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Early Arthritis: A Rapid and Sustained Response to Treatment over one Year Follow-up

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Abstract

Aim: We aimed to assess the evolution in a group of patients diagnosed with early arthritis, by using clinical outcome measures and to find possible predictors for the clinical response.
Methods: The study was conducted in the Rheumatology Department between January 2010 - December 2011. Thirty-six patients between 18-75 years of age with arthritis of at least one peripheral joint less then 12 months duration were consecutively included; other definite causes for arthritis were clinically excluded. The visits were performed at baseline, 3, 6 and 12 months. Clinical examination and biological investigations related to the disease activity were performed. Clinical remission and the EULAR ("European League Against Rheumatism") response criteria were assessed based on the disease activity score 28 (DAS28).
Results: At baseline 91.67% of patients received treatment indication with disease modifying antirheumatic drugs. A significant decrease in the number of tender, swollen joints, erythrocyte sedimentation rate was obtained at 3 months ($p<0.001$). The mean DAS28 decreased from 5.02 ± 1.31 at baseline to 3.54 ± 1.36 at 3 months ($p<0.001$). At 3 months, 33.3% of patients were good and 50% moderate responders ($p<0.001$), while at 6 months 47.2% were good and 33.3% moderate responders ($p<0.001$). Remission and low disease activity were achieved by 47.2% of patients at 3 and 12 months.
Conclusions: A rapid response to treatment was obtained at 3 months. Low disease activity and remission were achieved by almost a half of patients at each visit. The favorable response rate was preserved at 6 and 12 months of follow-up.

Keywords: Early arthritis; Rheumatoid arthritis; Disease activity; Clinical remission; Methotrexate.

Introduction

Rheumatoid arthritis (RA) is the most frequent among the inflammatory rheumatological conditions. If untreated, the disease can lead to joint damage, functional impairment and increased mortality. Early arthritis (EA) represents an inflammatory arthritis with recent onset, which do not fulfill the classification criteria for any definite disorder. The disease course may be towards rheumatoid arthritis (RA), other rheumatic autoimmune diseases, towards remission or sometimes the disease may remain an undifferentiated arthritis. Most of the authors define a very early stage of the disease less than 12 weeks from the onset and an early stage between 3 months and 12 months of evolution of the disease. Early referral to the Rheumatologist as well as early aggressive

treatment, are mandatory in order to prevent the progression of rheumatoid arthritis. Disease modifying drugs (DMARDs) given early in the disease state might lead to a sustained clinical remission, influencing the disease course [1].

This study aimed to assess the evolution over one year of treatment in a group of patients diagnosed with early arthritis, by using clinical outcome measures and to find possible predictors for the response to treatment.

Material and Method

Selection and Description of Participants

Patients between 18-75 years of age with arthritis of at least one peripheral joint less then 12 months duration were consecutively included in the study. Other definite causes for arthritis were clinically excluded: definite spondylarthritides, definite connective tissue diseases, microcrystal-induced arthritis, paraneoplastic syndromes, osteoarthritis and trauma.

Study Design

The study was conducted in the Rheumatology Department of a tertiary referral center. Patients were visited by their current rheumatologist of the department at baseline and then at 3, 6 months and at one year. Data collection was performed after the 12 months visit was ended. Clinical remission and the EULAR response criteria [2] were assessed based on the disease activity score 28 (DAS28) at 3, 6 and 12 months of follow-up. The relationship between demographic, clinical, biological and treatment parameters in relation with the response criteria was assessed.

Clinical Assessment and Laboratory Investigations

Complete clinical examination was performed at baseline and follow-up visits in order to exclude other possible causes for arthritis. Twenty eight joints were clinically assessed for tenderness and swelling. Patients' assessment of global health status (PGA) reported on 100 mm visual analogue scale and the duration of morning stiffness were recorded. Erythrocite sedimentation rate (ESR) (normal level < 28 mm/h) was performed at each visit. IgM rheumatoid factor (RF) (normal level < 32 UI/ml) and anti-cyclic citrullinated peptide (anti CCP) (normal level < 3 UI/ml) antibodies were determined at baseline.

Disease activity score 28 (DAS 28) was calculated for all patients at each visit. The EULAR response criteria based on DAS28 were noted at 3, 6 and 12 months of follow-up [2]. The new ACR/EULAR 2010 classification criteria were assessed for all patients at baseline [3].

Statistical Analysis

Baseline characteristics were reported as mean±standard deviation (SD), median (25%-75% percentiles) for quantitative variables or as numbers with corresponding percentages. Wilcoxon test was used for pairs, quantitative data and McNemar test for qualitative data. Normal distribution was assessed using Kolmogorov-Smirnov test. Student t test was used to compare means for normal distributed variables and Chi-square test to compare frequencies. To compare three or more means we used Anova test with Bonferroni pod-hoc analysis (normal distributed variables). Pearson correlation coefficient was used to estimate the correlation between two quantitative variables. Statistical analyses were performed using the Microsoft Office Excel and SPSS 15.0.

Results

Baseline Data in EA Patients

The study included 36 patients. A very early onset (less than 3 months duration) was seen in 19 (52.77%) patients. RF was positive in 13 (36.11%), while anti-CCP antibodies were found in 21 (58.33%) patients. The mean DAS28 showed a state of moderate disease activity at baseline. 2010

ACR/EULAR criteria were fulfilled in 19 (50%) patients. (Table 1).

Table 1 presents the summary of patients' demographic, clinical, laboratory data at baseline.

Table 1. Patients' demographic, clinical and laboratory data at baseline

Parameter	Statistics
Gender (F:M)	2.3:1
Age – years: mean±SD	46.66±13.16
Disease duration – months: median (25% - 75%)	3 (1.25-3)
Very Early EA: n (%[95% CI])	19 (52.77 [37.0-68.0])
Smoking (current or past): n of yes (% [95% CI])	11 (30.55 [17.8-46.9])
DAS28: mean±SD	5.01±1.30
Rheumatoid factor (positive): n (% [95% CI])	13 (36.11 [22.4-52.4])
Anti CCP antibodies (positive): n (% [95% CI])	21 (58.33 [42.1-72.8])
2010 ACR/EULAR classification criteria for RA: n (%[95% CI])	18 (50 [34.4-65.5])
Corticosteroids: n (% [95% CI])	23 (63.88 [47.5-77.5])

SD = standard deviation; CI = confidence interval

Changes from Baseline for Joints Counts and ESR

The changes from baseline for joints counts and ESR are presented in Table 2. At 3 months, the results showed an important decrease in the number of tender and swollen joints, the results being statistically significant (p=0.0008). No significant difference was noticed in tender or swollen joint count (TJC, SJC) from 3 to 6 month or from 6 to 12 month. The result are significant when TJC and SJC at 12 months were compared to baseline data. (Table 2). The results demonstrated a significant decrease of ESR at 3 months (Table 2). The changes in ESR from baseline to 12 months are also significant (p=0.006)

Table 2. The dynamics of number of tender and swollen joints and ESR in EA patients at 3, 6 and 12 months

	TJC	SJC	ESR (mm/h)
Baseline	10 (5-14)	4.5 (2.25-8)	29 (15.25-49.5)
3 months	4 (1-7)*	1.5 (0-4)*	18 (8-25)*
6 months	2 (0.25-5)	1 (0-2.75)	15 (8.5-22.75)
12 months	2 (0.25-4.75)+	1 (0-2)	17 (6.75-24.75)
p	< 0.001	< 0.001	< 0.001

TJC = tender joint count; SJC = swollen joint count; ESR= erythrocyte sedimentation rate;
* if p is significant for 0-3 m; ** 3-6 m; *** 6-12; +0-12; Data are presented as median (25%-75% percentiles)

The Evolution of the Disease Activity Score

Figure 1 shows the evolution of DAS28 in EA patients. An important decrease of DAS28 at 3 months was obtained, from a median value of 5.34 (IQR, 2.81-4.81) to 3.29 (IQR, 2.435-4.825), the results being statistically significant (p<0.001). At 6 months and at 12 months, the mean DAS28 was 3.18 (IQR, 2.305-4.195) and 3.22 (IQR, 1.78-3.925), respectively, without significance from 3 to 6 months (p=0.20) or from 6 to 12 months (p=0.96). The results were significant in terms of a decrease in mean DAS28 at 12 months when compared to baseline (p< 0.001).

The EULAR Response Criteria

The analysis of EULAR response criteria is presented in Figure 2. The results showed a good response for 33.33% and a moderate response for 50% of EA patients at 3 months (p<0.001). At 6 months, 47.22% of patients were good responders, while 33.33% were moderate responders, the results being significant for 3 to 6 month (p<0.001). The proportion of patients achieving a good and a moderate response at 12 months was 30.56% and 41.67%, respectively, with no difference from 6 to 12 months (p=0.20).

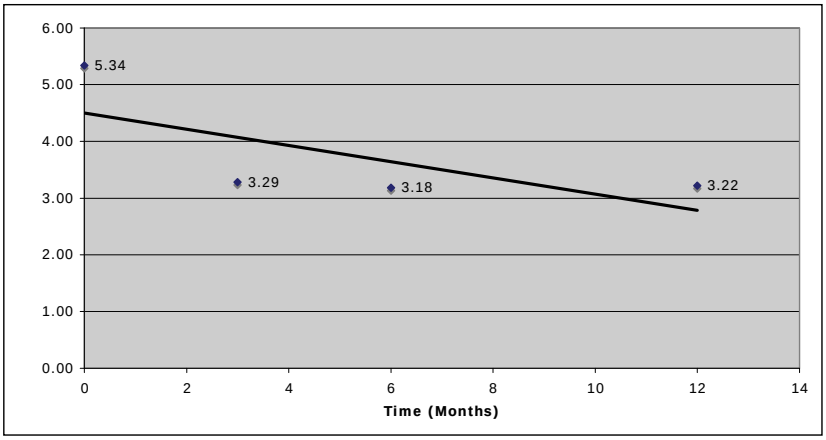

Figure 1. Disease activity measured by DAS 28, median at baseline (0), 3, 6 and 12 months

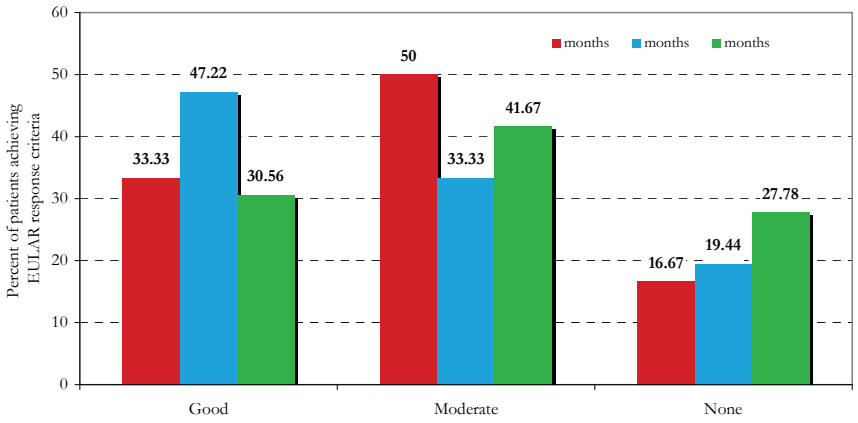

Figure 2. The distribution of patients fulfilling the EULAR response criteria at 3 months, 6 months, 12 months of follow-up

The Disease Activity States in EA Patients over the Follow-Up Time-Points

Figure 3 shows the percentage of patients achieving different disease activity states in the EA group at 3, 6 and 12 months. At baseline, the majority of patients were in high disease activity (HDA) (61.11%), followed by patients in moderate disease activity (MDA) (27.78%). A significant change was demonstrated at 3 months, by decreasing the number of patients in HDA (to 13.9%) and increasing the number of patients in remission (p<0.001); 36.11% of patients were in remission and 11.11% in LDA at 3 months. At 6 months, there was a decrease in the percentage of patients in HDA (5.56%), and increase in LDA patients (25%), significant from baseline to 6 months (p<0.001) and not significant from 3 to 6 months (p=0.10). The results at 12 months are similar to those at 3 months (p=0.01) with no significant changes from 3 to 12 months (p=0.34) or from 6 to 12 months (p=0.30).

In 13.9% of cases, moderate or high disease activity scores were obtained due to increased TJC and high PGA values (not shown).

Treatment with Disease Modifying Antirheumatic Drugs (DMARDs)

The proportion of patients in whom the treatment with Methotrexate (MTX), Hydroxichloroquine HQ), Salazopyrine (SSZ) or other combination of DMARDs was prescribed at baseline, 3, 6 and 12 months is shown in figure 4. MTX alone or in combination therapy was prescribed at baselie, 3, 6 and 12 months in 72.23 %, 80.56%, 74.99% and 63.89% of patients,

respectively. The number of patients taking a combination of DMARDs increased from 11.1% at baseline to 50% at 12 months. At baseline 63.88% of patients received concomitant corticosteroids (CS) (Table1), in small doses. The percentage of patients taking CS at 12 month decreased to 19.4%.

At 12 months, one quarter of patients received the indication for biological therapy.

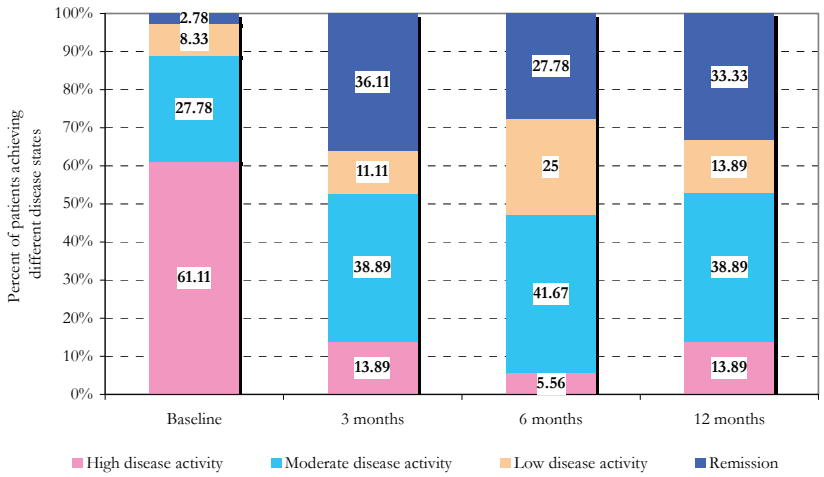

Figure 3. The distribution of patients achieving different disease activity states at 3, 6 and 12 months

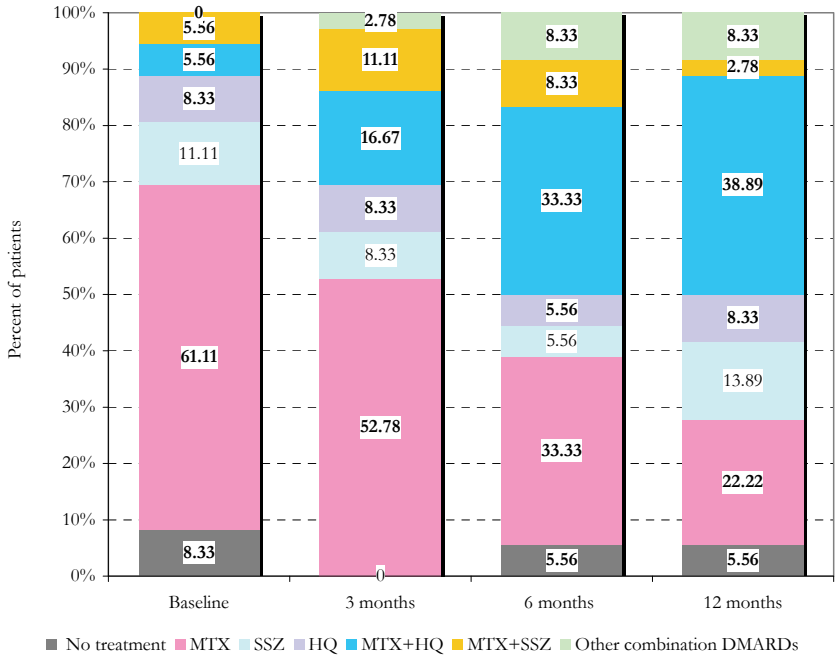

Figure 4. Percent of patients in whom DMARDs were prescribed at baseline and at follow-up time-points

Predictors for Clinical Response

The clinical response measured by DAS28 and/or EULAR response criteria in relation with age, sex, anti-CCP antibodies, treatment with CS and Methotrexate at baseline was investigated.

The data analysis demonstrated that the age at onset correlated with the EULAR response at 3 months: good responders had a mean age of 37.4 years versus moderate responders with a mean age of 50.88 (p=0.02). The age at onset did not influence the EULAR response (good/moderate) at 6 or 12 months (p=0.55, p=0.44 respectively). (Table 3) Anti-CCP antibodies positive patients were shown to have increased DAS28 scores at 12 months (mean DAS28=3.64) versus patients not presenting the antibodies (mean DAS28=2.13), p=0.01, with no influence over DAS28 at 3 and 6 months. (p=0.38, p=0.09), neither at baseline (p=0.18, not shown). (Table 3)

All patients (100%) with a moderate EULAR response at 6 months were receiving corticosteroids at baseline (p=0.05). Corticosteroids at baseline did not influence the EULAR response at 3 or 12 months (p=0.27, p=0.80). The treatment with MTX prescribed at baseline influenced the EULAR response at 12 months; 93.3% of patients presenting a moderate EULAR response were treated with MTX after the first visit (p=0.05, not shown).

Table 3. Age and anti-CCP antibodies in relation with clinical response (DAS28 and EULAR response rate)

	3 months		6 months		12 months	
	EULAR response (good / moderate)					
Mean age (years)	37.4 *	50.9	47	42.25	41.8	48.66
	Anti CCP antibodies (present / absent)					
Mean DAS28	3.60	3.18	3.47	2.57	3.64 *	2.13

*$p \leq 0.05$

Final Diagnosis at 12 Months

At one year of follow-up, the diagnosis established by the current physician was RA in 72.22% of cases, undifferentiated arthritis in 11.11%, the other cases being classified as seronegative spondylarthritides, overlap syndromes, palindromic rheumatism and polymyalgia rheumatica.

Discussion

Remission represents the main target in RA patients, including EA patients.[4] Early treatment with DMARDs is one of the key elements in the management of EA. [5] Biological agents can also be used in EA patients; studies have been proven that early and aggressive therapy improve outcome related to joint destruction, function and quality of life in RA [6,7]. However, the increased costs of biological agents reduce their use in early phases of RA. Identifying poor prognostic markers could improve the management of the early disease. [8]

The present study was aimed to investigate the evolution of patients diagnosed with early arthritis over one year of treatment, by using clinical outcome measures and to determine possible predictors for the response to therapy with synthetic DMARDs.

Ideally, remission means the absence of any sign and symptom of the disease as well as the absence of the radiographic progression and loss of physical function.[9,10] In daily clinical practice, remission means the absence of the disease activity or the presence of a minimal disease activity, using the composite indices.[11,12] In the present study, we used DAS28 score to assess the clinical remission, this score being the most frequently used in the daily clinical practice and the EULAR response criteria based on DAS28.

The analysis of the clinical assessment for TJC and SJC showed a decrease from 0 to 3 months as well as from 3 to 6 months, but statistically significant only at 3 months. Similar, our results demonstrated a significant decrease of ESR from 0 to 3 months. Although a slight increase of median values for ESR at 12 months were observed, a significant reduction in ESR was demonstrated from baseline to 12 months. In the study of Nell et al. it was demonstrated a decrease in TJC, SJC and ESR in patients with very early as well as with late early RA [13]. Our data at baseline shows that 52.77% were classified as having a very early arthritis, with symptom duration

less than 3 months.

The follow-up of the disease activity scores showed a decrease of the mean DAS28 corresponding to a moderate disease state at 3, 6 and 12 months, the mean values obtained at 6 and 12 months being very close to the upper limit of the low disease activity state (3.23 and 3.22 respectively compared to 3.2). The clinical benefit of early treatment versus delayed treatment with synthetic DMARDs was previously demonstrated [14,15]. A rapid response during the first 12 weeks of treatment was shown also in other papers [13,16,17]. We used DAS28 in order to assess the EULAR response criteria. The analysis of the EULAR response rates evidenced more than 80% of patients as good and moderate responders at 3 and 6 months. The rate of non-responders slightly increased at 12 months, one explanation being that some patients had increased DAS28 scores due to a high TJC and PGA values. An important divergence between the subjective parameters (TJC, PGA) and the objective measures of inflammation (SJC, ESR or C-reactive protein) and included in DAS score has to be identified when assessing the response to treatment. Associated fibromyalgia in patients with RA is not rare and can lead to difficulties in the management of these patients [18].

The results of the present study highlight that clinical remission evaluated by DAS28 was possible in a significant number of patients already at 3 months, this response being sustained over one year follow-up. It has been demonstrated that early and aggressive treatment can increase the rate of drug-induced remission in RA.[19-22] In our study, the majority of patients were taking DMARDs during the follow-up, in most of the cases MTX alone or in combination therapy. The number of patients taking combination therapy progressively increased from 3 to 6 and to 12 months. Despite that, no significant changes between 3 to 6 or 6 to 12 months were noticed in terms of joint involvement, ESR or DAS28. A significant change from 3 to 6 months was noticed only for the EULAR response rate, the rate of good responders being increased from one third to almost a half of the patients.

Previous studies demonstrated a rapid response, in the first months of treatment in early arthritis. Wevers-de Boer and colleagues recently published the results of the Improved study. A remission rate of 61% was obtained for 2010 classified RA patients treated with MTX and high doses of corticosteroids rapidly tapered [23].

Our results demonstrated a significant influence of CS prescribed at baseline on the EULAR response rate at 6 months. The value of CS in early rheumatoid arthritis has been demonstrated in other studies [24,25]. In our study we used low doses of corticosteroids (7.5-10 mg/day). A recent paper of Bakker et al showed that small doses of CS associated with MTX is more effective in reducing disease activity than MTX alone, 72% versus 61% patients with sustained remission [26].

The EULAR response at 12 months was influenced by treatment with MTX at baseline, 93.3% of patients presenting a moderate EULAR response being treated with MTX from the first visit.

The results of the present study also demonstrate that the frequent visits and measures of the disease activity can lead to a sustained good response to therapy. The international recommendations in this line are based on the TICORA study which demonstrated that tight control and clinical measure of the disease activity are associated with clinical remission [27].

During the last years, several predictive factors for the response to treatment were identified. Of the demographic, clinical or biological predictors, an older age at onset, female gender, increased number of affected joints were shown to be associated with a poor response to therapy. [28] Smoking and longer duration of the disease were also associated with a worse response to MTX in early RA [29]. Higher education, small number of comorbidities and regular exercises were demonstrated to be associated with remission. [30] Low or moderate DAS28 at baseline and a good response to treatment during the first months were also associated with clinical remission. [31] Similar to the published studies, our results highlighted that a younger age at onset was associated with a good EULAR response and that anti CCP antibodies were associated with higher disease activity scores. Identifying predictors of response to therapy and remission might help the clinician to develop a targeted-oriented approach to therapy in patients prone to develop a severe, destructive disease.

Conclusions

The majority of EA patients were treated with synthetic DMARDs, regardless to the fulfillment of the 2010 ACR/EULAR classification criteria or not. A rapid response to treatment was obtained at 3 months, more than 80% of patients being good and moderate responders. Low disease activity and remission were achieved by almost a half of patients at 3, 6 and 12 months, each. Forty percent of patients achieved a moderate disease activity at 3, 6 and 12 months, with a mean DAS28 close to the upper limit of a low disease activity state. Younger patients were good EULAR responders at 3 months. Anti CCP antibodies were associated with higher DAS28 scores at one year. MTX and CS influenced the EULAR response rate at 12 and 6 months, respectively. The EULAR response criteria and DAS 28 were preserved at 6 months and at one year follow-up.

List of abbreviations

RA – rheumatoid arthrtitis
EA – early arthritis
TJC – Tender joint count
SJC – Swollen joint count
ESR – erythrocite sedimentation rate
PGA – patient global health status assessment
FR – rheumatoid factor
Anti CCP antibodies – Anti cyclic citrullinated peptide antibodies
DAS 28 – disease activity score 28
DMARDs – disease modifying anti-rheumatic drugs
HAD – high disease activity
MDA – moderate disease activity
LDA – low disease activity
CS - Corticosteroids
MTX – Methotrexate
SSZ – Salazopyrine
HQ – Hydroxichloroquine
LEF – Leflunomide
EULAR – European League Against Rheumatism
ACR – American College of Rheumatology

Ethical Issues

The study was conducted according to the Declaration of Helsinki and local regulations. Approval of the institutional ethics committee was required and informed consent was obtained from all patients.

Conflict of Interest

The authors declare that they have no conflict of interests.

Authors' Contributions

MMT was involved in the study design, recruitment of patients, carried out data collection, performed statistical analysis and was the main contributor in the manuscript preparation. AP was involved in the recruitment of patients, data analysis and in the manuscript preparation. SR was involved in the study design and in the manuscript preparation. All authors read and approved the final manuscript.

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