Mortality in rheumatic diseases: introduction

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Premature mortality is the most severe medical outcome of any disease. Traditionally, cardiovascular and neoplastic diseases have been regarded most prominently as "fatal" diseases, while rheumatic diseases generally have been regarded by the medical community and general public as "non-fatal" diseases. Nonetheless, most rheumatic diseases have a natural history that includes premature mortality.

Some inflammatory rheumatic diseases such as systemic lupus erythematosus (SLE), systemic sclerosis, polymyositis, and vasculitis are associated with premature mortality rates comparable to or greater than most cardiovascular and neoplastic diseases. Mortality rates are lower in rheumatoid arthritis (RA) and gout, but nonetheless higher than in the general population. Even osteoarthritis (OA) is associated with premature mortality. The data to support the above statements are presented in this Supplement.

Examples of the "natural history" of mortality in inflammatory diseases may be seen in three reports published in 1971 – after glucocorticoids were available, but prior to modern use of cytotoxic drugs – concerning systemic sclerosis, polymyositis, and SLE. Survival data are compared to survival in patients with Hodgkin's disease at that time, published in 1972 (Fig. 1).

The 1972 analysis of mortality in patients with Hodgkin's disease indicated 5-year survival of approximately 80% in all patients (1), including 70% survival in patients with stage III disease and 45% in patients with stage IV disease, in contrast to 90% in patients with Stage I/Stage II disease (1) (Fig. 1A).

In 309 patients with systemic sclerosis seen between 1947 and 1970 (Fig. 1B), overall 5-year survival was about 50% and 7-year survival 35% (2). All 16 patients with renal disease died within one year! Five-year survival was about 25% in patients with cardiac but no renal involvement, 45% in patients with pulmonary but no cardiac or renal involvement, and 65% in patients with no pulmonary, cardiac, or renal involvement.

In 124 patients with polymyositis seen between 1947 and 1968 (Fig. 1C), overall survival at 2 years was about 72%, 60% after 5 years, and 55% after 7 years (3). Among 14 patients with pneumonitis, 2-year survival was about 30%, and 7-year survival was less than 10%.

In 150 patients with SLE (Fig. 1D), overall 5-year survival was 75%, including 95% in patients with discoid lupus, 85% with musculoarticular manifestations, 70% with malar rash, 60% with pulmonary SLE, 55% with cardiac SLE, and about 50% with central nervous system or renal SLE (4).

These data indicate that 5-year survival in the 1960s in patients with pulmonary, cardiac or renal systemic sclerosis, pneumonitis in polymyositis, or cardiac, neuropsychiatric or renal SLE was similar to or poorer than survival in patients with stage IV Hodgkin's disease. Significant improvement in survival has been seen since the 1970s in many diseases, as summarized in the chapters in this Supplement, attributable to many variables including more sensitive diagnostic tests, with increased early diagnosis; advances in general medical treatments; improved, earlier, and more aggressive specific treatment of rheumatic diseases; and others. Furthermore, the diseases may be milder at this time, due to secular trends (5), analogous to cardiovascular disease (6).

The relative lack of attention to mortality outcomes in rheumatic diseases may be explained in part by a number of factors (Table I):

1) The acute attributed causes of death tend to be similar in the aggregate in patients with rheumatic diseases to causes of death in the general population. Cardiovascular disease is listed as the most common cause

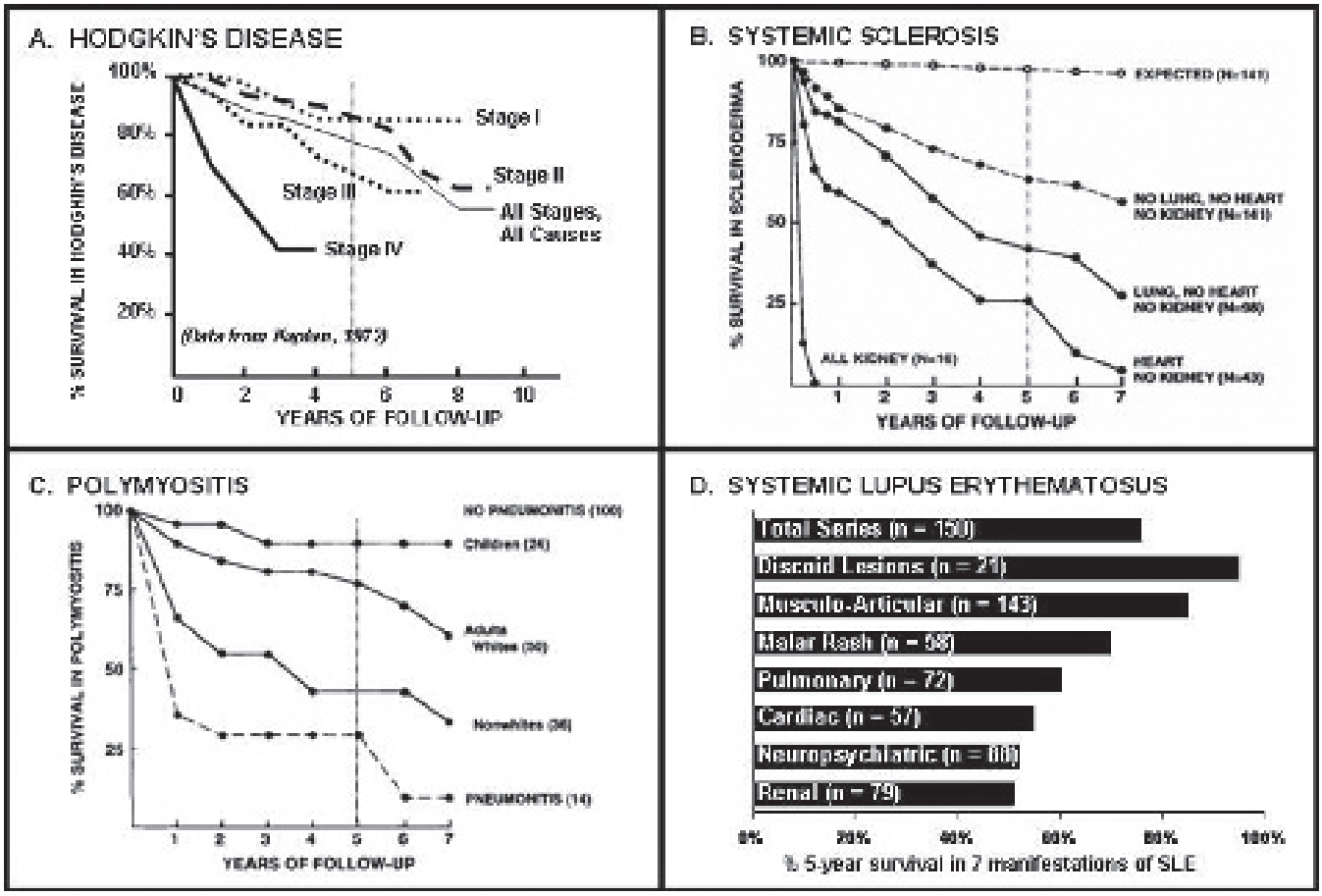

Fig. 1. Survival over time in Hodgkin's disease and in three inflammatory rheumatic diseases. **A**: Percent survival over 10 years of patients with Hodgkin's disease at all stages, and at Stages I, II, III, or IV at entry to study (1). **B**: Observed cumulative survival rates for systemic sclerosis patients with lung, heart or kidney involvement, and observed and expected cumulative survival rates for patients with none of these involvements at entry to study (2). **C**: Summary of observed cumulative survival rates for variables significantly affecting polymyositis survivorship (3). **D**: Percentage of 5-year survival in 150 patients with systemic lupus erythematosus (SLE), estimated from the time of appearance of each of 7 manifestations (4). These data are not corrected for age and gender, and therefore should not be compared directly, but illustrate that some patients with these rheumatic diseases experience survival comparable to a neoplastic disease.

of death, not necessarily in greater proportion than in the general population, but at an earlier age, indicating that rheumatic diseases serve as "risk factors" for cardiovascular disease. Infection is considerably more common as an acute cause of death in patients with inflammatory rheumatic diseases than in the general population, as are pulmonary, gastrointestinal, and renal disease, to a lesser extent. However, in a rheumatology practice caring for, say, 300 patients with RA and other inflammatory rheumatic diseases, patients might die at a rate of 1 or 2 per quarter, with acute attributed causes of death similar to the general population. Even 6 deaths in a year (1 every other month) attributed to infection would not trigger recognition of premature mortality, without data concerning long-term patient survival.

2) Few rheumatology settings maintain long-term databases concerning survival over 5 to 20 years, which are required to recognize premature mortality in a patient cohort compared to the general population. Without long-term data, it is not possible to recognize excess mortality rates.
3) The severe inflammatory rheumatic diseases with the highest mortality rates, including systemic lupus erythematosus (SLE), systemic sclerosis, vasculitis, and polymyositis, are rare diseases, *i.e.*, seen in fewer than 1 in 2,000 individuals. Therefore, mortality associated with these conditions has little impact on overall mortality statistics in the general population, compared to mortality in more prevalent chronic diseases such as hypertension or diabetes.
4) Again, due to low prevalence, most settings have too few patients to analyze long-term mortality rates in patients with most rheumatic diseases. Only specialized centers accumulate sufficient patients for analysis of mortality in diseases such as systemic sclerosis or polymyositis.
5) Death certificates of patients with chronic rheumatic diseases usually do not include mention of the rheumatic disease at all. Death generally is attributed to an acute process, such as infection or a cardiovascular event. Therefore, rheumatic diseases have even a lesser impact

Table I. Some reasons for relative neglect of attention to mortality outcomes in rheumatic diseases.

- Acute attributed causes of death similar to general population
- Few rheumatology settings maintain long-term databases of patients over 5-20 years
- Severe inflammatory rheumatic diseases with highest mortality rates are rare diseases – mortality rates have little impact on mortality in the population
- Because of rarity of diseases, few patients at most sites, even specialized centers
- Death certificates usually do not include the rheumatic disease at all
- Patient deaths often unknown at the rheumatology treatment site
- Clinical trials of mortality outcomes not possible in rheumatic diseases, unlike in asymptomatic diseases such as hypertension or hypercholesterolemia
- Resources for analyses of long-term mortality outcomes much smaller than in cardiovascular or neoplastic diseases
- Pathogenesis of comorbidities associated with rheumatic diseases, such as cardiovascular disease, has not been as well understood as in hypertension or diabetes
- Most patients experience some transient improvement upon treatment, which is emphasized in teachings of rheumatologists.

on population mortality statistics than might be expected on the basis of their low prevalence.

6) Patients may die at locations remote from the rheumatology site, and the rheumatologist administering specialty care possibly never learn of the deaths or causes of death.
7) Randomized controlled clinical trials over long periods, which provide an optimal method to analyze effects of therapies on mortality, are not possible in inflammatory rheumatic diseases. Clinical trials have been informative concerning mortality in hypertension or hypercholesterolemia, including reduction or prevention by various therapies. However, hypertension and hypercholesterolemia are asymptomatic conditions for which long-term placebo treatment was ethical to establish that mortality rates could be reduced by therapies. In addition, resources have been available for long-term clinical trials. In symptomatic diseases such as rheumatoid arthritis and all other inflammatory rheumatic diseases, long-term clinical trials are not possible due to logistical and ethical considerations (7), rarity of diseases, lack of resources, etc. Therefore, data concerning mortality outcomes in rheumatic diseases must be compiled from long-term observational data, which are methodologically less rigorous than clinical trial data to describe mortality outcomes, and less likely to be widely disseminated to the medical community.
8) Resources for studies of long-term outcomes, including mortality, in patients with rheumatic diseases are limited, in part as a consequence of their low prevalence and the general lack of recognition of their severity. By contrast, "tumor registries" to monitor cancer patients for mortality outcomes and possible changes over time have been established for many years. Such registries are now increasing for rheumatic diseases, although often only for selected patients, *e.g.*, patients receiving biological therapies in RA, limiting analyses of more general mortality rates compared to the general population.
9) The pathogenesis of comorbidities of rheumatic diseases, such as cardiovascular disease, has not been understood as well as in diseases such as hypertension or diabetes, which are more recognized as associated with later mortality. This situation has been changing recently, as discussed in the chapter on cardiovascular disease in RA and SLE (8).
10) Most patients experience some improvement upon treatment, sometimes transient and sometimes long-term. Treatment responses are emphasized (appropriately) in education of and by rheumatologists. However, long-term severe outcomes such as mortality may receive lesser or no attention.

This Supplement presents analytical reviews concerning mortality in specific rheumatic diseases by leading international experts, in two sections. An introductory section presents analyses of cardiovascular comorbidities in RA and SLE; poor musculoskeletal function and limited exercise as risk factors for mortality in rheumatic and other diseases as well as the general population; description of a proposed method whereby monitoring long-term outcomes, including mortality outcome in rheumatic diseases, could be as routine as laboratory tests; and associations of socioeconomic status with increased mortality rates.

The introductory section is followed by summaries of up-to-date information concerning mortality in specific rheumatic diseases including RA, psoriatic arthritis, Sjögren's syndrome, SLE, ankylosing spondylitis, systemic sclerosis, vasculitis, mixed cryoglobulinemia, polymyositis, gout, osteoarthritis, osteoporosis, and Behçet's syndrome. Each chapter includes a description of the mortality experience, acute attributed causes of death, and what is known concerning risk factors for premature mortality in each disease.

The ultimate rationale for studies of mortality in any disease is to identify and correct prognostic markers of premature mortality, such as elevated blood pressure, elevated cholesterol, and elevated hemoglobin A1c, in order to improve mortality outcomes. Similar advances are emerging in rheumatic diseases although, as noted, not documented in randomized controlled clinical trials (the most rigorous manner), but necessarily through long-term databases. A long-term database of consecutive patients can often be more informative than a randomized controlled clinical trial (9), and should be a component of all rheumatology care. The editors hope that this Supplement can stimulate greater interest in mortality in rheumatic diseases, leading to improved quality of care and patient outcomes.

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