Research Article

Comparison between the Improvements in Disease Activity Score 28 (DAS28) Using Erythrocyte Sedimentation Rate (DAS28-ESR) and Clinical Parameters in Cases of Waja-al-Mafasil (Rheumatoid Arthritis)

Mohd. Wasim Ahmad[1], Anirban Goswami[2], Rajesh[3], Md. Ishtiyaque Alam[4]

[1]Research Officer (U), Scientist L-1, Drug Standardization Research Institute (DSRI), Ghaziabad, under CCRUM, Ministry of Ayush, India
[2]Investigator (Statistics), Regional Research Institute of Unani Medicine, Patna, under CCRUM, Ministry of Ayush, India
[3]Research Officer (U), Scientist L-1, Regional Research Institute of Unani Medicine, Patna, under CCRUM, Ministry of Ayush, India
[4]Research Officer (U), Scientist L-4, Regional Research Institute of Unani Medicine, Patna, under CCRUM, Ministry of Ayush, India

Abstract *Waja-al-Mafasil* (Rheumatoid Arthritis) is a progressive, disabling, chronic multisystem disease of unknown cause characterized by pain, swelling and stiffness of synovial joints. The Disease Activity Score (DAS) is a major scoring system for evaluating disease activity of *Waja-al-Mafasil* (Rheumatoid Arthritis). DAS28 was originally using the erythrocyte sedimentation rate (ESR) as the inflammation marker and named DAS28-ESR. The aim of this study to compare the improvement in disease activity score 28 using erythrocyte sedimentation rate (DAS28-ESR) and clinical parameters in the patients of Rheumatoid Arthritis. Rheumatoid Arthritis patients registered in research OPD was used to calculate DAS28-ESR and clinical assessment. In this study, *Majun Jograj Gugal* (Semisolid) and *Raughan-e-Malkangani* (Oil) were administrated to patients for the period of twelve weeks. Improvements of DAS28-ESR were also evaluated according to the European League against Rheumatism response criteria and percentage improvement of clinical parameters in Rheumatoid Arthritis patients. Improvements in DAS28-ESR and Clinical Parameters criteria were compared by Woolf statistical test, Cohen's Kappa (κ) statistic for agreement and linear regression analysis. Classification of improvement in DAS28-ESR and clinical parameters among on the demographical characteristics and RA-Factor were generally identical (p-value >0.05) except patients' nature of work (p-value <0.05). Simple linear regression analysis showed a significant correlation between improvement between DAS28-ESR and clinical parameters (R^2 = 0.64; p-value <0.001). The Cohen's Kappa (κ) coefficient (95% CI) between of them was 0.43 (0.21 to 0.66), indicating good agreement (p-value <0.001). This study concluded that improvements in Disease Activity Score 28 (DAS28) using erythrocyte sedimentation rate (DAS28-ESR) and Clinical Parameters are same in cases of Rheumatoid Arthritis.

Keywords *Clinical Parameters; Disease Activity Score 28 (DAS-28); Improvement; Rheumatoid Arthritis (RA)*

1. Introduction

Waja-al-Mafasil (Rheumatoid Arthritis) is a progressive, disabling, chronic multisystem disease of unknown cause characterized by pain, swelling and stiffness of synovial joints. It is a common inflammatory disease characterized by poly-articular inflammation of the synovial tissue (Arnett et al., 1988). It is the most prevalent chronic disease of the world. In India, as per reports Arthritis affects 15% of total population. This prevalence is higher than many well-known diseases such as diabetes, AIDS and cancer. And in case of Bihar 1821 females per lakh than 1250 males per lakh are suffering from Arthritis as per the Annual Health Survey (2010-2011).

Unani system identifies and attributes diseases like *Waja'al-Mafasil* (rheumatoid arthritis) is a clinical condition of pain with or without stiffness in specific joint or more than one joint caused by accumulation of *Rutūbat Gharība* (foreign humour) in the joints. Indigestion, prolonged breast-feeding, poverty, getting wet, cold climate, worry etc are its predisposing factors. The diseases are due to the disproportionate distribution of humours or *Akhlat* (blood or *dam*, phlegm or *balgham*, bile or *safra*, black bile or *sauda)* inside the body. These humours, which are out of proportion, collect in various parts of the body, at times producing inflammation, and leading to presentation of various diseases. Arthritis is a troubling pain, which causes immobilization of the joint or cessation of function. In case of arthritis, the humours collect in the joints, thereby leading to pain, swelling and other articular tissue damage (Anjum et al., 2005).

According to the khilt waja al mufasil has four types which are *Balghamī*, *Damwī*, *Safrāwī* and *Sawdāwī*.

In *Waja'al-Mafāsil Balghamī*, colour of the skin over the affected joint is whitish and joint swelling is less. The pain is deep seated and the patients are often obese. Other symptoms of *Ghalaba-i-Balgham* (phlegm preponderance) are also present.

In *Waja'al-Mafāsil Damwī*, there is redness of the skin over the affected joint. Joint swelling is visibly marked and the pain is severe. Other symptoms of *Ghalaba-i-Dam* (blood preponderance) are also present.

In *Waja'al-Mafāsil Safrāwī*, there is a slight yellow discoloration of the skin over the affected joint. Joint swelling is less than that of *Damwī* type. Pain and burning sensation along with other symptoms of *Ghalaba-i-Safrā* (yellow bile preponderance) are also found.

In *Waja'al-Mafāsil Sawdāwī*, the skin over the affected joint is dry and blackish blue and joint swelling is hard. Other symptoms of *Ghalaba-i-Sawdā* (black bile preponderance) are also present (Khan et al., 2003; Ibn et al., 2007; Jurjani, 1887; Hakim, 1999; Razi, 2004). The Disease Activity Score (DAS) is a significant scoring system for evaluating disease activity of *Waja'al-Mafasil* (rheumatoid arthritis). The initial development of DAS was reported by van der Heijde et al in 1990 and 1992 (van der Heijde et al., 1990; van der Heijde et al., 1992) and then DAS was modified by a group of investigators from the Netherlands (Prevoo et al., 1995; van Gestel et al., 1996; Prevoo et al., 1996).

The use of DAS is officially recommended by the European League Against Rheumatism (EULAR) for evaluating disease activity and the improvement in disease activity in clinical trials and also in daily clinical practice. DAS combines tender and swollen joint counts, an inflammatory marker, and a patient-reported measure of general health. The first DAS was based on an examination of 44 joints (DAS44) (van der Heijde et al., 1990), and this was later followed by a reduced and simplified version based on 28 joints, DAS28 (Prevoo et al., 1995). Basically, DAS28 was using the erythrocyte

sedimentation rate (ESR) as the inflammation marker and named DAS28-ESR. DAS28-ESR was further extensively validated for its use in clinical trials (Prevoo et al., 1995; Prevoo et al., 1996; Cruyssen et al., 2005).

The disease activity score 28 (DAS-28) is based on 28 swollen joint counts (SJCs) and tender joint counts (TJCs), a self-determined assessment of patient general health on a visual analogue scale (VAS), and erythrocyte sedimentation rate (ESR) with a score ranging from 0 to 9.4 (van Gestel et al., 1998). Published thresholds define absolute DAS-28 scores representing remission (<2.6), mild (43.2), moderate or severe (>5.1) disease activity (Emery et al., 2009). The European League Against Rheumatism (EULAR) response criteria combine the DAS28 score at the time of evaluation with the change in DAS28 score between two-time points and to define improvement or response to treatment (Emery et al., 2009). While response categories and the sensitivity to change in absolute DAS-28 values are important outcomes when assessing treatment effect, in a number of European countries cross-sectional measurement of DAS-28 is crucial in determining which treatment a patient receives (Talstad et al., 1983). The DAS28 based on erythrocyte sedimentation rate (DAS28 (ESR)) has been extensively validated for its use in clinical trials in combination with the EULAR response criteria (Prevoo et al., 1995; Fransen and van Riel, 2005; Kushner, 1991; DAS-SCORE, 2017; Aletaha et al., 2010).

The aim of this study to compare the improvement in clinical parameters and disease activity score 28 using erythrocyte sedimentation rate (DAS28-ESR) in the patients of *Waja-al-Mafasil* (Rheumatoid Arthritis).

2. Materials and Methods

2.1. Study Place

An open level clinical study, approved by the institutional ethics committee, was carried- out on the patients of *Waja-al-Mafasil* (Rheumatoid Arthritis) in GOPD/IPD of Regional Research Institute of Unani Medicine, Patna during the 2014 to 2016.

2.2. Drugs Administrative

In this study unani pharmacopoeial formulation *Majun Jograj Gugal* was given 5 gm twice daily with water after meal and *Raughan-e-Malkangani* for local application in the patients of *Waja-al-Mafasil*. The total duration of treatment was 12 weeks. All clinical follow-ups were done once every 2 weeks.

2.3. Patients Selection

The patients were selected on the basis of inclusion and exclusion criteria in this protocol given below:

Inclusion Criteria

- Patients of either sex, in the age group between 18-65 years.
- Patients having *Waja'al-Mafasil* (rheumatoid arthritis) as defined by the following ACR-EULAR criteria (Aletaha et al., 2010)
    1) Definite clinical synovitis (pain, swelling, tenderness) in at least 1 joint
    2) Absence of an alternative diagnosis for the observed synovitis (arthritis)
    3) A total score of at least 6 from the individual scores in 4 domains:

a. Number and site of involved joints (range 0-5)
b. Serological abnormalities (range 0-3)
c. Elevated acute-phase reactants (range 0-1)
d. Duration of symptoms (range 0-1)

Exclusion Criteria

- Rheumatoid arthritis with extra-articular manifestations, joint deformities, and advanced radiological lesions (e.g. joint subluxation and collapse).
- Obese subjects (BMI ≥30)
- History or clinical evidence of any systemic inflammatory condition other than RA such as, juvenile chronic arthritis, spondyloarthropathy, IBD, psoriatic arthritis, active vasculitis, or gout that may interfere with evaluation.
- History or clinical evidence of any serious systemic illness, DM, TB, disseminated/ complicated herpes zoster (e.g., multi-dermatomal involvement, ophthalmic zoster, CNS involvement, or post-herpetic neuralgia), HIV infection or any other serious and/ or unstable illness that, in the opinion of the investigator, could constitute a risk when taking study drug or could interfere with the interpretation of data.
- Are currently receiving or have received intra-articular treatment (e.g., corticosteroids or hyaluronic acid), oral or parenteral corticosteroids, or NSAIDs within 2 weeks of study entry and DMARDs or IFN therapy within 4 weeks prior to study entry or are anticipated to require IFN therapy during the study.
- Screening laboratory test values, including SGOT, SGPT, ALP, S. creatinine, B. urea, and uric acid outside the reference range (raised >3 times the ULN) that, in the opinion of the investigator, could pose an unacceptable risk to the participant.
- History of hypersensitivity to study drug or any of its ingredients.
- Pregnant and lactating women
- H/o Addiction (alcohol, drugs)

2.4. ACR-EULAR Rheumatoid Arthritis Classification Criteria

1. Definite clinical synovitis (pain, swelling, tenderness) in at least 1 joint
2. Absence of an alternative diagnosis for the observed synovitis (arthritis)
3. A total score of at least 6 from the individual scores in 4 domains:
   a. Number and site of involved joints (range 0-5)
   b. Serological abnormalities (range 0-3)
   c. Elevated acute-phase reactants (range 0-1)
   d. Duration of symptoms (range 0-1)

2.5. Measures of Response Criteria on DAS28-ESR and Clinical Parameters

The improvement of disease using *Majun Jograj Gugal* and *Raughan-e-Malkangani* was assessed on clinical parameters of the Rheumatoid Arthritis. Clinical parameters included, Joint Tenderness, Joint Swelling, Early Morning Stiffness, Movement Restriction, Functional Disability and Joint Pain (on 0-100mm VAS). As, these clinical parameters differ in severity (such as absent, mild, moderate or severe) from patient to patient therefore severity of the clinical parameters were graded as absent=0, mild=1, moderate=2 and severe=3. The patients were followed up on 2nd, 4th,….,12th weeks and at every visit, they were clinically examined and asked about the improvement or worsening of their symptoms. And assessment of temperament of the patients was also done before and after the treatment.

The DAS28-ESR considers 28 tender and swollen joint counts, Patient's Global Assessment of Disease Activity(PGA) on VAS (0-100mm), plus levels of an acute phase reactant (ESR(mm/h)). DAS28(ESR) = 0.56*√(TJC28) + 0.28*√(SJC28) + 0.014*PGA + 0.70*ln(ESR), where TJC = tender joint count and SJC = swollen joint count. EULAR response states were classified as follows: good responders were patients with an improvement of >1.2 and a present score of ≤3.2; moderate responders were patients with an improvement of >0.6 to ≤1.2 and a present score of ≤5.1, or an improvement of >1.2 and a present score of >3.2; non responders were any patients with an improvement of ≤ 0.6, or patients with an improvement of >0.6 to ≤1.2 and a present score of >5.1. DAS28-defined remission was classified as a score of <2.6 (Chambers and Hastie, 1992).

Determine of percentage improvement base on clinical parameters in the patients were classified as following: good responders were patients with an improvement of ≥ 75%; moderate responders were patients with an improvement of >25% to <75 and non-responders were any patients with an improvement of ≤25%.

2.6. Statistical Analysis

All statistical analyses were carried out in R Software (version 3.3.2). Improvement of DAS28-ESR and clinical parameters over the classification of patients into disease activity were compared by Woolf statistical test (Woolf, 1955) on demographical characteristic of patients, RA-Factor & C-reactive protein(CRP), the hypothesis considered as null hypothesis (H0): The distribution among demographical Characteristic, RA-Factor & CRP and response of drugs are the identical in two different methodologies as response based on clinical parameters and DAS28-ESR vs alternative hypothesis (H1): The distribution among demographical Characteristic, RA-Factor & CRP and response of drugs are not identical in two different methodologies as response based on clinical parameters and DAS28-ESR, and values both of them compared by linear regression analysis (Chambers and Hastie, 1992). The null hypothesis set as Response based on clinical parameters and DAS28-ESR is identical on the distribution of demographical Characteristic, RA-Factor and CRP. The Cohen's Kappa (κ) statistic used to assess agreement between the improvement of DAS28-ESR and clinical parameters definitions over the classification of patients into disease activity (Landis and Koch, 1977).

3. Result and Discussion

3.1. Comparison between Response of the Drugs among of the Demographical Characteristics, RA-Factor and CRP based on DAS28-ESR and Clinical Parameters

In the sex distribution, moderate response based on DAS28-ESR was noted in 33 patients of female and 27 patients of male. Similarly, moderate response based on clinical parameters was noted in 48 patients of female and 12 patients of male. Generally, females are more prone to RA than male. The distribution between sex and drugs response were identical in two different methodologies as response based on DAS28-ESR and clinical parameters (p-value=0.73) (Table 1).

The highest numbers (16 & 24 patients) of moderate response were seen in the age group 31 to 40 years based on DAS28-ESR and respectively clinical parameters. The distribution between age group and drugs response were identical in two different methodologies as response based on DAS28-ESR and clinical parameters (p-value=0.12) (Table 1).

According to temperament, maximum number of patients belonged in balghami temperament (37 patients) out of which 24 patients have moderate response,13 patients have no response as per

DAS28-ESR and 30 patients have moderate response, 07 patients have no response as per clinical parameters. The distribution between temperament and drugs response were identical in two different methodologies as response based on DAS28-ESR and clinical parameters (p-value=0.89) (Table 1).

As per response of work, maximum number (55 patients) of moderate response was seen in sedentary work, out of which 28 patients have moderate response, 27 patients have no response as per DAS28-ESR and moderate response in 44 patients, no response in 11 patients as per clinical parameters. The distribution between temperament and drugs response were not same in two different methodologies as response based on DAS28-ESR and clinical parameters (p-value<0.05) (Table 1).

Table 1: *Effects of drugs response among the demographical characteristics, RA-Factor and CRP based on DAS28-ESR and clinical parameters*

Characteristic		Response based on DAS28-ESR			Response based on clinical parameters			Test statistic value	p-value
		Good Response (%)	Moderate Response (%)	No Response (%)	Good Response (%)	Moderate Response (%)	No Response (%)		
Sex	Male	-	9 (81.82)	2 (18.18)	-	8 (72.73)	3 (27.27)	2.35	0.12
	Female	-	33 (55.00)	27 (45.00)	-	48 (80.00)	12 (20.00)		
Age Group (Years)	18-30	-	7 (43.75)	9 (56.25)	-	10 (62.50)	6 (37.50)	0.11	0.73
	31-40	-	16 (57.14)	12 (42.86)	-	24 (85.71)	4 (14.29)		
	41-50	-	11 (57.89)	8 (42.11)	-	15 (78.95)	4 (21.05)		
	51-60	-	8 (100.00)	-	-	7 (87.50)	1 (12.50)		
Mizaj (Temperament)	Damvi (SANGUINE)	-	16 (57.14)	12 (42.86)	-	23 (82.14)	5 (17.86)	0.018	0.89
	Balghami (PHLEGMATIC)	-	24 (64.86)	13 (35.14)	-	30 (81.08)	7 (18.92)		
	Safravi (BILIOUS)	-	2 (40.00)	3 (60.00)	-	3 (60.00)	2 (40.00)		
	Saudavi (MELANCHOLIC)	-	-	1 (100.00)	-	-	1 (100.00)		
Nature of Work	Sedentary	-	28 (50.91)	27 (49.09)	-	44 (80.00)	11 (20.00)	4.42	0.035
	Moderate	-	14 (87.50)	2 (12.50)	-	12 (75.00)	4 (25.00)		
	Strenuous	-	-	-	-	-	-		
Chronicity (in month)	1 - 12	-	-	-	-	-	-	0.35	0.56
	13 - 24	-	1 (20.00)	4 (80.00)	-	3 (60.00)	2 (40.00)		
	> 24	-	41 (62.12)	25 (37.88)	-	53 (80.30)	13 (19.70)		
Occupation	House Wife	-	30 (56.60)	23 (43.40)	-	43 (81.13)	10 (18.87)	0.34	0.55
	Labour	-	1 (100.00)	-	-	1 (100.00)	-		
	Farmers	-	1 (100.00)	-	-	-	1 (100.00)		
	Business man/women	-	2 (66.67)	1 (30.33)	-	3 (100.00)	-		
	Teachers	-	-	2 (100.00)	-	1 (50.00)	1 (50.00)		
	Service man/women	-	1 (50.00)	1 (50.00)	-	2 (100.00)	-		
	Others	-	7 (77.78)	2 (22.22)	-	6 (66.67)	3 (33.33)		
Dietary Habits	Vegetarian	-	4 (100.00)	-	-	4 (100.00)	-	0.14	0.71
	Non-vegetarian	-	37 (56.92)	28 (43.08)	-	51 (78.46)	14 (21.54)		

	Mixed	-	1 (50.00)	1 (50.00)	-	1 (50.00)	1 (50.00)
Family History of the disease	Absent	-	18 (51.43)	17 (48.57)	-	25 (71.43)	10 (28.57)	0.12	0.72
	Present	-	24 (66.67)	12 (33.33)	-	31 (86.11)	5 (13.89)
RA-Factor	-ve	-	32 (58.18)	23 (41.82)	-	43 (78.18)	12 (21.82)	0.0001	0.99
	+ve	-	10 (62.50)	6 (37.50)	-	13 (81.25)	3 (18.75)
CRP	-ve	-	32 (55.17)	26 (44.83)	-	46 (79.31)	12 (20.69)	1.23	0.26
	+ve	-	10 (76.92)	3 (23.08)	-	10 (76.92)	3 (23.08)

According to chronicity, the maximum numbers of 66 patients were found in 24 months and above in chronicity, out of which 41 patients got moderate response, 25 patients got no response as per DAS28-ESR. Beside of that, 53 patients got moderate response, 13 patients got no response as per clinical parameters. The distribution between chronicity and drugs response were identical in two different methodologies as response based on DAS28-ESR and clinical parameters (p-value=0.56) (Table 1).

In this study, most of the patients were house wife (53 patients), out of which 30 patients got moderate response, 23 patients got no response as per DAS28-ESR. According to clinical parameter 43 patients have moderate response, 10 patients have no response. The distribution between occupation and drugs response were identical in two different methodologies as response based on DAS28-ESR and clinical parameters (p-value=0.55) (Table 1).

Table 2: *Comparison of the improvement in DAS28-ESR and clinical parameters*

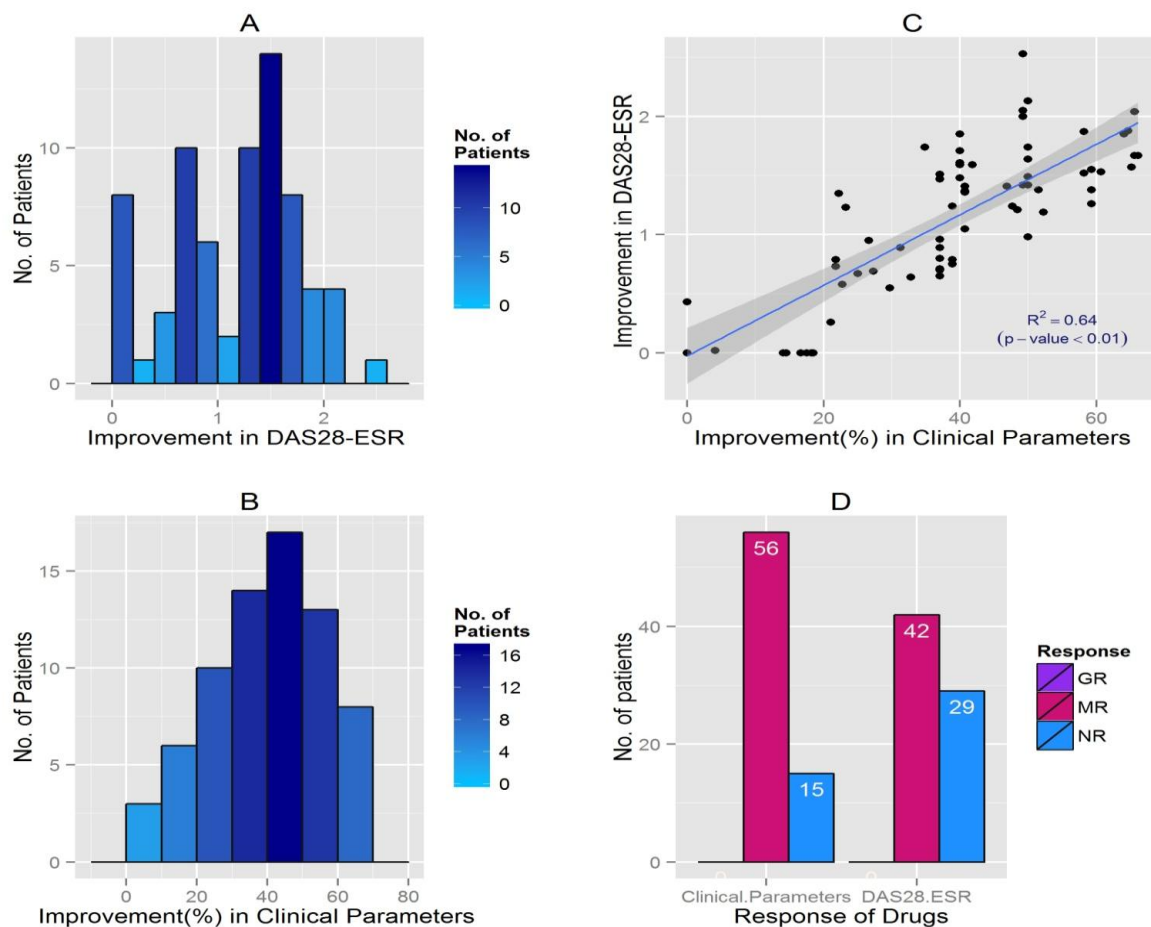|		DAS28-ESR			
		Good Response (%)	Moderate Response (%)	No Response (%)	Total (%)
Clinical Parameters	Good Response (%)	-	-	-	-
	Moderate Response (%)	-	40 (56.33)	16 (22.54)	56 (78.87)
	No Response (%)	-	2 (2.82)	13 (18.31)	15 (21.13)
	Total (%)	-	42 (59.15)	29 (40.85)	71 (100.00)
Cohen's Kappa (κ) coefficient (95% CI) between the improvement in DAS28-ESR and clinical parameters: 0.43 (0.21 to 0.66), p-value <0.001)					

Figure 1: *Distribution, correlation and response of the drugs of improvement in DAS28-ESR and Clinical Parameters. (A) Distribution of improvement in DAS28-ESR (B) Distribution of improvement in Clinical Parameters (C) correlation between of improvement in DAS28-ESR and Clinical Parameters (D) Response of drugs based on improvement in DAS28-ESR and Clinical Parameters*

In the dietary habit of patients, maximum numbers of 65 patients were non-vegetarian, out of which 37 patients got moderate response, 28 patients got no response as per DAS28-ESR. Beside of that, 51 patients got moderate response, 14 patients got no response as per clinical parameters. The distribution between dietary habit and drugs response were identical in two different methodologies as response based on DAS28-ESR and clinical parameters (p-value=0.71). The Family history of the disease and drugs response were identical in two different methodologies as response based on DAS28-ESR and clinical parameters (p-value=0.72) (Table 1).

According to RA-Factor wise distribution, maximum numbers of 55 patients were '-ve' factor, out of which 32 patients got moderate response, 23 patients got no response as per DAS28-ESR. 43 patients got moderate response, 12 patients got no response as per clinical parameters. The RA-Factor and drugs response were identical in two different methodologies as response based on DAS28-ESR and clinical parameters (p-value=0.99) (Table 1).

In the CRP distribution, maximum numbers of 58 patients were '-ve' factor, out of which 32 patients have moderate response, 26 patients have no response as per DAS28-ESR and moderate 46 patients, no response 12 patients as per clinical parameters. The CRP and drugs response were

identical in two different methodologies as response based on DAS28-ESR and clinical parameters (p-value=0.26) (Table 1).

3.2. Comparison between Response based on DAS28-ESR and Clinical Parameters

The patients were classified as good, moderate, and no response according to their improvement in DAS28-ESR and clinical parameters after completed the study. The result found a good agreement between the response indices based on DAS28-ESR and clinical parameters by Cohen's Kappa (κ) coefficient of 0.43 (95% CI: 0.21 to 0.66), p-value<0.001. The correlation between the two DAS28-ESR and clinical parameters is shown in Table 2. However, 40 (56.33%) of the 71 patients who have 'moderate' response according to their improvement in DAS28-ESR and also in clinical parameters. 16 (22.54%) showed 'no' response of improvement in DAS28-ESR at all.

3.3. Relationship between Improvement in DAS28-ESR and Clinical Parameters

The maximum number of patients were found in between 0.6 to 2.2 of improvement in DAS28-ESR (Figure 1-A) and the maximum number of patients were present in between 20 to 70 percent of improvement in clinical parameters (Figure 1-B). Simple linear regression analysis showed a significant correlation between the differences of improvement in Clinical Parameters and DAS28-ESR values, which could be fitted to the equation: improvement in DAS28-ESR= -0.11 + 0.031 x improvement in Clinical Parameters, R^2= 0.64, p-value<0.001 (Figure 1-C). Out of 71 patients, 42 patients were moderate, 29 patients were no response of drugs based on improvement in DAS28-ESR and 56 patients were moderate, 15 patients were no response of drugs based on improvement (%) in Clinical Parameters (Figure 1-D).

4. Conclusion

This study concluded that Comparison between the improvements in Disease Activity Score 28 (DAS28) using erythrocyte sedimentation rate (DAS28-ESR) and Clinical Parameters in cases of Waja-al-Mafasil (Rheumatoid Arthritis) are same as per among of the demographical characteristics, RA-Factor and CRP. So, it's say that the result has no any difference either use the clinical parameters or DAS28-ESR. The demographic data (age, sex, mizaj, chronicity, occupation, dietary habits and family history) have also same result except the nature of work. The Improvement is also there and almost being same either using the DAS28-ESR or using the clinical parameters.

Acknowledgment

References

Aletaha, D., Neogi, T., Silman, A.J., Funovits, J., Felson, D.T. and Bingham, C.O. 2010. Rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League against rheumatism collaborative initiative. *Arthritis & Rheumatism*, 62(9), pp.2569-2581.

Anjum, N., Jamil, S., Hannan, A., Akhtar, J. and Ahmad, B. 2005. Clinical Efficacy of Hijamat (Cupping) in Waja-ul-Mafasil (Arthritis). *Indian Journal of Traditional Knowledge*, 4(4), pp.412-415.

Arnett, F.C., Dworthy, S.M.E. and Blochetal, D.A. 1988. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis and Rheumatism*, 31(3), pp.315-324.

Chambers, J.M. and Hastie, T.J. 1992. *Statistical Models in S* (*Linear models,* Chapter 4). Chapman and Hall/CRC.

Cruyssen, B.V., van Looy, S. and Wyns, B. 2005. DAS28 best reflects the physician's clinical judgment of response to infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment. *Arthritis Research & Therapy*, 7, pp.R1063-R1071.

DAS-SCORE. 2017. *Home of the DAS: Disease activity score in rheumatoid arthritis*. Available from: http://www.das-score.nl.

Emery, P., van Vollenhoven, R. and Ostergaard M. 2009. Guidelines for initiation of anti-tumour necrosis factor therapy in rheumatoid arthritis: similarities and differences across Europe. *Ann Rheum Dis.*, 68, 456-459.

Fransen, J. and van Riel, P.L. 2005. The Disease Activity Score and the EULAR response criteria. Clin Exp Rheumatol., 23, pp.S93-S99.

Hakīm, M. 1999. Sharh al-Asbāb (Tarjama al-Kabīr). Vol. III, Hikmat Book Depot, Hyderabad, pp.213-221.

Ibn, S. 2007. Al-Qānūn fi'l Tibb, Urdu Translation by Hakīm Ghulām Hasnayn Kintūrī. Vol. V, Part-II, Idāra Kitāb al-Shifa, Daryaganj, Delhi, pp.1119-1130.

Jurjānī, S. 1887. Zakhīra Khawārizm Shāhī, Urdu translation by Hakīm Muhammad Hādī Husayn Khān. Vol. II, Matba' Munshi Naval Kishore, Lucknow, pp.1848-1859.

Khān, A. and Hakīm, M. 2003. Iksīr-i-A'zam, I'jāz. Publishing House, New Delhi, pp.618-628.

Kushner, I. 1991. C-reactive protein in rheumatology. *Arthritis Rheum.*, 34, pp.1065-1068.

Landis, J.R. and Koch, G.G. 1977. The measurement of observer agreement for categorical data. *Biometrics*, 33, pp.59-174.

Prevoo, M.L., van Gestel, A.M., van T Hof, M.A., van Rijswijk, M.H., van de Putte, L.B. and van Riel, P.L. 1996. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. *Br J Rheumatol.*, 35, pp.1101-1105.

Prevoo, M.L., van't Hof, M.A., Kuper, H.H., van Leeuwen, M.A., van de Putte, L.B. and van Riel, P.L. 1995. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum.*, 38, pp.44-48.

Rāzī, A. 2004. Kitāb al-Hāwī fi'l Tibb. Vol. XI, CCRUM, New Delhi, pp.75-188.

Talstad, I., Scheie, P., Dalen, H. and Roli, J. 1983. Influence of plasma proteins on erythrocytemorphology and sedimentation. *Scand J Haematol.*, 31, pp.478-484.

van der Heijde, D.M., van't Hof, M.A., van Riel, P.L., Theunisse, L.A., Lubberts, E.W. and vanLeeuwen, M.A. 1990. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis.*, 49, pp.916-920.

van der Heijde, D.M., van't Hof, M.A., van Riel, P.L., van Leeuwen, M.A., van Rijswijk, M.H. and van de Putte, L.B. 1992. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. *Ann Rheum Dis.*, 51, 177-181.

van Gestel, A.M., Haagsma, C.J. and van Riel, P.L. 1998. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum.*, 41, pp.1845-1850.

van Gestel, A.M., Prevoo, M.L., van't Hof, M.A., van Rijswijk, M.H., van de Putte, L.B. and van Riel, P.L. 1996. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum.*, 39, pp.34-40.

Woolf, B. 1955. On estimating the relation between blood group and disease. *Ann Human Genet.*, 19; pp.251-253.