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The Co-Morbidities and Mortality Rate among Rheumatoid Arthritis Patients at the Western Region of Saudi Arabia

A Retrospective Cross-Sectional Study

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Abstract. To evaluate the mortality rate in a well defined hospital; based patients diagnosed with rheumatoid arthritis over a three year period and to investigate the causes of death with their associated risk factors. A retrospective cross-sectional study was conducted for rheumatoid arthritis patients over a three year period (2006-2008) at King Abdulaziz University Hospital in Jeddah at the western region of Saudi Arabia. The causes of death and the associated co-morbidities were registered and compared statistically in relation to the mortality rate. Patients who fulfilled the criteria of the study were included (n = 116). The mortality rate was 16%. The most important causes of death and contributing factors were cardiovascular system diseases and infections (58%), followed by respiratory system diseases (47%) and renal impairment (32%). The most common co-morbidities were diabetes mellitus, hypertension and obesity ($p < 0.001$, 0.01, 0.03). This study gives important information of the variables associated with the mortality in rheumatoid arthritis and the associated factors which may accelerate the occurrence of an earlier death.

Keywords: Rheumatoid arthritis, Co-morbidities, Mortality, Death.

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by joint symptoms in the form of symmetrical inflammatory chronic polyarthritis with extra-articular features (ExRA) including systemic symptoms[1]. Because of these manifestations, the patients physical and psychosocial function deteriorate rapidly and subsequently, their life expectancy. It has been demonstrated that RA is associated with four fold increase in mortality in comparison to the general population[2] and therefore, the life expectancy is shortened by 3-10 years[3]. The first study about the mortality in RA was published in 1953, and there was 29% increase in the mortality in comparison to the general population[4]. Since then, many studies came out reporting similar results in RA patients[5]. Further studies have addressed possible predictors of early death and whether the mortality is related to the underlying disease (9.8% of the deaths)[6] or other factors contributing the premature death. The different factors that have been studied in the past with regards to increased risk of premature mortality in RA patients are: Increasing age of the patient and male sex[7]; young age of onset of the disease[8]; low socioeconomic factors (*e.g.,* level of education)[9]; poor functional status [10] and high or low Body Mass Index (BMI)[11,12]. The presence of sever extra-articular disease manifestation, especially defined previously by Turesson as factors (pericarditis, pleuritis, Felty's syndrome, vasculitis, neuropathy, sever eye involvement and glomerulonephritis)[13]; increased clinical severity of the disease (documented either clinically, biochemically in the form of positive Rheumatoid Factor [RF]); elevated acute-phase response (erythrocyte sedimentation rate [ESR]); C-reactive protein [CRP] or radiologically via joint damage[14]. Smoking has also been a suggested factor due to the formation of atherosclerotic plaque found on carotid Doppler without evidence of CVD[15]. Associated diseases include: cardiovascular disease[16], cancer[17], infections[18], respiratory disease, renal disease in the form of amyloidosis, GI bleeding, lymphoproliferative disorders, liver disease and finally use of steroid[19-22].

The acute cause of death in RA is unlike the general population. Many studies showed that the number one cause of death in RA is cardiovascular diseases[23], this is followed by respiratory diseases, gastrointestinal, renal and finally infection. From our previous study[24], it was demonstrated that the mortality rate in RA patients with ExRA was

16%. The aim of this study was to evaluate the mortality rate among patients with RA treated actively in a tertiary centre; evaluate the acute causes of death and to investigate the possible risk factors for the early death in our patients and compare them to the previously published data in the western studies.

Method

Study Design, Population and Setting

A retrospective study was conducted at King Abdulaziz University Hospital (KAUH), a governmental university teaching hospital in Jeddah, western region of Saudi Arabia (KSA). The facility provides health care to a multinational population of mixed socio-economic status. A computerized retrieval system was used to identify all patients with a registered diagnosis of RA who received treatment at the hospital during a 3 years period (January 2006 – December 2008). Rheumatoid arthritis (RA) patients (n = 116) were identified according to the 1987 ACR (American College of Rheumatology) classification criteria for RA[25]. All were included in the study and evaluated. The following information were obtained: Age [in years , which was further divided into to the following groups; group (a) less than 40 years , group (b) 40-50 years, group (c) between > 50-60 years and group (d) more than 60 years.], gender, nationality, and disease duration in years (< 10 years and > 10 years). Socioeconomic factors via the level of education (low education level less than 8th grade)[9], poor functional status (if the patient needs wheelchair or unable to do his usual daily activities), smoking, plus high BMI / Obesity (which was calculated as weight in kilograms divided by height in meters squared). Obesity was considered if the BMI is > 30 kg/m^2, as per WHO classification for obesity in 2000)[26], extra-articular features were recorded (pericarditis, pleuritis, Felty's syndrome, vasculitis, neuropathy, severe eye involvement and glomerulonephritis) the exact diagnosis of each feature has been described in detail in our previous study([24]. Activity of the disease was defined as more than 8 tender joints (from 68 joint count), 8 swollen joints (from 66 joint count), ESR > 28 mm/ hr, CRP > 15mg/L[27] or if the 28 disease activity score index (DAS28) is > 5.1[28]; positive RF with normal range (0 IU/L), elevated acute-phase response (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP] and joint damage per X-ray. Other diseases include: cardiovascular disease (ischemic heart

disease [IHD], arrhythmias, congestive heart failure [CCF] and peripheral vascular disease[PVD]), malignancy (any type including lympho-proliferative disorders), respiratory disease (pneumonias, non-cardiogenic pulmonary edema, chronic obstructive pulmonary disease [COPD] or preexisting radiographic interstitial infiltrates indicating lung fibrosis or bronchiectasis), *diabetes mellitus* (DM), which was defined according to the WHO definition as fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l)[29]. Hypertension (HTN), which was classified according to the World Health Organization-International Society of Hypertension (WHO-ISH) guidelines as a diastolic blood pressure > 90 mmHg[30] or the patient is on antihypertensive agent, renal disease (Kidney amyloidosis, nephrotic syndrome or chronic renal failure), infections (localized or systemic as pneumonia or sepsis), tuberculosis (TB) (pulmonary & extra-pulmonary). Treatment was reviewed, which include Non Steroidal Anti-Inflammatory Drugs (NSAIDs), Disease Modifying Antirheumatic Agents (DMARDs), steroids and biologics.

Statistical Analysis

Data analysis was done using the Statistical Package for Social Sciences (SPSS software version-16). Mean ± SD was calculated for quantitative data and proportions for categorical variables. The unpaired students' "*t"* test was used for comparing means of continuous variables. Proportions were compared by Chi-square test. The predictive value of mortality for the various co-morbidities was calculated using the multivariate logistic regression analysis (Enter method); with a confidence interval 95%.

The Kaplan-Meier Curve was plotted to describe the survival rate in relation to the disease duration. Results were considered significant if the p-value was less than 0.05 throughout the analysis.

Results

This study included 116 patients. Their age range was 13-81 years old, with a mean value 48.7 $\pm$ 15.1 years for both genders. Patients were classified according to age into 4 groups: Group A less than 40 years (n = 31) (27%), Group B between 40-50 years (n = 39) (34%), Group C > 50-60 years (n = 18) (15%) and Group D more than 60 years of age (n = 28) (24%). Women constituted (75%) (n - 87) while 29 (25%) were men. Table 1 shows the general demographic features of RA

patients including the duration of their disease; and the treatment, which was recorded in the form of DMARDs; including one or combination in almost 95% of patients; steroids were used by 20 (17%) patients and only 2 (2%) patients received biologics. A total of 59 (51%) patients had features of ExRA. Activity of the disease which was supported by the high acute phase reactant in the form of elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) was registered in 70 (60%) patients. RF was positive in 63 (54%) patients and joint damage per X-ray in 52 (45%) patients. The total deaths were 19 (16%) patients during the study period. The age range of their death was 40 - 80 years with a mean value 59.7 $\pm$ 12.6 years.

Table 1. General characteristics of RA patients at the time of the study.

Character of the patients	Number of patients 116	(100) %
Age group (years)		
<40	31	27 %
40-50	39	34 %
>50-60	18	15 %
>60	28	24 %
Sex		
Male	29	25 %
Female	87	75 %
Nationality		
Saudi	69	60 %
Non Saudi	47	40 %
Duration of RA in years		
<1 years	6	5%
1-5 years	23	20%
>5-10 years	30	26%
>10 years	57	49 %
Treatment		
NSAIDs	89	77 %
DMARDs	110	95 %
Steroids	20	17 %
Biologics	2	2 %
Extra-articular Manifestations	59	51 %
Joint damage per X-ray	52	45%
Activity of the disease	70	60%
Rheumatoid factor (present)	63	54%
Mortality	19	16%

RA: Rheumatoid arthritis, NSAIDs: Non steroidal anti-inflammatory drugs, DMARDs: Disease modifying antirheumatic drugs.

Table 2 illustrates the co-morbidities which were found in our RA patients. Hypertension was found in 61 (53%) patients, DM in 50 (43%)

patients, obesity in 42 (36%) patients, cardiovascular disease in 24 (21%) patients; including IHD, CCF and PVD in elderly. Patients having respiratory system diseases constituted (19%) (n = 22) in the form of: lung fibrosis (7%), bronchiectasis (4%) and COPD (8%). Patients with renal disease represented (16%) (n = 18); infection was recorded in 23 (20%) patients in the form of sepsis (12%), pneumonia (16%) and tuberculosis (7%). Five of the eight TB patients were pulmonary and the last three were Pott's disease (n = 2) and Tuberculoma (n = 1). Malignancies were considered as co-morbidity in 12 (10%) patients: as followed; bronchogenic cancer (n = 4), breast cancer (n = 2) and two with multiple myeloma. Other malignant diseases included were cancers of the thyroid, brain, urinary bladder and lymphoma affecting four patients. Fourteen patients were smokers (12%); in addition 27 (23%) patients were registered as poor functional status and ICU admission was required in 14 patients.

Table 2. Associated Co-morbidities in 116 RA patients.

Co-morbidities	Number of Patients	%
Age > 60	33	28%
RA duration > 10 years	57	49%
HTN	61	53 %
DM	50	43%
High BMI /Obesity	42	36%
Cardiovascular disease	24	21%
Respiratory disease	22	19%
Renal disease	18	16%
Malignancy	12	10%
Smoking	14	12 %
Tuberculosis	8	7%
Poor functional status	27	23%
Infections	23	20%
Sepsis	14	12%
Pneumonia	18	16%
ICU admissions	14	12%

RA: Rheumatoid Arthritis, DM: Diabetes Mellitus, HTN: Hypertension, BMI: Body Mass Index , ICU: Intensive Care Unit.

Table 3 shows the demographic features and the co-morbidities compared between dead and surviving patients. Eleven (58%) of 19 dead patients and 22 (23%) of 97 surviving patients were > 60 years (p = 0.003). The RA duration more than 10 years was significantly higher in dead patients (74%) compared to (44%) of the survivors (p = 0.017). Poor functional status was significantly higher in the dead group (63%)

than in those who survived (16%) and showed a significant association with mortality ($p < 0.001$). The presence of extra-articular manifestations of RA was found in 14 (74%)/19 dead patients, which was significantly higher than those in the surviving group 45(46%)/97 with ($p = 0.026$). Co-morbidities as DM, CVS diseases, HTN, obesity and renal involvement were significantly associated with mortality with p-values (< 0.001, < 0.001, 0.01, 0.03, 0.04), respectively. Respiratory system involvement, whether due to infection or non-infectious causes (lung fibrosis, bronchiactasis and COPD) was significantly associated with mortality ($p < 0.001$). Infection was higher among dead patients than survivors ($p < 0.001$). Patients admitted to the ICU showed a higher mortality ($p < 0.001$). Malignancy was significantly associated with mortality, 26% of the dead patients versus 7% of the survivors ($p = 0.026$). Gender, activity of the disease, presence of RF, joint damage per X-ray, and smoking did not show any significant difference in mortality between dead and surviving patients.

Table 3. Comparison of Demographic Features and Co-morbidities between dead and survived patients using Chi-Square Test ($\chi 2$).

Demographic Features/Co-morbidities	Dead N = 19		Survived N = 97		p - Value
	No.	%	No.	%	
Age >60y	11	58	22	23	0.003†
Gender; M/F	5/14	36/64	24/73	33/67	0.54
RA duration>10y	14	74	43	44	0.017*
Activity of disease	12	63	59	61	0.53
Joint damage per x-ray	11	58	41	42	0.16
Poor functional status	12	63	15	16	< 0.001‡
Presence of RF	9	47%	54	56%	0.34
Extra-RA	14	74	45	46	0.026*
Smoking	4	21	10	10	0.17
Obesity	11	58	31	32	0.031*
HTN	15	79	46	47	0.01*
DM	15	79	35	36	< 0.001‡
CVS disease	11	58	13	13	< 0.001‡
Respiratory disease.	9	47	10	10	< 0.001‡
Renal disease.	6	32	12	12	0.045*
Malignancy	5	26	7	7	0.026*
Infection	11	58	12	12	< 0.001‡
Sepsis	10	53	4	4	< 0.001‡
Pneumonia	8	42	10	10	0.002†
ICU admission	10	53	4	4	< 0.001‡

RA: Rheumatoid Arthritis, RF: Rheumatoid factor, HTN: Hypertension, DM: Diabetes Mellitus, CVS: Cardiovascular System, TB: Tuberculosis. p - value* < 0.05 , † <0.01, ‡ <0.001.

Table 4 demonstrates the acute causes of death as recorded in the death certificates. The most common causes of death were cardiovascular diseases, infections and respiratory system involvement (58%, 58%, 47%), respectively. Sepsis was the major cause of death in 10(53%)/19 patients, four deaths were secondary to pneumonia while the others were; cellulites (n = 2), osteomylities (n = 2) and the last 2 were due to septic arthritis. However, malignancy, CNS involvement and thromboembolism showed lesser relative frequencies (25%, 15%, 10%), respectively.

Table 4. The frequency (%) of the main causes of death in Rheumatoid Arthritis patients.

Causes of Death	Number of Patients 19	100 (%)
Cardiovascular diseases.	**11**	**58%**
CCF	6	32%
IHD	5	26%
Infection:	**11**	**58%**
Sepsis	10	53%
Pneumonia	8	42%
Pulmonary TB.	3	16%
Respiratory system diseases	**9**	**47%**
Malignancy	**5**	**25%**
Bronchogenic carcinoma	1	5%
Breast cancer	1	5%
Brain tumer	1	5%
Lymphoma	1	5%
Multiple myeloma	1	5%
Central Nervous system	**3**	**15%**
Intracerebral infarction	2	10%
Tuberculoma	1	5%
Thromboembolism	**2**	**10%**
Inferior vena cava obstruction	2	10%

IHD = Ischemic Heart Disease, CCF = Congestive Heart Failure

As shown in Table 5, the multivariate logistic regression analysis (Enter method) was used to determine the most significant predictors that affect the mortality. Poor functional status, DM and respiratory system involvement had the most significant association to mortality with p-values of (0.008, 0.009, 0.014), respectively. Other co-morbidities (CVS diseases, infections and older age group) were not significant predictors for mortality in this analysis. Although these factors were frequently seen as co-morbidity, other factors like poor functional status, DM and respiratory system involvement seem to have more impact on mortality.

Kaplan-Meier Curve illustrated in Fig. 1 shows the relation between the survival rate and RA duration. The survival rate of patients with disease duration < 1 year was (97%), while it was (76%) in patients with disease duration between 1-5 years; (52%) in those with RA duration > 5-10 years and (< 20%) in those with RA duration > 10years.

Table 5. Determination of the most significant predictors of mortality using the Multivariate Logistic Regression Analysis (Enter Method).

Pedictors	B-Coefficient	p-value	Exact Risk	95% CI
(A) Significant Predictors				
1. Poor functional status	2.05	**0.008**†	8	(1.7 – 36)
2. DM	2.13	**0.009**†	8.5	(1.7 – 43)
3. Respiratory disease	1.91	**0.014***	6.5	(1.5 – 31)
(B) Non-Significant Predictors				
1. CVS disease	0.71	0.32	2	(0.5 – 8)
2. Infection	0.24	0.75	1.3	(0.3 – 6)
3. Age	0.22	0.77	1.2	(0.3 – 6)

*p-value *< 0.05, †<0.01.*

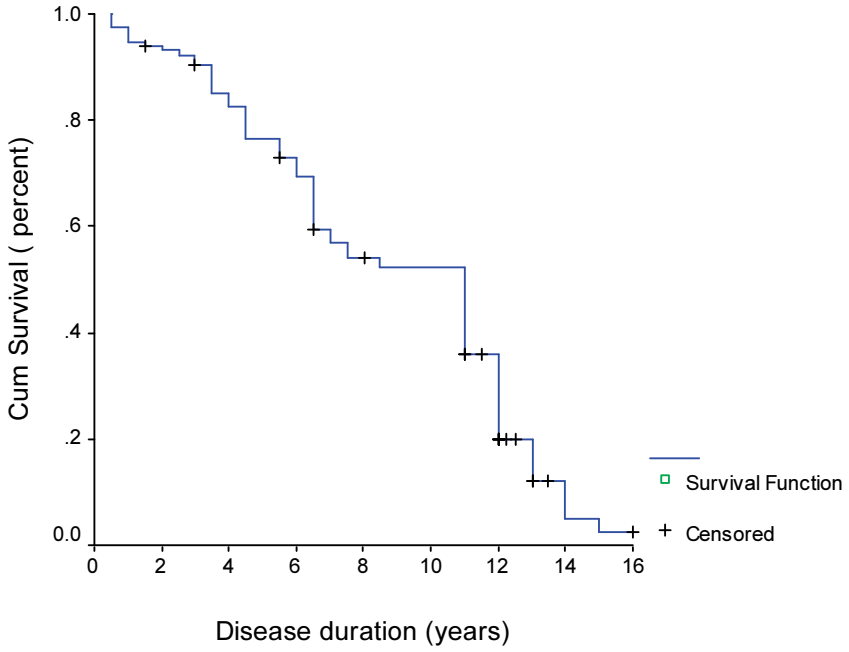

Fig. 1. Kaplan-Meier Curve shows the relation between the survival rate and RA duration.

Discussion

Rheumatoid Arthritis is a heterogeneous chronic disease characterized by remissions and relapses with variable outcome. Over the past 60 years, the mortality rate of RA patients remained higher than that of the general population(15-29%)[1-5].

The current study showed a mortality rate of 16% over 3 years which goes with the rate of mortality over the world[1-5]. The common cause of death in RA population is cardiovascular disease which is similar to the general control group but at a younger age group[31]. Cardiovascular involvement is a very well known cause of death due to multiple factors which could be related directly or indirectly such as; its association with atherosclerosis risk factors (including old age, male sex, smoking, family history, high blood pressure, high cholesterol, increased weight and reduced exercise) or the inflammatory process in RA or the steroid use[32].

The predictors of premature mortality in RA patients are controversial. Reilly *et al*.[33] found no significant difference in the mean ESR between patients who died of RA-related causes and the controls. This goes with our findings as there were no significant association between the activity of the disease and the mortality ($p = 0.53$). On the other hand, Scott *et al*.[34] found that a high initial ESR (> 50 mm/hr) and positive RF were related to a poor outcome .

Our team reported before, neither sex difference nor the presence of rheumatoid factor played a role on mortality[24]. This finding is supported by the results of the current study which showed that the presence of RF does not influence the poor outcome of RA patients ($p = 0.34$). In addition male sex was not significantly associated with mortality in RA ($p = 0.54$). On the other hand Western studies showed that male sex was a significant predictor of mortality in longitudinal analysis but not in retrospective evaluation of the death certificates[7].

The major cause of death in our patients was CVS diseases mainly (IHD and CCF), which affected 11 (58%)/19 patients. Infections were the cause of death in 11 (58%)/19 patients, 10 of them were complicated with sepsis. The CVS diseases and infections were significantly associated with morality ($p < 0.001$). Respiratory system involvement, whether related to the exacerbation of previous lung disease

superadded the infection, or in a normal lung, it was the cause of death in 47% of patients with ($p < 0.001$). Six (32%) patients were suffering from renal impairment. 25% of our patients had malignancies with RA. The reason of excess death from cancer could be related to the altered function of the body's immune system, however drugs used for treatment of RA also have an impact on the immune system (*Immunosuppressant* and Chemotherapy) and they can be implicated as a cause of death. Other co-morbidities which were strongly associated with the mortality included DM, HTN and obesity ($p < 0.001$, 0.01, 0.031), respectively. The multivariate regression analysis test supported that DM, poor functional status and respiratory diseases increase the exact risk of death by (8.5, 8, and 6.5), respectively. The percentages of CVS diseases were higher among diabetics (67%) and that explained the higher risk of mortality in diabetics. CVS diseases, infections and older age group showed lower degree in increasing the mortality. It is well established that with controlling the disease activity and the associated co-morbid illnesses, the risk of dying from rheumatoid arthritis will be decreased[35]. Despite all the efforts in finding risk factors that may predispose to mortality, all the recently published data in the United States confirmed that RF positive patients with a high level are still associated with both cardiovascular and respiratory death[36-37], even in patients with no joint symptoms[38]; but data from the current study did not confirm that, as seropositive patients were not significantly associated with high mortality. Furthermore, it has been suggested that a high CRP in RA patients may predict the development of cardiovascular morbidity[39], but as mentioned previously this was not supported in our study.

A main deficiency in this study is that; socioeconomic factors, the level of education, liver diseases and GI problems could not be assessed thoroughly and were not added as variables due to the insufficient data in the patient's medical records.

The discussion that has been raised in previous studies still remain[24], why such an inflammatory disorder is milder in the population at the Kingdom of Saudi Arabia than in the Western countries and could this be explained by the different genetic association of the disease or the lower risk factors; as Human leukocyte antigen (HLA) associations with RA differ between Caucasian and other populations. Rheumatoid Arthritis in the Saudi population is associated with HLA DR10, where as in Caucasians it is associated with HLA DR4 and HLA DR1[40,41].

Keeping in mind that none of the studied patients died from the RA itself, and with no associated co-morbiditis.

A further prospective multicenter trial is recommended to assess the mortality rate over a longer period of, and to evaluate the relationship between the co-morbidities and mortality.

Summary

In summary, this study confirms that older age, longer RA duration and the presence of extra-articular manifestations play a significant role in increasing the mortality rate in RA patients, while male sex, high rheumatoid factor titer and disease activity were not considered as predictors for mortality. CVS diseases, infections, respiratory system involvement, renal impairment were considered the major causes of death, while DM, HTN, obesity, malignancies, previous lung diseases were the most common associated co-morbidities.

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نسبة الوفيات في مرضى التهاب المفاصل الرثاوي (الروماتويد)

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المستخلص. تستهدف هذه الدراسة إيجاد نسبة الوفيات في المرضى المنومين بمرض الروماتويد (الالتهاب الرثاوي) لمدة ثلاث سنوات وبحث أسباب الوفيات والعوامل المؤثرة في زيادة نسبة الوفيات. تم دراسة حالات المرضى المنومين ولمدة ثلاث سنوات في مستشفى جامعة الملك عبدالعزيز بجدة في المملكة العربية السعودية، وتم إيجاد أهم الأسباب المؤدية للوفاة ، وتم دراسة الأمراض الملازمة للالتهاب الرثاوي. كانت نسبة الوفيات ١٦٪، وأهم الأسباب المؤدية للوفاة المصابون بأمراض القلب والأمراض الوبائية، ومن ثم أمراض الجهاز التنفسي. ومن أهم الأمراض الملازمة للالتهاب الرثاوي مرض السكري، ومرض ارتفاع ضغط الدم، والسمنة .