Editorial

Do Improved Survival Rates of Patients with Systemic Lupus Erythematosus Reflect a Global Trend?

Systemic lupus erythematosus (SLE) is a chronic disease that affects many organ systems and manifests a broad spectrum of laboratory and clinical features. Clinically, it is generally a remitting/recurring disease. While it is of mild severity in a significant number of patients, it can be severe and refractory to therapy in others.

Mortality and survival rates are important outcome measures that have long been the subject of research in SLE. Mortality studies have addressed causes of death, survival rates, and standardized mortality ratios (SMR), and have identified predictors associated with early and late death[1-3]. The development of various valid and reproducible outcome measures in SLE has been a major step in the exploration of variables associated with morbidity and mortality in these patients. The inclusion of the SLE Disease Activity Index (SLEDAI), Systemic Lupus International Collaborating Clinics (SLICC), British Isles Lupus Activity Group, the Medical Outcome Study Short Form-36, and many other variables as primary predictors associated with mortality enables comparisons between prognostic studies from various centers despite diversity in clinical manifestations of the disease.

The survival rate of patients with SLE has improved significantly over the last 5 decades, from less than 50% at 5 years in 1955 to 85% at 10 years in recent studies[3-5]. This improvement in SLE survival rates is the result of continuous improvement in the survival of the general population over the last half-century, advances in therapeutic modalities, more judicious use of existing therapies, in particular steroids and cytotoxic agents, and the change in prognostic factors[3,6]. Despite this encouraging improvement, patients with SLE followed at various centers in North America have a 2.4 to 3-fold increased risk (SMR) of death compared with the general population[3,5].

A review of the literature identified more than 50 prognostic and mortality studies in SLE reported from different lupus clinics around the globe. While all studies suggested improved survival, there is no agreement with regard to the causes of death or the type of predictors associated with mortality. A wide range of demographic, clinical, laboratory, and quality of life variables have been associated with reduced survival in SLE. Among those variables are female/male gender, low socioeconomic status, low income, unemployment, Black/African American race, nephritis, antiphospholipid syndrome, low platelets, fixed renal damage, high SLEDAI and SLICC scores, and many others[7]. This diversity in results of the various studies is related to differences in their design, the patient populations and referral types, definitions of causes of death, and types of analyses of predictor variables for mortality.

A comprehensive and informative mortality study should gather data on causes of death, present life-table analyses, identify predictors of death, and compare the mortality of SLE with the general population by calculating the SMR. Such studies could be based on the data of a single center, multiple centers, or a national or international registry. The SLE population should be based on an inception cohort and on patients from primary, secondary, and tertiary referral. The data need to be recorded prospectively at fixed intervals in a validated protocol that includes demographic, clinical, and laboratory variables. Those variables must be based on the glossary of the American College of Rheumatology and/or the committees for prognosis studies in SLE. All of the variables should be collected and recorded at each assessment. Identifying loss-to-followup patients is the first stage of all mortality studies. A thorough attempt should be made to contact and recruit all patients not seen 6–12 months or more prior to the start of the study.

The definition of causes of death is based on the primary mechanism and pathological process that was directly responsible for death, and not necessarily the terminal event. This is important when defining SLE as a primary

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cause of death since this concept has not been well defined. It should not be based on the absolute number of a disease activity index but on an SLE-related clinical manifestation that is directly related to the death. Identification of predictor variables for mortality should be based only on prospectively collected variables, which are recorded in the study protocol.

In this issue of *The Journal*, Mok, *et al*[8] claim that survival rates for patients with SLE in southern China have improved over the last decade. The authors previously reported survival rates and predictors for mortality for SLE patients living in Hong Kong. In their current study, they calculated the annual SMR over 7 years and identified a trend of improvement in SMR as a result of a reduction in infection rates. The 5, 10, and 15-year survival rates of the SLE patients were 92%, 83%, and 80%, respectively. These rates are encouraging and similar to reports from Europe and North America.

Their study is important since there is a paucity of information in general and relatively little has been published on survival rates for SLE in Asia. In addition, this study provides important additional information on lupus in Asia, a population thought to have a high prevalence of severe lupus. Ethnic background, socioeconomic status, and higher incidence of nephritis are variables that adversely affect the survival of these patients in Asia. Previous mortality studies from India and Indonesia[9,10] reported lower survival rates compared with data from the West. Despite the encouraging data of Mok, *et al*[8], it is not clear whether they indicate improved survival of SLE patients in developing countries. Additional mortality studies are clearly needed.

Limitations of the study from Mok, *et al*[8] are related to the structure of the cohort. Although the study was conducted in a referral center, it is not an inception cohort. Most of the patients were recruited from family physicians, pediatricians, hematologists, and nephrologists, and the cohort increased rapidly in size over a short period of time. No information is provided regarding those patients who were not recruited and those who were lost to followup. The characteristics of patients who were followed by nephrologists and their influence on the cohort are missing.

In 60% of cases infection was the main cause of death[8]. This is considerably higher than the reported rate of death from infection in other cohorts. However, in this cohort death as a result of active SLE was not defined and was not considered a cause of death. This was missed by the authors. The data of the cohort show that SMR for early death (SLE disease duration less than 5 years) did not change significantly during the 2000-2006 period and the improved survival rate is mainly the result of reduction in the rate of late deaths. This suggests that active SLE is still a major cause of death in SLE. Patients with active disease may develop a major infection prior to death, but in those cases the cause of death should be active SLE and not infection. Identifying SLE as a primary cause of death is crucial in developing strategies for further improvement in the survival of patients with SLE.

The bimodal distribution of SLE mortality was first described by Urowitz, *et al* in 1976[11], and was found to be valid in subsequent studies[1,5]. This model suggests that early death is largely the result of active disease and infections, while a significant portion of late deaths are the result of atherosclerosis and cardiovascular disease. This model was the first to posit that accelerated atherosclerosis is a significant contributor to the morbidity and mortality of SLE.

It is no longer a matter of controversy that SLE patients have an increased risk of developing cardiovascular disease, particularly before the age of 50[12-14]. In a recent large multicenter study[5] the risk of death due to vascular disease did not change despite reduction in the risk for death from active disease. In the study by Mok, *et al*[8] only 13% of the patients died from vascular disease. This low rate is most likely due to the young cohort and short followup period and not necessarily due to a change in the pattern of vascular mortality in SLE patients living in Asia.

The improved survival in SLE is not the result of changing demographics, disease activity at enrollment into the clinic, major changes in disease patterns, or new modalities of therapy. This confirms that the improved survival rate in SLE is greater than overall health improvement in the general population. However, mortality rates remain higher in SLE patients compared with the general population[3].

Additional research is needed to further improve morbidity and mortality rates in SLE. This should be directed at the development of new therapeutic modalities for SLE, prevention of infections, unraveling the etiology and pathogenesis of accelerated atherosclerosis in SLE, early detection and treatment of risk factors associated with cardiovascular diseases, and management of the antiphospholipid syndrome in SLE.

Adopting guidelines for the management of atherosclerotic risk factors among patients with diabetes mellitus and ischemic heart disease is reasonable for patients with SLE. This includes tight control of hypertension with blood pressure levels below 130/80, an LDL cholesterol target below 100 mg/dl, and the use of aspirin.

Currently, SLE therapeutic research is poised at the inception of a new era of biologic and therapeutic modalities including, among others, anti-BlyS, anti-CD20, atacicept, and anti-tumor necrosis factor. Possibly these modalities will facilitate the induction of remission in SLE, with a lower toxicity risk. This is important, since the risk of death from active and refractory disease remains high. Detecting variables associated with refractory SLE is also of great interest and will allow aggressive therapy in that group of patients[6].

Up to 30% of deaths in SLE are due to infections. The study by Mok, *et al* in this issue[8] reports a trend to fewer

deaths from major infection over the course of a decade. In addition to advances in the diagnosis and treatment of severe infections, the routine recommendation for vaccination against influenza virus, *Streptococcus pneumonia*, tetanus toxoid, *Hemophilus influenza,* and other viral and bacterial infections is a major step towards reducing morbidity and mortality associated with infections. These vaccinations are safe and efficacious[15,16].

In summary, despite the improvement in survival rates for patients with SLE the SMR are still 3-fold higher than for the general population. It may be possible to further improve survival by treating refractory SLE with new therapies and tightly controlling all disease-related morbidity. Further studies are needed to confirm that improved survival of SLE is a global trend and not limited to certain regions in the world.

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