香港中文大學
The Chinese University of Hong Kong

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

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

PhD candidate: Xianfeng Yan
Supervisor: Prof. Lai-shan Tam
Co-supervisor: Prof. Ho So
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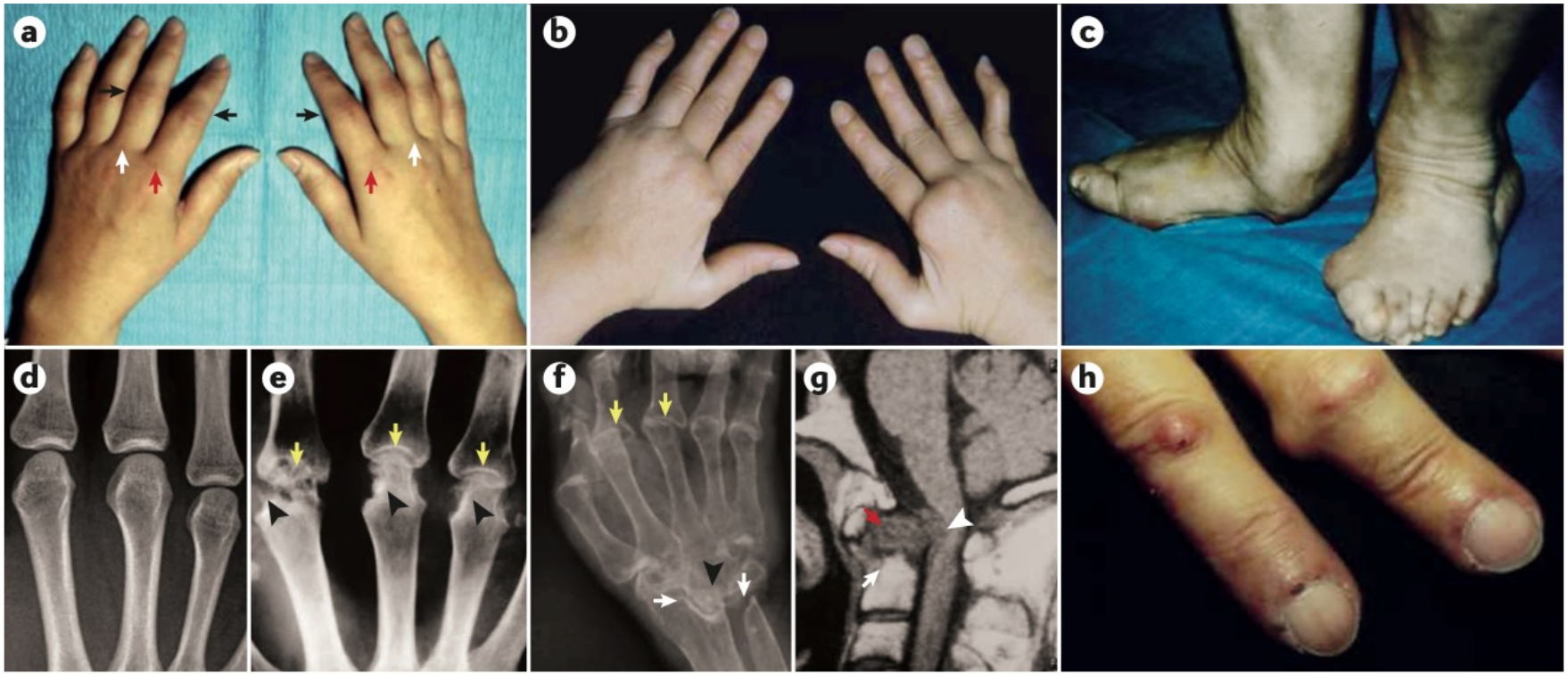
CONTENTS

Background » Rheumatoid arthritis (RA)



- ❑ Chronic, autoimmune, inflammatory arthritis. Heterogeneous clinical course.
- ❑ Characterized by synovitis, joint destruction, and functional disability.

Ref.: Smolen JS, et al. Nat Rev Dis Primers. 2018:doi:10.1038/nrdp.2018.1.

Background » Bone erosion in RA

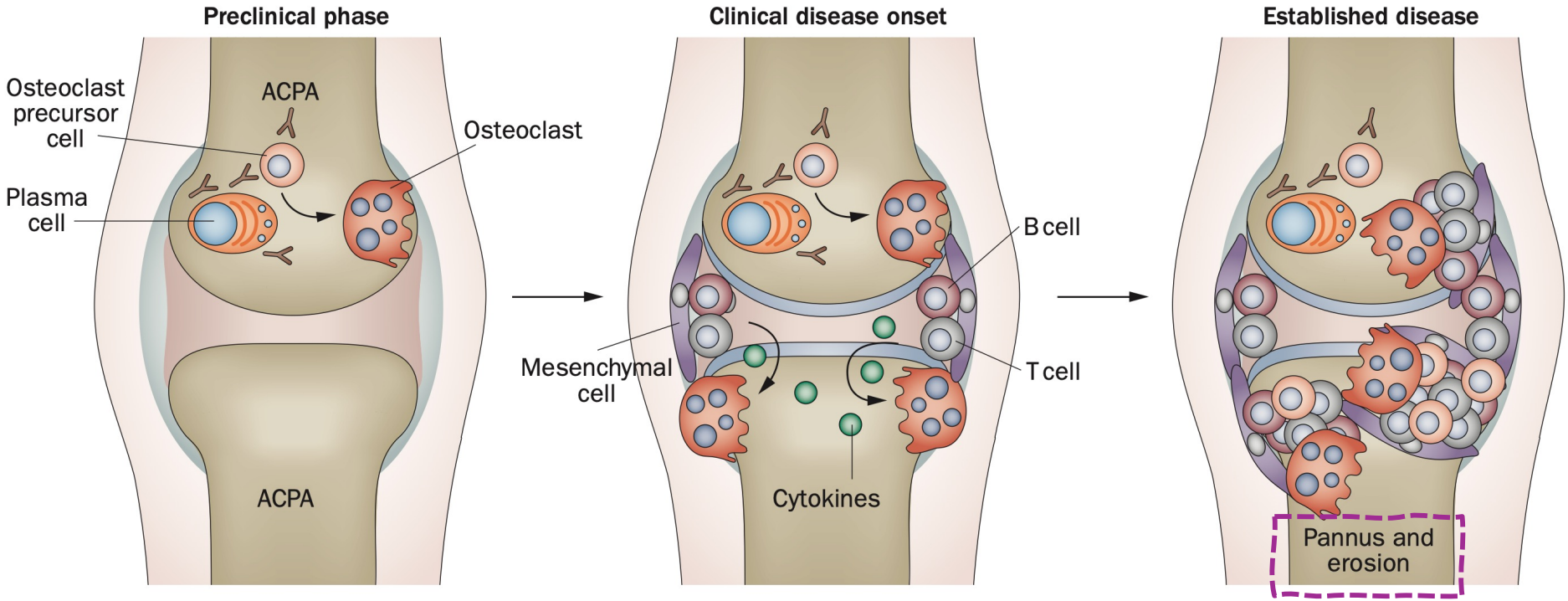
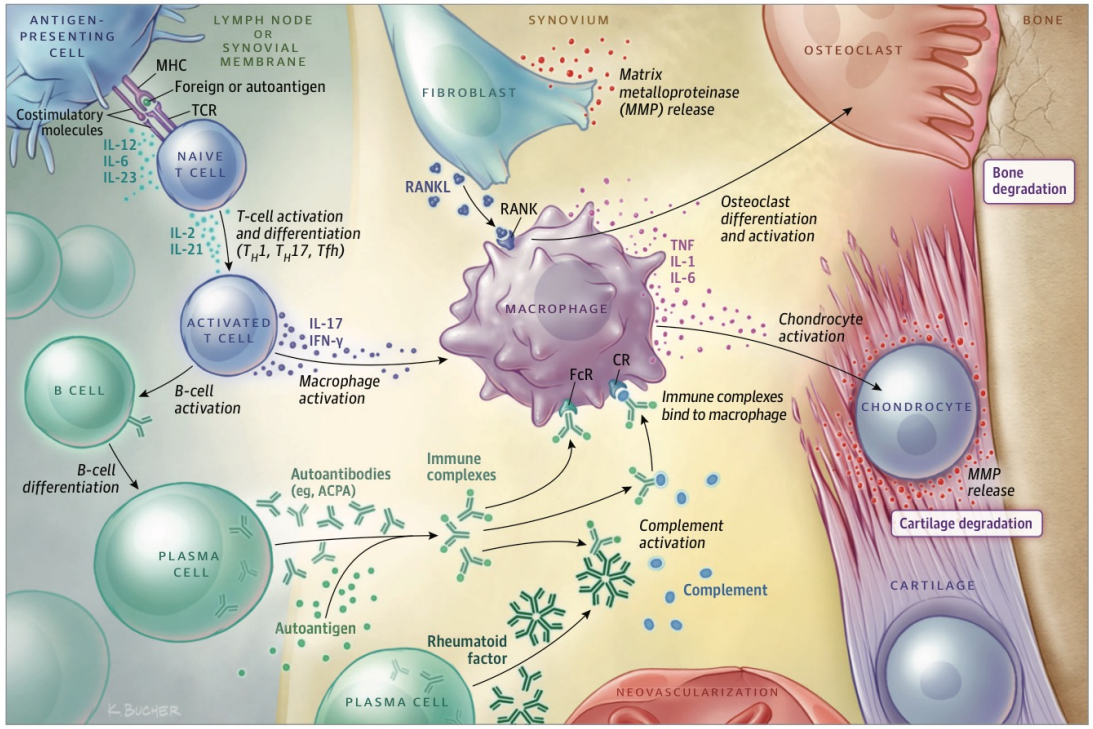


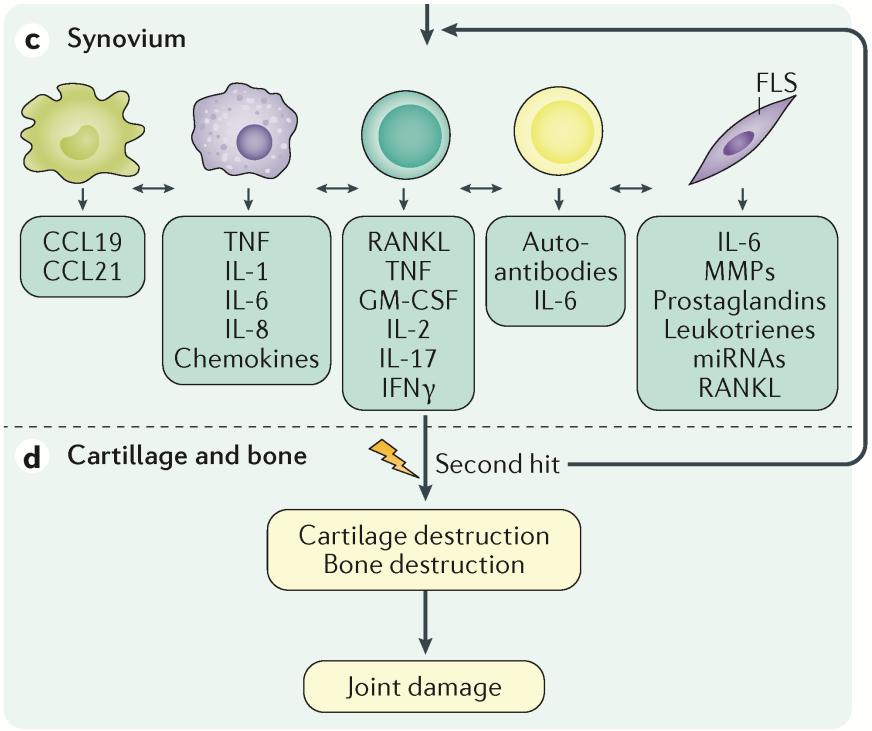
Figure - Evolution of bone erosion in the course of RA

❑ Bone erosion: A hallmark of the development of RA, represents localized bone loss at the margins of affected joints

Ref.: Schett, G. & Gravallese, E. Nat. Rev. Rheumatol. 8, 656-664 (2012).

Background » Pathogenesis of RA

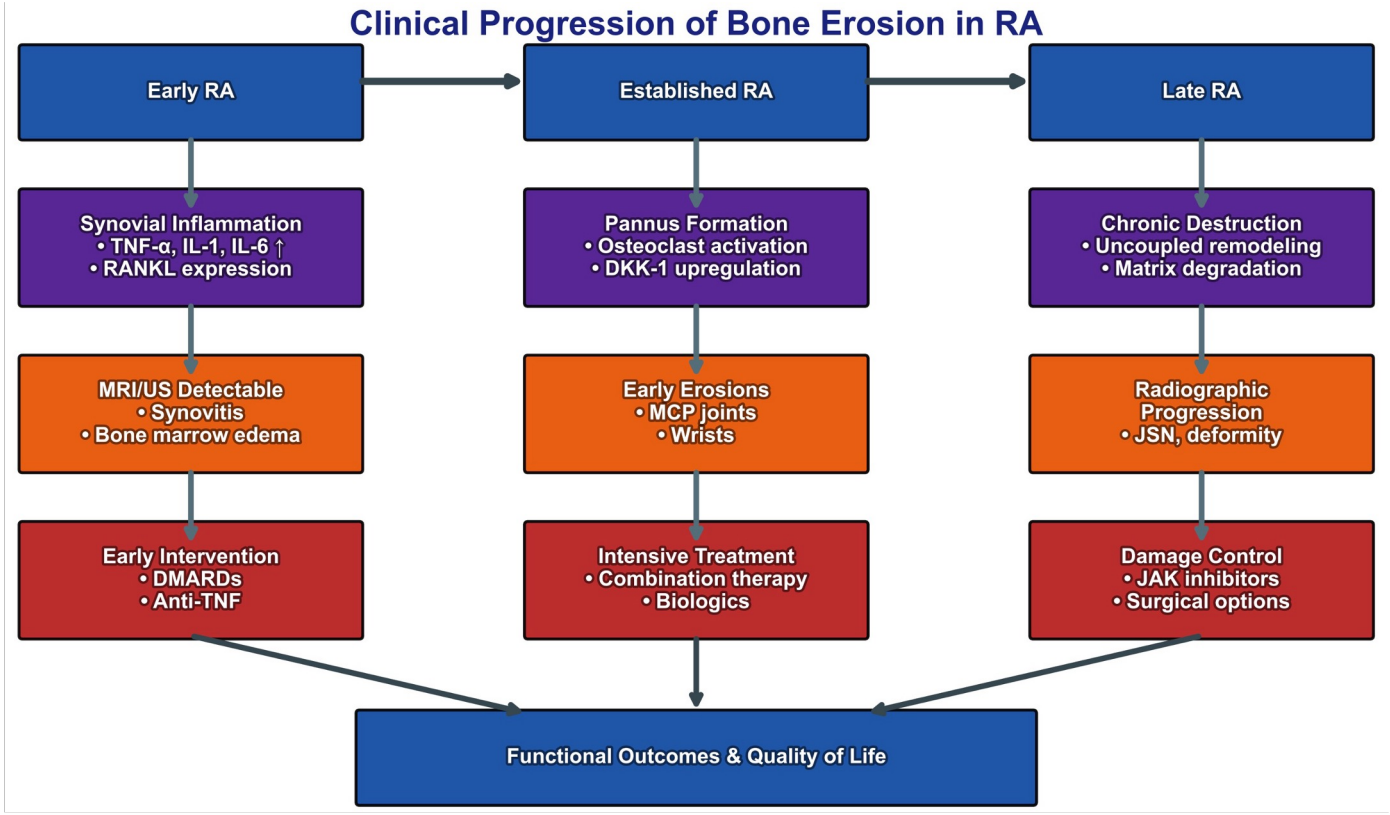




The pathophysiology of bone erosion in RA is primarily driven by aberrant osteoclast activation through the RANK/RANKL/OPG signaling axis

Ref.: Smolen JS, et al. Nat Rev Dis Primers. 2018:doi:10.1038/nrdp.2018.1.

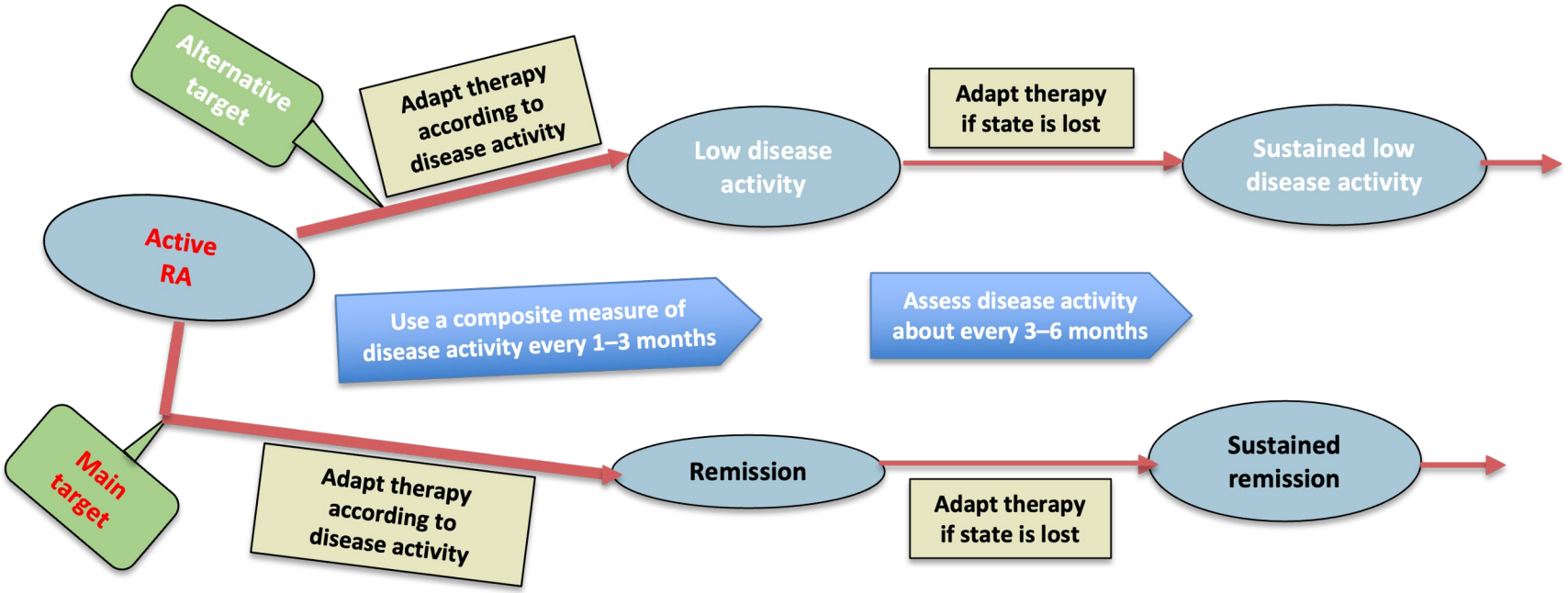
Background » Disease Course in RA



○ Early identification of early RA enables timely intervention, preventing irreversible joint damage and disability

Ref.: Smolen JS, et al. Nat Rev Dis Primers. 2018:doi:10.1038/nrdp.2018.1.

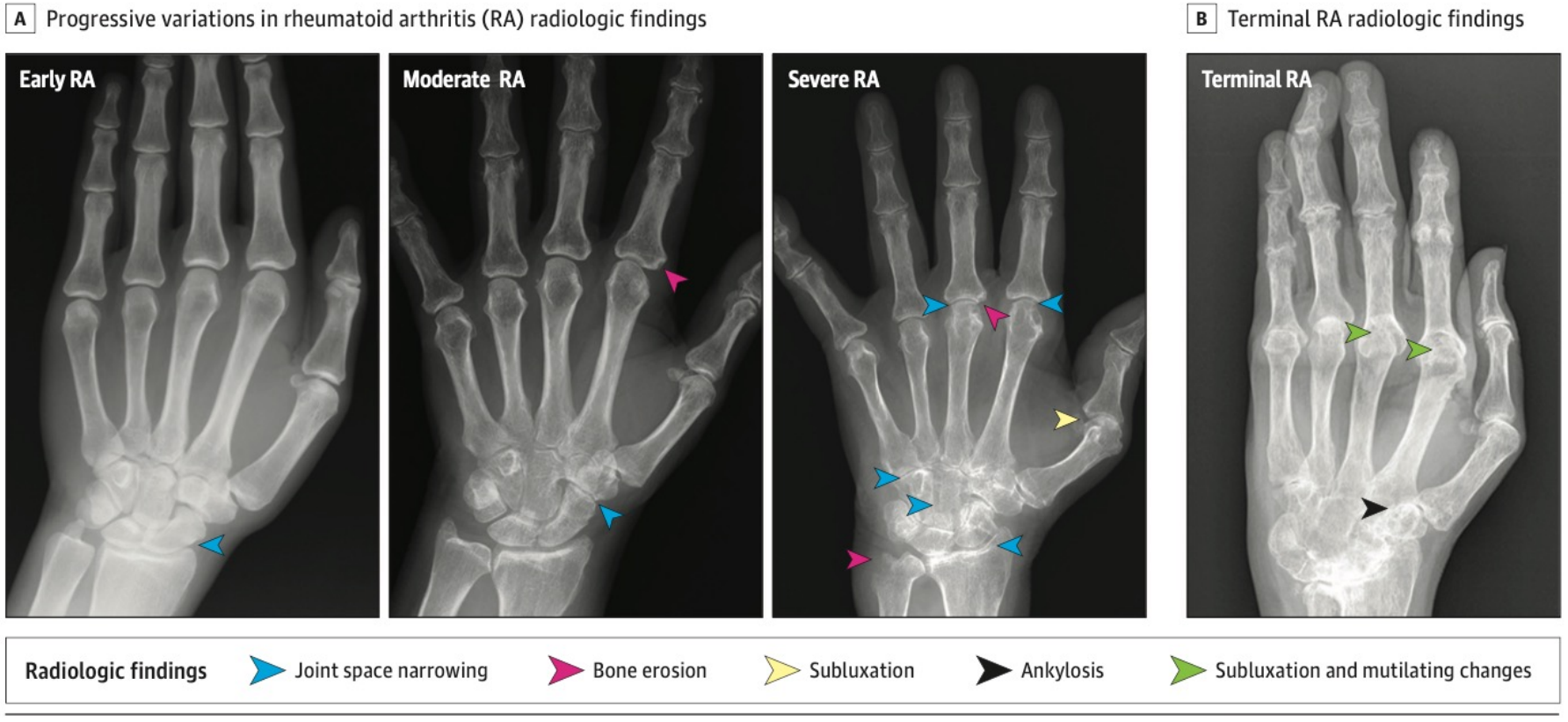
T2T implementation algorithm in RA



Treatment initiated within **12 weeks** of symptom onset achieves superior outcomes compared to delayed intervention

Ref.: 1. Smolen JS, et al. Ann Rheum Dis 2010;69:631-637. doi:10.1136/ard.2009.123919

Background » Radiographic features in RA



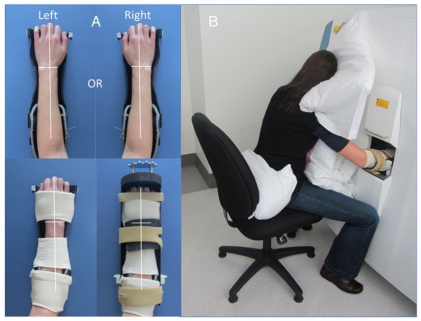
❑ Its two-dimensional protectional format is not sensitive to detecting small-to-medium-sized erosions

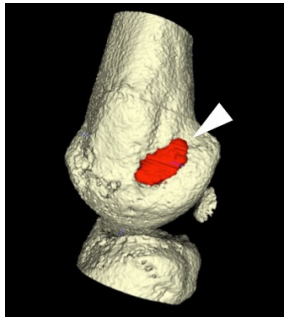
Ref.: Therkildsen J, et al. Rheumatology (Oxford). 2025 Mar 1; 64(3):1092-1101.

Background: Imaging in RA » HR-pQCT

HR-pQCT: <u>High-resolution peripheral quantitative CT</u>

- ✓ High spatial resolution (82 µm voxel)
- ✓ High sensitivity
- ✓ Low radiation exposure
- ✓ 3D visualization and volumetric quantification of erosions

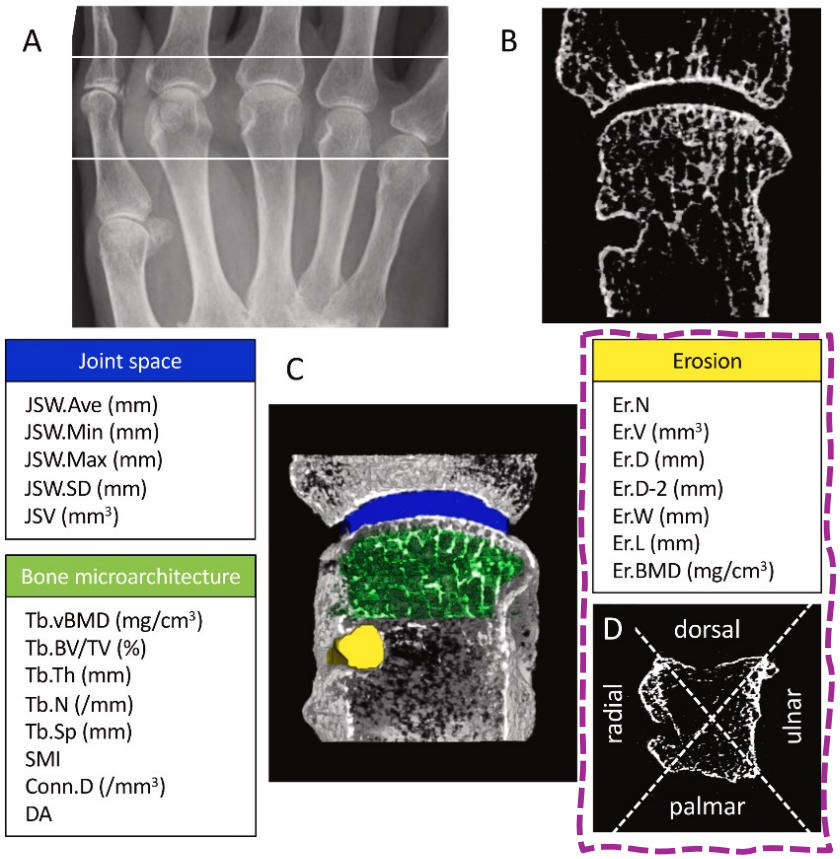


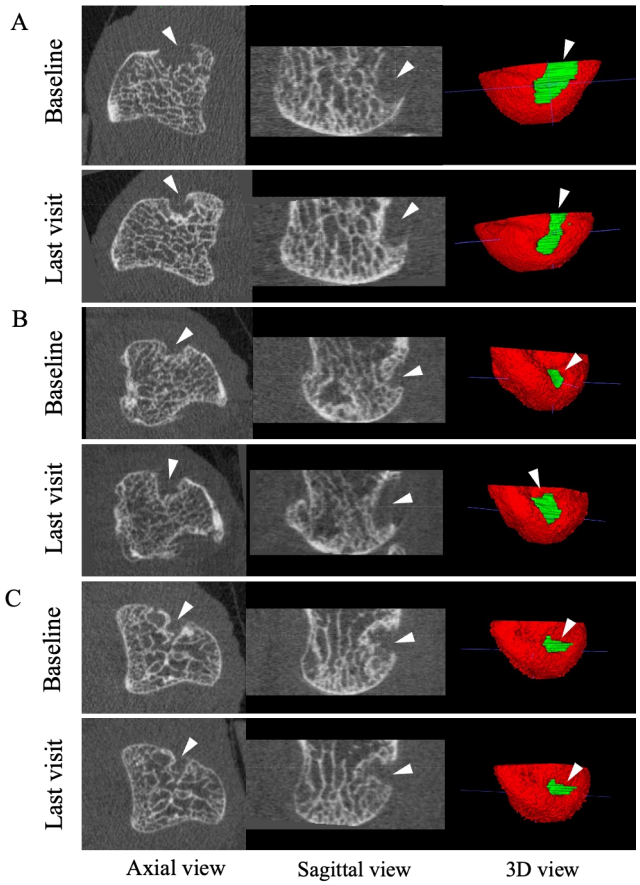


❑ Introduces a new dimension for erosion, detects cortical breaks earlier than radiography or MRI

Ref.: Geusens P et al, Nat Rev Rheumatol . 2014 May;10(5):304-13.

Background: Imaging in RA » HR-pQCT

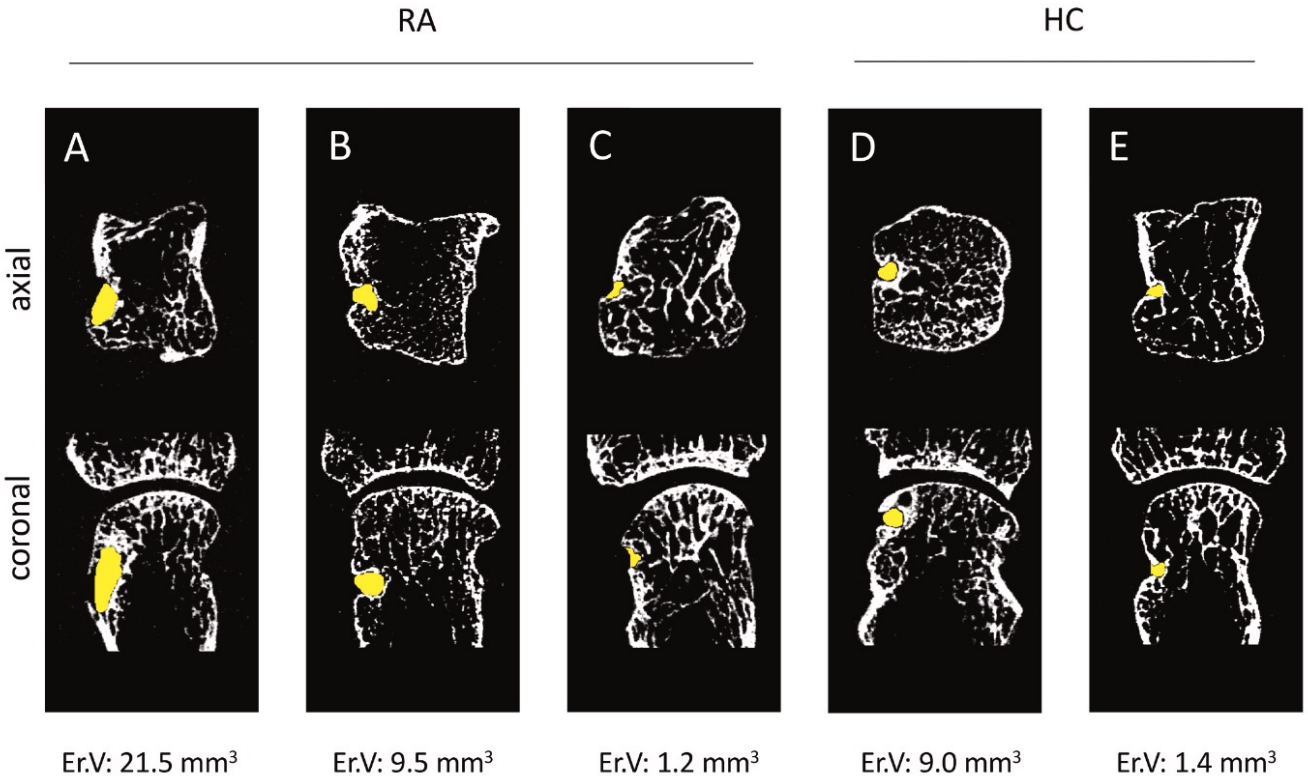




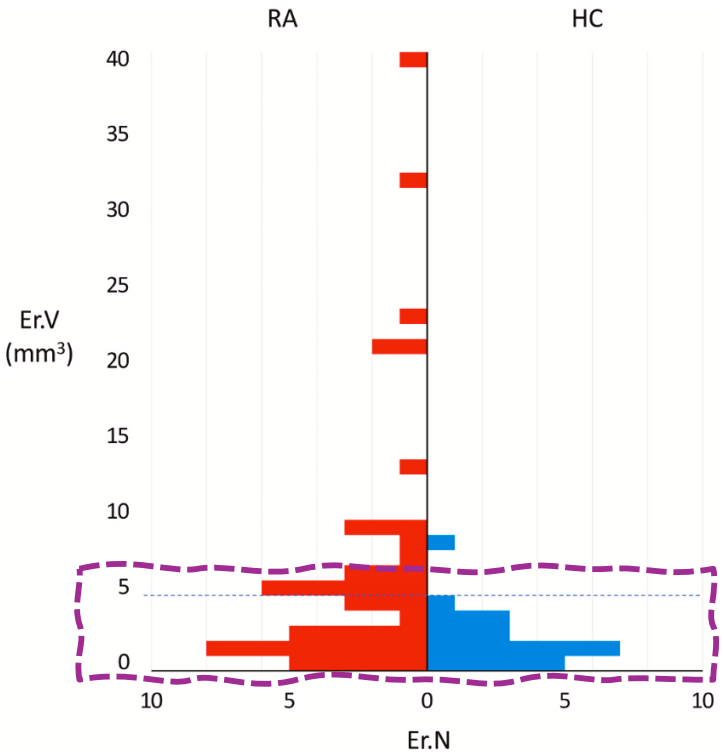
❑ HR-pQCT can detect bone erosion trajectories by volumetric quantification

Ref.: Watanabe Ket al., Bone. 2024 Dec; 189:117250.

Background » Research Gaps



Various sizes of erosion occurring in RA and HCs



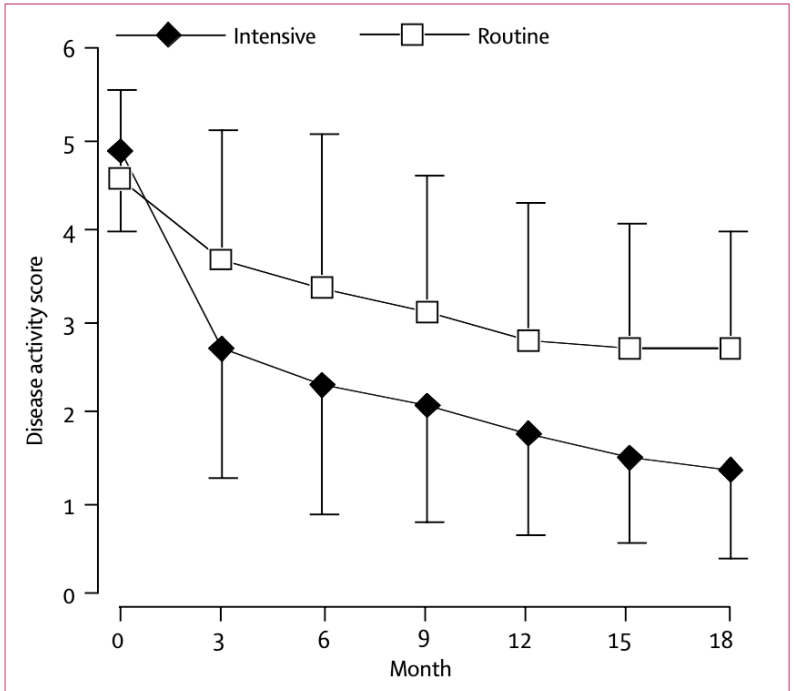
Most erosions of HCs had volumes < 5mm³.No differences in location/morphology for erosion < 5mm³ in RA and HCs.

Key question 1: The clinical significance and long-term evolution of small (<5 mm³), intermediate (1–5 mm³), and large (>5 mm³) erosions in RA remain unclear

Ref.: Watanabe Ket al., Bone. 2024 Dec; 189:117250.

Background » Research Gaps

Remission rate: 65% vs 16%



Reduced radiographic progression and improved function

	Intensive group (n=53)	Routine group (n=50)	Difference (95% CI)	p*
Disease activity score	−3·5 (1·1)	−1·9 (1·4)	1·6 (1·1 to 2·1)	<0·0001
Joint swelling count	−11 (5)	−8 (5)	3 (1 to 5)	0·0028
Joint tenderness count	−20 (9)	−12 (12)	8 (4 to 12)	0·0003
Patient global assessment	−51 (30)	−21 (34)	30 (17 to 42)	<0·0001
Assessor global assessment	−58 (22)	−34 (28)	24 (14 to 34)	<0·0001
Pain score	−45 (24)	−20 (31)	25 (14 to 36)	<0·0001
Erythrocyte sedimentation rate	−30 (28)	−12 (24)	18 (8 to 28)	0·0007
C-reactive protein	−30 (53)	−14 (40)	16 (−3 to 34)	0·09
Health assessment questionnaire	−0·97 (0·8)	−0·47 (0·9)	0·5 (0·2 to 0·8)	0·0025
Short form-12 physical summary score	9·3 (12)	4·0 (11)	5·3(0·8 to 9·8)	0·021
Short form-12 mental health summary score	10·9 (16)	6·0 (18)	5·0 (−1·6 to 11·6)	0·138
Erosion score†	0·5 (0–3·375)	3 (0·5–8·5)	n/a	0·002‡
Joint space narrowing†	3·25 (1·125–7·5)	4·5 (1·5–9)	n/a	0·331‡
Total Sharp score†	4·5 (1–9·875)	8·5 (2–15·5)	n/a	0·02‡

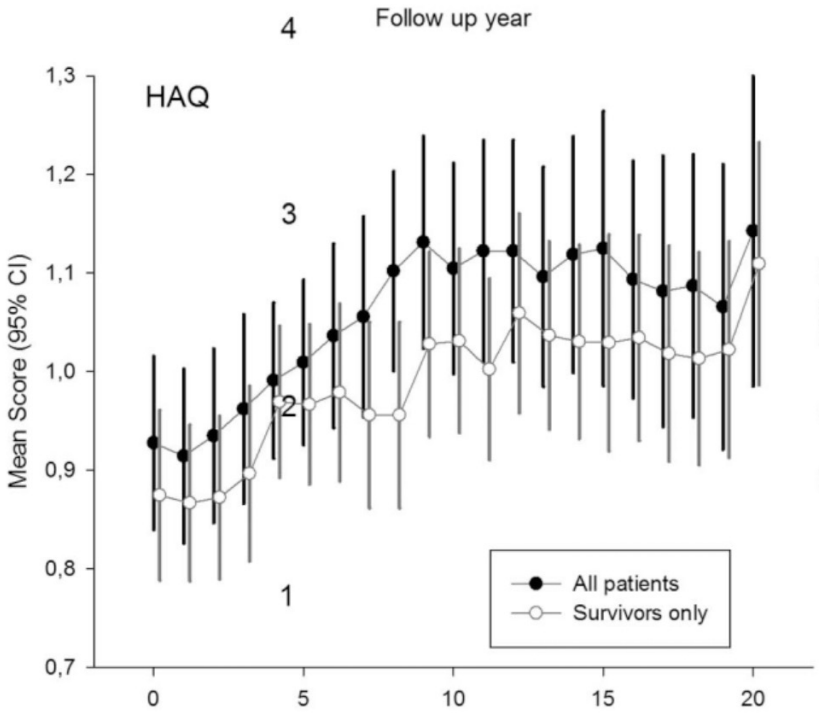
Data are mean (SD) unless otherwise indicated. n/a=not applicable. *Students' *t* test used. †Median (IQR) increase in score. ‡Mann-Whitney test used.

Key question 2: whether inflammation resolution through T2T in ERA patients improves erosion healing compared to usual care is unclear

Ref.: Grigor C, et al. Lancet. 2004 Jul 17-23; 364(9430):263-269.

Background » Research Gaps

The development of disability in RA over 20 years



Structural changes over a short period are associated with functional assessments in RA

Table Associations between quantitative structural changes and clinical and functional changes.

Variables	% ΔSynovitis Volume	% ΔBME Volume	% ΔErosion Volume	% ΔJSV Wrist
ΔHAQ Total	**β = 0.623 p = 0.027**	**β = 0.592 p = 0.033**	**β = 0.496 p = 0.043**	β = 0.176 p = 0.485
ΔHAQ Dressing	β = 0.201 p = 0.592	β = 0.391 p = 0.107	β = 0.320 p = 0.296	β = –0.126 p = 0.682
ΔHAQ Arising	β = 0.500 p = 0.122	β = 0.428 p = 0.150	**β = 0.522 p = 0.036**	β = 0.201 p = 0.471
ΔHAQ Eating	**β = 0.604 p = 0.040**	β = 0.439 p = 0.120	β = 0.031 p = 0.920	β = 0.065 p = 0.800
ΔHAQ Walking	β = 0.596 p = 0.058	β = 0.181 p = 0.549	β = –0.077 p = 0.791	**β = 0.668 p = 0.004**
ΔHAQ Hygiene	β = 0.259 p = 0.497	β = 0.536 p = 0.124	β = 0.368 p = 0.213	β = –0.216 p = 0.448
ΔHAQ Reach	β = 0.409 p = 0.174	β = 0.326 p = 0.286	β = 0.364 p = 0.223	β = 0.142 p = 0.584
ΔHAQ Grip	**β = 0.871 p = 0.002**	β = 0.345 p = 0.237	**β = 0.521 p = 0.037**	β = 0.119 p = 0.651
ΔHAQ Activities	β = 0.138 p = 0.715	β = 0.444 p = 0.210	β = 0.123 p = 0.722	β = 0.094 p = 0.756

Key question 3: whether the carpal erosion burden is associated with functional disability in RA patients is uncertain

Ref.: Kapetanovic MC, et al. Arthritis Care Res (Hoboken). 2015 Mar; 67(3):340-348.
Tomohiro S, et al. The Journal of Rheumatology 2019; 46:7.

Hypothesis & Objectives

Hypothesis

We hypothesize that the majority of small erosions (<1 mm') 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.

Hypothesis & Objectives

1: Cross-sectional Analysis

- To quantify and compare the volumetric distribution patterns of bone erosions across three size categories (small <1mm^3, intermediate 1-5mm^3, large >5mm^3) between RA patients and healthy controls.

2: Longitudinal Trajectory Analysis

- To characterize the 8-year erosion trajectories in the second metacarpal head (MCH2), examining:

  a) Volumetric changes stratified by baseline erosion size

  b) Frequencies of stabilization, progression, and regression within each size category

  c) Comparative outcomes between early RA (ERA) and established RA (EstRA) cohorts

3: Structure-Function Relationship

- To investigate the association between carpal erosive burden (quantified by total erosion volume and counts) and functional disability measures in RA patients.

General Methodology

Study Cohorts

- ❑ ***Established RA (EstRA) Cohort (n=247)***

i. Recruited: 2010-2017 from the general rheumatology clinic

ii. Treatment: Usual care (pre-T2T era)

- ❑ ***Early RA (ERA) Cohort (n=148)***

i. Recruited: 2012-2018 from the rheumatology research clinic

ii. Symptom onset: <2 years at diagnosis

iii. Treatment: T2T algorithm for 1 year, followed by usual care

Imaging

i. HR-pQCT of MCH2 (baseline & final visit) and wrist (final visit)

General Methodology

Inclusion criteria:

Fulfilling 2010 ACR/EULAR RA classification criteria

Exclusion criteria:

1) had severe clinical deformity at the 2nd MCP / wrist joint precluding a reliable HR-pQCT examination

2) were pregnant or breastfeeding

General Methodology » Study Population

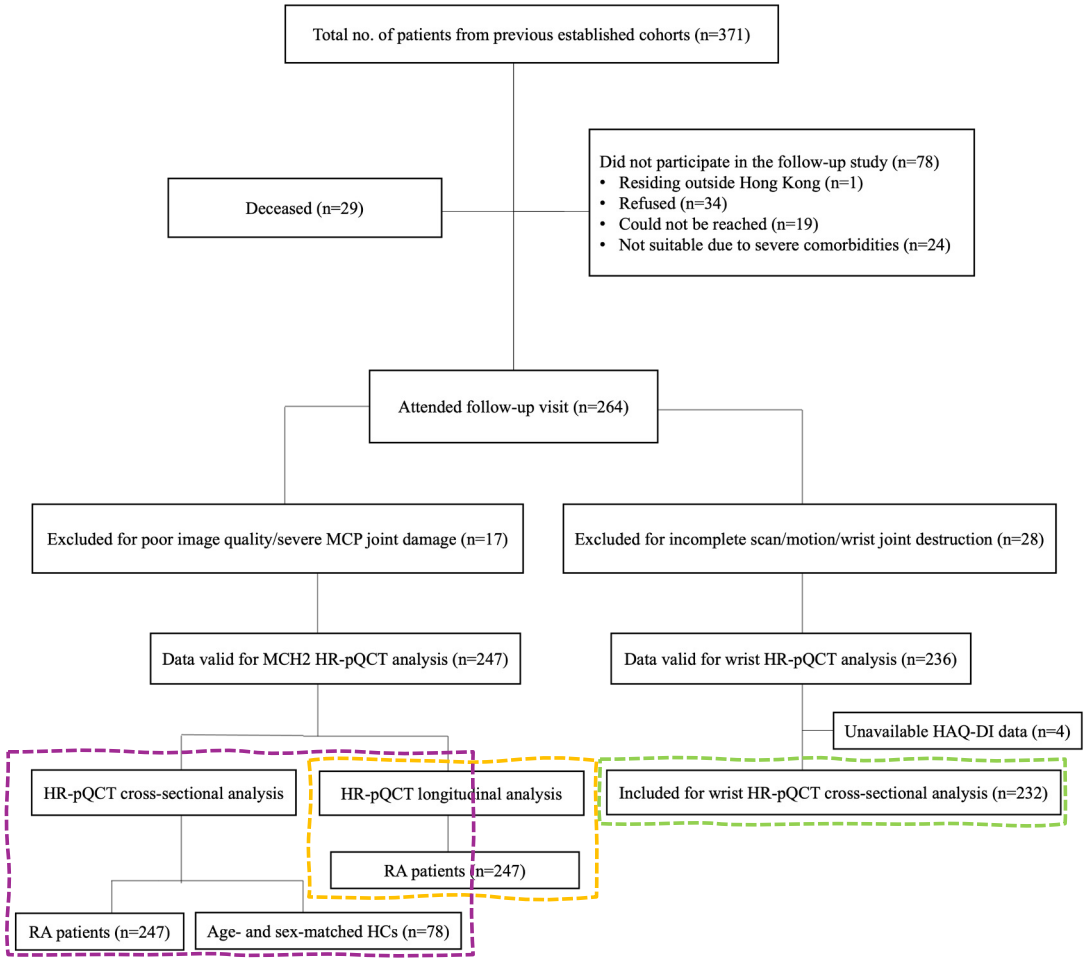


Figure 3.1 Flow diagram of patient enrollment and data inclusion for HR-pQCT analysis

General Methodology

Clinical assessment: including disease activity parameters, laboratory, and treatment

Functional assessment: Health Assessment Questionnaire-Disability Index (HAQ-DI)

Structure of HAQ-DI:
- Component: 20 questions across eight functional domains
- 4-point Likert scale: 0 (no difficulty) to 3 (unable to perform)
- Score range: 0 (no disability) to 3 (severe disability)

Disability Classification based on HAQ-DI:

- Presence of disability: HAQ-DI ≥0.5
- Degree of disability:
  - No/minimal disability: 0 to <0.5
  - Mild disability: 0.5 to <1.0
  - Moderate/severe disability: 1.0 to 3.0

HR-pQCT Assessment Protocol

High-Resolution Peripheral Quantitative Computed Tomography

IMAGE ACQUISITION

System: XtremeCT I (Scanco Medical AG, Switzerland)

Resolution: Isotropic voxel size: 82 µm

Scanning Protocol:

- **MCH2:** 9.02mm coverage (110 slices), 2.8 min
- **Wrist:** 27.06mm coverage (330 slices), 9 min

Radiation Dose: ~16 µSv (≈ daily background)

Quality Control: Motion scores 1-5 (excluded if ≥4)

EROSION IDENTIFICATION

SPECTRA Criteria:

- ✓ Sharply marginated juxta-articular lesions
- ✓ Cortical break visible in ≥2 adjacent slices
- ✓ Accompanied by trabecular bone loss

Exclusions:

- ✗ Physiological vascular channels
- ✗ Pseudo-erosions from osteophytes

Assessment Sites:

Palmar • Ulnar • Dorsal • Radial aspects of MCH2

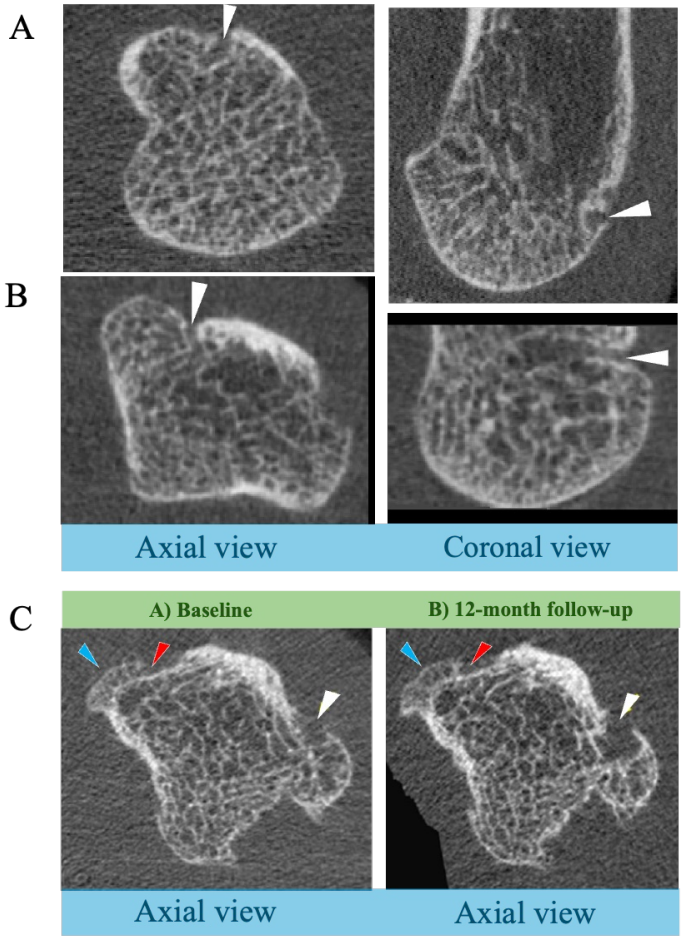


Figure 3.2 Cortical breaks on high-resolution imaging

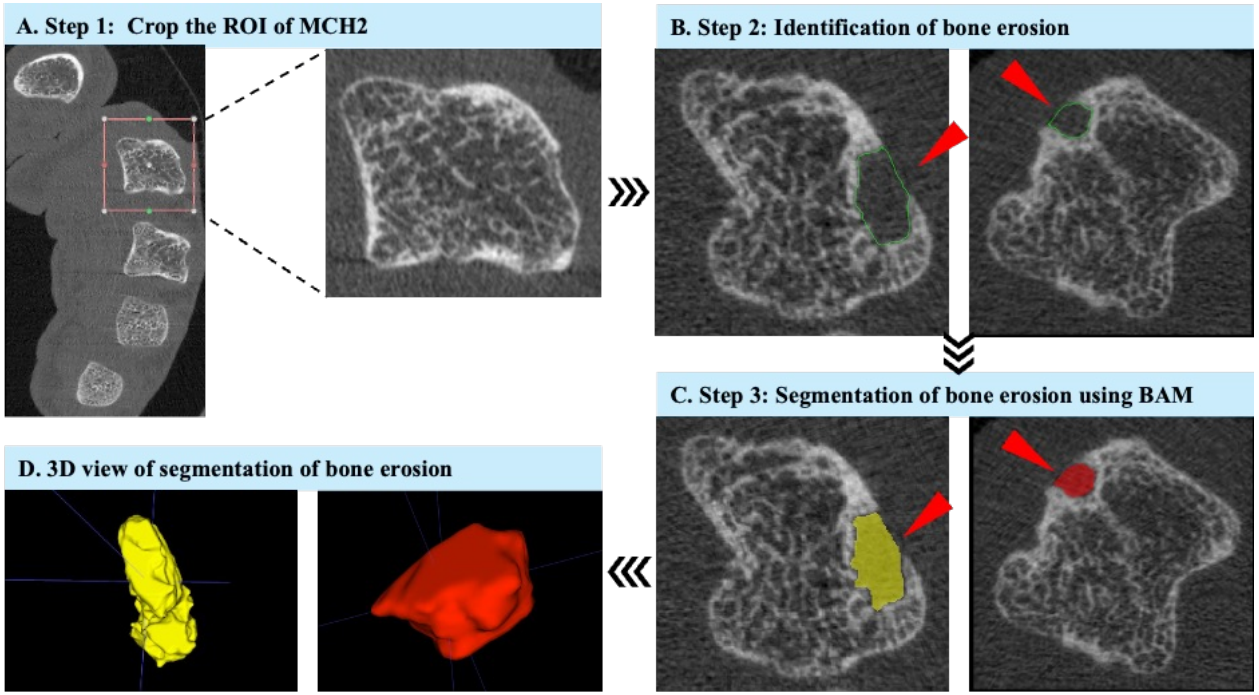


Figure 3.3 Identification and quantification of bone erosion

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.

Study 1 » Objectives

1: Cross-sectional Analysis

- To quantify and compare the volumetric distribution patterns of bone erosions across three size categories (small <1mm^3, intermediate 1-5mm^3, large >5mm^3) between RA patients and healthy controls.

2: Longitudinal Trajectory Analysis

- To characterize the 8-year erosion trajectories in the second metacarpal head (MCH2), examining:
  - a) Volumetric changes stratified by baseline erosion size
  - b) Frequencies of stabilization, progression, and regression within each size category
  - c) Comparative outcomes between early RA (ERA) and established RA (EstRA) cohorts

3: Structure-Function Relationship

- To investigate the association between carpal erosive burden (quantified by total erosion volume and counts) and functional disability measures in RA patients.

Study 1 » Methodology

i. Cross-sectional, comparative study

ii. Population: 247 RA patients and 78 age- and sex-matched HCs who underwent HR-pQCT scans of the MCH2

iii. Comparing the erosion parameters between the two groups, stratified by erosion size: small <1 mm^3, intermediate 1-5 mm^3, large >5 mm^3.

iv. Effect sizes (rank-biserial correlation, Cliff‘s delta, and Hodges-Lehmann estimates with 95% CI) were used to assess the between-group difference in erosive changes.

Study 1 » Results

Table 4.1 Characteristics of RA patients and healthy individuals

	RA (n=247)	HCs (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]		
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 [IQR] or n (%). HCs, healthy controls.

Study 1 » Results

Table 4.2 Erosion parameters of MCH2 between RA patients and HCs

	RA patients	HCs	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^3)	1.1 [0.3, 3.0]	0 [0, 0.5]	< 0.001
[#] Presence of erosion according to size (n, %)			< 0.001[†]
Large erosion (>5 mm^3)	42 (17)	2 (3)	0.002
Intermediate erosion (1-5 mm^3)	79 (32)	10 (13)	0.003
Small erosion (<1 mm^3)	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. [#] Defined based on the size of the largest erosion per patient. [†] 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.

- RA patients had higher prevalence of both large and intermediate erosions
- The prevalence of small erosions was comparable between groups

Study 1 » Results

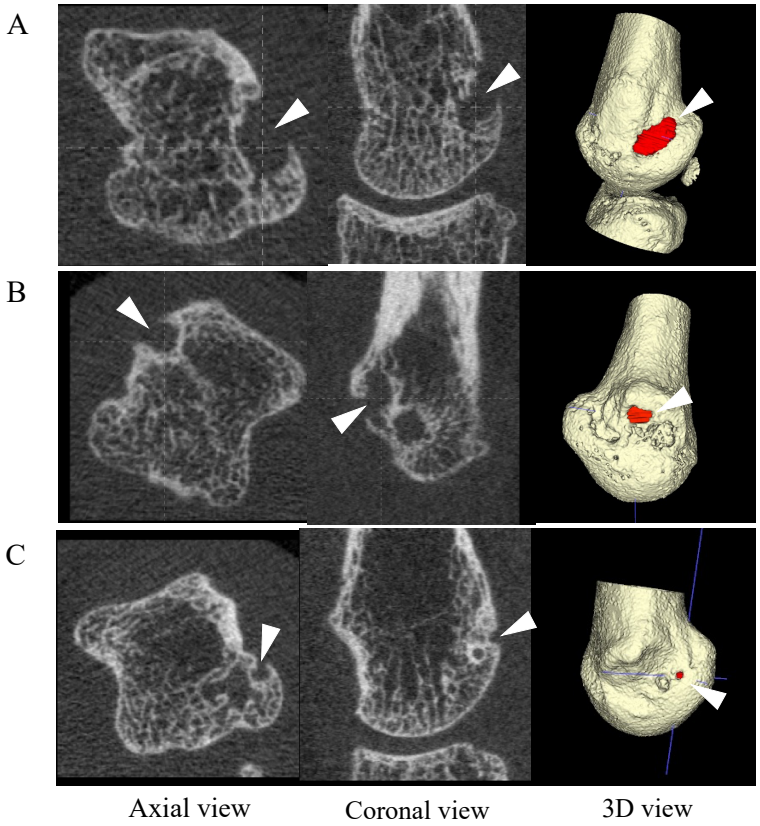


Figure 4.1 Typical images depicting erosion by size in MCH2
Erosion size categories: large erosion: > 5 mm^3, intermediate erosion: 1-5 mm^3, small erosion: <1 mm^3. (A) Large erosion (volume = 32.18 mm^3); (B) intermediate erosion (volume = 2.66 mm^3); (C) small erosion (volume = 0.98 mm^3). The erosion 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.

Study 1 » Results

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

	Small erosion (<1 mm^3)			Intermediate erosion (1-5 mm^3)			Large erosion (>5 mm^3)		
	RA (n=110)	HCs (n=24)	P	RA (n=104)	HCs (n=11)	P	RA (n=45)	HCs (n=2)	P
Individual erosion volume (mm^3)	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 [IQR]. RA, rheumatoid arthritis. HCs, healthy controls.

- Small erosions: the Hodges-Lehmann estimate indicated a slight absolute difference of 0.1 mm^3 between groups.
- Intermediate erosions: no significant difference between groups was observed.
- Large erosions: a substantially higher volume in RA patients compared to HCs was observed

Study 1 » Conclusions

Small erosions were common in HCs and did not differentiate from RA, whereas large erosions were more frequent and of larger size in RA, and may be associated with RA pathology.

Study 2 » Objectives

1: Cross-sectional Analysis

- To quantify and compare the volumetric distribution patterns of bone erosions across three size categories (small <1mm^3, intermediate 1-5mm^3, large >5mm^3) between RA patients and healthy controls.

2: Longitudinal Trajectory Analysis

- To characterize the 8-year erosion trajectories in the second metacarpal head (MCH2), examining:

  a) Volumetric changes stratified by baseline erosion size

  b) Frequencies of stabilization, progression, and regression within each size category

  c) Comparative outcomes between early RA (ERA) and established RA (EstRA) cohorts

3: Structure-Function Relationship

- To investigate the association between carpal erosive burden (quantified by total erosion volume and counts) and functional disability measures in RA patients.

Study 2 » Primary & secondary outcome

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.

Secondary outcome

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.

Study 2 » Methods » Erosion Status Classification

Least Significant Change (LSC) Framework for Erosion Volume Analysis

Individual erosion-level analysis with size-specific thresholds for precise longitudinal tracking

A

Methodology

- Sample: 60 erosions (20 per size category)
- Reader: Single observer (XY)
- Measurements: Duplicate assessments
- Formula: LSC = $\pm 2.77 \times \sqrt{((\Sigma(a-b)^2)/2n)}$
- Purpose: Distinguish true biological changes from measurement error

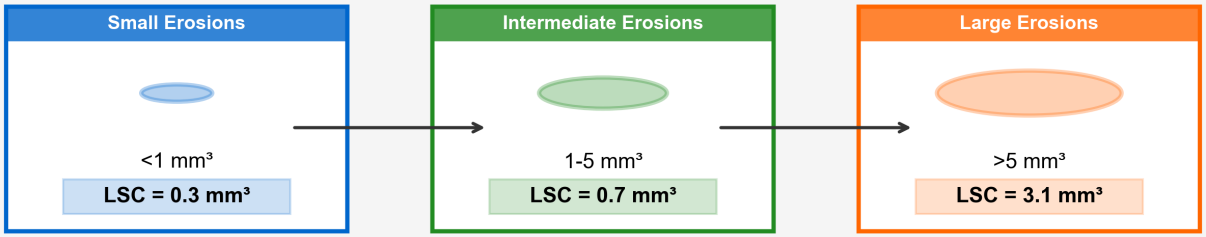
B

Erosion Status Classification

Progression	Stable	Partial Repair
Volume increase > LSC	Volume change within ±LSC	Volume decrease > LSC

C

Size-Specific LSC Thresholds



LSC thresholds increase proportionally with erosion size to maintain measurement precision

LSC, least significant change; ΔV, volume change

Study 2 » Results

Part I: Long-term outcomes of bone erosion in MCH2 in the entire cohort

1. Clinical characteristics of the overall cohort at baseline and follow-up
2. Longitudinal assessment of erosions by size in the overall cohort

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

3. Clinical characteristics between both cohorts at baseline and follow-up
4. Erosion parameters assessed by HR-pQCT between the two cohorts
5. Outcome of erosions according to erosion size
6. Subgroup analysis of patients with large erosions (> 5 mm^3)

Study 2 » Results » (Part I) Long-term changes in entire cohort

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
Physician's global assessment, NRS 0-10	2.5 (0.8, 5.0)	1.0 (0.0, 3.0)	<0.001
Tender joint count (0-28)	3.0 (0.0, 7.0)	0.0 (0.0, 2.0)	<0.001
Swollen joint count (0-28)	2.0 (0.0, 4.0)	0.0 (0.0, 1.0)	<0.001
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)	<0.001
SDAI score	13.0 (6.0, 24.2)	6.1 (2.1, 11.3)	<0.001
DAS28-CRP score	3.5 (2.3, 4.7)	2.3 (1.5, 3.2)	<0.001

	Baseline	Last visit	P-value†
SDAI category			<0.001
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)	0.005
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)	0.002
NSAIDs	163 (67.6)	114 (47.3)	<0.001
csDMARDs	164 (68.0)	206 (85.5)	<0.001
b/tsDMARDs	15 (6.2)	34 (14.1)	0.004
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.

Study 2 » Results » (Part I) Long-term changes in entire cohort

Table 5.2 Comparison of pre-existing erosion in MCH2 in RA patients from baseline to last visit

	Small erosion (<1 mm^3) (n=110)			Intermediate erosion (1-5 mm^3) (n=104)			Large erosion (>5 mm^3) (n=45)		
	Baseline	Last visit	P-value	Baseline	Last visit	P-value	Baseline	Last visit	P-value
Individual erosion volume (mm^3)	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 [IQR]. Individual erosion volume was analyzed between two time points using the Wilcoxon signed-rank test.

- Small erosions: the magnitude of increase in median volume was minimal (Hodges-Lehmann estimate: 0.05 mm^3).
- Intermediate erosions: demonstrated remarkable stability, with unchanged median volumes across two time points.
- Large erosions: showed a significant decrease in median volumes, with a notable Hodges-Lehmann estimate of -5.6 mm^3.

Study 2 » Results » (Part I) Long-term changes in entire cohort

Table 5.3 The status of individual erosion in MCH2 from baseline to last visit

	Small erosion (<1 mm^3) (n=110)	Intermediate erosion (1-5 mm^3) (n=104)	Large erosion (>5 mm^3) (n=45)
Erosion status			
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 (mm^3)	OR	95% CI	P-value
Overall distribution			0.008
< 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.

- Small erosions were more likely to remain stable compared to both intermediate and large erosions

Study 2 » Summary of Part I

Part I: Long-term outcomes of bone erosion in MCH2 in the entire cohort

Small erosions were stable over an 8-year follow-up in RA, whereas large erosions were more likely to regress under the contemporary treatment.

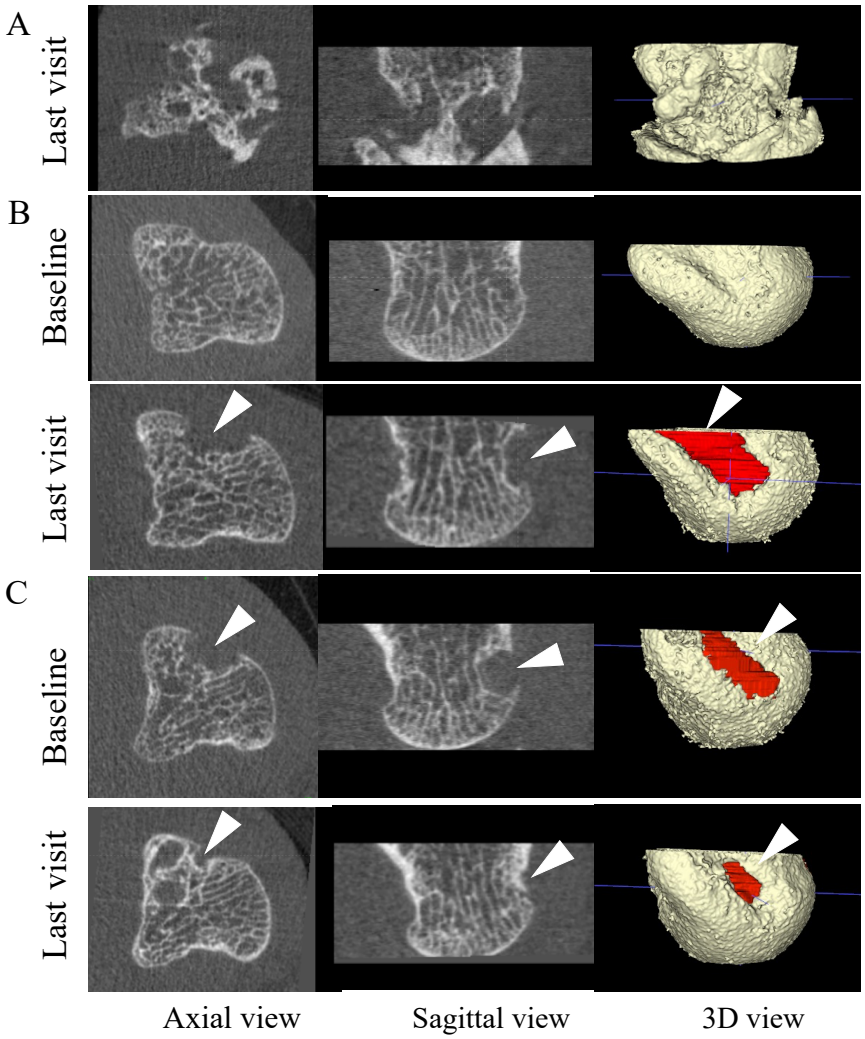
Study 2 » Results » (Part II) Long-term outcomes for ERA vs EstRA

Table 5.4 Clinical characteristics between patients from the ERA and EstRA cohorts

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

Study 2 » Results » (Part II) Long-term outcomes for ERA vs EstRA



- Panel A illustrates joint destruction detected at the last visit in the EstRA cohort.
- Panel B demonstrates the new large erosion detected in the EstRA cohort.
- Panel C shows the regression of large erosion in the ERA cohort.

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^3) 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^3 at baseline to 5.58 mm^3 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.

Erosion parameters assessed by HR-pQCT between the two cohorts

Table 5.5 Comparison of erosion parameters of MCH2 between two cohorts at two time points

	Baseline			Last visit				
	ERA (n=98)	EstRA (n=149)	P-value †	ERA (n=98)	EstRA (n=149)	P-value †	P-value ¶	P-value §
Presence of erosion (n, %)	75 (77)	118 (79)	0.620	80 (82)	126 (85)	0.545	0.125	**0.021**
Presence of erosion according to size (n, %)								
Large erosion (>5mm^3)	16 (16)	26 (17)	0.818	13 (13)	37 (25)	**0.027**	0.549	**0.013**
Intermediate erosion (1-5mm^3)	27 (28)	52 (35)	0.226	45 (46)	51 (34)	0.065	**0.004**	1.000
Small erosion (<1mm^3)	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^3)	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.

- Over an 8-year follow-up, the prevalence of large erosion was significantly increased in the EstRA cohort.
- The prevalence of large erosions was significantly higher in the EstRA cohort compared to the ERA cohort.

Incident erosions

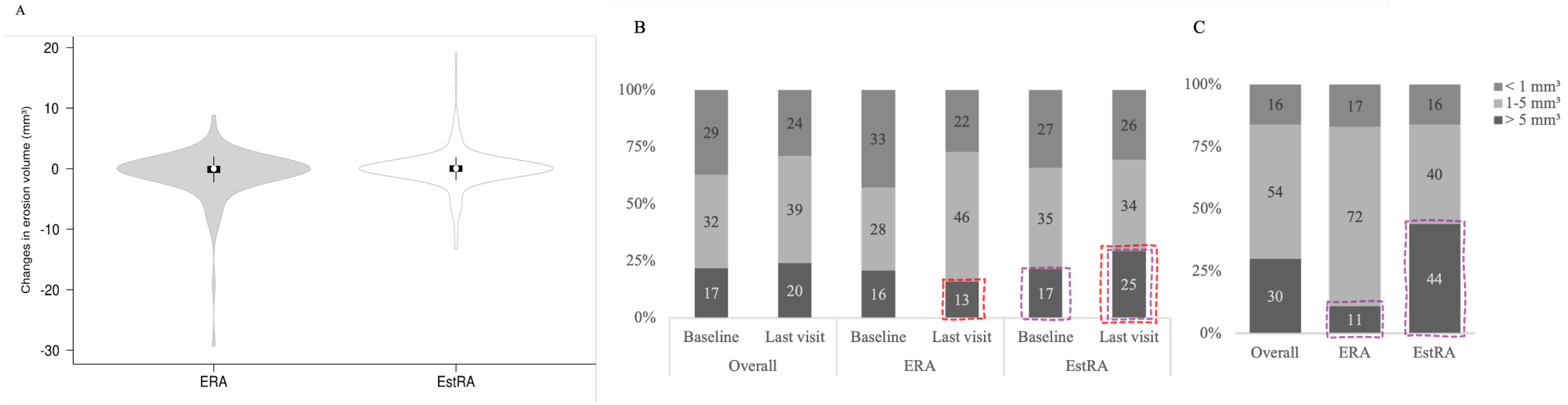


Figure 5.2 Changes in pre-existing erosion volume and distribution of erosions of MCH2 by size between cohorts A: Violin plot illustrating the distribution of changes in pre-existing erosion volumes (n = 259; 91 from ERA, 168 from EstRA). B: Prevalence of erosions stratified by size in the entire cohort (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.

Table 5.6 Erosion size distribution of new erosions in MCH2 detected at the last visit

	ERA (n=18)	EstRA (n=25)	P-value
Volume >5 mm³ (n=13)	2 (11)	11 (44)	**0.041**
Volume 1-5 mm³ (n=23)	13 (72)	10 (40)	0.062
Volume <1 mm³ (n=7)	3 (17)	4 (16)	1.000

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

For new erosion detected at the last visit, a significantly lower frequency of incident large erosions was observed in the ERA cohort compared to the EstRA cohort.

Erosion regression

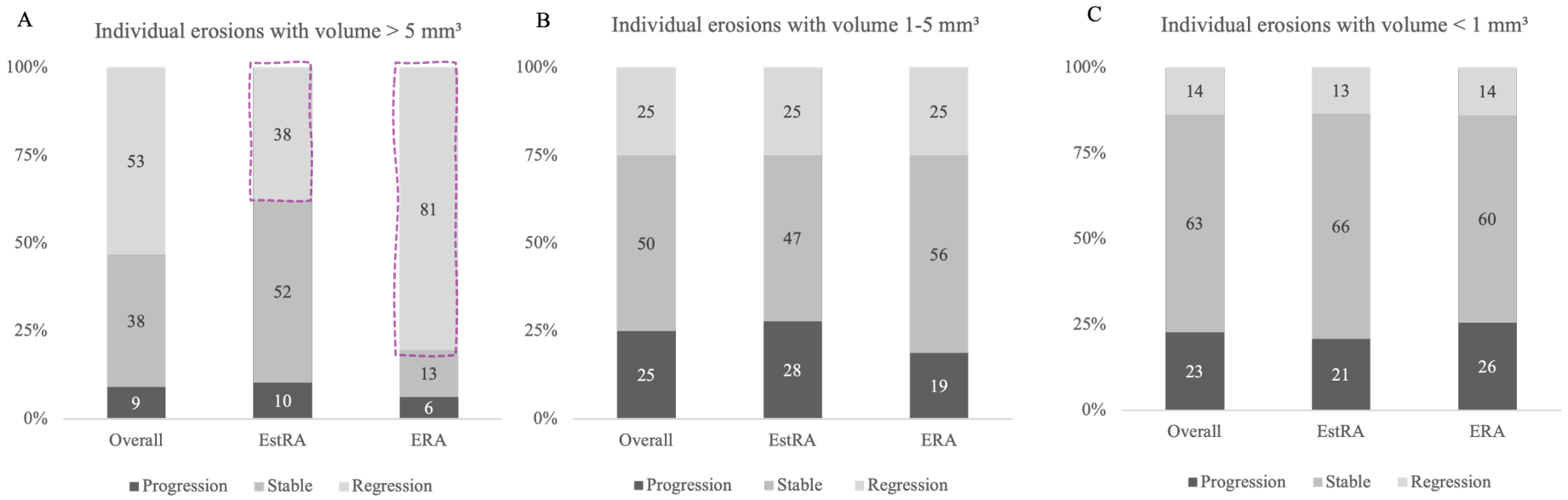


Figure 5.3 Outcome of erosions stratified by erosion volume categories in MCH2 between the two cohorts
Total number of erosions =259, including 168 and 91 erosions from patients in the EstRA and ERA cohort, respectively.

- Large erosions in the ERA cohort were more likely to regress and less prone to remain stable compared to the EstRA cohort

Study 2 » Results » Subgroup analysis of patients with large erosions

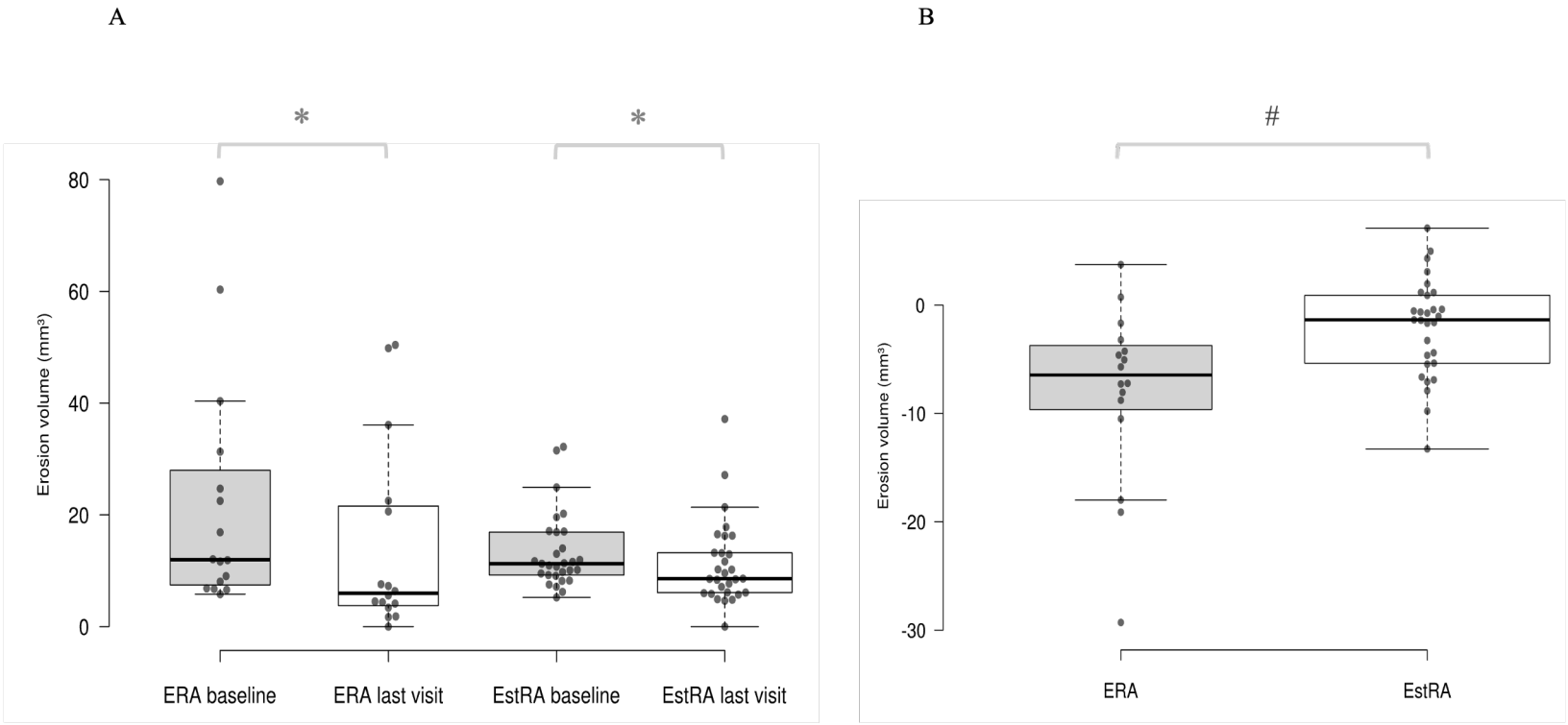


Figure 5.4 Comparison of MCH2 pre-existing erosion with baseline volume > 5 mm^3 in two cohorts

- Over an 8-year follow-up, both cohorts showed a significant reduction in erosion volume.
- The reduction in erosion volume was significantly greater in the ERA compared to the EstRA.

Study 2 » Summary of Part II

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

- Early intervention with the T2T strategy significantly promotes regression of large erosions and prevents the formation of new large erosions in the ERA cohort compared to the EstRA cohort.

Study 3 » Objectives

1: Cross-sectional Analysis

- To quantify and compare the volumetric distribution patterns of bone erosions across three size categories (small <1mm^3, intermediate 1-5mm^3, large >5mm^3) between RA patients and healthy controls.

2: Longitudinal Trajectory Analysis

- To characterize the 8-year erosion trajectories in the second metacarpal head (MCH2), examining:
  - a) Volumetric changes stratified by baseline erosion size
  - b) Frequencies of stabilization, progression, and regression within each size category
  - c) Comparative outcomes between early RA (ERA) and established RA (EstRA) cohorts

3: Structure-Function Relationship

- To investigate the association between carpal erosive burden (quantified by total erosion volume and counts) and functional disability measures in RA patients.

Functional Assessment Methods in Rheumatoid Arthritis

Standardized Clinical Protocols for Research and Practice

Grip Strength Assessment

EQUIPMENT & PROTOCOL

- Dynamometer: Grip D TKK5401 (Takei, Japan) | Range: 0-90 kg
- ASHT Protocol: Shoulder adducted, elbow 90°, neutral forearm
- Bilateral assessment with standardized rest intervals

MEASUREMENT PROTOCOL

1 Familiarization → 2 Position Setup → 3 Bilateral Testing → 4 Score Calculation

CLINICAL THRESHOLDS (EWGSOP2)

♂ Men: <27 kg

♀ Women: <16 kg

Reliability: ICC >0.90 | Strong predictor of functional decline

Fine Motor Function (CAIMS2)

HIERARCHICAL STRUCTURE

SCORING METHODOLOGY

- Binary Assessment: Able (0) vs Unable (1) to perform
- Raw Score Range: 0-5 failures
- Linear Transformation: 0-100 scale
- **Higher scores = Greater functional impairment**

CLINICAL APPLICATIONS

- ✓ **Sensitive detection of functional changes in RA**
- ✓ **Embedded within comprehensive CAIMS2 assessment**
- ✓ **Validated for clinical trials and research**
- ✓ **Administration time: 10-15 minutes**

ICC >0.85

Study 3 » Primary & Secondary Outcomes

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.

Secondary outcomes

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).

Study 3 » Results

Table 6.1 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
Disease activity parameters						
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¶
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
Current treatment, n (%)						
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
Ever treatment, n (%)						
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 ≥ 0.5. Moderate to severe disability was defined as HAQ-DI ≥1 to ≤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 ≤ 3.3, Low Disease Activity (LDA) with SDAI > 3.3 to ≤ 11, Moderate Disease Activity (MDA) with SDAI > 11 to ≤ 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.

- Patients with disability were more often female than those without, and demonstrated higher disease activity.
- Ever use of prednisolone and b/tsDMARDs was higher among patients with disability than those without.

Study 3 » Results

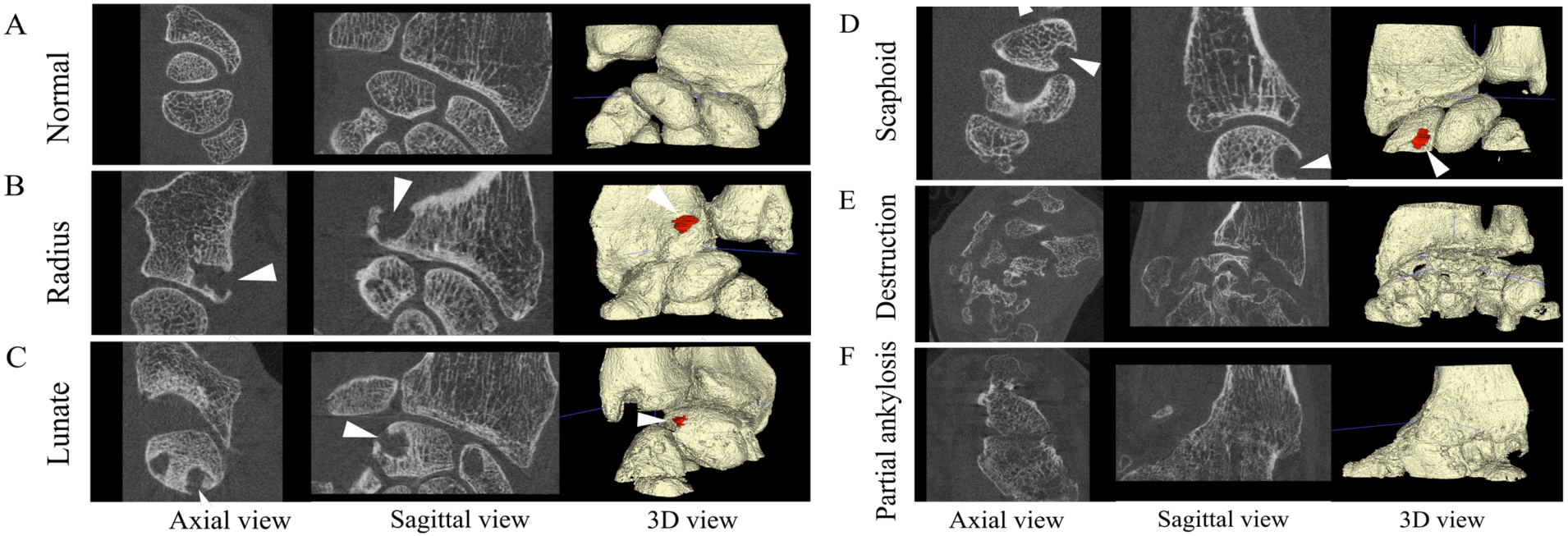


Figure 6.1 Typical images depicting wrist bone erosions and joint destruction
(A) Normal wrist bone; (B) Bone erosions in the radius; (C) Bone erosions in the lunate; (D) Bone erosions in the scaphoid; (E) Wrist joint destruction; (F) Wrist joint partial ankylosis. The erosion size is depicted by the red segmentation of the bone in the 3D view. White triangles indicate the presence of erosion in axial, sagittal, and 3D views.

Table 6.2 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^3), Mean±SD	12.7±34.7	8.4±14.3	5.5±10.9	26.5±47.1
Total erosion volume per patient (mm^3), 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]

- The presence of carpal erosion was 88%, most frequently in the lunate, followed by the scaphoid and radius.
- The lunate had the highest erosion counts but smaller volumes, while the radius showed fewer erosion counts but larger volumes.

Study 3 » Results

Table 6.3 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)	**0.021**	25 (55.6%)	73 (39.0%)	**0.044**
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%)	**0.040**	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]	**<0.001**	3.0 [1.0, 4.0]	2.0 [1.0, 3.0]	**0.002**
In scaphoid	1.0 [0.0, 2.0]	0.0 [0.0, 1.0]	**0.002**	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]	**<0.001**	5.0 [1.0, 8.0]	3.0 [1.0, 4.0]	**0.011**
Total erosion volume (mm^3)						
In radius	0.7 [0.0, 14.4]	0.0 [0.0, 3.1]	**0.015**	2.9 [0.0, 14.4]	0.0 [0.0, 4.9]	**0.033**
In lunate	5.4 [1.7, 15.3]	2.9 [0.8, 7.3]	**0.003**	7.8 [2.4, 15.8]	3.4 [0.9, 8.1]	**0.012**
In scaphoid	1.1 [0.0, 9.6]	0.0 [0.0, 4.0]	**0.035**	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]	**0.003**	16.0 [2.8, 43.8]	6.7 [2.1, 23.1]	**0.032**

Data are presented as median [IQR] or n (%). † P-values from Mann-Whitney U tests for continuous variables and Chi-square or Fisher's exact test for categorical variables.

- Compared to patients without disability, those with disability had a higher prevalence of radial erosions and nearly doubled total wrist bone erosive burden.
- A similar pattern was observed in patients with moderate-to-severe disability, with higher radial erosion prevalence, greater erosion counts of wrist bones, and larger erosion volumes of wrist bones.

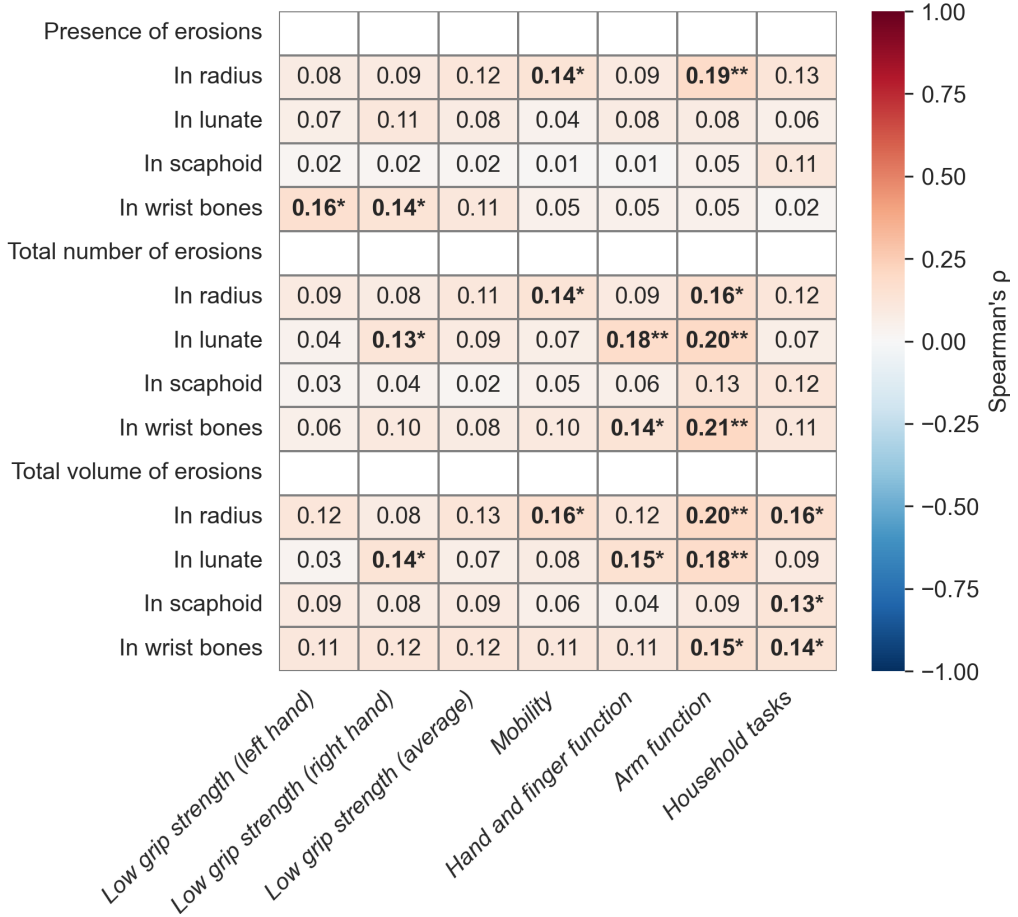
Study 3 » Results

Table 6.4 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	
	ρ	P value	ρ	P value	ρ	P value	ρ	P value
Presence of erosions								
In radius	**0.14**	**0.034**	**0.15**	**0.021**	**0.16**	**0.013**	**0.13**	**0.044**
In lunate	0.11	0.090	0.09	0.162	0.10	0.129	0.08	0.200
In scaphoid	0.09	0.179	**0.14**	**0.040**	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
Total number of erosions								
In radius	0.10	0.111	0.12	0.077	0.13	0.051	0.11	0.090
In lunate	**0.22**	**0.001**	**0.23**	**<0.001**	**0.24**	**<0.001**	**0.20**	**0.002**
In scaphoid	**0.14**	**0.029**	**0.20**	**0.002**	**0.18**	**0.005**	0.08	0.224
In wrist bones	**0.19**	**0.003**	**0.23**	**<0.001**	**0.24**	**<0.001**	**0.17**	**0.011**
Total volume of erosions								
In radius	**0.14**	**0.026**	**0.16**	**0.014**	**0.17**	**0.009**	**0.14**	**0.032**
In lunate	**0.19**	**0.004**	**0.19**	**0.003**	**0.21**	**0.001**	**0.17**	**0.011**
In scaphoid	0.10	0.136	**0.14**	**0.035**	0.13	0.054	0.06	0.387
In wrist bones	**0.17**	**0.007**	**0.19**	**0.003**	**0.20**	**0.002**	**0.14**	**0.032**

- Lunate erosion count and volume showed the strongest correlation with HAQ-DI scores, presence of disability, and degree of disability.
- The total wrist bone erosion metrics had a similar correlation across all disability measurements.

Study 3 » Results



- Radius erosions were correlated with reduced mobility and arm function.
- Lunate erosive burden was associated with reduced grip strength, hand/finger dexterity, and arm function.
- Wrist-bone erosion metrics showed the strongest relationships with hand/finger and arm functional impairments.

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.

Study 3 » Results

Table 6.5 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

All models were adjusted for age, sex, disease duration, SDAI remission status, and ever use of b/tsDMARDs and prednisolone during the study period.

- Erosive burden in wrist bones was independently associated with a higher degree of disability

Study 3 » 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.

Summary & Discussion

Cross-Sectional Analysis

Key Finding: Size-dependent erosion patterns distinguish physiological from pathological processes

- **Small erosions** (<1 mm^3): Comparable prevalence in RA patients vs. healthy controls
  - **Implication**: Likely represents physiological phenomena
- **Large erosions** (>5 mm^3): Significantly higher frequency and volume in RA patients
  - **Implication**: Specific pathological markers of bone damage

✓ **Hypothesis confirmed: Small erosions are likely physiological in nature**

Summary & Discussion

Longitudinal Analysis

Key Finding: Distinct 8.4-year evolutionary trajectories based on baseline erosion size

Small Erosions:

Predominantly stable over time

Reinforces physiological nature

Large Erosions:

Significant regression under contemporary treatment

Better outcomes with early intervention

Treatment Impact:

ERA (T2T strategy): Enhanced large erosion regression & prevention of new erosion formation

EstRA (usual care): Less favorable structural outcomes

✓ **Structural "window of opportunity" concept validated**

Summary & Discussion

Structure-Function Correlation

Key Finding: HR-pQCT detected carpal erosive burden independently associated with functional disability

Radial erosions and **greater wrist erosive burden** → functional impairment

Volumetric quantification of carpal erosion correlates with functional capacity

Enables enhanced risk stratification and personalized intervention

✓ **Structure-function relationship hypothesis confirmed**

Study Limitations

Cross-Sectional Study

Methodological Constraints:

- **Anatomical scope**: Limited to MCH2 only
  - May underestimate broader hand erosive patterns
- **Volumetric thresholds**: Literature-based but somewhat arbitrary
  - Alternative cutoffs could influence prevalence findings
- **Classification challenges**: Small erosions vs. physiological interruptions
  - Potential bias despite SPECTRA adherence

Study Limitations

Longitudinal Study

Design Limitations:

Non-randomized treatment timing: Potential selection bias

EstRA cohort lacked protocol-driven decisions

Variable imaging intervals: Treatment initiation to baseline HR-pQCT

May influence large erosion healing assessment

Anatomical restriction: MCH2 focus only

Limited understanding of multi-joint dynamics

Imaging frequency: No intermediate assessments

Erosion evolution dynamics are unclear

Observational design: Constrains causal interpretations

Despite "window of opportunity" evidence

Study Limitations

Functional Correlation Study

Analytical Constraints:

Cross-sectional design: No temporal relationship determination

Despite multivariable adjustment

Missing baseline data: No wrist HR-pQCT trajectory analysis

Selection bias: Excluded severe joint destruction cases

May underestimate extreme damage associations

Technology limitation: HR-pQCT availability restricts translation

Generalizability: Requires external validation in diverse populations

Manuscripts in Preparation

1. Yan X, Cheng I, et al. “Bone Erosion Progression and Regression in Rheumatoid Arthritis - An Eight-Year HR-pQCT Follow-Up Study.” Ready for submission.
2. Yan X, Cheng I, et al. “Comparative Study of Bone Erosions in Rheumatoid Arthritis: Insights from an HR-pQCT Examination and Long-term Follow-up.” In Preparation.
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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- Department of Medicine & Therapeutics, The Prince of Wales Hospital, The Chinese University of Hong Kong
- Department of Imaging and Interventional Radiology, The Prince of Wales Hospital, The Chinese University of Hong Kong
- Bone Quality and Health Centre of the Department of Orthopedics & Traumatology, The Prince of Wales Hospital, The Chinese University of Hong Kong
- Centre for Clinical Research and Biostatistics, The Jockey Club School of Public Health & Primary Care, The Chinese University of Hong Kong
- Department of Medicine, Queen Elizabeth Hospital, Hong Kong

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Faculty of Medicine
The Chinese University of Hong Kong

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Table 6.4 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)
Total volume of erosions (mm^3)					
In radius	7.60 ± 19.11	16.45 ± 35.83	21.82 ± 58.24	**0.037***	
	0.00 (0.00, 3.12)	0.00 (0.00, 12.61)	2.90 (0.00, 14.41)	**0.032***	Group A vs C: **0.037***
In lunate	5.95 ± 8.46	11.20 ± 22.83	11.36 ± 11.89	**0.018***	
	2.94 (0.76, 7.32)	4.85 (1.28, 10.95)	7.75 (2.37, 15.76)	**0.007****	Group A vs C: **0.008****
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	**0.009****	Group A vs C: **0.033***
	5.38 (1.96, 16.11)	9.13 (3.84, 40.66)	15.99 (2.82, 43.79)	**0.011***	Group A vs C: **0.026***

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).