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ANALYSIS OF VARIABLES INVOLVE IN RHEUMATOID ARTHRITIS DIAGNOSIS USING LOGISTIC REGRESSION

Ausaf Ahmad[*1], T. B. Singh [1], Usha [2] and Navin Kumar [1]

Division of Biostatistics [1], Department of Community Medicine, Department of Pathology [2], Institute of Medical Sciences, Banaras Hindu University, Varanasi - 221005, Uttar Pradesh, India.

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Correspondence to Author:
Ausaf Ahmad

Research Scholar, Division of Biostatistics, Department of Community Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi - 221005, Uttar Pradesh, India.

E-mail: ausafahmad86@gmail.com

ABSTRACT: Rheumatoid Arthritis (RA) is a auto-immune disease in which body mistakenly considers some parts of its own system as pathogens and attacks them. RA is a chronic systemic inflammatory illness with prevalence of approximately 0.75% in India. It leads to irreversible joint damage and systemic complications. It is associated with substantial morbidity and increased mortality Better understanding of its pathophysiology has led to the progress of besieged therapies that have significantly enhanced outcomes. The key to beneficial achievement lies in identifying those who will have rigorous critical disease as early as possible, so that efficient management can be initiated prior to unalterable injure occurs. The primary aim of this study is to find out what factors play a significant role in determine the disease. From the brief account of discussion on observation and results of multivariate techniques are established, such techniques are important for they make it possible to encompass all the data from an investigation in one analysis. They in fact result in a clearer and better account of the research effort than do the piecemeal analyses of portions of data. Anti-cyclic citrullinated peptide (anti-CCP) antibody testing is mostly useful in the diagnosis of rheumatoid arthritis, with high specificity, presence early in the disease process, and ability to identify patients who are likely to have severe disease and unalterable injure. As of this observation concluded that disease also affects the quality of life *i.e.* disablement enhances.

INTRODUCTION: Rheumatoid arthritis (RA) is a chronic inflammatory joint disease characterized by a distinctive pattern of bone and joint destruction. RA is also a systemic disease, and several patient subsets can be distinguished based on the presence of extra-articular manifestations. For example, the concomitant presence or absence of anti-cyclic citrullinated peptide antibody (ACPA) and rheumatoid factor (RF) defines two important patient subsets [1].

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Several epidemiological studies of RA have been published. They show variations in the incidence and prevalence of RA across populations. Further variation occurs as a result of differences in statistical methods and case-ascertainment criteria. Several large prospective studies have improved our knowledge of the risk factors for RA. Unfortunately, the available epidemiological data often come from retrospective studies and underpowered case–control studies.

In addition, the effects of several environmental factors on the risk and outcome of RA have been studied. Environmental factors that affect RA may act many years before the disease becomes clinically apparent [2]. While genetic factors contribute 50% to 60% of the risk of developing RA.

The gene most strongly associated with RA is the HLA-DRB1 gene in the major histocompatibility complex, where specificalleles within the DRB1*04 and *01 clusters encode the "share depitope" sequences within the expressed DRB1 molecule. Rheumatoid arthritis, are the number one cause of early retirement, disability payments, and loss of employment [4]. The social and economic consequences for the individual are drastic even in the first years of the disease. Within seven years, up to 40 percent of patients are no longer able to work in their profession [5]. According to the WHO, this percentage rises significantly as rheumatoid arthritis progresses: ten years after onset of the disease, nearly 60 percent of RA patients are no longer able to work [6].

It is now accepted that those affected by these diseases must be genetically predisposed toward them. Many autoimmune diseases occur more frequently within families, and in some families there is an increased tendency toward autoimmune diseases [7]. For some autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, the genetic component of the disease has already been scientifically verified [8-10]. The primary aim of this study is to find out what factors play a significant role in determine the disease.

MATERIALS AND METHODS: This was a cross-sectional observational study. The study was carried out from between August 2012 and February 2014 in UGC Advanced Immuno-diagnostic Training and Research Centre (AITRC), Department of Pathology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh. The cases were referring by different OPD's of Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, with RA who fulfilled the American College of Rheumatology (ACR)/ European League against Rheumatism (EULAR) 2010 criteria [11], were selected in a random manner. The study was approved by the appropriate ethics committee, and written informed consent was obtained from each patient before inclusion.

Statistical Analysis: Statistical analyses were conducted using SPSS for Windows (version 16.0). Descriptive statistics were obtained for all participants. Data has been presented in number and percentage. Step wise binary logistic regressions have been applied to correctly predicted percentage among study subjects.

RESULTS AND DISCUSSION: Table 1 provides the summary of demographic and clinical measures obtained from 290 clinically suspected patients. In present study 48 (16.6%) were RA positive. The burden of RA in the developing countries is enormous and almost similar to that described in the West [12-13]. The prevalence of RA was 0.45% in India [14].

TABLE 1: PERCENT DISTRIBUTION OF STUDY SUBJECTS WITH RESPECT TO SOCIO-DEMOGRAPHIC AND ENVIRONMENTAL CHARACTERISTICS

S. No.	Variables		RA (%)	Non-RA (%)	Chi-Square value	p - value
1	Age Group	≤ 20	8(16.7)	58(23.9)	2.85	0.415
		21-40	24(50.0)	114(47.2)		
		41-60	13(27.1)	64(26.4)		
		>60	3(6.2)	6(2.5)		
2	Gender	Male	14(29.2)	96(39.7)	1.877	0.177
		Female	34(70.8)	146(60.3)		
3	Food Habits	Veg.	21(43.8)	105(43.4)	0.002	0.963
		Non-Veg.	27(56.2)	137(56.6)		
4	Occupation	Student	10(20.8)	84(34.7)	4.949	0.293
		House wife	25(52.1)	94(38.8)		
		Farmer	3(6.3)	13(5.4)		
		Working Person	7(14.6)	42(17.4)		
		Other	3(6.2)	9(3.7)		
5	Type of Occupation	Sedentary	33(68.8)	99(40.9)	12.52	0.000
		Active	15(31.2)	143(59.1)		
6	Family History	Yes	12(25)	25(10.3)	7.744	0.005
		No	36(75)	217(89.7)		
7	Place of Residence	Urban	16(33.3)	106(43.8)	1.801	0.1796
		Rural	32(66.7)	136(56.2)		

		≤ Primary	19(39.6)	61(25.2)		
8	Education	Primary to Inter	22(45.8)	95(39.3)	8.915	0.0116
		>Inter	7(14.6)	86(35.5)		
9	Milk consumption	Yes	21(43.8)	126(52.1)	1.108	0.292
		No	27(56.3)	116(47.9)		

Age and Sex: It has been observed that 47.6% of the clinically suspected cases fell in the middle age group of 21-40 years. Followed by age group 41-60 shows the second most predominance age group in study subject *i.e.* 77 (26.6%). 66 (22.8%) clinically suspected case belongs to the lower age group which belongs less than age twenty. Among all the clinically suspected cases the positivity rate is directly proportional to the age whereas according to Therapeutics in Malaysia. Bio-medicine News (2009) [15], RA affects about 0.5 per cent of adults between the ages of 25 and 50. Percentage of female clinically suspected cases that referred from OPDs was 62.1% and 37.9% male among the total study subjects. Noticed that positivity was also higher in female (70.81%) than male (29.2%).

Some previous study exhibit mixed pattern of prevalence according to the age-groups, such as, in the study of symmons (2002) [16], the incidence and prevalence of RA increase with age. Globally, the peak incidence of RA occurs between the ages of 55 and 64 years in women and 65-75 years in men and the age of onset is rising (Symmons, 2002) [17]. According to Malaviya *et al*., (1993) [18] that female were more prone to R.A. Lawrence (1998) [19] said that there are 2.5 times as many women as there are men with RA.

Rural Urban Background: The data were distributed in two category *i.e.* Urban, Rural. Results undoubtedly indicate the predomination of rural study subjects *i.e.* 57.9%. Most of the studies conclude that RA is more prevalent to the developed countries [18]. RA is rare in undeveloped and rural areas [17], and the incidence of RA is higher among groups residing in urban areas. As a result, urbanization and air quality have been proposed as risk factors for the condition [20-21] although reports of such an association are conflicting [22-23].

Education Status: Education programs employing behavioural interventions have small but significant effects on disability and depression, whereas programs focused solely on providing information do not demonstrate any significant effects or trends [24]. It has been observed that 66 (22.7%) subjects were graduate. Approximately educational status of 75% subjects was above the high school.

In addition, study in Sweden (the EIRA study), the risk of RA was studied vis-à-vis level of formal education; people without university degree had an increased risk of RA (relative risk = 1.4, 95% CI; 1.2-1.8) compared to those with a degree [25]. An Australian study demonstrated that the prevalence of RA was lowest among those who attended university and highest among those leaving school before 15 years of age [26]. Therefore, it appears that education programs need to provide information in combination with problem-solving skills and motivational activities [27].

Occupations and their Nature: An association between type of occupation and the risk of developing RA has not been confirmed. There is some evidence of an association between organic dust exposure and the incidence of RA in men [28]. In the present house wife was more prone to as compare to the other occupation; about 32.4% clinically suspected cases belong to students in which only 10.6% had RA. Some studies have evaluated the importance of occupational determinants; an increased frequency of RA has been observed in several occupational categories [29-32].

Food Habits: Many studies shown associations between RA and factors such as diet [33-35]. Approximately fifty seven percent study subjects belong to the non-vegetarian and rest of them in vegetarian group. Wherein positivity in non vegetarian as compared to vegetarian was higher *i.e.* (56%). Total two ninety clinically suspected RA cases, 56.2% subjects were not taking milk directly or indirectly. And 43.8% of study subject were taking milk or any type of milk product including tea, coffee *etc*. Conflicting reports exist concerning coffee consumption as a possible risk factor for development of RA. A few reports have suggested that coffee is a risk factor [36, 37].

Family History: In this study found that more that 87% of clinically suspected cases having no family history of RA. The familial nature of RA suggests that genetic risk factors play a role in susceptibility to RA [38]. Based on twin studies, the genetic contribution to RA susceptibility is estimated to be 60% [39]. Genetic variation in the human leukocyte antigen region is a contributing factor to the genetic risk of RA [40]. The disease also exhibits a higher concordance rate in identical twins than in fraternal twins [41].

Presence of Opportunistic Infections (Signs and Symptoms): In addition to present study distribution of positivity rate among the study subjects in **Table 2** provides the summary according to their signs and symptoms. However, in 10% to 15% of patients, the onset of disease is explosive, with polyarthritis, fever, lympha-denopathy, and splenomegaly developing over days to weeks [42, 43].

The positivity rate was 29.8% among the suspects suffering from fever and 13.3% among those not suffering with fever. Positivity rate was approximately 4 times higher in suspects suffering from dizziness than those who were not having dizziness Positivity rate was more than double in subjects suffering from tiredness than those not having 31.8% positivity was observed in suspects suffering from joint pain, 12.1% in those not having joint pain. Assessments in RA mainly look at joint inflammation [44]. Moreover in present study joint swelling, ankle swelling and neck pain positivity rate where approximately more than 2 times higher in suspects suffering from these signs and symptoms than those who were not suffering from these signs and symptoms. Out of total RA patient only 8.3% RA patient were having ankle swelling. The differences among them were statistically highly significant. 11.1% positivity was observed in suspects suffering from muscle pain, 16.9% in those not having muscle pain.

TABLE 2: PERCENT DISTRIBUTION OF STUDY SUBJECTS WITH RESPECT TO SIGN AND SYMPTOMS

Sign / Symptoms		RA (%)	Non-RA (%)	Chi-Square value	p - value
Fever	Yes	17(29.8)	40(70.2)	9.049	0.005
	No	31(13.3)	202(86.7)		
Dizziness	Yes	13(50.0)	13(50.0)	23.13	0.000
	No	35(13.3)	229(86.7)		
Tiredness	Yes	33(45.8)	39(54.2)	12.52	0.000
	No	15(6.9)	209(93.1)		
Joint Pain	Yes	21(31.8)	45(68.2)	14.418	0.000
	No	27(12.1)	197(87.9)		
Joint Swelling	Yes	17(29.8)	40(70.2)	9.049	0.003
	No	31(13.3)	202(86.7)		
Ankle Swelling	Yes	4(80.0)	1(20.0)		0.003
	No	44(15.4)	241(84.6)		
Back Pain	Yes	15(32.6)	31(67.4)	10.205	0.001
	No	33(13.5)	211(86.5)		
Muscle Pain	Yes	2(11.1)	16(88.9)		0.747
	No	46(16.9)	226(83.1)		
Neck Pain	Yes No	6(33.3)	12(66.7)	3.913	0.048

Joints Involvement of the Study Subjects: RA is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality [45-48]. The significant body ache with RA were Finger, Wrist, Toes, Shoulders, Neck, Back, Elbow, Ankle, Knee and Hips. Present study positivity rate was 41.3% among the suspects suffering from finger pain and 7.9% among those not suffering with finger pain. The course of established RA can range from mild disease to rapidly progressive multisystem inflammation. About 70% of patients who have RA display a slow insidious disease onset; 20% have an intermediate onset; and 10% have a sudden acute onset. Patients predominantly complain of pain, stiffness, and swelling of their peripheral joints as the cardinal features of the disease. Physical examination of the joints reveals tenderness to palpation, synovial thickening, Joints effusion, and sometimes erythema and warmth.

TABLE 3: PERCENT DISTRIBUTION OF STUDY SUBJECTS WITH RESPECT TO INVOLVE JOINTS

Involve Joints		RA (%)	Non-RA (%)	Chi-Square value	p - value
Finger	Yes	31(41.3)	44(58.7)	44.980	0.000
	No	17(7.9)	198(92.1)		
Wrist	Yes	33(55.0)	27(45.0)	80.968	0.000
	No	15(13.3)	215(86.7)		
Toes	Yes	10(55.6)	8(44.4)	21.138	0.000
	No	38(14.0)	234(86.0)		
Shoulders	Yes	16(30.2)	37(69.9)	8.732	0.003
	No	32(13.5)	205(86.5)		
Neck	Yes	11(31.4)	24(68.6)	6.378	0.012
	No	37(14.5)	218(85.5)		
Back	Yes	21(25.6)	61(74.4)	6.791	0.013
	No	27(13.0)	181(87.0)		
Elbow	Yes	8(44.4)	10(56.6)	10.810	0.001
	No	40(14.7)	232(85.3)		
Ankle	Yes	17(39.5)	26(60.5)	19.308	0.000
	No	31(16.9)	216(83.1)		
Knee	Yes	40(22.3)	139(77.7)	11.369	0.001
	No	8(7.2)	103(92.8)		
Hips	Yes	22(43.1)	29(56.9)	31.667	0.000
	No	26(10.9)	213(89.1)		

TABLE 4: PERCENT DISTRIBUTION OF STUDY SUBJECTS WITH RESPECT TO INVESTIGATION PROFILE

Blood Test		RA (%)	Non-RA (%)	Chi-Square	p - value
RF	+	37(77.1)	24(9.9)	108.79	P<0.001
	-	11(22.9)	218(91.1)		
AntiCCP	+	36(75)	26(10.7)	98.39	P<0.001
	-	12(25)	216(91.3)		
CRP	+	45(93.8)	49(20.2)	98.78	P<0.001
	-	3(6.2)	193(79.8)		
CRP or AntiCCP	+	47(97.9)	65(26.9)	85.32	P<0.001
	-	1(2.1)	177(73.1)		
CRP and AntiCCP	+	32(66.7)	7(2.9)	139.96	P<0.001
	-	16(33.3)	235(93.1)		
RF or AntiCCP	+	48(100.0)	47(19.4)	118.07	P<0.001
	-	0(0.0)	195(80.6)		
RF and AntiCCP	+	25(89.6)	2(0.80)		P<0.001
	-	23(10.4)	240(99.20)		
RF or CRP	+	46(95.8)	60(24.8)	87.16	P<0.001
	-	2(4.2)	182(25.2)		
RF and CRP	+	34(70.8)	12(4.9)	130.24	P<0.001
	-	14(29.2)	230(95.1)		
RF or AntiCCP or CRP	+	48(100.0)	80(33.0)	72.80	P<0.001
	-	0(0.0)	162(67.0)		
RF and AntiCCP and CRP	+	23(89.6)	3(90.5)		P<0.001
	-	25(10.4)	239(9.5)		

With longer duration of disease, there may be decreased range of motion with the much later possibility of joint ankylosis and subluxation. Initial involvement occurs in the upper extremities in over half of patients, with multiple joints affected in one-third and hand only involvement in about one-quarter of the cases. Joint symptoms are initially symmetric in 70% patients or become symmetric by 1 year after onset in 85%. The joints most commonly affected are the proximal inter-phalangeal (PIP) and metacarpo-phalangeal (MCP) joints of the hand and wrist, followed by the metatarso-phalangeal (MTP) joints of the feet, ankles, and shoulders. According to Dr. Friederike Hammar (2010) [49] RA usually begins subtly, with swelling, pain and problems with movement of the small and middle finger joints, as well as with unspecific symptoms like rapid fatigue and general weakness. If the disease is not stopped it leads to complete destruction of the joints.

TABLE 5: FORWARD STEPWISE LIKELIHOOD MODEL WITH CORRECTLY PREDICTED PERCENTAGE

Forward stepwise likelihood model	Variable included in the model	Regression coefficient (B)	Standard error (B)	-2log likelihood	Nagelkerke R^2*100	Correctly predicted %			χ^2/ p-value
						RA	Non-RA	Overall	
I Step	RF	-3.419	.405	170.023	45.1	90.1	77.1	87.9	90.22
	Constant	.433	.262						P<0.001
II Step	RF	-4.364	.761	105.823	69.7	99.2	52.1	91.4	154.42
	AntiCCP	-4.185	.761						P<0.001
	Constant	3.427	.769						
III Step	Tiredness	2.438	.578	84.923	76.6	95.9	87.5	94.5	175.32
	RF	-4.439	.805						P<0.001
	AntiCCP	-4.136	.795						
	Constant	2.344	.794						
IV Step	Tiredness	2.518	.664	71.335	80.8	98.8	68.8	93.8	188.91
	Wrist	2.363	.688						P<0.001
	RF	-4.314	.870						
	AntiCCP	-4.245	.875						
	Constant	1.527	.860						
V Step	Tiredness	1.821	.721	63.540	83.1	97.5	87.5	95.9	196.71
	Fingers	2.024	.775						P<0.001
	Wrist	2.444	.729						
	RF	-4.642	.946						
	AntiCCP	-4.160	.919						
	Constant	1.166	.913						
VI Step	Tiredness	1.921	.793	54.788	85.7	97.9	91.7	96.9	205.46
	Fingers	2.899	.982						P<0.001
	Wrist	2.696	.811						
	Hips	2.510	.945						
	RF	-4.412	1.029						
	AntiCCP	-4.245	.999						
	Constant	-.221	1.083						
VII Step	Tiredness	2.066	.878	48.640	87.4	98.3	89.6	96.9	211.61
	Fingers	3.013	1.077						P<0.001
	Wrist	3.234	.938						
	Toes	3.340	1.430						
	Hips	2.610	1.005						
	RF	-5.031	1.192						
	AntiCCP	-4.359	1.075						
	Constant	-.534	1.132						
VIII Step	Tiredness	2.504	1.019	44.271	88.7	98.3	87.5	96.6	215.97
	Fingers	2.990	1.131						P<0.001
	Wrist	3.782	1.086						
	Toes	4.423	1.606						
	Back	1.989	1.040						
	Hips	2.883	1.091						
	RF	-5.530	1.346						
	AntiCCP	-4.305	1.159						
	Constant	-1.589	1.423						
IX Step	Tiredness	2.375	1.105	39.322	90.0	98.8	91.7	97.6	220.92
	Fingers	2.989	1.144						P<0.001
	Wrist	3.770	1.241						
	Toes	4.171	1.791						
	Back	2.442	1.191						
	Hips	2.552	1.071						
	RF	-4.666	1.393						
	AntiCCP	-3.402	1.175						
	CRP	-2.249	1.103						
	Constant	-1.789	1.571						

With periodic flare-ups, the disease marches inexorably onward, affecting more and more joints. Positivity rate was approximately more than 2 times higher in suspects suffering from wrist involvement than those who were not having problem in wrist. Positivity rate was approximately one-fourth in subjects suffering from toes pain than those not having any difficulties in toes, 30.2% positivity was observed in suspects suffering from shoulder involvement, 13.5% in those not suffering from shoulder problem.

Positivity rate in involvement of neck and back where approximately more than 2 times higher in suspects suffering from neck and back problem than those who were not suffering from neck and back problem. Out of total RA patient only 16.7% RA patient were having difficulty in elbow. 39.5% positivity was observed in suspects suffering from ankle problem, 16.9% in those not having ankle problem. Maximum percentages of RA patients having knee difficulty *i.e.* 83.3%. Out of total hips affected subjects 43.1% were RA patients. The differences among them were statistically highly significant ($P < 0.001$). In Indian context, reason behind majority in knee difficulties was reported by Kumar *et al*., (2002) [50] that sitting cross-legged on the floor is a standard practice in India.

Even the higher socio-economic strata of the society practice it in social or religious assemblies. This posture requires acute flexion of the knees besides abduction, flexion and external rotation of the hip joints. A similar set of joint movements is needed for another important activity in the Indian population, *i.e.* squatting in the toilet. Inability to perform either of these two activities means a major functional disability.

Investigation Profile of the Study Subjects: The presence of "rheumatoid factor" (RF) was identified in patients with RA over 50 years ago [51]; assays for RF remain one of the ACR classification criteria for RA. 61 (21.0%) out of 290 subjects found positive for RF, and out of 61 subjects, 37 had RA. This compared with 62 / 290 (21.4%) subjects found positive for anti-CCP. In which 36 had RA. Besides, over the past few years, many studies have evaluated the diagnostic performance of anti-CCP on a variety of diagnostic platform [52-56].

High levels of C-reactive protein (CRP) are also indicators of active inflammation. Like the ESR, a high result does not indicate what part of the body is inflamed, or what is causing the inflammation [57]. Whereas in present study 94 (32.4%) out of 290 subjects observed positive for acute phase reactant CRP and 93.8% positivity of RA out of total RA patients. The differences observed among the various blood tests and positivity rate was found statistically highly significant ($p < 0.001$).

If considered combinations of serology tests and acute phase reactant CRP or AntiCCP, CRP and AntiCCP, RF or AntiCCP, RF and AntiCCP, RF or CRP, RF and CRP, RF or AntiCCP or CRP and RF and AntiCCP and CRP. It was observed that RF and AntiCCP and CRP showed minimum percentage of RA patients from total RA patients. Whereas RF or AntiCCP and RF or AntiCCP or CRP both the combination had 100% outcome. The differences observed among the combination of various blood tests and positivity rate was found statistically highly significant ($p<0.001$). Detection of anti-CCP is very useful for the diagnosis of RA, in fact even RF also very useful for diagnosis of RA and combination of testing for both RF and anti-CCP may be even more useful in comparison to individual test.

Early treatment of RA is important as it can prevent irreversible damage of the joints. Despite the strong diagnostic value of anti-CCP and RF, there is strong demand for novel serological biomarkers to further improve the early diagnostic of this abundant disease [58].

Multivariate Technique: From the brief account of discussion on observation and results of multivariate techniques are demonstrated below, such techniques are important for they make it possible to encompass all the data from an investigation in one analysis. They in fact result in a clearer and better account of the research effort than do the piecemeal analyses of portions of data. According to van der Helm-van Mil AH *et al*., (2007), using regression analysis the variables that were independent predictors for the development of RA was selected. This resulted in the construction of prediction rule. In present study using step wise binary logistic regression, RA patients correctly categorized according to their positivity status.

In the first step blood test of RF of subjects has categorized 90.1% and 77.1% RA and non-RA respectively. By including the blood test of AntiCCP the percentage was increased up to 99.2% and 52.1%, in the third step by adding symptom of tiredness, these percentages were 95.9% and 87.5% correctly. At the fourth step by including the involvement of wrist joint has categorized the 98.8% RA and 68.8% non RA. In the fifth step involvement of finger joint of subjects has categorized 97.5% and 87.5% RA and non-RA respectively.

By including the involvement of hip joint the percentage was increased up to 97.9% and 91.7% in the seventh step by adding involvement of toe joint, these percentages were 98.3% and 89.6% correctly. At the eight step by including the attachment of back pain has categorized the 98.3% RA and 87.5% non RA. By including the blood test of CRP in ninth step the percentage was increased up to 98.8% and 91.7%.

CONCLUSION: The finding of this study illustrates that there is no single variable or screening test is suitable to diagnose the RA disease. Females are more prone for this disease as compared to male. The suspected cases having the family history had more chances to become diseased as compared to cases not having the family history of RA. This disease also affects the quality of life *i.e.* disability increases.

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