

Bone Erosion Trajectories and Functional Correlates in  
Rheumatoid Arthritis: Cross-Sectional and Longitudinal  
Evidence from an 8-Year HR-pQCT Study

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## **DECLARATION**

The work contained in this thesis is original research carried out by the author in the Division of Rheumatology, Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong. No proportion of the thesis has been submitted to this university or to any other universities or institutions for a degree, diploma, or other qualifications.

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# **ABSTRACT**

Abstract of thesis entitled:

Bone Erosion Trajectories and Functional Correlates in Rheumatoid Arthritis: Cross-Sectional and  
Longitudinal Evidence from an 8-Year HR-pQCT Study

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## **Background**

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by progressive joint destruction leading to functional disability. High-resolution peripheral quantitative computed tomography (HR-pQCT) offers superior sensitivity for detecting early cortical breaks and enables precise quantification of erosive burdens. Analysis via HR-pQCT showed cortical breaks across RA patients and healthy controls (HCs) groups, with erosions in HCs being characteristically small, as 95% less than 5 mm<sup>3</sup>. Notably, no differences in location or morphology of erosions <5 mm<sup>3</sup> were observed between HCs and RA patients with long-standing disease, though it remains uncertain if these findings apply to early RA (ERA). The clinical significance and long-term evolution of small (<5 mm<sup>3</sup>), intermediate (1–5 mm<sup>3</sup>), and large (>5 mm<sup>3</sup>) erosions in RA remain unclear. Although joint destruction is detrimental, long-term data on the rate or extent of erosion progression or healing are lacking. Exploring whether inflammation resolution through treat-to-target (T2T) in ERA patients improves erosion healing compared to usual care warrants further investigation. Previous studies highlight the significant impact of wrist erosions and MCP joint narrowing on disability, though conventional radiography may underestimate the functional effects of MCP erosions. It remains unclear if the relationship between erosion volume and physical functioning varies by location (wrist vs. MCH2) as assessed via HR-pQCT. Addressing these gaps could refine site-specific evaluations to better assess treatment efficacy.

## **Hypothesis**

We hypothesize that most small erosions (<1 mm<sup>3</sup>) may represent physiological rather than pathological lesions, and that early RA (ERA) patients treated with a treat-to-target (T2T) strategy may exhibit better long-term outcomes, such as greater erosion healing in the second metacarpal

head (MCH2), compared to established RA (EstRA) patients receiving usual care. Additionally, carpal erosion burden assessed by HR-pQCT may be associated with functional disability in RA patients.

## **Objectives**

1. To compare the prevalence of erosions between RA patients and HCs, stratified by erosion size: small <1 mm<sup>3</sup>, intermediate 1-5 mm<sup>3</sup>, large >5 mm<sup>3</sup>.
2. To ascertain the long-term change in MCH2 erosion volume, stratified by size, over a median follow-up period of 8 years in RA patients, and also to assess the frequency of erosions exhibiting stability, progression, or regression over time within each size category in patients with ERA vs EstRA.
3. To elucidate whether erosion volume in the wrist measured by HR-pQCT is related to disability in RA patients.

## **Methods**

The present investigation involved three studies.

Study 1 was a cross-sectional study comparing the erosion parameters of 247 RA patients with 78 age- and sex-matched HCs who underwent HR-pQCT scans of the MCH2 at baseline.

Study 2 was a follow-up study of the 247 RA patients, including patients from an ERA cohort (n=98; baseline symptom duration ≤ 2 years, received T2T management within the first year followed by usual care), and an EstRA cohort (n=149, received usual care) who had undergone HR-pQCT of MCH2 after a median of 8.4 years to assess changes in erosive parameters.

Study 3 was a cross-sectional study examining the relationship between erosion parameters in the wrist bones and functional outcomes in RA patients. A total of 232 RA patients who underwent wrist HR-pQCT imaging were enrolled. Disability was assessed in three different ways: the Health Assessment Questionnaire Disability Index (HAQ-DI), grip strength, and the dexterity component of the Chinese Arthritis Impact Measurement Scales 2 (CAIMS2).

## Results

Study 1: Compared to healthy controls, erosions in RA patients were significantly more prevalent ( $P<0.001$ ), with higher numbers ( $P<0.001$ ) and larger total volumes ( $P<0.001$ ). Based on the largest erosion volume per patient, large erosions ( $>5 \text{ mm}^3$ ,  $P=0.002$ ) and intermediate erosions ( $1-5 \text{ mm}^3$ ,  $P=0.003$ ) were significantly more common in RA patients, whereas the prevalence of small erosions ( $<1 \text{ mm}^3$ ) was comparable between RA patients and healthy controls.

Study 2: In RA patients, small erosions showed minimal change magnitude (Hodges-Lehmann estimate:  $0.052 \text{ mm}^3$ ); intermediate erosions remained stable, while large erosions demonstrated a significant reduction in volume ( $11.6$  to  $5.7 \text{ mm}^3$ ,  $P<0.001$ ) after a median follow-up of 8 years. Small erosions exhibited the highest (64%) stability, compared with intermediate ( $P=0.044$ ) and large erosions ( $P=0.003$ ).

Comparing the ERA and EstRA cohorts, destruction of MCH2 precluding image assessment by HR-pQCT occurred in seven patients in the EstRA cohort compared to zero in the ERA cohort (4% vs. 0%,  $P=0.046$ ) at the last visit. Images of 247 RA patients (mean age  $54\pm10$  years, 81% female) were assessed. Baseline comparison showed equivalent erosion profiles across both cohorts. At the last visit, the prevalence of large erosions ( $> 5 \text{ mm}^3$ ) was significantly higher in the EstRA cohort compared with the ERA cohort (25% vs. 13%,  $P=0.027$ ). A notably greater rate (81% vs.

38%, p=0.005) of large erosions regressed in the ERA than in the EstRA cohort between baseline and follow-up. Reduction in erosion volume was also significantly greater in the ERA cohort compared to the EstRA cohort.

Study 3: The investigation analyzed 232 RA patients (mean age 62±10 years, 80% female). Carpal erosions were detected in 88% of patients, most frequently in the lunate (80%), followed by the scaphoid (53%) and radius (42%). Both the number and volume of erosions in the radius and lunate significantly correlated with functional disability ( $\rho$  up to 0.21, P<0.01). Multivariate ordinal analysis adjusting for potential confounders identified the presence of radial erosions (OR=2.16, 95% CI 1.26–3.71, P=0.005), erosion counts (OR=1.20-1.41, p<0.001), and volume (OR=1.01-1.02, P=0.001) in the wrist bones were independently associated with higher disability grades in RA patients. Additionally, wrist joint destruction independently conferred a threefold higher odds of higher disability grades in RA patients (p=0.021).

## Conclusion

The volumetric properties of small and intermediate erosions were similar in RA patients and HC, and small erosions remained stable over long-term follow-up in RA patients, suggesting that small erosions may represent physiological rather than pathological lesions. Early intervention with a T2T approach may limit long-term bone erosion progression and promote partial erosion healing in ERA patients. HR-pQCT-detected carpal erosions were independently associated with functional disability in RA patients.

## 摘要

論文題目：類風濕性關節炎骨侵蝕演變軌跡與功能關聯性：基於八年高解像度外周定量電腦斷層掃描（HR-pQCT）研究的橫斷面與縱向證據

### 背景

類風濕性關節炎（RA）是一種以進行性關節破壞為特徵的慢性炎症性疾病，可導致功能殘疾。高解像度外周定量電腦斷層掃描（HR-pQCT）對早期皮質斷裂的檢測具有更高敏感性，並可精準量化骨侵蝕負荷。研究發現，RA 患者和健康對照者（HCs）中均存在皮質中斷，但健康人群中 95% 的侵蝕竈體積  $< 5 \text{ mm}^3$ 。值得注意的是，長病程 RA 患者與健康對照的小型侵蝕竈 ( $< 5 \text{ mm}^3$ ) 在位置和形態學上無差異，但此現象是否適用於早期 RA (ERA) 尚不明確。此外，不同體積（小型  $< 1 \text{ mm}^3$ 、中型  $1-5 \text{ mm}^3$ 、大型  $> 5 \text{ mm}^3$ ）骨侵蝕的臨床意義及長期演變規律仍不清楚。儘管關節破壞具有明確危害性，但關於侵蝕進展或修復速率及程度的長期數據仍缺乏。通過達標治療（T2T）策略緩解炎症是否可促進 ERA 患者骨侵蝕修復（相較於常規治療）值得深入探討。既往研究表明腕關節侵蝕和掌指關節（MCP）間隙狹窄對功能障礙影響顯著，但傳統放射學可能低估 MCP 侵蝕的功能影響。目前尚不明確 HR-pQCT 測量的不同部位（腕關節 vs. 第二掌骨頭）侵蝕體積與軀體功能的關係是否存在差異。解決這些知識缺口將有助於優化特定部位評估，從而更精準評價治療療效。

### 假設

本研究假設：小型侵蝕竈 ( $<1 \text{ mm}^3$ ) 可能多為生理性而非病理性損傷；接受達標治療 (T2T) 策略的 ERA 患者在第二掌骨頭 (MCH2) 的長期侵蝕修復效果可能優於接受常規治療的已確診 RA (EstRA) 患者；此外，HR-pQCT 評估的腕骨侵蝕負荷可能與 RA 患者功能障礙相關。

## 目標

1. 比較 RA 患者與健康對照者不同體積骨侵蝕（小型 $<1 \text{ mm}^3$ 、中型 $1-5 \text{ mm}^3$ 、大型 $>5 \text{ mm}^3$ ）的患病率差異
2. 評估 RA 患者 MCH2 侵蝕體積（按體積分層）在 8 年中位隨訪期的長期變化，並比較 ERA 與 EstRA 患者各體積侵蝕竈的穩定性、進展或消退頻率
3. 探討 HR-pQCT 測量的腕部侵蝕體積與 RA 患者功能障礙的關係

## 方法

本研究包含三項子研究：

研究 1 為橫切面研究，納入基線接受 MCH2 HR-pQCT 掃描的 247 例 RA 患者和 78 例年齡性別匹配的健康對照，比較兩組骨侵蝕參數。

研究 2 為縱向隨訪研究，對 247 例 RA 患者（包括 98 例 ERA 隊列[症狀持續時間 $\leq 2$  年，首年接受 T2T 治療後轉為常規管理]和 149 例 EstRA 隊列[全程常規治療]）進行中位 8.4 年的 MCH2 HR-pQCT 複查，分析侵蝕參數演變。

研究 3 為橫切面研究，納入 232 例接受腕關節 HR-pQCT 成像的 RA 患者，通過健康評估問卷殘疾指數 (HAQ-DI)、握力及中國關節炎影響量表 2 (CAIMS2) 手功能分量表評估腕部侵蝕參數與功能障礙的關係。

## 結果

研究 1：RA 患者總體侵蝕患病率 ( $P<0.001$ )、侵蝕數量 ( $P<0.001$ ) 及總體積 ( $P<0.001$ ) 均顯著高於健康對照。按最大侵蝕體積分層分析顯示，RA 患者大型 ( $>5 \text{ mm}^3$ ,  $P=0.002$ ) 及中型 ( $1-5 \text{ mm}^3$ ,  $P=0.003$ ) 侵蝕竈更常見，而小型侵蝕竈 ( $<1 \text{ mm}^3$ ) 患病率組間無差異。

研究 2：RA 患者小型侵蝕竈體積變化微小 (Hodges-Lehmann 估計值： $0.052 \text{ mm}^3$ )，中型保持穩定，大型侵蝕體積顯著減少 ( $11.6 \rightarrow 5.7 \text{ mm}^3$ ,  $P<0.001$ )。小型侵蝕穩定性最高 (64%)，顯著優於中型 ( $P=0.044$ ) 和大型 ( $P=0.003$ )。EstRA 組 7 例 (4%) 出現 MCH2 嚴重破壞致無法影像評估 (ERA 組 0 例,  $P=0.046$ )。末次隨訪時 EstRA 組大型侵蝕患病率顯著高於 ERA 組 (25% vs. 13%,  $P=0.027$ )，且 ERA 組大型侵蝕消退比例更高 (81% vs. 38%,  $P=0.005$ )，侵蝕體積降幅亦更顯著。

研究 3：88%患者存在腕骨侵蝕，月骨 (80%)、舟骨 (53%) 和橈骨 (42%) 最常見。橈骨及月骨侵蝕數量與體積均與功能障礙顯著相關 ( $\rho$  最高 0.21,  $P<0.01$ )。多因素分析顯示，橈骨侵蝕存在 ( $OR=2.16$ , 95%CI 1.26-3.71)、腕骨侵蝕數量 ( $OR=1.20-1.41$ ) 及體積 ( $OR=1.01-1.02$ ) 均為功能障礙的獨立預測因子 ( $P$  均 $<0.01$ )。腕關節破壞使重度殘疾風險增加 3 倍 ( $P=0.021$ )。

## 結論

小型與中型侵蝕的容積特徵在 RA 患者與健康人群中相似，且小型侵蝕在長期隨訪中保持穩定，提示其可能為生理性損傷。早期達標治療可抑制 ERA 患者骨侵蝕進展並促進部分修復。HR-pQCT 檢測的腕部侵蝕與 RA 患者功能障礙獨立相關，凸顯腕關節精準評估的臨床價值

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3. Yan X, Cheng I, et al. "Wrist Bone Erosion Burden Assessed by HR-pQCT Is Associated with Functional Disability in Patients with Rheumatoid Arthritis." In Preparation.

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## LIST OF ABBREVIATIONS

<b>Abbreviation</b>	<b>Full Form</b>
RA	Rheumatoid Arthritis
ERA	Early Rheumatoid Arthritis
EstRA	Established Rheumatoid Arthritis
HCs	Healthy Controls
MCP	Metacarpophalangeal
MCH2	Second Metacarpal Head
HR-pQCT	High-Resolution Peripheral Quantitative Computed Tomography
MRI	Magnetic Resonance Imaging
LSC	Least Significant Change
BAM	Bone Analysis Modules
ROI	Region of Interest
HAQ-DI	Health Assessment Questionnaire-Disability Index
CAIMS2	the Chinese Arthritis Impact Measurement Scales 2
CDAI	Clinical Disease Activity Index
DAS28	Disease Activity Score in 28 joints
DAS28-CRP	Disease Activity Score 28-CRP
SDAI	Simplified Disease Activity Index
SDI	Sustained SDAI remission
LDA	Low Disease Activity
MDA	Moderate Disease Activity
HDA	High Disease Activity
VAS	Visual Analog Scale
RF	Rheumatoid Factor
ACPA	Anti-Citrullinated Protein Antibodies
Anti-CCP	Anti-Cyclic Citrullinated Peptide antibody

<b>Abbreviation</b>	<b>Full Form</b>
CRP	C-Reactive Protein
ESR	Erythrocyte Sedimentation Rate
T2T	Treat-to-Target
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
MTX	Methotrexate
DMARDs	Disease-Modifying Antirheumatic Drugs
csDMARDs	Conventional Synthetic Disease-Modifying Antirheumatic Drugs
bDMARDs	Biological Disease-Modifying Antirheumatic Drugs
bsDMARDs	Biosimilar Disease-Modifying Antirheumatic Drugs
tsDMARDs	Targeted Synthetic Disease-Modifying Antirheumatic Drugs
b/tsDMARDs	Biologic/Targeted synthetic Disease-Modifying Anti-rheumatic drug
TNF	Tumor Necrosis Factor
TNF- $\alpha$	Tumor Necrosis Factor Alpha
RANK	Receptor Activator of Nuclear Factor $\kappa$ B
RANKL	Receptor Activator of Nuclear Factor $\kappa$ B Ligand
MMPs	Matrix Metalloproteinases
OPG	Osteoprotegerin
ADAMTS	A Disintegrin and Metalloproteinase with Thrombospondin motifs
DKK-1	Dickkopf-1
IFN	Interferon
IL	Interleukin
IL-1	Interleukin-1
IL-1 $\beta$	Interleukin-1 beta
IL-6	Interleukin-6
IL-17	Interleukin-17
IL-23	Interleukin-23
Wnt	Wingless-related Integration Site signaling pathway
CTLA4	Cytotoxic T-Lymphocyte-Associated Protein 4

<b>Abbreviation</b>	<b>Full Form</b>
JAK	Janus Kinase
mAb	Monoclonal Antibody
PAD	Peptidylarginine Deiminase
SPECTRA	Study GrouP for XTrEme-CT in Rheumatoid Arthritis
BeSt	Behandeling van Reumatoïde Arthritis (Dutch trial)
CAMERA	Computer Assisted Management in Early Rheumatoid Arthritis
SWEPFOT	Swedish Farmacotherapy
TICORA	Tight Control of Rheumatoid Arthritis
ACR	American College of Rheumatology
APLAR	Asia-Pacific League of Associations for Rheumatology
EULAR	European League Against Rheumatism
IM	Intramuscular
IV	Intravenous
PO	Per Os (oral)
SC	Subcutaneous

# **Chapter 1: Introduction**

## **1.1 Rheumatoid arthritis (RA)**

Rheumatoid arthritis (RA) represents a chronic, inflammatory, autoimmune joint disease characterized by the production of autoantibodies against immunoglobulin G (rheumatoid factor) and citrullinated proteins (anti-citrullinated protein antibodies, ACPAs). This complex disorder manifests through persistent synovitis, systemic inflammation, and ultimately progressive joint destruction, resulting in substantial functional disability and reduced quality of life[[1](#), [2](#)]. The heterogeneity of RA is profound, clinical presentations, disease trajectories, and underlying pathogenic mechanisms demonstrate remarkable variability even among patients with identical classification or disease stage[[3](#)]. Despite considerable advances in understanding disease mechanisms and developing novel therapeutic approaches, RA remains incurable, though remission has emerged as an achievable clinical target for many patients [[4](#), [5](#)]

## **1.2 Epidemiology**

The global prevalence of RA exhibits geographical, ethnic, and temporal variations. Cross-sectional population studies indicate prevalence rates of 0.5-1% in North American and European populations, with lower rates in Southern European and Asian regions[[6](#), [7](#)]. The annual incidence ranges from 20 to 50 cases per 100,000 population, with temporal fluctuations observed over recent decades[[8](#)]. Across all populations, RA demonstrates female predominance, particularly in reproductive years, suggesting hormonal influences on disease pathogenesis[[9](#)].

Recent epidemiological investigations reveal declining incidence in certain regions, potentially attributable to environmental modifications, reduced smoking prevalence, or altered hormonal

exposures[[10](#)]. Conversely, longitudinal cohort studies demonstrate reduced disability and mortality among contemporary RA cohorts compared to historical populations, reflecting therapeutic advances and implementation of treat-to-target strategies[[11](#), [12](#)].

### **1.3 Mechanisms**

#### **1.3.1 Disease Course**

##### ***1.3.1.1 Preclinical RA***

The preclinical phase of RA represents a critical period during which immunological abnormalities precede clinical manifestations, providing potential windows for disease interception[[13](#)]. This phase encompasses several stages, beginning with genetic risk, followed by environmental exposures in susceptible individuals that trigger loss of tolerance to self-antigens, and culminating in systemic autoimmunity evidenced by autoantibody production, particularly rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs)[[14](#)]. These autoantibodies may appear years to decades before clinical symptoms, with progressively increasing titers and epitope spreading as disease onset approaches[[15](#)]. The preclinical phase also features alterations in circulating cytokines and chemokines, creating a pro-inflammatory milieu that ultimately transitions to clinically apparent arthritis[[16](#)].

##### ***1.3.1.2 Early and established RA***

The transition from preclinical to early clinical RA represents a pivotal phase characterized by synovitis, which may initially manifest subtly but progressively evolves into persistent inflammatory arthritis[[17](#)]. Early RA (ERA), typically defined as disease duration less than 12-24 months, constitutes a critical therapeutic window during which intervention may substantially alter disease trajectory[[18](#)]. This "window of opportunity" concept is supported by evidence that

treatment initiated within the first 12 weeks of symptoms achieves significantly better outcomes, including higher remission rates and reduced radiographic progression, compared to delayed intervention[[5](#), [19](#)].

The progression from early to established RA (EstRA) marks the transition to chronic, often refractory disease[[20](#)]. While previously considered inevitable, this progression can now be significantly modified through aggressive therapeutic strategies[[21](#)]. Nonetheless, established disease typically demonstrates more treatment resistance and accumulated structural damage, with consequent functional limitations. The transition from reversible synovitis to irreversible joint destruction represents a critical pathophysiological threshold that therapeutic strategies aim to prevent[[22](#)]. Longitudinal studies reveal distinct disease trajectories among RA cohorts, with different levels of disease activity despite conventional treatment[[23](#)]. These trajectories correlate with genetic profiles, autoantibody status, and baseline disease characteristics, underscoring the heterogeneity of RA and suggesting potential for personalized therapeutic approaches[[24](#), [25](#)] (Figure 1.1).

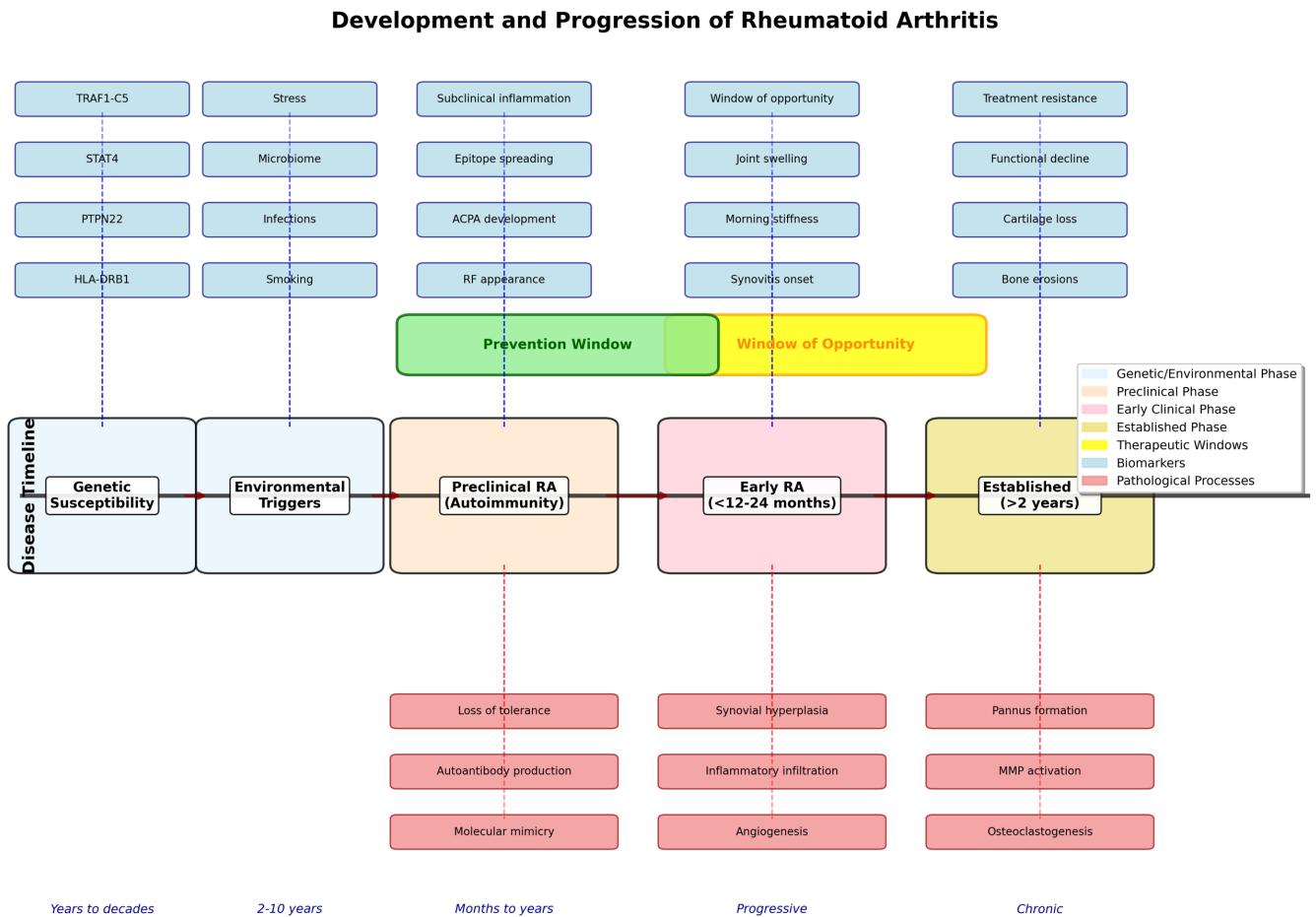


Figure 1.1 Development and progression of RA

This diagram illustrates the stages from genetic susceptibility and environmental triggers, through preclinical RA, early RA, to established RA. Key intervention windows, clinical features, and underlying pathological processes are highlighted. Abbreviations: RA, rheumatoid arthritis; TRAF1-C5, TNF receptor-associated factor 1-complement component 5; STAT4, signal transducer and activator of transcription 4; PTPN22, protein tyrosine phosphatase non-receptor type 22; HLA-DRB1, human leukocyte antigen-DR beta 1; MMP, matrix metalloproteinase. Source: Created by the author based on the content presented in this chapter and references cited therein, with primary reference to Deane KD, Holers VM. The Natural History of Rheumatoid Arthritis. Clin Ther 2019;41:1256-1269. doi:10.1016/j.clinthera.2019.04.028; and Smolen JS, et al. Rheumatoid arthritis. Nat Rev Dis Primers 2018;4:18001. doi:10.1038/nrdp.2018.1

### 1.3.2 Pathogenesis

#### 1.3.2.1 The synovium

The synovium, a specialized connective tissue lining diarthrodial joints, represents the primary site of inflammatory pathology in RA[26]. Activated synoviocytes develop invasive, tumor-like

properties, secreting matrix metalloproteinases and cathepsins that degrade cartilage and bone, while producing chemokines and cytokines that perpetuate inflammation[[27](#)]. The transformed synovium (pannus) ultimately invades adjacent cartilage and bone, mediating the characteristic joint destruction of RA[[28](#)].

### ***1.3.2.2 Joint damage***

Joint destruction in RA emerges from the complex interplay between inflammatory mediators and effector cells at the synovial-bone interface, culminating in progressive cartilage degradation and bone erosion[[29](#)]. This process represents the primary pathological feature of RA and correlates strongly with functional disability and disease progression[[30](#)]. The temporal sequence begins with synovial inflammation triggering initial cartilage matrix degradation through protease-mediated mechanisms, followed by osteoclast-mediated bone erosion and eventually joint space narrowing as cartilage loss becomes substantial[[31](#)].

Cartilage degradation results from both direct enzymatic degradation and chondrocyte dysfunction[[32](#)]. Inflammatory cytokines, particularly IL-1 $\beta$ , TNF- $\alpha$ , and IL-6, induce chondrocyte expression of matrix-degrading enzymes, including matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family members[[33](#)]. Concurrently, these cytokines suppress proteoglycan and type II collagen synthesis while promoting chondrocyte apoptosis, creating an imbalance favoring cartilage catabolism over anabolism[[34](#)]. The resulting loss of cartilage integrity contributes to joint space narrowing, visible radiographically, and compromises mechanical joint function[[35](#)].

Bone erosion, the characteristic radiographic feature of RA, occurs predominantly at the bone-synovium interface where the hyperplastic synovium invades into bone[[36](#)]. The temporal

relationship between cartilage degradation and bone erosion remains incompletely characterized, though modern imaging modalities have revealed that erosions may develop remarkably early in the disease course, within weeks to months of symptom onset[37]. Erosions predominantly affect periarticular bone at sites lacking protective periosteum, particularly metacarpophalangeal (MCP) joints (including the second metacarpal head, MCH2), metatarsophalangeal joints, and wrist articulations[38, 39]. Once established, erosions can contribute to permanent functional impairment even after inflammation resolution.

The metacarpophalangeal joints represent sentinel locations for erosive damage due to their anatomical vulnerability (thin overlying cartilage and minimal protective soft tissue) and early involvement in disease course[40]. Among MCP joints, the second metacarpal head (MCH2) has garnered particular attention as a standardized region of interest in both conventional radiography and advanced imaging studies due to its reliability for sequential comparison[41]. The wrist complex, with its intricate articulations and thin cortical bone surfaces, similarly demonstrates high susceptibility to erosive damage with significant functional implications due to its crucial role in upper extremity mechanics[42].

#### ***1.3.2.3 Cytokine and signalling networks***

The immunopathogenesis of RA involves complex cytokine networks orchestrating and perpetuating inflammatory responses within the synovial microenvironment[43] (Figure 1.2). This dysregulated cytokine milieu emerges from interactions between activated immune cells, resident synoviocytes, and stromal elements, creating self-sustaining inflammatory circuits resistant to endogenous regulatory mechanisms[44]. Multiple cytokine pathways operate simultaneously, with both hierarchical organization and redundancy contributing to therapeutic challenges[45].

## Cytokine and Signaling Networks in Rheumatoid Arthritis

Pathophysiological Cascade from Initial Activation to Joint Destruction

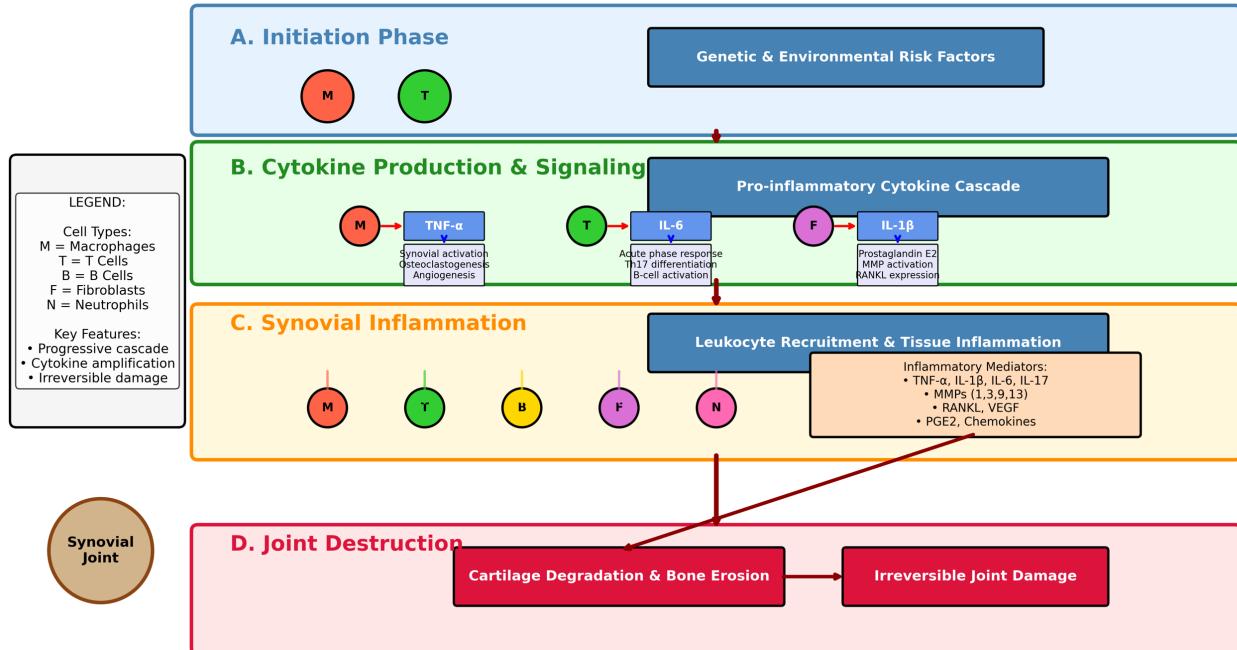


Figure 1.2 Cytokine and signaling networks in RA

Schematic overview of the pathophysiological cascade from initial activation to joint destruction in RA. Abbreviations: RA, rheumatoid arthritis; TNF- $\alpha$ , tumor necrosis factor alpha; IL-6, interleukin-6; IL-1 $\beta$ , interleukin-1 beta; MMPs, matrix metalloproteinases; RANKL, receptor activator of nuclear factor  $\kappa$ B ligand; VEGF, vascular endothelial growth factor; PGE2, prostaglandin E2; Th17, T helper 17 cell; B cell, B lymphocyte. Source: Created by the author based on the content presented in this chapter and references cited therein.

### 1.3.2.4 Pro-inflammatory Cytokines

The immunopathogenesis of RA involves complex cytokine networks that orchestrate and perpetuate inflammatory responses within the synovial microenvironment. Three fundamental pro-inflammatory cytokines with validated contributions to the pathogenic processes of RA include:

**Tumor Necrosis Factor Alpha (TNF- $\alpha$ ).** This pleiotropic cytokine occupies a hierarchical position in the inflammatory cascade and exhibits multifaceted contributions to RA pathophysiology[44].

TNF- $\alpha$  induces synovial fibroblast activation, promotes osteoclastogenesis through RANKL

upregulation, enhances matrix metalloproteinase production, and facilitates leukocyte recruitment through endothelial activation[[44](#), [46](#), [47](#)]. The pioneering success of TNF inhibition in RA established the cytokine as a preeminent therapeutic target and validated the cytokine-directed treatment paradigm[[48](#)].

**Interleukin-6 (IL-6).** This multifunctional cytokine mediates both local and systemic inflammatory responses in RA[[49](#)]. Locally, IL-6 promotes synovial hyperplasia, neutrophil recruitment, and osteoclast activation[[50](#)]. Systemically, IL-6 induces acute-phase reactant production, contributes to anemia of chronic disease, and modulates adaptive immune responses through effects on T-cell differentiation and B-cell antibody production[[51](#), [52](#)]. The efficacy of IL-6 receptor blockade in both DMARD-naïve and refractory RA cohorts underscores its pathogenic significance[[53](#)].

**Interleukin-1 (IL-1).** This canonical pro-inflammatory cytokine induces synovial inflammation through stimulation of prostaglandin synthesis, nitric oxide production, and subsequent cartilage-degrading enzyme activation[[54](#)]. IL-1 further contributes to bone destruction by enhancing RANKL expression on synovial fibroblasts and directly stimulating osteoclast differentiation[[55](#)]. While IL-1 inhibition has demonstrated modest efficacy compared to other cytokine-directed therapies, potentially due to redundant inflammatory pathways, the cytokine remains a significant contributor to joint inflammation and destruction[[56](#), [57](#)].

The intricate cytokine network in RA extends beyond these canonical mediators to include IL-17, IL-23, granulocyte-macrophage colony-stimulating factor, and various chemokines that collectively shape the inflammatory microenvironment[[58](#)]. Contemporary therapeutic strategies

increasingly target specific cytokine pathways, with efficacy heterogeneity suggesting pathogenic variability among RA subsets[59].

#### **1.3.2.5 Bone erosion-related pathways**

Bone erosion represents a distinctive pathological feature of RA, reflecting the progressive, irreversible structural damage that culminates in functional impairment[29]. The pathophysiological mechanisms underlying bone erosion in RA center on dysregulated osteoclast activation through the RANK/RANKL/OPG axis[60] (Figure 1.3).

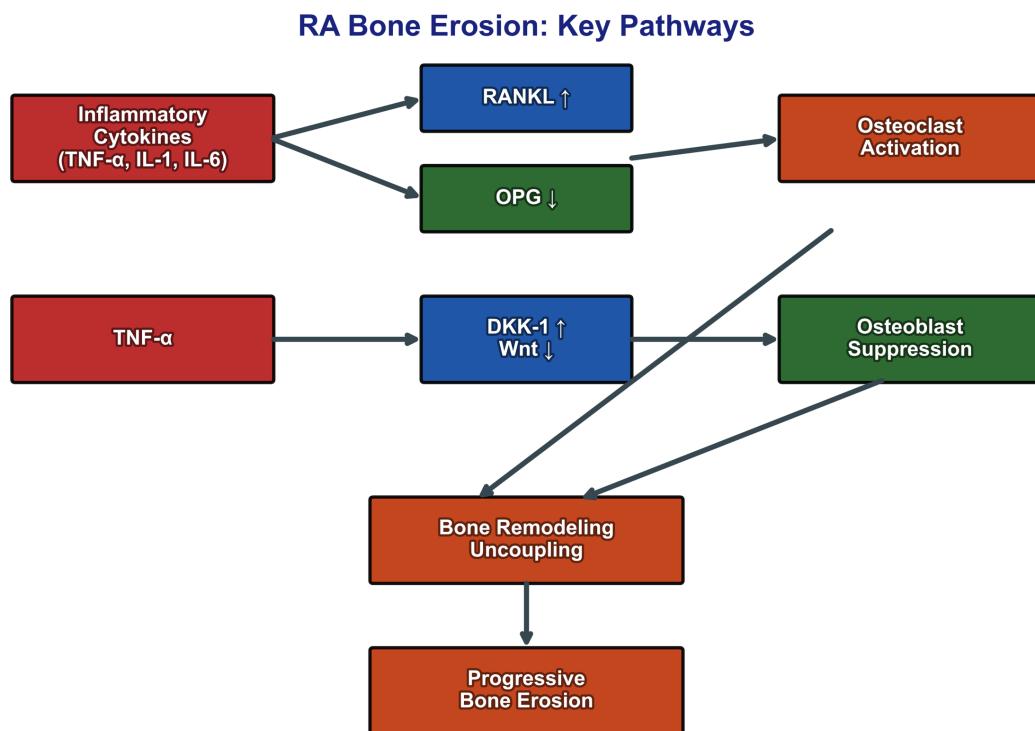


Figure 1.3 Key molecular pathways driving bone erosion in RA  
Pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1, and IL-6 induce osteoclast activation via upregulation of RANKL and suppression of OPG. TNF- $\alpha$  also promotes DKK-1 expression, which inhibits Wnt signaling, leading to osteoblast suppression. These processes converge to cause uncoupled bone remodeling and progressive bone erosion at the synovial-bone interface. Abbreviations: RA, rheumatoid arthritis; TNF- $\alpha$ , tumor necrosis factor alpha; IL, interleukin; RANKL, receptor activator of nuclear factor  $\kappa$ B ligand; OPG, osteoprotegerin; DKK-1, Dickkopf-1; Wnt, Wingless-

related integration site signaling pathway. Source: Created by the author based on the content presented in this chapter and references cited therein.

The receptor activator of nuclear factor κB (RANK) / RANK ligand (RANKL) / osteoprotegerin (OPG) system constitutes the principal regulatory mechanism governing osteoclastogenesis[[61](#)].

In the inflammatory milieu of RA, pro-inflammatory cytokines, particularly TNF-α, IL-1, IL-6, and IL-17, upregulate RANKL expression on synovial fibroblasts and activated T lymphocytes[[62](#), [63](#)] (Figure 1.3). Concurrently, these cytokines suppress OPG production, disrupting the RANKL:OPG ratio and favoring osteoclastogenesis[[64](#)]. Activated osteoclasts at the synovial-bone interface (pannus) mediate localized bone resorption, manifest radiographically as periarticular erosions[[36](#)].

Beyond direct effects on the RANK/RANKL/OPG axis, the inflammatory microenvironment promotes osteoclastogenesis through additional pathways. TNF-α induces expression of Dickkopf-1 (DKK-1), which inhibits Wnt signaling, a pathway critical for osteoblast differentiation and function[[65](#)]. This dual effect of promoting osteoclastogenesis while suppressing bone formation creates an "uncoupling" of bone remodeling that accelerates erosive damage[[66](#)]. Similarly, sclerostin, another Wnt antagonist, is upregulated in RA synovium and correlates with erosive progression[[67](#)].

The gradual emergence of evidence has implicated additional pathways in RA-associated bone destruction. The JAK/STAT signaling pathway, mediating effects of multiple cytokines including IL-6, contributes to osteoclastogenesis and represents both a pathogenic mechanism and therapeutic target[[68](#)]. Similarly, the role of microRNAs in regulating osteoclast differentiation and function offers potential biomarkers for erosive progression and novel therapeutic targets[[69](#)].

Bone erosions typically develop early in disease course, with approximately 75% of patients demonstrating radiographic evidence within the first two years[70]. The predilection sites for erosive damage include MCP joints, wrists, and metatarsophalangeal joints, locations characterized by thin cortical bone and extensive synovial tissue[71] (Figure 1.4). Modern imaging modalities have demonstrated that erosions occur substantially earlier than detectable by conventional radiography, with MRI and ultrasound identifying erosive changes within months of symptom onset[37, 72].

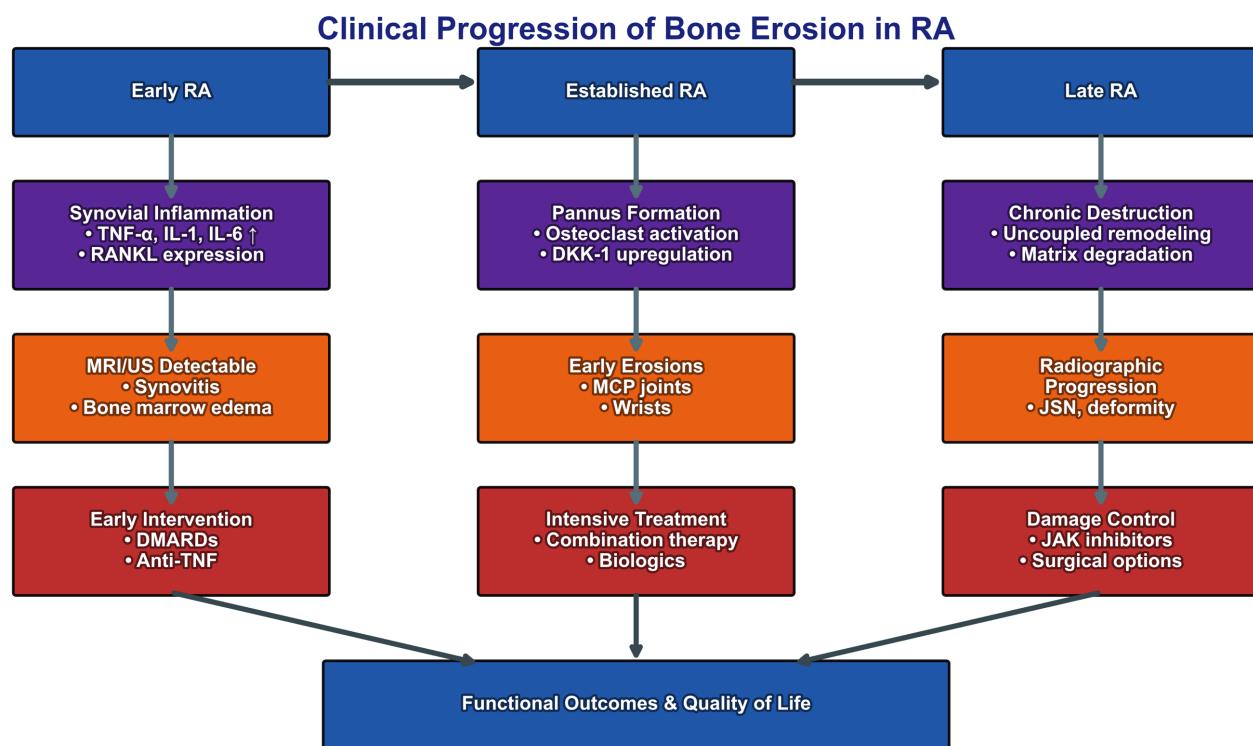


Figure 1.4 Clinical progression of bone erosion in RA

Inflammatory cytokines induce osteoclast activation and inhibit osteoblast function through modulation of the RANKL–OPG and DKK–1–Wnt signaling axes, leading to uncoupled bone remodeling and progressive bone erosion. **Abbreviations:** RA, rheumatoid arthritis; DKK-1, Dickkopf-related protein 1; IL, interleukin; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor  $\kappa$ B ligand; TNF- $\alpha$ , tumor necrosis factor alpha; Wnt, Wingless-related integration site signaling pathway. **Source:** Created by the author based on the content presented in this chapter and references cited therein.

## **1.4 Diagnosis and screening**

### **1.4.1 Diagnosis**

The diagnosis of RA represents a clinical determination integrating multiple elements: characteristic clinical features, serological markers, acute phase reactants, and radiographic findings[[73](#)]. This multifaceted assessment acknowledges the condition's heterogeneous presentation and absence of pathognomonic features, necessitating both inclusion of supportive findings and exclusion of alternative diagnoses[[74](#)]. The evolving conceptualization of RA as a disease continuum emphasizes the importance of early diagnosis during the therapeutic window when intervention yields disproportionate long-term benefits[[18](#)].

#### ***1.4.1.1 Joint manifestations***

The articular manifestations of RA typically present as symmetric polyarthritis, predominantly affecting small joints in the hands and feet, though any synovial joint may be involved[[20](#)]. Primary clinical features include prolonged morning stiffness (typically exceeding 60 minutes), joint tenderness, swelling characteristically soft and boggy (reflecting synovial proliferation and effusion), and progressive functional limitation[[20, 75](#)]. The metacarpophalangeal joints, proximal interphalangeal joints, wrists, and metatarsophalangeal joints constitute the most frequently involved sites, particularly in early disease[[76](#)]. As disease progresses, characteristic deformities may develop, including ulnar deviation of the metacarpophalangeal joints, boutonnière and swan-neck deformities of the fingers, and subluxation of the metatarsophalangeal joints[[77](#)].

#### ***1.4.1.2 Systemic manifestations***

Beyond articular involvement, RA may manifest with diverse extra-articular features reflecting systemic inflammatory processes[[78](#)]. These manifestations range from constitutional symptoms

(fatigue, low-grade fever, weight loss) to specific organ system involvement, including rheumatoid nodules, interstitial lung disease, vasculitis, scleritis, and Felty's syndrome[[79](#)]. Previous cohort studies demonstrate declining frequency of severe extra-articular manifestations, potentially reflecting earlier diagnosis, more aggressive treatment strategies, and reduced smoking prevalence[[80](#)]. Nevertheless, these manifestations contribute to both morbidity and mortality, particularly cardiovascular complications attributed to accelerated atherosclerosis mediated by systemic inflammation[[81](#)].

#### ***1.4.1.3 Classification criteria***

The evolution of RA classification criteria reflects advancing understanding of disease pathophysiology and the critical importance of early intervention. The 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria represented a paradigm shift from the 1987 criteria, prioritizing earlier disease recognition through incorporation of serological markers and acute phase reactants[[82](#)] (Table 1.1). These criteria incorporate weighted assessments of four clinical domains: symptom duration, joint involvement, serological markers (RF and ACPA), and acute-phase reactants [[83](#)]. This approach demonstrates superior sensitivity for early disease identification compared to previous criteria, facilitating earlier therapeutic intervention[[84](#)] (Figure 1.5).

The inclusion of autoantibodies, particularly ACPA, as classification criteria components acknowledges their pathogenic significance and predictive value for erosive disease[[85](#)]. ACPA positivity precedes clinical manifestations by years and confers heightened risk for aggressive disease progression and radiographic damage[[15](#), [86](#)]. Nevertheless, approximately 30% of RA

patients remain seronegative, representing a distinct clinical entity with potentially different pathogenetic mechanisms[[87](#)].

Table 1.1 The ACR/EULAR 2010 classification criteria for RA

Criterion	Category	Score
<b>Joint Involvement</b>	1 large joint	0
	2-10 large joints	1
	1-3 small joints (with or without large joints)	2
	4-10 small joints (with or without large joints)	3
	>10 joints (at least 1 small joint)	5
<b>Serology*</b>	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
<b>Acute-phase Reactants*</b>	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
<b>Duration of Symptoms</b>	<6 weeks	0
	≥6 weeks	1

\* One or more test results are required for classification. Classification as 'definite RA' requires: Total score  $\geq 6/10$  + Synovitis in  $\geq 1$  joint + No alternative diagnosis. Abbreviations: ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor. Source: Adapted from Aletaha D, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-1588. doi:10.1136/ard.2010.1384614

## 2010 ACR/EULAR RA Classification Process

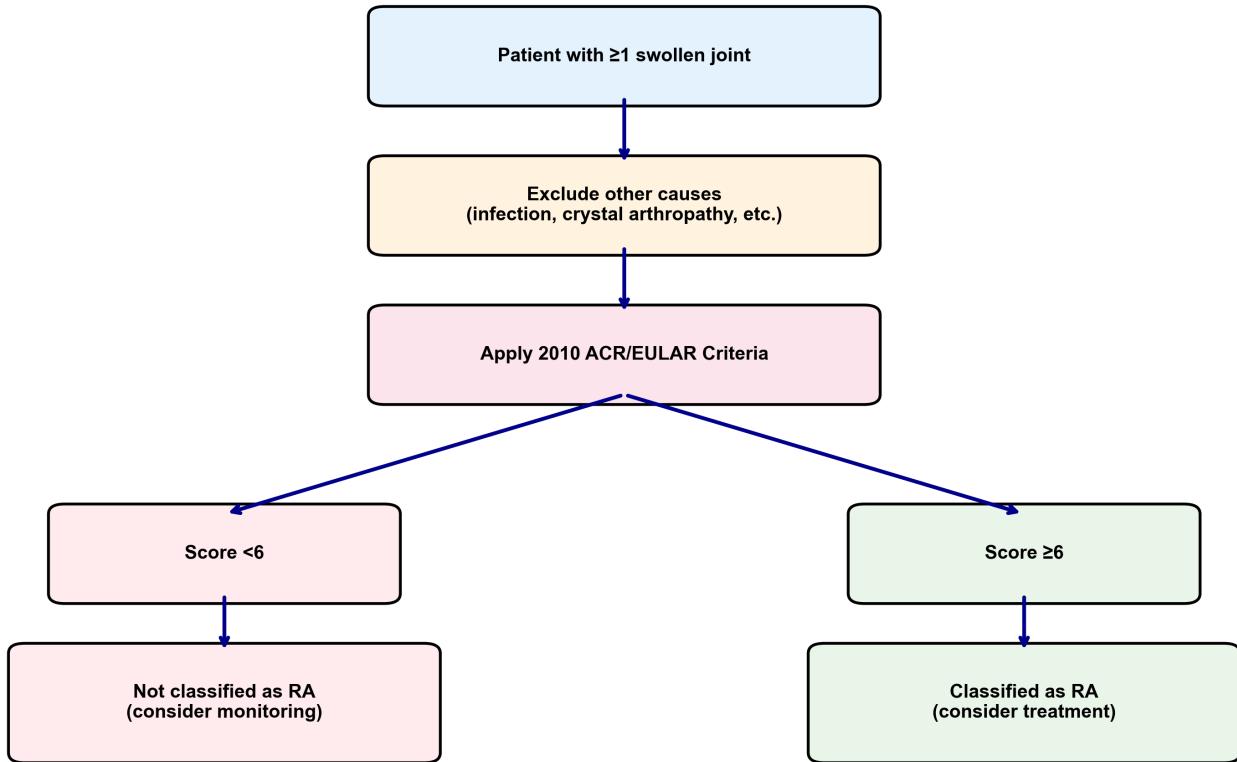


Figure 1.5 2010 ACR/EULAR RA classification process

Algorithm illustrating the 2010 classification criteria for rheumatoid arthritis developed by ACR and EULAR showing the systematic approach to RA diagnosis based on joint involvement, serology, acute-phase reactants, and symptom duration. Abbreviations: ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis. Source: Adapted from Aletaha D, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-1588. doi:10.1136/ard.2010.1384614

### 1.4.2 Screening

Systematic screening for RA in general populations lacks cost-effectiveness given the condition's relatively low prevalence and imperfect predictive value of available biomarkers[[88](#)]. However, targeted screening of high-risk populations—particularly first-degree relatives of RA patients and individuals with arthralgias and seropositivity—may identify preclinical disease amenable to preventive intervention[[88](#), [89](#)]. Evolving screening approaches incorporate serological markers

(particularly high-titer, high-specificity ACPA), genetic risk factors, and sensitive imaging techniques to identify individuals at imminent risk for developing clinical disease[[14](#)].

## **1.5 Management**

### **1.5.1 Treat-to-target strategy**

The treat-to-target (T2T) paradigm represents a transformative approach to RA management, based on systematic disease activity monitoring and protocol-driven therapeutic escalation to achieve predefined targets[[90](#)] (Figure 1.6). This strategy emerged from mounting evidence that sustained inflammatory control significantly mitigates radiographic progression and functional deterioration, fundamentally altering disease trajectory[[91](#)]. The key principles include: (1) establishing a specific therapeutic target (typically remission or low disease activity); (2) systematically measuring disease activity using validated composite indices; (3) adjusting therapy at predefined intervals until target achievement; and (4) maintaining the target through continued monitoring and therapeutic adjustment as needed[[92](#)]. Multiple randomized controlled trials have demonstrated the superiority of T2T approaches compared to conventional care across various outcomes, including remission rates, radiographic non-progression, and functional preservation[[93](#)]. The landmark TICORA (Tight Control of Rheumatoid Arthritis) study demonstrated a remission rate of 65% with intensive management versus 16% with routine care, along with significantly reduced radiographic progression and improved function [[94](#)]. Subsequent trials including CAMERA, BeSt, and SWEFOT confirmed these findings across diverse patient populations and treatment regimens[[93](#), [95](#), [96](#)].

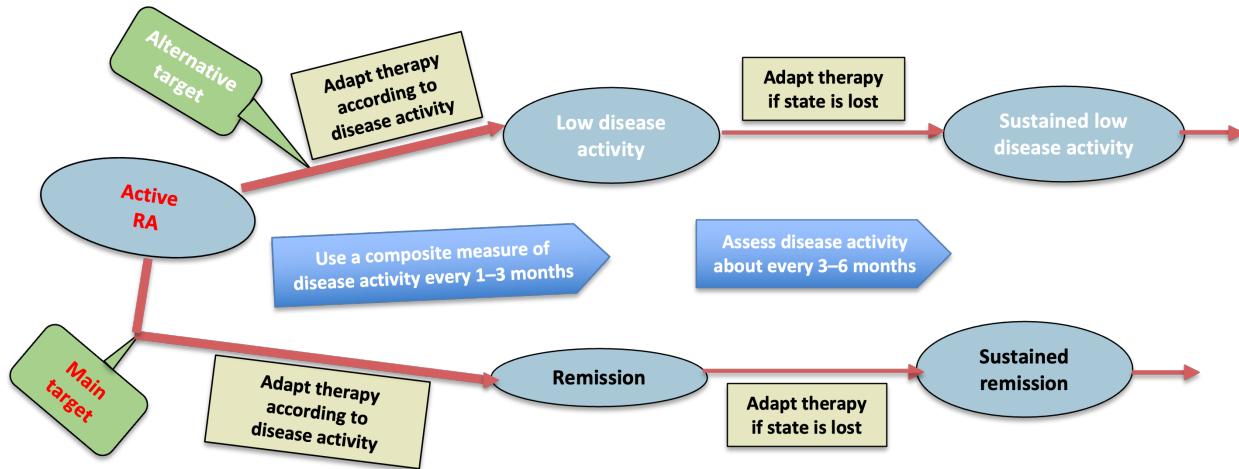


Figure 1.6 T2T strategy in RA management

Algorithm illustrating the T2T approach for management of RA patients, emphasizing regular assessment of disease activity and therapy adjustment to achieve and maintain remission or low disease activity. Abbreviations: RA, Rheumatoid arthritis; T2T, Treat-to-target.

Source: Adapted from Smolen JS, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-637. doi:10.1136/ard.2009.123919

The implementation of T2T principles has proven particularly impactful in early disease, where the "window of opportunity" concept suggests heightened responsiveness to therapeutic intervention before structural damage becomes established[97]. Studies demonstrate that treatment initiated within 12 weeks of symptom onset achieves superior outcomes compared to delayed intervention, including higher sustained remission rates, reduced radiographic progression, and greater likelihood of drug-free remission[5, 21]. Beyond clinical benefits, T2T strategies demonstrate cost-effectiveness through reduced long-term disability, decreased hospitalization rates, and lower requirements for orthopedic interventions[98]. The approach has been universally endorsed by international guidelines, including those from ACR, EULAR, and Asia-Pacific League of Associations for Rheumatology (APLAR)[99-101]. This approach has fundamentally transformed RA management philosophy from symptom control to disease modification with specific, measurable targets[102] (Figure 1.7).

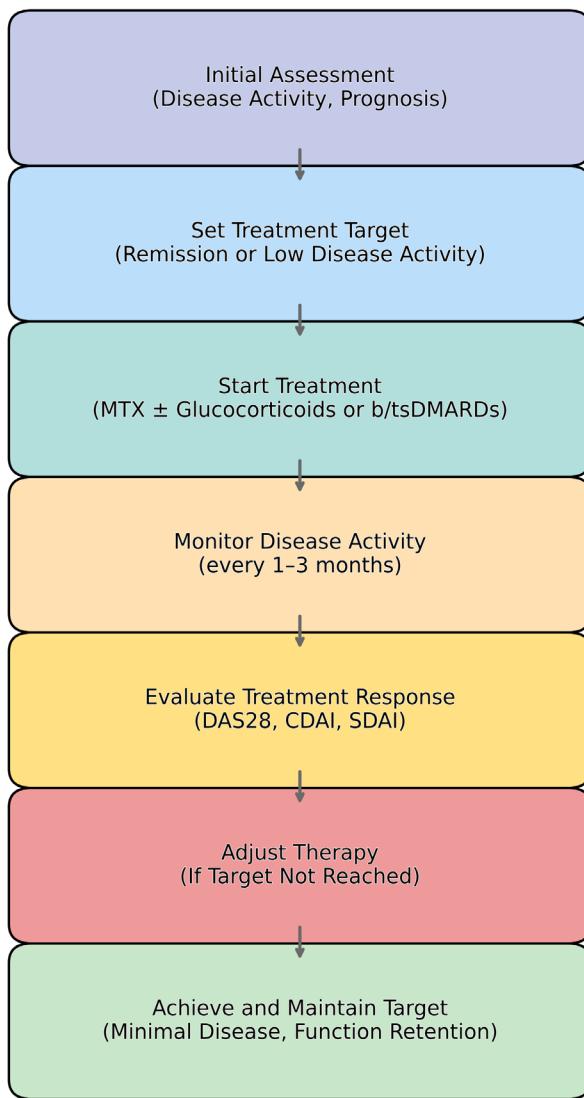


Figure 1.7 T2T implementation algorithm in RA

Stepwise flowchart outlining the T2T approach in RA, including initial assessment, target setting, treatment initiation, regular monitoring, evaluation of treatment response, therapy adjustment, and achievement of sustained remission or low disease activity. Abbreviations: bDMARDs, biological disease-modifying antirheumatic drugs; CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score in 28 joints; MTX, methotrexate; RA, rheumatoid arthritis; SDAI, Simplified Disease Activity Index; T2T, treat-to-target; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs. Source: Adapted from Smolen JS, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-637. doi:10.1136/ard.2009.123919

The impact of T2T strategies on radiographic outcomes has been particularly noteworthy. Multiple studies demonstrate significantly reduced radiographic progression rates among patients managed

with T2T compared to conventional care, with some cohorts demonstrating radiographic non-progression in up to 90% of patients over 2-5 years[[103](#), [104](#)]. This effect appears partially dissociated from clinical disease activity, suggesting that T2T may suppress radiographic progression through mechanisms beyond symptom control[[104](#), [105](#)]. The potential for T2T strategies to promote erosion healing, rather than merely preventing new erosions, represents an evolving area of investigation[[106](#)]. Limited evidence suggests that sustained disease control through T2T may facilitate partial erosion repair, particularly for smaller, more recent erosions[[107](#)]. This healing manifests radiographically as recortication of erosion margins and filling of erosion cavities, though complete healing appears exceptional[[108](#)]. The likelihood of erosion healing exhibits inverse correlation with erosion size and chronicity, suggesting a potential therapeutic window during which intervention might facilitate structural repair[[109](#), [110](#)]. This observation underscores the importance of therapeutic strategies that achieve rapid inflammatory control, potentially preserving reparative capacity before chronic erosive changes become established[[111](#)]. The potential functional benefit of erosion healing in the long term, particularly in early disease treated with T2T strategies that lead to more rapid remission of disease activity[[112](#)], warrants longitudinal investigation through sensitive volumetric techniques.

## 1.5.2 Measuring disease activity

### 1.5.2.1 Disease activity parameters

Quantitative assessment of disease activity guides therapeutic decision-making and outcome evaluation in RA. Validated composite indices, including the Disease Activity Score in 28 joints (DAS28), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI), incorporate joint counts, patient/physician global assessments, and acute phase reactants to

categorize disease activity and define treatment targets[[113](#), [114](#)]. These instruments facilitate implementation of treat-to-target strategies and serve as standardized endpoints in clinical trials[[90](#)].

Patient-reported outcomes, particularly functional capacity measured by Health Assessment Questionnaire-Disability Index (HAQ-DI), complement clinical disease activity metrics and correlate more robustly with long-term outcomes than isolated disease activity measures[[115](#), [116](#)].

Functional assessment provides insight into disease impact beyond inflammation, reflecting accumulated joint damage and extra-articular manifestations[[117](#)].

#### ***1.5.2.2 Remission criteria***

Remission, the optimal therapeutic target for most RA patients, has undergone evolving definition, reflecting changing treatment expectations and outcome measures[[114](#)]. Remission definitions include both index-based criteria (SDAI  $\leq 3.3$ , CDAI  $\leq 2.8$ , DAS28  $< 2.6$ ) and the 2011 ACR/EULAR Boolean criteria (tender joint count  $\leq 1$ , swollen joint count  $\leq 1$ , C-reactive protein  $\leq 1$  mg/dL, patient global assessment  $\leq 1$  on 0-10 scale)[[118](#)] (Table 1.2). These definitions exhibit hierarchical stringency, with Boolean criteria typically most restrictive, followed by SDAI, CDAI, and DAS28[[114](#)]. Importantly, achieving remission by these clinical criteria does not always correspond to complete absence of synovitis on sensitive imaging techniques or cessation of radiographic progression, though residual disease activity detected solely by imaging may not necessarily warrant therapeutic escalation[[119](#)].

Table 1.2 RA disease activity assessment criteria

Assessment Tool	Remission	Low Activity	Moderate Activity	High Activity
DAS28	< 2.6	≤ 3.2	3.2 - 5.1	> 5.1
CDAI	≤ 2.8	≤ 10	10.1 - 22	> 22
SDAI	≤ 3.3	≤ 11	11.1 - 26	> 26
Boolean Criteria*	TJC ≤1, SJC ≤1 CRP ≤1, PGA ≤1	—	—	—

\*Boolean: ACR/EULAR criteria (all 4 items must be met). ACR/EULAR, American College of Rheumatology/European League Against Rheumatism.

### 1.5.3 Treatment paradigms

#### 1.5.3.1 DMARDs

Disease-modifying antirheumatic drugs (DMARDs) represent the cornerstone of RA management, distinguished from symptomatic therapies by their capacity to suppress inflammatory disease activity and retard structural damage progression[22]. The DMARD classification includes diverse agents categorized as conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs), biosimilar DMARDs (bsDMARDs), and targeted synthetic DMARDs (tsDMARDs)[120] (Table 1.3). These agents target different components of the immune-inflammatory cascade, with varying mechanisms of action, pharmacokinetic properties, and safety profiles[121].

Conventional synthetic DMARDs, including methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide, represent first-line agents due to established efficacy, favorable cost-effectiveness, and extensive safety data[122]. Methotrexate plays a particularly central role in RA therapeutics, functioning both as monotherapy and the foundational component of combination

regimens[[123](#)]. Its pleiotropic mechanisms include antiproliferative effects, adenosine-mediated anti-inflammatory actions, and modulation of cellular adhesion molecule expression[[124](#)].

Biological DMARDs, including cytokine inhibitors (TNF, IL-6), cell-targeted therapies (anti-CD20, costimulation blockade), and the IL-1 receptor antagonist, have revolutionized outcomes for patients with inadequate response to conventional agents[[59](#), [125](#)]. These targeted therapies demonstrate capacity to induce rapid symptomatic improvement, sustained disease control, and retardation of radiographic progression in patients with treatment-refractory disease[[126](#), [127](#)]. Contemporary guidelines recommend bDMARD initiation following inadequate response to optimal csDMARD therapy, with agent selection guided by comorbidities, patient preference, and cost considerations[[128-130](#)].

Table 1.3 Classification of DMARDs in RA: current therapeutic paradigms

Category	Drug Class	Agent	Mechanism/Target	Route	Evidence level†
csDMARDs	Antifolate	Methotrexate	Dihydrofolate reductase inhibition	PO/SC /IM	IA
	Sulfonamide	Sulfasalazine	Anti-inflammatory/immunomodulatory	PO	IA
	Antimalarial	Hydroxychloroquine	Lysosomal enzyme inhibition	PO	IIaB
	Pyrimidine synthesis inhibitor	Leflunomide	Dihydroorotate dehydrogenase inhibition	PO	IA
tsDMARDs	JAK1/3 inhibitor	Tofacitinib	Janus kinase 1/3 inhibition	PO	IA
	JAK1/2 inhibitor	Baricitinib	Janus kinase 1/2 inhibition	PO	IA
	JAK1 selective inhibitor	Upadacitinib	Selective Janus kinase 1 inhibition	PO	IA
	JAK1 selective inhibitor	Filgotinib	Preferential Janus kinase 1 inhibition	PO	IA
bDMARDs	TNF-α inhibitor (mAb)	Adalimumab	Anti-TNF-α monoclonal antibody	SC	IA
	TNF-α inhibitor (fusion protein)	Etanercept	TNF receptor p75-Fc fusion protein	SC	IA
	TNF-α inhibitor (mAb)	Infliximab	Anti-TNF-α chimeric monoclonal antibody	IV	IA
	IL-6 receptor antagonist	Tocilizumab	Anti-IL-6 receptor monoclonal antibody	IV/SC	IA
	IL-6 receptor antagonist	Sarilumab	Anti-IL-6 receptor monoclonal antibody	SC	IA
	T-cell co-stimulation modulator	Abatacept	CTLA4-Ig fusion protein	IV/SC	IA
	B-cell depleting agent	Rituximab	Anti-CD20 monoclonal antibody	IV	IA

† Evidence levels based on 2022 EULAR recommendations and 2021 ACR guidelines: IA = Meta-analysis of randomised controlled trials or ≥ 1 randomised controlled trial; IIaB = ≥ 1 well-designed controlled study without

randomization. Abbreviations: ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; bDMARDs, biological disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; CTLA4-Ig, cytotoxic T-lymphocyte-associated protein 4-immunoglobulin; DMARDs, disease-modifying antirheumatic drugs; Fc, fragment crystallizable; IL-6, interleukin-6; IM, intramuscular; IV, intravenous; JAK, Janus kinase; mAb, monoclonal antibody; CD20, cluster of differentiation 20; RA, rheumatoid arthritis; SC, subcutaneous; TNF- $\alpha$ , tumor necrosis factor alpha; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; PO, per os (oral). Source: Adapted from Smolen JS, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023;82(1):3-18; and Fraenkel L, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2021;73(7):1108-1123.

### ***1.5.3.2 Biosimilars***

Biosimilar DMARDs represent biological agents demonstrating high similarity to reference bDMARDs in terms of structure, biological activity, efficacy, safety, and immunogenicity[[131](#)]. These agents undergo rigorous comparative assessment through comprehensive analytical characterization, preclinical studies, and clinical trials demonstrating equivalent pharmacokinetics, efficacy, and safety[[132](#)]. The introduction of bsDMARDs has greatly improved treatment accessibility through cost reduction while maintaining therapeutic efficacy equivalent to reference products[[133](#)]. Multiple randomized controlled trials and real-world registry data have confirmed comparable efficacy and safety profiles between biosimilars and reference products, supporting their integration into treatment algorithms[[134](#)].

## **1.6 Bone erosive outcomes**

### **1.6.1 Bone erosion progression**

Bone erosion progression represents a critical outcome measure in both clinical trials and longitudinal observational studies, reflecting cumulative inflammatory burden and therapeutic efficacy. Longitudinal studies demonstrate strong correlations between persistent disease activity and erosive progression, supporting the concept that sustained inflammatory control mitigates

structural damage[[135](#)]. This relationship highlights the treat-to-target (T2T) paradigm, posing that stringent inflammatory control through targeted therapy will reduce structural damage progression[[136](#)].

The kinetics of erosion progression exhibit great heterogeneity among patients, with genetic factors, autoantibody status, baseline radiographic damage, and treatment intensity all influencing progression rates[[23](#)]. ACPA-positive patients demonstrate accelerated erosive progression compared to seronegative counterparts, potentially reflecting direct osteoclastogenic effects of these autoantibodies through PAD enzymes and citrullinated protein recognition[[137](#)]. Similarly, patients with early erosive damage at presentation exhibit higher risk for subsequent progression, potentially reflecting both intrinsic disease severity and established osteoclastogenic pathways[[24](#)] (Figure 1.6).

### **1.6.2 Bone erosion healing**

The longstanding paradigm of irreversibility in RA-associated bone erosions has been challenged by abundant evidence of partial erosion repair following effective anti-inflammatory therapy [[106](#), [138](#), [139](#)]. This phenomenon, termed "erosion healing," manifests as sclerotic margin formation, erosion cavity filling, and cortical reconstitution[[106](#)]. The biological mechanisms underlying this repair involve activation of osteoblastic activity at erosion borders, with subsequent new bone formation partially restoring cortical integrity[[140](#)].

The likelihood of erosion healing exhibits inverse correlation with erosion size and chronicity, suggesting a potential therapeutic window during which intervention might facilitate structural repair[[107](#)]. This observation underscores the importance of therapeutic strategies that achieve

rapid inflammatory control, potentially preserving reparative capacity before chronic erosive changes become established[[111](#)].

While T2T clearly mitigates radiographic progression, its specific impact on erosion healing, particularly for erosions of varying sizes, remains incompletely characterized. Early RA patients managed with T2T strategies may theoretically exhibit enhanced erosion healing potential compared to established RA cohorts receiving usual care, given both shorter erosion chronicity and more rapid inflammatory resolution[[21](#)]. However, longitudinal HR-pQCT studies examining erosion healing stratified by disease duration, erosion size, and anatomical location are lacking. Further investigation is warranted to examine the long-term outcomes of bone erosion under T2T management strategies.

### **1.6.3 Evolution trajectories of variably-sized erosions**

Previous studies mainly focus on tracking the bone erosion as a whole (either at the patient level or at the erosion level) in a relatively short period. The longitudinal evolution of erosions stratified by size remains unclear, particularly regarding their potential for progression, stability, or regression. Recent study reported that the morphology and location of erosions with size  $<5\text{ mm}^3$  are similar between healthy controls and RA patients [[141](#)], raising interesting questions regarding their pathophysiological significance and natural history. The lack of long-term HR-pQCT data tracking erosion evolution by size category leaves significant knowledge gaps regarding whether small cortical interruptions represent stable physiological variants, nascent pathological lesions with progression potential, or dynamic structures capable of both progression and healing depending on inflammatory context. Understanding these evolutionary trajectories holds crucial clinical relevance for distinguishing between benign findings and early pathology requiring

therapeutic intervention, particularly in patients with early inflammatory arthritis or those at risk for RA development.

## **1.7 Functional outcomes**

### **1.7.1 Health-related quality of life**

Functional assessment represents a critical component of RA management, capturing disease impact beyond inflammatory activity and structural damage[[142](#)]. The Health Assessment Questionnaire-Disability Index (HAQ-DI), the most extensively validated and widely employed functional measure in RA, assesses limitations across eight categories of daily activities, generating a composite score ranging from 0 (no disability) to 3 (severe disability)[[115](#)]. This instrument demonstrates robust psychometric properties, including reliability, validity, and responsiveness to change, with established correlations to work disability, healthcare utilization, and mortality[[143](#)].

### **1.7.2 Relationship between disease activity, structural damage, and function**

The relationship between disease activity, structural damage, and functional capacity exhibits dynamic evolution throughout disease course[[144](#), [145](#)]. In early disease, functional limitation correlates predominantly with inflammatory activity, demonstrating substantial reversibility with effective anti-inflammatory therapy[[135](#), [146](#)]. As disease progresses, structural damage, particularly erosive changes and joint space narrowing, contributes increasingly to functional impairment, with this component demonstrating limited reversibility despite inflammation suppression[[135](#)] [[146](#)]. Structural damage seen on radiograph was reported to be associated with

functional limitation, underscoring the importance of early intervention to prevent irreversible structural changes[[147](#)].

Metacarpophalangeal joint and wrist involvement confer particular functional significance given their critical roles in hand function, with specific structural changes at these locations demonstrating distinct functional implications[[148](#)]. Conventional radiographic studies suggest a link between joint damage and functional disability, indicating that more joint damage correlates with greater disability over time[[145](#), [149](#)]. Different structural pathologies, erosions versus joint space narrowing[[30](#), [148](#)], may confer distinct functional implications, with conventional radiographic studies suggesting potentially greater disability impact from joint space narrowing[[147](#)]. However, these studies employed two-dimensional radiography, which inadequately captures erosion severity, potentially underestimating erosive contributions to functional impairment.

The relationship between structural damage and functional impairment has important implications for therapeutic strategies and outcome prediction[[21](#)]. The volumetric assessment capability of HR-pQCT enables precise quantification of the relationship between erosion burden and functional outcome[[41](#)]. This technique may facilitate exploration of whether volumetric erosion measures at specific anatomical sites exhibit correlations with functional parameters. It remains unclear which degree of HR-pQCT-detected erosive progression (or repair) translates into declines or improvements in clinical assessments, patient quality of life, or physical function. The differential functional impact of MCH2 versus wrist erosions, when assessed using precise volumetric quantification, represents a critical knowledge gap with implications for both prognostication and therapeutic prioritization.

## **1.8 Imaging in RA**

### **1.8.1 Overview**

Imaging modalities serve essential roles in RA diagnosis, prognostication, and therapeutic monitoring, with evolving technologies providing increasingly sensitive detection of both inflammatory and structural changes[[150](#)]. Each modality offers distinct advantages and limitations, with selection guided by specific clinical questions, anatomical regions of interest, and balance between sensitivity and specificity[[151](#)]. The spectrum of available techniques includes conventional radiography, ultrasonography, magnetic resonance imaging, computed tomography, nuclear medicine studies, and positron emission tomography[[152](#)]. The gradient of imaging modality sensitivity for erosion detection spans from conventional radiography (least sensitive) to computed tomography (most sensitive), with ultrasonography and MRI showing modest sensitivity[[39](#)].

### **1.8.2 Radiography**

Conventional radiography, despite limited sensitivity for early changes, remains the standard for long-term structural damage assessment, clinical routine practice, and trial endpoints[[153](#)]. This technique requires demineralization (typically 30-40%) before erosions become radiographically visible, resulting in detection delays compared to more sensitive modalities. Additionally, the two-dimensional nature of radiography confounds erosion quantification and progression assessment, particularly at anatomically complex sites like the wrist[[154](#)]. Despite these limitations, radiography's wide availability, standardized scoring methods, and extensive longitudinal data support its continued clinical utility, particularly for long-term monitoring.

### **1.8.3 HR-pQCT**

High-resolution peripheral quantitative computed tomography (HR-pQCT) represents a transformative advancement in erosion assessment, offering isotropic resolution of 82 $\mu\text{m}$  that permits three-dimensional visualization and precise volumetric quantification of erosive lesions[[38](#)] (Figure 1.8). This modality enables detection of erosions much smaller than the detection threshold of conventional radiography or MRI, with particular utility for the metacarpophalangeal joints and wrist[[155](#)]. The superior sensitivity of HR-pQCT permits visualization of early cortical breaks before they expand into frank erosions, providing a potential opportunity for therapeutic intervention before irreversible structural damage occurs[[156](#)].

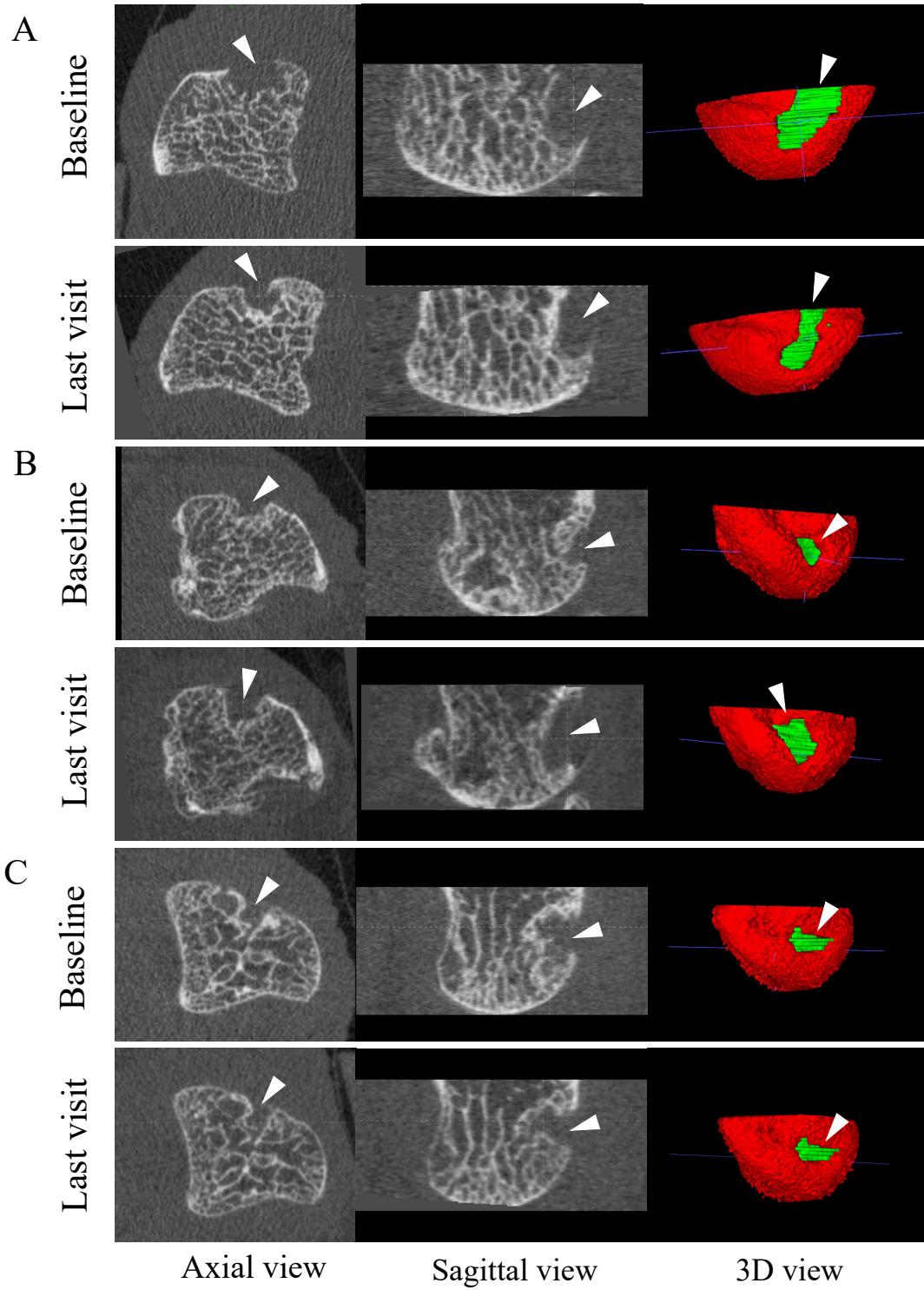


Figure 1.8 HR-pQCT assessment of bone erosion progression, regression, and stability in RA  
 Representative axial, sagittal, and 3D HR-pQCT images showing (A) erosion regression, (B) erosion progression, and (C) stable erosion over time in RA patients. The erosion size is depicted by the green segmentation of the bone in the 3D view. White triangles indicate the location of erosion in axial, sagittal, and 3D views. RA: Rheumatoid arthritis;

HR-pQCT: High-resolution peripheral quantitative computed tomography. Source: Created by the author using original imaging resources.

Beyond erosion detection, HR-pQCT enables comprehensive assessment of periarticular bone microarchitecture, revealing trabecular thinning, increased porosity, and density changes that precede frank erosions[[157](#)]. These microstructural alterations, mediated by inflammatory cytokines through mechanisms distinct from erosion formation, contribute to biomechanical compromise and fracture risk beyond articular damage[[158](#), [159](#)]. Longitudinal HR-pQCT studies have demonstrated that inflammatory control can preserve or even partially restore bone microarchitecture, highlighting the reversible component of these changes with appropriate therapeutic intervention.

The enhanced sensitivity of HR-pQCT has revealed cortical interruptions in both RA patients and healthy controls[[160](#)], and Studies demonstrate that most erosions (95%) in healthy individuals measure <5mm<sup>3</sup>, prompting critical questions regarding the pathological significance of smaller lesions[[161](#)]. The morphological similarity between small cortical interruptions (<1mm<sup>3</sup>) in healthy controls and RA patients raises questions regarding whether these represent true pathology or physiological variants. This distinction holds clinical significance, as misclassification of physiological findings as pathological erosions might lead to unnecessary therapeutic escalation or misinterpretation of treatment efficacy.

## **Chapter 2: Hypothesis and objectives**

### **2.1 Hypothesis**

We hypothesize that the majority of small erosions ( $<1 \text{ mm}^3$ ) may be physiological phenomena rather than inflammatory-mediated bone structural pathology, and that early rheumatoid arthritis (ERA) patients managed through a treat-to-target (T2T) approach may demonstrate better structural outcomes in the long turn, with greater opportunities for erosion healing at the second metacarpal head (MCH2), compared to patients in the established RA (EstRA) cohorts receiving conventional care. This differential response likely reflects the temporal window during which structural repair remains feasible. Additionally, we anticipate that volumetric erosive burden within the carpus, as quantified via HR-pQCT, may potentially correlate with functional capacity metrics in patients with RA.

### **2.2 Objectives**

1. To delineate the differential distribution patterns of size-variety erosions, categorized as small ( $<1 \text{ mm}^3$ ), intermediate ( $1\text{-}5 \text{ mm}^3$ ), or large ( $>5 \text{ mm}^3$ ), between RA patients and healthy controls through volumetric quantification.
2. To characterize the longitudinal evolution trajectories of erosive lesions in MCH2 over an extended observation period (median 8 years), with particular emphasis on: (a) volumetric changes stratified by baseline erosion size; (b) comparative analysis on the frequencies of stabilization, progression, or regression within each size category in RA patients; and (c) subgroup analysis between the ERA and EstRA cohorts to address whether early intervention has a significant impact on the long-term outcomes of bone erosions.

3. To investigate the relationship between carpal erosive burden, as quantified by erosion volume and counts, and functional capacity parameters in RA patients.

## **Chapter 3: Methodology**

### **3.1 Study design**

The present investigation involved three separate studies.

Study 1 was a cross-sectional study comparing the erosion parameters of 247 RA patients with 78 age- and sex-matched HCs who underwent HR-pQCT scans of the MCH2 at baseline.

Study 2 was a follow-up study of the 247 RA patients, including patients from an ERA cohort ( $n=98$ ; baseline symptom duration  $\leq 2$  years, received T2T management within the first year followed by usual care), and an EstRA cohort ( $n=149$ , received usual care) who had undergone HR-pQCT of MCH2 after a median of 8.4 years to assess changes in erosive parameters.

Study 3 was a cross-sectional study examining the relationship between erosion parameters in the wrist bones and functional outcomes in RA patients. A total of 232 RA patients who underwent wrist HR-pQCT imaging were enrolled. Disability was assessed in three different ways: the Health Assessment Questionnaire Disability Index (HAQ-DI), grip strength, and the dexterity component of the Chinese Arthritis Impact Measurement Scales 2 (CAIMS2).

### **3.2 Patients**

From September 2011 to March 2024, all patients who (a) fulfilled the 2010 ACR/EULAR classification criteria for RA [162], (b) were followed up in one of 11 regional hospitals in Hong Kong, and (c) who had previously undergone an HR-pQCT of the MCH2, were invited to participate in this follow-up study. MCH2 was selected as the target joint given its predominance among affected metacarpophalangeal (MCP) joints and its propensity for erosive progression in RA [163]. The established RA (EstRA) cohort (n=247) was assembled from the general rheumatology clinic between 2010 and 2017, and received usual care as T2T management was not standard treatment at that time. The early RA (ERA) cohort (n=148) was assembled between 2012 and 2018 from the rheumatology research clinic, consisting of patients with symptom-onset of less than 2 years at diagnosis. These patients were initiated on a T2T treatment algorithm immediately after diagnosis for one year, followed by usual care thereafter. Certain aspects of these cohort populations have been previously described in our previous studies [138, 158, 164-166]. Based on information retrieved from the citywide Clinical Data Analysis and Reporting System (CDARS), 371 patients were eligible for potential follow-up assessment at the Prince of Wales Hospital (PWH) at the commencement of the study. Among these, 29 patients were deceased, and 78 patients did not participate in the follow-up assessment due to various reasons as outlined in Figure 3.1. As a result, 264 patients attended the follow-up visit. At baseline, 78 age- and sex-matched healthy individuals without inflammatory joint disease were also recruited. Ethics approval was granted by the Joint Chinese University of Hong Kong (CUHK) - New Territories East Cluster (NTEC) Clinical Research Ethics Committee (Ethics approval number: CREC 2020.704). All participants signed written consent agreements. All study methods and procedures adhered to the ethical standards outlined in the Declaration of Helsinki.

### ***Exclusion criteria***

Patients were excluded if they: 1) had severe clinical deformity at the 2<sup>nd</sup> MCP or wrist joint, which precluded a reliable HR-pQCT examination, or 2) were pregnant or breastfeeding.

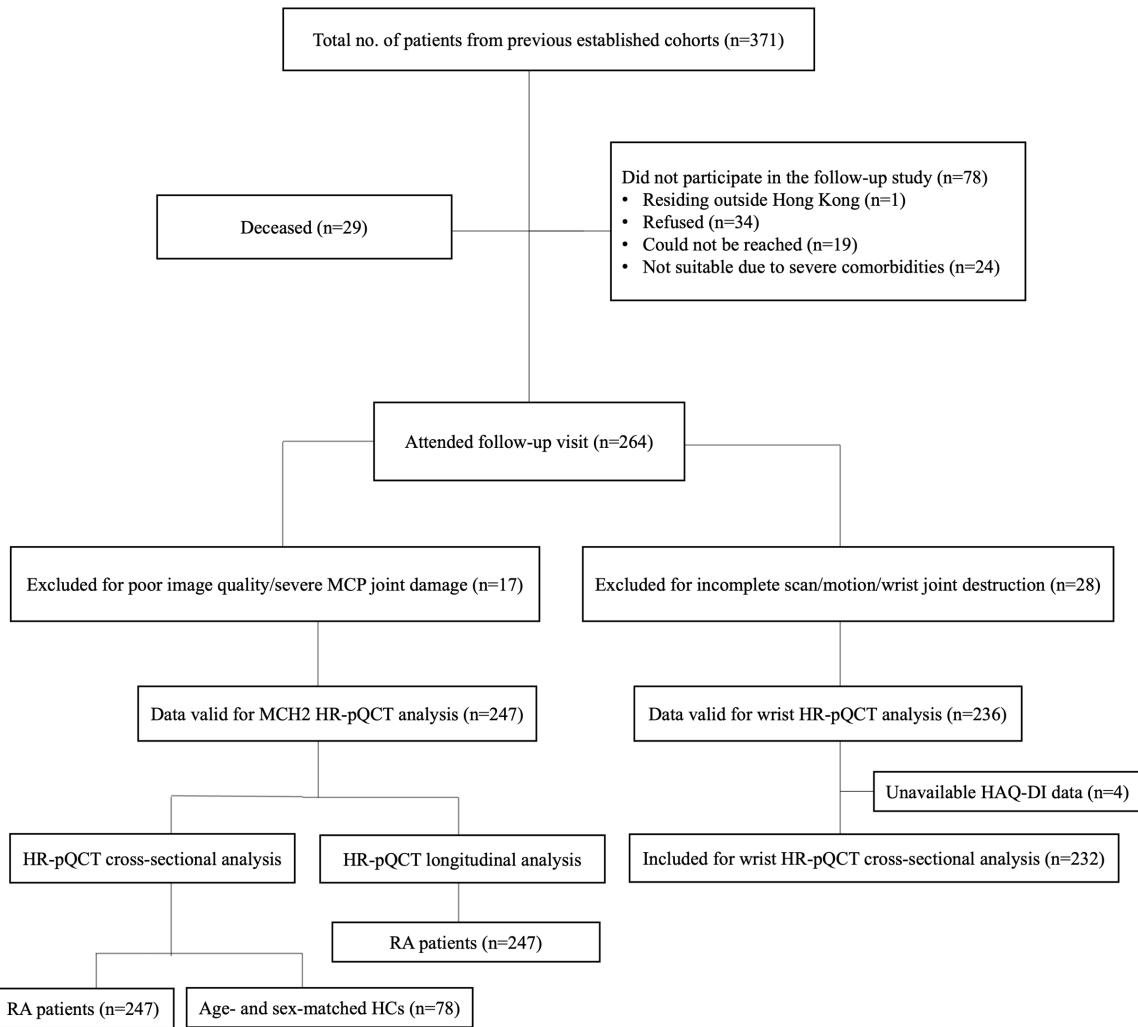


Figure 3.1 Flow diagram of patient enrollment and data inclusion for HR-pQCT analysis  
 RA, rheumatoid arthritis; MCP, metacarpophalangeal; MCH2, second metacarpal head; HR-pQCT, high-resolution peripheral quantitative computed tomography; HAQ-DI, Health Assessment Questionnaire–Disability Index; HCs, healthy controls.

### **3.3 Clinical assessment**

The present investigation included 264 RA patients who underwent comprehensive clinical, laboratory, and HR-pQCT assessments of the MCH2 at baseline and last visit and wrist joint at last visit. Clinical, laboratory, and HR-pQCT assessments were performed on all study subjects. Clinical and laboratory assessments conducted at baseline and final evaluation consisted of erythrocyte sedimentation rate (ESR, mm/h), C-reactive protein (CRP), swollen and tender joint counts (0–28), visual analogue scale (VAS) for pain assessment (0–100 mm=most pain), VAS for patient global assessment (0–100 mm=worst score), VAS for physician global assessment (0–100 mm=worst score), simplified disease activity score (SDAI), and disease activity score 28-CRP (DAS 28-CRP). The status of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACCP) was determined at baseline only. Treatment regimen at each visit was also retrieved from CDARS, including prednisolone, nonsteroidal anti-inflammatory drugs (NSAIDs), csDMARDs, and biologic/targeted DMARDs (b/tsDMARDs).

### **3.4 Functional assessment**

#### **HAQ-DI**

The HAQ-DI was administered as the primary patient-reported outcome measure of functional disability [[115](#)]. This validated instrument comprises 20 questions across eight domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities. For each question, patients rated their difficulty performing specific tasks on a four-point Likert scale (0=without difficulty, 1=with some difficulty, 2=with much difficulty, 3=unable to perform). Domain scores were calculated as the highest score within each category, with adjustment for assistive device usage or help from others (increasing scores by 1 point when applicable, not exceeding 3). The overall HAQ-DI score was computed as the mean of the eight domain scores, yielding a final score

ranging from 0 (no disability) to 3 (severe disability). The HAQ-DI demonstrates robust psychometric properties and well-established convergent validity with other functional measures [115, 167]. All questionnaires were administered in a standardized setting by trained research personnel who provided uniform instructions but no assistance with interpretation or completion. The presence of disability was established based on HAQ-DI scores  $\geq 0.5$ . The degree of disability was graded by HAQ-DI score as follows: No or minimal disability:  $\geq 0$  to  $<0.5$ ; Mild disability:  $\geq 0.5$  to  $<1$ ; Moderate to severe disability:  $\geq 1$  to  $\leq 3$  [168-171].

### **3.5 HR-pQCT assessment**

#### **3.5.1 Image acquisition**

Bone erosion was assessed in the MCH2 and wrist of the same hand that had been scanned at baseline, using an HR-pQCT system (XtremeCT I; Scanco Medical AG, Bruttisellen, Switzerland). This system enables the simultaneous acquisition of CT slices with an isotropic resolution (voxel size) of 82  $\mu\text{m}$ . All HR-pQCT scanning procedures were carried out by a single investigator blinded to patients' clinical details. Because motion artefacts are a concern in image acquisition, scanning protocols and position holders were developed to stabilize the area of interest. An anteroposterior scout view was used to define the region of interest (ROI). The wrist acquisition was performed in the standard forearm cast provided by the manufacturer, with the hand in a thumb-up orientation. The wrist scan covered 27.06 mm (330 slices) with a total scan time of about 9 min and an effective dose of 12.6  $\mu\text{SV}$ [172]. At the second metacarpal bone, the scan region started at the distal end of the MCH and spanned proximally 9.02 mm (110 slices) with a total scan time of about 2.8 min and an effective dose of 3  $\mu\text{SV}$ . The total radiation dose was similar to a daily background radiation ( $10\mu\text{Sv}$ ) but significantly less than a standard chest plain radiograph

( $50\mu\text{Sv}$ ). The Scan time was around 12 min per patient, comparable to conventional computed tomography (10–15 min) and shorter than MRI (20–45 min). Longitudinal 3D rigid body image registration was implemented to align and superimpose the follow-up image with the baseline image[[173](#)]. Each scan was evaluated for motion in each stack using the manufacturer’s standard scoring system from 1–5. Scans with motion scores of 4 or 5 were excluded from analysis.

### **3.5.2 Erosion identification**

Erosions are defined as sharply marginated bone lesions with juxta-articular localisation with a cortical break seen in at least two adjacent slices, which are often accompanied by loss of the adjacent trabecular bone following the recommended definitions and procedures developed by the Study GrouP for XTrEmE-CT in Rheumatoid Arthritis (SPECTRA)[[174](#)]. Erosions were differentiated from physiological breaks, indicating entry of blood vessels by the linear shape and occurrence on predilection sites. Pseudo-erosions, structures similar to cortical breaks presented by osteophytes, were also excluded (Figure 3.2). Assessment included the palmar, ulnar, dorsal as well as the radial sides of MCH2.

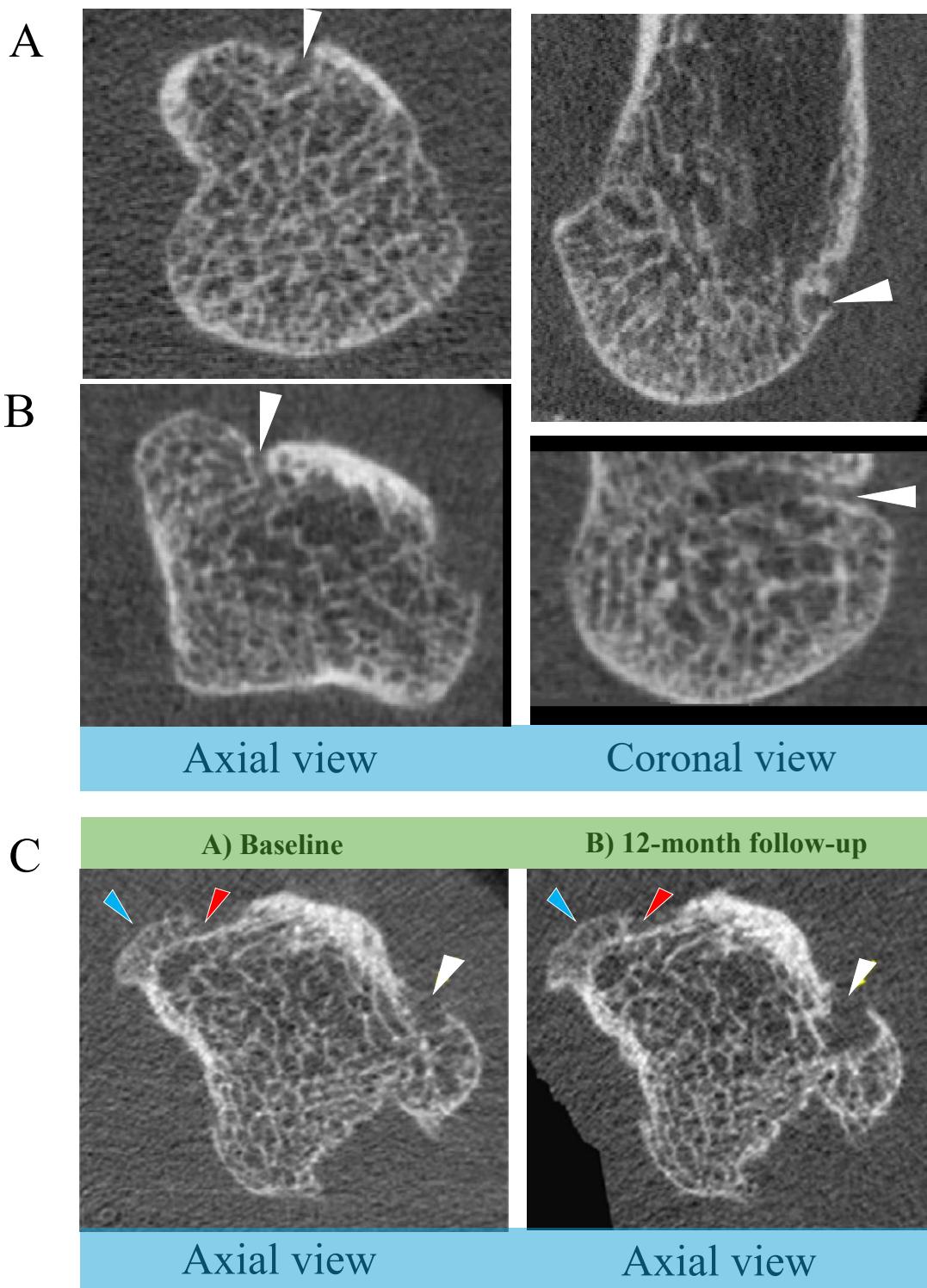


Figure 3.2 Cortical breaks on high-resolution imaging

Axial and coronal views are shown, with white triangles indicating the site of cortical interruption. (A) bone erosion, pathological cortical break; (B) vascular channel, physiological cortical interruption; (C) pseudo erosion due to osteophyte/new bone formation. The red triangle indicating an apparent concave region caused by an osteophyte (blue triangle) is not counted as erosion.

### 3.5.3 Erosion volume measurement

The volume of the erosions were calculated according to the methodology published by Fouque-Aubert et al[155]. The volume of erosions (using either per-erosion or per-patient volume of interest) of the MCH2, wrist bones including distal radius, lunate, and scaphoid was determined by manually defining the ROI, and then was quantified automatically by segmentation utilizing the Bone Analysis Modules (BAM) of the open-source software 3D Slicer[175] and ITK-SNAP as a viewer [175, 176] (Figure 3.3). Mean pixel attenuation was used to determine the density within the region of interest. All erosion measurements were independently assessed by an experienced reader (XY), blinded to clinical information. Based on our previous HR-pQCT data, intra-observer reproducibility was 0.982 for erosion volume (XY) while inter-observer reproducibility, as determined by intraclass correlation coefficient, was 0.962 (XY and ITC).

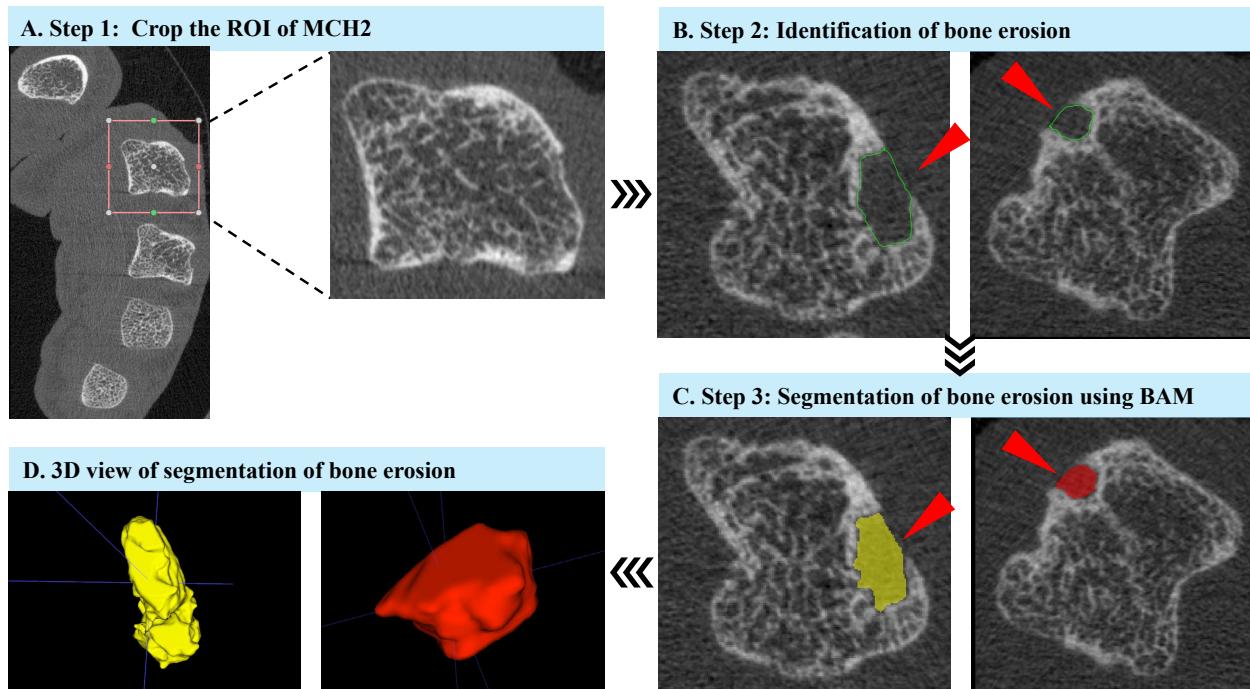


Figure 3.3 Identification and quantification of bone erosion

This figure illustrates A: defining the ROI including the MCH2; B: identification and delineation of bone erosion; C: automated segmentation of bone erosion using BAM; and D: 3D reconstruction of the identified erosion. The red triangular arrows in panel B indicate the location of bone erosion identified on the HR-pQCT image, while in panel C, the arrows indicate the corresponding region segmented as bone erosion using BAM. HR-pQCT, High-Resolution Peripheral Quantitative Computed Tomography; ROI, Region of Interest; MCH2, Second metacarpophalangeal joint; BAM, Bone Analysis Model.

# **Chapter 4: Comparative Study of Bone Erosions in Rheumatoid Arthritis and Healthy Controls: Insights from an HR-pQCT Examination**

## **4.1 Introduction**

Rheumatoid arthritis (RA) is a persistent inflammatory disorder that leads to gradual joint damage, frequently resulting in decreased physical function and disability [29]. A hallmark of RA is the development of bone erosion, which represents localized bone loss at the margins of affected joints and which serves as an important radiographic marker of disease severity and is predictive of long-term clinical outcomes [153, 177] [29]. The development and progression of bone erosions in synovial joints, including the metacarpophalangeal (MCP) joints [178], are driven by complex interactions between inflammatory cytokines, autoantibodies, and osteoclast activation [179].

Radiography has traditionally been used to assess erosive changes in RA, but its two-dimensional projectional format is not sensitive at detecting small to medium-sized erosions [180]. High-resolution peripheral quantitative computed tomography (HR-pQCT) is a powerful cross-sectional imaging modality that offers superior sensitivity for detecting and quantifying bone erosions, allowing for detailed assessment of erosion volume [155]. It facilitates understanding the morphology, spatial distribution, and evolution of juxta-articular bone erosions through 3D visualization and quantification [155, 180]. Semiautomated image analysis algorithms have further enhanced their capacity to discriminate and quantify a broader morphological spectrum of erosive changes, including early and established disease states [175].

HR-pQCT identifies a spectrum of cortical interruptions in the finger joints of RA patients and healthy individuals[[141](#), [160](#), [161](#), [181](#), [182](#)]. Larger cortical interruptions, which are often accompanied by an underlying void in the trabecular bone, typically indicate the presence of erosions. In contrast, smaller interruptions, such as vascular channels, are frequently considered physiological in nature, rather than true erosion[[161](#)]. Previous studies comparing RA patients to healthy controls (HCs) using HR-pQCT mainly focused on visually detecting pathological interruptions[[106](#), [155](#), [156](#), [183-186](#)]. Using an automated algorithm, the number and size of cortical interruptions are significantly greater in the MCP joints of RA patients compared to HCs [[187](#), [188](#)].

Recent investigation results showed that most erosions of HC had volumes below 5 mm<sup>3</sup> [[141](#)]. Analysis comparing erosions <5 mm<sup>3</sup> between HCs and RA patients found no differences in morphological characteristics or anatomical location. However, it remains uncertain whether these findings apply to patients with early RA. To address these knowledge gaps, we conducted an HR-pQCT study of the second metacarpal head (MCH2) in a large cohort of RA patients and compared the findings with age- and sex-matched HCs.

## 4.2 Objective

To compare the prevalence of erosions between RA patients and HCs, stratified by erosion size: small <1 mm<sup>3</sup>, intermediate 1-5 mm<sup>3</sup>, large >5 mm<sup>3</sup>.

## 4.3 Methods

### 4.3.1 Study population and design

This cross-sectional study included 264 RA subjects and 78 age- and sex-matched HCs. All HCs were recruited previously through word-of-mouth recommendation from the staff of the Prince of Wales Hospital. All eligible controls had no history of autoimmune disease, arthritis, or known metabolic disorder that could affect bone metabolism. Distal radial densitometric and microstructural features of the HCs were published previously[[158](#), [165](#)]. Further details pertaining to additional patient characteristics have been comprehensively addressed in the general methodology section (Chapter 3) presented earlier.

#### **4.3.2 Clinical assessment**

All RA subjects had clinical, laboratory, and HR-pQCT assessments of MCH2, while all HCs only had HR-pQCT assessments of MCH2. Symptom duration was determined as the interval between symptom onset and diagnosis, and disease duration was determined as the time between diagnosis and HR-pQCT scan. Details of clinical assessment have been described in the general methodology section (Chapter 3).

#### **4.3.3 HR-pQCT assessment**

HR-pQCT assessment, including image acquisition, erosion identification, and measurement of erosion volume, and the reliability of erosion size and image motion assessment, have already been described in detail in the general methodology section (Chapter 3).

#### **4.3.4 Statistical analyses**

Data were presented as median with interquartile range [IQR] for continuous variables and frequency with percentage for categorical variables. For group comparisons between RA and HCs, continuous data were analyzed using the Mann-Whitney U test, while categorical data were

evaluated with the Chi-square or Fisher's exact test. Effect sizes were calculated using rank-biserial correlation, Cliff's delta, and Hodges-Lehmann estimates with 95% confidence intervals (CI). IBM SPSS Statistics Version 30.0 (IBM, Armonk, NY, USA) and Python 3.13 were used to perform all statistical procedures. Statistical significance was established at a two-tailed p-value of <0.05.

## 4.4 Results

### 4.4.1 Demographics and clinical characteristics

Out of the 264 RA patients who underwent clinical and HR-pQCT assessment, 17 patients were excluded due to poor image quality (n=10) or severe joint damage (n=7), leaving 247 patients for inclusion in the final analysis (Figure 3.1 in chapter 3). Age (P = 0.119) and gender distribution (P = 0.072) showed no significant differences between RA patients and HCs. RA patients had a median symptom duration of 0.6 years and a disease duration of 1.8 years, and had a high (60.3%) prevalence of anti-CCP antibody and a moderate disease activity. Disease-modifying therapeutic agents were used in most RA patients, with 68.4% receiving csDMARDs and 6.5% receiving b/csDMARDs (Table 4.1).

Table 4.1 Characteristics of RA patients and healthy individuals

	RA (n=247)	HC (n=78)	P-value
Demographic characteristic			
Age (yrs)	54.8 [48.0, 61.3]	53.3 [48.7, 58.0]	0.119
Female, n (%)	200 (81)	55 (71)	0.072
Clinical characteristic			
Symptom duration (yrs)	0.6 [0.3, 1.3]		
Disease duration (yrs)	1.8 [0.1, 7.2]		
Follow-up interval (yrs)	8.4 [5.9, 10.9]		
RF positive, n (%)	149 (60.3)		
Anti-CCP positive, n (%)	192 (81.0)		
Disease activity parameters			
Patient VAS pain	5.0 [2.0, 6.0]		
Patient's global assessment, NRS 0–10	5.0 [3.0, 6.0]		
Physician's global assessment, NRS 0–10	2.5 [1.0, 5.0]		
Tender joint count (0–28)	3.0 [0, 7.0]		
Swollen joint count (0–28)	2.0 [0, 4.0]		
ESR (mm/h)	30 [19, 53]		
CRP (mg/L)	4.0 [1.1, 11.5]		

	RA (n=247)	HC (n=78)	P-value
SDAI score	12.8 [5.9, 24.2]		
HAQ-DI (0-3)	0.5 [0.1, 1.1]		
Current treatment, n (%)			
Prednisolone	42 (17.0)		
NSAIDs	166 (67.2)		
csDMARDs	169 (68.4)		
b/tsDMARDs	16 (6.5)		

Data are reported as median [interquartile range] or number (%). Symptom duration represents the time period from symptom initiation to diagnostic confirmation. Disease duration is defined as the duration between diagnosis and HR-pQCT scan at baseline. Abbreviation: RA: rheumatoid arthritis. HCs: healthy controls. SDI: sustained SDAI remission. RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide antibody; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: simplified disease activity score; DAS 28-CRP: disease activity score 28- CRP; HAQ-DI: health assessment questionnaire - disability index; NSAIDs: Nonsteroidal Anti-inflammatory Drugs. csDMARDs: conventional synthetic disease-modifying anti-rheumatic drug. b/tsDMARDs: biologic/targeted synthetic disease-modifying anti-rheumatic drug.

#### 4.4.2 Erosion parameters in the MCH2

HR-pQCT analysis of the MCH2 showed significant differences in erosive parameters between RA patients and HCs (Table 4.2). The prevalence of erosions was significantly greater in RA patients than in HCs (78% vs 41%, P<0.001). Significantly higher median erosion counts per person (1 [IQR: 1, 1] vs 0 [IQR: 0, 1], P<0.001) and total erosion volumes per person (1.1 mm<sup>3</sup> [IQR: 0.3, 3.0] vs 0 mm<sup>3</sup> [IQR: 0, 0.5], P<0.001) were observed in RA patients compared with HCs.

Table 4.2 Erosion parameters of MCH2 between RA patients and HCs

	RA patients	H Cs	P-value
Total no. of patients (n)	247	78	
Presence of erosion (n, %)	193/247 (78)	32/78 (41)	< 0.001
Total no. of erosion (n)	259	37	
Total no. of erosions per patient	1 [1, 1]	0 [0, 1]	< 0.001
Total erosion volume per patient, (mm <sup>3</sup> )	1.1 [0.3, 3.0]	0 [0, 0.5]	< 0.001
# Presence of erosion according to size (n, %)			< 0.001 <sup>†</sup>

	RA patients	HCs	P-value
Large erosion (>5 mm <sup>3</sup> )	42 (17)	2 (3)	0.002
Intermediate erosion (1-5 mm <sup>3</sup> )	79 (32)	10 (13)	0.003
Small erosion (<1 mm <sup>3</sup> )	72 (29)	20 (26)	1.000
Erosion site (n, %)			0.076*
Dorsal	61 (24)	3 (8)	
Ulnar	29 (11)	2 (5)	
Palmar	48 (19)	9 (24)	
Radial	121 (47)	23 (62)	

Data are presented as median [IQR] or n (%). RA, rheumatoid arthritis; HCs, healthy controls. <sup>#</sup> Defined based on the size of the largest erosion per patient. <sup>†</sup> Presence of erosion by size was compared using Fisher's exact test; post hoc pairwise comparisons used Fisher's exact test with Bonferroni correction. \* Overall comparisons for erosion site used Fisher's exact test with a Monte Carlo simulation.

When stratified by baseline erosion size (Figure 4.1), the prevalence of large erosions (17% versus 3%, P=0.002) and intermediate erosions (32% vs 13%, P=0.003) were significantly higher in RA patients compared to HCs, while the prevalence of small erosions (<1 mm<sup>3</sup>) was comparable between both groups (29% in RA vs 26% in HC, P=1.000).

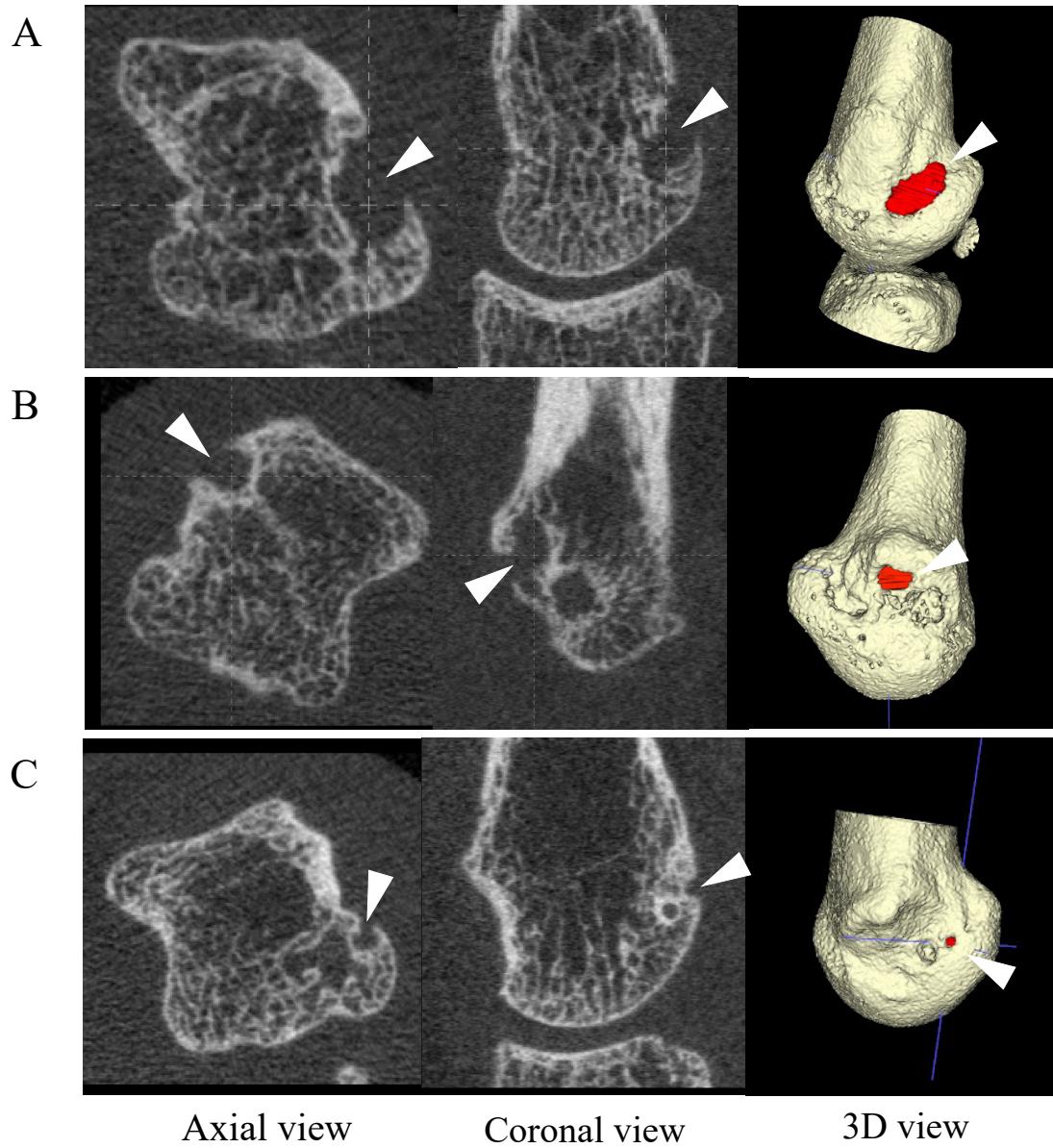


Figure 4.1 Typical images depicting erosion by size in MCH2

Erosion size categories: large erosion:  $> 5 \text{ mm}^3$ , intermediate erosion:  $1-5 \text{ mm}^3$ , small erosion:  $< 1 \text{ mm}^3$ . (A) Large erosion (volume =  $32.18 \text{ mm}^3$ ); (B) intermediate erosion (volume =  $2.66 \text{ mm}^3$ ); (C) small erosion (volume =  $0.98 \text{ mm}^3$ ). The erosion size is depicted by the red segmentation of the bone in the 3D view. White triangles indicate the presence of erosion in axial, coronal, and 3D views.

Anatomical distribution analysis showed that the radial aspect was the predominant erosion site in both RA patients (47%) and HCs (62%). RA patients exhibited proportionally higher involvement

of dorsal (24% vs 8%) and ulnar (11% vs 5%) aspects compared to HCs, while the control group showed relatively greater involvement of palmar and radial aspects.

#### **4.4.3 Volumetric analysis of erosions by size in the MCH2 between both groups**

Table 4.3 presents a detailed volumetric comparison of erosions stratified by size in the MCH2 between RA patients and HCs. Small erosions with volumes <1 mm<sup>3</sup> were present in 110 RA patients and 24 HCs. RA patients have a slightly larger median erosion volume than HCs (0.5 vs 0.4 mm<sup>3</sup>, P=0.025). The effect size analysis demonstrated a slight difference between groups, with a rank-biserial correlation of 0.294 (95% CI: 0.130 to 0.441) and a Cliff's delta of 0.294 (95% CI: 0.048 to 0.523). The Hodges-Lehmann estimate indicated a slight absolute difference of 0.119 mm<sup>3</sup> (95% CI: 0.022 to 0.216) between groups.

Intermediate erosions (1-5 mm<sup>3</sup>) were identified in 104 RA patients and 11 HCs, with erosion volumes showing no significant inter-group differences (P=0.091). Effect size measures suggested moderate differences between groups, with a rank-biserial correlation of 0.311 (95% CI: 0.136 to 0.468) and a Cliff's delta of 0.311 (95% CI: -0.065 to 0.659). The Hodges-Lehmann estimate indicated a difference of 0.276 mm<sup>3</sup> (95% CI: -0.083 to 0.551), but the confidence interval crossing zero reflected the non-significant nature of this comparison.

Large erosions (>5 mm<sup>3</sup>) demonstrated the most pronounced volumetric disparities, with substantially higher volumes in RA patients (median: 11.6 mm<sup>3</sup> in RA vs 6.6 mm<sup>3</sup> in HC, P=0.046). The effect size analysis revealed substantial differences between groups, with a rank-biserial correlation of 0.822 (95% CI: 0.700 to 0.897) and a Cliff's delta of 0.822 (95% CI: 0.600 to 0.978). The Hodges-Lehmann estimate quantified this substantial difference as 4.838 mm<sup>3</sup> (95% CI: 3.127 to 6.456).

Table 4.3 Comparison of the individual erosion volume of MCH2 between RA patients and HCs

	Small erosion (<1 mm <sup>3</sup> )			Intermediate erosion (1-5 mm <sup>3</sup> )			Large erosion (>5 mm <sup>3</sup> )		
	RA (n=110)	HCs (n=24)	P-value	RA (n=104)	HCs (n=11)	P-value	RA (n=45)	HCs (n=2)	P-value
Individual erosion volume (mm <sup>3</sup> )	0.5 [0.3, 0.7]	0.4 [0.3, 0.5]	0.025	1.7 [1.3, 2.7]	1.2 [1.2, 2.2]	0.091	11.6 [9.0, 17.1]	6.6 [6.4, 6.8]	0.046
Effect size for RA vs. HCs									
Rank-biserial correlation (95% CI)	0.294 (0.130 to 0.441)			0.311 (0.136 to 0.468)			0.822 (0.700 to 0.897)		
Cliff's delta (95% CI)	0.294 (0.048 to 0.523)			0.311 (-0.065 to 0.659)			0.822 (0.600 to 0.978)		
Hodges-Lehmann Estimate (95% CI)	0.119 (0.022 to 0.216)			0.276 (-0.083 to 0.551)			4.838 (3.127 to 6.456)		

Data are reported as median [interquartile range]. Erosion volume differences between groups were analyzed using the Mann-Whitney U test. RA, rheumatoid arthritis. HCs, healthy controls.

#### 4.5 Discussion

This HR-pQCT-based comparative study provides essential insights into the prevalence and distribution of bone erosions in RA and HCs, suggesting that small erosions were common in HCs and did not differentiate from RA patients. The key findings include: 1) higher prevalence of erosions in RA patients compared to HCs (78% vs 41%), 2) comparable prevalence of small erosions ( $<1 \text{ mm}^3$ ) between RA patients and HCs.

The present study systematically excluded vascular channels from all erosion analyses. The identification and exclusion of vascular channels, recognised by their linear morphology and characteristic anatomical locations [161, 189], ensured that all small erosions included in our dataset were not physiological vascular channels but instead represented discrete cortical breaks with features consistent with SPECTRA-defined erosions [190]. Regarding the anatomical distribution of erosions, the radial aspect was the predominant erosion site in both RA patients and HCs. This pattern is consistent with previous anatomical studies showing that the radial aspect of the MCP joint experiences the greatest mechanical stress during hand use [191, 192].

While the volume of small erosions was slightly larger in RA patients than in HCs, the effect size was minimal (Cliff's delta: 0.294), and the magnitude of difference between groups was also minor (Hodges-Lehmann Estimate: 0.119). No significant difference was observed between groups with regard to intermediate erosion. The common emergence of small erosions in HCs also aligns with previous work proposing that small cortical breaks might represent normal anatomical variants or age-related changes rather than pathological erosions, since it was also found in healthy individuals [191].

Our findings have important implications for interpreting HR-pQCT findings in clinical practice and research. Given that small erosions are also observed in healthy individuals, their isolated presence warrants caution and should not be construed as definitive evidence of structural joint damage or an adverse prognosis. Instead, attention should focus on larger erosions, which appear more specific to RA and show greater differentiation value not only in the prevalence but also in the volume of erosion. This nuanced understanding may help avoid overtreatment in patients with predominantly small-to-intermediate erosions and direct therapeutic interventions toward those with larger, potentially more clinically significant erosions.

#### **4.6 Limitations**

The present investigation has several limitations that merit discussion. First, our analysis only focused on the MCH2, which, while being the most commonly affected MCP joint in RA [178], may not represent the full spectrum of erosive changes throughout the hand. Analysis of multiple joints might provide a more comprehensive picture of erosion patterns. Second, the erosion size categorization (small, intermediate, large) was based on volume thresholds that remain somewhat arbitrary, while generally used in the literature [141]. Different threshold selections might yield different patterns of prevalence and distribution. Future studies with larger cohorts might enable more data-driven approaches to size-variety erosion categorization. Finally, while we carefully excluded vascular channels from our erosion analysis, the differentiation between small erosions and other physiological cortical interruptions can be challenging, even with high-resolution imaging. Some misclassification cannot be entirely ruled out, though our image analysis protocol, based on the SPECTRA definition [190], was designed to minimize such errors.

#### **4.7 Conclusions**

This cross-sectional HR-pQCT study showed that small erosions were common in HCs and did not differentiate from RA, whereas large erosions were more frequent and of greater size in RA, and may be associated with RA pathology.

## **Chapter 5: Bone Erosion Progression and Regression in Rheumatoid**

### **Arthritis - An Eight-Year HR-pQCT Follow-Up Study**

#### **5.1 Introduction**

HR-pQCT, with an isotropic resolution of  $82\mu\text{m}$ , can detect small cortical interruptions ( $>0.41\text{mm}$ ), which are more prevalent in RA patients compared to controls [193]. Small ( $<5 \text{ mm}^3$ ) erosions are similar in terms of location and morphology in RA patients as controls, while larger ( $>5 \text{ mm}^3$ ) erosions are more likely to characterise RA [141]. In study 1, our findings also showed that small erosions were common in HCs and did not distinguish from RA, whereas large erosions were more frequent and larger in RA and may be associated with RA pathology. Early HR-pQCT study reported that interruption volumes are larger in longstanding RA than in early-stage disease [187]. The clinical importance of detecting small cortical interruptions lies in the hypothesis that vascular channels may serve as initial sites for developing pathological cortical breaks, offering a pathway for osteoclast-driven bone destruction[29, 140, 194]. Nevertheless, the long-term evolution and clinical implications of these variably-sized erosions quantified by HR-pQCT remain unclear. Longitudinal monitoring of these small cortical interruptions may enhance our understanding of RA pathogenesis and provide valuable insights into the progression of structural joint damage or the effectiveness of therapeutic interventions. Currently, the clinical significance, natural history, and long-term evolution of small ( $<1 \text{ mm}^3$ ), intermediate ( $1-5 \text{ mm}^3$ ), and large ( $>5 \text{ mm}^3$ ) erosions in RA remain unknown. In particular, it is uncertain whether small erosions observed on high-resolution imaging represent harmless anatomical variants, early precursors to pathological erosions, or initial indicators of structural damage that necessitate timely therapeutic intervention.

Longitudinal studies evaluating the evolution of erosions according to their size are also limited [186]. While prior research indicates that larger erosions tend to either progress or undergo repair over time[106, 138, 180, 195], whether small-to-intermediate erosions may progressively enlarge during long-term follow-up is unknown.

Over the past two decades, substantial evidence has emerged supporting the concept of a "window of opportunity" in RA treatment, a critical early period during which therapeutic intervention may significantly alter disease trajectory and potentially prevent irreversible joint damage [1, 19, 196].

While the impact of early intervention on clinical outcome has been well-documented [197], the long-term effects of early treatment on structural damage, such as bone erosion, remain incompletely understood.

Several HR-pQCT studies have shown that effective immunosuppression leads to, not only retardation of erosion progression, but also erosion repair in RA. Partial erosion repair by inhibiting tumour necrosis factors (TNF), interleukin-6 (IL-6), receptor activator of nuclear factor kappa B ligand (RANKL), and Janus kinases (JAK) has been demonstrated [106, 138, 183, 195].

In patients with early RA (ERA), we have demonstrated that erosion volume at the second metacarpal head (MCH2) reduced after 1 year of tight control treatment with conventional disease-modifying anti-rheumatic drugs (csDMARDs) [164]. A limitation of previous studies is the relatively short follow-up duration, which may not allow sufficient time to observe complete erosion repair. It is also unclear whether erosion healing is more achievable in ERA patients under a treat-to-target (T2T) approach compared to usual care. In patients with long-standing RA who achieved sustained low-disease activity (LDA) or remission, erosions can continue to progress, even though patients may be asymptomatic, most likely due to sub-clinical, low-grade

inflammation/synovitis [180]. While any joint destruction is clearly unfavourable, no long-term data addresses the precise degree or rate of erosion progression or healing. Exploring whether inflammation resolution through T2T in ERA patients results in improved erosion healing compared to usual care in the long term warrants further investigation.

The present HR-pQCT-based study aimed to evaluate the changes in erosive parameters over time in RA patients who underwent a follow-up assessment after a median of 8 years, and to compare long-term erosion volume in ERA patients treated to target (T2T) and established RA (EstRA) patients receiving usual care, so as to provide insight into whether early intervention can result in meaningful modification of erosive outcome long term.

## **5.2 Primary outcome**

Long-term change in erosion volume in MCH2 assessed by HR-pQCT, stratified by size, over a median follow-up period of 8 years.

## **5.3 Secondary outcomes**

1. Frequency of erosions exhibiting stability, progression, or regression over time within each size category in the entire cohort.
2. Long-term outcome of bone erosions between ERA patients receiving the T2T strategy and EstRA patients receiving usual care.

## **5.4 Methods**

### **5.4.1 Patients**

Details of patient characteristics have been comprehensively described in the general methodology section (Chapter 3) presented earlier.

#### **5.4.2 Clinical assessment**

This follow-up study included 247 RA patients followed for a median duration of 8 years. Details of clinical assessment have been described in the general methodology section (Chapter 3).

#### **5.4.3 HR-pQCT assessment**

HR-pQCT assessment, including image acquisition, erosion identification, and measurement of erosion volume, and the reliability of erosion size and image motion assessment, have already been described in detail in the general methodology section (Chapter 3).

#### **Definition of partial erosion repair and progression**

Partial erosion repair was defined as a decrease in erosion volume exceeding the least significant change (LSC), whereas an increase beyond the LSC denoted erosion progression; changes within  $\pm$ LSC were considered stable [138, 198, 199]. This threshold-based approach aligns with established methods for quantifying longitudinal volumetric change of erosions detected by HR-pQCT, and LSC was applied to ensure robust discrimination of true biological effects from measurement error [200]. To determine the LSC, the reader (XY) performed two volume assessments on 60 randomly selected erosions from the study cohort. These erosions were stratified into 3 categories based on the volume: small ( $<1 \text{ mm}^3$ ), intermediate ( $1\text{--}5 \text{ mm}^3$ ), and large ( $>5 \text{ mm}^3$ ), with 20 cases in each category. The LSC value was calculated using the formula  $\text{LSC} = \pm 2.77 \times \sqrt{\frac{\sum(a-b)^2}{2n}}$ , where a and b were the first and second measurements, respectively, and n is the

number of observations rescored [201]. Erosion status was determined based on the individual erosion approach. The corresponding LSC was 0.3 mm<sup>3</sup>, 0.7 mm<sup>3</sup>, and 3.1 mm<sup>3</sup>, for the individual erosion of the three volume categories (<1 mm<sup>3</sup>, 1–5 mm<sup>3</sup>, and >5 mm<sup>3</sup>), respectively.

#### 5.4.4 HAQ-DI assessment

The details of the HAQ-DI assessment have previously been described in Chapter 3.

#### 5.4.5 Statistical analyses

Numeric variables were presented as median with interquartile range (IQR) or frequency with percentage where appropriate. Longitudinal within-cohort changes were assessed using the Wilcoxon signed-rank test for continuous variables and the McNemar test for categorical variables. Effect sizes were calculated using rank-biserial correlation, Cliff's delta, and Hodges-Lehmann estimates with 95% confidence intervals (CI). Odds ratios (OR) with 95% CI were calculated to compare the prevalence of erosions that remained stable in size within each size category. Logistic regression was used to analyze the association between erosion size and its stability. Mann-Whitney U test for continuous data and Chi-square test or Fisher's exact test for categorical data were employed in between-cohort comparisons (ERA versus EstRA). Statistical significance was determined by 2-tailed probability values of  $p < 0.05$ . Statistical analyses were performed using IBM SPSS Statistics Version 30.0 (IBM, Armonk, NY, USA).

### 5.5 Results

#### Part I: Long-term changes in erosion volume in MCH2 assessed by HR-pQCT

### 5.5.1 Clinical characteristics of the overall cohort at baseline and follow-up

The total number of patients included for analysis was 247, as mentioned previously in Chapter 4.

In addition, 6 patients were unavailable for HAQ-DI scores, leaving 241 patients included in the current cohort analysis. At baseline, RA patients presented with symptom duration of 2.7 (0.8, 8.9) years and disease duration of 1.7 (0.1, 7.1) years. A high prevalence of anti-CCP antibodies (81%) was observed, along with moderate disease activity (Table 5.1). Most RA patients were receiving NSAIDs (67.6%), DMARDs (68% on csDMARDs and 6.2% on b/tsDMARDs), and 17.4% were on prednisolone.

After a follow-up interval of 8.3 (5.9, 10.9) years, the use of csDMARDs (85.5%) and b/tsDMARDs (14.1%) was significantly increased, while a significant reduction in prednisolone (7.9%) and NSAID (47.3%) use was observed. Significant improvement in disease activity was observed, with the majority of patients reaching SDAI low disease activity (40.2%) and remission (31.1%), accompanied by significantly improved HAQ-DI scores.

Table 5.1 Demographic and clinical characteristics of RA patients

	Baseline	Last visit	P-value†
Age (yrs)	54.7 (48.0, 61.3)	63.0 (55.0, 69.5)	<0.001
Female, n (%)	196 (81.3)	-	
Cohort (ERA), n (%)	97 (40.2)	-	
Symptom duration (years)	2.7 (0.8, 8.9)		
Disease duration (years)	1.7 (0.1, 7.1)		
Follow-up interval (years)	-	8.3 (5.9, 10.9)	
RF positive, n (%)	146 (60.6)		
Anti-CCP positive, n (%) *	189 (81.1)		
Disease activity parameters			
Patient VAS pain	5.0 (2.0, 6.0)	3.0 (1.0, 5.0)	<0.001
Patient's global assessment, NRS 0-10	5.0 (2.8, 6.0)	3.0 (1.0, 5.0)	<0.001

	Baseline	Last visit	P-value†
Physician's global assessment, NRS 0-10	2.5 (0.8, 5.0)	1.0 (0.0, 3.0)	<b>&lt;0.001</b>
Tender joint count (0-28)	3.0 (0.0, 7.0)	0.0 (0.0, 2.0)	<b>&lt;0.001</b>
Swollen joint count (0-28)	2.0 (0.0, 4.0)	0.0 (0.0, 1.0)	<b>&lt;0.001</b>
ESR (mm/h)	32.0 (19.0, 53.0)	28.0 (18.0, 45.5)	0.098
CRP (mg/L)	4.0 (1.1, 11.5)	2.0 (0.7, 4.8)	<b>&lt;0.001</b>
SDAI score	13.0 (6.0, 24.2)	6.1 (2.1, 11.3)	<b>&lt;0.001</b>
DAS28_CRP score	3.5 (2.3, 4.7)	2.3 (1.5, 3.2)	<b>&lt;0.001</b>
SDAI category			<b>&lt;0.001</b>
Remission	32 (13.3)	75 (31.1)	
LDA	78 (32.4)	97 (40.2)	
MDA	79 (32.8)	58 (24.1)	
HDA	52 (21.6)	11 (4.6)	
Change in SDAI	-	-6.4 (-18.2, 0.6)	
Change in DAS28_CRP	-	-1.2 (-2.4, 0.1)	
HAQ-DI §	0.5 (0.1, 1.1)	0.4 (0.0, 0.9)	<b>0.005</b>
Change in HAQ-DI	-	-0.1 (-0.7, 0.3)	
Worsening disability	-	39 (16.2)	
Current treatment, n (%)			
Prednisolone	42 (17.4)	19 (7.9)	<b>0.002</b>
NSAIDs	163 (67.6)	114 (47.3)	<b>&lt;0.001</b>
csDMARDs	164 (68.0)	206 (85.5)	<b>&lt;0.001</b>
b/tsDMARDs	15 (6.2)	34 (14.1)	<b>0.004</b>
Ever treatment during study period, n (%)			
Prednisolone	-	114 (47.3)	-
csDMARDs	-	241 (100.0)	-
b/tsDMARDs	-	56 (23.2)	-

Data are reported as median (interquartile range) or number (%). † P-values from Mann-Whitney U tests for continuous variables and Chi-square test for categorical variables. Bold values indicate statistical significance ( $P < 0.05$ ). § Missing HAQ-DI (n=6), leaving 241 patients included for the current analysis. Abbreviations: ERA: early rheumatoid arthritis (RA); SDI: sustained SDAI remission. RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide antibody; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: simplified disease activity score; DAS 28-CRP: disease activity score 28-CRP; HAQ-DI: health assessment questionnaire - disability index; Worsening disability: increase in HAQ-DI  $>0.5$  from baseline to the last visit; NSAIDs: Nonsteroidal Anti-inflammatory Drugs. csDMARDs: conventional synthetic disease-modifying anti-rheumatic drug. b/tsDMARDs: biologic/targeted synthetic disease-modifying anti-rheumatic drug.

## 5.5.2 Longitudinal assessment of erosions by size in the overall cohort

## **Outcome of erosions**

Over the 8-year period, erosion prevalence remained stable between the two time points (78% vs. 83%, p = 0.168) (Table 5.2). The formation of new erosions was seen in 43/241 (17.8%) patients. The total number of erosions per person (p=0.01) and the total erosion volume per person (P=0.049) were significantly increased.

For erosions present at baseline (n = 259), the individual erosion volume showed no significant change (Table 5.2). However, based on the LSC, 21.2% of erosions progressed, 25.1% regressed, and 53.1% remained stable.

Table 5.2 Erosion parameters of MCH2 in RA patients

	Baseline	Last visit	p-value
Presence of erosion (n, %)	188/241 (78.0)	200/241 (83.0)	0.168
Total no. of erosions per patient	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	<b>0.010</b>
Total erosion volume per patient (mm <sup>3</sup> )	1.0 (0.3, 3.0)	1.4 (0.3 4.9)	<b>0.049</b>
Mean erosion volume per patient (mm <sup>3</sup> )	0.9 (0.3, 2.4)	1.2 (0.3, 3.2)	0.107
New erosion development (n, %)	-	43 (17.8)	
Pre-existing erosions (n=259)			
Individual erosion volume (mm <sup>3</sup> )	1.2 (0.5, 3.2)	1.3 (0.5, 3.2)	0.549
Progression (n, %)	-	55 (21.2)	
Stable (n, %)	-	139 (53.7)	
Regression (n, %)	-	65 (25.1)	

Data are reported as median (interquartile range) or number (%). MCH, the second metacarpal head. RA, rheumatoid arthritis.

## **Changes in erosion volume by size**

Changes in erosion volume over time in the overall cohort of RA patients exhibited variability across three size categories (Table 5.3). Small erosions (n=110) showed an increase in median volume from 0.5 mm<sup>3</sup> [IQR: 0.3, 0.7] to 0.6 mm<sup>3</sup> [IQR: 0.3, 1.2] (P<0.001), with an effect size of small-to-moderate change (rank-biserial correlation: 0.325, 95% CI: 0.131 to 0.484). Nevertheless, the change magnitude was minimal as evidenced by a minor Hodges-Lehmann estimate of 0.052 mm<sup>3</sup> (95% CI: 0.022 to 0.161). Intermediate erosions (n=104) demonstrated remarkable stability, with unchanged median volumes of 1.7 mm<sup>3</sup> at both time points (P=0.402). The negligible effect size (r=0.082, 95% CI: 0.005 to 0.259) and Hodges-Lehmann estimate near zero (0.039 mm<sup>3</sup>, 95% CI: -0.265 to 0.290) confirmed the minimal longitudinal change in intermediate erosions. In contrast, large erosions (n=45) showed a significant decrease in median volume from 11.6 mm<sup>3</sup> to 5.7 mm<sup>3</sup> (P<0.001). This substantial reduction was supported by a large effect size (r=0.697, 95% CI: 0.534 to 0.817; Rank-biserial correlation: 0.759, 95% CI: 0.507 to 0.812) and a notable Hodges-Lehmann estimate of -5.580 mm<sup>3</sup> (95% CI: -8.052 to -4.260), suggesting considerable repair of these larger erosions.

Table 5.3 Comparison of pre-existing erosion in MCH2 in RA patients from baseline to last visit

	Small erosion (<1 mm <sup>3</sup> ) (n=110)			Intermediate erosion (1-5 mm <sup>3</sup> ) (n=104)			Large erosion (>5 mm <sup>3</sup> ) (n=45)		
	Baseline	Last visit	P-value	Baseline	Last visit	P-value	Baseline	Last visit	P-value
Individual erosion volume (mm <sup>3</sup> )	0.5 [0.3, 0.7]	0.6 [0.3, 1.2]	<0.001	1.7 [1.3, 2.7]	1.7 [1.0, 3.5]	0.402	11.6 [9.0, 17.1]	5.7 [1.8, 13.0]	<0.001
Effect size for changes in erosive volume from baseline to last visit									
Rank-biserial correlation	0.325 (0.131 to 0.484)			0.082 (0.004 to 0.273)			0.759 (0.507 to 0.812)		
Effect Size (r) (95% CI)	0.325 (0.154 to 0.494)			0.082 (0.005 to 0.259)			0.697 (0.534 to 0.817)		
Hodges-Lehmann Estimate (95% CI)	0.052 (0.022 to 0.161)			0.039 (-0.265 to 0.290)			-5.580 (-8.052 to -4.260)		

Data are reported as median [interquartile range]. Individual erosion volume was analyzed between two time points using the Wilcoxon signed-rank test.

## **Erosion status by size**

When classified by erosion status, small erosions had the highest stability, with 64% remaining stable, while 23% progressed and 14% regressed. Intermediate erosions ( $1\text{-}5 \text{ mm}^3$ ) showed equal proportions of progression and regression (25% each), with 50% remaining stable. Large erosions ( $>5 \text{ mm}^3$ ) exhibited a predominant pattern of regression (53%), with minimal progression (9%) and moderate stability (38%). When stable erosion was further analysed, erosion stability was significantly associated with baseline erosion size ( $P=0.008$ ). Small erosions were more likely to remain stable compared to both intermediate (OR: 1.75, 95% CI: 1.01 to 3.02,  $P=0.044$ ) and large erosions (OR: 2.88, 95% CI: 1.41 to 5.90,  $P=0.003$ ; Table 5.4).

Table 5.4 The status of individual erosion in MCH2 from baseline to last visit

	Small erosion ( $<1 \text{ mm}^3$ ) (n=110)	Intermediate erosion ( $1\text{-}5 \text{ mm}^3$ ) (n=104)	Large erosion ( $>5 \text{ mm}^3$ ) (n=45)
<b>Erosion status</b>			
Progression	25 (23)	26 (25)	4 (9)
Regression	15 (14)	26 (25)	24 (53)
Stable	70 (64)	52 (50)	17 (38)
Stable erosion according to size category			
Size category ( $\text{mm}^3$ )	OR	95% CI	P-value
<b>Overall distribution</b>			
< 1 vs. 1-5	1.75	1.01 to 3.02	0.044
< 1 vs. > 5	2.88	1.41 to 5.90	0.003
1-5 vs. > 5	1.65	0.81 to 3.37	0.170

Erosion size categories were defined according to baseline volume. Progression and regression were determined by erosive volume changes (increase/decrease) exceeding the least significant change (LSC) thresholds. Erosions showing neither progression nor regression were classified as stable.

## **Part II: Long-term outcomes of bone erosions between ERA and EstRA cohorts**

### **5.5.3 Clinical characteristics between both cohorts at baseline and follow-up**

Of the 247 patients, 98 patients had ERA while 149 patients had EstRA. At baseline, the ERA cohort had a significantly shorter symptom duration (from symptom onset to diagnosis) and disease duration (from diagnosis to HR-pQCT assessment), a higher prevalence of anti-CCP antibody, and a higher disease activity compared to the EstRA cohort (Table 5.5). At baseline, the ERA cohort had more NSAID usage, less csDMARD usage, and no b/ts DMARD usage.

The entire cohort had a median (IQR) follow-up period of 8.4 (5.9-10.9) years. The ERA cohort had a shorter follow-up interval ( $p<0.001$ ) and a greater reduction in disease activity ( $p<0.001$ ) than the EstRA cohort (Table 5.5). Throughout the study period, overall drug usage was similar ( $p=0.669$  for b/csDMARDs and  $p=1.000$  for csDMARDs) for both cohorts. However, at the final visit, fewer ERA patients used csDMARDs ( $p=0.002$ ) (Table 5.5).

Table 5.5 Clinical characteristics between patients from the ERA and EstRA cohorts

	Baseline			Last visit			P-value <sup>†</sup>	P-value <sup>¶</sup>	P-value <sup>§</sup>
	ERA (n=98)	EstRA (n=149)	P-value <sup>†</sup>	ERA (n=98)	EstRA (n=149)	P-value <sup>†</sup>			
Age	54 [46, 62]	55 [49, 61]	0.209	60 [54, 68]	64 [59, 70]	<b>0.011</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Female, n (%)	77 (79)	123 (83)	0.372						
Symptom duration (yrs)	0.6 [0.3, 0.9]	0.7 [0.3, 1.9]	<b>0.032</b>						
Disease duration (yrs)	0.05 [0.02, 0.11]	6.28 [2.68, 10.91]	<b>&lt;0.001</b>	7.67 [6.30, 8.89]	14.68 [11.48, 21.42]	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
Follow-up interval (yrs)				7.6 [6.2, 8.8]	10.7 [5.9, 11.1]	<b>&lt;0.001</b>			
RF positive, n (%)	52 (53)	97 (65)	0.058						
Anti-CCP positive, n (%) <sup>*</sup>	87 (90)	105 (75)	<b>0.005</b>						
<b>Disease activity parameters</b>									
Patient VAS pain	6.0 [5.0, 7.1]	3.0 [1.5, 5.0]	<b>&lt;0.001</b>	2.0 [1.0, 5.0]	3.0 [1.0, 5.0]	0.148	<b>&lt;0.001</b>	0.275	
Patient's global assessment, NRS 0–10	6.0 [5.0, 7.1]	3.5 [2.0, 5.0]	<b>&lt;0.001</b>	2.0 [0.9, 5.0]	3.0 [1.0, 5.0]	0.085	<b>&lt;0.001</b>	0.019	
Physician's global assessment, NRS 0–10	6.0 [4.0, 8.0]	1.0 [0, 2.0]	<b>&lt;0.001</b>	1.0 [0, 2.5]	1.0 [0, 3.0]	0.539	<b>&lt;0.001</b>	0.066	
Tender joint count (0–28)	7.0 [5.0, 12.0]	1.0 [0, 3.0]	<b>&lt;0.001</b>	0 [0, 2.0]	1.0 [0, 2.0]	0.729	<b>&lt;0.001</b>	0.153	
Swollen joint count (0–28)	4.0 [2.0, 6.0]	1.0 [0, 2.0]	<b>&lt;0.001</b>	0 [0, 1.0]	0 [0, 1.0]	0.423	<b>&lt;0.001</b>	<b>0.010</b>	
ESR (mm/h)	51 [32, 81]	23 [15, 38]	<b>&lt;0.001</b>	26 [16, 40]	29 [18, 47]	0.398	<b>&lt;0.001</b>	<b>&lt;0.001</b>	
CRP (mg/L)	11 [4, 26]	2.1 [0.7, 5.3]	<b>&lt;0.001</b>	2.0 [0.6, 4.2]	2.2 [0.8, 5.5]	0.182	<b>&lt;0.001</b>	0.964	
SDAI score	24.9 [18.0, 34.5]	7.1 [3.6, 11.4]	<b>&lt;0.001</b>	5.2 [1.3, 10.2]	6.8 [3.1, 12.1]	0.204	<b>&lt;0.001</b>	0.243	
SDAI category			<b>&lt;0.001</b>			0.240	<b>&lt;0.001</b>	0.112	
Remission	0 (0)	33 (22)		39 (40)	48 (32)				
LDA	3 (3)	78 (52)		38 (39)	64 (43)				
MDA	49 (50)	31 (21)		18 (18)	36 (24)				
HDA	46 (47)	7 (5)		3 (3)	1 (1)				
Change in SDAI				-19.1 [-25.7, -14.1]	-1.6 [-5.9, 4.0]		<b>&lt;0.001</b>		
HAQ-DI (0–3) <sup>**</sup>	0.5 [0.1, 1.0]	0.6 [0.1, 1.1]	0.606	0.4 [0.1, 0.6]	0.4 [0, 1.0]	0.354	<b>0.019</b>	<b>0.029</b>	
<b>Current treatment, n (%)</b>									
Prednisolone	18 (18)	24 (16)	0.644	8 (8)	11 (7)	0.822	<b>0.031</b>	<b>0.002</b>	
NSAIDs	78 (80)	88 (59)	<b>&lt;0.001</b>	40 (41)	78 (52)	0.076	<b>&lt;0.001</b>	0.253	
csDMARDs	29 (30)	140 (94)	<b>&lt;0.001</b>	76 (78)	136 (91)	<b>0.002</b>	<b>&lt;0.001</b>	0.523	
b/tsDMARDs	0 (0)	16 (11)	<b>&lt;0.001</b>	17 (17)	17 (11)	0.185	<b>&lt;0.001</b>	1.000	
<b>Ever treatment, n (%)</b>									
Prednisolone ever use during study period				50 (51)	65 (44)	0.254			
csDMARDs ever use during study period				98 (100)	149 (100)	1.000			
b/tsDMARDs ever use during study period				24 (25)	33 (22)	0.669			

Data are reported as median [interquartile range] or number (%). ERA: early rheumatoid arthritis (RA); EstRA: established RA. Symptom duration represents the interval from symptom initiation until diagnosis. Disease duration is defined as the duration between diagnosis and HR-pQCT scan at baseline. Remission: SDAI score ≤ 3.3; LDA (Low Disease Activity): SDAI score > 3.3 to ≤ 11; MDA (Moderate Disease Activity): SDAI score > 11 to ≤ 26; HDA (High Disease Activity):

SDAI score > 26. \* Anti-CCP status data at baseline were available for 237 subjects only. \*\* Subjects available for the HAQ-DI at baseline and the last visit were 245 and 243, respectively. † Between-cohort analyses compared baseline or last visit differences. ¶ Comparing the within-cohort changes in the ERA cohort from baseline to the last visit. § Comparing the within-cohort changes in the EstRA cohort from baseline to the last visit. Abbreviation: SDI: sustained SDAI remission. RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide antibody; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: simplified disease activity score; DAS 28-CRP: disease activity score 28- CRP; HAQ-DI: health assessment questionnaire - disability index; NSAIDs: Nonsteroidal Anti-inflammatory Drugs. csDMARDs: conventional synthetic disease-modifying anti-rheumatic drug. b/tsDMARDs: biologic/targeted synthetic disease-modifying anti-rheumatic drug.

#### 5.5.4 Erosion parameters assessed by HR-pQCT between the two cohorts

Four patients in the EstRA cohort had destruction of MCP2 at baseline, precluding image assessment by HR-pQCT, increasing to 7 patients at the last visit (Figure 5.1A). MCP2 joint destruction was more common in the EstRA cohort than the ERA cohort at the last visit (4% vs. 0%, P = 0.046).

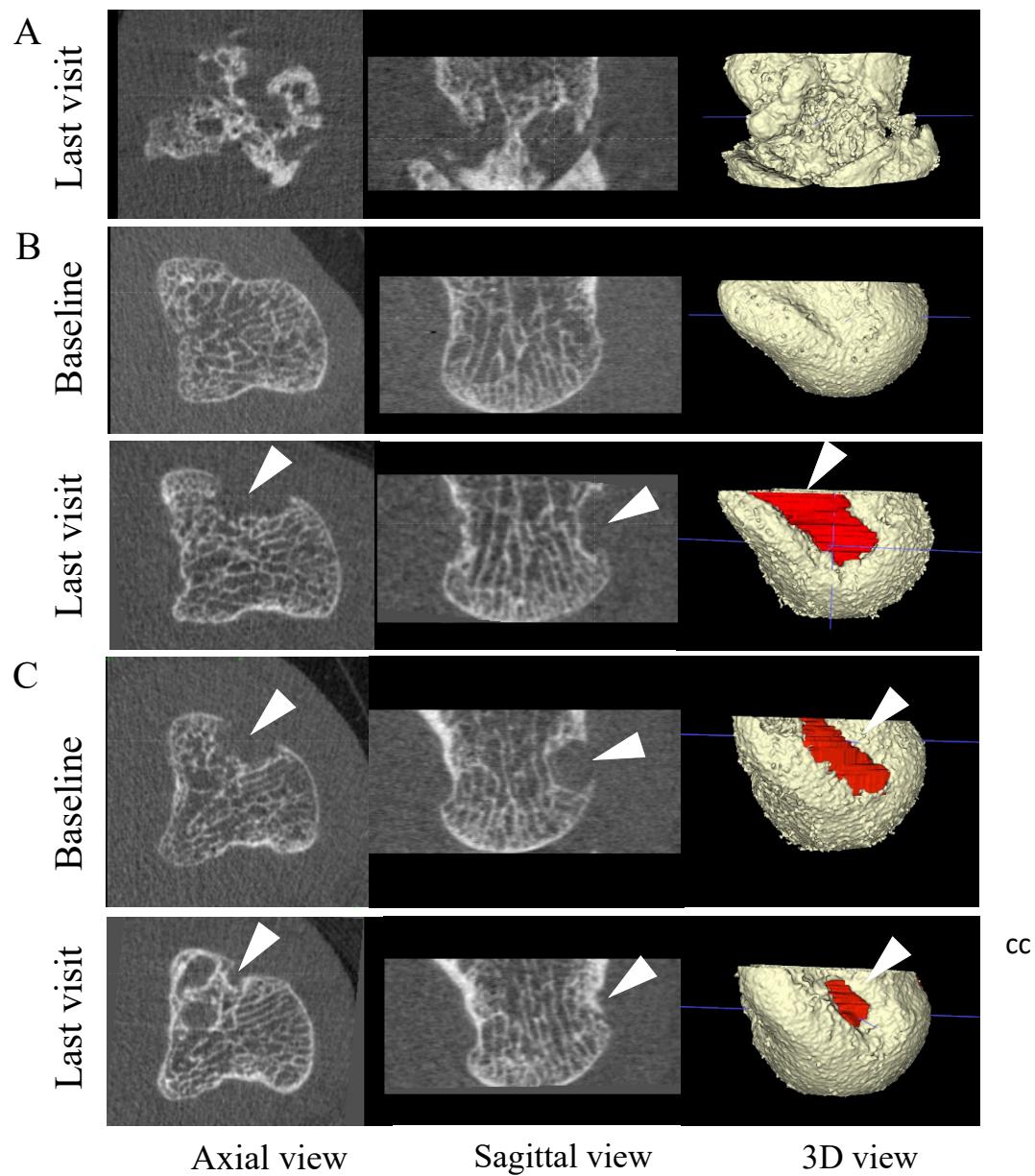


Figure 5.1 Representative images depicting joint destruction and changes in erosion size in MCH2 over two visits (A) Joint destruction detected at the last visit in the EstRA cohort; (B) Large erosion (volume = 37.53 mm<sup>3</sup>) newly detected at the last visit in the EstRA cohort. (C) Regression of large erosion in the ERA cohort (volume decrease from 24.69 mm<sup>3</sup> at baseline to 5.58 mm<sup>3</sup> at the last visit). The erosion size is depicted by the red segmentation of the bone in the 3D view. White triangles indicate the presence of erosion in axial, sagittal, and 3D views.

At baseline, similar percentages of ERA patients (77%) and EstRA (79%) patients had erosions (Table 5.6). At the last visit, erosion prevalence was significantly increased in the EstRA cohort (79% vs. 85%, p = 0.021) but not in the ERA cohort. Total erosion volumes remained stable in both cohorts. For erosions present at baseline (n = 259; 91 from ERA and 168 from EstRA), the total erosion volume remained unchanged in both cohorts (ERA: -0.01 [-0.65, 0.39] vs. EstRA: 0.03 [-0.48, 0.47], P=0.232, Figure 5.2A).

Table 5.6 Comparison of erosion parameters of MCH2 between two cohorts at two time points

	Baseline			Last visit				P-value ¶	P-value §
	ERA (n=98)	EstRA (n=149)	P-value †	ERA (n=98)	EstRA (n=149)	P-value †	P-value ¶		
Presence of erosion (n, %)	75 (77)	118 (79)	0.620	80 (82)	126 (85)	0.545	0.125	<b>0.021</b>	
Presence of erosion according to size (n, %)									
Large erosion (>5mm <sup>3</sup> )	16 (16)	26 (17)	0.818	13 (13)	37 (25)	<b>0.027</b>	0.549	<b>0.013</b>	
Intermediate erosion (1-5mm <sup>3</sup> )	27 (28)	52 (35)	0.226	45 (46)	51 (34)	0.065	<b>0.004</b>	1.000	
Small erosion (<1mm <sup>3</sup> )	32 (33)	40 (27)	0.326	22 (22)	38 (26)	0.584	0.052	0.815	
Total no. of erosion (n)	91	168	-	112	192	-	-	-	
Total erosion volume, (mm <sup>3</sup> )	0.8 [0.1, 2.2]	1.2 [0.3, 3.3]	0.192	1.4 [0.3, 2.6]	1.4 [0.3, 5.8]	0.209	0.411	0.075	

Data are reported as median [interquartile range] or number (%). † Comparing the between-cohort difference at baseline or the last visit using the Mann-Whitney U test for continuous variables and the Chi-Square/Fisher's exact test for categorical variables. ¶ Comparing the ERA within-cohort difference across two time points using the Wilcoxon signed-rank test for continuous variables and the McNemar test for categorical variables. § Comparing the EstRA within-cohort difference across two time points using the Wilcoxon signed-rank test for continuous variables and the McNemar test for categorical variables. ERA: early rheumatoid arthritis (RA); EstRA: established RA.

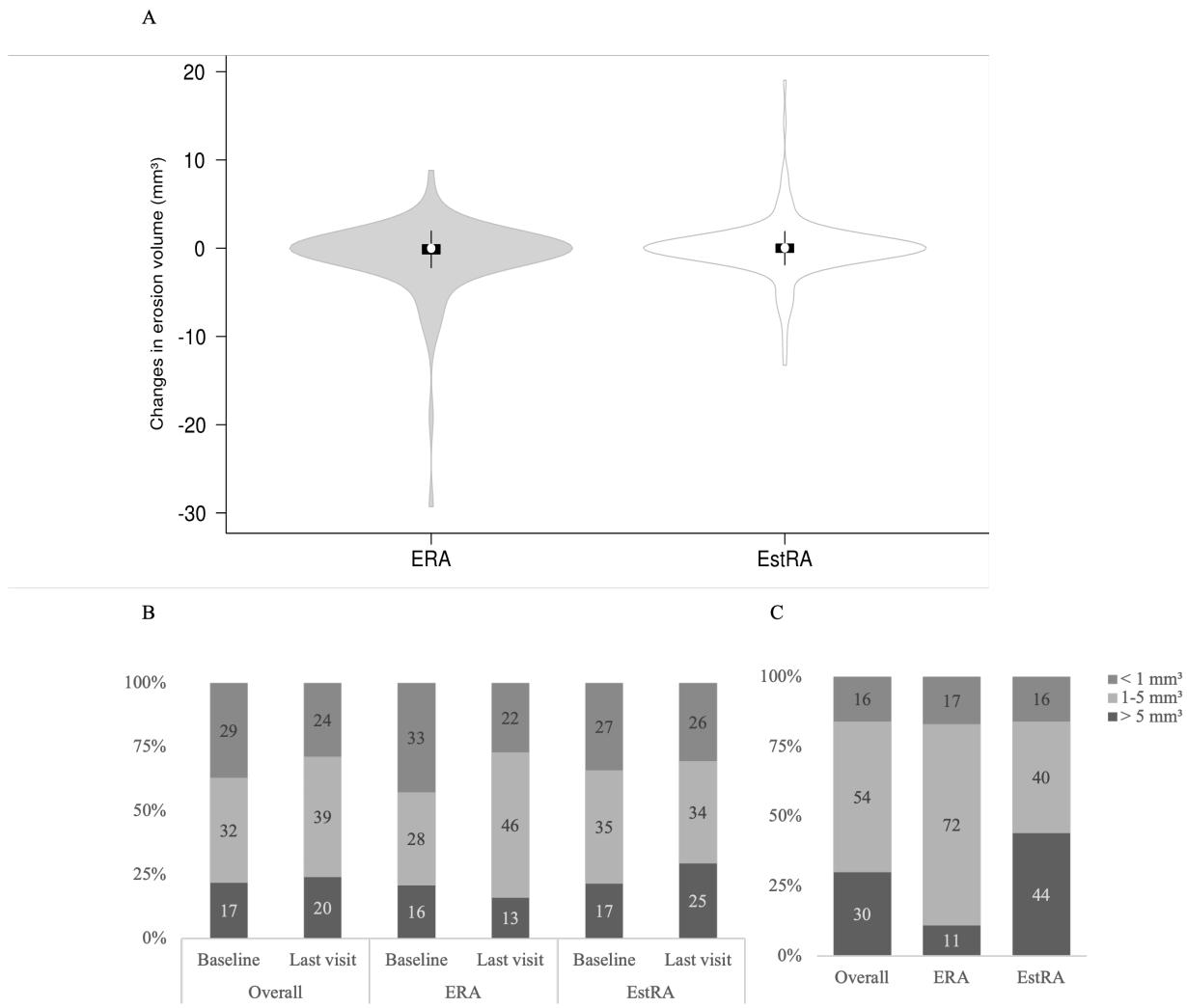


Figure 5.2 Changes in pre-existing erosion volume and distribution of erosions of MCH2 by size between cohorts  
A: Violin plot illustrating the distribution of changes in pre-existing erosion volumes ( $n = 259$ ; 91 from ERA, 168 from EstRA). B: Prevalence of erosions stratified by size in the entire cohort (total number of patients = 247). C: Prevalence of newly detected erosions at the last visit (total number of patients = 43). ERA: early rheumatoid arthritis (RA); EstRA: established RA.

### 5.5.5 Outcome of erosions according to erosion size

Although total erosion volumes remained unchanged, differences were seen when erosions of different sizes were analysed. When erosions were stratified by size (small:  $<1 \text{ mm}^3$ , intermediate:

1–5 mm<sup>3</sup>, and large: >5 mm<sup>3</sup>) at the patient level (defined by the largest erosion per patient), erosion size variability was similar between the ERA and EstRA cohorts at baseline (Table 5.6). However, by the last visit, the proportion of patients with large erosions had significantly increased in the EstRA cohort (from 17% to 25%, p = 0.013, Table 5.6), while intermediate erosions became more prevalent in the ERA cohort (from 28% to 46%, p = 0.004; Figure 5.2B). The prevalence of large erosions was significantly higher in the EstRA cohort compared with the ERA cohort at the last visit (25% vs. 13%, P = 0.027, Table 5.6).

### **Incident erosions**

At the last visit, 54 newly detected (incident) erosions were identified in 43 patients (Figure 5.1B), with a similar prevalence between both cohorts (18/98 [18%] in the ERA cohorts, 25/149 [17%] in the EstRA cohort, p = 0.747). When stratified by erosion size, a significantly lower frequency of incident large erosions was observed in the ERA cohort compared to the EstRA cohort (11% vs. 44%, p = 0.041, Table 5.7, Figure 5.1B). No significant differences were noted in the prevalence of incident intermediate or small erosions between the two cohorts.

Table 5.7 Erosion size distribution of new erosions in MCH2 detected at the last visit

	ERA (n=18)	EstRA (n=25)	P-value
Volume >5 mm <sup>3</sup> (n=13)	2 (11)	11 (44)	<b>0.041</b>
Volume 1-5 mm <sup>3</sup> (n=23)	13 (72)	10 (40)	0.062
Volume <1 mm <sup>3</sup> (n=7)	3 (17)	4 (16)	1.000

Data are reported as n (%). Differences between cohorts were assessed using Chi-Square or Fisher's exact test. ERA, early rheumatoid arthritis (RA); EstRA, established RA.

### **Erosion regression**

Based on the LSC thresholds, large erosions in the ERA cohort were more likely to regress (81% vs. 38%, P = 0.005) and less prone to remain stable (13% vs. 52%, P = 0.009) compared to the EstRA cohort (Figure 5.3A, Figure 5.1C). In contrast, there were no significant differences in erosion volume between the two cohorts with respect to intermediate and small erosions.

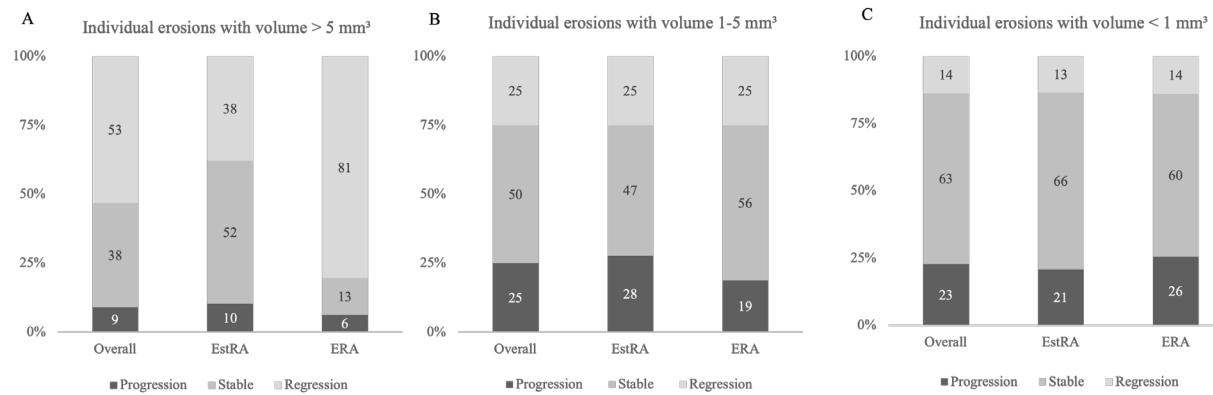


Figure 5.3 Outcome of erosions stratified by erosion volume categories in MCH2 between the two cohorts  
Total number of erosions =259, including 168 and 91 erosions from patients in the EstRA and ERA cohort, respectively.  
Progression: increase in erosion volume > least significant change (LSC); Regression: decrease in erosion volume > LSC; Stable: did not meet criteria for progression or regression. The LSC values were calculated based on the baseline erosion volume for each erosion, using the following size-based cut-off intervals: <1 mm<sup>3</sup>: LSC = 0.3 mm<sup>3</sup>; 1–5 mm<sup>3</sup>: LSC = 0.7 mm<sup>3</sup>; >5 mm<sup>3</sup>: LSC = 3.1 mm<sup>3</sup>. ERA: early rheumatoid arthritis (RA); EstRA: established RA.

### 5.5.6 Subgroup analysis of patients with large erosions (> 5 mm<sup>3</sup>)

In a subgroup analysis of patients with large erosions (n = 44; Table 5.8), ERA patients (n = 16) had significantly shorter disease duration compared to EstRA patients (n = 28). Despite having higher baseline levels of disease activity, the ERA cohort with large erosions demonstrated significantly greater improvements in disease activity, leading to significantly lower disease activity scores at the last visit. Treatment patterns in this subgroup were similar between the two cohorts. Within-cohort comparison revealed that both cohorts demonstrated a significant reduction

in erosion volume (Table 5.9, Figure 5.4). However, the reduction in erosion volume was significantly greater in the ERA cohort compared to the EstRA cohort.

Table 5.8 Clinical characteristics in the subgroup of patients with baseline erosion volume > 5 mm<sup>3</sup> in MCH2 from two cohorts

	Baseline			Last visit				P-value <sup>†</sup>	P-value <sup>¶</sup>	P-value <sup>§</sup>
	ERA (n=16)	EstRA (n=28)	P-value <sup>†</sup>	ERA (n=16)	EstRA (n=28)	P-value <sup>†</sup>	P-value <sup>¶</sup>			
Age	59 [47, 65]	55 [51, 61]	0.510	66 [54, 73]	65 [58, 69]	0.845	<0.001	<0.001		
Female, n (%)	9 (60)	18 (64)	0.782							
Symptom duration (yrs)	0.7 [0.5, 1.5]	1.0 [0.2, 3.5]	0.329							
Disease duration (yrs)	0.06 [0.03, 0.13]	6.64 [3.33, 15.62]	<0.001	7.19 [5.83, 8.89]	15.59 [11.33, 25.75]	<0.001	<0.001			
Follow-up interval (yrs)				7.1 [5.6, 8.7]	10.3 [5.9, 11.1]	0.062				
RF positive, n (%)	10 (63)	22 (79)	0.303							
Anti-CCP positive, n (%) *	14 (93)	19 (86)	0.633							
<b>Disease activity parameters</b>										
Patient VAS pain	6.0 [5.0, 7.0]	3.5 [1.6, 5.0]	0.003	1.5 [0.3, 4.1]	4.3 [1.3, 5.0]	0.040	0.002	0.794		
Patient's global assessment, NRS 0–10	6.0 [5.0, 7.4]	3.8 [1.0, 5.0]	<0.001	2.0 [0, 3.0]	4.3 [1.5, 5.0]	0.007	<0.001	0.896		
Physician's global assessment, NRS 0–10	6.5 [5.0, 9.8]	1.5 [0.5, 3.0]	<0.001	0 [0, 1.8]	2.3 [1.0, 4.0]	0.003	<0.001	0.367		
Tender joint count (0–28)	7.5 [5.0, 11.8]	1.0 [0, 4.4]	<0.001	0 [0, 0]	1.0 [0, 4.0]	0.006	<0.001	0.398		
Swollen joint count (0–28)	6.0 [3.3, 7.0]	1.5 [0, 2.0]	<0.001	0 [0, 0]	1.0 [0, 3.0]	0.004	<0.001	0.706		
ESR (mm/h)	49 [28, 68]	25 [17, 44]	0.008	25 [12, 39]	31 [17, 68]	0.236	0.001	0.052		
CRP (mg/L)	9 [5, 29]	1.3 [0.6, 4.6]	<0.001	1.7 [0.6, 2.7]	1.6 [0.7, 8.8]	0.606	<0.001	0.882		
SDAI score	27.3 [22.1, 39.8]	7.4 [4.1, 14.9]	<0.001	2.1 [0.5, 7.9]	9.5 [5.1, 16.3]	<0.001	<0.001	0.849		
SDAI category			<0.001			<0.001	<0.001	1.000		
Remission	0 (0)	6 (21)		11 (69)	5 (18)					
LDA	0 (0)	10 (36)		5 (31)	11 (39)					
MDA	7 (44)	11 (39)		0 (0)	12 (43)					
HDA	9 (56)	1 (4)		0 (0)	0 (0)					
Change in SDAI				-26.3 [-29.9, -18.2]	-0.5 [-8.0, 7.5]		<0.001			
HAQ-DI (0-3)	0.7 [0, 1.5]	0.3 [0, 0.6]	0.844	0.4 [0.1, 0.6]	0.6 [0, 1.0]	0.200	0.059	0.676		
<b>Current treatment, n (%)</b>										
Prednisolone	3 (19)	3 (11)	0.652	0 (0)	3 (11)	0.541	0.250	1.000		
NSAIDs	11 (69)	20 (71)	1.000	6 (38)	20 (71)	0.028	0.180	1.000		
csDMARDs	4 (25)	26 (93)	<0.001	11 (69)	24 (86)	0.250	0.065	0.687		
b/tsDMARDs	0 (0)	2 (7)	0.526	3 (19)	1 (4)	0.129	0.250	1.000		
<b>Ever treatment, n (%)</b>										
Prednisolone ever use during study period				7 (44)	13 (46)		0.864			
csDMARDs ever use during study period				16 (100)	28 (100)		-			
b/tsDMARDs ever use during study period				3 (19)	4 (14)		0.692			

Data are reported as median [interquartile range] or number (%). ERA: early rheumatoid arthritis (RA); EstRA: established RA. Symptom duration refers to the time period from symptom initiation until diagnosis. Disease duration is defined as the duration between diagnosis and HR-pQCT scan at baseline. Disease activity levels were established as: Remission with SDAI  $\leq 3.3$ , Low Disease Activity (LDA) with SDAI  $> 3.3$  to  $\leq 11$ , Moderate Disease Activity (MDA) with SDAI  $> 11$  to  $\leq 26$ , and High Disease Activity (HDA) with SDAI  $> 26$ . \* Baseline anti-CCP status was accessible for 37 study participants. Data are reported as median [interquartile range] or number (%). † Comparing the difference between two cohorts at the baseline or last visit. ¶ Comparing the within-cohort changes in the ERA cohort from baseline to the last visit. § Comparing the within-cohort changes in the EstRA cohort from baseline to the last visit. SDI: sustained SDAI remission. Abbreviation: RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide antibody; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: simplified disease activity score; DAS 28-CRP: disease activity score 28- CRP; HAQ-DI: health assessment questionnaire - disability index; NSAIDs: Nonsteroidal Anti-inflammatory Drugs; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drug. b/tsDMARDs: biologic/targeted synthetic disease-modifying anti-rheumatic drug.

Table 5.9 Comparison of MCH2 pre-existing erosion with baseline volume  $> 5 \text{ mm}^3$  in two cohorts

	Baseline	Last visit	P-value *	Change in erosion volume	P-value **
ERA (n=16)	12.0 [7.1, 29.6]	6.0 [3.6, 22.0]	<b>0.001</b>	-6.5 [-10.1, -3.5]	<b>0.005</b>
EstRA (n=29)	11.3 [9.2, 17.0]	8.6 [6.0, 14.7]	<b>0.027</b>	-1.4 [-5.4, 1.0]	

Analysis of erosion volume using the per-erosion approach. Data are reported as median [interquartile range]. \* Comparing the within-cohort changes across two time points using the Wilcoxon signed-rank test. \*\* Comparing the between-cohort differences in erosion volume changes across two time points using the Mann-Whitney U test. ERA: early rheumatoid arthritis (RA); EstRA: established RA.

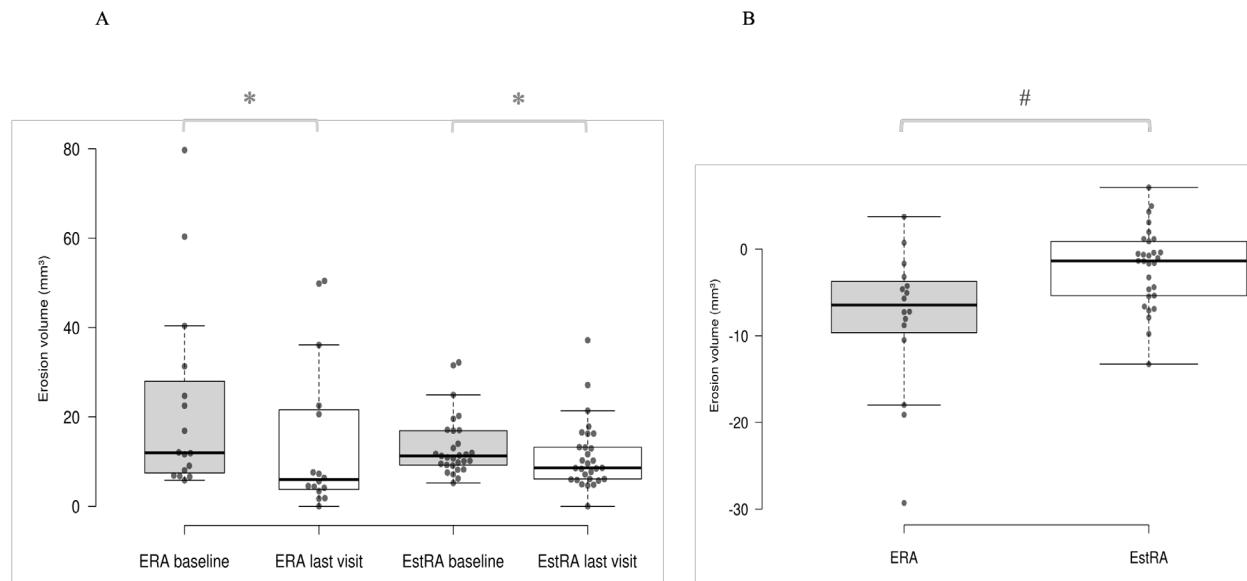


Figure 5.4 Comparison of MCH2 pre-existing erosion with baseline volume  $> 5 \text{ mm}^3$  in two cohorts

Analysis of erosion volume using the per-erosion approach. Analysis was conducted on a total of 45 erosions.

A: Within-cohort comparison showed a significant reduction in erosion volume from baseline to the last visit in both cohorts. B: Between-cohort comparison showed a significantly greater reduction in erosion volume changes in the ERA ( $-6.5 \text{ mm}^3$ ) than EstRA ( $-1.4 \text{ mm}^3$ ) ( $p = 0.005$ ). \* Indicating  $p < 0.05$  for within-cohort comparison in erosion volume across two time points using the Wilcoxon signed-rank test. # Indicating  $p < 0.05$  for between-cohort comparison of erosion volume changes across two time points using the Mann-Whitney U test. ERA: early rheumatoid arthritis (RA); EstRA: established RA.

## 5.6 Discussion

This eight-year longitudinal HR-pQCT study reveals essential insights into the natural history of bone erosions in RA, suggesting that erosion evolution may follow more complex, size-dependent patterns. The key findings include: 1) remarkable stability of small erosions in RA patients over long-term follow-up, and 2) significant regression of large erosions in RA patients over time. This is also the first study to assess the long-term impact of early treatment on erosion outcomes in RA using HR-pQCT over a period of 8 years. The results support the long-term benefits of early, tight-control treatment, not only in preventing bone damage with fewer incident large erosions in the ERA cohort compared with the EstRA cohort, but also in facilitating partial erosion healing.

Over an eight-year follow-up period for small-to-intermediate erosions in RA patients, the magnitude of volumetric changes over time was nearly negligible (Hodges-Lehmann Estimate: 0.052 and 0.039, respectively). When defining erosion states using the LSC threshold, small erosions showed remarkable stability over time, with 64% remaining unchanged, and were significantly more likely to remain stable than intermediate (OR: 1.75) and large erosions (OR: 2.88). Clinically, despite significant improvement in disease activity over time, most small-to-intermediate erosions remained on a stable long-term trajectory rather than showing regression. These observations indicate that complete reversal of small erosions may not be achievable or necessary, even with effective therapy leading to disease control. These findings together suggest that many small erosions may represent innocuous anatomical variants or physiological microstructural features rather than pathological erosions. These findings also align with previous work proposing that small cortical breaks might represent normal anatomical variants or age-related changes rather than pathological erosions [[191](#)].

In contrast, our data showed a significant regression in large erosions ( $>5 \text{ mm}^3$ ) in RA patients over an eight-year follow-up period. This substantial volumetric reduction, supported by a large

effect size (rank-biserial correlation: 0.759) and considerable Hodges-Lehmann estimate (-5.580 mm<sup>3</sup>), suggests significant repair potential in these larger erosions. This observation aligns with previous studies demonstrating erosion repair with biologic therapies [106, 138, 183, 195], but the present study extends these findings to a larger cohort with longer follow-up. The pronounced regression of large erosions, in comparison to the stability of smaller erosions, suggests that active inflammatory bone destruction is most relevant for large erosions, while small erosions often remain static and may not contribute to radiographic progression. Whether these small erosions may contribute to functional impairment would need to be addressed in future studies.

The considerable regression of large erosions observed in our cohort warrants exploration of possible influencing factors. To address whether early intervention has a significant impact on the long-term outcomes of bone erosions, we performed a subgroup analysis between the ERA and the EstRA cohorts. We have demonstrated that early T2T management in the ERA group resulted in less joint destruction, reduced formation of new large erosions, and greater regression of large erosions, compared to the EstRA cohort.

Strong evidence from several high-quality randomized controlled trials concluded that early DMARD treatment results in less erosion progression radiographically, over a period of 6 months to five years [202-206]. This benefit is less evident when treatment was delayed 6–12 months after diagnosis due to the use of placebo medication [202-206]. In the current study, using HR-pQCT to focus on erosive change in a single joint, we demonstrated less erosion progression over 8 years in the ERA cohort, despite MCH2 being the most commonly involved joint in disease progression [163]. Following the exclusion of seven patients from the EstRA cohort with joint destruction, the remaining patients in both cohorts had comparable erosive change at baseline. Although disease

activity was initially higher in the ERA cohort, progression was significantly greater in terms of incident erosion development in the EstRA cohort compared to the ERA cohort. The EstRA cohort also had a greater propensity to develop large erosions [141]. The finding of a slower progression observed in the ERA cohort suggests actual disease modification achieved through early, tight-control treatment during the first year after diagnosis, confirming a long-term benefit beyond the initial improvement seen after one year [164].

In accordance with the “window of opportunity” theory, the potential reversibility of autoimmunity decreases over time in RA, which in turn alters the potential efficacy of therapy. This early phase is characterized by increased proinflammatory cytokines, leading to synovitis, osteoclast activation, and bony erosion. During this critical phase, aggressive therapy yields disproportionate benefits, offering patients a good chance of remission [207]. In the current study, we demonstrated that partial healing of large erosions was more frequently observed in the ERA cohort compared to the EstRA cohort. This trend likely mirrors the swift inflammation suppression seen in this T2T cohort. This aligns with our previous report on the substantial decrease in the SDAI from  $28.2 \pm 11.5$  at baseline to  $6.2 \pm 5.9$  at one year, with 43% of patients achieving SDAI remission after the first year [164]. Erosion repair in ERA is known to occur only in joints that are clinically inactive [208]. Previous studies have provided ample evidence that longer durations of sustained remission result in a greater likelihood of radiographic erosion repair [209]. Conversely, persistent moderate disease activity in the first year [210] and disease flares [211] lead to greater radiographic erosion progression and more severe joint damage [212]. It is clear that reducing inflammation to a degree that achieves remission is beneficial in RA patients in promoting erosion repair and limiting disease progression. Our previous 1-year report showed that achieving sustained SDAI remission for 6 months is associated with less erosion progression and more erosion repair [164]. After an

eight-year period, a greater proportion of patients in the ERA cohort achieved SDAI remission (69% compared to 18% in the EstRA cohort), indicating a trend that may potentially explain a higher probability of erosion repair in the ERA cohort.

Overall, the strength of our study lies in the extended follow-up of the ERA cohort from disease onset, which enabled us to capture an 8-year trajectory closely resembling the natural evolution of RA. Additionally, the transition from T2T to usual care after the initial year, akin to the EstRA cohort, offered essential insights highlighting the critical impact of rapid inflammation control in the first year after diagnosis. Data from the EstRA cohort was also valuable given the current widespread adoption of the T2T approach and the established benefits of early csDMARD treatment on long-term functional and structural outcomes [213]. It would be questionable ethically to perform future randomized trials comparing early and delayed treatment in patients with RA.

## **5.7 Limitations**

Several limitations were present in our study. First, the initiation timing of DMARDs was not randomized, potentially leading to a mixture of patient and environmental factors influencing when DMARD therapy commenced, particularly in the EstRA cohort, which was not protocol-driven. Second, the HR-pQCT conducted at baseline occurred before or soon after the initiation of DMARDs in the ERA cohort, whereas such timing was not mandated in the EstRA cohort. As such, a substantial interval may have existed between the onset of DMARD treatment (though usually soon after diagnosis) and baseline HR-pQCT assessment in the EstRA cohort. Whether this affected the likelihood of large erosion healing in the EstRA cohort is uncertain. Third, HR-pQCT of only the second MCP joint was performed, so whether changes seen here are mirrored in other

affected joints is unclear. Fourth, the absence of serial imaging between baseline and final assessments restricts insight into erosion dynamics over time. Lastly, while our results provided evidence supporting the "window of opportunity" concept, the observational design precludes definitive causal inferences.

## **5.8 Conclusions**

This longitudinal HR-pQCT study shows that most small erosions remained stable over time, while large erosions exhibited significant regression with contemporary treatment and may be associated with RA pathology, suggesting that many small erosions detected by high-resolution imaging may be physiological rather than pathological lesions. The current study also provides evidence for a structural "window of opportunity" in RA management. Early intervention with T2T strategy significantly promotes regression of large erosions and prevents the formation of new large erosions in the ERA cohort compared to patients with established RA.

# **Chapter 6: Wrist Bone Erosion Burden Assessed by HR-pQCT Is Associated with Functional Disability in Patients with Rheumatoid Arthritis**

## **6.1 Introduction**

Bone erosion of RA, particularly in peripheral joints including the wrist, indicates both disease severity and subsequent functional impairment[[29](#), [135](#), [148](#)]. In the initial phase of RA, functional ability is driven primarily by inflammatory activity, whereas in later stages it reflects the extent of accumulated joint damage[[146](#)]. Despite significant advances in therapeutic strategies over the past two decades, including treat-to-target (T2T) approaches and biological disease-modifying antirheumatic drugs (bDMARDs)[[2](#)], approximately one-third of early RA patients still experience progressive joint damage and resulting functional disability[[30](#), [82](#), [214](#)]. Disease progression in RA follows heterogeneous patterns[[215](#)], with varying rates of erosion development and functional decline among patients[[1](#), [135](#)]. This heterogeneity complicates clinical decision-making, necessitating more precise imaging markers to identify patients at higher risk of functional disability.

The functional impact of RA-related joint damage extends beyond pain and inflammation, profoundly affecting patients' ability to perform daily activities[[74](#)]. The Health Assessment Questionnaire Disability Index (HAQ-DI) serves as the primary tool for assessing functional disability in RA patients, evaluating limitations within eight daily functioning domains [[115](#)]. A HAQ-DI greater than 0.5 points represents a clinically meaningful disability in functional status

and quality of life[[216](#)]. While previous work has established associations between radiographic joint damage and physical disability[[146](#)], the relationship between carpal erosive burdens and subsequent functional disability requires further elucidation.

The carpal bones were reported to be the earliest and most sensitive affected sites in RA[[178](#), [217](#), [218](#)]. Previous studies have primarily focused on erosion detection and quantification, with limited investigation into the association between carpal erosive burden and functional outcomes in RA. Different structural pathologies, erosions versus joint space narrowing[[30](#), [148](#)], may confer distinct functional implications, with radiographic studies suggesting potentially greater disability impact from joint space narrowing[[147](#)]. Previously study also reported that erosive damage in the wrist was an independent predictor for functional disability, as wrist movement constitute a large proportion of daily activities [[219](#)]. However, these studies employed two-dimensional radiography, which inadequately captures erosion severity, potentially underestimating erosive contributions to functional impairment. The prevalence and burden of erosions across different carpal bones quantified using high-resolution imaging may have varying implications for wrist biomechanics and function, potentially linking to functional disability. Understanding the association between specific carpal erosion patterns and functional disability could enhance risk stratification and personalized treatment strategies for RA patients. This is particularly relevant in the context of evolving remission-targeted treatment paradigms, where identifying patients at high risk for radiological damage leading to functional disability despite apparent clinical remission remains challenging[[214](#)].

In the current study, we hypothesized that erosive parameters in the wrist bones quantified by HR-pQCT are correlated with functional disability in RA patients. We aimed to determine the

relationship between erosive burden in specific carpal bones and functional disability as assessed by HAQ-DI, grip strength, and dexterity measures. Such an investigation could potentially identify additional imaging indicators for improved risk stratification and more tailored therapeutic approaches in RA management.

## **6.2 Primary outcome**

The association between erosion parameters in the wrist bones measured by HR-pQCT and functional disability determined by HAQ-DI in RA patients.

## **6.3 Secondary outcomes**

1. The correlation between erosion parameters in the wrist bones and functional measurements, including grip strength and the dexterity component of the Chinese Arthritis Impact Measurement Scales 2 (CAIMS2).
2. The association between wrist joint destruction and functional outcomes.

## **6.4 Methods**

### **6.4.1 Patients**

Details pertaining to patient characteristics have been comprehensively described in the general methodology section (Chapter 3).

### **6.4.2 Clinical assessment**

This cross-sectional study included 264 participants who underwent comprehensive clinical, laboratory, and HR-pQCT assessments of the wrist joint. Details of clinical assessment have also been described in the general methodology section (Chapter 3).

### **6.4.3 Functional assessment**

Functional assessment employing three complementary measures to comprehensively evaluate patient-reported disability, objective physical function, and arthritis-specific quality of life. This multi-dimensional approach facilitates exploration of distinct yet interrelated aspects of functional impairment and its relationship with structural damage in RA.

#### **HAQ-DI**

The details of HAQ-DI assessment have previously been described in Chapter 3.

#### **Grip strength**

Grip strength was quantified bilaterally as an objective surrogate of overall musculoskeletal function using a calibrated handheld dynamometer (Grip D TKK5401 Digital Hand Dynamometer, Takei, Japan, recording forces from 0 to 90 kg), following the American Society of Hand Therapists' standardized posture (shoulder adducted, elbow flexed at 90°, forearm neutral, wrist in slight extension) and testing protocol. After familiarization trials, participants performed two maximal-effort squeezes per hand, alternating sides with a one-minute rest interval to mitigate fatigue, and each attempt was recorded in kilograms. The highest value from two attempts per hand was averaged to determine overall grip strength. Low grip strength was defined according to the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) consensus, with cut-offs of <27 kg for men and <16 kg for women[220]. Due to its strong correlation with upper-limb

function and daily living activities, grip strength serves as a sensitive indicator of disease impact in RA populations. Its excellent reproducibility (intraclass correlation coefficients >0.90) and well-established normative benchmarks enable precise detection of clinically meaningful changes over time [221].

## **CAIMS2**

Fine motor function was quantified using the Chinese Arthritis Impact Measurement Scales 2 (CAIMS2) dexterity scale, which evaluates motor skills of the fingers, hands, and arms through five hierarchical items arranged in ascending difficulty based on Guttman scaling[222]. Embedded within CAIMS2's broader domains of mobility, pain, and psychosocial health, this dexterity scale offers a concise, robust measure of hand function tailored for clinical trials. During assessment sessions, trained assessors recorded each participant's binary responses (able vs. unable). Raw scores (number of failures, 0–5) were linearly transformed to a 0–100 scale, where higher values indicate greater functional impairment.

### **6.4.4 HR-pQCT assessment**

HR-pQCT assessment, including image acquisition, erosion identification, and measurement of erosion volume, and the reliability of erosion size and image motion assessment, have already been described in detail in the general methodology section (Chapter 3).

### **6.4.5 Statistical analyses**

Continuous variables were presented as medians with interquartile ranges (IQR), and categorical variables were reported as frequencies and percentages, as appropriate. The Mann-Whitney U test, Kruskal-Wallis H test, or ANOVA (for continuous data) and the Chi-square test or Fisher's exact

test (for categorical data) were used to evaluate the difference between patients with and without functional disability, and post-hoc analysis with Bonferroni correction was used when necessary. Spearman's correlation was used to determine the correlations between erosion parameters in the wrist bones and functional outcomes. Multivariate logistic and ordinal regression analyses were used to ascertain the association between erosion parameters in the wrist bones and functional assessment after adjustment for potential clinical covariates, including age, sex, disease duration, disease activity (SDAI remission), and medication use (b/tsDMARDs and prednisolone). Two-tailed p values < 0.05 were used to determine statistical significance. Statistical procedures were performed using IBM SPSS Statistics version 30.0 (IBM Corp., Armonk, NY, USA), and figures were plotted using Python 3.1.3.

## 6.5 Results

### 6.5.1 Clinical characteristics between RA patients with and without disability

Out of the 264 patients who underwent clinical and HR-pQCT assessment, 32 patients were excluded due to severe wrist joint destruction (n=25), incomplete scan (the absence of lunate and scaphoid; n=2), motion artefacts (n=1), and unavailable HAQ-DI data (n=4), leaving 232 patients included in the current analysis (Figure 3.1, in chapter 3). Among 232 patients, 105 (45.3%) presented with disability, and 45 (19.4%) exhibited moderate-to-severe disability (Table 6.1). Patients with disability were more often female than those without ( $P < 0.001$ ), and demonstrated higher disease activity, reflected by a higher median SDAI score (8.1 vs 4.2,  $P < 0.001$ ) and a lower remission rate (24% vs 45%,  $P = 0.001$ , Table 6.2). Patients with moderate-to-severe disability were older and exhibited markedly higher disease activity, with elevated SDAI scores (9.5 vs 5.0;

$P < 0.001$ ) and a substantially lower remission rate (13% vs 41%;  $P = 0.001$ ). Ever use of prednisolone ( $P = 0.030$ ) and b/tsDMARDs ( $P = 0.040$ ) was higher among patients with disability than those without, while prednisolone use was also more common in patients with moderate-to-severe disability than those with mild or no disability ( $P = 0.011$ ).

Table 6.1 Prevalence of disability grades stratified by HAQ-DI scores (n=232)

	N	%
No or minimal disability: HAQ $\geq 0$ to $< 0.5$	127	55
Presence of disability	105	45
Mild disability: HAQ $\geq 0.5$ to $< 1$	60	26
Moderate to severe disability: HAQ $\geq 1$ to $\leq 3$	45	19

Table 6.2 Clinical characteristics between RA patients with and without disability/moderate to severe disability

	Presence of disability			Moderate to severe disability		
	Yes (n=105)	No (n=127)	P-value†	Yes (n=45)	No (n=187)	P-value†
Age (yrs)	63.0 [57.0, 71.0]	63.0 [54.5, 68.0]	0.166	68.0 [60.0, 72.0]	62.0 [55.0, 68.8]	0.007
Sex (female), n (%)	94 (90)	91 (72)	<0.001	39 (87)	146 (78)	0.198
Cohort (ERA), n (%)	51 (49)	49 (39)	0.1264	16 (36)	84 (45)	0.255
Disease duration (yrs)	9.5 [7.4, 16.4]	10.1 [7.8, 14.4]	0.812	9.9 [7.4, 20.7]	9.6 [7.6, 14.5]	0.404
<i>Disease activity parameters</i>						
Patient VAS pain	4.0 [2.0, 5.0]	2.0 [0.8, 4.0]	<0.001	5.0 [3.0, 6.0]	2.0 [1.0, 4.0]	<0.001
Patient's global assessment, NRS 0-10	3.0 [2.0, 5.0]	2.0 [0.5, 3.5]	<0.001	5.0 [3.0, 6.0]	2.0 [0.8, 4.0]	<0.001
Physician's global assessment, NRS 0-10	2.0 [1.0, 3.0]	1.0 [0.0, 2.0]	0.003	2.0 [1.0, 3.0]	1.0 [0.0, 2.0]	0.004
Tender joint count (0-28)	1.0 [0.0, 3.0]	0.0 [0.0, 2.0]	<0.001	2.0 [0.0, 3.0]	0.0 [0.0, 2.0]	0.002
Swollen joint count (0-28)	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.102	0.0 [0.0, 2.0]	0.0 [0.0, 1.0]	0.080
Damage joint count (0-28)	1.0 [0.0, 3.0]	0.0 [0.0, 1.0]	0.003	1.0 [0.0, 4.0]	0.0 [0.0, 1.0]	0.002
ESR (mm/h)	30 [17, 48]	25 [17, 40]	0.349	31 [16, 54]	25 [18, 40]	0.534
CRP (mg/L)	2.1 [0.7, 3.9]	1.6 [0.7, 3.9]	0.376	1.9 [0.7, 5.2]	1.8 [0.7, 3.7]	0.473
SDAI score	8.1 [4.1, 13.2]	4.2 [1.1, 8.4]	<0.001	9.5 [5.6, 15.5]	5.0 [1.4, 9.2]	<0.001
SDAI category			<0.001			0.001
Remission	25 (24)	57 (45)	0.001¶	6 (13)	76 (41)	0.001¶
LDA	47 (45)	54 (43)		22 (49)	79 (42)	
MDA	30 (29)	15 (12)	0.002¶	15 (33)	30 (16)	0.015¶

	Presence of disability			Moderate to severe disability		
	Yes (n=105)	No (n=127)	P-value†	Yes (n=45)	No (n=187)	P-value†
HDA	3 (3)	1 (1)		2 (4)	2 (1)	
HAQ-DI (0-3) **	0.8 [0.5, 1.2]	0.1 [0.0, 0.2]	<0.001	1.2 [1.1, 1.5]	0.2 [0.0, 0.5]	<0.001
<i>Current treatment, n (%)</i>						
Prednisolone	11 (11)	4 (3)	0.024	6 (13)	9 (5)	0.083
NSAIDs	52 (50)	52 (41)	0.191	24 (53)	80 (43)	0.201
csDMARDs	92 (88)	106 (84)	0.373	41 (91)	157 (84)	0.223
b/tsDMARDs	20 (19)	16 (13)	0.177	8 (18)	28 (15)	0.641
<i>Ever treatment, n (%)</i>						
Prednisolone ever use during study period	58 (55)	52 (41)	0.030	29 (64)	81 (43)	0.011
csDMARDs ever use during study period	105 (100)	127 (100)	-	45 (100)	187 (100)	-
b/tsDMARDs ever use during study period	32 (31)	24 (19)	0.040	15 (33)	41 (22)	0.108

Data are reported as median [interquartile range] or number (%). †P-values were determined through Mann-Whitney U tests for continuous data and Chi-square or Fisher's exact tests for categorical measures. **Bold** text denotes statistical significance ( $P < 0.05$ ). ¶ signifies post-hoc analysis employing Bonferroni correction. \*\* Four subjects were absent for HAQ-DI at the last visit, resulting in the total number of patients included being 232 (236-4). The presence of disability was determined by HAQ-DI scores  $\geq 0.5$ . Moderate to severe disability was defined as HAQ-DI  $\geq 1$  to  $\leq 3$ . Disease duration is defined as the duration between diagnosis and HR-pQCT scan at baseline. Disease activity states were established as: Remission with SDAI  $\leq 3.3$ , Low Disease Activity (LDA) with SDAI  $> 3.3$  to  $\leq 11$ , Moderate Disease Activity (MDA) with SDAI  $> 11$  to  $\leq 26$ , and High Disease Activity (HDA) with SDAI  $> 26$ . Abbreviation: ERA: early rheumatoid arthritis. ERA: early rheumatoid arthritis. SDI: sustained SDAI remission. RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide antibody; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: simplified disease activity score; DAS 28-CRP: disease activity score 28- CRP; HAQ-DI: health assessment questionnaire - disability index; NSAIDs: Nonsteroidal Anti-inflammatory Drugs. csDMARDs: conventional synthetic disease-modifying anti-rheumatic drug. b/tsDMARDs: biologic/targeted synthetic disease-modifying anti-rheumatic drug.

### **6.5.2 Erosion patterns in the carpal bones of RA patients**

Among 232 patients, 88% had at least one erosion, most frequently in the lunate (80% prevalence, 56% of total erosions) (Table 6.3). The radius and scaphoid were less commonly affected (42% and 53%, respectively; Figure 6.1 B-D). Erosion count per patient averaged  $4 \pm 3$  (median 3, IQR 1–5), with a corresponding mean total erosion volume of  $26.5 \pm 47.1 \text{ mm}^3$  per patient. The lunate had the highest number of erosions but smaller erosion volumes, while the radius showed fewer erosion counts but larger erosion sizes. Patients with greater disability exhibited significantly larger wrist bone erosion volumes, particularly in the radius, lunate, and total wrist bones (all  $p < 0.05$ ; Supplementary Table 2). Post-hoc analysis confirmed that patients with moderate to severe disability had markedly greater erosion volumes in these regions compared to those with no or minimal disability.

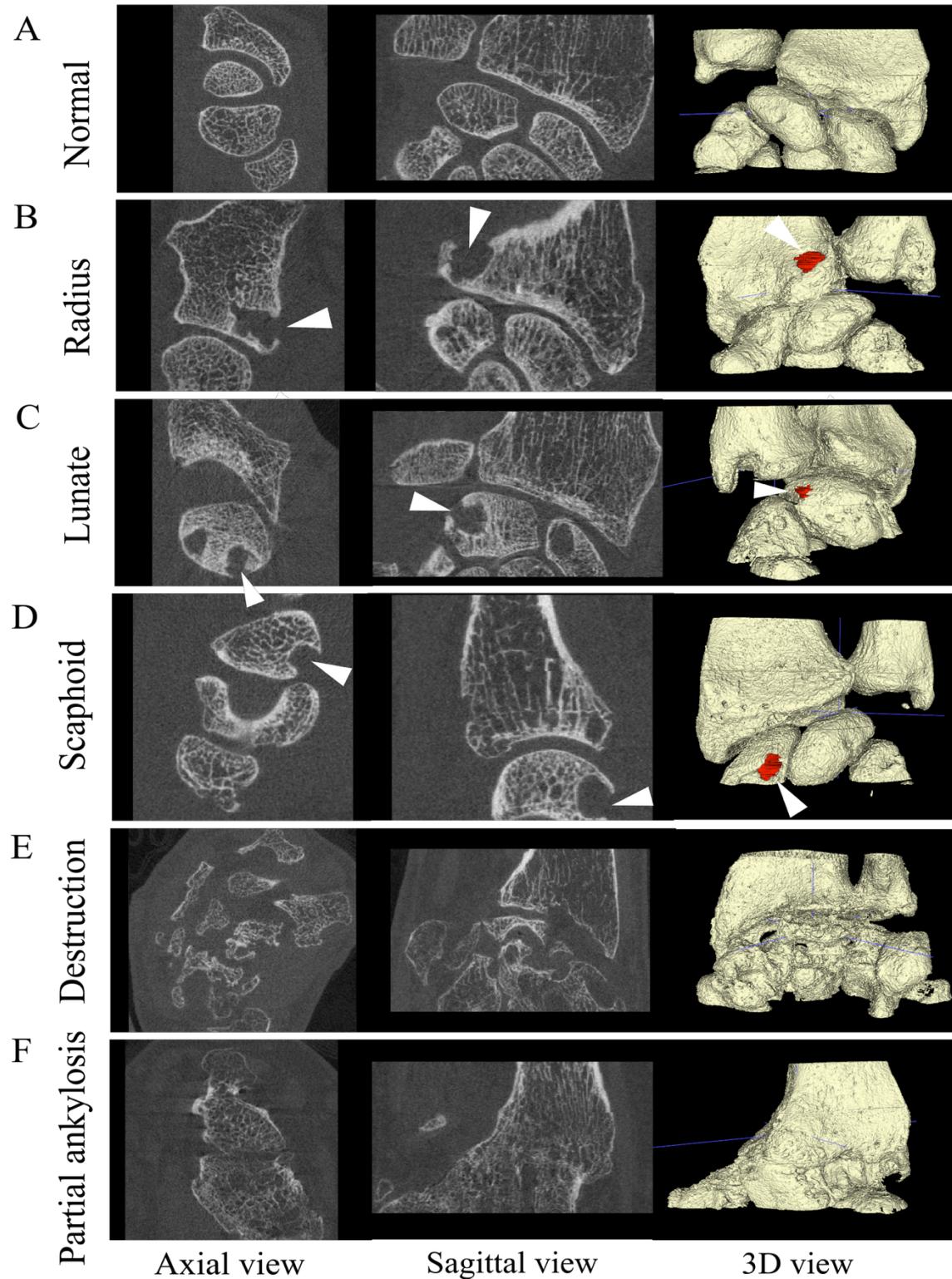


Figure 6.1 Typical images depicting wrist bone erosions and joint destruction

(A) Normal wrist bone; (B) Bone erosions in the radius; (C) Bone erosions in the lunate; (D) Bone erosions in the scaphoid; (E) Wrist joint destruction; (F) Wrist joint partial ankylosis. The erosion size is depicted by the red

segmentation of the bone in the 3D view. White triangles indicate the presence of erosion in axial, sagittal, and 3D views.

Table 6.3 Erosion parameters of wrist bone (n=232)

	Radius	Lunate	Scaphoid	Total
Total numbers of erosions (n)	156	463	209	828
Total numbers of patients presented erosion (n)	98	186	122	203
Presence of erosion (n, %)	98 (42)	186 (80)	122 (53)	203 (88)
Total numbers of erosions per patient (n), Mean±SD	1±1	2±2	1±1	4±3
Total numbers of erosions per patient (n), median [IQR]	0 [0, 1]	2 [1, 3]	1 [0, 1]	3 [1, 5]
Maximum of erosion per patient (n)	6	8	5	13
Total erosion volume per patient (mm <sup>3</sup> ), Mean±SD	12.7±34.7	8.4±14.3	5.5±10.9	26.5±47.1
Total erosion volume per patient (mm <sup>3</sup> ), median [IQR]	0.00 [0.00, 7.4]	3.9 [1.0, 10.1]	0.6 [0.00, 6.6]	7.7 [2.3, 34.4]

### 6.5.3 Erosion parameters of wrist bones between RA patients with and without disability

#### *Overview*

Compared with patients without disability, those with disability had a higher prevalence of radial erosions (50.5% vs 35.4%; P=0.021) and nearly doubled total wrist erosion burden (count: 4 [2–7] vs 2 [1–4]; P<0.001; volume: 12.0 [3.1–41.9] vs 5.4 [2.0–16.1] mm<sup>3</sup>; P=0.003, Table 6.4). Erosion counts and volumes at the lunate were also increased (count: 2 [1–4] vs 1 [1–2]; P<0.001; volume: 5.4 [1.7–15.3] vs 2.9 [0.8–7.3] mm<sup>3</sup>; P=0.003). A similar pattern was observed in moderate-to-severe disability, with higher radial erosion prevalence (55.6% vs 39.0%; P=0.044), greater counts of wrist bone erosions (5 [1–8] vs 3 [1–4]; P=0.011), and larger erosion volumes (16.0 [2.8–43.8] vs 6.7 [2.1–23.1] mm<sup>3</sup>; P=0.032). Compared those with no or minimal disability,

patients with moderate to severe disability had significant larger total erosions volume in wrist bones (15.99 [2.82, 43.79] vs 5.38 [1.96, 16.11] mm<sup>3</sup>, p = 0.026; Table 6.5).

Table 6.4 Erosion parameters of wrist bone between RA patients with and without disability/moderate to severe disability

	Presence of disability			Moderate to severe disability		
	Yes (n=105)	No (n=127)	P-value†	Yes (n=45)	No (n=187)	P-value†
Presence of erosion, n (%)						
In radius	53 (50.5)	45 (35.4)	<b>0.021</b>	25 (55.6%)	73 (39.0%)	<b>0.044</b>
In lunate	88 (83.8)	97 (76.4)	0.161	39 (86.7%)	146 (78.1%)	0.198
In scaphoid	63 (60.0%)	59 (46.5%)	<b>0.040</b>	26 (57.8%)	96 (51.3%)	0.437
In wrist bones	93 (88.6%)	105 (82.7%)	0.206	40 (88.9%)	158 (84.5%)	0.454
Total no. of erosion (n)						
In radius	1.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.077	1.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.091
In lunate	2.0 [1.0, 4.0]	1.0 [1.0, 2.0]	< <b>0.001</b>	3.0 [1.0, 4.0]	2.0 [1.0, 3.0]	<b>0.002</b>
In scaphoid	1.0 [0.0, 2.0]	0.0 [0.0, 1.0]	<b>0.002</b>	1.0 [0.0, 2.0]	1.0 [0.0, 1.0]	0.224
In wrist bones	4.0 [2.0, 7.0]	2.0 [1.0, 4.0]	< <b>0.001</b>	5.0 [1.0, 8.0]	3.0 [1.0, 4.0]	<b>0.011</b>
Total erosion volume (mm <sup>3</sup> )						
In radius	0.7 [0.0, 14.4]	0.0 [0.0, 3.1]	<b>0.015</b>	2.9 [0.0, 14.4]	0.0 [0.0, 4.9]	<b>0.033</b>
In lunate	5.4 [1.7, 15.3]	2.9 [0.8, 7.3]	<b>0.003</b>	7.8 [2.4, 15.8]	3.4 [0.9, 8.1]	<b>0.012</b>
In scaphoid	1.1 [0.0, 9.6]	0.0 [0.0, 4.0]	<b>0.035</b>	0.9 [0.0, 7.5]	0.5 [0.0, 5.3]	0.387
In wrist bones	12.0 [3.1, 41.9]	5.4 [2.0, 16.1]	<b>0.003</b>	16.0 [2.8, 43.8]	6.7 [2.1, 23.1]	<b>0.032</b>

Data are presented as median [interquartile range] or n (%). † P-values from Mann-Whitney U tests for continuous variables and Chi-square or Fisher's exact test for categorical variables. Four patients were excluded due to missing HAQ-DI scores, resulting in 232 patients for analysis. HAQ-DI scores ≥ 0.5 indicated the presence of disability. Moderate to severe disability was defined as HAQ-DI ≥1 to ≤3.

Table 6.5 Comparison of wrist bone erosion volume across RA patients with different degrees of disability

	Group A (n=127)	Group B (n=60)	Group C (n=45)	P-value	Post-hoc analysis (p-value)
<b>Total volume of erosions (mm<sup>3</sup>)</b>					
In radius	7.60 ± 19.11	16.45 ± 35.83	21.82 ± 58.24	<b>0.037*</b>	
	0.00 (0.00, 3.12)	0.00 (0.00, 12.61)	2.90 (0.00, 14.41)	<b>0.032*</b>	Group A vs C: <b>0.037*</b>
In lunate	5.95 ± 8.46	11.20 ± 22.83	11.36 ± 11.89	<b>0.018*</b>	
	2.94 (0.76, 7.32)	4.85 (1.28, 10.95)	7.75 (2.37, 15.76)	<b>0.007**</b>	Group A vs C: <b>0.008**</b>
In scaphoid	4.59 ± 11.03	6.30 ± 9.99	6.93 ± 11.75	0.374	
	0.00 (0.00, 3.96)	1.26 (0.00, 9.74)	0.88 (0.00, 7.54)	0.104	
In wrist bones	18.14 ± 31.11	33.95 ± 58.09	40.12 ± 62.74	<b>0.009**</b>	Group A vs C: <b>0.033*</b>
	5.38 (1.96, 16.11)	9.13 (3.84, 40.66)	15.99 (2.82, 43.79)	<b>0.011*</b>	Group A vs C: <b>0.026*</b>

Data are presented as mean ± standard deviation or median (Q1, Q3). Assessment of differences between groups employed ANOVA or Kruskal-Wallis H testing. \* p < 0.05, \*\* p < 0.01. Group A: No or minimal disability (HAQ ≥ 0 to < 0.5); Group B: Mild disability (HAQ ≥ 0.5 to < 1); Group C: Moderate to severe disability (HAQ ≥ 1 to ≤ 3).

### ***Correlation of wrist bone erosions with functional outcomes in RA patients***

Correlation analyses (Table 6.6) pinpointed lunate and overall wrist-bone erosion burden as the most sensitive imaging correlates of disability in RA. Lunate erosion count and volume showed the strongest associations with HAQ-DI ( $\rho=0.22$  and  $0.19$ ; both  $P\leq 0.004$ ), presence of disability ( $\rho=0.23$  and  $0.19$ ;  $P\leq 0.003$ ), and degree of disability ( $\rho=0.24$  and  $0.21$ ;  $P\leq 0.001$ ). Total wrist erosion metrics had similar correlations across all disability measurements ( $\rho=0.14-0.24$ ;  $P<0.007$ ). The presence and volume of radial erosion demonstrated moderate links to HAQ-DI and disability status ( $\rho=0.13-0.17$ ;  $P\leq 0.044$ ), whereas scaphoid erosions correlated relatively weakly ( $\rho=0.14-0.20$ ;  $P\leq 0.035$ ).

Table 6.6 Correlations of wrist bone erosion parameters with functional outcomes in RA patients (n=232)

	HAQ-DI score		Presence of disability		Degree of disability		Moderate to severe disability	
	$\rho$	P value	$\rho$	P value	$\rho$	P value	$\rho$	P value
<b>Presence of erosions</b>								
In radius	<b>0.14</b>	<b>0.034</b>	<b>0.15</b>	<b>0.021</b>	<b>0.16</b>	<b>0.013</b>	<b>0.13</b>	<b>0.044</b>
In lunate	0.11	0.090	0.09	0.162	0.10	0.129	0.08	0.200
In scaphoid	0.09	0.179	<b>0.14</b>	<b>0.040</b>	0.12	0.064	0.05	0.439
In wrist bones	0.05	0.474	0.08	0.208	0.08	0.220	0.05	0.456
<b>Total number of erosions</b>								
In radius	0.10	0.111	0.12	0.077	0.13	0.051	0.11	0.090
In lunate	<b>0.22</b>	<b>0.001</b>	<b>0.23</b>	<0.001	<b>0.24</b>	<0.001	<b>0.20</b>	<b>0.002</b>
In scaphoid	<b>0.14</b>	<b>0.029</b>	<b>0.20</b>	<b>0.002</b>	<b>0.18</b>	<b>0.005</b>	0.08	0.224
In wrist bones	<b>0.19</b>	<b>0.003</b>	<b>0.23</b>	<0.001	<b>0.24</b>	<0.001	<b>0.17</b>	<b>0.011</b>
<b>Total volume of erosions</b>								
In radius	<b>0.14</b>	<b>0.026</b>	<b>0.16</b>	<b>0.014</b>	<b>0.17</b>	<b>0.009</b>	<b>0.14</b>	<b>0.032</b>
In lunate	<b>0.19</b>	<b>0.004</b>	<b>0.19</b>	<b>0.003</b>	<b>0.21</b>	<b>0.001</b>	<b>0.17</b>	<b>0.011</b>
In scaphoid	0.10	0.136	<b>0.14</b>	<b>0.035</b>	0.13	0.054	0.06	0.387
In wrist bones	<b>0.17</b>	<b>0.007</b>	<b>0.19</b>	<b>0.003</b>	<b>0.20</b>	<b>0.002</b>	<b>0.14</b>	<b>0.032</b>

Presence of disability was defined as HAQ-DI  $\geq 0.5$ . Moderate to severe disability was defined as HAQ-DI  $\geq 1$  to  $\leq 3$ . The degree of disability was graded by HAQ-DI score as follows: No or minimal disability:  $\geq 0$  to  $< 0.5$ ; Mild disability:  $\geq 0.5$  to  $< 1$ ; Moderate to severe disability:  $\geq 1$  to  $\leq 3$ .

Correlation analyses (Figure 6.2) revealed a modest but significant correlation between carpal erosions and multiple functional impairments. Distal radius erosions (whether by presence, count, or volume) were correlated with reduced mobility and arm function ( $\rho = 0.14\text{--}0.20$ ;  $P < 0.05\text{--}0.01$ ).

Lunate erosive burden was associated with reduced grip strength, hand/finger dexterity, and arm function ( $\rho = 0.13\text{--}0.20$ ;  $P < 0.05\text{--}0.01$ ). Combined wrist-bone erosion metrics showed the strongest relationships with hand/finger and arm impairments ( $\rho = 0.14\text{--}0.21$ ;  $P < 0.05$ ). In contrast, scaphoid erosions correlated only with household task difficulty ( $\rho = 0.13$ ;  $P < 0.05$ ).

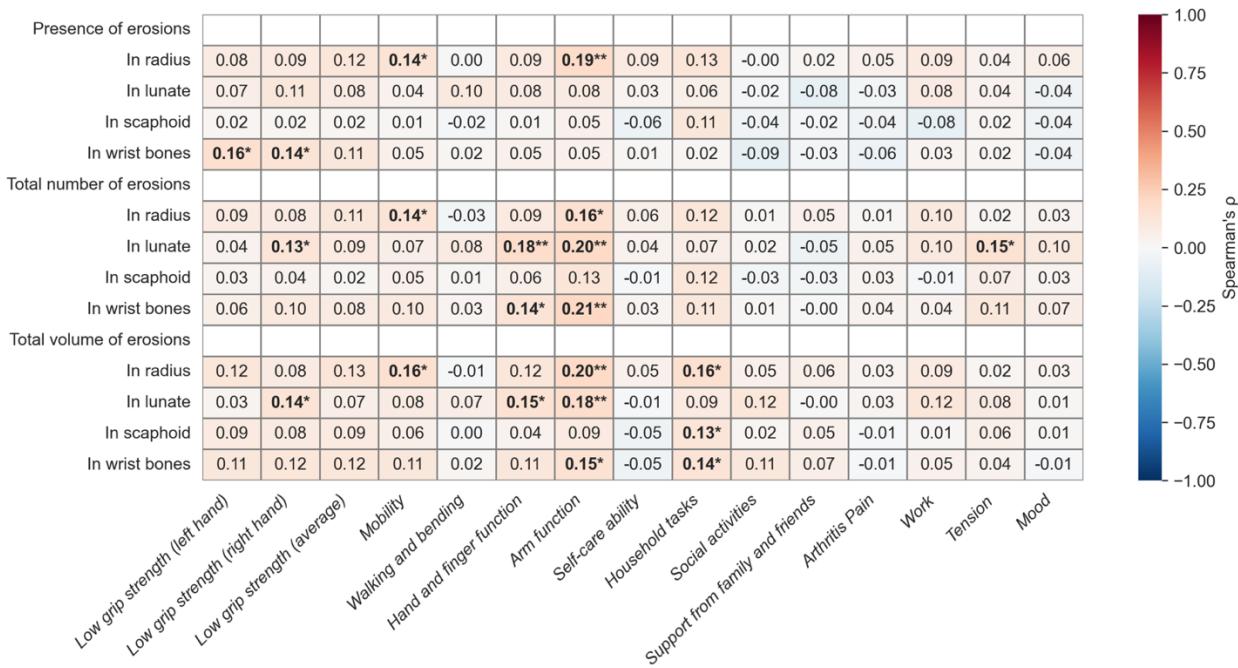


Figure 6.2 Heatmap of correlation matrix of wrist bone erosion parameters and functional outcomes in RA patients. Spearman correlation analysis with significance denoted as: \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ . Functional outcomes included grip strength and CAIMS2. Low grip strength was defined according to the EWGSOP2 criteria, using cut-off values of  $< 27$  kg for men and  $< 16$  kg for women. The best performance of the two attempts in each hand was used to calculate the average grip strength in both hands. The CAIMS2 includes items assessing: mobility, walking

and bending, hand and finger function, arm function, self-care ability, household tasks, social activities, support from family and friends, arthritis pain, work, tension, and mood. CAIMS2: Chinese Arthritis Impact Measurement Scales 2.

### ***Association between wrist bone erosions and functional disability in RA patients***

Univariate logistic regression analysis showed that the presence of erosions in the radius, and total number/volume of erosions in wrist bones were associated with the presence of disability/moderate to severe disability in RA patients (Table 6.7). Multivariable ordinal regression analysis (Table 6.8) demonstrated that erosive burden in wrist bones, as measured by the presence, number, and volume of erosions, determined higher degrees of disability, independent of age, sex, disease duration, disease activity (SDAI remission), and medication use (b/tsDMARDs and prednisolone). The presence of erosions in the radius (adjusted OR 2.16, 95% CI 1.26–3.71, p=0.005), as well as increased erosion numbers in the lunate/scaphoid/total wrist bones (adjusted ORs 1.20–1.41 per additional erosion, p<0.01) and volumes in the radius/lunate/total wrist bones (adjusted ORs 1.01–1.02 per mm<sup>3</sup>, p<0.01), were independently associated with higher degree of disability.

Table 6.7 Univariate logistic regression analysis for factors associated with the presence of disability/moderate to severe disability in RA patients (n=232)

	Presence of disability			Moderate to severe disability		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.02	[0.99, 1.05]	0.119	1.05	[1.01, 1.09]	<b>0.006</b>
Sex (female)	3.38	[1.62, 7.04]	<b>0.001</b>	1.83	[0.72, 4.61]	0.203
Disease duration	1.02	[0.98, 1.05]	0.419	1.05	[1.00, 1.09]	<b>0.045</b>
Cohort (ERA vs EstRA)	1.50	[0.89, 2.54]	0.127	0.68	[0.34, 1.33]	0.256
SDAI remission	0.38	[0.22, 0.68]	<b>0.001</b>	0.22	[0.09, 0.56]	<b>0.001</b>

	Presence of disability			Moderate to severe disability		
	OR	95% CI	P value	OR	95% CI	P value
b/tsDMARDs ever use	1.88	[1.02, 3.46]	<b>0.042</b>	1.78	[0.88, 3.62]	0.111
Prednisolone ever use	1.78	[1.06, 3.00]	<b>0.031</b>	2.37	[1.21, 4.66]	<b>0.012</b>
<b>Presence of erosions</b>						
In the radius	1.86	[1.10, 3.15]	<b>0.022</b>	1.95	[1.01, 3.77]	<b>0.046</b>
In lunate	1.60	[0.83, 3.10]	0.163	1.83	[0.72, 4.61]	0.203
In scaphoid	1.73	[1.02, 2.92]	<b>0.040</b>	1.30	[0.67, 2.50]	0.438
In wrist bones	1.62	[0.76, 3.46]	0.209	1.47	[0.53, 4.03]	0.456
<b>Total number of erosions</b>						
In radius	1.18	[0.91, 1.53]	0.219	1.16	[0.86, 1.57]	0.343
In lunate	1.36	[1.14, 1.61]	<b>&lt;0.001</b>	1.42	[1.17, 1.73]	<b>&lt;0.001</b>
In scaphoid	1.56	[1.21, 2.02]	<b>0.001</b>	1.27	[0.97, 1.68]	0.086
In wrist bones	1.20	[1.09, 1.32]	<b>&lt;0.001</b>	1.18	[1.06, 1.31]	<b>0.003</b>
<b>Total volume of erosions</b>						
In radius	1.01	[1.00, 1.02]	<b>0.027</b>	1.01	[1.00, 1.02]	0.074
In lunate	1.04	[1.01, 1.07]	<b>0.005</b>	1.01	[0.99, 1.04]	0.163
In scaphoid	1.02	[0.99, 1.04]	0.181	1.01	[0.99, 1.04]	0.331
In wrist bones	1.01	[1.00, 1.02]	<b>0.007</b>	1.01	[1.00, 1.01]	<b>0.043</b>

Presence of disability was defined as HAQ-DI  $\geq 0.5$ . Moderate to severe disability was defined as HAQ-DI  $\geq 1$  to  $\leq 3$ .

Table 6.8 Ordinal regression analysis for factors associated with a higher degree of disability in RA patients (n=232)

		OR	95% CI	P value		OR	95% CI	P value		OR	95% CI	P value
	Age	1.04	[1.01, 1.07]	0.008								
	Female	4.05	[1.85, 8.87]	<0.001								
	SDAI remission	0.40	[0.22, 0.71]	0.002								
Model 1	Presence of erosions											
	Radius	2.16	[1.26, 3.71]	0.005								
	Age	1.03	[1.01, 1.06]	0.018		1.03	[1.01, 1.06]	0.019		1.04	[1.01, 1.07]	0.013
	Female	3.32	[1.53, 7.22]	0.002		3.55	[1.63, 7.70]	0.001		3.62	[1.66, 7.91]	0.001
Model 2	SDAI remission	0.37	[0.20, 0.66]	<0.001		0.41	[0.23, 0.73]	0.003		0.39	[0.22, 0.70]	0.002
	Number of erosions											
	Lunate	1.41	[1.19, 1.67]	<0.001	Scaphoid	1.38	[1.10, 1.74]	0.006	Wrist bones	1.20	[1.09, 1.31]	<0.001
	Age	1.03	[1.01, 1.06]	0.017		1.04	[1.01, 1.07]	0.006		1.04	[1.01, 1.06]	0.013
	Female	4.35	[1.94, 9.73]	<0.001		3.65	[1.69, 7.89]	0.001		4.38	[1.96, 9.77]	<0.001
Model 3	SDAI remission	0.41	[0.23, 0.73]	0.003		0.38	[0.21, 0.68]	0.001		0.40	[0.22, 0.72]	0.002
	Total erosion volume											
	Radius	1.01	[1.00, 1.02]	0.006	Lunate	1.02	[1.01, 1.04]	0.007	Wrist bones	1.01	[1.00, 1.01]	0.001

The degree of disability was graded by HAQ-DI score as follows: No or minimal disability:  $\geq 0$  to  $<0.5$ ; Mild disability:  $\geq 0.5$  to  $<1$ ; Moderate to severe disability:  $\geq 1$  to  $\leq 3$ . All models were adjusted for the following covariates: age, sex, disease duration, SDAI remission status, and ever use of b/tsDMARDs and prednisolone during the study period.

#### **6.5.4 Subgroup analysis of patients with wrist joint destruction at the last visit**

Among 25 patients who exhibited severe wrist joint destruction (Figure 6.1E) that precluded accurate volumetric erosion assessment, 21 (84%) presented with wrist joint partial ankylosis (Figure 6.1F). All 25 patients were EstRA patients, with longer disease duration ( $P < 0.001$ ), greater burden of disease activity ( $P = 0.007$ ), and more frequent use of prednisolone ( $P = 0.036$ ) but no use of b/csDMARDs ( $P = 0.032$ ) compared to those without joint destruction (Table 6.9). Those patients also had higher HAQ-DI (median 1.0 vs 0.4,  $P < 0.001$ ) and poorer outcomes in multiple functional domains, including mobility, hand and finger function, arm function, walking and bending, self-care, and arthritis pain (all  $P < 0.05$ ; Table 6.10). More importantly, patients with wrist joint destruction had a higher prevalence and severity of disability compared to those without (21.7% vs 4.5%,  $p < 0.001$ ; Table 6.11). Multivariable logistic regression analysis showed that wrist joint destruction conferred a threefold higher odds of higher degrees of disability in RA patients (adjusted OR 2.91, 95% CI 1.17 to 7.23,  $p = 0.021$ ), independent of age, sex, disease duration, SDAI remission status, and treatment regimen (Table 6.12).

Table 6.9 Clinical characteristics between RA patients with and without wrist joint destruction

	Baseline			Last visit		
	Wrist joint destruction at last visit		P-value†	Wrist joint destruction at last visit		P-value†
	Yes (n=25)	No (n=239)		Yes (n=25)	No (n=239)	
Age (yrs)	56.0 [48.6, 58.2]	55.0 [48.3, 61.4]	0.784	66.0 [59.0, 68.0]	63.0 [55.5, 70.0]	0.572
Female, n (%)	21 (84)	191 (80)	0.794			
Cohort (ERA vs EstRA), n (%)	0 (0) vs 25 (15.3)		<0.001			
Symptom duration (yrs)	1.0 [0.5, 1.6]	0.6 [0.3, 1.3]	0.207			
Disease duration (yrs)	15.0 [6.7, 19.7]	1.1 [0.1, 6.6]	<0.001	23.2 [16.9, 28.9]	9.7 [7.6, 15.8]	<0.001
Follow-up interval (yrs)				10.9 [9.9, 11.1]	8.1 [5.9, 10.8]	0.003
RF positive, n (%)	14 (56)	146 (61)	0.620			
Anti-CCP positive, n (%) *	20 (87)	187 (81)	0.776			
Disease activity parameters						
Patient VAS pain	4.0 [2.0, 5.5]	5.0 [2.0, 6.5]	0.179	4.0 [2.5, 5.0]	3.0 [1.0, 5.0]	0.079
Patient's global assessment, NRS 0-10	4.0 [2.0, 6.0]	5.0 [3.0, 6.5]	0.275	4.0 [2.0, 5.0]	2.5 [1.0, 5.0]	0.046
Physician's global assessment, NRS 0-10	2.0 [1.0, 3.0]	2.5 [1.0, 5.0]	0.206	2.0 [1.0, 4.0]	1.0 [0.0, 2.5]	0.064
Tender joint count (0-28)	1.0 [0.0, 4.0]	4.0 [1.0, 7.5]	0.028	1.0 [0.0, 2.0]	0.0 [0.0, 2.0]	0.770
Swollen joint count (0-28)	1.0 [0.0, 3.0]	2.0 [0.0, 4.0]	0.463	1.0 [0.0, 3.0]	0.0 [0.0, 1.0]	0.004
Damage joint count (0-28)				4.5 [3.0, 7.0]	0.0 [0.0, 2.0]	<0.001
ESR (mm/h)	33 [19, 53]	32 [19, 54]	0.985	45 [32, 69]	26 [17, 42]	<0.001
CRP (mg/L)	4.5 [1.5, 9.1]	4.0 [1.1, 12.0]	0.850	6.3 [2.3, 19.7]	1.9 [0.7, 4.0]	<0.001
SDAI score	7.4 [5.6, 16.0]	14.3 [6.5, 24.5]	0.091	10.6 [5.5, 16.2]	5.7 [2.1, 10.3]	0.007
SDAI category			0.204			0.146
Remission	3 (12)	30 (13)		7 (28)	84 (35)	
LDA	12 (48)	72 (30)		8 (32)	105 (44)	
MDA	8 (32)	83 (35)		10 (40)	46 (19)	
HDA	2 (8)	54 (23)		0 (0)	4 (2)	
Change in SDAI				-1.2 [-6.3, 5.4]	-8.3 [-18.9, -0.6]	0.006
HAQ-DI (0-3) **	0.6 [0.0, 1.2]	0.5 [0.1, 1.1]	0.667	1.0 [0.8, 1.2]	0.4 [0.0, 0.8]	<0.001
Current treatment, n (%)						
Prednisolone	6 (24)	39 (16)	0.399	5 (20)	16 (7)	0.036
NSAIDs	17 (68)	162 (68)	0.982	13 (52)	108 (45)	0.515
csDMARDs	24 (96)	160 (67)	0.003	21 (84)	205 (86)	0.767
b/tsDMARDs	4 (16)	15 (6)	0.091	0 (0)	36 (15)	0.032
Ever treatment, n (%)						
Prednisolone ever use during study period				11 (44)	113 (47)	0.755
csDMARDs ever use during study period				25 (100)	239 (100)	1.000
b/tsDMARDs ever use during study period				3 (12)	57 (24)	0.179

Data are reported as median [interquartile range] or number (%). † P-values calculated through Mann-Whitney U tests for continuous measures and Chi-square or Fisher's exact tests for categorical measures. Bold values indicate statistical significance ( $P < 0.05$ ). \* Only 253 subjects were available for the anti-CCP status at baseline. \*\* Only 257 subjects were available for the HAQ-DI (3 missing values at baseline and 4 at the last visit. SDI: sustained SDAI remission. Symptom duration represents the interval from symptom initiation until diagnosis. Disease duration is defined as the duration between diagnosis and HR-pQCT scan at baseline. Disease activity states were established as: Remission with SDAI  $\leq 3.3$ , Low Disease Activity (LDA) with SDAI  $> 3.3$  to  $\leq 11$ , Moderate Disease Activity (MDA) with SDAI  $> 11$  to  $\leq 26$ , and High Disease Activity (HDA) with SDAI  $> 26$ . Abbreviation: ERA: early rheumatoid arthritis (RA); EstRA: established RA. RF: Rheumatoid factor; Anti-CCP: Anti-cyclic citrullinated peptide antibody; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: simplified disease activity score; DAS 28-CRP: disease activity score 28- CRP; HAQ-DI: health assessment questionnaire - disability index; NSAIDs: Nonsteroidal Anti-inflammatory Drugs. csDMARDs: conventional synthetic disease-modifying anti-rheumatic drug. biologic/targeted synthetic disease-modifying anti-rheumatic drug.

Table 6.10 Comparison of functional outcomes of RA patients with or without wrist joint destruction

	Wrist joint destruction		P-value
	Yes (n = 25)	No (n = 239)	
HAQ-DI			
HAQ-DI (0-3) at baseline	0.6 [0.0, 1.2]	0.5 [0.1, 1.1]	0.667
HAQ-DI (0-3) at last visit	1.0 [0.8, 1.2]	0.4 [0.0, 0.8]	<b>&lt;0.001</b>
Change in HAQ-DI (0-3)	0.3 [-0.4, 1.0]	-0.1 [-0.8, 0.2]	<b>0.004</b>
Grip strength			
Average grip strength in both hands †	16.9 [13.4, 18.6]	17.1 [14.0, 21.9]	0.310
Average grip strength in both hands (male)	22.0 [18.0, 23.9]	26.5 [20.0, 33.8]	0.156
Average grip strength in both hands (female)	15.4 [13.5, 18.3]	16.1 [13.4, 19.5]	0.562
CAIMS2			
Mobility	2.5 [0.5, 5.5]	1.0 [0.0, 2.5]	<b>0.018</b>
Walking and bending	4.0 [2.0, 5.0]	2.0 [1.0, 3.9]	<b>0.008</b>
Hand and finger function	2.9 [0.8, 4.6]	1.3 [0.4, 2.5]	<b>0.004</b>
Arm function	3.0 [1.5, 4.0]	1.0 [0.0, 2.5]	<b>&lt;0.001</b>
Self-care ability	0.0 [0.0, 1.0]	0.0 [0.0, 0.0]	<b>0.011</b>
Household tasks	2.0 [0.0, 7.0]	1.0 [0.0, 3.0]	0.062
Social activities	7.0 [6.0, 7.5]	6.5 [5.5, 7.9]	0.839
Support from family and friends	3.0 [3.0, 5.0]	4.0 [3.0, 6.0]	0.571
Arthritis Pain	4.5 [3.0, 5.5]	3.0 [2.0, 4.9]	<b>0.012</b>
Work	1.0 [0.0, 3.2]	1.0 [0.0, 3.0]	0.899
Tension	3.5 [2.5, 5.0]	3.0 [1.5, 5.0]	0.557
Mood	3.0 [1.5, 4.0]	2.5 [1.0, 3.5]	0.187

Data are presented as median [interquartile range]. Between-group P-values were obtained utilizing Mann-Whitney U tests. Bold values indicate statistical significance (P < 0.05). † The best performance of the two attempts of grip strength in each hand was used to calculate the average grip strength in both hands. HAQ, Health Assessment Questionnaire. CAIMS2, Chinese Arthritis Impact Measurement Scales 2.

Table 6.11 Difference in functional outcomes in RA patients with or without wrist joint destruction

	Presence of disability		P-value
	Yes	No	
Wrist Joint Destruction	19 (15.0)	6 (4.5)	0.004
	Moderate to severe disability		
	Yes	No	
Wrist Joint Destruction	13 (21.7)	12 (6.0)	<0.001
	No/ minimal disability	Mild disability	Moderate to severe disability
Wrist Joint Destruction	6 (4.5)	6 (9.0)	13 (21.7)
			<0.001

Data was presented as (n, %). The presence of disability was determined by HAQ-DI scores  $\geq 0.5$ . The degree of disability was graded by HAQ-DI score as follows: No or minimal disability:  $\geq 0$  to  $< 0.5$ ; Mild disability:  $\geq 0.5$  to  $< 1$ ; Moderate to severe disability:  $\geq 1$  to  $\leq 3$ .

Table 6.12 Ordinal regression analysis for factors associated with higher degree of disability in RA patients (n=260)

	Adjusted OR	95% CI	P value
Age	1.37	[1.05, 1.79]	0.022
Sex (Female)	3.08	[1.52, 6.24]	0.002
Disease duration	1.34	[1.01, 1.77]	0.046
SDAI remission	0.37	[0.22, 0.64]	<0.001
Prednisolone ever use	1.80	[1.07, 3.02]	0.027
Wrist joint destruction	2.91	[1.17, 7.23]	0.021

The number of patients enrolled was 264, and 4 patients were unavailable for HAQ-DI data, leaving 260 included for the analysis above. The degree of disability was graded by HAQ-DI score as follows: No or minimal disability:  $\geq 0$  to  $< 0.5$ ; Mild disability:  $\geq 0.5$  to  $< 1$ ; Moderate to severe disability:  $\geq 1$  to  $\leq 3$ . Adjusted for the following covariates: age, sex, disease duration, SDAI remission status, and ever use of b/tsDMARDs and prednisolone during the study period.

## 6.6 Discussion

To our knowledge, this study is the first to leverage detailed volumetric and count-based erosion metrics at specific carpal sites to examine their association with functional disability in RA patients. This study demonstrated that the presence of radial erosions and greater erosion counts and volume in the wrist bones quantified by HR-pQCT were independently associated with functional disability. Wrist joint destruction was also a strong independent indicator for functional disability.

Carpal erosive burden may capture dimensions of wrist bone structural damage that lead to functional disability in RA, which was not fully explained by conventional clinical metrics.

Our findings extend prior observations that high disease activity results in subsequent progression of radiographic joint damage[[223](#)], which consequently drives functional disability in RA[[135](#)].

The present study demonstrated that carpal erosion assessed by high-resolution imaging was independently associated with functional disability, independent of age, sex, disease duration, disease activity burden, and treatment regimen, thereby corroborating and refining the established link between radiographic joint damage and functional capacity in RA. Early studies have shown that overall radiographic joint damage was associated with worsening HAQ scores over time in long-standing disease of RA[[146](#)], and subsequent observation from randomized controlled trials confirmed that the level of radiographic damage and the rate of radiographic progression were correlated with a higher degree of disability[[135](#)]. However, conventional radiography remains relatively insensitive to early erosive changes. High-resolution techniques like MRI can detect new wrist bone erosions a median of two years before they become apparent on X-ray[[224](#), [225](#)], and wrist MRI-detected erosions are associated with functional outcomes at 6 years in early RA[[226](#)]. Short-term HR-pQCT-detected structural damage in wrist bone has also been associated with functional declines in RA[[218](#)]. These findings underscore the clinical relevance of microstructure assessment for monitoring structural damage to wrist bones and their linkage to disability. Importantly, our study extends this paradigm by demonstrating that erosive changes in wrist bones exhibit distinct associations with functional disability in RA, independent of disease activity and duration.

The preferential association of erosions in the lunate and radius with functional outcomes likely reflects the biomechanical importance of these bones in wrist stability and load transmission. Given the central biomechanical roles of the lunate as the fulcrum for wrist flexion and extension, and the distal radius as the principal load-bearing surface of the radiocarpal joint[[227-231](#)], erosive damage at these sites may disproportionately disrupt wrist mechanics[[217](#)]. Microstructural deterioration around the lunate and distal radius interferes with the intricate kinematics of the radiocarpal and midcarpal joints[[217](#), [229](#), [230](#)], thereby amplifying deficits in physical function such as dexterity and grip strength. Future biomechanical investigations should seek to elucidate the pathways linking localized bone loss to global wrist dysfunction.

Clinically, quantifying erosion number offers clear advantages over volumetric measures, as it is simpler, faster, and more readily integrated into routine imaging workflows, enhancing translational feasibility. In contrast, although volumetric assessment offers valuable insights, it demands time-intensive segmentation and specialized software; nonetheless, our findings demonstrate its significant association with functional disability. Incorporation of HR-pQCT-derived carpal erosion metrics into risk-stratification algorithms may allow earlier identification of RA patients at high risk for irreversible functional impairment, even when disease activity indices indicate quiescent inflammation[[214](#), [232](#)]. This finding reinforces the notion that joint damage and inflammation can have partially dissociated trajectories in RA, particularly in the context of contemporary treatment strategies that may achieve clinical remission without fully preventing structural progression[[214](#), [232](#)]. Such precision imaging biomarkers may guide timely escalation to b/tsDMARDs to preserve joint integrity and function in RA patients, and may potentially serve as sensitive imaging endpoints in trials of interventions aimed at structural preservation and repair.

## **6.7 Limitations**

Nevertheless, certain limitations merit consideration. First, the cross-sectional nature of the analysis precludes definitive causal inferences. Despite multivariable adjustment, residual confounding by unmeasured factors cannot be excluded. Second, carpal erosion parameters were assessed only at the last study visit, as no baseline HR-pQCT measurements were available. We therefore could not characterise the trajectory of wrist bone structural change over time, and longitudinal HR-pQCT data are required to validate and refine the temporal relationship between erosion progression and functional outcomes. Third, patients with severe wrist joint destruction that precluded volumetric HR-pQCT analysis were excluded, potentially underestimating the association between extreme structural damage and functional impairment. Fourth, although HR-pQCT provides high-resolution quantification of bone erosions, it remains primarily a research modality with limited availability in routine clinical practice. Its cost-effectiveness and logistical feasibility across diverse clinical settings warrant further evaluation. Finally, while the sample size was substantial and included both early and established RA cohorts, external validation in independent populations is necessary to confirm the generalisability and robustness of the observed associations.

## **6.8 Conclusions**

HR-pQCT detected radial erosions and greater erosion counts and volumes in the wrist bones are independently associated with functional disability in RA patients. These imaging markers may enhance risk stratification and inform personalized treatment strategies to preserve physical function for RA patients. Longitudinal studies are essential to validate their impact on long-term functional outcomes.

## **Chapter 7: Summary & Discussion**

### **7.1 Main findings**

The aims of the whole study were achieved, and the hypotheses proposed were answered.

#### ***Cross-sectional study***

In chapter 4, the comparative study demonstrated that small erosions ( $<1 \text{ mm}^3$ ) were comparable in prevalence and size in both RA patients and HCs, suggesting these small erosions may potentially represent physiological phenomena rather than disease-specific pathology. In contrast, large erosions ( $>5 \text{ mm}^3$ ) occurred with significantly higher frequency and magnitude in RA patients, suggesting their specificity as pathological markers of bone structural damage. These findings validate our initial hypothesis regarding the physiological nature of small erosions.

#### ***Longitudinal study***

In chapter 5, the longitudinal investigation spanning a median of 8.4 years revealed that bone erosions had distinct evolutionary trajectories based on baseline erosion size. Small erosions predominantly maintained stability, reinforcing their likely physiological nature, while large erosions exhibited significant regression under contemporary treatment management. ERA patients managed with T2T strategies demonstrated better structural outcomes, including enhanced large erosion regression and prevention of new large erosion formation, compared to EstRA patients receiving usual care. These observations substantiate the concept of a structural "window of opportunity" in RA management, wherein early intervention yields favorable long-term structural preservation.

### ***Functional correlation study***

In chapter 6, the functional correlation analysis showed that HR-pQCT-detected radial erosions and greater erosive burden in wrist bones independently associate with functional disability in RA patients. This relationship between volumetric erosive quantification and functional capacity confirms our hypothesis regarding structure-function correlations in RA. These findings highlight the value of wrist HR-pQCT on erosive burden assessment, offering potential for enhanced risk stratification and personalized intervention strategies to preserve physical function in RA patients.

### **7.2 Study limitations**

Study 1 was subject to several methodological limitations. The anatomical scope was limited to the MCH2, potentially underestimating the broader erosive pattern across the hand. The volumetric thresholds used for erosion categorization, while consistent with literature, remain somewhat arbitrary and could influence prevalence patterns if alternate cutoffs were employed. Despite rigorous adherence to SPECTRA definitions, the technical challenge of differentiating small erosions from unusual physiological cortical interruptions introduces a potential classification bias that may affect the interpretation of findings regarding small erosions.

Study 2 had limitations related to treatment timing and imaging parameters. The non-randomized timing of DMARD initiation introduced potential selection bias, particularly in the EstRA cohort where treatment decisions were not protocol-driven. The variable interval between treatment initiation and baseline HR-pQCT assessment in the EstRA group may have influenced the healing potential of large erosions. The restricted anatomical focus (MCH2 only) and absence of intermediate imaging between baseline and final assessment limited a comprehensive understanding of erosion dynamics across multiple joints over time. The observational design,

despite showing evidence for a structural "window of opportunity," constrains definitive causal interpretations.

Study 3 was primarily limited by its cross-sectional design, preventing the determination of temporal relationships between erosive burden and functional outcomes despite multivariable adjustment. The absence of baseline wrist HR-pQCT measurements precluded analysis of structural change trajectories over time. Selection bias may have been introduced by excluding patients with severe wrist joint destruction, potentially underestimating the association between extreme damage and functional impairment. While providing high-resolution quantification, the limited clinical availability of HR-pQCT raises questions about translational applicability. External validation in diverse populations remains necessary to confirm the generalizability of observed structure-function associations.

### **7.3 Future therapeutic perspectives**

The findings from this comprehensive investigation into bone erosion trajectories in RA offer several promising directions for future therapeutic approaches. The differentiation between physiological small erosions and pathological large erosions is not merely academic. It could fundamentally change how we approach treatment. Rather than targeting all erosions with equal vigor, clinicians might soon focus their therapeutic efforts primarily on preventing and healing larger erosions ( $>5 \text{ mm}^3$ ), which our data suggest represent genuine pathological processes. The smaller lesions, often indistinguishable from those in healthy individuals and tend to be stable over time, might not warrant aggressive intervention. This enhanced therapeutic targeting offers practical benefits. Patients might be spared unnecessary medication intensification when small erosions are detected on high-resolution imaging. In clinical practice, this could translate to more

judicious use of potent immunosuppressants, potentially reducing both treatment costs and adverse events without compromising structural outcomes.

Our longitudinal findings strongly support the implementation of early aggressive intervention using T2T strategies as standard of care. Better structural outcomes in ERA patients receiving T2T management validate the "window of opportunity" concept, suggesting universal adoption of treatment protocols with systematic disease activity monitoring and predefined adjustments in early disease. Future therapies may involve earlier intervention, possibly at the pre-clinical or arthralgia stage, to maximize prevention of pathological erosion. Integrating HR-pQCT metrics with serological and clinical parameters in predictive models could improve risk stratification and allow preemptive therapy in high-risk individuals before significant structural damage.

The demonstrated association between wrist bone erosive burden and functional impairment extends beyond volumetric measurements to include erosion counts. This represents a significant advantage in translational potential, as erosion counting demands considerably less technical expertise and computational resources than volumetric analysis, facilitating broader clinical implementation. Integration of wrist erosion assessment into routine radiological evaluation could enable risk stratification for functional deterioration, allowing clinicians to identify high-risk patients requiring more aggressive intervention before irreversible disability develops. Integrating erosion analyses with JAK inhibitors and IL-6 antagonists may reveal different effects on healing, guiding personalized treatment for optimal functional preservation in RA patients. Future longitudinal studies combining established and novel therapies with standardized functional assessments are essential to validate these associations and determine if erosion-targeted approaches lead to significant improvements in patient outcomes.

Our observations raise fundamental questions about bone biology that extend beyond clinical practice. Why do some erosions heal while others prove intractable to treatment? This differential response likely reflects underlying biological mechanisms we have not yet characterized. Histological examination correlated with HR-pQCT data may illuminate these processes. Future investigations are needed to examine the cellular microenvironment around erosions of varying sizes, examining osteoclast activity, angiogenesis patterns, and synovial-bone interactions. Such studies might reveal whether large erosions have distinct biological features that could become targets for novel therapeutics on bone repair rather than general inflammation suppression.

Looking ahead, artificial intelligence could revolutionize how we analyze erosion data. Machine learning algorithms might detect subtle patterns in volumetric measurements that human observers may miss. These computational approaches could identify early predictors of structural deterioration, potentially years before conventional assessment methods. We envision a future where treatment decisions integrate not just clinical findings and laboratory values, but sophisticated structural characterization from advanced imaging. This represents a paradigm shift toward truly personalized medicine. Healthcare systems globally prioritize value-based care due to the high costs of biologic therapies. Rigorous studies on targeted erosion management are essential to confirm its effectiveness in preventing functional decline and reducing long-term healthcare costs for widespread adoption.

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## Chapter 9: Appendix





## IMPROVING POSTGRADUATE LEARNING

### Certificate of Attendance 2023-2024

This Certificate is awarded to

**YAN Xianfeng  
1155185977**

Division of Medical Sciences  
*MED / MESC / PHD*

**Who has attended the following course(s):**

Advanced Data Analysis for Quantitative Research by SPSS

Managing and Creating Reference Citations with EndNote

LaTeX Basics - Professional Document Preparation

LaTeX Advanced - Thesis Preparation

Introduction to Research & Thesis Writing For Engineering, Medicine & Science

Communication Skills Workshop

Features of Spoken English II: Improving Pronunciation and Oral Delivery Skills

Total No. of Course(s) Taken: 7

30 June 2024

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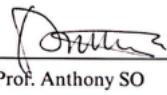
# Research Poster Exhibition 2024

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*For participating in the Poster Presentation Session held on 21 May 2024.*



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