recurrent painful symptoms, accompanying pustulosis palmoplantaris or acne” (Ferguson, 2013). However, delay of diagnosis remains a barrier for CNO/CRMO due to the lack of clinical exam findings, high potential of ongoing onset of symptoms, relatively normal lab results, and until physicians can create a singular distinct diagnostic criterion (Nico et al., 2022). A setback of this diagnosis barrier is that this can lead patients to be on extensive treatment plans for lengthy periods, have reoccurring bone biopsies, MRI’s, or even increased anxiety in patients of a delayed diagnosis when waiting for results (Nico et al., 2022). It has been documented that it on average takes two years for an official diagnosis and typically “69% of patients consulted with 2–5 physicians before receiving the final diagnosis” (Nico et al., 2022). Due to the various geographical locations and socio-economic differences amongst patients with CNO/CRMO seeking physician aid, this may pose more challenges and many patients may not have equitable access to clinics or physicians to seek treatment.

Treatment

Due to the various clinical presentations CNO/CRMO can display in patients, amongst the differences in locations and quantity of lesions on the body, this does not allow for any singular specific treatment plan for physicians to give to all patients with this disease. Lack of a detailed remission definition of CNO/CRMO makes it troublesome for physicians to be able to

thoroughly assess patients treatment options (Cebecauerová et al., 2022). The treatment that physicians decide to use to help their patients deeply relies on which location of the body is being affected and the number of lesions formed on the body. As well, family hesitancy poses another barrier, due to many families being hesitant to put their children on many medications, which can also disrupt and delay their child's overall health development.

Nonsteroidal Anti-Inflammatory Drugs commonly known as "NSAIDS" are typically used as first line treatment plans, unless there is confirmed spinal lesions in the patient (Cebecauerová et al., 2022). Physicians use Nonsteroidal Anti-Inflammatory Drugs due to their nature in providing a quick response to symptomatic relief when it deals with controlling the bone inflammation in the patients (Zhao et al., 2021). NSAIDs are typically taken differently based on which one the patient is prescribed. Some possible side effects of NSAIDS include digestion issues, high blood pressure, fluid preservation, heart problems and kidney issues (Petryna, 2024). A setback of NSAIDS is that it has been documented that over 50% of all CNO/CRMO patients will have recurrent flares with this treatment within the first two years of using this treatment option (Zhao et al., 2021). Some examples of commonly prescribed NSAIDS for CNO/CRMO patients are Naproxen, Indomethacin, Meloxicam, and Ibuprofen (Petryna, 2024). Normally these NSAIDS are taken twice daily by patients, however it is common to be different based on the patient and prescribing physician (Petryna, 2024). Due to the quantity of patients that continue to flare after termination of their NSAID prescription, and the related side-effects reported that can cause concerning health issues in patients, it is suggested to not be on NSAIDS for long term durations (Zhao et al., 2021).

Disease-Modifying Anti-Rheumatic Drugs (DMARDs) and Short-Course Corticosteroids tend to the best next line of treatment physicians prescribe to help intensify therapy with their

patients (Cebecauerová et al., 2022). Examples of DMARDS that tend to be prescribed to patients in need of the additional therapy are Methotrexate and Sulfasalazine (Ursani, 2023). Children who are on DMARDS or other biologic therapies, will be more susceptible to infections due to their immunosuppressive effects, therefore, this is something that families are counseled on at the time of initiating therapy and require monitoring while on therapy (Ursani, 2023). Some other possible side effects to DMARD usage in early stages of treatment are nausea, sun sensitivity, and discolored urine (Chan, 2024). Common and similar to NSAIDs, Corticosteroids are prescribed and used to aid in the reduction of prostaglandin creation (Zhao et al., 2021). These have been reported to help control bone inflammation in 79% of CNO/CRMO cases, remission long-term is often not found (Zhao et al., 2021).

Bisphosphonates such as Pamidronate or Zoledronic Acid are used when there are lesions on the spine of if the patient has already had a lack of response form the NSAID treatment (Ursani, 2023). Bisphosphonates are known to have a “biological half-life” and used to aid in prevention of osteoclast movement, with the urge to stop bone loss in patients (Zhao et al., 2021). Pamidronate usage will help patients move towards remission and prevent against inflammatory cytokine countenance (Zhao et al., 2021). Bisphosphonates tend to be taken as often as daily, weekly or every four weeks via infusion (Zhao et al., 2021). Due to it being noted that Bisphosphonates tend to have stronger potential side effects such as cardiac diseases or thyroid complications, it is essential that they are mainly used when there is spinal involvement or already damage to the vertebrae (Zhao et al., 2021).

Another common form of treatment that physicians prescribe in patients are biological agents such as Tumor Necrosis Factor (TNF) Inhibitors, which have been noted to induce radiological and clinical remission in patients (Zhao et al., 2021). TNF inhibitors can be

administered through self-injection with a needle typically in the abdomen or thigh, or through infusions (Chan, 2024). TNF inhibitors are typically given on a weekly basis or every four weeks (Chan, 2024). Some possible side effects that have been noted are skin reactions, anaphylaxis, low blood pressure, or heart failure (Chan, 2024). The most commonly prescribed TNF Inhibitors for CNO/CRMO patients are Infliximab, Adalimumab, Etanercept, Golimumab, and Certrolizumab (Chan, 2024). It has been noted that TNF Inhibitors are expensive which presents challenges to patients; therefore, this is typically used when patients have failed to respond to other treatments prior. There are also reports of usage of other biological agents such as the IL-1 inhibitor Anakinra, or T still co-stimulation blocker Abatacept.

It is important to continue to spread awareness that there is no set cure for CNO/CRMO in patients. The biggest priority with treatment is to try to help patients feel they are living a normal life, pain free. Columbia University's Pediatric Rheumatology program noted that the overall goal many physicians depend on is to "reduce pain, prevent bone growths and deformities, and help your child lead a normal, productive life" (Columbia University, 2021).

Disease Outcomes

It is imperative to know that CNO/CRMO follows a relapsing and reemitting course, however complete remission is possible! For CNO/CRMO, there is a broad definition of remission, which is stated to be "no pain, a decrease in inflammatory markers back to normal values and no radiological progression" (Sadeghi et al., 2011). This can be considered to be vague because there is no timeline duration given of how long a patient needs to be expressing no pain, normal inflammatory markers, and no radiological progression for, therefore this leaves room for a lot of misunderstanding regarding physicians and patients. Some complications that

can occur are if this disease goes untreated is it can potentially induce limb length discrepancies, deformity of extremities, and/or vertebral fractures on a patient (Sergi et al., 2022). The most commonly documented outcome complications that have occurred in CNO/CRMO patients are leg length inequities, bony overgrowth in the clavicle, bone deformities and vertebral fractures (Zhao et al., 2021). It is critical to point out that in much of the published literature, there is much data lacking regarding larger longitudinal studies of following patients prospectively from childhood to adulthood (Zhao et al., 2021). Currently observed data demonstrates that if treated early and adequately, the outcomes are generally favorable for those living with this disease (Zhao et al., 2021). Those that experience fractures within the spine, may not be able to resolve this issue. More recently published literature has proposed that 50% of CNO/CRMO patients continue to have flare ups on average 29 months after treatment (Zhao et al., 2021). The timing of diagnosis is critical regarding CNO/CRMO outcomes due to the verities that can present themselves with inadequate treatment options in a timely manner. The complications that this disease can present to a patient's health can be impactful at the first moment of diagnosis and then accumulate over time causing more health concerns such as vertebral fractures, pustulosis, arthritis, and gastrointestinal inflammation (Zhao et al., 2021). Data from a study in Germany points in the direction that due to inadequate treatment, unfavorable outcomes have a higher likelihood of occurring such as inflammatory bowel disease, psoriasis, and arthritis (Zhao et al., 2021).

The early literature published on CNO/CRMO displayed that it is self-limiting, however it is now coming to light that the symptoms of CNO/CRMO can be extended. In a study that was conducted, it found that on average patients will have active disease for about a range of 3-12 years before having no active lesions or having remission (Catalano-Pons et al., 2008).

Additionally having active-disease at physician follow up appointments was very common, and patients reported having severe pain consequences in their daily life routines (Catalano-Pons et al., 2008). Many patients also reported that they had "long-term sequelae such as growth delay, bone deformities, kyphosis and thoracic outlet syndrome, a high rate of orthopedic complications at maturity" with many resulting in having surgery due to these harmful outcomes (Catalano-Pons et al., 2008).

Overall, it is imperative to understand that for a patient to have a higher likelihood of living a healthier lifestyle with CNO/CRMO unless already in remission, is to seek medical care from physicians and be consistent with all diagnosed treatment plans. Staying active with physicians while having active disease will help the patient learn ways on how to live productively and give the patient the best possible opportunity to try to control the active bone lesions and pain that may arise.

Conceptual Framework

The research question being posed here is what are the clinical features and outcomes of patients at their last clinical visit who are diagnosed with CNO/CRMO at this institution. The appendix 1 aims to display the conceptual framework that describes what has been described in the literature review, which is the various factors that come into play with each patient having different scenarios that present themselves with their Chronic Non-Bacterial Osteomyelitis or Chronic Recurrent Multifocal Osteomyelitis. Much of the literature displays the various clinical features and the barriers that can be present with diagnosing cases due to the verities of clinical features that can be existent in patients. As well, the literature points out that due to the lack of diagnosis and lack of unified successful treatment options, this can lead patients to developing

other co-morbidities such as inflammatory bowel disease, psoriasis, and arthritis (Cebecauerová et al., 2022). There is a lack of data regarding the quality of life of those living with CNO/CRMO from childhood through adulthood, but it has been noted that it can cause patients to be more likely to miss school due to being in pain and ultimately leading them to better health (Zhao et al., 2021). Previous literature has suggested a negative outcome that is produced from delay in diagnosis of this disease is how patients can have radiation exposure from consistent x-rays or being on high demanding treatment options which can all have negative impacts on one's body and overall development (Nico et al., 2022).

The purpose of appendix 1 is to display the various trajectories a patient can have with their disease pathway. It begins with the various demographic factors that were collected being age, sex, and ethnicity. It is important to point out that when collecting hospital patient data, there are many PHI barriers put in place regarding protecting patient data, therefore for this descriptive study from the Center for Advanced Pediatrics, the demographic factors collected was limited to keep patient protection as a priority. An arrow shows any association found in a patients CNO/CRMO pathway. The descriptive indicators that were collected from the patient subjects were clinical features, diagnosis methods, treatment plans, number of hospital admissions related to CNO/CRMO, blood test abnormalities, and date of onset vs. diagnosis. These indicators were carefully chosen due to the literature that described the impact these factors had on a patient's overall disease pathway. Time itself pertains to the period prior to diagnosis from onset of symptoms in a patient. This was another very important factor that impacted all of these descriptive indicators. As well, a familial history of autoimmunity was another driving factor that impacted a patients disease pathway. All three of the demographic factors have an association arrow directly linked with time. From time, there is an association

arrow connected to a familial history of autoimmunity to display those who have that versus those who may not. Time plays a critical role in a patients CNO/CRMO trajectory; therefore, it is linked to affecting both those who have a familial history of autoimmunity and those who may not. Many studies conducted regarding CNO/CRMO collected data explaining how a delay in diagnosis and ineffective treatment plans can lead to various co-morbidities are such as inflammatory bowel disease, psoriasis, and arthritis developing or being present in a patient, which is displayed in appendix 1 with a correlation arrow coming from the descriptive indicators to present this relationship. Stemming from the descriptive indicators whether the patient has other co-morbidities or not is "outcome". The "outcome" in appendix 1 displays if the patient is either in remission, if they may have may have experienced any adverse health outcomes, or if they are continuing to live consistently with CNO/CRMO. Appendix 1 demonstrates the various levels and factors embedded in a patients CNO/CRMO process that can affect the development of the disease and the outcome.

From this study, the aim is to answer the research question of what are the clinical features and outcomes of patients at their last clinical visit who are diagnosed with CNO/CRMO at this institution. The information collected can be used to increase knowledge and understanding for Pediatric Rheumatologists who care for patients with CNO/CRMO. As well, it can spread awareness to the various clinical features that may present themselves in patients. By assessing the different treatment options and medications, a potential benefit that can be derived is seeing which medications may be more suitable for distinct clinical features in patients. There will be a complete comprehensive chart review done of pediatric patients who have been diagnosed with CNO/CRMO from the last ten years who have been seen at the Children's Center for Advanced Pediatrics, who have undergone various treatments, documented clinical features

and identified various outcomes. Additionally, there will be a complete comparison analysis done between the varying treatment plans, clinical features, and outcomes. It is important to point out that this study will aid to the previous knowledge on the clinical features and outcomes of CNO/CRMO and help to add more awareness of this disease.

III. Data and Methods

Study Population

The inclusion criteria to be involved in this study is one must be a pediatric patient seen at this particular single center large academic children's hospital that was diagnosed with Chronic Nonbacterial Osteomyelitis or Chronic Recurrent Multifocal Osteomyelitis, have at least one whole body MRI, and age <21 years old at time of enrollment. The exclusion criteria for the data being used is, patients without a clear diagnosis of Chronic Recurrent Multifocal Osteomyelitis or Chronic Nonbacterial Osteomyelitis and patients with osteomyelitis as a result of infections. This exclusion criteria were set in place to create the most accurate descriptive study of the cohort here at CAP with CNO/CRMO. The study population consists of pediatric subjects that have been diagnosed with CNO/CRMO here at the Children's Healthcare of Atlanta's Center for Advanced Pediatrics. They have also been cared for by Pediatric Rheumatology physicians at the Center for Advanced Pediatrics date ranging from August 1st, 2013-August 1st, 2023. There are a total of 111 subjects, making this one of the largest cohorts of CNO/CRMO. Subjects include those living in the state of Georgia and nearby states. The members who are from other states are those that have been recommended to be seen by the physicians at CAP by their current providers where they reside.

Data Extraction

The procedures for data collection begin with retrieving a list of patients with rheumatology encounters who also have ICD-9 or ICD-10 codes consistent with CNO/CRMO with assistance of the informatics team. From that list, those who fit the inclusion criteria were a

part of the study sample. Clinical, demographic, laboratory, imaging and if available, histopathology data was collected. An extensive amount of data was extracted from each patient's medical records. The information collected was, data of onset, data of diagnosis, method of diagnosis, first MRI, familial history of autoimmunity, # of hospital related CNO/CRMO admissions, blood test abnormalities, treatments/medications, most recent MRI, outcome at last visit, how often seen at CAP, muskoskeletal exam findings, physical exam findings, if the patient receives infusions, frequency of illnesses, HLA B27 status, frequency of flares, medication adverse events, areas sensitive to touch, and other co-morbidities present. These were solely collected from medical record extraction, none of the patients answered any questionnaires nor were approached. All of these data points were from clinical assessment.

Data Analysis

Regarding all the vital data points that were extracted, the next step was identifying the areas on the body where each patient had bone lesions. The locations on the body were broken up into three sections central skeleton, spine, and extremities. The central skeleton consisted of the skull, mandible, clavicle, ribs, sternum, scapula, pelvis, and SI joints. The spine consisted of the cervical, thoracic, lumbar, and sacrum. The extremities contained any part of the femur, knee, tibia, fibula, ankle/feet and humerus, radius, ulna, wrist, and hand. Regarding each body part, the data was given a "1" to display if the patient had this lesion unilaterally or a "2" to display if the patient had lesions bilaterally in this location. The locations on the body where bone lesions were present are one of the priorities in identification regarding how data analysis will be conducted. Locations were identified by whole body MRI images and disease activity was indicated by abnormal increased T2 signal within the bone. From this information there was a skeleton diagram created of the human body that displays the various percentages of the different

locations on the body that had bone lesions. This will help identify the locations that had the highest rates of bone lesions and the locations where it was less prevalent. Other co-morbidities present was another key point that was collected. The only co-morbidities that were documented from the patient sample were inflammatory bowel disease (IBD), psoriasis, and arthritis, as these have been noted in much literature to have a potential correlation with CNO/CRMO. With this information, this can help aid in potentially drawing conclusions regarding which of the three sections of the body that were divided up had higher rates of co-morbidities being present in comparison to the others. Also, there was a comparison done regarding the different forms of treatments patients have received and the clinical outcomes following the treatments. From this, comparisons were made on the post therapy MRI lesions and if sites of disease had improved or worsened, along with overall clinical outcomes. Also, there were two cohorts formed for comparison, being those with a familial history of autoimmunity to those with no familial history of any autoimmune diseases. The number of hospital admissions relating to CNO was collected to analyze the rate of patients going to the hospital regarding CNO prior to diagnosis. There was a comparison done regarding the races and ethnicities of the patients to see if there are distinct races and ethnicities where this was more prevalent regarding the sample population. With this data there was a group of descriptive statistics formed and a set of two-way tables that compared statistics between males and females and tested for differences between them using SAS 9.4 software. The tests conducted within these analysis' were a fisher's exact test, a chi square analysis, or a two-sample t-test.

Methods

Data Work:

This specific study population was available form EPIC. EPIC is a software platform that many health systems and hospitals use to keep electronic medical records of their patients. For the purpose of this specific study, we will only use those who have been diagnosed with CNO/CRMO via CAP. In order to obtain access to these medical records, one must be on the IRB for this specific descriptive study along an employee of CAP's rheumatology department. The IRB process for this descriptive study was creating a protocol for this descriptive study that laid out all that was going to be done for this study, the information that was being collected, how it would be collected, and the inclusion/exclusion criteria, which was then sent over to the IRB submission board to be approved to get this study moving forward.

Outcome Variables:

For this specific analysis, the outcome variables that were used to examine were clinically assessed by physicians at CAP, these being modality of diagnosis (whole body (WB) MRI, bone biopsy, x-ray), anatomical variables on skeleton, which places on the body have most lesions, medications, who has extra osseous features present, and if there is a familial history of autoimmunity. The demographic variables such as age, sex, race, and ethnicity were assessed by physicians asking the patient or the patients family member present if they were too young to answer their preference regarding those variables.

1. *Age*

All patients had their birthdates on file via EPIC which was reported by the patient or the family member present if the patient was too young to answer. Age was calculated by subtracting their birthdate from August 1st, 2023 which was the date that their birthdate was collected for the purpose of this study. All ages were reported as whole numbers.

2. *Sex*

Gender was determined via the EPIC listed on file being male, female, or chose not to disclose, which was based on the patients preference or if the patient was too young to answer by their family member present.

3. *Race*

For this analysis, patients race was collected via EPIC where they chose from White, Native Hawaiian or Other Pacific Islander, Black or African American, Asian, and American Indian or Alaska Native.

4. *Modality of diagnosis*

For this analysis, the modality of each patients diagnosis was collected. These variables being, whole body MRI, bone biopsy, and diagnostic radiology (x-ray). Each patients modality of diagnosis was documented and each of these variables was summed to see which had the highest rates of each.

5. *Anatomical variables on the skeleton*

For this analysis, the human skeleton was split into three sections. The locations on the body were broken up into three sections central skeleton, spine, and extremities. The central skeleton consisted of the skull, mandible, clavicle, ribs, sternum, scapula,

pelvis, and SI joints. The spine consisted of the cervical, thoracic, lumbar, and sacrum. The extremities contained any part of the femur, knee, tibia, fibula, ankle/feet and humerus, radius, ulna, wrist, and hand. Regarding each body part, the data was given a "1" to display if the patient had this lesion unilaterally or a "2" to display if the patient had lesions bilaterally in this location.

6. *Which locations on the body have the most lesions*

For this analysis, each column was summed for each location on the body in order to see based on this specific cohort, which locations on the body had the highest rates of lesions. Regarding each body part, the data was categorized by the total number of lesions each patient had and the total count of the number of locations on the body each patient had.

7. *Treatments/medications*

For this analysis, regarding each patient, their treatment and medication plans were documented. The specific medications documented are Nonsteroidal Anti-Inflammatory Drugs commonly known as "NSAIDS", Disease-Modifying Anti-Rheumatic Drugs (DMARDs), Short-Course Corticosteroids Bisphosphonates, and Tumor Necrosis Factor (TNF) Inhibitors. Each patient that used these medications was documented in order to see which treatments were used the most. Regarding each medication, there was a separate column for each of the four medications above and the data was given a "1" to display if the patient was on that specific medication and a "0" to display they were not on that medication.

8. *Extra osseous features present*

For this analysis, it was collected if the patients had any extra osseous features present, these being inflammatory bowel disease, psoriasis, and arthritis. This was collected in order to see within this cohort which patients with lesions also had these diseases present. Regarding each osseus feature, there was a separate column for each of the three features above and the data was given a "1" to display if the patient had that feature and a "0" to display they did not have that feature.

9. *Familial history of autoimmunity*

For this analysis, it was collected via each patient's medical records if they had a familial history of autoimmunity diseases the maternal or paternal side. This was collected due to the genetic aspect of autoimmune diseases in regard to CNO that much literature has touched upon. The data was categorized as a column for a familial history on the maternal side or a familial history on the paternal side, the data was given a "1" to display if the patient had a parent with a history of autoimmunity and a "0" to display there was no autoimmunity on that specific side.

10. *Clinical status at last visit*

For this analysis, it was collected via each patient's medical records with the most recent physician note posted on EPIC. Each physician has noted whether the patient still has active disease, meaning lesions still presently forming and the patient on medication treatment. On the other hand, the patient was possibly noted to be in clinical remission meaning they do not have any active lesions present and no longer needing to be on medication. Regarding if the patient had active disease or was in remission, , the data was

given a “1” to display if the patient had active disease and a “0” to display they were in clinical remission.

11. *HLA B27 Gene*

For this analysis, it was collected via each patient’s medical records with their most recent lab test results regarding being tested for the HLA B27 Gene. Regarding if the patient had active disease or was in remission, , the data was given a “1” to display if the patient was positive with the HLA B27 Gene and a “0” if they tested negative for the HLA B27 Gene.

Outcome:

Regarding each patient due to the most present chart note, it was reported whether they still have active disease or if they were deemed to be in clinical remission. Active disease meaning they are still in pain, have active lesions, and need to still be on their medications. Clinical remission means that they are completely off medications, or their medications are prescribed as needed and are living with no pain and have no current active lesions present on imaging.

Data Cleaning and Coding:

Following the data variables being selected, the data that was collected was cleaned to be analyzed. There was a univariate analysis completed to make sure there were no foreseeable errors in the categorical data. Regarding categorical variables, the data was coded as a “1” meaning yes and a “0” meaning no. Regarding gender, “1” referred to females, “0” referred to males, and “2” referred to those who chose to not disclose their gender. There are no missing

values for the data since all data was collected via patient medical history reported by physicians. Regarding the variables for arthritis, IBD, psoriasis, medication subtype (TNF-I, Biologic, Pamidronate, Bisphosphonates, Steroids, DMARDS, NSAIDS), WB MRI, X-RAY, bone biopsy, familial history on maternal side, familial history on paternal side, race (White, Black or African American, Native Hawaiian or Pacific Islander, Asian, American Indian or Alaska Native) was coded as "1" for yes if the specific patient reported that and "0" as no. Age was calculated by subtracting their birthdate from August 1st, 2023 which was the date that their birthdate was collected for the purpose of this study. Regarding each body part, the data was given a "1" to display if the patient had this lesion unilaterally or a "2" to display if the patient had lesions bilaterally in this location and a "0" if there was no lesion present in that location.

Data Analysis:

The research question of this study was what are the clinical features and outcomes of patients at their last clinical visit who are diagnosed with CNO/CRMO at a single center large academic children's hospital from August 1st, 2013 to August 1st 2023. Data was analyzed using SAS 9.4 Software. First, a descriptive analysis was completed to describe and assess the frequency of those for each race that was reported. Next, there was an analysis conducted to assess the frequency of if the patient had a familial history of autoimmunity on the mothers or fathers side, or even both. Another analysis was conducted to assess the frequency between the genders that were reported. As well, there was a frequency analysis conducted to assess the frequency of each of the medication subtypes each patient was on. These were calculated via chi square analysis' and fisher exact tests.

Another descriptive analysis was completed which was done to assess the frequency between those who have extra osseous features with CNO/CRMO. The three extra osseous features accounted for were arthritis, psoriasis, and inflammatory bowel disease. This was completed by conducting Fisher's exact tests and chi square analysis'. As well, there was a descriptive analysis completed to assess the frequency of each modality of diagnosis each patient had which was done via a chi square analysis.

The next descriptive analysis that was completed which was done to assess the frequency of the places on the body that had lesions. This was done by using equal variance t tests. Another descriptive analysis that was conducted was at the patients last visit if they had active disease or were in clinical remission. To assess this, a chi square analysis was used. To evaluate the average age of onset and diagnosis, an equal variance two sample t-test was used and to calculate the date difference between onset and diagnosis, an unequal two sample t-test was used. It is important to note all of these analysis' were stratified by gender.

Ethical Considerations:

IRB submission before this study was required and approved due to all variables were obtained via electronic medical records on the patients files via EPIC. The IRB number for this study is STUDY00001800.

IV. Results

Descriptive Statistics Results

Table 1: Descriptive Statistics of Entire Sample Population Frequency Counts

Table 1 displays the basic descriptive statistics that were included in this study. There was a total of 111 participants in this study who either self-reported their gender or the present caregiver reported for them if they were too young. 44.1% of the study participants identified as males and 54.1% of the study participants identified as females. There were two respondents (1.8%) who either self-reported or their present caregiver chose not to disclose their gender. The mean age of those involved in this descriptive study was 14 years old. Regarding races, there was 1 study participant (0.9%) who identified as American Indian or Alaskan Native, 6.3% who identified as Asian, 23.4% who identified as Black or African American, and 70.3% who identified as White. Regarding medication treatment plans, 96.4% of the study participants received non-steroidal anti-inflammatory drugs (NSAIDS), 64% received disease-modifying antirheumatic drugs (DMARDS), 63.1% received at least one dose of Tumor Necrosis Factor-Inhibitors (TNF-I), 52.3% of the participants received steroids, 19.8% received pamidronate infusions, 6.3% received biologic drugs, 2.7% received bisphosphonates.

Table 2: Descriptive Statistics Stratified by Gender

Table 2 displays the descriptive statistics that were stratified by gender being male and female. The two patients who chose not to identify as a gender were excluded. An analysis that was conducted was the time difference in days of when the patient had reported onset of disease

to when it was officially diagnosed. It was found that the average difference in days between onset to diagnosis for males was 282 days and for females was 98 days.

Another important data aspect that was reported in literature was any familial history of autoimmunity on the patient's maternal or paternal side. It is important to point out that dependent on the patient's ability to self-report it was either self-reported by them or the caregiver who was present at the visit when the physician asked these questions. In regard to if there was a familial history of autoimmunity on the mothers side, 40.8% of the male study participants had a history and 41.7% female study participants also had a history. For those who had a familial history of autoimmunity on their fathers side, 18.4% male study participants reported having a history and 23.3% female participants also reported having a history. In much literature published thus far with associations of CNO/CRMO to other diseases, these three are noted to be commonly seen in patients with CNO/CRMO. Regarding arthritis, 6.1% of the male study participants have been diagnosed with this condition and 8.3% of the female participants have been diagnosed. Regarding psoriasis, there were no male reports with this condition, while 11.7% of the female study participants were diagnosed. For inflammatory bowel disease (IBD), 4.1% of the male participants reported having this condition and 5% of the female participants reported as well.

Table 3: Comparison of those with at least 1 extra osseous feature to those with solely bone lesions by gender

Table 3 has been stratified by gender and displays those who have at least one of the three extra osseous features present compared to those with just bone lesions. Many published studies on CNO/CRMO report a relationship between patients with CNO/CRMO and extra

osseous features present such as arthritis, psoriasis, and inflammatory bowel disease (IBD). Overall, it was noted that 5 males had at least one extra osseous feature out of the three and 14 females had at least one extra osseous feature. This was tested from looking at the patient's medical records to see if any prior note was made by physicians in regard to the patient having any of these extra osseous features. The significance behind looking at this was seeing the group of children that go beyond the confines of just the bones, but also have skin, joint, and intestinal involvement and seeing if it is a known risk factor for CRMO/CNO.

Table 4: Comparison of those with Sacroiliac Joint involvement and extra osseous features

Table 4 displays the comparison of those who had sacroiliac joint involvement within their CNO/CRMO diagnosis to those with sacroiliac joint involvement and also had at least one of the extra osseous features present. This comparison was conducted to assess if there was any association between having sacroiliac joint involvement and extra osseous features. This table combined frequency counts for the entire study population, meaning genders were not accounted for. The collection of those who had sacroiliac joint involvement was conducted to display if the patient had involvement unilaterally, meaning only on one side of the body or bilaterally, meaning on both sides of the body. After conducting the analysis, it was noted that two members within the sample population had unilateral sacroiliac joint involvement and at least one extra osseous feature present. As well, three study participants had bilateral sacroiliac joint involvement with at least one extra osseous feature present. It was found that six study participants had unliteral joint involvement with no extra osseous features present and one study participant had bilateral sacroiliac joint involvement with no extra osseous features. Under the Fisher's Exact Test that was conducted, the results were noted to be statistically significant

which means the probability of this relationship is considered random variation instead of an actual relationship between the variables. A Fisher's Exact Test was used because 50% of the cell counts within this table were below the value of five. The Table Probability (P) was 0.0037 and the Pr<=P being 0.0115, which shows the test was significant at or below the 0.05 level. It is important to note that due to the cell counts being such small values, one should be cautious when generalizing this table.

Table 5: Comparison of those who are positive for HLA B27 gene to those who are negative by gender

Table 5 displays a comparison of those who tested positive for having the HLA B27 gene to those who tested negative. The HLA B27 gene is a very common gene seen in many adolescents who have rheumatic diseases such as arthritis and CNO/CRMO (Açoğlu et al., 2019). In regard to the male participants, it was found that 17.9% were positive with the HLA B27 gene. As well, it is important to note that 21 male participants did not receive the laboratory test for this, so they were considered missing values in this table. In regard to the female participants, it was found that 16.3% were positive with the HLA B27 gene. It was documented that 18 female participants did not receive the laboratory test for this, so they were considered missing values in this table. These findings are deemed significant as the overall frequency of HLA B27 for the US population is 7.6% (Reveille, 2017).

Table 6: Comparison of those with a follow up whole body MRI post treatment to those with no follow up whole body MRI by gender

Table 6 displays a comparison of those who had a follow up whole body MRI completed once being on treatment compared to those who did not receive a follow up whole body MRI. An inclusion criterion for those to be involved in this descriptive study is to have received at least one whole body MRI. However, something of importance that was assessed within this study was seeing who within this cohort received a follow up whole body MRI after being prescribed medication. This is meaningful because whole body MRI's are deemed as the gold standard in terms of assessing CNO/CRMO bone lesions due to getting a full body picture of what lesions are considered as "active" or "resolved" (Swidrowska-Jaros et al., 2019). Physicians will decide whether their patients should receive an MRI or not due to the of the importance of seeing the current lesion status. This is of high significance because many times lesions can be "asymptomatic," meaning the patient is not experiencing any pain or physical deformity. Therefore, they can go unseen and undetected if only receiving partial lower extremely or upper extremely MRI imaging. Regarding the female participants, it was noted that 68.3% of the study participants received follow up whole body MRI's. For the male participants, it was noted that 77.6% received follow up whole body MRI's.

Table 7: Average age at onset of disease and diagnosis of disease by gender

Table 7 displays the average age of the date of onset that was reported within the patient's medical charts and the average age of diagnosis that was reported in the patient's medical chart. Regarding average age of onset, the average age for both males and females was 9 years old. The average age of diagnosis for males was 9 years old and the average age of

diagnosis for females was 10 years old. These tests were meaningful as they support the published literature regarding the mean age for onset and diagnosis of CRMO/CNO being 9 (Cebecauerová et al., 2022). The tests conducted for both of these measures was two sample t-tests.

Table 8: Comparison of those with active disease at last clinical visit to those with noted clinical remission by gender

Table 8 shows a comparison of those who had noted active disease at their last clinical visit to those who had noted clinical remission at their last visit. Active disease pertains to if the patient has current active lesions on the most recent MRI images from persistent abnormal hyperintense bone marrow signal and if the patient is still on medication. Clinical remission pertains to the notion of the patient not having any current active lesions on the most recent MRI imaging and is either no longer receiving medication or PRN meaning to take as needed. Regarding males, 12.2% were noted to be in remission at their last visit and 87.8% reported having active disease. For females, 28.3% reported being in remission while 71.7% reported having active disease at their last visit.

Appendix 2: Frequencies of the lesions on different body parts

Appendix 2 displays the frequencies of bone lesions that were present within the entire study population, with a summed total of 604 lesions. It is important to point out that to calculate the locations on the body, it was measured by summing up the total amount of lesions that were present in each distinct location. This was done by the patient either receiving a 0 for the location on the body if no lesions were present, a 1 if the lesion was unilateral meaning only in one

distinct location, or a 2 which meant bilaterally due to it being on both parts of the body. The 16 distinct locations on the body noted are thoracic spine, mandible, clavicle, scapula, ribs, sacrum/sacroiliac joint, pelvis, humerus, radius/ulna, hand/wrist, proximal femur, mid femur, distal femur, hind/midfoot, and tibia/fibula. Some locations on the body were placed together in a broader category for totaling purposes. For example, the sacrum and sacroiliac joint were combined together for a total amount of lesions in both of those locations. The radius/ulna category contained the forearm, radius, and ulna all into one. The proximal femur also contained the lesions that were noted in the greater trochanter. The hind/midfoot consisted of all the bones of the foot exclusive of metatarsals and phalanges. As well, the tibia and fibula were conjoined together into one category. The locations that had the greatest number of lesions were the tibia/fibula N=141, hind/midfoot N=111, mid femur N=76, pelvis N=69, sacrum/sacroiliac joint N=36, radius/ulna N=33, and the humerus N=30. The three locations that had the least number of lesions reported were the ribs N=4, hand/wrist N=6, and scapula N=7.

V. Discussion

This descriptive study examined the clinical features and outcomes of patients at their last clinical visit who are diagnosed with CNO/CRMO at this single center large academic children's hospital from August 1st, 2013 to August 1st 2023. The criteria for a participant to be included in this study consisted of adolescent patients less than 21 years old whom have been seen by physicians at CAP since August 1st, 2013 to August 1st, 2023, that have been diagnosed with CRMO or CNO and have received at least one whole body MRI. Much of the literature published on CNO and CRMO thus far shows various clinical features and outcomes with adolescents who are diagnosed with the disease, along with those who also have extra osseous features present such as arthritis, psoriasis, and inflammatory bowel disease. The purpose of this study was to add to the overall understanding and knowledge from previous literature by collecting data on the clinical features and outcomes of those who are diagnosed with Chronic Nonbacterial Osteomyelitis (CNO) and Chronic Recurrent Multifocal Osteomyelitis (CRMO) at the Children's Healthcare of Atlanta's Center for Advanced Pediatrics (CAP). As well, the study focused on seeing the various discrepancies across genders, age, and familial history of autoimmunity if any amongst the study population.

Main Findings

Within this study population it is important to note that there was no significant difference between genders in regard to treatment regiments that physicians prescribed their patients at CAP. Within much of the literature, there has been no discrepancy between males and females being prescribed one form of medication over the other and this descriptive study

supports the literature with the forms of treatments diagnosed being relevantly even between genders dependent on their lesion quantity and locations. The first main finding present within this study population that supports the literature that is published regarding this topic is the most common areas on the body that are affected by CNO/CRMO being the vertebrae, pelvis, clavicles, femurs, and tibias (O'Leary et al., 2021). The research conducted at this institution supports this as the areas that had the most lesions within this study population were the tibia, femurs, pelvis, clavicles, and thoracic spine. A notable distinction between literature and our research is the hind/midfoot being a common site of disease within the cohort at our clinic versus what has been reported in literature. The areas of the body that were categorized within the hind/midfoot for this study were all the bones of the foot exclusive of metatarsals and phalanges. These had a total of 60 lesions within the cohort, and due to the literature that supports the most common locations on the body, lesions in the hind/midfoot are generally less described in comparison to the most common locations of lesions previously mentioned.

The second main finding from this descriptive study stemmed from examining the clinical features present, by the total amount of whole-body MRI's that were performed within this study population. One of the inclusion criteria's for being able to be included in this study is the patient must receive at least one whole body MRI. Therefore, a total of 111 patients that have been diagnosed with CNO and CRMO at the Children's Healthcare of Atlanta's Center for Advanced Pediatrics have received at least one whole body MRI. However, a significant direction after procedural plans is the follow up imaging results to assess the disease status once the patient has been on a treatment plan from their physician. It was documented that 85 total patients (73%) within this cohort received a follow up whole body MRI after being on treatment. Those that were not included within this are those who either did not receive any follow up MRI

imaging or solely received site specific MRI imaging, as in only distinct locations on the body. Whole body MRI's are considered the gold standard for assessing CNO/CRMO bone lesions on the body. After Children's Healthcare of Atlanta's Center for Advanced Pediatrics patients having assessed 111 patients, this should be considered significant for this data. To back this statement up, one of the larger studies published where the entire study population received a whole-body MRI was a population of 61 total patients receiving at least one whole body MRI (Suo et al., 2022). To magnify the significance from our study, our study population is 111 patients that all underwent whole body MRI's, which is almost double compared to the 61 patients, and 81 of our study participants received another follow up whole body MRI, which is also greater than 61. This larger data set allowed us to enhance our understanding through nuances found within each patient's clinical features.

The final main finding from this study that supports literature was the average age of those who are diagnosed with CNO and how the prevalence amongst CNO across genders was greater for females compared to males. Much of the literature published regarding this matter concludes that across the genders male and female, CNO/CRMO is more prevalent amongst girls (Cebecauerová et al., 2022). Within our research conducted for this descriptive study there were more female patients (N=60) compared to male patients (N=49), with two patients who chose not to disclose their gender. As well, the average age of onset for this disease for both males and females within this study was nine years old. Both of these statistics support the published literature regarding these subject matters.

Other Relevant Findings

There was an analysis that was conducted that was looking at within the patients in this study population, which have a particular set of extra osseous features present alongside their CNO or CRMO diagnosis. In previous literature, children diagnosed with CNO/CRMO may present other co-morbidities such as inflammatory bowel disease, psoriasis, and arthritis (Hedrich et al., 2013). Therefore, there was an analysis that looked at which patients within this cohort had any of these features present along with their current CRMO/CNO diagnosis. Additionally, patients that had these extra osseous features present, which supported the literature that is present regarding this topic. The final analysis that was conducted dealt with those with solely sacroiliac joint involvement within their CNO/CRMO lesions, compared to those across the entire cohort that had sacroiliac joint involvement and at least one of the three previously mentioned extra osseous features present. Due to this center location in the rheumatology department, it is very common to see patients with diseases that impact the sacroiliac joint, such as arthritis. Therefore, seeing if there was any sort of relevance between this particular cohort amongst those with extra osseous features and sacroiliac joint involvement was of high interest. There was an established relationship within the cohort of patients that had both unilateral and bilateral sacroiliac joint involvement and at least one of the extra osseous features present.

Limitations and Future Directions

It is important to point out that this study did have some limitations present. One of the first limitations is due to the earliest data collection for this study being from 2013, at this time electronic medical record systems were not nearly as advanced as to where it is present day,

therefore, some notes from paper chart were missing. There could be missing data in the patients' medical records via EPIC where all the data was extracted from which could affect certain variables such as locations on the body, missing MRI image results, or documentation of medication plans. For example, since this is a retrospective chart review, there may be missing data regards to family history. In regard to this, with several physicians at the clinic (~10 including those that have left over the last years), there is likely subjective variation in assessment. There is no standardized clinical exam for CNO/CRMO unlike other rheumatic diseases such as juvenile idiopathic arthritis, where there is a joint count to standardize the disease status. This leads to patients being unaware that their additional symptoms are in association with CRMO/CNO, due to physicians not routinely asking these questions, which can make errors and inconsistencies within patient reporting global pain scores and physician global scores.

A second limitation that is present is due to the nature of the disease being possibly asymptomatic, this can result in a lack of awareness on the patients end for the patient to be alerted to go into see their physicians for updates on disease status or collection of follow up imaging results. A byproduct of this could be delays in diagnosis due to the unawareness of the disease that may be present. This in return would impact treatment plans, which ultimately could be detrimental to the patient.

A third limitation that is existent is due to many of the beginning symptoms of disease onset being similar to cold and flu like symptoms such as fevers, fatigue, and body aches, this can cause a delay in a proper diagnosis, also impacting the calculation of age of onset for the patient (Cebecauerová et al., 2022). Recall bias may also play a role due to the patient not

remembering exactly where they are experiencing pain on their body, along with when that pain began, which are critical points for physicians knowledge.

A fourth limitation that should be included is the impact of the COVID-19 pandemic. During this time many physicians were only able to see what was deemed as "emergency cases," which CNO/CRMO may not be deemed an "emergency case." Therefore, this made it challenging for patients to come into the clinic during this time and/or receive certain critical diagnosing modalities such as MRI's, X-rays, or bone biopsies. This did impact and cause delays in patients being diagnosed and treated for CNO/CRMO at the clinic. As well, this presented barriers with helping those already diagnosed that needed consistent routine follow ups with their physicians on the progress of their treatment. As resulted, this created loss to follow ups as many patients may not have comeback post pandemic.

Future directions

In terms of future directions, it would be important to follow this cohort over time to describe the outcomes of the patients with regards to remission, active disease or development of complications. This will help in improved understanding of the disease and treatments. Secondly, another area or research that would be beneficial is to systematically compare the follow up images to the initial images to discern the MRI outcome of lesions and whether these were impacted by treatment. A question this study raises is to narrow down the specific clinical questions asked by physicians when observing new potential patients to diagnose with CNO/CRMO.

Strengths

The strengths of this study were the large sample size and the inclusion of the entire sample cohort receiving at least one whole body MRI. Additionally, to the best of our knowledge this is one of the largest studies conducted on a cohort of children with CNO/CRMO (N=111), that all have received at least one whole body MRI, along with (N=85) receiving a follow up whole body MRI. The strength allowed us to examine the clinical features and outcomes of patients that have been seen and treated in our clinic at Children's Healthcare of Atlanta's Center for Advanced Pediatrics from 2013 to August 1st, 2023.

Conclusion

This study aimed to answer the research question of what are the clinical features and outcomes of patients at their last clinical visit who are diagnosed with CNO/CRMO at a single center large academic children's hospital from August 1st, 2013 to August 1st 2023. Improved understanding the signs and symptoms of CNO/CRMO and knowing the utility of whole-body MRI can lead to timely treatment of CNO/CRMO with the appropriate medication that can lead to improvement of pain and dysfunction. This study also provides important information on the anatomical locations of involvement in CNO/CRMO that will help pediatric rheumatologists in recognizing bone involvement. From the descriptive statistics that were conducted, this helps describe the clinical features and outcomes that were present amongst the 111 study participants. This information is vital when disseminating knowledge and understanding to other treating physicians to patients with CNO and CRMO. The results produced from this study magnify the importance of continuing to further understand the various clinical features and outcomes that

can be present amongst patients with this disease through looking at their pre-and post-diagnosis characteristics via electronic medical records.

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VII. Tables

Table 1: Descriptive Statistics of Entire Sample Population	Frequency Counts	
Variables	Yes N=111	No N=111
Race		
American Indian/Alaskan Native	0.9%	99.1%
Asian	6.3%	93.7%
Native Hawaiian/Pacific Islander	0%	100%
Black or African American	23.4%	76.6%
White	70.3%	29.7%
Gender		
Female	54.1%	
Male	44.1%	
Undisclosed	1.8%	
Medications		
Tumor Necrosis Factor-Inhibitors (TNF-I)	63.1%	36.9%
Pamidronate	19.8%	80.2%
Biologic	6.3%	93.7%
Bisphosphonates	2.7%	97.3%
Steroid	52.3%	47.7%
Disease-modifying antirheumatic drugs (DMARDS)	64%	36%
Non-steroidal anti-inflammatory drugs (NSAIDS)	96.4%	3.6%
Modalities of Diagnosis		
Whole Body MRI	100%	
XRAY	85.6%	14.4%
Bone Biopsy	39.6%	60.4%
Extra Osseous Features	7.2%	92.8%
Arthritis	6.3%	93.7%
Psoriasis	4.5%	95.5%
IBD		
Family History of Autoimmunity	40.5%	59.5%
Maternal	20.7%	79.3%
Paternal	73%	27%
Follow up Whole Body MRI		
Disease Status at last visit	78.4%	
Active Disease	21.6%	
Disease in Remission		
HLA B27 Gene	16.7% (N=11)	
Tested Positive	83.3% (N=61)	
Tested Negative		

Table 2: Descriptive Statistics Stratified by Gender

Variables	Female (N=60)	Male (N=49)	P-Value
Medications			
Tumor Necrosis Factor-Inhibitors (TNF-I)	65%	59.2%	0.5329[3]
Pamidronate	21.7%	14.3%	0.3220[3]
Biologic	6.7%	6.1%	1.0000[4]
Steroid	53.3%	51%	0.8099[3]
Bisphosphates	1.7%	4.1%	0.5869[4]
Disease-modifying antirheumatic drugs (DMARDS)	63.3%	63.3%	0.9942[3]
Non-steroidal anti-inflammatory drugs (NSAIDS)	95%	98%	0.6258[4]
Modalities of Diagnosis			
Whole Body MRI	100%	100%	
XRAY	85%	85.7%	0.9165[2]
Bone Biopsy	43.3%	36.7%	0.4849[2]
Extra Osseous Features			
Arthritis	8.3%	6.1%	0.7280[3]
Psoriasis	11.7%	0%	0.0158[3]
IBD	5%	4.1%	1.0000[3]
Family History of Autoimmunity			
Maternal	41.7%	40.8%	0.9285[2]
Paternal	23.3%	18.4%	0.5273[2]
Follow up Whole Body MRI	68.3%	77.6%	0.2838[2]
Disease Status at last visit			
Active Disease	71.7%	87.8%	0.0406[3]
Disease in Remission	28.3%	12.2%	0.0406[3]
HLA B27 Gene			
Tested Positive	16.3%	17.9%	0.8623[2]
Tested Negative	83.7%	82.1%	0.8623[2]
Mean Number of lesions	5	5	0.2757[1]
Average age at onset	9	9	0.3107[1]
Average age at diagnosis	10	9	0.5212[1]
Average difference between onset and diagnosis (In days)	182	282	0.2231[1]

**[1]Equal variance two sample t-test; [2]Unequal variance two sample t-test; [3]Chi-Square p-value, [4]Fisher Exact p-value

**Note 2 missing values for the two who identified as undisclosed gender

Table 3: Comparison of those with at least 1 extra osseous feature to those with solely bone lesions by gender

Variables:	Female	Male	P-Value
Those with extra osseous features	14	5	0.0723[2]
Those solely with bone lesions	46	44	

**[2]Unequal variance two sample t-test
**Note 2 missing values for the two who identified as undisclosed gender

Table 4: Comparison of those with Sacroiliac Joint involvement to those with Sacroiliac Joint involvement and at least 1 extra osseous feature

Variables:	Unilateral	Bilateral
Those with SI Joint Involvement with just bone involvement	6	1
Those with SI Joint involvement with extra osseous features	2	3

**Fisher's Exact Test
**Note 2 missing values for the two who identified as undisclosed gender

Table 5: Comparison of those who are positive for HLA B27 gene to those who are negative by gender

Variables:	Female	Male	P-Value
Tested positive with HLA B27	7	5	0.8623[2]
Tested negative with HLA B27	36	23	

**[2]Unequal variance two sample t-test
**Note 2 missing values for the two who identified as undisclosed gender

Table 6: Comparison of those with a follow up whole body MRI post treatment to those with no follow up whole body MRI post treatment by gender

Variables:	Female	Male	P-Value
Those with Follow up WB MRI	41	38	0.2838[2]
Those without Follow up WB MRI	19	11	

**[2]Unequal variance two sample t-test
**Note 2 missing values for the two who identified as undisclosed gender

Table 7: Average age at onset of disease and diagnosis of disease by gender

Variables:	Female	Male	P-Value
Average age at date of Onset	9	9	0.3107[1]
Average age at date of Diagnosis	10	10	0.5212[1]

**[1]Equal variance two sample t-test
**Note 2 missing values for the two who identified as undisclosed gender

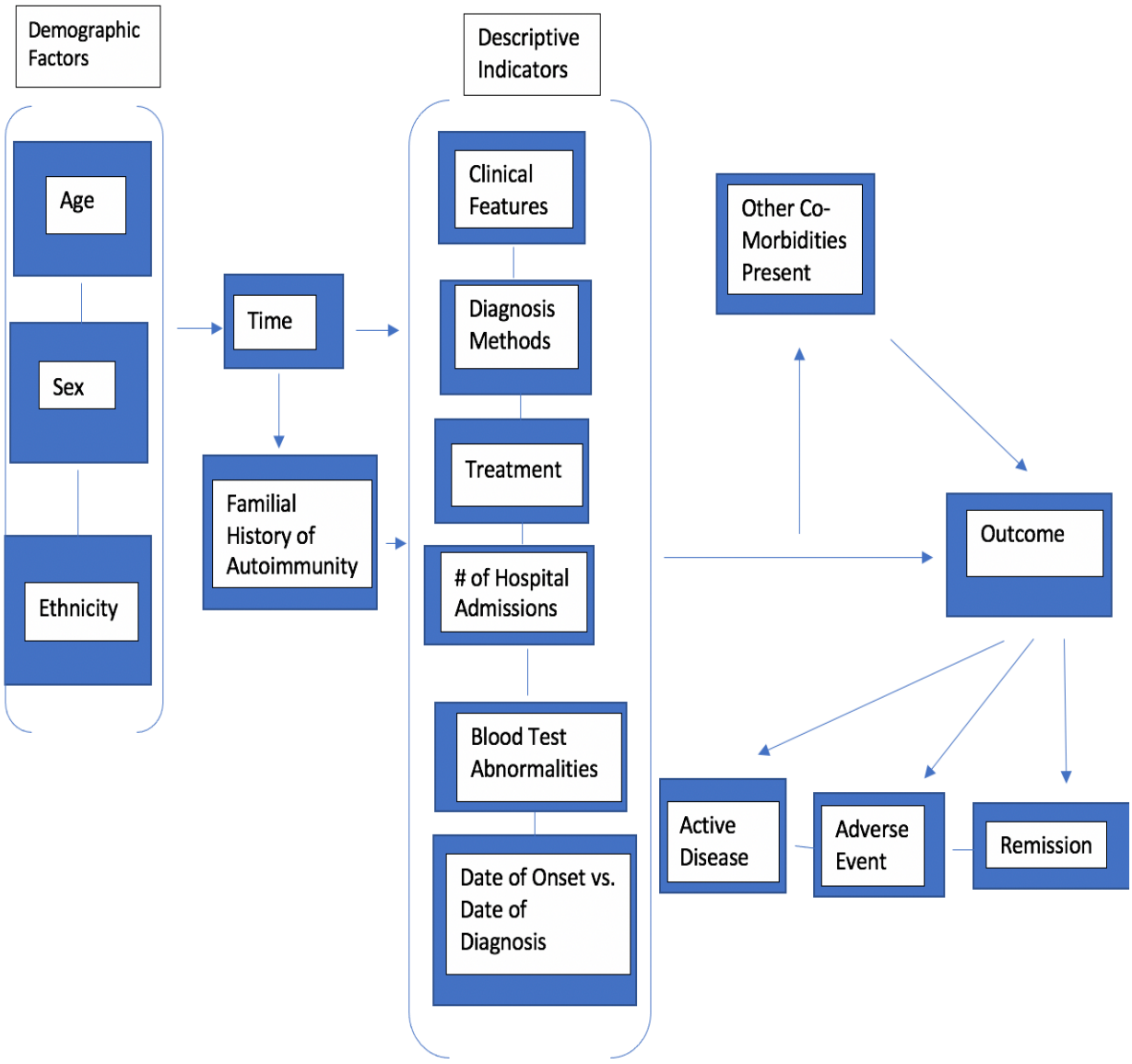
Table 8: Comparison of those with active disease at last clinical visit to those with noted clinical remission by gender

Variables:	Female	Male	P-Value
Active Disease	43	43	0.0406[2]
Clinical Remission	46	44	

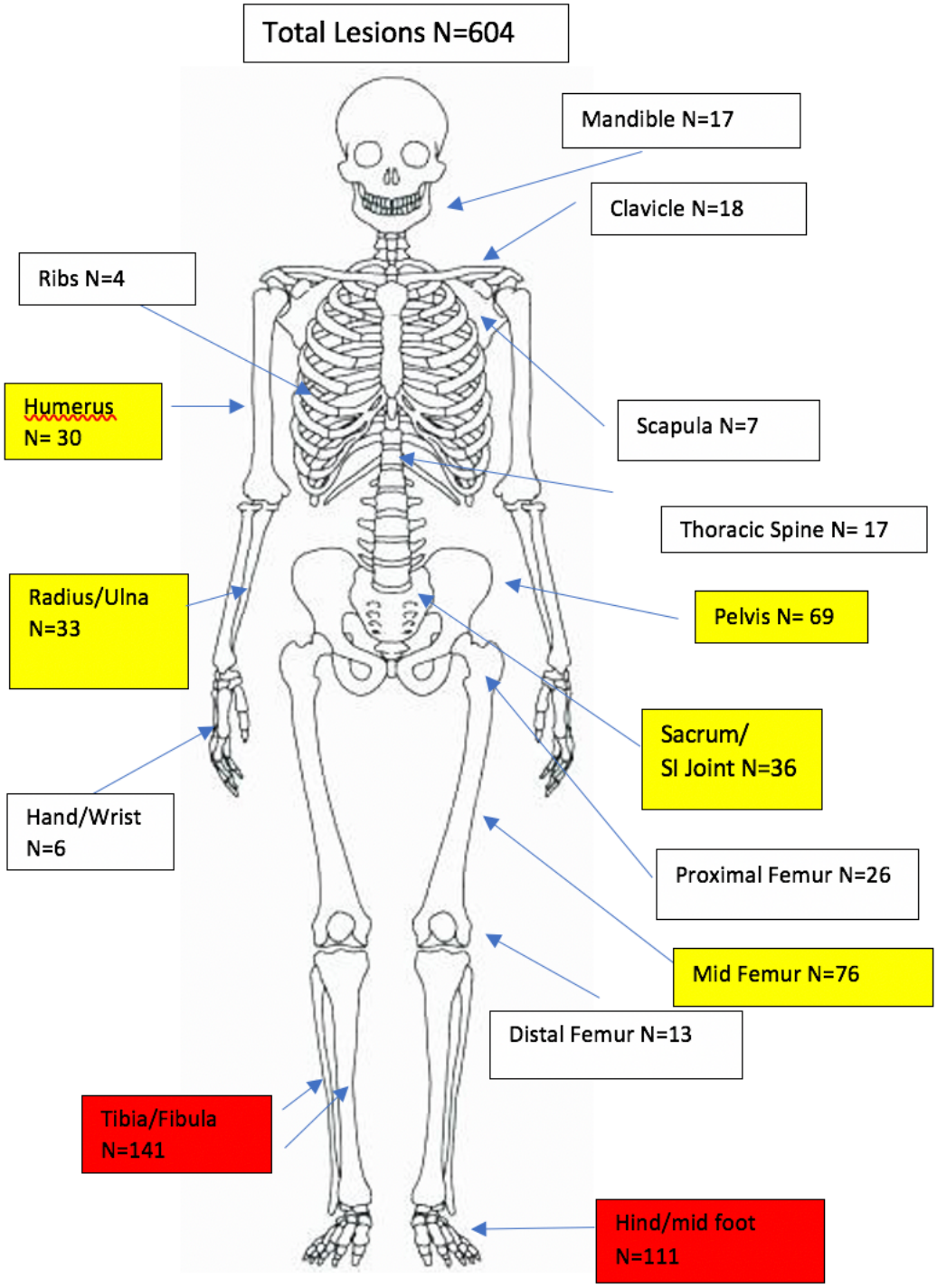
**[2]Unequal variance two sample t-test
**Note 2 missing values for the two who identified as undisclosed gender

VIII. Appendices

Appendix 1: Representation of Conceptual Framework



Appendix 2: Figure 1: Full body skeleton showing total lesion counts at each location for entire sample population (See Below)



The red coloring displays the locations that have the greatest number of lesions present and the yellow coloring displays the locations with the next highest amounts of lesions present within the study population.