

Original Research Article

Five year retrospective study of mortality in systemic inflammatory rheumatologic disorders

Krutika R. Kale, Tukaram V. Kumbhar, Seema H. Kini*

Department of Medicine, Topiwala Nair Medical College, Mumbai, Maharashtra, India

Received: 19 December 2019

Revised: 04 January 2020

Accepted: 24 January 2020

***Correspondence:**

Dr. Seema H Kini,

E-mail: shkini@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Inflammatory systemic rheumatologic disorders are responsible for significant morbidity and premature deaths. The present study was done to assess causes of mortality in these patients.

Methods: In the retrospective study, the death records of patients with inflammatory rheumatologic illnesses from January 2012 to January 2017 were studied. The demographic details, disease activity, organ involvement, treatment received and evidence of infection were noted.

Results: 50 records were analyzed (25 systemic lupus erythematosus (SLE), 13 rheumatoid arthritis (RA), four immune myositis, three systemic sclerosis (SS), two takayasu's arteritis (TA), two ankylosing spondylitis (AS) and one granulomatosis with polyangiitis (GPA)). The mean age of death was 39.94 years. Sixteen patients had disease related organ damage, 17 had active disease. Infection was present in 31 patients (gram negative organisms most commonly isolated), being the major contributor of mortality. Only two patients succumbed to acute coronary syndrome.

Conclusions: Infection, disease activity and organ damage due to the disease are the major contributors to of death in hospitalized patients with inflammatory rheumatological disorders.

Keywords: Disease activity, Inflammatory systemic rheumatologic diseases, Infection, Mortality

INTRODUCTION

The common inflammatory rheumatologic disorders are systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis, autoimmune myositis, systemic sclerosis and related disorders and various types of vasculitis. Their course is characterized by flares and remissions affecting various organ systems. Due to immune dysregulation, these diseases are treated with immunosuppression which increase the risk of infection and drug toxicities. Cardiovascular mortality has been found significant in Swedish, Danish, Dutch and French studies.¹⁻⁶ Similar results have been found in studies from America, Canada and Asia.⁷⁻¹¹ Mortality due to infections

has been observed mainly in Asian, British and some European studies, including a few studies from America.¹²⁻²² There are fewer Indian studies dealing with mortality in inflammatory rheumatologic disorders.²³⁻²⁴ Hence, it was decided to study causes of mortality in the above population.

METHODS

This descriptive retrospective study was done from January 2012 to August 2017 in the tertiary care teaching hospital in western India. Death records of 62 patients with a diagnosis of inflammatory rheumatologic conditions were collected from medical record office

from the period of January 2012 to August 2017. Ethical approval from ethics committee of academic research project (ECARP) was obtained.

Inclusion criteria

Deaths due to inflammatory rheumatologic disorders in our hospital with the diagnosis mentioned on the death certificate.

Exclusion criteria

Incomplete patient records and non-inflammatory rheumatologic diseases.

Methodology

The demographic details were recorded, duration of hospital stays, cause of death, duration of the rheumatologic disorder, treatment records, co morbidities, infections, disease activity. Twelve records of patients who were not on follow up in the rheumatology clinic were excluded due to insufficient details.

Statistical analysis

The data was analyzed using descriptive analysis, and data represented in the form of charts and diagrams.

RESULTS

Distribution of rheumatologic diseases is shown in Figure 1. The commonest disease in the study was SLE followed by RA. Female preponderance was present (79%). Mean age at death was 39.94 years with SD (standard deviation) 16.95.

The overall contributors to mortality in all inflammatory rheumatologic diseases were infection 44%, disease related organ damage 23%, disease activity 24%, drug toxicity 6%, ACS 3% and malignancy 1%.

Disease-wise results were as follows:

SLE (n = 25)

Ten SLE patients out of total 25 had survival for less than a year after diagnosis. Duration of survival after diagnosis was ranging from 1 day to 10 years and average duration of last hospital stay ranged from 9 hours to 27 days. Commonest organ involvement was lupus nephritis (Figure 2). Amongst 25 SLE patients, 13 patients had active disease at the time of hospitalization. Ten patients had coexistent infection and active disease; whereas three patients had only active disease. Infection as the most common cause of mortality in SLE is shown in Figure 3. Active Infection was seen in 18 patients. Of these, 11 patients had Lower respiratory tract infection (4 patients had *Klebsiella Pneumoniae* on sputum culture, two

patients had tubercular pleural effusion, one patient had military TB, 4 were culture negative). One patient each had culture negative infective endocarditis of the mitral valve, urinary tract infection (*E. coli*), and dengue fever. Two patients had pseudomonas skin infection. Three patients had tinea corporis. Oral candidiasis and herpes labialis were present in two patients. Three of the patients with bacterial infection had sepsis. They were on the following immunosuppressants: Long term steroids (10), cyclosporine (6), cyclophosphamide (6) and azathioprine (4). Two patients received rituximab, out of which one patient succumbed to infection and other to disease activity. Two patients had intracranial hemorrhage. One patient had acute myocardial infarction and one patient had colorectal malignancy. Comorbidities associated with SLE patients were hypertension (5), cardiomyopathy (2), ASD (1).

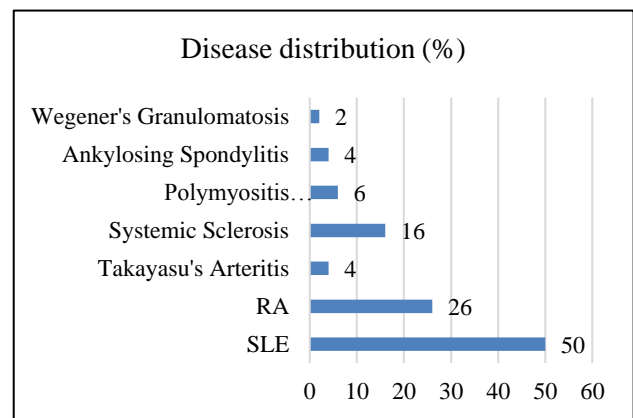


Figure 1: Distribution of rheumatologic diseases.

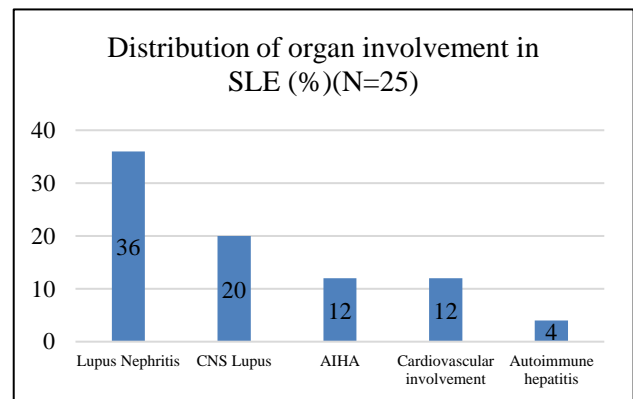


Figure 2: Organ involvement in SLE.

RA (N = 13)

Duration of last hospitalization was ranging from 8 hours to 23 days and survival after diagnosis was ranging from 3 years to 21 years. Among 13 RA patients, four patients had urinary tract infections (*E. coli* in two patients and two culture negative). Four patients had lower respiratory tract infections (*Klebsiella* and *Acinetobacter* infection in one patient each). Tinea corporis infection was present in three patients. One patient each had acute pancreatitis and

acute coronary syndrome. Interstitial lung disease of NSIP pattern was seen in three patients. They were on following immunosuppressant drugs: steroids (3), methotrexate (10), sulfasalazine (3) and azathioprine (1). Methotrexate induced bone marrow suppression was seen in 3 patients. Comorbidities associated in these patients were hypertension (7), DM (4), ischemic heart disease (1) and chronic liver disease (2).

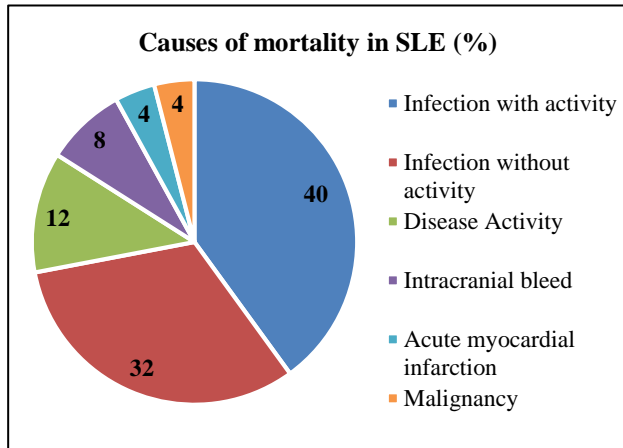


Figure 3: Causes of mortality in SLE.

SS (N = 4)

Among patients with systemic sclerosis 3 had interstitial lung disease. 2 patients had LRTI and one patient had UTI. One patient succumbed to presumptively diagnose tubercular pericardial effusion with cardiac tamponade within hours of admission. Three patients were on long term steroids and one patient each received cyclophosphamide, methotrexate and MMF.

TA (N = 2)

Both the Takayasu arteritis patients succumbed to acute decompensated heart failure in dilated cardiomyopathy and low ejection fraction, one of which was in second stage of labor.

AS (N = 2)

Urinary tract infections (*E. coli*) were seen in both the cases of ankylosing spondylitis who were on sulfasalazine, out of which one patient had pyelonephritis and another patient had preexisting chronic kidney disease due to hypertension.

Immune myositis (N = 3)

The patient with polymyositis had dilated cardiomyopathy with poor left ventricular ejection fraction and succumbed to acute decompensated heart failure. Both the patients with dermatomyositis had lower respiratory tract infections (*Acinetobacter*) causing respiratory failure.

GPA (N = 1)

Only one patient who was documented to have granulomatosis with polyangiitis had pseudomonal sepsis, tinea corporis infection and multiple renal infarcts.

DISCUSSION

Systemic rheumatologic disorders have been known to cause significant morbidity and mortality. Numerous studies have dealt with causes of mortality in these diseases, most of them from foreign countries.

SLE

Predictors of mortality in SLE have been identified as time from onset to diagnosis > 1-year, renal involvement, high SLEDAI (SLE disease activity index) and severe organ involvement.²⁵ EULAR task force identified infection, hypertension, dyslipidemias, diabetes, osteoporosis and malignancies as comorbidities that increase SLE mortality.²⁶

A Chinese metanalysis showed that infection causes 25-50% overall mortality.¹² A UK based study showed 25% mortality due to infection in SLE.¹⁶ A multiple cause of death analysis done by Souza DC et al concluded that there is increase in SLE deaths associated with infections like pneumonia and septicemia in developing countries.²² In a Korean study of 110 SLE patients, risk factors for infection were high disease activity at diagnosis (low complement levels, high ds DNA titers), frequent flares and duration of follow up (>8 years), lupus nephritis, leukopenia, immunosuppressive drugs and using steroids in high doses for a longer duration.^{13,17,21} SLE patients have a predisposition to tuberculosis and bacterial infections especially respiratory urinary and skin infections, due to defective immune system and immunosuppressive therapies.^{14,16,18,19} High disease activity and concomitant infections are known in SLE.^{13,23} In keeping with the above study, present study, 72% patients succumbed to infection, bacterial pneumonia being most common. Other infections included infective endocarditis, urinary tract infection due to *E. coli* and cutaneous fungal infections due to herpes and candidiasis. One SLE patient had rituximab induced bone marrow suppression and neutropenia contributing to *Pseudomonas* septicemia. Active disease was seen in 52% (13) patients, amongst which 76% (10) patients also had infection.

Cardiovascular disorders (related to atherosclerosis) were found to be the top cause of mortality in SLE patients in various studies.^{1,8} SLE patients have accelerated coronary atherosclerosis.⁷ Risk factors for the same were found to be dyslipidemia, endothelial dysfunction, steroid induced atherogenesis and active inflammation along with obesity, sedentary lifestyle.⁹ Salmon et al found that higher homocysteine levels, renal impairment, elevated LDL oxidation are the nontraditional risk factors are

responsible for cardiovascular diseases in SLE.⁷ Conflicting results have been obtained in the Chinese study by Wang et al where deaths due to cardiovascular diseases were minimum.¹² Contrary to the western studies, in present study, only one patient had acute myocardial infarction.

Lupus nephritis was found to be a major contributor in mortality. Lupus nephritis is associated with markedly increased morbidity from Ischemic heart disease (IHD) in SLE patients.² In present study, 44% of patients had lupus nephritis. Lupus nephritis is known to be associated with increased infection rates in SLE.²¹ In present study, 90% of patients with lupus nephritis also had infection.

Neuropsychiatric lupus in the form of acute confusional state, seizures has seen to contribute to high mortality in SLE in the studies conducted in Asia and Europe.^{12,25} Three of the cases had vasculitic infarcts in CNS contributing to mortality.

Pulmonary hypertension, diffuse alveolar hemorrhage, interstitial lung diseases in SLE have been found to be common causes of death.¹² Four patients had moderate pulmonary hypertension in the study (three secondary to SLE and one due to underlying ASD.)

RA

Various cohort studies show that cardiovascular involvement, respiratory causes and infections are mainly the causes of death in RA.^{3,4} A German study by Joachim has shown that patients with persistent high disease activity of RA are at increased risk of mortality along with diabetes, chronic lung, renal and cardiac diseases. Significant association has been found between mortality in RA and glucocorticoid use.²⁸ Four patients in the study had HTN and CKD, 4 patients had DM, and 3 patients were on long term steroids. Infections (UTI and LRTI) caused death in RA in 8 patients in the study. Methotrexate caused bone marrow suppression in 3 cases causing neutropenic sepsis.

SS

Studies on systemic sclerosis show that cardiopulmonary involvement is the most frequent cause of death.^{5,10} A Spanish metanalysis showed that pulmonary involvement was the commonest cause of fatality in these patients. In present study, all patients had ILD and three patients had respiratory tract infections.²⁹

TA

In Takayasu arteritis, secondary systemic hypertension and aortic regurgitation causing heart failure are the leading causes of death followed by ischemia and pulmonary infections.¹¹ In present study, both the patients succumbed to acute heart failure, out of which one patient was in second stage of labor.

Immune myositis

Malignancy, cardiopulmonary complications and infections are the most common causes of deaths as shown by various studies.^{6,20} In present study, two patients succumbed to LRTI and one patient had cardiogenic shock as the terminal events with 2 patients having cardiomyopathy as a comorbidity. A patient with dermatomyositis had methotrexate induced lung toxicity leading to respiratory failure and azathioprine induced hepatotoxicity which contributed to the mortality.

AS

Cardiovascular events were the commonest observed cause of mortality in AS followed by malignancies and infection.²⁷ In present study, both the patients succumbed to infection among which one patient had hypertension and chronic kidney disease as a contributory factor.

GPA

Mortality in Granulomatosis with Polyangiitis patients has been attributed to infection, active vasculitis and renal failure.¹⁵ The patient with GPA had vasculitis, orbital granuloma, lung cavitation and renal failure.

In present study, infections are the most common contributor to the mortality in systemic inflammatory rheumatologic disorders. Gram negative bacteria were most commonly isolated organisms in cultures. Other contributors of mortality were disease activity, associated organ damage and drug toxicities. Unlike in the studies by western countries, atherosclerotic cardiovascular diseases and malignancy were comparatively low in our study. Systemic inflammatory rheumatologic diseases require aggressive immunosuppression for disease control. In our setup, it's a challenging task to titrate the immunosuppression to lower the disease activity without increased risk of infection.

The study had some limitations. The hospital caters mostly to poor socioeconomic strata patients, who have limited resources for diagnosis as well as treatment. Other factors were small sample size and incomplete patient records leading to exclusion. (These deaths occurred in various departments of the hospital, not necessarily in rheumatology ward.) Microbiologic diagnosis of infection was not possible in all patients due to early death of the patient and/or unavailability of suitable sample. These diseases are not as common in the general population and often death certificate fails to mention the underlying rheumatologic disease, especially if the disease is in remission. The study only included the patients who had died in the public tertiary care center. Greater use of biologics in the private setup would perhaps influence the patient outcome. Hence multicentric population-based studies or cohort follow up survival studies can throw more light on the mortality causes in inflammatory rheumatologic disease.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

- Gustafsson JT, Simard JF, Gunnarsson I. Risk factors for cardiovascular mortality in patients with systemic lupus erythematosus, a prospective cohort study. *Arthritis Res Ther.* 2012;14(2):46-9.
- Faurschou M, Mellemkjaer L, Starklint H, Kamper A, Tarp U, Voss A, et al. High risk of ischemic heart disease in patients with lupus nephritis. *J Rheumatol.* 2011;38(11):2400-5.
- Butt S, Jeppesen J, Fuchs C, Mogensen M, Engelhart M, Pedersen C. Trends in incidence, mortality, and causes of death associated with systemic sclerosis in Denmark between 1995 and 2015: a nationwide cohort study. *BMC Rheumatol.* 2018;2:36-9.
- Van DHJ, Boshuizen HC, Roorda LD, Tijhuis GJ, Nurmohamed MT, Bos GA, et al. Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study. *Rheumatol Int.* 2017;37(4):487-93.
- Bronner IM, Van MFG, Visser M, Kalmijn S, Venrooij WJ, Voskuyl AE. Long-term outcome in polymyositis and dermatomyositis. *Curr Rheumatol Rep.* 2012;14(3):275-85.
- Avouac J, Amrouche F, Meune C, Rey G, Kahan A, Allanore Y. Mortality profile of patients with rheumatoid arthritis in France and its change in 10 years. *Arthr Rheumat.* 2017;46(5):537-43.
- Salmon JE, Roman MJ. Accelerated atherosclerosis in systemic lupus erythematosus: implications for patient management. *Curr Opin Rheumatol.* 2001;13(5):341-4.
- Nieves CE, Izmirlly PM. Mortality in systemic lupus erythematosus: an updated review. *Curr Rheumatol Rep.* 2016;18(4):21-7.
- Petri M, Gutthann PS, Spence D, Hochberg MC. Risk factors for coronary artery disease in patients with systemic lupus erythematosus. *Am J Med.* 1992;93:513-9.
- Nikpour M, Baron M. Mortality in systemic sclerosis: lessons learned from population-based and observational cohort studies. 2014;26(2):131-7.
- Park SJ, Kim HJ, Park H. Incidence, prevalence, mortality and causes of death in takayasu arteritis in korea a nationwide, population-based study. *Int J Cardiol.* 2017;235:100-4.
- Wang Z, Wang Y, Zhu R, Tian X, Xu D, Wang Q, et al. Long-term survival and death causes of systemic lupus erythematosus in China: a systemic review of observational studies. *Med Baltimore.* 2015;94:79-84.
- Jeong SJ, Choi H, Lee HS, Han SH, Chin BS, Baek JH, et al. Incidence and risk factors of infection in a single cohort of 110 adults with systemic lupus erythematosus. *Scand J Infect Dis.* 2009;41:268-74.
- Teh CL, Wan SA, Ling GR. Severe infections in systemic lupus erythematosus: disease pattern and predictors of infection-related mortality. *Clin Rheumatol.* 2018;37(8):2081-6.
- Luqmani R, Suppiah R, Edwards CJ, Phillip R, Maskell J, Culliford D. Mortality in wegener's granulomatosis: a bimodal pattern. *Rheumatol.* 2011;50(4):697-702.
- Goldblatt F, Chambers S, Rahman A, Isenberg DA. Serious infections in British patients with systemic lupus erythematosus: hospitalizations and mortality. *Lupus.* 2009;18(8):682-9.
- Danza A, Irastorza RG. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. *Clin Rheumatol.* 2018;37(8):2081-6.
- Erdozain JG, Irastorza RG, Egurbide MV, Berriotxoa MA, Aguirre C. High risk of tuberculosis in systemic lupus erythematosus? *Lupus.* 2006;15(4):232-5.
- Franco MD, Lucchino B, Spaziante M. Lung infections in systemic rheumatic disease: focus on opportunistic infections. *Int J Mol Sci.* 2017;18(2):293-6.
- Murray S, Schmajuk G, Trupin L. Infection is the leading cause of hospital mortality in patients with dermatomyositis/polymyositis: data from a population-based study. *Arthritis Care Res.* 2015;67(5):673-80.
- Feldman CH, Hiraki LT, Winkelmayr WC, Marty FM, Franklin JM, Kim SC. Serious infections among adult medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. *Arthritis Rheumatol.* 2015;67(6):1577-85.
- Souza DC, Santo AH, Sato EI. Mortality profile related to systemic lupus erythematosus: a multiple cause-of-death analysis. *J Rheumatol.* 2012;39(3):496-503.
- Bharath G, Kumar P, Makkar N, Singla P, Soneja M, Biswas A, et al. Mortality in systemic lupus erythematosus at a teaching hospital in India: a 5-year retrospective study. *Rheumatol.* 2019;8(7):2511-5.
- Sharma A, Shamanna SB, Kumar S, Wanchu A, Bamberg P, Singh S, et al. Causes of mortality among inpatients with systemic lupus erythematosus in a tertiary care hospital in North India over a 10-year period. *Lupus.* 2013;22(2):216-22.
- Piraquive OV, Aristizábal NI, Cañas CA, Tobón GJ. Mortality in systemic lupus erythematosus: causes, predictors and interventions. *Expert Rev Clin Immunol.* 2018;14(12):1043-53.
- Bertsias G, Ioannidis JP, Boletis J. EULAR recommendations for the management of systemic lupus erythematosus report of a task force of the EULAR. *Expert Rev Clin Immunol.* 2018;14(12):1043-53.

27. Bakland G, Gran JT, Nossent JC. Increased mortality in ankylosing spondylitis is related to disease activity. *Ann Rheum Dis.* 2011;70(11):1921-5.
28. Listing J, Kekow J, Manger B, Burmester GR, Pattloch D, Zink A, et al. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNF α inhibitors and rituximab. *Ann Rheum Dis.* 2015;74:415-21.
29. Aznar CP, Pla´ FV, Vilella TC, Garriga EG, Grau CM, Casals RM, et al. Registry of the Spanish network for systemic sclerosis survival, prognostic factors, and causes of death. *Medicine.* 2015;94(43):77-83.

Cite this article as: Kale KR, Kumbhar TV, Kini SH. Five year retrospective study of mortality in systemic inflammatory rheumatologic disorders. *Int J Res Med Sci* 2020;8:979-84.