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Do it fast! Early access to specialized care improved long-term outcomes in rheumatoid arthritis: data from the REAL multicenter observational study

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Abstract

Background Early rheumatoid arthritis (RA) offers an opportunity for better treatment outcomes. In real-life settings, grasping this opportunity might depend on access to specialized care. We evaluated the effects of early versus late assessment by the rheumatologist on the diagnosis, treatment initiation and long-term outcomes of RA under real-life conditions.

Methods Adults meeting the ACR/EULAR (2010) or ARA (1987) criteria for RA were included. Structured interviews were conducted. The specialized assessment was deemed "early" when the rheumatologist was the first or second physician consulted after symptoms onset, and "late" when performed afterwards. Delays in RA diagnosis and treatment were inquired. Disease activity (DAS28-CRP) and physical function (HAQ-DI) were evaluated. Student's t, Mann-Whitney U, chi-squared and correlation tests, and multiple linear regression were performed. For sensitivity analysis, a propensity score-matched subsample of early- vs. late-assessed participants was derived based on logistic regression. The study received ethical approval; all participants signed informed consent.

Results We included 1057 participants (89.4% female, 56.5% white); mean (SD) age: 56.9 (11.5) years; disease duration: 173.1 (114.5) months. Median (IQR) delays from symptoms onset to both RA diagnosis and initial treatment coincided: 12 (6–36) months, with no significant delay between diagnosis and treatment. Most participants (64.6%) first sought a general practitioner. Notwithstanding, 80.7% had the diagnosis established only by the rheumatologist. Only a minority (28.7%) attained early RA treatment (≤ 6 months of symptoms). Diagnostic and treatment delays were strongly correlated (rho 0.816; $p < 0.001$). The chances of missing early treatment more than doubled when the assessment by the rheumatologist was belated (OR 2.77; 95% CI: 1.93, 3.97). After long disease duration, late-assessed

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participants still presented lower chances of remission/low disease activity (OR 0.74; 95% CI: 0.55, 0.99), while the early-assessed ones showed better DAS28-CRP and HAQ-DI scores (difference in means [95% CI]: -0.25 [-0.46, -0.04] and −0.196 [-0.306, -0.087] respectively). The results in the propensity-score matched subsample confirmed those observed in the original (whole) sample.

Conclusions Early diagnosis and treatment initiation in patients with RA was critically dependent on early access to the rheumatologist; late specialized assessment was associated with worse long-term clinical outcomes.

Keywords Rheumatoid arthritis, Delivery of healthcare, Health care outcome and process assessment, Accessibility of health services, Rheumatology

Background

Rheumatoid arthritis (RA) is a systemic inflammatory disease associated with severe structural damage, frequently leading to [1]. The current concepts of RA treatment emphasize the importance of early diagnosis and prompt initiation of a disease-modifying anti-rheumatic drug (DMARD). Chronically established RA is not easily managed, often requiring drugs in combination to control the inflammatory process. Many patients with long-standing RA must go through different pharmacological schemes until finding one with acceptable effectiveness and tolerability. Some patients never achieve complete remission even after trying several drug combinations, thus facing no practical alternative but to tolerate low levels of disease [2].

Early treatment provides better chances of attaining long-term disease remission, function preservation, and structural damage [3–8]. These observations underpin the concept of a window of opportunity for early RA treatment, with an upper limit generally situated at approximately 3 to 6 months of symptoms [9–11]. However, in real-life health care settings, grasping this opportunity might depend on timely access to a physician able to establish the diagnosis and initiate the first DMARD, generally methotrexate, without [12–14].

The first physician sought by the patient with novel articular symptoms is usually the general practitioner (GP). However, even if RA is suspected at this moment, prescribing DMARDs may not be a trivial procedure to the GP. Managing DMARDs requires experience and high confidence in the diagnosis, considering the many potentially severe adverse events associated with these drugs. Moreover, the differential diagnosis of arthritis itself might not also be trivial to the non-rheumatologist. It demands ruling out several mimics of RA, including certain infections for which immunosuppressive treatments could be disastrous.

If arthritis was suspected, but the GP is not confident about the diagnosis or treatment, the patient should come immediately to a rheumatologist. Unfortunately, this does not always happen. Instead, some patients seek other doctors before eventually reaching the specialist. This could be driven by difficulties in access to the specialized care or simply by unawareness regarding the nature of RA, its potential destructiveness, the role of the rheumatologist in managing the disease, and the consequences of missing the window of opportunity for early [15]. Regardless of the motives for interposing other doctors between the first health care provider and the rheumatologist in this diagnostic journey, the result might be excessive delays in diagnosis and/or treatment, with possible long-term clinical consequences.

In this study, we evaluated the effects of early versus delayed assessment by the rheumatologist on the timing of RA diagnosis and DMARD initiation, as well as on the long-term control of the disease under real-life conditions.

Methods

This work was part of the REAL study, a cohort designed to evaluate the prevailing patterns of clinical management concerning RA in real-life [16]. Between August 2015 and April 2016, the study included participants attending outpatient clinics from eleven public tertiary hospitals in different regions of Brazil. As inclusion criteria, ascertained during eligibility screening, the participants should be ≥18 years old, meet the ACR/EULAR (2010) or ARA (1987) classification criteria for RA [17, 18] and have been followed up at their respective outpatient clinics for at least 6 months by study inclusion. The participants underwent structured clinical interviews with physical examination, and their medical records were thoroughly reviewed. Individuals with cognitive impairment that impeded the interview were excluded.

Data analyzed herein were collected at the baseline assessment in the REAL study, thus being cross-sectional in nature. However, the participants had long mean disease duration by the time of inclusion in the study (see Results). Therefore, the clinical conditions evaluated upon study inclusion relate to a point in time long after the disease onset. In other words, aspects such as disease activity and physical function, and other clinical conditions assessed upon study inclusion are inherently long-term outcomes relative to any exposure or intervention that may have occurred by the time of disease onset and/or its first medical evaluations. (Fig. 1)

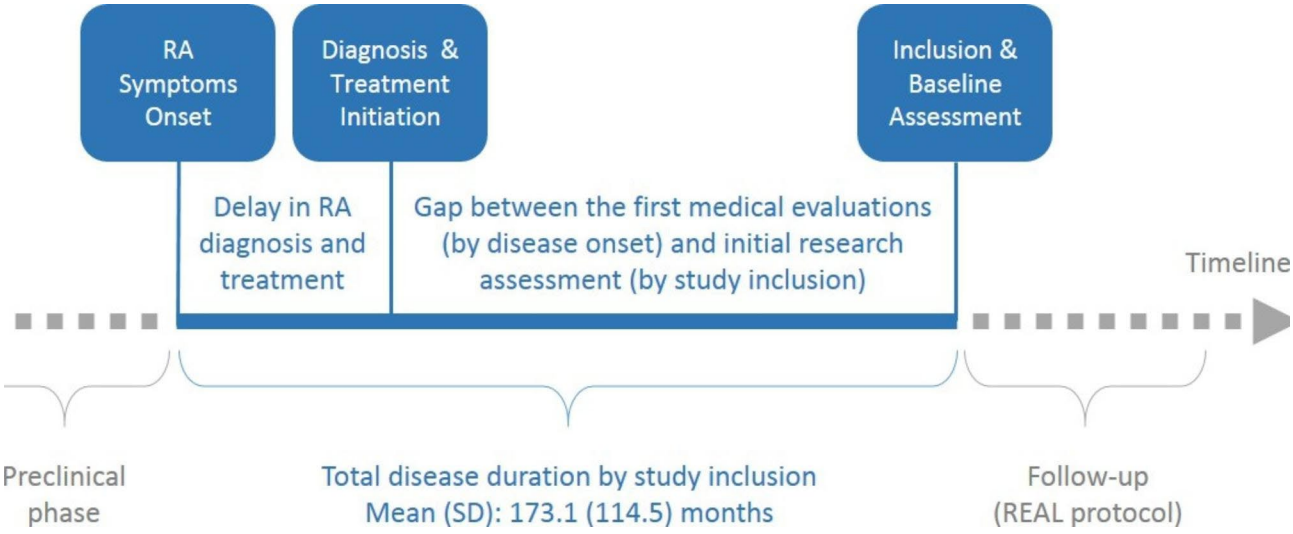

Fig. 1 Timeline of landmark events covered in the current study (blue area)

[Legends] The participants with rheumatoid arthritis (RA) had long-standing disease (long mean disease duration) upon study inclusion. The events surrounding the disease onset and its first medical evaluations preceded the study baseline assessment by a considerable amount of time. Hence, the clinical outcomes observed upon study inclusion are long-term ones relative to all exposures or interventions that took place by the time of RA onset and diagnosis. Outcomes measured upon study inclusion: disease activity (DAS28) and physical function (HAQ-DI). Other background and clinically relevant features ascertained upon study inclusion: age, sex, race, schooling, disease duration, current medications and rheumatoid factor status. Past events inquired, related to the disease onset, diagnosis and initial treatment: delays in RA diagnosis and treatment, the sequence of physicians (medical specialties) consulted initially and their role in RA diagnosis and treatment initiation. Events in the gray areas of the figure (preclinical phase of RA, follow-up phase of the REAL study) are not covered in the present study. The timeline is not in scale for real length of time. SD: standard deviation.

The participants were inquired about sociodemographic characteristics, disease duration, interval from symptoms onset to RA diagnosis and initiation of the first DMARD, as well as the specialties of the physicians who firstly assessed them for their articular symptoms and who established the diagnosis of RA. Current medication use and rheumatoid factor (RF) status were ascertained from the patients' medical records. Disease activity was evaluated using the Disease Activity Score-28 joints with C-reactive protein (DAS28-CRP). Patients were deemed in disease remission when exhibiting DAS28-CRP scores <2.6; scores above that limit but still <3.2 were classified as low disease activity. Physical function was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI).

Adequacy in the access to specialized care was evaluated by inquiring how many physicians had assessed the patients for their articular complaints before the first consultation with a rheumatologist. We assumed that the rheumatologist should be, at most, the second physician to see a patient with suspected arthritis when considering a proper transition from primary to specialized care. The specialized consultation was classified as "early" when the rheumatologist was the first or second physician to be ever consulted, for the ongoing articular symptoms, and "late" when the rheumatologist was seen only after two or more other doctors. Therefore, "late assessment", by this working definition, indicated a flaw in the transition of cases with suspected arthritis from primary to specialized care. All mentions to "early" or "late" assessment by the rheumatologist in the current study allude to this sequence-based working definition, not to time intervals.

To evaluate missed opportunities for early RA treatment, we adopted three different cutoffs regarding the upper limit of the so-called "window of opportunity": ≤ 3 months, ≤ 6 months, and ≤ 12 months after symptoms onset, respectively. This approach acknowledged and incorporated the current uncertainty about the precise moment when the window of opportunity really [9]. Moreover, this triple cut-off approach allowed for sensitivity analysis regarding the consistency of the results.

Continuous variables were compared across groups using students' t tests with Welch's correction (equal variances not assumed) or Mann-Whitney U tests, as appropriate. Associations between categorical variables were assessed through Pearson's chi-squared tests. Correlation was assessed by Spearman's rho.

Table 1 General characteristics of the studied population of RA patients

Population characteristics	Results	N*
Female sex	89.4% (n = 945)	1057
Race, White	56.5% (n = 597)	1057
Positive rheumatoid factor	78.2% (n = 813)	1039
Corticosteroid use	47.3% (n = 500)	1057
Biological DMARD use	35.5% (n = 375)	1057
Disease activity levels**		886
Remission	38.4% (n = 340)	
Low	15.3% (n = 136)	
Moderate	34.7% (n = 307)	
High	11.6% (n = 103)	
Age in years, mean (SD)	56.9 (11.5)	1057
Years of schooling, mean (SD)	8.1 (4.3)	1021
Disease duration, mean (SD)***	173.1 (114.5)	1056
Delay to diagnosis, median [IQR]***	12 [6–36]	1024
Delay to first DMARD, median [IQR]***	12 [6–36]	944
HAQ-DI score, median [IQR]	0.875 [0.250–1.500]	1053
DAS28-CRP score, mean (SD)	3.27 (1.37)	886

RA: rheumatoid arthritis; DMARD: disease-modifying anti-rheumatic drug; DAS28-CRP: disease activity score-28 joints with C-reactive protein; SD: standard deviation; IQR: interquartile range [Q1–Q3]. * Number of patients with available information on each characteristic. ** Based on DAS28-CRP scores. *** Values in months.

Given the observational design, with possible imbalances between subgroups, we used a propensity score-based matching procedure to obtain a subsample with more balanced probabilities of assignment to early or late assessment by the rheumatologist. The predicted probabilities of assignment (propensity scores, PS) were calculated through multivariate binomial logistic regression, adjusted for age, sex, race, total disease duration and rheumatoid factor status. Then, the early-assessed cases were matched 1:1 with appropriate late-assessed controls based on their multivariate PS, being randomly selected from all possible matches without replacement, allowing for a tolerance margin of 0.003 in the PS. This margin was chosen *a priori*, aiming at achieving precision in the matches, while preserving a sizeable subsample.

Comparisons between subgroups were performed in the general (unadjusted) sample, as well as in the propensity score-matched subsample, to allow for sensitivity analysis. Finally, we used multiple linear regression to assess the relationship between the "position of the rheumatologist" (predictor variable) and DAS28-CRP and HAQ scores (outcome variables) in the matched subsample, while adjusting for the propensity scores (covariate). p-values <0.05 were deemed significant. No data imputation was performed. Statistical analyses were conducted using SPSS 25.

The study was approved by a central ethics review board and by local institutional boards in each participating center (https://plataformabrasil.saude.gov.br/, protocol number CAAE 45781015.8.1001.5259). All participants granted informed consent; all procedures were in accordance with the ethical standards of the Brazilian National Research Committee and with the 1964 Helsinki declaration and its later amendments.

Table 2 Medical specialty who first consulted the patient and first established the diagnosis of RA, respectively

Medical Specialty	First consulted the patient Number of cases (%)	First established RA diagnosis Number of cases (%)
Rheumatologist	202 (19.3)	838 (80.7)
General practitioner	674 (64.6)	156 (15.0)
Orthopedist	131 (12.5)	29 (2.8)
Other	37 (3.5)	15 (1.4)
Total*	1044 (100)	1038 (100)

RA: rheumatoid arthritis. * Numbers of cases with data available for the analyses.

Results

We included a total of 1057 participants. Table 1 displays the general characteristics of the sample, which consisted predominantly of female (89.4%), white (56.5%), middle-aged patients with RA. The participants typically presented long disease duration, low to moderate disease activity, high rates of positive RF, and frequent corticosteroid use (Table 1). Participants were of predominantly low socioeconomic status, with low to medium educational levels.

Most participants (64.6%) first sought a GP for their initial assessment. In 52.9% of the cases the rheumatologist was the second physician to assess the participant, and in 28.8% the specialist was consulted only after two or more other doctors. Notwithstanding, in 80.7% of all cases the rheumatologist was the professional who established the diagnosis of RA, whereas the GP was able to do so in only 15% of the occasions (Table 2).

The proportions of RA patients diagnosed by the GP were not significantly different between individuals with seropositive and seronegative RF status (23.7% vs. 17.5%; OR=1.46; 95% CI: 0.90, 2.37; p=0.124; Pearson's chi-squared test). Likewise, the frequency of a seropositive RF status was not significantly different between patients who presented to the rheumatologist early or late (79.4% vs. 75.4%; OR 0.80; 95% CI: 0.58, 1.09; p=0.157; Pearson's chi-squared test). Moreover, seronegative and seropositive patients showed similar time delays to RA diagnosis [median (interquartile range): 12 (6–36) months for both groups; p=0.817; Mann-Whitney U test] and to treatment initiation [again 12 (6–36) months for both seropositive and seronegative groups; p=0.763; Mann-Whitney U test].

Overall, 52% of the patients started the first DMARD within 12 months of symptoms onset, whereas 28.7% managed to do so in the first 6 months; only 13.1% of all

Table 3 Missed opportunities for early RA treatment according to access to the rheumatologist in the diagnostic journey

Considered window for early RA treatment (thresholds)	Position of the rheumatologist in the sequence of attending physicians *		Chances of missing the window of opportunity with belated assessment OR [95% CI] **
	1st or 2nd (N = 665)	3rd or later (N = 279)	
12 months	42.7% (n = 284)	60.6% (n = 169)	2.06 [1.55, 2.74]
6 months	65.9% (n = 438)	84.2% (n = 235)	2.77 [1.93, 3.97]
3 months	84.2% (n = 560)	93.2% (n = 260)	2.57 [1.54, 4.27]

RA: rheumatoid arthritis; OR: odds ratio; CI: confidence intervals. * The values in the cells represent the relative and absolute frequencies of patients who missed the opportunity for early RA treatment within the considered windows (thresholds). ** Odds ratios for missing the opportunity of early RA treatment when the consultation by the rheumatologist was belated (position 3rd or later) compared to early consultation (positions 1st or 2nd); all differences were significant at $p<0.001$, on Pearson's chi-squared test.

Table 4 Comparisons between patients with RA according to access to the rheumatologist in the diagnostic journey

Characteristics	Position of the rheumatologist in the sequence of attending physicians*		Difference in means** [95% CI]
	1st or 2nd (N = 753)	3rd or later (N = 304)	
Years of schooling	8.40 (4.38)	7.19 (3.92)	1.22 [0.67, 1.77]
Total disease duration[(a)]	167.04 (112.56)	188.03 (118.20)	-20.99 [-36.58, -5.41]
Delay to diagnosis[(a)]	26.90 (46.67)	44.55 (60.07)	-17.65 [-25.28, -10.02]
Delay to first DMARD[(a)]	32.48 (58.53)	50.58 (69.98)	-18.10 [-27.46, -8.73]
HAQ-DI score	0.877 (0.715)	1.074 (0.857)	-0.196 [-0.306, -0.087]
DAS28-CRP score	3.20 (1.32)	3.45 (1.48)	-0.25 [-0.46, -0.04]

RA: rheumatoid arthritis; CI: confidence intervals; DMARD: disease-modifying anti rheumatic drug; HAQ-DI: health assessment questionnaire disability index; DAS28-CRP: disease activity score-28 joints with C-reactive protein. (a) Results expressed in months, counting from symptoms onset. * The values in cells are the observed means (standard deviations) for each feature. ** Differences between groups of patients consulted by the rheumatologist early (as the 1st or 2nd physician) or late (as the 3rd physician or later on); all differences were significant at $p<0.05$, on bivariate (unadjusted) students' t tests.

patients received a DMARD within 3 months of symptoms onset. Table 3 shows the frequencies of missed opportunities for starting early RA treatment, within these predefined windows (thresholds), according to the position of the rheumatologist in the sequence of consulted physicians.

Patients with early access to the rheumatologist showed lower mean delays to RA diagnosis and DMARD initiation (Table 4). The delay in treatment was strongly correlated to the delay in diagnosis (rho 0.816; $p<0.001$). The median (interquartile range) delay to initiate the first DMARD once the diagnosis of RA had been established was 0 (0–1) months.

Upon study inclusion, patients who had been assessed early by the rheumatologist still exhibited lower HAQ and DAS28-CRP scores compared to those who had been assessed late (Table 4). The status of remission / low disease activity (on study inclusion) was less frequent among the late-assessed patients compared to the early-assessed group [48.4% vs. 55.9%; OR 0.74; 95% CI: 0.55, 0.99; $p=0.045$; Pearson's chi-squared test]. Other characteristics associated with early assessment by the rheumatologist were shorter disease duration (upon study inclusion), and higher educational levels (Table 4).

To assess the consistency of the results observed in the general sample (sensitivity analysis), a propensity score-matched subsample of 578 individuals (289 early- and 289 late-assessed patients) was derived. The subsample achieved balance across the early- and late-assessed groups, regarding sex (female: 94.1% vs. 92%, $p=0.325$), race (white: 54% vs. 51.6%, $p=0.560$), RF status (positive: 76.1% vs. 77.2%, $p=0.768$), age [mean(SD): 55.5 (11.7) vs. 56.4 (11.7), $p=0.318$] and disease duration [175.3 (112.7) vs. 181.2 (110.8), $p=0.523$]; chi-squared tests for categorical and t tests for continuous variables.

However, in the PS-matched subsample, the late-assessed group (compared to early-assessed patients) still presented higher disease activity [mean(SD), DAS28-CRP scores: 3.17 (1.32) vs. 3.47 (1.50); mean difference=0.30; 95% CI: 0.04, 0.55; $p=0.022$] and worse physical function [HAQ scores: 0.870 (0.701) vs. 1.088 (0.862); mean difference=0.217; 95% CI: 0.089, 0.346; $p=0.001$], as well as higher delays in treatment initiation [36.7 (63.6) vs. 48.7 (69.3) months; mean difference=12.1 months; 95% CI: 0.62, 23.5 months; $p=0.039$] and lower educational levels [schooling years: 8.25(4.63) vs. 7.22 (3.89); mean difference = -1.02; 95% CI: -1.73, -0.32; $p=0.005$]; all based on students' t tests. The status of remission / low disease activity was still less frequent among the late-assessed patients compared with their PS-matched counterparts (59.4% vs. 48.8%, OR 0.65; 95% CI: 0.45, 0.93; $p=0.018$; chi-squared test).

Finally, in the multivariate linear regression models, the position of the rheumatologist (predictor variable) adjusted to the PS for early or late assessment (as covariate) remained significantly associated with (the outcomes variables of) disease activity [DAS28-CRP scores:

β=0.295; 95% CI: 0.045, 0.544; p=0.021] and physical function [HAQ scores: β=0.217; 95% CI: 0.089, 0.345; p=0.001], with higher, that is, worse scores observed among the late-assessed participants.

Discussion

Approximately half of the participants started their treatment within 12 months of symptoms onset; less than one-third initiated treatment within 6 months; only 13.1% received a DMARD in the first 3 months of symptoms. Therefore, an alarmingly high proportion of patients missed the so-called window of opportunity for early RA treatment, whatever the cutoff adopted for that window. The more stringent (narrow) the considered window, the higher the frequency of missed opportunities.

The delay in treatment initiation appeared higher in our data (median: 12 months) than reported in other countries, which could indicate limited access to healthcare services and/or suboptimal awareness about the disease in Brazil. Kimsey et al. found a mean delay of approximately 4 months from symptoms onset to the first DMARD in the [19]. Jamal et al. reported a median delay of 6.4 months to treatment in [20]. Corominas et al. observed a mean delay to treatment of 11 months in [21]. Rosa et al. found a median delay to DMARD initiation of 7 months in Buenos [22]. Kiely et al. reported a median delay to treatment of 8 months in the UK and [23].

Our data refer to a population of long-standing RA (mean disease duration > 14 years). Therefore, a substantial proportion of our participants started their disease before the years 2000, when the concept of a window of opportunity for early RA management was not yet firmly established or widely disseminated. Studies that have enrolled participants with more recent disease might show better scenarios, as decreasing delays in RA diagnosis and treatment have been reported recently in many [20, 35].

Most patients firstly consulted a GP for their articular symptoms; less than one-fifth came to a rheumatologist firsthand. Nevertheless, approximately 80% of the patients had the final diagnosis of RA established only when the rheumatologist was consulted. This finding suggests the differential diagnosis of arthritis may not be trivial to the non-specialist, who usually requires the assistance of the rheumatologist for that purpose.

More than one-fourth of the patients with RA visited a rheumatologist for the first time only after consulting two or more non-rheumatologists. This finding indicates difficult access to the specialist and/or unawareness by the population about RA, its potential destructiveness, the role of the rheumatologist in the management of the disease, and the consequences of missing the window of opportunity for early [15].

Seropositivity for RF did not increase the frequency of RA diagnoses by the GP. Moreover, seropositive patients did not present earlier to the rheumatologist, nor exhibited shorter delays to diagnosis or treatment. However, a positive RF must at least have raised suspicion of RA in the primary care setting. These findings once again suggest difficulties in the differential diagnosis of arthritis by the GP, possibly combined with limitations in access to the specialist. Limited access to specialized care is a common problem for people with low socioeconomic status, which was the predominant status among our [16]. Socioeconomic disadvantage has indeed been associated with longer delays to RA diagnosis and [24, 25].

A strong correlation was found between the delays to RA diagnosis and treatment. Moreover, the median delay (in months) to initiate the first DMARD once RA diagnosis had been established was zero. Jamal et al. also reported no delay in initiating treatment once the RA diagnosis was established by a [19]. Hence, the bottleneck to early RA treatment in our study lay on the establishment of the diagnosis, for which the input from a rheumatologist proved to be critical.

When the rheumatologist was seen early in the sequence of consulted physicians, after symptoms onset, the delays in diagnosis and treatment were reduced, and more patients could grasp the window of opportunity for early RA treatment (whatever the threshold adopted for that window: 3, 6 or 12 months). The odds of missing the window (for all thresholds) more than doubled when the rheumatologist was consulted late.

Corominas et al. found that facilitated access to the rheumatologist in dedicated outpatient clinics or through a liaison program in the primary care setting resulted in shorter delays to DMARD initiation in early [21]. Vega-Morales et al. reported low concordance between the primary care physician and the rheumatologist regarding RA diagnosis in patients with articular [26]. These findings, in line with ours, argue for an early referral of suspected cases of arthritis to the rheumatologist, always avoiding undue delays. Accordingly, the health care systems should be structured to provide these patients with timely access to the specialist as [27, 28].

Upon study inclusion, thus long after the disease onset, patients who had been consulted late by the rheumatologist still presented lower chances of being in remission or low disease activity status, and had worse physical function compared to those who had been seen by the specialist early in the beginning of the disease. Obviously, being assessed by a rheumatologist is not a therapeutic intervention per se, nor has it any plausible effect on the pathophysiology of RA. Rather, we interpret these long-term worse outcomes as consequences of missed opportunities for early RA treatment, due to delayed access to the specialist.

Several studies have reported worse outcomes associated with late initiation of RA [10, 24, 29, 30]. Fewer studies, though, have specifically investigated the effects of late assessment by a specialist on RA long-term management outcomes. van der Linden et al. observed that late assessment by the rheumatologist (>12 weeks of symptoms onset) was associated with greater structural damage and lower chances of DMARD-free remission over 6 years of follow-[31].

Evidence indicates the existence of an early, limited phase in the course of RA when its immunopathological abnormalities seem most susceptible to [32, 33]. Grasping this window of opportunity, however, depends on the timely access of the patients to a professional able to establish the diagnosis and manage the treatment without delays. Fautrel et al. reported that a direct appointment with the rheumatologist (even before seeing a GP) for patients with suspected arthritis increased the chances of reaching the specialist within the first 6 weeks of synovitis, thus allowing for early [34]. We have demonstrated herein that interposing other doctor(s) between the first consulted physician (usually the GP) and the rheumatologist in the diagnostic journey of RA decreased the chances of grasping the window of opportunity for early treatment, with worse long-term outcomes.

In our study, the participants who had consulted the rheumatologist early, by the time of symptoms onset, showed higher educational levels. Patient-originated delay, i.e., belatedness in seeking medical attention, may represent a sizeable fraction of the total delay for treatment [24, 36–38]. Educational, cultural and psychosocial aspects are determinants of this kind of [39, 40]. Hence, educational interventions to promote awareness of RA in the general population are advisable, for they could potentially reduce this component of the total [15]. However, the success of these initiatives could be attenuated if equivalent awareness is not to be found among the GPs, who are likely to see the suspected cases firsthand. Therefore, any educational intervention directed at the general public, in this regard, should ideally be coupled with proper training of primary care providers to maximize its potential effectiveness.

Given the observational design of the study, hence susceptible to potential imbalances and biases, we derived a PS-matched subsample, in order to probe the consistency of the results (sensitivity analysis), particularly concerning the long-term outcomes associated with early or late assessment by a rheumatologist. In that scheme, the general sample is more akin to real-life settings, while the PS-matched subsample approaches a quasi-experimental design, in that some covariates are statistically modeled to derive groups (of early- and late-assessed participants) with more balanced conditions regarding some known [41].

The PS-matched subsample, as intended, achieved statistical balance for age, sex, race, disease duration and RF status. The results in the general sample were consistent with those in the PS-matched subsample, which strengthens the overall reliability of the findings. Participants assessed by a rheumatologist, for the first time, only late in the course of the disease showed in both unadjusted (general sample) and adjusted settings (PS-matched subsample) higher disease activity, lower chances of being in remission / low disease activity status, and worse physical function. Likewise, late assessment by the rheumatologist was consistently associated to higher delays in treatment initiation and lower educational levels (in both settings).

One specific limitation in our study was that data regarding the delays in diagnosis and treatment and the sequence of the physicians in the initial diagnostic journey relied to a great extent on patients' recall. Thus, some imprecision should be expected in these estimates; confidence intervals are provided. Whenever available, these data were cross-checked from medical records. Another limitation was that the RF status of the participants (seropositive or seronegative) was ascertained upon study inclusion. Therefore, all inferences related to the initial RF status should be interpreted with caution since an unknown proportion of seropositive participants may have been seronegative at symptoms onset.

The outcomes in the study were not adjusted for the treatment modalities the participants were exposed to, whether currently or over time. That procedure would be very difficult to conduct and interpret in a real-life study with a sample of such long mean disease duration and diverse treatment exposure over time. Trying to separate (statistically) the effects of every single DMARD or combination in this mixed and sequential treatment milieu could be misleading. Our study just reproduced the conditions commonly found in real-life clinical practice settings.

We adopted a working definition for early / late specialized assessment based on the number of physicians consulted prior to the rheumatologist. We acknowledge that analyzing the time delay from symptoms onset to the first rheumatologic consultation would also have been informative. Unfortunately, we don't have this data. However, we did compute time delays from symptoms onset to diagnosis and treatment, and our working definition for early/late specialized assessment was proven associated to these delays (in diagnosis and treatment), as well as to the proportions of patients treated within the window of opportunity. Keep in mind that the diagnosis of RA (and consequently, treatment initiation) was highly dependent on the rheumatologist (for about 80% of the cases in our data). Therefore, the long delay we observed in diagnosis and treatment (median: 12 months) indicates to a great extent long delay in rheumatologic consultation, which

in turn (once again) points out to difficulties in accessing the specialist. Moreover, our sequence-based working definition for early/late specialized assessment allowed us to evaluate inadequacy in the transition from primary to specialized care.

Finally, we understand that investigating long-term outcomes specifically related to damage accrual such as radiographic scores and permanent disability would have been nice. Unfortunately, we also lack these data. Nonetheless, we assessed physical function through HAQ. Although HAQ scores may fluctuate to some extent over time due to inflammatory activity, they reflect damage and disability as well, exhibiting a 'floor effect' in their levels, below which the scores cannot go in patients with significant structural damage. Moreover, it is well recognized that persistent inflammatory activity (as indicated by elevated DAS28 scores) predicts structural damage accrual in RA.

One last question arising from this study, as yet unsolved, is whether proper training of the GP to recognize RA and initiate the first DMARD timely, while still in the primary care setting, could provide outcomes in the long term equivalent to (or even better than) those we found in association with early assessment by the rheumatologist. That is an interesting topic for a future research.

Conclusions

Patients with RA often missed the window of opportunity for early treatment. Failure in the transition from primary to specialized care was common. Input from the specialist appeared critical to RA diagnosis. Belatedness in the assessment by the rheumatologist was associated to delays in treatment, with worse long-term outcomes. When not confident about the diagnosis or management, primary care providers should, therefore, refer the suspected cases of arthritis to the rheumatologist promptly. Health care systems should be organized to provide quick access to the specialist on demand. Educational interventions to raise awareness in the general population, as well as among primary care providers, about RA features, the importance of early diagnosis and treatment, and the role of the rheumatologist in the process are advisable.

List of abbreviations

ACR	American College of Rheumatology
ARA	American Rheumatism Association
CI	confidence interval
DAS28-CRP	disease activity score – 28 joints, with C-reactive protein
DMARD	disease-modifying anti-rheumatic drugs
EULAR	European League Against Rheumatism
GP	general practitioner
HAQ-DI	health assessment questionnaire disability index
IQR	interquartile range
OR	odds ratio
RA	rheumatoid arthritis
RF	rheumatoid factor
SD	standard deviation

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Author contribution

All authors made substantial contributions to the acquisition of data, have been involved in drafting the manuscript or revising it critically for important intellectual content, gave final approval of the version to be published and have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. In addition, GRCP, ABVS, and LMHM made substantial contributions to study conception and design; CPA made substantial contributions to study conception and design and data analysis.

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Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Not applicable for materials.

Declarations

Ethics approval and consent to participate

The study was approved by a central ethics review board and by local institutional boards in each participating center (https://plataformabrasil.saude.gov.br/, protocol number CAAE 45781015.8.1001.5259). All participants granted informed consent; all procedures were in accordance with the ethical standards of the Brazilian National Research Committee and with the 1964 Helsinki declaration and its later amendments.

Consent for publication

All participants granted informed consent for publication.

Competing interests

CPA reports personal fees and/or non-financial support from Pfizer, AbbVie, AstraZeneca, Janssen, Bristol-Myers Squibb, Roche, Novartis and UCB, outside the submitted work. APMG reports personal support and consulting fees from Pfizer. ABVS reports support for international medical events from AbbVie and Janssen. MBB reports having participated in clinical and/or experimental studies related to this work and sponsored by Roche and having delivered speeches at events related to this work and sponsored by AbbVie and Pfizer. PLJ reports support for international congresses from Bristol-Myers Squibb, UCB; and consulting fees from Pfizer; RDNG reports consulting fees, speaking fees and support for international congresses from Roche, Pfizer, Bristol-Myers Squibb, UCB, Eli-Lilly, AbbVie, Abbott and EMS. SCR reports consulting and speaking fees from AbbVie, Janssen, Pfizer, Roche and UCB. MFBRG reports speaking fees and support for congresses from AbbVie, Bristol-Myers Squibb, Janssen, Novartis, Pfizer, Roche and UCB. KRB reports speaking fees and support for international congresses from Roche, Pfizer, Bristol-Myers Squibb, AbbVie and Janssen. MFLCS reports no financial disclosures. IAP reports consulting fees, speaking fees and support for internationals congresses from Roche, Pfizer, UCB Pharma, Eli-Lilly, AbbVie and Janssen. CVB reports having participated in clinical and/or experimental studies related to this work and sponsored by AbbVie, BMS, Janssen, Pfizer and Roche; having received personal or institutional support from AbbVie, BMS, Janssen, Pfizer and Roche; having delivered speeches at events related to this work and sponsored by AbbVie, Janssen, Pfizer and Roche. LMHM reports personal or institutional support from AbbVie, Janssen, Pfizer and Roche; and having delivered speeches at events related to this work and sponsored by AbbVie, Janssen, Pfizer, Roche and UCB. LSN reports no financial disclosures. GRCP reports consulting fees from AbbVie, Bristol-Myers Squibb, Eli Lilly, Glaxosmithkline, Janssen, Pfizer, Sanofi Genzyme and Roche.

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