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ORIGINAL ARTICLE

Major trends in the manifestations and treatment of rheumatoid arthritis in a multiethnic cohort in Singapore

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Abstract We analyzed the epidemiological changes of rheumatoid arthritis (RA) over three decades using patients from a single center in Singapore. All patients who fulfill the 1987 American College of Rheumatology criteria for RA were invited to enroll in a prospective disease registry. We analyzed the patient demographics, disease manifestation, management and patient-reported outcomes, including quality of life (QoL), in the three categories according to the year of disease onset: before 1989 (group I), 1990–1999 (group II) and after 2000 (group III). There were 1,153 patients with 231, 532 and 390 in groups I, II and III, respectively. The mean disease durations were 25, 12 and 4.8 years, respectively. The majority was female (84.1 %) and Chinese (76.6 %) with no socio-demographic differences across the three periods. The age of onset rises and the prevalence of rheumatoid factor falls with the proximity of disease onset. Patients with most recent disease onset had the earliest access to the rheumatologist. They also had the highest tender and swollen joint counts, lowest deformed joint count and highest remission rate. Patients in group I report better mental and emotional QoL though many developed marked disability. We have documented changes of the manifestations of RA that are dependent and independent of improved treatment. Significant differences in accessibility to the rheumatologist, RA activity, functional capacity, quality of life and comorbidities were seen in subsequent cohorts due to treatment evolution and more efficient healthcare delivery.

Keywords Rheumatoid arthritis · Asian · Epidemiology · Functional status · Quality of life · Outcome measures

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Introduction

We are witnessing major secular changes in the epidemiology of rheumatoid arthritis (RA). Some changes may be explained by better treatment; for example, RA is becoming milder, with lower disease activity, fewer erosions and fewer extra-articular features (EAF) [1–3]. Improved diagnosis and physician awareness may explain why fewer RA patients now test positive for the rheumatoid factor [4–7]. But the reasons for the increasing age of disease onset [8–10] or the U-shaped incidence of RA are unclear [11–13].

Our knowledge of the epidemiology of RA is derived primarily from studies in Western populations [14, 15]. Studies of Chinese patients have been largely population-based prevalence surveys [16, 17]. These retrospective small-scale studies suggest that RA in Asians behaves differently from that in Caucasians, such as the predilection for the wrist joint and milder course [18, 19]. Because of this, we wanted to understand the major trends in disease expression and management in this country.

We studied the clinical features, patient-reported and treatment outcomes of a large multiethnic Asian

(predominantly Chinese) RA cohort according to the year of disease onset: 1960–1989 (group I), 1990–1999 (group II) and 2000–2005 (group III). These arbitrary periods were chosen to provide representative numbers of patients for the analysis and to mark the treatment epochs (1990 saw the introduction of methotrexate (MTX) and 2000 the biologics in this country). This report provides three different kinds of temporal information: the secular change in disease phenotype (such as age of onset and serology results), RA features that manifest at different times in the course of illness (such as joint damage, disease activity, EAF and comorbidity) and the effects of treatment (such as types and number of drugs used, access to specialists and tempo of initiating and escalating therapy) [20].

Patients and methods

RA patients attending the outpatient clinic of the Department of Rheumatology, Allergy and Immunology at Tan Tock Seng Hospital (TTSH) were invited to participate in the study. Patients at least 18 years of age who fulfill the 1987 American College of Rheumatology revised criteria for RA were recruited [21]. Informed consent was obtained from patients or their legal guardians according to the Helsinki Declaration. The work was approved by the Institutional Review Ethics Board.

Our center, established in 1994, is the first and largest Rheumatology specialist unit in the country. We estimate that 90 % of RA patients in Singapore are managed by rheumatologists in three public hospitals, and about 75 % of these are treated in our center. About 75 % of RA patients managed in our institution have been enrolled into the study. Therefore, this cohort is a good representation of RA in this country.

Data collection

The RA patients entered a disease registry that collects these data prospectively: socio-demographic profile, clinical data including the presence of comorbidities, EAF, physician's global assessment of RA activity, tender (TJC), swollen (SJC) and damaged (DJC) joint counts, DAS28 score [22], visual analog scale score for patient-reported general health, RA activity and pain, drug treatment, ACR functional capacity [23], health assessment questionnaire (HAQ) [24], QoL measurement using the Short-Form 36 [25, 26], radiographic erosion and laboratory tests. For this report, we analyzed the latest study visit of every enrolled RA patient. If the patient was illiterate, a research assistant helped in the administration of the questionnaire. The attending rheumatologists performed the joint assessment and completed the protocol at every study visit.

DAS28 was used to catalog RA activity. Remission was defined as DAS28 below 2.6 [27]. Mild, moderate and highly active disease was defined by DAS scores between 2.6 and 3.2, 3.3 and 5.1 and above 5.1, respectively.

Statistical analysis

Statistical analysis was performed with Stata 9.0 (College Station, Texas 77845, USA). Continuous variables were presented as mean ± standard deviation (SD) and categorical variables as numbers and percentages. Chi-square test was used to compare associations between period of onset of RA and categorical variables. One-way ANOVA test was used to compare variable means between the three periods. In the event of nonnormality in the data, we used the Kruskal–Wallis test. The level of statistical significance was set at 5 %.

Results

Description of patient cohort

We recruited 1,153 RA patients (Table 1). According to our predefined periods of disease onset, 231 patients were classified to group I (onset between 1960 and 1989), 532 to group II (onset between 1990 and 1999) and 390 to group III (onset between 2000 and 2005). The mean disease duration for groups I, II and III was 25, 12 and 4.8 years, respectively.

The mean age of the entire cohort was 57.1 years and the majority (84.1 %) was female. With regard to ethnicity, 76.6 % were Chinese, 12.1 % Indian and 8.5 % Malay. The most common first languages spoke and/or written were Chinese and English. The majority (67.7 %) of the patients was married and had attained a highest education level of secondary school and below (equivalent to less than ten years of education). Monthly household income was generally below S$4,000 (79.7 %) with median household income in the $2,000–$2,999 bracket. Most patients were homemakers (40.6 %), clerical/service industry workers (17.4 %) and retirees (15.9 %). The three groups were comparable in gender, ethnicity, marital status, language background, educational level and household income despite a span of 45 years in RA onset (1960–2005).

The majority of our patients were nonsmokers (85.6 %); only 7.6 % were current smokers as of the last study visit and 6.8 % were ex-smokers. Smoking does not play a significant role in the pathogenesis of RA in Asians in this country.

Clinical and laboratory features

The number of tender and deformed joints (but not swollen joints) were significantly different across the three groups,

Table 1 Socio-demographic characteristics of the cohort of 1,153 RA patients

Characteristics	Whole cohort	Onset 1960–1989	Onset 1990–1999	Onset 2000–2005	*p* value
Age at study visit (years)					
Mean (SD)	57.1 (12.6)	60.8 (11.4)	57.6 (12.2)	54.2 (13.2)	<0.001‡
Median (IQR)	56.8 (49.5–65.6)	60.8 (53.7–68.8)	56.9 (50.4–65.1)	54.8 (46.1–62.8)	
Gender					
Female	970 (84.1 %)	204 (88.3 %)	450 (84.6 %)	316 (81 %)	0.052†
Ethnicity					
Chinese	883 (76.6 %)	178 (77.1 %)	410 (77.1 %)	295 (75.6 %)	0.713†
Malay	98 (8.5 %)	18 (7.8 %)	46 (8.7 %)	34 (8.7 %)	
Indian	139 (12.1 %)	29 (12.6 %)	57 (10.7 %)	53 (13.6 %)	
Others	33 (2.9 %)	6 (2.6 %)	19 (3.6 %)	8 (2.1 %)	
Marital status					
Single	160 (13.9 %)	33 (14.3 %)	69 (13 %)	58 (14.9 %)	0.766†
Married	780 (67.7 %)	148 (64.1 %)	366 (68.8 %)	266 (68.2 %)	
Widowed	156 (13.5 %)	36 (15.6 %)	73 (13.7 %)	47 (12.1 %)	
Divorced	57 (4.9 %)	14 (6.1 %)	24 (4.5 %)	19 (4.9 %)	
First language					
English	329 (28.5 %)	55 (23.8 %)	164 (30.8 %)	110 (28.2 %)	0.702†
Chinese	311 (27.0 %)	70 (30.3 %)	131 (24.6 %)	110 (28.2 %)	
Malay	92 (8.0 %)	17 (7.4 %)	46 (8.7 %)	29 (7.4 %)	
Chinese dialect	309 (26.8 %)	67 (29.0 %)	142 (26.7 %)	100 (25.6 %)	
Tamil	99 (8.6 %)	20 (8.7 %)	44 (8.3 %)	35 (8.6 %)	
Others	13 (1.1 %)	2 (0.9 %)	5 (0.9 %)	6 (1.5 %)	
Educational level					
No formal education	244 (21.2 %)	45 (24.5 %)	89 (21.1 %)	64 (20.1 %)	0.187†
Primary	280 (24.3 %)	49 (26.6 %)	104 (24.6 %)	73 (22.9 %)	
Secondary	453 (39.3 %)	64 (34.8 %)	165 (39.1 %)	133 (41.7 %)	
A level/polytechnic	98 (8.5 %)	19 (10.3 %)	33 (7.8 %)	25 (7.8 %)	
Tertiary	78 (6.8 %)	7 (3.8 %)	31 (7.4 %)	24 (7.5 %)	
Household income					
No income	148 (12.9 %)	25 (10.8 %)	74 (13.9 %)	49 (12.6 %)	0.637†
$1–999	91 (7.9 %)	17 (7.4 %)	37 (6.97 %)	37 (9.49 %)	
$1,000–1,999	305 (26.5 %)	59 (25.5 %)	151 (28.4 %)	95 (24.4 %)	
$2,000–2,999	239 (20.8 %)	46 (19.9 %)	101 (19 %)	92 (23.6 %)	
$3,000–3,999	134 (11.6 %)	30 (13.0 %)	59 (11.1 %)	45 (11.5 %)	
$4,000–4,999	90 (7.8 %)	21 (9.1 %)	45 (8.5 %)	24 (6.2 %)	
$>5,000	144 (12.5 %)	33 (14.3 %)	63 (11.9 %)	48 (12.3 %)	
Age at diagnosis, years					
Mean (SD)	47.5 (13.3)	42.7 (14.2)	47.6 (12.6)	50.1 (12.9)	<0.001‡
Median (IQR)	47.4 (38.8–55.9)	42.4 (32.6–53.3)	46.8 (39.3–55.4)	50 (42–58.3)	
Disease duration, years					
Mean (SD)	12.1 (8.2)	25 (6.5)	12 (3.4)	4.8 (2.4)	0.0001*
Median (IQR)	10.5 (6.2–16.2)	23.4 (20–28.3)	12.1 (9.3–14.7)	4.9 (3–6.9)	
Interval from onset to first visit, months					
Mean (SD)	41.1 (70.0)	123.5 (111.0)	30 (36.3)	7.7 (11.4)	0.0001*
Median (IQR)	12.5 (4.1–48.8)	121.8 (30.5–183.5)	13 (5–46.4)	5.2 (2.8–12.2)	
Interval from onset to diagnosis, months					
Mean (SD)	29.4 (54.7)	79.2 (97.1)	23.6 (30.0)	8 (9.6)	0.0001*

Table 1 continued

Characteristics	Whole cohort	Onset 1960–1989	Onset 1990–1999	Onset 2000–2005	*p* value
Median (IQR)	9.1 (3–28.4)	40 (4.1–121.8)	12.2 (3.1–36.5)	5 (3–12.2)	

Household income is reported in Singapore currency. At the time of writing, one Singapore dollar was worth US$0.70

Not all columns add up to the same total because of missing values

* Kruskal–Wallis test

† Chi-square test

‡ ANOVA test

Table 2 Clinical and laboratory features and outcome measures in the cohort of RA patients

Parameter	Whole cohort	Onset 1960–1989	Onset 1990–1999	Onset 2000–2005	*p* value
Duration of morning stiffness (min)					
Mean (SD)	11.8 (39.3)	12.0 (46.7)	8.6 (29.0)	16.0 (46.0)	0.0232*
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–5.0)	
Tender joints (continuous)					
Mean (SD)	0.6 (1.9)	0.3 (1.4)	0.4 (1.3)	0.9 (2.7)	0.0004*
Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–1.0)	
Swollen joints (continuous)					
Mean (SD)	1.1 (2.3)	1.1 (2.7)	0.9 (1.7)	1.3 (2.8)	0.1013*
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–2.0)	
Deformed joints (continuous)					
Mean (SD)	3.1 (4.8)	6.9 (7.2)	3.0 (4.0)	1.0 (1.9)	0.0001*
Median (IQR)	1.0 (0.0–4.0)	4.0 (1.0–11.0)	2.0 (0.0–4.0)	0.0 (0.0–1.0)	
Radiographic erosions	855 (74.2)	162 (70.1 %)	407 (76.5 %)	286 (73.3 %)	<0.001†
ESR (mm/h)					
Mean (SD)	29.3 (26.2)	29.9 (26.6)	28.4 (24.9)	30.1 (27.7)	0.8208*
Median (IQR)	24.0 (10.0–43.0)	25.5 (8.0–45.0)	24.0 (10.0–43.0)	22.5 (10.0–41.0)	
Rheumatoid factor					
Positive at diagnosis	672 (58.3 %)	173 (74.9 %)	352 (66.2 %)	147 (37.7 %)	<0.001†
Anti-CCP**					
Positive	494 (76.7 %)	94 (71.8 %)	238 (76.8 %)	138 (68.0 %)	–
ACR functional class					
Class I	827 (71.7 %)	126 (54.6 %)	377 (70.9 %)	324 (83.1 %)	<0.001†
Class II	230 (20.0 %)	66 (28.6 %)	113 (21.2 %)	51 (13.1 %)	
Class III	60 (5.2 %)	21 (9.1 %)	28 (5.3 %)	11 (2.8 %)	
Class IV	36 (3.1 %)	18 (7.8 %)	14 (2.6 %)	4 (1.0 %)	
HAQ					
<0.5	772 (67.4 %)	118 (51.5 %)	366 (69.2 %)	288 (74.2 %)	<0.001†
0.5–1.5	272 (23.7 %)	70 (30.6 %)	116 (21.9 %)	86 (22.2 %)	
>1.5	102 (8.9 %)	41 (17.9 %)	47 (8.9 %)	14 (3.6 %)	
DAS28 (continuous)					
Mean (SD)	2.6 (1.2)	2.6 (1.3)	2.6 (1.2)	2.7 (1.4)	–
Median (IQR)	2.6 (2–3.3)	2.7 (2.1–3.3)	2.6 (2.0–3.2)	2.6 (1.8–3.4)	
DAS28 (categorical)					
Remission	572 (49.6 %)	101 (43.7 %)	270 (50.8 %)	201 (51.5 %)	0.030†
Low activity	269 (23.3 %)	67 (29 %)	122 (22.9 %)	80 (20.5 %)	
Moderate activity	273 (23.7 %)	57 (24.7 %)	128 (24.1 %)	88 (22.6 %)	
High activity	39 (3.4 %)	6 (2.6 %)	12 (2.3 %)	21 (5.4 %)	

Table 2 continued

Parameter	Whole cohort	Onset 1960–1989	Onset 1990–1999	Onset 2000–2005	*p* value
Patient's assessment of general health					
Mean (SD)	25.3 (29.9)	31.3 (33.9)	23.9 (28.8)	23.7 (28.4)	0.0495*
Median (IQR)	10.0 (0.0–50.0)	20.0 (0.0–60.0)	10.0 (0.0–50.0)	10.0 (0.0–47.0)	
Physician's assessment of disease activity					
Mean (SD)	8.7 (16.1)	7.2 (13.9)	7.8 (13.9)	11.0 (19.5)	0.2461*
Median (IQR)	1.0 (0.0–10.0)	1.0 (0.0–9.0)	1.0 (0.0–10.0)	2.0 (0.0–12.0)	
Patient's assessment of disease activity					
Mean (SD)	16.7 (22.8)	19.7 (26.0)	16.2 (22.5)	15.7 (21.1)	0.4631*
Median (IQR)	6.0 (0.0–27.0)	10.0 (0.0–38.0)	5.0 (0.0–25.0)	7.0 (0.0–23.0)	
Patient's assessment of pain					
Mean (SD)	18.9 (26.7)	22.1 (30.2)	18.4 (26.2)	17.9 (25.1)	0.5550*
Median (IQR)	5.0 (0.0–30.0)	5.0 (0.0–40.0)	4.0 (0.0–30.0)	5.0 (0.0–28.0)	

Some boxes do not add up to 100 % of the column because of missing values

† Chi-square test

* Kruskal–Wallis test

** 644 patients were tested for anti-CCP

Table 3 Extra-articular manifestations of RA

Extra-articular feature *n* (%)	Whole cohort	Onset 1960–1989	Onset 1990–1999	Onset 2000–2005	*p* value†
Sicca	110 (9.5 %)	27 (11.7 %)	49 (9.2 %)	34 (8.7 %)	0.448
SC nodule	72 (6.2 %)	21 (9.1 %)	39 (7.3 %)	12 (3.1 %)	0.004
AA subluxation	49 (4.3 %)	24 (10.4 %)	25 (4.7 %)	0 (0 %)	<0.001
Interstitial lung disease	37 (3.2 %)	8 (3.5 %)	22 (4.1 %)	7 (1.8 %)	0.133
Fever	22 (1.9 %)	8 (3.5 %)	9 (1.7 %)	5 (1.3 %)	0.140
Entrapment neuropathy	27 (2.3 %)	4 (1.7 %)	17 (3.2 %)	6 (1.5 %)	0.205
Eye inflammation	14 (1.2 %)	6 (2.6 %)	3 (0.6 %)	5 (1.3 %)	0.062
Cutaneous vasculitis	10 (0.9 %)	6 (2.6 %)	3 (0.6 %)	1 (0.3 %)	0.006
Cervical myelopathy	13 (1.1 %)	7 (3 %)	5 (0.9 %)	1 (0.3 %)	0.006
Raynaud's phenomenon	7 (0.6 %)	2 (0.9 %)	5 (0.9 %)	0 (0 %)	0.164
Lymphadenopathy	6 (0.5 %)	0 (0 %)	4 (0.8 %)	2 (0.5 %)	0.415
Pleural effusion	5 (0.4 %)	2 (0.9 %)	3 (0.6 %)	0 (0 %)	0.234
Polyneuropathy	5 (0.4 %)	1 (0.4 %)	3 (0.6 %)	1 (0.3 %)	0.782
Mononeuropathy	3 (0.3 %)	2 (0.9 %)	0 (0 %)	1 (0.3 %)	0.098
Amyloidosis	1 (0.1 %)	0 (0.0 %)	1 (0.2 %)	0 (0.0 %)	0.558

† Chi-square test

with the most recent group showing the highest proportion with joint tenderness ($p = 0.0004$) but the lowest with joint deformity ($p = 0.0001$) (Table 2).

Deformity of the wrist was found in 46.4 % of the cohort, the elbow in 20.4 %, the proximal interphalangeal joints of the hands in 18.5 %, the metacarpophalangeal joints in 16.5 %, the knee in 16.2 %, the ankle in 9.2 %, the shoulder in 6.2 % and the hip in 1.5 %. The pattern of joint involvement did not differ across the three periods.

The proportion of patients with rheumatoid factor (RF) was 58.3 %. RF positivity became successively lower over the three time periods (74.9 %, 66.2 % and 37.7 %, respectively, $p < 0.001$). Anti-cyclic citrullinated peptide antibody (anti-CCP) was found in 76.7 % of the 644 tested patients. We could not compare the prevalence of anti-CCP antibody in the three groups because of incomplete data. Radiographic erosions of hand joints were found in over 70 % with a similar prevalence across the three groups.

Extra-articular features (EAF) of RA were found in 24.4 % of the cohort, of which sicca was the commonest (9.5 %) (Table 3). The prevalence of subcutaneous nodules ($p = 0.004$), cutaneous vasculitis ($p = 0.006$), atlantoaxial

Table 4 Comorbid conditions in the cohort

Comorbid condition *n* (%)	Whole cohort	Onset 1960–1989	Onset 1990–1999	Onset 2000–2005	*p* value[†]
Hypertension	458 (39.7 %)	117 (50.7 %)	219 (41.2 %)	122 (31.3 %)	<0.001
Diabetes mellitus	134 (11.6 %)	25 (10.8 %)	57 (10.7 %)	52 (13.3 %)	0.431
Ischemic heart disease	62 (5.4 %)	19 (8.2 %)	32 (6 %)	11 (2.8 %)	0.010
Cardiovascular accident	37 (3.2 %)	13 (5.6 %)	15 (2.8 %)	9 (2.3 %)	0.060
Cancer	31 (2.7 %)	11 (4.8 %)	13 (2.4 %)	7 (1.8 %)	0.078
Peptic ulcer	88 (7.6 %)	32 (13.9 %)	48 (9 %)	8 (2.1 %)	<0.001
Thyroid disease	93 (8.1 %)	26 (11.3 %)	43 (8.1 %)	24 (6.2 %)	0.078
Liver disease	40 (3.5 %)	13 (5.6 %)	18 (3.4 %)	9 (2.3 %)	0.091
Renal disease	47 (4.1 %)	18 (7.8 %)	18 (3.4 %)	11 (2.8 %)	0.006
Osteoporosis	268 (23.2 %)	95 (41.1 %)	124 (23.3 %)	49 (12.6 %)	<0.001
Hyperlipidemia	194.0 (16.8 %)	41 (17.8 %)	96 (18.1 %)	57 (14.6 %)	0.356
Cataract	119 (10.3 %)	43 (18.6 %)	55 (10.3 %)	21 (5.4 %)	<0.001

[†] Chi-square test

subluxation ($p < 0.001$) and cervical myelopathy ($p = 0.006$) was higher in patients in groups I and II compared with those in group III.

The commonest comorbidities were hypertension (39.7 %), osteoporosis (23.2 %), hyperlipidemia (16.8 %) and diabetes mellitus (11.6 %) (Table 4). As expected, due to age, drug effects and RA itself, the cardiovascular comorbidities were more common in group I compared to group III [28]. Other comorbidities such as cataracts, osteoporosis, renal disease and peptic ulcer disease were also more common in group I compared with groups II and III. Surprisingly, the prevalence of diabetes mellitus, hyperlipidemia and cancer did not change across the three patient groups.

Functional status and quality of life

The majority of our patients remained in ACR functional class I (71.7 %). More patients in the recent-onset group had better ACR functional class than patients in the more remote groups ($p < 0.001$). The HAQ score was generally low across all groups; 67.4 % of the cohorts have a HAQ score below 0.5. Over the three time periods, from the most recent to the most remote, the patients progressed to worse functional classes and developed higher HAQ scores.

The proportion of patients in remission at the last study visit assessed with DAS28 was higher in groups II and III (50.8 % and 51.5 %) as compared to group I (43.7 %) though this was not statistically significant ($p = 0.030$). The patient's and physician's assessment of disease activity were not significantly different across the 3 groups.

Group II and III patients report higher physical and social functioning, better role physical, better general health and less pain than group I patients, but the latter have better mental health (Table 5).

Treatment

About 50 % of the patients in the entire cohort were treated with one DMARD, 30.5 % with two and 12.8 % with three or more in the last study visit (Tables 6, 7). Two-thirds of the 75 patients not receiving any DMARD were in remission.

Patients with longer follow-up durations tend to be exposed to a greater number of DMARDs; 46–49 % of group I and II patients had received two or more DMARDs compared to 34 % of group III patients. The use of biologic DMARDs (infliximab, etanercept and adalimumab) was low (fewer than 2 %) and not significantly different across the 3 groups.

The median interval between diagnosis and initiation of first DMARD was significantly shorter in group III compared with groups II and I (1 month vs. 15 and 77 months), respectively. The median interval between onset of symptoms and initiation of first DMARD was also significantly shorter in group III.

MTX, sulfasalazine (SSZ) and hydroxychloroquine (HCQ) were the commonest DMARDs ever used and in use at the time of the study. Prednisolone (dose < 10 mg/day) was used most frequently in patients with more recent disease onset ($p = 0.012$), likely reflecting a change in practice and a better appreciation of the symptom-relieving and disease-modifying role of corticosteroids in RA. Intramuscular gold injections ($p < 0.001$) and D-penicillamine ($p < 0.001$) were used more often in group I compared with groups II and III.

Discussion

Our single-center patient group is, to our knowledge, one of the largest Asian RA series ever reported. Description of

Table 5 Quality of life of RA patients represented by the SF-36

SF-36	Whole cohort	Onset 1960–1989	Onset 1990–1999	Onset 2000–2005	*p* value*
Physical functioning					
Mean (SD)	58.2 (39.5)	46.7 (38.9)	61.1 (35.7)	60.9 (43.5)	0.0001
Median (IQR)	70.0 (35.0–90.0)	50.0 (20.0–80.0)	70.0 (40.0–90.0)	75.0 (45.0–90.0)	
Role physical					
Mean (SD)	52.3 (57.2)	48.7 (55.1)	57.0 (53.6)	48.1 (62.6)	0.0566
Median (IQR)	75.0 (0.0–100.0)	50.0 (0.0–100.0)	100.0 (0.0–100.0)	75.0 (0.0–100.0)	
Bodily pain					
Mean (SD)	66.4 (24.9)	63.7 (25.5)	67.3 (25.2)	66.6 (24.0)	0.1239
Median (IQR)	64.0 (50.0–84.0)	62.0 (41.0–84.0)	72.0 (50.0–84.0)	72.0 (50.0–84.0)	
General health					
Mean (SD)	56.3 (20.7)	52.2 (20.7)	57.0 (20.9)	57.7 (20.2)	0.0017
Median (IQR)	57.0 (42.0–72.0)	52.0 (40.0–67.0)	57.0 (45.0–72.0)	60.0 (45.0–72.0)	
Vitality					
Mean (SD)	54.9 (19.9)	52.8 (19.2)	55.8 (20.2)	55.0 (19.7)	0.0847
Median (IQR)	50.0 (45.0–70.0)	50.0 (40.0–65.0)	55.0 (45.0–70.0)	50.0 (45.0–70.0)	
Social functioning					
Mean (SD)	78.6 (29.8)	73.5 (30.2)	80.7 (32.5)	78.8 (25.0)	0.0405
Median (IQR)	87.5 (62.5–100.0)	87.5 (50.0–100.0)	87.5 (62.5–100.0)	87.5 (62.5–100.0)	
Role emotional					
Mean (SD)	64.8 (64.1)	66.1 (55.0)	67.7 (52.4)	60.2 (81.1)	0.0912
Median (IQR)	100.0 (33.3–100.0)	100.0 (33.3–100.0)	100.0 (33.3–100.0)	100.0 (0.0–100.0)	
Mental health					
Mean (SD)	68.6 (21.1)	69.3 (21.7)	69.6 (21.2)	66.8 (20.5)	0.0814
Median (IQR)	72.0 (52.0–84.0)	72.0 (56.0–84.0)	72.0 (56.0–84.0)	68.0 (52.0–84.0)	
Physical component summary					
Mean (SD)	38.0 (14.0)	34.1 (14.1)	39.1 (13.2)	38.8 (14.7)	0.0001
Median (IQR)	40.0 (27.9–50.0)	34.5 (21.7–46.6)	41.0 (29.7–50.2)	42.2 (28.5–50.7)	
Mental component summary					
Mean (SD)	49.0 (13.0)	49.8 (12.1)	49.5 (12.5)	47.7 (14)	0.0087
Median (IQR)	51.1 (40.2–58.4)	51.7 (42.7–58.9)	52.0 (41.4–58.8)	49.7 (37.8–57.3)	

* Kruskal–Wallis test

Asian RA cohorts from Malaysia, India and Japan have been published [19, 29, 30]. Our cohort showed comparable educational levels, age of onset, prevalence of rheumatoid factor and anti-CCP positivity, and HAQ scores as those in other reports. On the other hand, the prevalence of EAF was lower and the interval from diagnosis to initiation of DMARD was shorter, at least in our subset of patients with recent disease onset.

Singapore has a population of 5.07 million comprising three main ethnic groups, the Chinese (74.1 %), Malays (13.4 %) and Indians (9.2 %) [31]. Compared to the proportion in the population, Indian patients are overrepresented and Malay ones are underrepresented. The genetic basis of the different RA prevalence in these ethnicities merits further research.

The age of onset of RA has increased in our patients who developed the disease more recently, and this trend may well be worldwide [8–10]. Though ours is not an inception cohort and patients of remote disease onset could have died or failed to return, this finding of increasing age of onset is too compelling to dismiss. Since the age of onset is not determined genetically, unlike in systemic lupus erythematosus, the trend may be due to the environment [32, 33]. The proportion of patients with positive RF became lower in the groups with recent onset, while that for anti-CCP remained the same. Whether this is due to an actual increase in the prevalence of RF-negative RA is unknown [6].

Recent-onset RA patients experienced the least delay in receiving the appropriate diagnosis, referral to a rheumatologist and initiation of DMARD therapy, also reported in other series [34–36]. Care improvements include heightened awareness of the morbidity of RA, care by rheumatologists rather than by physicians of other disciplines,

Table 6 Ever and current treatment in the cohort of RA patients

Drug *n* (%)	Whole cohort	1960–1989	1990–1999	2000–2005	*p* value[†]
Prednislone					
Now	652 (56.6 %)	136 (58.9 %)	289 (54.3 %)	227 (58.2 %)	0.365
Ever	1078 (93.5 %)	215 (93.1 %)	487 (91.5 %)	376 (96.4 %)	0.012
Methotrexate					
Now	675 (58.5 %)	123 (53.3 %)	319 (60 %)	233 (59.7 %)	0.188
Ever	906 (78.6 %)	189 (81.8 %)	436 (82 %)	281 (72.1 %)	0.001
Sulfasalazine					
Now	549 (47.6 %)	110 (47.6 %)	263 (49.4 %)	176 (45.1 %)	0.433
Ever	826 (71.6 %)	188 (81.4 %)	407 (76.5 %)	231 (59.2 %)	<0.001
Hydroxychloroquine					
Now	358 (31.1 %)	78 (33.8 %)	185 (34.8 %)	95 (24.4 %)	0.002
Ever	584 (50.7 %)	133 (57.6 %)	310 (58.3 %)	141 (36.2 %)	<0.001
Leflunomide					
Now	60 (5.2 %)	10 (4.3 %)	30 (5.6 %)	20 (5.1 %)	0.753
Ever	112 (9.7 %)	22 (9.5 %)	61 (11.5 %)	29 (7.4 %)	0.124
Gold					
Now	11 (1 %)	1 (0.4 %)	8 (1.5 %)	2 (0.5 %)	0.205
Ever	108 (9.4 %)	58 (25.1 %)	39 (7.3 %)	11 (2.8 %)	<0.001
D-penicillamine					
Now	20 (1.7 %)	4 (1.7 %)	13 (2.4 %)	3 (0.8 %)	0.157
Ever	128 (11.1 %)	73 (31.6 %)	49 (9.2 %)	6 (1.5 %)	<0.001
Azathioprine					
Now	26 (2.3 %)	8 (3.5 %)	10 (1.9 %)	8 (2.1 %)	0.378
Ever	61 (5.3 %)	23 (10 %)	25 (4.7 %)	13 (3.3 %)	0.001
Cyclosporin A					
Now	10 (0.9 %)	2 (0.9 %)	7 (1.3 %)	1 (0.3 %)	0.230
Ever	29 (2.5 %)	8 (3.5 %)	16 (3 %)	5 (1.3 %)	0.150
Cyclophosphamide					
Now	2 (0.2 %)	1 (0.4 %)	1 (0.2 %)	0 (0.0 %)	0.453
Ever	16 (1.4 %)	11 (4.8 %)	5 (0.9 %)	0 (0.0 %)	<0.001
Biologics					
Now	2 (0.2 %)	0 (0 %)	1 (0.2 %)	1 (0.3 %)	0.755
Ever	13 (1.1 %)	3 (1.3 %)	9 (1.7 %)	1 (0.3 %)	0.120

[†] Chi-square test

accessible rheumatology service and active education of the public. Nevertheless, even in group with disease onset after 2000, the mean interval from disease onset to specialist attention is 7.7 months, so efforts to expedite access to specialist care must continue.

The HAQ scored above 1.5 in 18 % of patients in group I and 4 % of patients in group III. This is not surprising because group I patients experienced the longest delay between onset of symptoms and access to specialist care. Despite the high prevalence of radiographic erosions, about half of group I and three quarters of group III patients had no functional disability (HAQ score <0.5). Indeed, the HAQ scores of our patients are low compared to those reported in studies conducted before 2005 [1, 37, 38], but similar to those in the more recent ones [30, 35, 39]. We postulate three reasons to explain why the HAQ is low. First, our patients may have better functional status as suggested by the good score in the physical functioning subscale of the SF-36 and ACR functional class. We have shown that, of the eight subscales, this correlates best with HAQ [25]. Second, the majority of our patients are not engaged in physically demanding work, resulting in lower perceived disability. Third, most patients settle their medical bills

Table 7 Current DMARD use in the cohort of RA patients

No of DMARD *n* (%)	Whole cohort	Onset 1960–1989	Onset 1990–1999	Onset 2000–2005	*p* value
Number of DMARDs currently used					
0	75 (7.1 %)	21 (10.2 %)	29 (6 %)	25 (6.9 %)	<0.001†
1	521 (49.6 %)	90 (43.7 %)	217 (44.8 %)	214 (59.4 %)	
2	320 (30.5 %)	70 (34.0 %)	165 (34.1 %)	85 (23.6 %)	
3 and more	134 (12.8 %)	25 (12.1 %)	73 (15.1 %)	36 (10 %)	
Interval between disease onset to first use of DMARD, months					
Mean (SD)	67 (77.1)	175.3 (95.8)	58.6 (46.7)	18.7 (19.8)	0.0001*
Median (IQR)	37.7 (10.9–95.5)	164.1 (104.7–242.5)	49.8 (17.7–88.4)	10.5 (4.6–25.7)	
Interval between diagnosis to first use of DMARD, months					
Mean (SD)	37.3 (58.4)	94.1 (91.9)	34.3 (42.6)	10.2 (17.8)	0.0001*
Median (IQR)	9.2 (1–55.1)	77.2 (6.4–152.9)	15.4 (1.4–58.3)	1.2 (0.6–10.9)	

Not all columns add up to the same total because of missing data

* Kruskal–Wallis test

† Chi-square test

out-of-pocket as they do not have insurance coverage, so there is no need to overstate their disability. The ACR functional class of the patients in the three groups was consistent with the HAQ score findings.

Contrary to previous reports, the presence of radiographic erosions in more than 70 % of our patients across the three periods suggests RA in Asians is as aggressive in the Caucasian populations [40]. The findings confirm that radiographic erosions occur early in the course of the disease and that reduction in disease activity may not halt radiographic progression [41, 42].

More patients in group III achieved remission compared to those in groups I and II. The prevalence of joint deformity was significantly lower compared to the earlier two groups. This may be explained by the significantly shorter disease duration, aggressive therapy of contemporary practice and the higher responsiveness to such treatment earlier in the disease course during the "window of opportunity" [30–35].

The physical component summary score measured by SF-36 concurred with the HAQ score. Interestingly, the mental component summary score was better in group I than group III, probably because the remote group had better coping mechanisms developed over 20 years of living with the condition.

The prevalence of EAF in our cohort is relatively low compared to other populations; for example, it is 38.4 % in Turkey, 41 % in Italy, 36.2 % in Spain and 40.6 % in the United States [43–46]. This low prevalence of EAF in Asians has also been reported in Pakistan and Malaysia [47, 48]. In Southern Chinese, EAFs are uncommon despite a high prevalence of erosive and severe disease [49]. Certain EAFs were present early in disease course (such as sicca symptoms and entrapment neuropathy), while others take years to develop (such as nodulosis, vasculitis and atlantoaxial subluxation).

The prevalence of cardiovascular comorbidities was lower in patients from the most recent group. Fewer patients in that group had hypertension, ischemic heart disease and cerebrovascular accidents, likely due to the association of cardiovascular disease with RA activity and traditional risk factors [50]. The prevalence of other risk factors such as diabetes mellitus and hyperlipidaemia did not differ significantly among the three groups. Complications of treatment including osteoporosis, peptic ulcer disease and cataract were more prevalent in the most remote group. Interestingly, there was no significant increase in cancer prevalence over time. A US Veteran's Health Administration study with mainly male RA patients also reported a decreasing prevalence of most EAF, except for lung disease, in patients of more recent disease onset [51].

In our institution, rheumatologists usually employ a step-up combination strategy with MTX or SSZ as the first-line DMARDs. Consequently, MTX, SSZ and HCQ are the commonest DMARDs prescribed to our cohort, alone or in combination. About 58.5 % of the patients are currently on MTX treatment, and this is not significantly different across the three groups. This is comparable to the incidence of MTX use in other reported cohorts including the QUEST-RA study (ranging from 49 to 74.1 %) and IORRA cohort in Japan [30, 52]. In contrast, SSZ usage in our RA population was much higher. Intramuscular gold injections and D-penicillamine were used more commonly in group I compared with groups II and III, reflecting the availability of different DMARDs over time.

In Singapore, most patients receive subsidized care, involving co-payment with partial subsidy by public funds

and the use of generic drugs. Many medications, including the newer anti-rheumatic agents, have to be paid out-of-pocket unless the patients qualify for additional financial assistance known as Medifund. Therefore, the biologics and newer agents such as leflunomide are not often prescribed. Even though the use of biologics across the three patient groups is similarly low, some patients from the more recent group achieve disease remission, suggesting optimal use of available drugs and a trend toward treating the disease to target. On the other hand, although 31–49 % of the patients received at least two DMARDs, a significant proportion of the cohort remains in moderate and high disease activity (23.7 and 3.4 %, respectively). These patients require aggressive treatment including the biologics, and there is a need to develop alternate means of funding these drugs, whether from private insurance, charity organizations, or support groups.

The main limitation of our study is that our cohort is not an inception cohort. Also, we report the disease activity at only one time point which does not reflect the fluctuating course of RA. The design of our study does not allow us to determine the incidence and prevalence of RA in the population.

In summary, this study shows improved RA management across the last three decades coinciding with the introduction of new treatments and more efficient health care infrastructure. Patients with more recent disease onset had better outcomes and generally better quality of life. A significant proportion of patients continue to manifest active disease and means to access newer and more expensive forms of treatment must be found. Increasing age of disease onset and lower prevalence of RF observed over time are probably not related to the treatment.

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