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Differences in the response to TNF inhibitors at distinct joint locations in patients with psoriatic arthritis: results from nine European registries

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Abstract

Background Efficacy of tumour necrosis factor inhibitors (TNFi) for peripheral arthritis in patients with psoriatic arthritis (PsA) has been established in randomized clinical trials that have used improvement in summated joint counts as an outcome. Whether joints at different anatomical locations might respond differentially to TNFi remains unknown. The aim of the study was to investigate potential variations in the responsiveness to a first tumour necrosis factor inhibitor (TNFi) among joints at distinct locations in patients with psoriatic arthritis (PsA) treated in routine clinical care.

Methods Bionaive PsA patients from nine European countries were included in this observational cohort study if ≥ 1 joint was swollen at the initiation of a first TNFi as monotherapy or added to methotrexate. Only the 28-joint count was available without imaging data confirming the presence of synovitis. The primary outcome was time to first resolution of joint swelling at each joint level. Hazard ratios (HR) for resolution comparing different joint locations were estimated using interval-censored mixed-effects Cox proportional hazards models, including a random effect for country and patient, adjusted for age and sex.

Results A total of 1729 patients with 8397 swollen joints at the start of TNFi were included. Considering the upper extremity, a higher rate of resolution of joint swelling (HR, 95% CI) was observed for the shoulder (1.65, 1.16–2.35) and elbow (1.90, 1.38–2.61), while a lower rate was found for the wrist (0.72, 0.62–0.83) compared to the joints of digit 3. Within fingers, and using the same reference, joint swelling resolved fastest in digit 4 (1.77, 1.49–2.11) and digit 5 (1.88, 1.53–2.31). A lower rate of resolution of joint swelling was found for the knee in comparison to the elbow, the corresponding joint on the upper limb (0.56, 0.40–0.78).

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Conclusion The time to resolution of joint swelling upon treatment with TNFi in patients with PsA seems to depend on the localisation of the affected joints.

Introduction

Psoriatic arthritis (PsA) presents with a diverse range of clinical manifestations, including peripheral arthritis, enthesitis, dactylitis, and axial involvement, accompanied by psoriasis and other extra-musculoskeletal features [1–3]. Various conventional synthetic, biological, and targeted synthetic disease-modifying antirheumatic drugs (cs-, b-, and ts-DMARDs, respectively) have demonstrated efficacy in PsA [4–6]. Emerging evidence suggests that different PsA manifestations may respond differently to particular modes of action of immunosuppressive drugs, necessitating personalized treatment plans based on the domains affected [7]. In the context of peripheral arthritis, disease activity measurements and assessments of treatment response commonly rely on composite indices [8]. Their use has been shown to be superior to the assessment of individual variables [9]. It is assumed that joints at different sites respond similarly to immunosuppressive treatment in general and to specific DMARDs, justifying the use of summated joint counts in composite scores rather than evaluating synovitis changes in individual joints. However, manifold reasons might exist for possible differences in response to DMARDs at distinct articular sites, such as the size of the joint, the degree or volume of synovitis, the weight-bearing load, or the function of the specific joints [10]. Moreover, recent research has revealed transcriptomic differences in human fibroblasts from distinct anatomic regions [11], as well as in synovial fibroblasts from different joint locations in rheumatoid arthritis (RA) [12–14]. These differences translated into joint-specific synovial fibroblast phenotypes with distinct characteristics and responsiveness to cytokines. These differences could impact the response to specific immunosuppressive treatments at the individual joint level [15].

Leveraging a sizable observational cohort within the European Spondyloarthritis (EuroSpA) research collaboration network [16], this study aimed to explore potential differences in the rate of resolution of joint swelling upon treatment with a first tumour necrosis factor inhibitor (TNFi) between different joint locations in patients with PsA treated in routine clinical care.

Methods

Study design and patient population

The EuroSpA research collaboration network uses aggregated data on spondyloarthritides from routine clinical care, comprising information from 16 rheumatology registries across Europe [16]. Nine registries provided data on individual joints in patients registered as having PsA at start of the current study: DANBIO (Denmark), SCQM (Switzerland), ATTRA (Czech Republic), Reuma.pt (Portugal), ICEBIO (Iceland), ROB-FIN (Finland), RRBR (Romania), GISEA (Italy), and TURKBIO (Turkey). A PsA cohort was established between 2000–2013 in the respective registries: DANBIO 2002, SCQM 2006, ATTRA 2002, Rheuma.pt 2009, ICEBIO 2008, ROB-FIN 2000, RRBR 2013, GISEA 2010, and TURBIO 2011. All registries longitudinally collect a broad range of information on patients with inflammatory rheumatic diseases relevant to the real-life management of these patients and particularly on treatment with DMARDs. All nine registries are nationwide, except ROB-FIN and GISEA, which cover only part of Finland and Italy, respectively. The basis for registration of the PsA diagnosis in the different registries is expert rheumatological opinion in DANBIO, SCQM, ATTRA, Reuma.pt, TURKBIO, and ICD-10 in ICEBIO, ROB-FIN, and GISEA [16]. Patients are not only included from the rheumatology departments of non-academic and academic hospitals, but also from private rheumatology practices, with the exception of ROB-FIN and GISEA. The mean number of clinical visits per year is 2–3 in the first year and 1–2 in subsequent years. Electronic data entry is established in all registries. Data completeness for the swollen joint count (28 joints) ranged between 70–100% (DANBIO 80%, SCQM 90%, ATTRA 100%, Reuma.pt 80%, ICEBIO 90%, ROB-FIN 80%, RRBR 100%, GISEA 70%) in a recent study [16]. With regards to PsA treatment, an inadequate response to at least one csDMARD is required before start of a TNFi in all nine countries [17]. Some differences in TNFi retention could be observed between the registries in a previous investigation [18]. The TNF retention rate at 24 months in patients with ≥ 1 swollen joint was 58% in DANBIO, 65% in SCQM, 79% in ATTRA, 80% in Reuma.pt, 57% in ICEBIO, 80% in ROB-FIN, 88% in RRBR, and 86% in TURKBIO. The proportion of TNFi treated patients with concurrent use of a csDMARD differed between the registries: DANBIO 70%, SCQM 65%, ATTRA 80%, Reuma.pt 63%, ICEBIO 53%, ROB-FIN 78%, GISEA 21% [19]. When co-medication was used, methotrexate was the preferred medication in 79% of the patients.

Inclusion criteria for participants in this study were a diagnosis of PsA by the treating rheumatologist, age 18 years or older, and at least one swollen or tender

joint out of 28 at start of a first TNFi between 2000 and 2021 in bio-naïve patients. Considering the fact, that different therapeutic agents might have a distinct influence on the likelihood of specific articular responses [20], as well as the common co-administration of methotrexate with TNFi in patients with PsA in EuroSpA [17, 19], the study included only those patients who commenced their first TNFi either as added to exclusively methotrexate (MTX) or as monotherapy.

Information on swollen and tender joints based on the 28-joint count was used, aligning with the data collection practices on peripheral arthritis in the majority of participating registries [16]. No information was available from the registries regarding the continuity of patient care, specifically the proportion of patients assessed by the same rheumatologist at baseline and during follow-up. We present data on the proportion of patients with involvement of small joints (finger joints and wrists) versus large joints (shoulders, elbows, knees) among the population experiencing swollen joints at baseline. No imaging data to confirm the presence of synovitis at individual joint locations was available [21].

Swollen and tender joints were followed up from the baseline clinical visit, defined as the assessment closest to and within a 30-days window before the registered start of TNFi. Follow-up visits were defined as clinical assessments at 6 months (90–270 days), 12 months (271–450 days), 18 months (451–630 days), and 24 months (631–810 days) after the initiation of the first TNFi. If multiple visits were recorded within a follow-up window, we selected the visit with the most comprehensive information available. In cases where two visits were equally complete, we prioritized the one closest to the midpoint of the follow-up window.

This retrospective observational study on prospectively collected data was performed in accordance with the Declaration of Helsinki. The study was approved by the respective national data protection agencies and research ethical committees according to legal regulatory requirements in the participating countries, as detailed in the supplementary appendix.

Analysis of resolution of joint swelling

The primary outcome was time to first resolution of clinical synovitis, defined as the time to first documented absence of clinical joint swelling after start of the TNFi in joints that were swollen at treatment start. If a joint was swollen at both baseline and a subsequent follow-up visit, we assumed that it had remained swollen between visits. Comparisons between joints were predefined in the protocol according to previous observations regarding the topographic diversity of synovial fibroblasts found to be genetically imprinted according the body axes [12]. A first comparison was performed on the proximal–distal axis of the upper limb (shoulder, elbow, wrist, and joints of digit 3). A second comparison was performed on the anterior–posterior axis of the hand between the joints of digits 1–5. The joints of digit 3 were included in both analyses and therefore served as a reference for both comparisons. Resolution at the level of metacarpophalangeal (MCP) joint versus proximal interphalangeal (PIP) joint of digit 3 was considered a priori to be comparable. This assumption was tested in a sensitivity analysis. Finally, resolution of joint swelling at the knee was compared to the elbow, the corresponding joint on the upper limb.

Analysis of resolution of joint tenderness

A secondary outcome of our study was resolution of joint tenderness, defined as the time to first documented absence of joint tenderness after start of the TNFi in joints that were tender at treatment start, regardless of whether the joints were also swollen. If a joint was tender at both baseline and a subsequent follow-up visit, we assumed that it had remained tender between visits. Tender joints have only been analysed as a secondary outcome, as joint tenderness has a low association with imaging signs of inflammation in PsA [22, 23]. Additionally, tender joints have been found to be less predictive of structural damage progression in PsA compared to swollen joints [24]. The choice of comparisons between individual tender joints was performed in analogy to the analyses of swollen joints.

Statistical methods

We used interval-censored mixed-effects Cox proportional hazards models to estimate the hazard ratios (HR) of resolution of synovitis between different joint locations. All patients receiving at least one dose of TNFi were considered in the analysis. Resolution of joint swelling and resolution of joint tenderness were modelled separately as interval-censored outcome events occurring in the event window between the last visit with and the first visit without swelling or tenderness, respectively, as the status of joint affection was only available at recorded visits. Interval-censoring effectively accounts for the uncertainty of the exact time-point of resolution between visits and for missing visits through using larger intervals. We accounted for the nested data structure by country (multiple patients per country), as well as by patient (multiple joints per patient) by including random effects (tramME R package) [25, 26]. The main models were adjusted for age at TNFi start and sex. In a first sensitivity analysis, we performed an additional adjustment for disease duration, body mass index (BMI), and the use of a csDMARD in the months before start of TNFi (i.e. MTX, as treatment

with other csDMARDs at start of TNFi was restricted to MTX in our study to reduce complexity).

As comparisons included joints from different patients in the main analyses, we addressed potential unknown confounding with respect to baseline patient characteristics with the following sensitivity analyses: Pairwise comparisons between two joint locations were performed exclusively among patients who had affected joints at both locations, ensuring an identical distribution of patient characteristics for both types of joints. The same reference joint(s) were used in this sensitivity analysis as in the main models. To address the issue whether different patient profiles with separate clusters of specific joint involvement might affect the results, we performed an additional sensitivity analysis with adjustment for polyarticular vs. oligoarticular disease based on the 28-joint count. This differentiation defined populations with distinct proportions of large vs. small joint involvement. All types of analysis were also performed in patients starting TNFi as a monotherapy only.

Importantly, the sole availability of the 28-joint count, without data on feet and axial involvement, precluded adjustment for the known subtypes of PsA [27, 28], originally described by Moll and Wright (distal interphalangeal joint involvement only, asymmetrical oligoarthritis, polyarthritis, spondylitis, and arthritis mutilans) [29]. A patient with oligoarticular disease utilizing a 28-joint count might have been classified as having polyarticular PsA if information on all joints had been available.

All analyses were performed with the R language and environment for statistical computing (version 4.2.2, 2022) along with R Markdown, a format for writing reproducible, dynamic reports with R [30, 31].

Results

Patient characteristics at the initiation of a first TNF inhibitor

A total of 1729 bionaive PsA patients had at least one swollen joint out of 28 at start of their first TNFi (8397 swollen joints). The number of patients included from each of the nine European registries is indicated in the supplemental Table S1. The baseline characteristics of the patients at start of TNFi are detailed in Table 1. The mean (SD) age and symptom duration was 49.4 (12.1) and 9.0 (8.6) years, respectively. The proportion of women was 54%. The mean DAS28-CRP was 4.7 (1.0), the mean number of swollen joints was 4.8 (4.1), and the mean

Table 1 Characteristics of patients with PsA and at least one swollen joint at start of first TNFi, pooled across all countries

	All patients starting TNFi (TNFi monotherapy and TNFi added to methotrexate) *N* = 1729		**Subgroup of patients starting TNFi as monotherapy *N* = 406**	
	N		**N**	
Female sex, N (%)	1729	799 (53.8)	406	210 (51.7)
Age, years	1729	49.4 (12.1)	406	49.8 (11.8)
Symptom duration, years	1409	9.0 (8.6)	352	9.8 (9.1)
CRP, mg/l	1645	15.0 (21.5)	376	13.6 (17.3)
DAS28-CRP	1476	4.7 (1.0)	312	4.6 (1.0)
Physician global score	1602	4.9 (2.3)	370	5.2 (2.1)
Patient global score	1559	6.6 (2.3)	339	6.6 (2.2)
Use of methotrexate, N (%)	1729	1323 (76.5)	406	0 (0.0)
Details regarding peripheral arthritis	1729		406	
Tender joints (28 joints count)		7.4 (6.0)		7.0 (5.9)
Swollen joints (28 joints count)		4.9 (4.1)		4.9 (4.1)
Number of joints involved, N (%)				
• < 5 (out of 28)		1043 (60.3)		246 (60.6)
• ≥ 5 (out of 28)		686 (39.7)		160 (39.4)
Type of joints involved, N (%)				
• Only small joints		1034 (59.8)		255 (62.8)
• Only large joints		210 (12.1)		42 (10.3)
• Small and large joints		485 (28.1)		109 (26.8)

Except where indicated otherwise, values represent the mean and SD. Small joints: finger joints and wrist; large joints: elbow, knee, shoulder; *CRP* C-reactive protein, *DAS28-CRP* Disease Activity Score using the 28 joints count and CRP

TNFi Tumour Necrosis Factor inhibitors

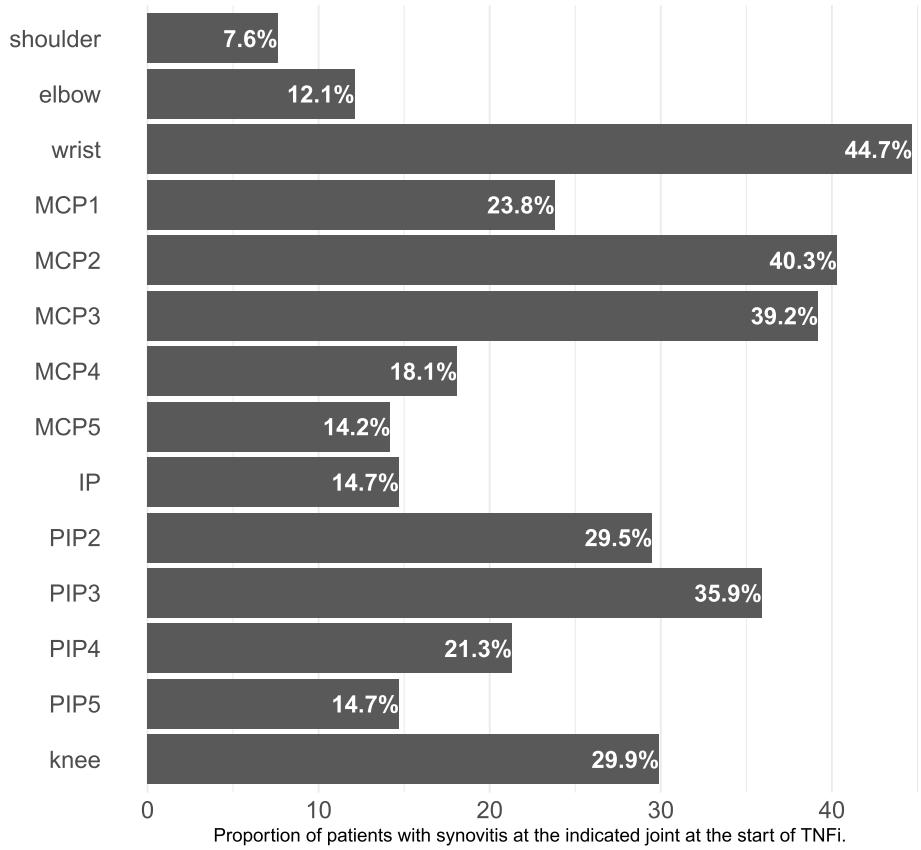

Fig. 1 Proportion of patients with joint swelling at start of treatment with the first tumour necrosis factor inhibitor by joints of the 28-joint set in 1729 patients with PsA and at least one swollen joint at treatment start

number of tender joints was 7.4 (6.0). While the use of the 28-joint count precluded differentiation between patients with true oligoarthritis and polyarthritis, the proportion of patients with involvement of < 5/28 joints and ≥ 5/28 joints was 60% and 40%, respectively (Table 1). Comparable patient characteristics were observed in the subgroup of PsA patients starting TNFi as monotherapy ($N = 406$; Table 1).

Figure 1 depicts the proportion of patients presenting with joint swelling at individual joint locations at TNFi start. This ranged from 44.7% at the wrist to 7.6% at the shoulder. Besides the wrist, the most commonly affected joints included the MCP and PIP joints of digits 2–3 and the knee (Fig. 1). Stratification by the number of involved joints (< 5 vs. ≥ 5) lead to identification of patient profiles with different clusters of involvement at specific locations (patient profiles 1 and 2 in the supplemental table S2). Large joints (particularly the knee) and the wrist were more often involved in oligoarthritis, while finger joints synovitis was more prevalent in polyarthritis.

Site-specific resolution of joint swelling in PsA

Resolution of synovitis was observed in 5604 out of 8397 joints that were swollen at baseline (67%). The number of events (resolutions of swollen joints) per individual location is presented in the supplemental table S3. Median (lower, upper quartile) duration to resolution as measured by the event windows (time between the start and end of the event interval) was 189 (168, 259) days. Time to study exit (time to loss to follow-up if resolution of joint swelling was not observed or to the end of the event interval if resolution of joint swelling was observed was 203 (168, 364) days. For 79% of the assessed joints, treatment with the first TNFi continued until study exit.

In a descriptive analysis of joints that were swollen at various locations at the start of TNFi, we assessed the proportion of joints that remained swollen at 6, 12, 18, and 24 months within patients with evaluated joints. The results are shown in Fig. 2A for the proximal–distal axis of the upper limb and the knee and in Fig. 2B for the anterior–posterior axis (digits 1–5 of the hand). Clinical synovitis resolved in over 75% of joints assessed

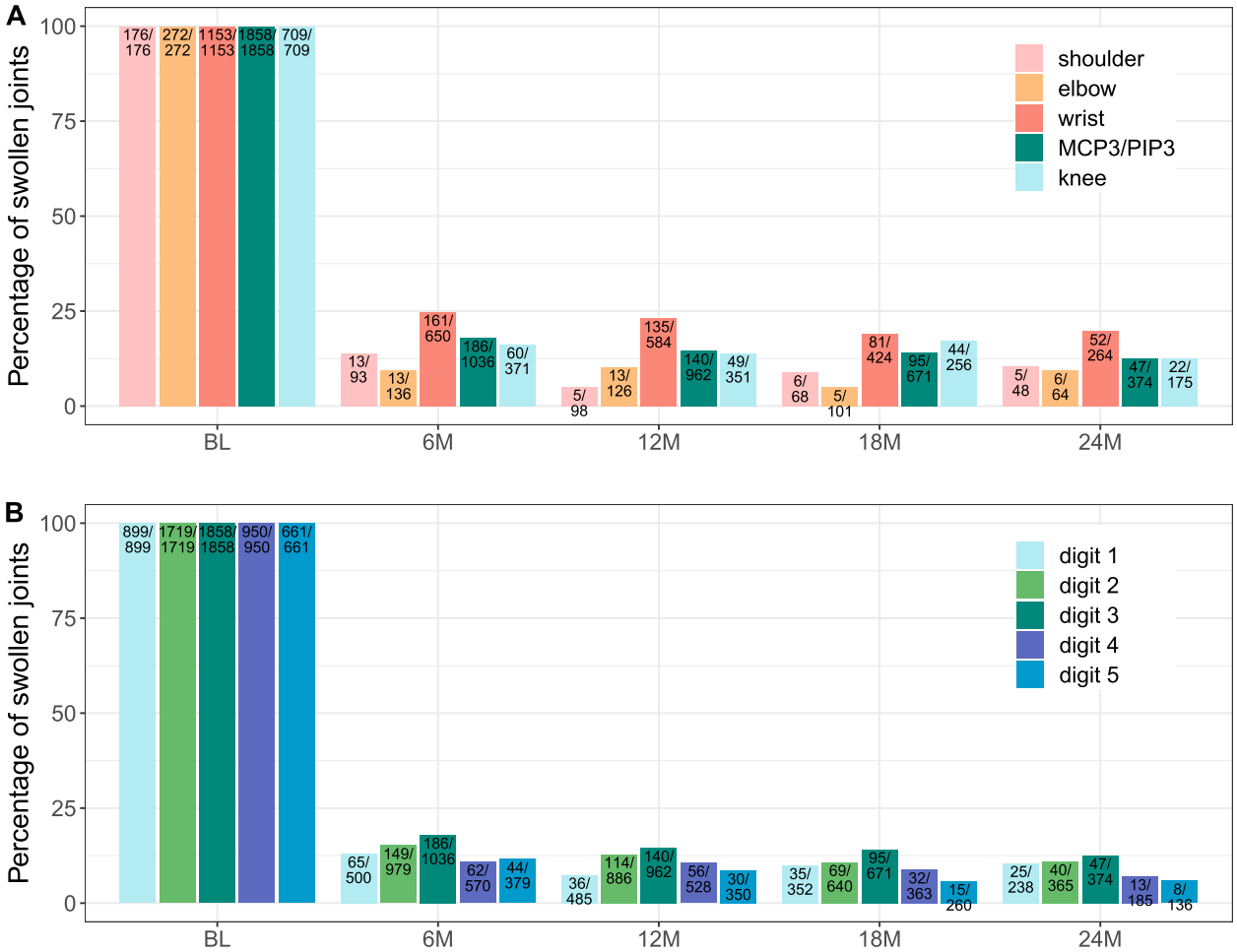

Fig. 2 Proportion of swollen joints at individual locations of the 28-joint count at follow-up visits after start of treatment with the first tumour necrosis factor inhibitor (TNFi) in joints that were swollen at baseline (BL). The proportions were calculated in relation to the total number of joints assessed at 6, 12, 18, and 24 months. **A** Joints located along a proximal–distal axis of the upper extremity and the knee. **B** Joints positioned along an anterior–posterior axis of the hand (digits 1–5). Metacarpophalangeal and proximal interphalangeal joints of each digit were combined for analysis

at all locations within the initial 6 months. Along the proximal–distal axis of the upper extremity, the wrist exhibited a higher persistence of swelling compared to the other joints (Fig. 2A). Minor differences were noted between digits, with the index and middle fingers retaining joint swelling slightly more frequently at follow-up compared to the thumb and more ulnar fingers (Fig. 2B). Notably, only a few joints (< 7%) developed palpable synovitis during TNFi treatment among those not affected at baseline (supplemental figure S1). New joint swelling most commonly emerged at the wrist and the finger joints of the digits 2 and 3.

Adjusted mixed-effect Cox proportional hazards analyses were conducted to explore the rate of resolution of clinical synovitis at different sites. All joints with follow-up assessment(s) contributed to this analysis (6197 joints, from 1173 patients). Baseline characteristics of these patients are shown in the supplemental Table S4. On the proximal–distal axis of the upper limb and compared to the joints of digit 3, a significantly higher rate of joint

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Fig. 3 Rate of resolution of swollen joints (HR and 95% CI) after start of tumour necrosis factor inhibitor treatment estimated using overall interval-censored mixed-effects Cox proportional hazards models adjusted for age and sex for different comparisons: **A** joints along the proximal–distal axis of the upper limb, **B** finger joints along the anterior–posterior axis of the hand (digits 1–5), **C** knee compared to elbow. The reference joint(s) are indicated in each panel. The number of swollen joints and the number of patients are shown for each joint location. MCP3 = metacarpophalangeal joint of digit 3; PIP3 = proximal interphalangeal joint of digit 3

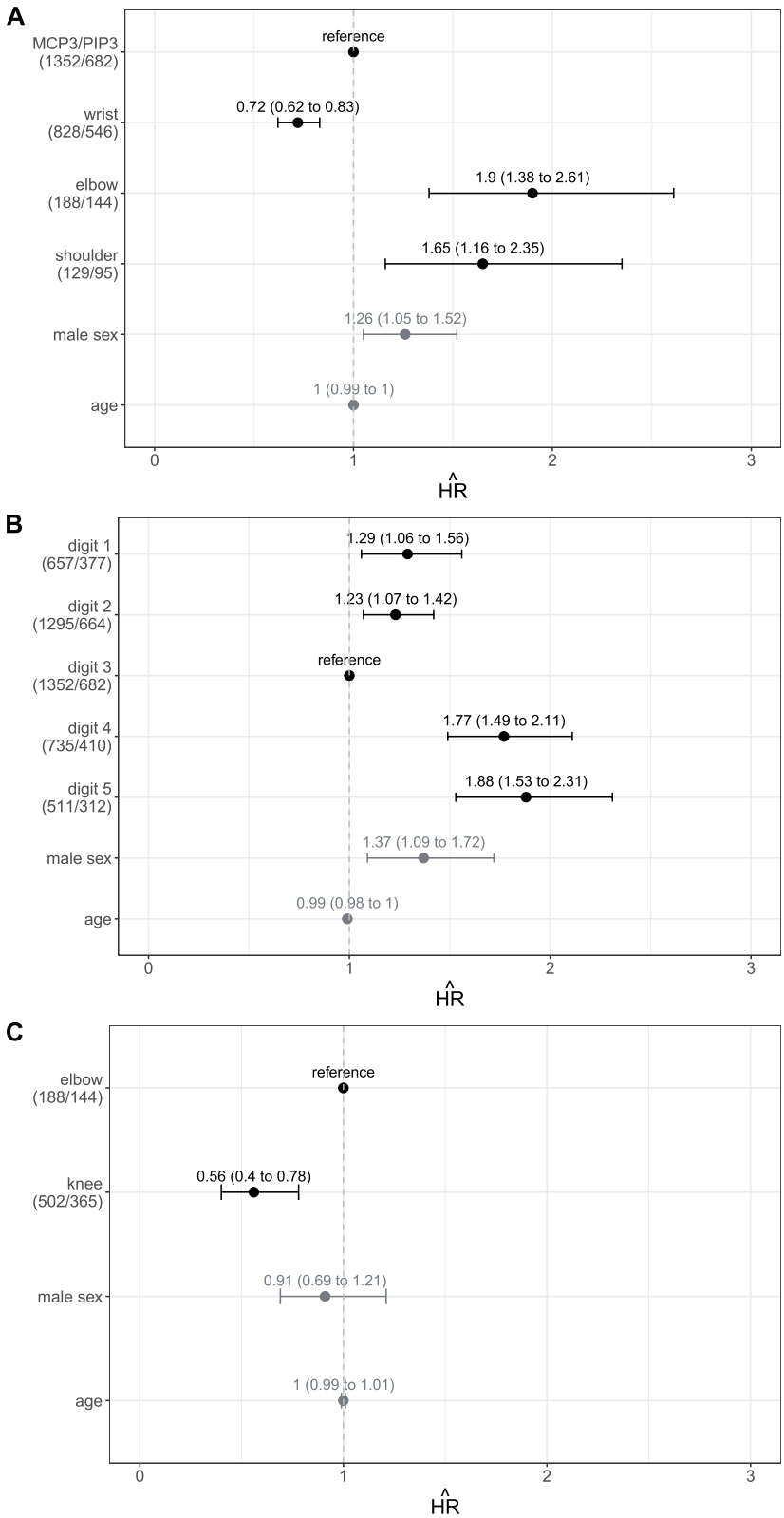

Fig. 3 (See legend on previous page.)

swelling resolution was identified for the elbow and the shoulder (HR 1.90, 95% CI 1.38–2.61 and HR 1.65, 95% CI 1.16–2.35, respectively, Fig. 3A). Conversely, a lower rate of joint swelling resolution was observed at the wrist (HR 0.72, 95% CI 0.62–0.83) compared to the joints of digit 3. These estimates were confirmed in a model that analyzed resolution of synovitis at MCP3 and PIP3 separately on the proximal–distal axis, with PIP3 serving as reference (supplemental figure S2). A comparable rate of joint swelling resolution was found for MCP3 in comparison to PIP3 (HR 0.91, 95% CI 0.75–1.10).

The joints of digit 3 also served as a reference to compare resolution of synovitis along the anterior–posterior (radio-ulnar) axis of the hand (Fig. 3B). We found an U-shaped pattern of response with a significantly higher rate of joint swelling resolution in joints of digits 1, 2, 4, and 5, compared to digit 3. The best response was observed in digits 4 and 5 (HR 1.77 (95% CI 1.49–2.11), and HR 1.88 (95% CI 1.53–2.31), respectively. We also compared the resolution of joint swelling between the knee, as the only weight-bearing joint and only representative of the lower limb on the 28-joint count, and the elbow, the corresponding joint on the upper limb with a similar range of motion (Fig. 3C). A lower rate of resolution of joint swelling was found for the knee vs. the elbow (HR 0.56, 95% CI 0.40–0.78). In contrast, the responses at the knee and digit 3 levels were comparable (HR 1.11, 95% CI 0.90–1.36).

Differences in hazards of resolution of joint swelling found between individual joints in all three major comparisons were also confirmed after adjustment for the patient profiles with distinct joint involvement clusters identified through stratification by the number of involved joints (<5 vs. ≥ 5; Fig. 4A-C), as well as after adjustment for MTX treatment prior to TNFi start, disease duration, and BMI (supplemental figure S3). All findings were also confirmed in pairwise comparisons of joints affected simultaneously in the same patients, which were performed to avoid residual confounding by differences in patient characteristics (Table 2). In comparison to the joints of digit 3, a significantly higher rate of resolution of joint swelling was found for the shoulder, the elbow, and joints of digits 1, 2, 4, and 5, while a lower rate of resolution was observed for the wrist. Digits 4 and 5 consistently exhibited higher estimates of synovitis resolution rates compared to the other fingers. A comparable lower rate of resolution of joint swelling was estimated for the knee vs. the elbow (0.55, 95% CI 0.27–1.10; Table 2). However, given the much lower number of joints, statistical significance was not reached in this sub-analysis.

The same trends were confirmed in patients with PsA starting TNFi as monotherapy (23% of the whole population; Fig. 5). An exception involved the comparison between the wrist and the reference joints on the proximal–distal axis of the upper limb (finger joints of digit 3). No evidence for a difference in the rate of resolution of joint swelling was found at these sites during TNFi monotherapy in both the overall model (HR 1.04, 95% CI 0.74–1.44, Fig. 5A) and in a pairwise comparison in patients affected with synovitis at both sites (HR 1.23, 95% CI 0.83–1.83). A numerically lower rate of resolution of joint swelling was also found for the knee in comparison to the elbow (HR 0.42, 95% CI 0.11–1.68; Fig. 5C).

Site-specific resolution of joint tenderness in PsA

The assessment of agreement between clinical synovitis and joint tenderness yielded a moderate Cohen's Kappa value of 0.54 (95% CI 0.53–0.55). The patterns observed for resolution of joint tenderness on the proximal–distal and the anterior–posterior axes, as well as for the knee vs elbow were consistent with the patterns observed for synovitis resolution (Fig. 6A-C). The most notable discrepancy was found for the shoulder. A lower rate of resolution of tenderness was found at this site in comparison to the joints of digit 3 (Fig. 6D).

Discussion

In this multinational study, which included over 1700 patients with PsA, and 8000 individual joints, we present compelling evidence that the clinical response to TNFi may also be contingent upon the specific joint location. Employing a 28-joint count, our findings revealed that the most favourable responses to TNFi were observed in the proximal joints of the upper limb and the MCP

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Fig. 4 Rate of resolution of swollen joints (HR and 95% CI) after start of TNFi with *additional adjustment for patient profiles with different joint involvement clusters* in comparison to Fig. 3. The rate of resolution of synovitis for different comparisons (**A**, **B**, **C**) is estimated using overall interval-censored mixed-effects Cox proportional hazards models: **A** joints along the proximal–distal axis of the upper limb, **B** finger joints along the anterior–posterior axis of the hand (digits 1–5), **C** knee compared to elbow. The reference joint(s) are indicated in each panel. The numbers of swollen joints and of patients are shown for each joint location. MCP3 = metacarpophalangeal joint of digit 3; PIP3 = proximal interphalangeal joint of digit 3

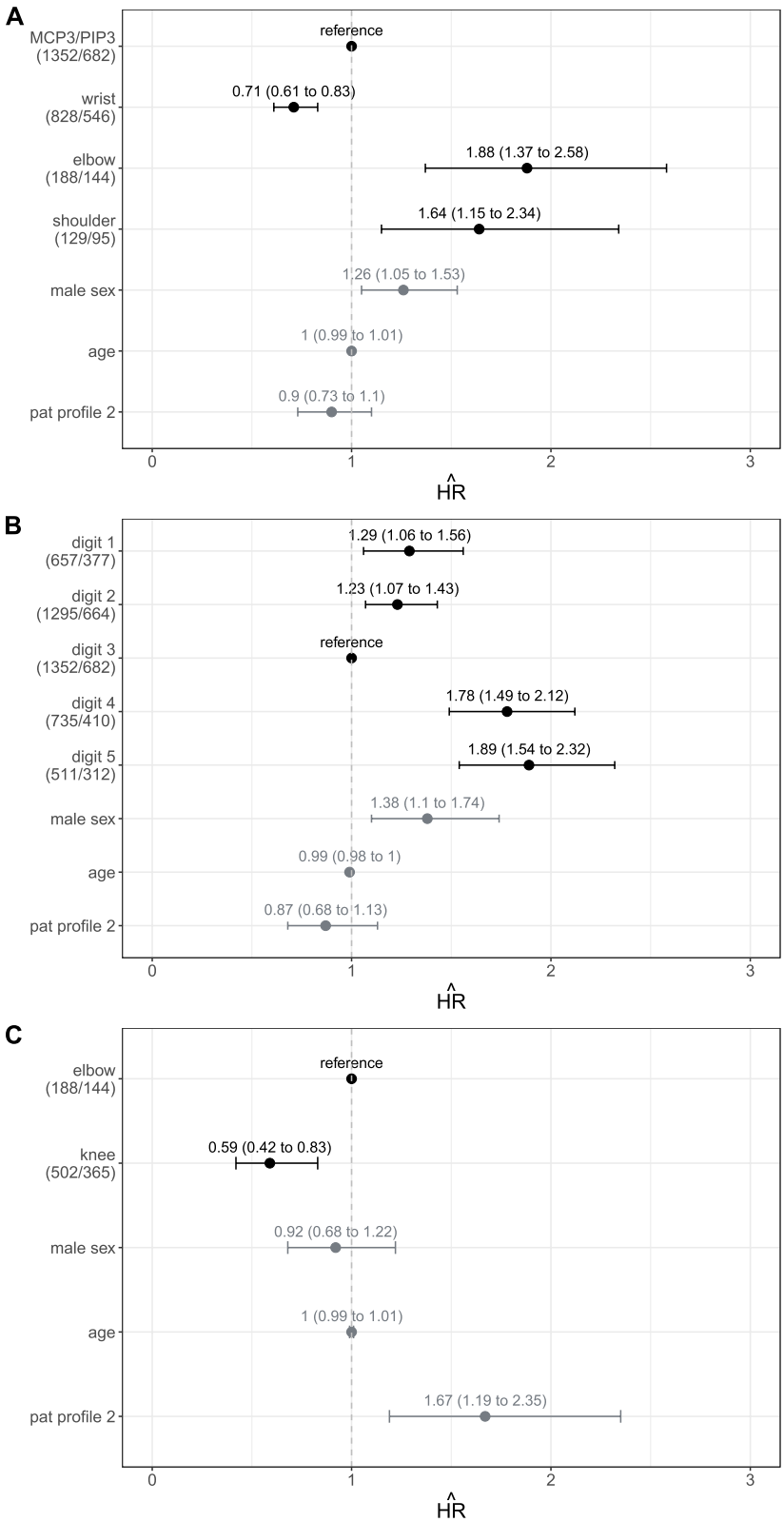

Fig. 4 (See legend on previous page.)

Table 2 Rate of resolution of swollen joints after start of TNFi in pairwise comparisons of joints (subgroups of patients affected at both sites)

	Site of joint	Number of affected joints/ patients	Reference joint(s)	HR (95% CI)
Proximal–distal axis of upper limb	Shoulder	(74/56)	MCP3/PIP3	3.27 (1.27; 8.42)
	Elbow	(99/78)	MCP3/PIP3	3.89 (1.80; 8.40)
	Wrist	(537/338)	MCP3/PIP3	0.75 (0.63; 0.90)
Anterior–posterior axis of the hand (digits 1–5)	MCP1/PIP1	(490/264)	MCP3/PIP3	1.43 (1.14; 1.79)
	MCP2/PIP2	(1107/539)	MCP3/PIP3	1.24 (1.05; 1.46)
	MCP4/PIP4	(650/352)	MCP3/PIP3	2.01 (1.65; 2.44)
	MCP5/PIP5	(431/247)	MCP3/PIP3	2.33 (1.83; 2.96)
Knee vs. elbow	Knee	(103/75)	Elbow	0.55 (0.27; 1.10)

Estimates of resolution rates (HR and 95% CI) from individual interval-censored mixed-effects Cox proportional hazards models. Confounding is minimized since patient characteristics are equally distributed for both joint sites in each comparison

and PIP joints of fingers 4 and 5 when compared to the joints of the third digit. In contrast, the estimated rate of response was lowest for the wrist, the joints of the third finger, and the knee. The results were consistent over several sensitivity analyses. The data on the time required for synovitis to resolve after start of TNFi in individual joints was used to estimate the hazard (or rate) of resolution for specific articular sites. Our approach also indirectly identified those joints that were less likely to resolve despite TNFi treatment. New synovitis occurred in < 7% of joints not involved at baseline.

Potential unknown confounding related to differences in baseline patient characteristics was addressed by analyzing the resolution of joint swelling through pairwise comparisons of joints in subgroups of patients with simultaneous involvement at both locations. Additionally, sensitivity analyses were conducted, adjusting for diverse patient profiles characterized by distinct joint clusters. These supplementary evaluations supported the robustness of our findings. Nevertheless, our reliance on the 28-joint count, lacking data on involvement of distal interphalangeal joints, feet, and the axial skeleton, constrained our ability to test potential confounding from established subtypes of PsA [27–29]. Furthermore, we recognize the potential for bias, particularly concerning joints like the shoulder that are inherently more challenging to assess or potential differences in the degree of synovitis at individual joints. This difficulty is compounded by the absence of imaging data to validate the presence and the degree of synovitis at specific joint sites.

The wrist was the most commonly affected joint at the start of treatment with TNFi in the current analysis. This finding is consistent with data from a randomized controlled study of PsA patients starting tofacitinib or methotrexate, which also reported individual joint information [20]. In a broader, unselected PsA population, the wrist may be less frequently affected, although it ranked third, following the MCP 2 and 3 joints, in terms of joint involvement in a national PsA registry of patients under real-life conditions [32]. The wrist, along with the knee and the PIP3 joint, is also among the most commonly affected joint in oligoarticular PsA [33]. However, wrist involvement seems to be more frequently observed in late PsA as compared to early PsA [34].

Various factors contributing to potential variations in treatment response across distinct joint sites have been proposed: disparities in joint size, mechanical stress linked to the function of specific joints or to weight-bearing, and differences in the profiles of local cells, with a particular emphasis on synovial fibroblasts at various sites [15].

The role of mechanical stress, particularly at entheseal sites, in the pathogenesis of spondyloarthritides is established [35]. The concept of the synovio-entheseal complex provides the linkage between microdamage associated with mechanical loading and

(See figure on next page.)

Fig. 5 Rate of resolution of swollen joints (HR and 95% CI) in the subgroup of patients on tumour necrosis factor inhibitor monotherapy estimated using overall interval-censored mixed-effects Cox proportional hazards models adjusted for age and sex for different comparisons: **A** joints along the proximal–distal axis of the upper limb, **B** finger joints along the anterior–posterior axis of the hand (digits 1–5), **C** knee compared to elbow. The reference joint(s) are indicated in each panel. The number of swollen joints and the number of patients is shown for each joint location. MCP3 = metacarpo-phalangeal joint of digit 3; PIP3 = proximal interphalangeal joint of digit 3

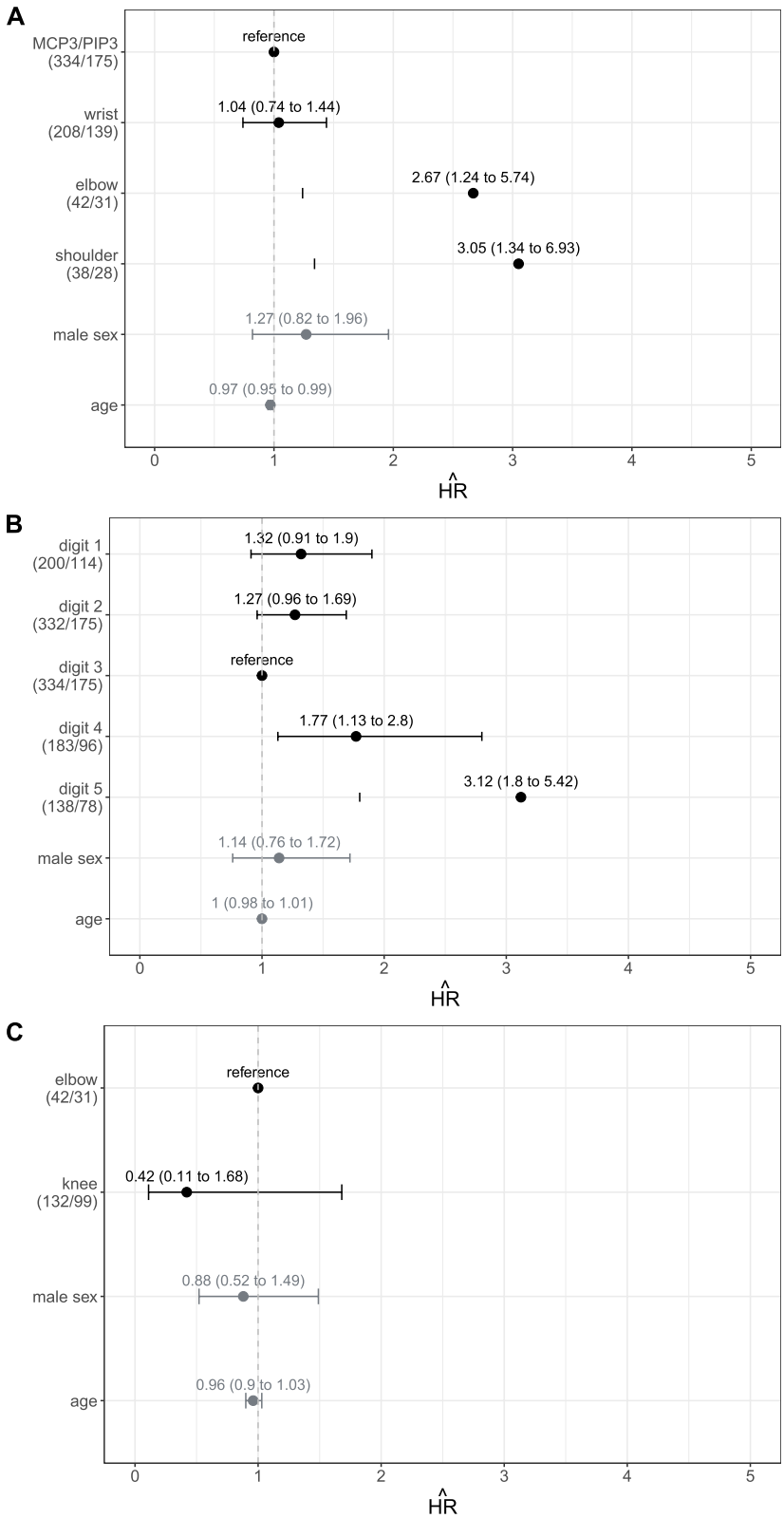

Fig. 5 (See legend on previous page.)

joint inflammation in PsA and axSpA [36]. An association also exists between a physically traumatic event and the onset of musculoskeletal manifestations at specific sites in PsA and is known as the "deep Koebner" phenomenon [37, 38]. A correlation between occupational-related mechanical stress and radiographic damage has been previously found in PsA, but the results were presented as summed damage scores and not tied to specific locations [39]. The observation that the rate of synovitis resolution was lower for the knee, the sole weight-bearing joint in the 28-joint count, compared to the elbow, could suggest that joints more susceptible to mechanical stress respond less effectively to TNFi. However, the joints of the third digit, which exhibited the lowest rate of resolution of synovitis along the anterior–posterior axis of the hand, are not the most biomechanically affected joints of the hand [40]. Moreover, adjustment for BMI did not affect our results.

More common persistence of synovitis at the wrist, as well as at digits 2 and 3, has also indirectly been shown for RA, making confounding by the type of PsA unlikely. In a prospective Swedish RA cohort study, the wrist, the PIP-3 joint, and the MCP-2 joint were the first joints of the hand to develop radiographic damage [41]. A more recent sub-analysis of the BeSt study, a Dutch RA strategy trial including a TNFi arm, revealed that, compared to all other joints in the 66-joint count, the wrist and the MCP and PIP joints of the index and middle fingers were most frequently associated with recurrent synovitis after initial resolution with targeted treatment [42]. Long-term cumulative local joint inflammation in these joints was further linked to joint damage progression [43]. Whether these findings in RA and our results in PsA here are related to the recently unveiled important transcriptional and epigenetic diversity encoded in the homeobox (HOX) gene loci in synovial fibroblasts found in hand and finger joints versus more proximal joints in RA, which translated into specific joint phenotypes [12–14], remains unknown.

In order to investigate a potential relationship between putative transcriptomic, epigenomic, and phenotypical cell differences at distinct joints in PsA and their varied response to treatment, sequential synovial biopsies taken from different sites during treatment would be needed in future studies. Moreover, exploring whether a particular joint response pattern in PsA is associated with distinct therapeutic modes of action seems warranted.

We utilized swollen joints as the primary outcome in the present study to specifically address joint inflammation. A noteworthy discrepancy in the resolution of swollen vs. tender joints was particularly evident at the level of the shoulder. This may be attributed to the greater clinical challenge in assessing shoulder synovitis. Moreover, shoulder tenderness could result from more common pathologies such as rotator cuff tendinopathy. The shoulder should therefore be omitted from comparable analyses in the absence of imaging data confirming the presence of synovitis.

Several limitations in our study have to be acknowledged. Data on individual joints, in contrast to summed swollen or tender joint counts, was only available for a subgroup of patients followed in the EuroSpA research network [16]. Furthermore, most registries employed the 28-joint count. Enhancing the feasibility of observational multinational studies, the 28-joint count seems reasonable for a proof-of-concept study aimed at exploring potential differences between joints. The use of the 28-joint count, in comparison to the 66/68-joint count, demonstrated significantly higher concordance between different examiners [44], proving advantageous in the context of an observational study conducted by rheumatologists in primary, secondary, and tertiary centres across nine European countries. While DAS28 response criteria have been validated for PsA [45], they might be particularly problematic in patients with oligoarticular disease [33].

Another limitation arises from the lack of information on the use of systemic glucocorticoids or local steroid injections at specific joints before and after start of TNFi treatment in the EuroSpA dataset available for analysis.

While our focus in this study was exclusively on peripheral arthritis, it is worth noting that site-specificity of response may also be observed for other PsA manifestations, like enthesitis [46], dactylitis, and psoriatic skin disease [47].

Strengths of our analyses include the prospective assessment of treatment response at individual joint sites during real-life clinical follow-up throughout Europe and statistical methods that effectively account

(See figure on next page.)

Fig. 6 Rate of resolution of tender joints (HR and 95% CI) after start of tumour necrosis factor inhibitor treatment estimated using overall interval-censored mixed-effects Cox proportional hazards models adjusted for age and sex for different comparisons: **A** joints along the proximal–distal axis of the upper limb, **B** finger joints along the anterior–posterior axis of the hand (digits 1–5), **C** knee compared to elbow. The reference joint(s) are indicated in each panel. The number of swollen joints and the number of patients is shown for each joint location. MCP3 = metacarpophalangeal joint of digit 3; PIP3 = proximal interphalangeal joint of digit 3

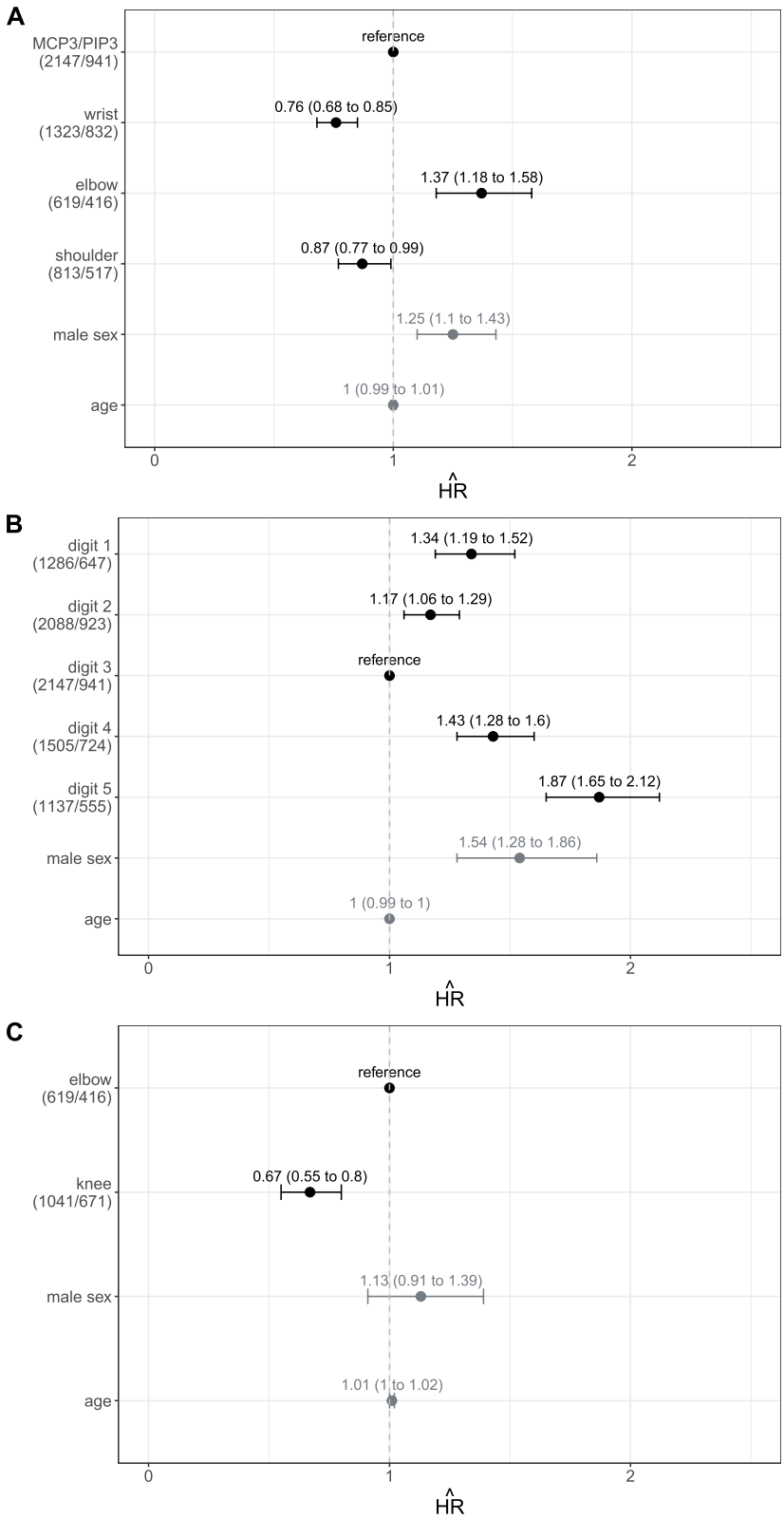

Fig. 6 (See legend on previous page.)

for the complex grouped data structure within the EuroSpA research collaboration network.

In conclusion, our analysis suggests that the clinical response to TNFi treatment in PsA with regards to peripheral arthritis is influenced by the specific location of the affected joint.

Supplementary Information

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Supplementary Material 1.

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Patient and public involvement statement
Patients were involved in the reporting and dissemination plans of this research.

Authors' contributions
All coauthors have contributed significantly in accordance with contributorship guidelines, as detailed in the CRediT statement provided in the supplementary table S5 of the manuscript.

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Data availability
Data are not publicly available for legal and logistical reasons. It would require permissions from the data owners, represented by each contributing registry.

Declarations

Ethics approval and consent to participate
The study was approved by the respective national data protection agencies and research ethical committees according to legal regulatory requirements in the participating countries (online supplemental table S6).

Consent for publication
Not required.

Competing interests
AG reports a grant from Novartis (paid to employer). AGL reports a research grant from Novartis; speaking and/or consulting fees from Abbvie, Janssen, Eli Lilly, MSD, Novartis, Pfizer, and UCB; and being a paid instructor for Pfizer. BeG reports a grant from Novartis (paid to institution); grants from Abbvie, BMS, and Sandoz paid to the institution, outside the submitted work. BrM reports a research grant from Novartis paid to the employer (outside the submitted work); speaker fees from Novartis; grants from the Research Council of Norway to the Centre for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY). CC reports speaking and consulting fees from Abbvie, Amgen, Boehringer-Ingelheim, Ewopharma, Eli Lilly, Novartis, and Pfizer. 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