An update on mortality in systemic lupus erythematosus

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ABSTRACT

Objective. *Both systemic lupus erythematosus (SLE) and its treatments can contribute to increased mortality rates. The main focus of this review is recent studies on mortality during the last 5 years.*

Methods. *A literature search using PUBMED was performed for articles relating to lupus mortality with a specific focus on literature published within the last 5 years.*

Results. *Survival rates for lupus patients have improved greatly with the ability to treat disease-specific manifestations and infections and to lessen the impact of comorbid conditions. Nonetheless, disparities in mortality rates still exist based on ethnicity, socioeconomic status, age, and gender. Cardiovascular disease, infection, and severe disease activity remain common causes of mortality.*

Conclusions. *Despite advances in the treatment of SLE-associated infection, and renal failure, increased mortality remains a major concern in patient management.*

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Introduction

SLE is associated with an approximate two- to five-fold risk of death compared to the general population (1, 2). Lupus has long been associated with a bimodal pattern of mortality (3). Early mortality (less than 1 year since diagnosis) is thought to be more likely related to severe disease activity, and later mortality is more likely associated with complications of long-standing disease and treatment with immunosuppressive agents. Infection and accelerated atherosclerosis are causes of late mortality. The concept of early and late mortality was recently challenged by Nossent *et al.* (4) in a report that demonstrated a low frequency of death in a large European multicenter cohort within the first year. The median disease duration at the time of death was 10 years. These authors suggested that "early death" be redefined as death within the first 5 years, rather than within the first year.

Numerous studies have addressed mortality in various populations of SLE patients. Recently, Borchers *et al.* (25) and Kasitanon *et al.* (2) published detailed reviews of the international literature on lupus-related mortality. This study will focus on updates and advances made over the course of the last 5 years (Table I).

Historically, lupus was considered a rapidly fatal disease, as treatment options were limited or nonexistent. For example, the 5-year survival of a lupus patient in the 1950s was a dismal 50% (5). Today, the approximate 5-, 10-, and 15-year survival rates are 96%, 93%, and 76%, respectively (2, 6, 7, 8-13, 15, 16, 20, 81). Table I provides an overview of some of the more recent studies to specifically address mortality rates. Even over the course of the last 20 years, there has been a steady decline in mortality. In North America, the 5-year survival was 50% to 75% in the period from 1950 to 1975. The period from 1975 to 1990 saw a dramatic improvement; 10-year survival increased from 64% to 87%. Still more improvements took place in the period from 1990 to 2004, when 20-year survival increased to 78% (2). The decrease in mortality rates is likely due to improved classification of disease, early diagnosis, inclusion of milder cases in many cohorts, and improved therapeutics, as well as improvements in treating concomitant comorbidities such as hypertension, infection, and renal failure (6, 17, 18).

Interestingly, Doria *et al.* (6) found that the survival curves for SLE patients were quite similar for the first 10 to 15 years for patients with mild versus severe disease or for patients with or without glomerulonephritis. After this time, though, the curves clearly diverged. The authors propose that the similar survival noted over the first decade highlights the improved efficacy of initial treatment

Table I. Recent mortality studies in Systemic Lupus Erythematosus.

Study (ref)	Year	Number of patients	W (%)	B (%)	H (%)	A (%)	O (%)	Location	Survival 5	10	15	20
Al-Saleh (20)	2008	151	2	4	0	35	110	United Arab Emirates	94	-	-	-
Cervera (7)	2003	1000	1000	0	0	0	0	Europe	95	92	-	-
Doria (6)	2006	207	207	0	0	0	0	Italy	96	93	76	-
Funauchi (81)	2007	306	0	0	0	306	0	Japan	94	92	-	77
Heller (15)	2007	92	0	7	0	7	78	Saudi Arabia	92	-	-	-
Kasitanon (2)	2006	1378	767	543	-	-	68	USA	95	91	85	78
Mok (40)	2005	285	0	0	0	285	0	China	92	83	80	-
Sun (16)	2008	100	0	0	0	100	0	China	98	98	-	-
Wadee (69)	2007	226	2	210	0	7	7	South Africa	57-72%	-	-	-

W: White; B: Black (African, African-American, African-Caribbean); H: Hispanic; A: Asian; O: Other

regimens, even in patients with severe disease or glomerulonephritis. They further hypothesize that divergence of survival curves may be associated with complex disease-related variables or may be secondary to aggressive immunosuppressive therapy.

Despite numerous advances in diagnosis and treatment of SLE and associated comorbid conditions, this disease remains a source of significant morbidity and mortality. Even with the clear improvement in overall mortality over the last 5 decades, a patient diagnosed at 20 years of age still has a 1 in 6 chance of dying by the age of 35 (14) and higher likelihood of a shortened lifespan.

Factors associated with mortality in SLE

Mortality in SLE is clearly multifactorial. Various studies have examined demographic variables such as ethnicity, socioeconomic status, gender, age, and even geography in relation to mortality.

The role of ethnicity and mortality has been evaluated at length. Previous studies have consistently shown increased morbidity and mortality in those of African-American/African-Caribbean and Hispanic ethnic origin as compared to Caucasians (1, 22, 23, 30, 36, 47-49). For example, Fernandez *et al*. (47) determined 5-year survival rates for Texan-Hispanics and African-Americans to be 86.9% and 89.8%, respectively compared to 94% for Caucasians. By contrast, disparities between ethnicity and mortality did not exist in a Canadian cohort of SLE patients (52).

In addition, genetic variation, increased disease severity (especially as defined by renal disease) in minority populations, environmental exposures, and numerous socioeconomic factors all play a significant role in determining disease activity and mortality. Using genetic markers such as HLA alleles and ancestral informative markers (AIMs), several studies have examined the contribution of genetics to disease activity. Alarcon *et al*. (30) found higher disease activity in African-American and Texan Hispanic patients compared with Caucasian and Puerto Rican Hispanic patients on both univariate and multivariate analysis. In another study (29), genetic factors better explained the increased incidence of renal involvement seen in minority populations than did socioeconomic status. Finally, Fernandez *et al*. (47) found that African American and Texan Hispanic patients had higher disease activity (as measured by Systemic Lupus Activity Measure scores [SLAM-R] and physician global assessment), a higher incidence of renal involvement, increased damage accrual, and poorer 5- and 10-year survival when compared to Caucasians and Puerto Rican Hispanics. Although some of these relationships failed to retain significance on multivariate analysis, these results lend further support to the importance of genetic factors in SLE.

In addition to genetic factors, environmental exposures may also contribute to mortality in SLE (55). Tsai *et al*. (21) studied the effect of polychlorinated biphenyls/dibenzofurans on the mortality of SLE patients and found standardized mortality ratios (SMR) of 19.8 eight to fifteen years after exposure and 18.9 sixteen to twenty three years after exposure.

Renal complications cause significant morbidity and mortality in SLE patients; standardized mortality ratios (SMR) for such complications are estimated at 4.3 (1). Studies have shown that minority populations manifest renal disease more commonly, which has resulted in poorer outcomes for these groups (19, 22, 28, 35, 47). Korbet *et al*. (22) found both 10-year survival and renal survival were significantly worse in black patients compared with whites even on multivariate analysis. Similarly, Contreras *et al*. (19) found an increased risk for the doubling of creatinine, progression to end-stage renal disease (ESRD), and death in African Americans and Hispanics compared with Caucasians. A study done in the United Kingdom (28) again confirmed the ethnic disparities in renal failure, with 62% of the renal failure patients being of African descent. Moreover, health care in the UK is free to all, making socioeconomic factors less of an issue as compared to the studies done in US populations. Although other factors, such as adherence, may be affecting outcomes, these findings lend further support to ethnicity as an independent risk factor for poor outcome.

Education levels, economic status, and access to health care are some of the varied demographic variables studied in SLE patient populations. Many research efforts have focused on these

disparities as potential risks for increased disease activity and poor outcomes (30, 47, 50, 51). Kasitanon *et al*. (2) found that an annual family income of <$25,000 led to poor survival (HR=1.7; *p*=0.040). Alarcon *et al*. (27) found an association between poverty and increased disease activity using the Physicians Global Assessment (PGA) as the measure of activity. However, this association was not apparent when the SLAM score was used to assess disease activity. Using the Systemic Lupus International Collaborating Clinic and ACR Damage Index scores (SDI) as measures of early damage, Cooper *et al*. (36) found that household income of <$30, 000 was independently associated with increased damage. Ward (37), using education levels as a measure of socioeconomic status, found that mortality was higher among whites with lower education levels (<12 years) compared to whites with higher education levels (>12 years). In contrast, minority patients with lower education levels actually had lower mortality rates. While this may be due to either underreporting of SLE related deaths or the underdiagnosis of SLE in minorities, this seemingly contradictory association underscores the difficulty of examining complicated socioeconomic factors as they relate to morbidity and mortality.

SLE preferentially affects females, with a female to male ratio of approximately 10:1. Males with SLE have higher mortality rates than do females with the disease. (1, 2, 6, 31, 33, 38, 39).

Other studies have found a link between the age at diagnosis and mortality (31,24). In a univariate analysis, Mok *et al*. (40) found that late-onset lupus (after age 50) was associated with increased mortality; 5, 10, and 15-year survival rates were 66%, 44%, and 44%, respectively. Bujan *et al*. (39), Kasitanon (2) *et al*., and Bertoli *et al*. (32) all found that diagnosis after age 50 was an independent risk factor for mortality. Bertoli *et al*. (53) examined the effect of acuity of onset and outcome (mortality and damage). Patients with more acute onset of SLE (as defined by the accrual of 4 ACR criteria in <4 weeks) were younger, of lower socioeconomic status, and had more severe disease manifestations, but the acuity of onset did not influence overall mortality.

Other authors have studied the role of damage accrual and disease severity as predictive markers of mortality. Kasitanon *et al*. (2) found that a SLEDAI score of >10 in the first year was associated with increased mortality, but this relationship did not achieve significance after adjusting for demographic variables. Nossent *et al*. (4) used the European Consensus Lupus Activity Measure (ECLAM) score and the Systemic Lupus International Collaborating Clinic and ACR Damage Index scores (SDI) and did see an association with severe disease and poorer survival. But it should be noted that these studies did not use the same disease activity measures (SLEDAI *vs*. ECLAM). In addition, Ibanez *et al*. (24) noted that the Adjusted Mean SLEDAI-2K was a predictor of survival.

Other studies have focused on damage accrual as a marker for mortality. Persistent disease activity (as measured by ECLAM, SLEDAI) and damage accrual (the SLICC/ACR Damage Index) were associated with mortality (4). Only 12% of patients had not accrued damage at the time of death, suggesting a causal relationship between these two variables. Merok *et al*. (54) showed that damage accrual occurs linearly as a function of time over the first 10 years of disease and then plateaus. While a weighted average SLEDAI score (WAS) was associated with persistent disease activity and increased damage accrual, damage accrual was not shown to be an independent risk factor for mortality either by univariate analysis or by a Cox regression model. Furthermore, Chambers *et al*. (80) found that SLE patients had a tendency to develop additional autoimmune diseases and that patients with coexistent autoimmune disease accrued more damage than did patients with SLE alone. They further postulated that the combination of autoimmune pathology predisposed patients to increased mortality. In patients with acute, severe disease, both disease activity (by SLEDAI and SLAM) and damage (by SDI) were associated with poor outcomes (46). Thus, both disease activity and accrual of damage affect mortality.

Many centers have studied the relationship between laboratory markers and mortality in SLE. Ramos-Casals *et al*. (41) prospectively evaluated complement levels in SLE and antiphospholipid syndrome (APS) patients and found that, although hypocomplementemia was associated with accumulated hospitalizations, there was no correlation with survival at 5 years. Conversely, Kasitanon *et al*. (2) found that low complement activity during the first year after diagnosis was associated with worse survival in SLE. In a Puerto Rican SLE population, Vilá *et al*. (34) found that the presence of anti-dsDNA, anti-Smith, and anti-Ro autoantibodies was associated with higher SDI scores. Although that study did not specifically address long-term outcomes, these findings might suggest an association of damage accrual and increased mortality rates in patients with these autoantibodies. Other groups have studied serologic markers, including anti-dsDNA, ANA, anti-Smith, anti-Ro, anti-La, anti-RNP, lupus anticoagulant, and anti-cardiolipin antibodies, but there is an overall lack of consensus about possible associations of these markers and mortality (2, 6, 30, 31, 34, 56, 57). Regression analysis showed that marked lymphopenia (<500 per mm^3) and moderate lymphopenia (500-999 per mm^3) were independently associated with higher SLAM scores, Physician Global Assessment (PGA), and SLICC/ACR-Damage Index scores (56). Thrombocytopenia was also found to be an independent risk factor for mortality (58).

Krishnan (45) studied mortality in hospitalized SLE patients in the US Nationwide Inpatient Sample from 1998 to 2002. Not only are hospitalizations costly, about US $10,000 per incident, but 1 in 30 ended in death. In a multivariate analysis, socioeconomic factors, such as private health insurance and a higher income category, were also factors in determining a favorable outcome.

Several other studies specifically examined outcomes in SLE patients admitted to a critical care setting. Alzeer

et al. (42) studied a population of Saudi Arabian SLE patients admitted to an ICU setting (n=48). They found an overall mortality of 29% in their patient population; an APACHE II score >20, poor health status, thrombocytopenia associated with sepsis/DIC, and multiorgan dysfunction were correlated with poorer outcomes in the ICU (42). Whitelaw *et al*. (43) retrospectively analyzed clinical data from South African SLE patients admitted to the ICU from 1992 to 1999 (n=14). The mortality in this female patient population of mixed race was a dismal 79%, with the majority of deaths occurring from either SLE flare (especially ARF secondary to lupus nephritis) or sepsis. Finally, Hsu *et al*. (44) found a mortality rate of 47% among Taiwanese SLE patients in the ICU (n=51). Multivariate logistic regression analysis revealed an association of gastrointestinal bleeding, intracranial hemorrhage, and septic shock with an increased likelihood of death. Unlike Alzeer *et al*., they found no association between APACHE II scores and mortality. Although these studies were relatively small and involved varied patient populations in different geographic locations, the results were universally poor, with mortality rates ranging from 30% to 79%.

Specific causes of mortality in SLE

Accelerated atherosclerosis and coronary artery disease (CAD)

Over the years, cardiovascular disease, infection, malignancy, and active disease have all been identified as specific causes of death in SLE populations. Premature atherosclerosis is a major concern in SLE (60, 61). The pathogenesis of CAD in SLE is complex and related not only to inflammation, but to endothelial damage as well. Recent work by Hahn and McMahon has offered insights into the mechanisms of accelerated atherosclerosis in SLE (82, 83).

Women with SLE have a particularly high risk of CAD. Manzi *et al*. (64) showed a 50-fold increase for myocardial infarction in women with SLE when compared to age- and sex-matched controls. In addition, SLE patients also have a 2- to 10-fold increased risk of stroke (65). Although all cause mortality in SLE has declined, the risk of death due to cardiovascular disease remains essentially unchanged (62) with an unadjusted SMR of 1.7 (1).

Atherosclerosis in SLE is associated with traditional risk factors such as hypertension, hypercholesterolemia, smoking, diabetes mellitus, obesity, and family history. In fact, several studies have shown that SLE patients have an increased prevalence of traditional risk factors such as obesity; sedentary lifestyle; hypercholesterolemia with low HDL, high VLDL and triglycerides; hypertension; and diabetes mellitus (86-89). But these variables cannot entirely account for the prevalence of CAD in SLE. Other nontraditional factors such as disease activity (renal disease in particular) and duration, exposure to steroids as well as antiphospholipid antibodies, homocysteine levels, and elevated CRP may also contribute to CAD (59, 61, 63, 88, 94).

Infection

Infection is a common cause of death in SLE (4, 6, 46, 69, 70). In the study by Cervera *et al*. (7), infection was one of the most common causes of death during the first 5 years of follow up, with the majority of infections originating in pulmonary, abdominal and urinary sites. One study found that infection was associated with a standardized mortality ratio (SMR) of 5 (1)! The increased risk of infection has been associated with the use of immunosuppressants (1) but may also represent an innate inability of the SLE immune system to ward off infectious agents effectively.

Malignancy

A multitude of cancers have been reported in SLE. There does seem to be an association between SLE and the overall development of a malignancy (1, 6, 7, 26). Using a large international cohort, Bernatsky *et al*. (72) determined that SLE patients had a slightly increased risk of cancer overall, but the risk of hematologic malignancies and lung cancer was more pronounced (standardized incidence ratio of 2.75 for hematologic and 1.37 for lung cancer). In another study by the same authors (1), the standardized mortality ratios for all malignancy, all hematologic cancer, non-Hodgkin's lymphoma, and lung cancer were 0.8, 2.1, 2.8, and 2.3 respectively. Other research has shown a link between SLE and Hodgkin's and non-Hodgkin's lymphoma (74-76) as well as lung cancer (73), but it is unclear if these associations are due to disease, use of immunosuppressants, traditional risk factors such as smoking, or a combination of all three.

Most studies have not shown a strong association of cancer and the use of immunosuppressants (4, 7). Bernatsky *et al*. (71) did not relate prior use of immunosuppressants (cyclophosphamide, azathioprine, or methotrexate) to overall cancer risk but suggested that exposure to these agents may be related to hematologic malignancies. Lung cancer was not associated with immunosuppressant use but was more commonly associated with smoking (71, 73).

It has been noted that SLE patients have an increased incidence of cervical dysplasia compared with the general population (97, 99, 100) and that this may be related to the use of immunosuppressants such as cyclophosphamide, azathioprine, and methotrexate (98).

Active disease

Lastly, active SLE itself is directly responsible for increased mortality (6, 7) with a standardized mortality ratio of about 3 (25). Nossent *et al*. (4) showed that at the time of death, 70% of patients had active disease by ECLAM, and 52% had active disease by SLEDAI, suggesting that active disease contributed to mortality. This study noted higher ECLAM and SLEDAI scores were associated with early death, while higher SLICC-DI scores were related to late deaths. Renal involvement is commonly seen in SLE patients, especially among minority populations, and is associated with significantly increased mortality (2, 69, 79). Hemolytic anemia, although not necessarily the cause of death, is associated with a 2-fold increase in mortality (2). This can be a difficult aspect of mortality to quantify as SLE is a multiorgan disease and many systems may contribute to mortality, often simultaneously.

Prevention

Given the increased risks from CAD and malignancy, how then should the practicing physician attempt to minimize these risks in SLE patients? Disease activity must be managed appropriately to avoid long-term sequelae leading to mortality. In order to prevent CAD, treating physicians must be vigilant in assessing and treating all modifiable traditional risk factors (93) such as hypertension, obesity, smoking cessation, and diabetes. The role of aspirin and statin therapy remains unclear. Statins are known to have antiinflammatory effects and have shown some benefit in rheumatoid arthritis (85) and in a murine model of SLE (84). These beneficial effects were not conclusively shown in SLE patients, though (67). Other studies have also suggested the potential benefits of aspirin therapy (66, 96) in preventing cardiovascular events, although one study did not show any benefit in patients with persistently positive antiphospholipid levels without APS (68). Considering the evidence for the role of accelerated atherosclerosis and cardiovascular disease in SLE, it is recommended that all modifiable CAD risk factors be treated aggressively. Although disease-specific goals for management of these comorbidities have been suggested (96), there is a clear need for large-scale prospective studies to help clinicians better identify appropriate treatment goals (95) in the SLE population.

Considering the aforementioned relationship between various malignancies and SLE, routine cancer screening must be an integral part of routine care. Unfortunately, this may not be the case. Bernatsky *et al*. (101) showed that routine cancer screening was often overlooked, with a consistently lower percentage of patients reporting mammogram, fecal occult blood check, and Pap testing compared to matched controls in the general population. As previously noted, there is an increased risk of cervical dysplasia in SLE. In addition to annual pap testing, the recently FDA-approved quadrivalent human papillomavirus vaccine (Gardasil/Merck), has been shown to reduce cervical neoplasia related to known oncogenic HPV subtypes in certain populations (102-104). Although there are no studies specifically related to efficacy in SLE populations, this vaccine should be discussed with patients and their gynecologists as a potential means of cancer prevention.

Novel therapeutics are currently being evaluated and may enter into the SLE armamentarium over time. However, recent studies have shown that hydroxychloroquine, a time-tested treatment traditionally prescribed for mild to moderate disease manifestations, has numerous potential benefits in SLE. Previous studies have shown that antimalarial agents lower total cholesterol, LDL cholesterol, and triglycerides, and increase HDL cholesterol (88, 90, 91). Hydroxychloroquine may also help prevent thrombosis. Espinola *et al*. (92) showed that hydroxychloroquine reversed platelet activation induced by antiphospholipid antibodies. In a univariate analysis, Ho *et al*. (105) suggested a protective effect of hydroxychloroquine in preventing thrombotic events. Ruiz-Irastorza *et al*. (106) suggested a protective effect of antimalarials against the development of malignancy. In addition, hydroxychloroquine has been associated with long-term benefits. Using the SLAM and SLICC/ACR Damage Index as damage indices, the study by Fessler *et al*. (107) showed that there was less damage accrual in patients using hydroxychloroquine. Finally, and perhaps most significantly, two recent studies revealed that hydroxychloroquine also may have an overall protective effect on survival (77, 78). Considering the many benefits of hydroxychloroquine and its limited toxicity, physicians should discuss this treatment option with each of their SLE patients.

Conclusions

Despite many advances in diagnosis and therapy, increased mortality remains part of the natural history of SLE. SLE patients still have 2 to 5 times the risk of death compared with the general population. In industrialized countries, the survival rates in the first 10 years range from approximately 92% to 98%. This still translates to a 2% to 8% chance of death within the first decade. But there is hope! Clearly, there has been a dramatic increase in survival rates over the last half century. Even over the course of the last 20 years, mortality rates have improved. In addition to focusing on the pathogenesis of disease and the development of novel SLE therapies, additional research should address the most appropriate management of the many comorbid conditions contributing to mortality. This is especially important in terms of accelerated atherosclerosis and CAD. The management of patients with SLE is undoubtedly complex and fraught with numerous pitfalls and complications. Despite the complexity of the disease itself, physicians must maintain a focus on routine care. Screening and prevention of likely complications play a particularly important role in such a susceptible population of patients. As we learn to better treat complications of SLE and its comorbid conditions, survival should continue to improve over the next decades as well.

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