ORIGINAL ARTICLE

DOI: 10.15713/ins.bhj.134

Cloud Cover and High Temperature Increase Disease Activity in Patients with Rheumatoid Arthritis: Inferences from a Tropical Setting

ABSTRACT

Background: The effect of weather on rheumatoid arthritis (RA) activity is contentious. Most of the studies checking this effect have been done in temperate climates. The climate in tropical countries like India is distinctive and studying its effect on RA disease activity could provide unique insights. **Objectives:** The objectives of this study were to prospectively study the effect of weather parameters on disease activity in patients with RA in tropical settings. **Methods:** We studied the effect of weather parameters such as minimum temperature, mean temperature, maximum temperature, humidity, cloud cover, atmospheric pressure, and rainfall on RA disease activity scores 68, (DAS) in 907 patients over a follow-up period of 61 months. The mean follow-up was 32.24 (±14. 25) months. **Results:** Multiple step-wise linear regressions were performed to assess influence of pressure, maximum temperature, minimum temperature, ultraviolet (UV) index, rainfall, humidity, and clouds on DAS. Maximum temperature (Beta = 0.665, $P < 0.01$) and clouds (Beta = 0.996, $P < 0.01$) had a significant direct, while rainfall (Beta = −0.575, $P < 0.05$) had a significant inverse effect on DAS. Minimum temperature, UV index, humidity, and pressure did not have any effect on RA disease activity. Overall model adjusted R^2 was 0.346. **Conclusion:** After comparing with previous literature, we conclude that extremes of temperatures have deleterious effect of RA activity. In tropical climate, cloud cover increases RA activity, while rainfall reduces it.

Key words: Cloud cover, Disease activity score 68, Rainfall, Rheumatoid arthritis, Temperature, Weather

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, immunoinflammatory, and systemic disease that mainly affects the synovial joints and extra-articular structures of the body. Many patients with RA report that weather conditions or changes in weather aggravate their symptoms, which include pain, stiffness, and swelling of the joints. Weather has a profound effect on human health and well-being. It has been shown to be associated with changes in birth rates and sperm counts, with outbreaks of respiratory tract infections, and with increased mortality in heat and cold waves.[1]

Earlier, numerous studies have been done to study the effect of weather on RA activity.[2-16] A meta-analysis studying the effect of weather on RA activity in 2004 could not come to a firm conclusion of the effect of weather, except possibly for the effect of humidity.[17] Most of the studies on this subject were done either in cooler or temperate climates. The effect of weather on RA activity could be different in tropical countries as compared to temperate countries. To the best of our knowledge, there have been no reports studying this effect from tropical countries.

India is a tropical country with three different seasons. There is a significant variation of weather in these three seasons, with a fairly clear cut demarcation during transition of seasons.

The aim of this study was to prospectively check the effect of weather parameters on RA activity in tropical setting.

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METHODS

This was a single-center study conducted in the city of Nasik situated in the state of Western Maharashtra of India. It is situated on 19.9° North latitude and 73.7° East longitude. It is situated 577 m above the sea level. It is has a climate which is classified as tropical. This center gets patients from a surrounding area of 100 km radius. This entire drainage area has a similar weather pattern. During the year, summer months range from mid March to mid-June, monsoon from mid-June to mid-October and winter from mid-October to mid-March, with a few days needed for transition into the next season.

This was a longitudinal observational study. The data recording started in October 2014. Patients registered till May 2019 were used for analysis (n = 2176). This center has computerized data recordings of all patients following up in the outpatient clinic. From this database all patients classified as RA based on the American College of Rheumatology 2010 criteria were assessed. These patients were followed up monthly for first 3 months or until their RA activity was controlled. Thereafter, they were followed up every 2–4 months. Interim visits were allowed if they had an emergent situation. At each visit, their total joint count (TJC), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), and physician's global assessment (PGA) of disease activity were recorded. Disease activity score 68 (DAS) was derived from this data. Furthermore, they were enquired about the Indian version of health assessment questionnaire (HAQ) and it was recorded.[18] Patients classified as Palindromic RA, by definition, were considered to have episodic rise in disease activity and hence were excluded from the analyses.

The weather parameters were collected from the site www.worldweatheronline.com. The parameters collected were minimum temperature (Celsius), maximum temperature (Celsius), mean temperature (Celsius), rainfall (millimeters), humidity (percentage), cloud cover (percentage), ultraviolet (UV) index, sun cover, sun days, and atmospheric pressure (mb). These were averaged as monthly data. The data collection was done from October 2014 to May 2019.

Data were analyzed using the SPSS software for Windows (version 26.0, 2019, SPSS Inc., Chicago, IL). Continuous variables were presented as mean with standard deviation for normally distributed variables and median with inter-quartile range for non-normally distributed variables. One-way analysis of variance (ANOVA) was used to examine differences in means parameters between groups. Multiple step-wise linear regressions were performed to assess influence of pressure, maximum temperature, minimum temperature, UV index, rainfall, humidity, and cloud cover on DAS. Regression assumptions colinearity, normality, and homoscedasticity were assessed using VIF, P-P plots, and scatter plot of residuals, respectively.

RESULTS

The consort diagram [Figure 1] explains the enrolment of patients for the study. We excluded first three visits of each patient, as we considered this as the time required for stabilization of disease activity with disease modifying anti rheumatic drugs (DMARDS). Their disease activity was high during this period due to the latency in activity of DMARDS. We sorted outpatients who had a gap more than 6 months in their subsequent visits as non-compliant (n = 1269, visits n = 1651) and excluded the visits thereafter from the study. Both these notions were based on a preliminary analysis of our data which suggested that DAS was stable after first 3 months of treatment and when the gap between two subsequent visits was <6 months. Beyond a gap of 6 months, the DAS became unstable and high, proving that noncompliance was affecting disease activity [Figure 2]. A total of 4885 visits from 907 patients were considered for analysis. Although, there was a significant drop in the number of patients included, we ensured that we had a population which was compliant, followed up regularly during the period of the analysis and their presentation to clinic was not due to flares of noncompliance.

The cohort included 907 patients (Male [M] 121 and female [F] 786) with 4885 (M 579, F 4306) visits. The duration of individual patient follow-up ranged from 3 months to 61 months. Of the 907 patients, 145 (16%) had a follow-up of <1 year, 210 (23.2%) between 1 and 2 years, 220 (24.3%) between 2 and 3 years, 189 (20.8%) between 3 and 4 years, 10 (12%) between 4 and 5 years, and 34 (3.7%) above 5 years.

Baseline characteristics and details of subsequent visits are mentioned in Table 1.

Mean age was significantly higher in males and average visits were significantly higher in females. There was a statistically significant difference between genders as determined by one-way ANOVA in age $F(1, 4883) = 29.1$, $P < 0.01$ and number of visits ($F[1, 4883] = 11.8$, $P < 0.01$). No significant difference was seen between genders in average gap between two visits.

Mean DAS was 3.6 ± 1.2 (M 3.2 ± 1.3, F 3.7 ± 1.2), and HAQ score was 0.62 ± 0.48 (M 0.58 ± 0.46, F 0.49 ± 0.1). There was a statistically significant difference between genders as determined by one-way ANOVA in DAS $F(1, 3861) = 60.6$, $P < 0.0$. No significant difference was seen between genders in HAQ. There was a statistically significant difference between age groups (<40 years, 41–50 years and >51 years) as determined by one-way ANOVA in DAS score, and HAQ. $F(2, 3860) = 14.1$, $P < 0.0$.

There was no statistically significant difference in pressure, maximum temperature, minimum temperature, UV index, rainfall, humidity, and cloud cover from 2014 to 2019 months as determined by one-way ANOVA.

Table 1: Important characteristics of patients

	Men	Women	TOTAL
N	121	786	907
Age	50.88±13.35	48.11±11.34	48.44±11.63
Total number of visits	579	4306	4885
Average number of visits	7.33±3.15	7.9±3.8	7.83±3.73
Average Interval between 2 visits	2.18±1.26	2.14±1.25	2.15±1.25
Average DAS	3.2±1.25	3.66±1.17	3.61±1.19
Average HAQ	0.58±0.45	0.62±0.48	0.62±0.48

Table 2: Regression analysis result

Model	B	Std. Error	Beta	t	Sig.
(constant)	2.215	0.282		7.868	<0.001
Maximum Temperature	0.042	0.008	0.665	4.996	<0.001
Rainfall	-0.003	0.001	-0.575	-2.417	0.019
Cloud cover	0.008	0.002	0.996	4.005	0.001

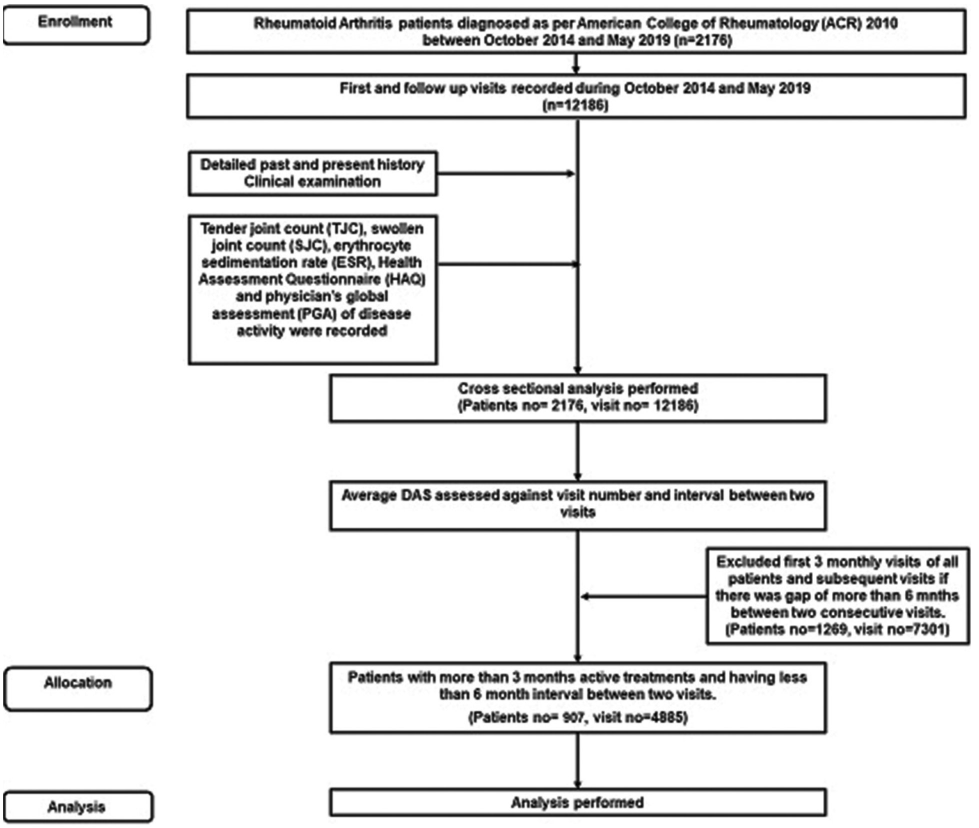

Figure 1: Consort diagram for patient enrollment

Multiple step-wise linear regressions were performed to assess influence of pressure, maximum temperature, minimum temperature, UV index, rainfall, humidity, and clouds on DAS scores. The results are shown in Table 2. Overall model adjusted R^2 was 0.346. Data also fulfilled normality, colinearity, and homoscedasity assumptions.

There was a strong correlation between the behavior of DAS and HAQ. Results of the Spearman`s correlation indicated that there was a significant positive association between DAS and HAQ, ($r = 0.492$, $n = 2179$, $P < 0.001$) [Figure 3].

DISCUSSION

In tropical country like India, maximum temperature and cloud cover have a direct relation with RA activity, whereas rainfall has inverse relation. This study highlights that weather does have effect on the RA disease activity. The previous studies examining the effects of weather on RA activity were limited by the virtue of their using subjective measures[2-4] being of short duration,[3,4] having fewer subjects,[4-6] and having unorthodox methodology.[7,8] A more recent study with a good design evaluated the effect of seasons in a large cohort. However, it could not draw a firm conclusion of the weather effect. This could have been due to the fact that the effect of seasons, rather than that of absolute weather parameters, were analyzed.[9]

This study can be said to be a fairer representation of the effects of weather on RA activity. First, this is a longitudinal study with a relatively large sample size. Second, the patients had an average follow-up of 32.24 (+14. 25) months. This can be considered a substantial time to know the effect of weather on RA activity indices. Third, both, subjective (TJC, PGA, HAQ) and objective (SJC, ESR) parameters, were used to calculate the weather effect rather than using the subjective data alone. Hence, in essence, each patient acted as a "control" of himself in studying the effect of various weather parameters over a period of time on his disease activity. Finally, this could be the first study done in a tropical setting to check the effect of weather on RA activity.

Temperature is the most studied weather parameter among all. Some studies did not find effect of temperature,[10-12] while others showed higher disease activity in cooler climates.[10,13-15] These studies were carried out in places with a cooler or temperate climates, where temperatures are extremely cool in winter. In our study, maximum temperature correlated directly and significantly with DAS (Beta = 0.665, $P < 0.01$). The weather pattern in this part of India has bimodal pattern of maximum temperature with peaks in April and October. The first peak reflects the peak summer, while second peak signals the end of monsoon. The graph of DAS moves synchronously and matches with the peaks of maximum temperature. Similar

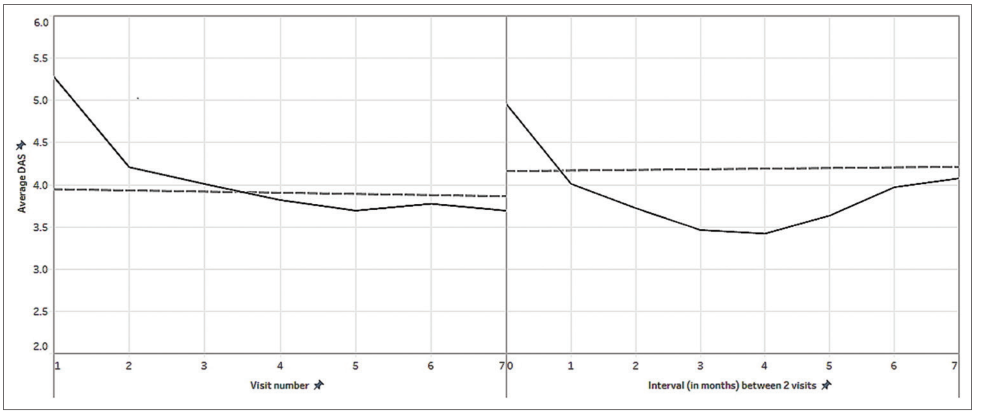

Figure 2: Correlation between DAScore and the number of patient visits

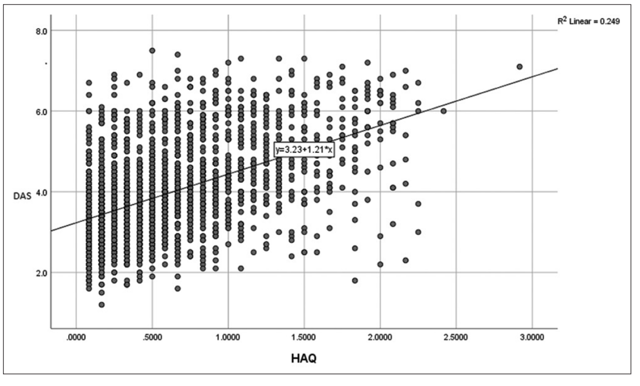

Figure 3: Correlation between DAScore and Health Assessment Questionnaire

findings of higher RA activity in warmer temperatures have been reported in a study from Israel with a Mediterranean and warm climate.[16]

There was no effect of minimum or mean temperature on RA activity. In India, winters are relatively pleasant, while summers are harsh and uncomfortable. In terms of discomfort, Indian summers correspond to winters of the colder countries. Our data shows that minimum temperatures in winters hardly went below 15°C and were not associated with deterioration in RA activity. Hence, we can conclude that extreme temperatures rather absolute temperatures affect the RA activity. This is corroborated by a study carried out in Madrid where RA activity was lowest at moderate temperatures (10–20°C) and increased when temperature dropped below 10°C or rose above 20°C.[7]

There is substantial evidence that extreme temperatures are responsible for an increased pain perception. Dorsal horn neurons that respond to noxious cold also respond to noxious heat, suggesting that pain evoked by extreme temperatures, hot or cold, may be processed similarly in the central nervous system. Furthermore, the differential information about stimulus quality is preserved in the cerebral cortex.[19] In fact, the unpleasantness ratings revealed that cold stimuli were more unpleasant than hot stimuli in the cool room and that noxious heat stimuli were more unpleasant in a warm environment.[20] This phenomenon may help explain the worsening disease activity at extremes of temperatures. We believe that this is the first study which checks the effect of maximum temperatures in a tropical setting. It suggests that maximum temperatures in tropical countries are as deleterious as minimum temperatures in cooler climates.

Tropical weather is peculiar, in that, there are three distinct seasons: Summer, winter and monsoon. Almost whole of the yearly rainfall happens in monsoon, dating mid-June to September. For most days of these months, there is a significant cloud cover ranging from 47% to 92%. Hence, monsoon is the best season to check the activity of cloud cover on RA activity. We found that of all the weather parameters, cloud cover has the strongest correlation with DAS (Beta = 0.996). There could be various mechanisms to explain this. In summer, cloud cover acts as a layer which prevents dissipation of heat into higher layers of environment. Hence, heat is trapped in lower layers of atmosphere. In the period of summer with already high temperatures, trapping of heat further increase the maximum temperature. Hence, cloud cover is responsible for further deterioration of RA activity. Another mechanism through which cloud cover could act is through psychological mechanisms. Psychological disorders such as seasonal affective disorder or depression are known to exacerbate during cloudy weathers and on days with lesser sunshine.[21] This may lead to increase perception of pain, especially in patients with these pre-existing conditions.

It will be intriguing to think about the effects of cloud cover in cooler climates. Many patients in the Western world vouch for the fact that their pain increases on a cold and humid day. This is aptly brought out in the blog www.cloudywithachanceofpain.com and many anecdotal reports. However, the data in this regard is sparse, inconclusive, and needs further research.[22] If properly designed studies prove this phenomenon, we can postulate a hypothesis based on the fact that cloudy skies reflect the sun's rays back into space and prevent them from reaching the cooler earth's surface in winter months. Further, cooling due to cloud cover will increase the RA activity which has already deteriorated by the minimum temperatures. Cloud cover in winters can also act by a mechanism seen in seasonal affective disorders. In some patients, mood and decision making may depend on cloudy weather,[23] which in turn can increase the perception of pain.

Another salient finding of the study was an inverse relation of rainfall with RA activity. The average monthly rainfall recorded in monsoon ranged from 12.98 to 226.33 mm. The average yearly rainfall was 330.91 mm concentrated in monsoon months. DAS indices had an inverse correlation with rainfall. The previous studies did not find a significant relation between rainfall and RA activity.[24] The inverse relation found here could be due to a peculiar phenomenon working for the tropical countries. Here, monsoon months are in summers when temperatures otherwise are supposed to reach high extremes. The precipitation brings respite in high temperatures and thus in the RA activity. In cooler climates, rainfall may be irrelevant in the summers, while precipitation in the form of snowfall may increase the disease activity by reducing the winter temperatures. We did not find any reports studying the effects of snowfall on RA activity. This avenue needs to be explored further.

Humidity has been studied extensively as a factor affecting RA activity. Some suggest a direct relation,[13,17] while others did not find any.[4] We did not find any effect of humidity on RA activity.

A good correlation of DAS and HAQ suggests that, that maximum temperature, cloud cover and rainfall have similar effect on subjective parameters like HAQ.

There could be some short comings in this study. First, the correlation of weather parameters and RA activity was done using monthly averages. It was presumed that this was a reflection of their association on a daily basis. It would have been ideal to correlate daily weather indices with indices of RA activity. However, unfortunately, managing this data would have been too tedious. Second, from this data, it could not be said if the rise in RA activity was due to flares or due to sustained increase in activity. It would have been ideal to get exact number of flares in each month and correlate with weather indices. However, even if there were flares during a particular period, they would act in a way as to affect the disease activity for that period. Third, this analysis does not study the residual effect of weather on RA activity spilling over to subsequent days. There is a possibility that a particular weather parameter affect RA activity days after it ceases to exist. Finally, it is possible that many patients may be immune to weather changes. Hence, these findings may not be generalized to an individual patient.

CONCLUSION

First, this study suggests that weather has significant effect on the RA activity. Second, the effect of weather on RA activity may depend on the patient's geographical area. In tropical climates, RA activity increases with maximum temperature and cloud cover. Tropical rainfall, that is, one in summer reduces the RA activity. Further larger prospective studies may confirm these findings.

These findings may have many possible implications. Knowing that a specific weather may improve or worsen patient's condition, the rheumatologist may be able guide his therapy for a good control over patients' RA activity. For the patient, the knowledge of upcoming weather may help to know and decide what to expect of their disease activity. This may, in turn, help guide their activities and schedules so that they pursue a better quality of life.

Future research can be guided by these findings. A computer model can be created that can study the contributions of effects of each of the weather parameters on RA activity. Researchers may be able to generate applications advising the rheumatologist and RA patients about their daily activities.

The Omkar Hospital Ethics committee granted permission for the patient data to be used for the preparation of manuscript.

ACKNOWLEDGMENT

We acknowledge the efforts of Dr Vinod Ravindran in preparation of the manuscript.

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How to cite this article: Jadhav P, Patwardhan V. Cloud cover and high temperature increase disease activity in patients with rheumatoid arthritis: Inferences from a tropical setting. Bombay Hosp J 2023;65(1):1-6.

Source of support: Nil, **Conflicts of interest:** None