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ORIGINAL ARTICLE

Death causes and pathogens analysis of systemic lupus erythematosus during the past 26 years

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Abstract Different causes of mortality have been described over different decades followed by description of pathogens identified from infective episodes that led to death. A retrospective review was performed in 3,831 hospitalized systemic lupus erythematosus (SLE) patients in Peking Union Medical College Hospital from January 1986 to April 2012. The primary causes of death were identified, and the constituent ratio of specific death causes during different periods was compared. Among 3,831 hospitalized SLE patients, 268 patients died, accounting for 7.0 %. No significant difference of death rate was found between men and women, $P=0.404$. The three most frequent death causes according to decade were as follows: for 1986–1995, renal involvement, lupus encephalopathy, and infections; for 1996–2005, infections, lupus encephalopathy, and renal involvement; and for 2006–2012, infections, lupus encephalopathy, and pulmonary hypertension. Certain types of deaths, primarily related to lupus activity, have decreased over time, whereas infections, often attributed to the use of corticosteroid and immunosuppressant medications, have increased gradually and changed to the most frequent death causes of SLE. Early mortality (<3 years) occurred more commonly in lupus encephalopathy, while late death (>3 years) happened more frequently in renal involvement, pulmonary artery hypertension, cardiovascular events, and cancer. In SLE death cases mainly dying from infection, mixed infections were more frequent than single pathogen infection (60.5 vs. 39.5 %), including common bacteria, fungal infection, and cytomegalovirus. *Aspergillus fumigatus* and *Pneumocystis carinii* were the two most commonly infected pathogens, and *Cytomegalovirus* was a frequent pathogen of mixed infection. Aggressive therapy has effectively reduced the mortality related to disease activity but also was associated with life-threatening infections. Mixed and fungal infection should be considered when SLE patients have severe infection.

Keywords Death causes · Infection · Systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease characterized by the presence of multiple autoantibodies and various clinical features, predominately affecting women. It has been reported that active SLE, infection, atherosclerotic cardiovascular disease, and malignancy are the most common death causes among SLE patients [1–5].

In the past decades, the survival rate of SLE patients has been greatly improved due to earlier diagnosis, inclusion of milder cases, and administration of high-dose glucocorticoid and other cytotoxic/immunosuppressive agents. With the more intensive schemes of treatment on SLE active disease

manifestation, the causes of death observed in patients with SLE in recent years are different from those reported in the past. Currently, the most frequent causes of death in patients with SLE have changed to infections [1, 3–5].

The aim of this study was to investigate the major death causes change in SLE patients during the past 26 years. We especially focused our attention on the pathogens of life-threatening infection.

Patients and methods

Patients

A retrospective medical records review was performed in 3,831 lupus patients hospitalized in Peking Union Medical College Hospital from January 1986 to April 2012. The clinical data were systematically retrieved over these decades. All lupus patients satisfied the diagnostic criteria of the American College of Rheumatology in 1982 or 1999.

Death causes

Causes of death were ascertained by review of case records, by discussion with the attending physician and when available, postmortem examination, in which the number of deaths were 242 and 26 cases, respectively. The main clinical or pathological process resulting in death were recorded as the primary causes of death, which were directly responsible for death, including infections, lupus encephalopathy, renal involvement, severe pulmonary hypertension, and diffuse alveolar hemorrhage, etc. The primary death causes were grouped under the following categories: those resulting from SLE and/or treatment-related morbidity, such as infection, malignancies, cardiovascular complications, etc.; those related to SLE activity, such as respiratory causes, renal lesions, encephalopathy, intestinal vasculitis, etc.; and those from unrelated causes. If SLE patients did not have severe organ function damage related to SLE disease activity, and they died directly from severe infection, probably resulting from SLE treatment, their death causes were defined as infection.

Statistical methods

The categorical data were presented as numbers (in percent) and the continuous variables as mean and standard deviation (SD) or median and interquartile range, depending on the data distribution type. The chi-square test was used to analyze the categorical variables; a value of $P<0.05$ was considered statistically significant. Statistics were performed using the SPSS statistical package version 16.0.

Results

Demographic characteristics

Among 3,831 hospitalized SLE patients in Peking Union Medical Hospital during the past 26 years, including 3,341 females and 490 males, 268 patients died, accounting for 7.0 %. In the 268 dead cases, 238 (88.8 %) were women, accounting for 7.2 % in the 3,341 female SLE patients and 30 (11.2 %) were men, accounting for 6.2 % in the 490 male SLE patients. There was no significant difference of death rate between men and women, $P=0.404$. The mean age at onset of SLE were 31.4± 14.0(7~70)years. The mean age at the time of death were 37.5± 14.5(10~74)years. The mean duration of disease from disease onset to death were 6.01±6.70(0.02~34)years.

Major death causes of SLE

Table 1 shows the major cause of death according to the ICD-9 codes. The principal causes of death were, in descending order of frequency, infections (37.3 %), lupus encephalopathy (18.7 %),

Table 1 Causes of death in the SLE patients during the past 26 years

Causes of death	Number (%)
Events caused by SLE disease activity	138 (51.5)
Lupus encephalopathy	50 (18.7)
Diffuse alveolar hemorrhage	13 (4.9)
Severe pulmonary hypertension	13 (4.9)
Interstitial pneumonia	7 (2.6)
Hematological abnormality	5 (1.9)
Intestinal vasculitis	3 (1.1)
Renal involvement	36 (13.4)
Acute pulmonary embolism	2 (0.7)
Myocarditis	2 (0.7)
Multiple system organ Failure*	6 (2.2)
Catastrophic antiphospholipid syndrome	1 (0.4)
Events caused by complications of the disease and/or its treatment but not disease activity	126 (47.0)
Infections	101 (37.3)
Gastrointestinal bleeding	5 (1.9)
Cancer	6 (2.2)
hepatic complication	2 (0.7)
Acute cardiovascular events	10 (3.7)
Myeloproliferative dysfunction caused by cytotoxic drugs	2 (0.7)
Events unrelated to SLE disease	4 (1.5)
Suicide	1 (0.4)
Asphyxia caused by jugular venous catheter hemorrhage	1 (0.4)
Intracerebral hemorrhage caused by hemodialysis	2 (0.7)
Total	268

*Multiple system organ failure was defined as at least three organs being involved simultaneously and led to organ function failure

renal involvement (13.4 %), severe pulmonary hypertension (4.9 %), and diffuse alveolar hemorrhage (4.9 %) etc.

The final event was caused by active disease manifestations in 138 patients (51.5 %). There were 36 SLE patients dying from end-stage renal failure, including 19 cases of acute renal dysfunction and 17 cases with chronic renal failure. Hematological abnormality included three patients with bleeding caused by thrombocytopenia and severe infection and one patient caused by agranulocytosis. Three patients died from intestinal vasculitis, who developed intestinal obstruction, necrosis, or/and perforation, respectively.

Five patients who died of gastrointestinal bleeding had taken cortisone and NSAIDs for a long time, despite correct gastric protection.

Constituent ratio of specific causes of death

Infections, lupus encephalopathy, and renal involvement were the most common causes of death among patients with SLE during the past 26 years, followed by severe pulmonary hypertension, and diffuse alveolar hemorrhage. However, there was a great change on constituent ratio of various causes of death across the different time periods (Table 2, Fig. 1).

From 1986 to 1990, renal involvement was the first common death cause, accounting for 31.4 % (11/35) in death cases and 4.0 % (11/274) in hospitalized SLE patients, whereas only three patients died from renal involvement during 2006 to 2012. Thus, the third common cause of SLE from 2006 to 2012 was severe pulmonary hypertension but not renal lesions, which accounted for 9.5 % (8/84) in death cases and 0.5 % (8/1,431) in hospitalized SLE patients. With the increase of severe infection in SLE patients, infections have changed to the first common death cause of SLE from 1996 to today.

The relationship between SLE death causes and other factors

Patient groups were characterized by the following: sex, age, or SLE duration. There was significant difference of death causes between male and female patients. Male accounted for 50.0 % of patients dying from cardiovascular events, whereas females were markedly more often seen than males in death cases of other causes, including infection, lupus encephalopathy, renal involvement, pulmonary hypertension, and diffuse alveolar hemorrhage etc., accounting for 87.6, 95.3, 80.6, 100, and 83.3 %, respectively.

The median of SLE duration from onset to death was 2 (quartile range 0.5~6), 5 (quartile range 1.3~13.5), 4.5 (quartile range 0.5~10.5), and 5 years (quartile range 4~10) for patients dying mainly from lupus encephalopathy, renal involvement, diffuse alveolar hemorrhage, and severe pulmonary hypertension, respectively, whereas the median of SLE duration was 3.8 (quartile range 0.8~9.3), 4 (quartile range 2.0~10.0), and 28.5 years (quartile range 24.0~33.0) for patients dying from infection, acute cardiovascular events, and cancer. The causes of early death differed significantly from those that caused late death (shown in Table 3). Early death due to renal involvement or pulmonary artery hypertension is now rare, while death caused by lupus encephalopathy occurred more commonly in early stage (<3 years). Late death (>3 years) took place more frequently in patients dying from cardiovascular events and cancer (Table 3).

The median of age at death was 38.5 (quartile range 24.8~46.0), 33.0 (quartile range 26.8~47.3), 23.0 (quartile range 17.3~47.3), and 29 years (quartile range 27~39) for patients dying mainly from lupus encephalopathy, renal involvement, diffuse alveolar hemorrhage, and severe pulmonary hypertension, respectively, whereas the median of age at death was 40.0 (quartile range 26.0~50.0), 59.0 (quartile range 49.0~64.0), and 56.0 years (quartile range 53.0~63.0) for patients dying from infection, acute cardiovascular events, and cancer.

Infection site of SLE death cases

In the present study, the most common infection site was lung, accounting for 64.9 % in death cases dying mainly from infections. In addition, sepsis, peritonitis, and meningitis were the frequent infection sites in death cases (Table 4).

Table 2 Constituent ratio and death rate of specific death causes in SLE during past 26 years

Death causes	1986–1990 cases (%)	1991–1995 cases (%)	1996–2000 cases (%)	2001–2005 cases (%)	2006–2012 cases (%)	*P* Anova	Total cases (%)
Infections	9 (3.28)	7 (2.42)	18 (2.96)	22 (1.85)	45 (3.05)	0.645	101 (2.64)
Lupus encephalopathy	9 (3.28)	7 (2.42)	12 (1.97)	13 (1.10)	9 (0.61)	0.000*	50 (1.31)
Renal involvement	11 (4.01)	8 (2.77)	9 (1.48)	5 (0.42)	3 (0.20)	0.000*	36 (0.94)
Death cases of the same period	35 (12.7)	29 (10.0)	57 (9.4)	63 (5.3)	84 (5.7)	0.013*	268 (7.0)
Hospitalized patients of the same period	274	289	609	1,186	1,473		3,831

$p<0.05$

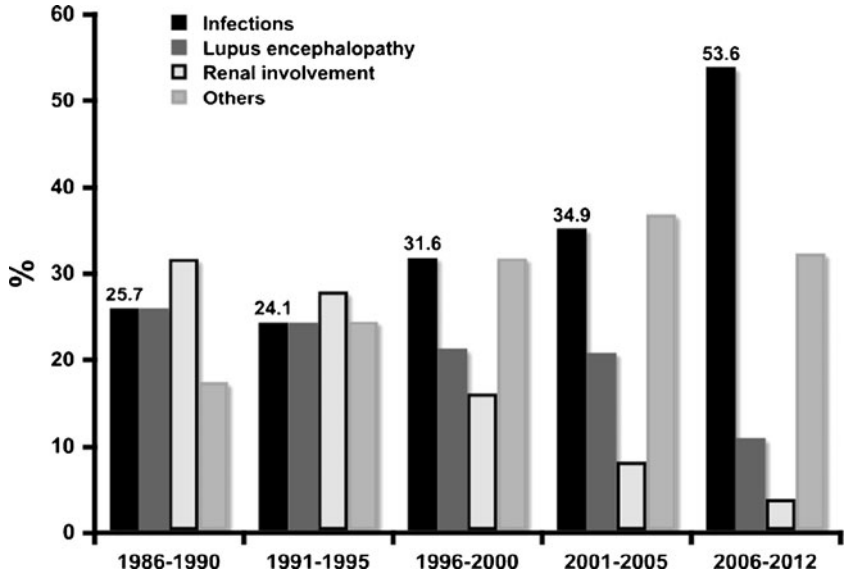

Fig. 1 Constituent ratio change of specific death causes in SLE during past 26 years

Pathogens of pulmonary infection in SLE death cases

Among 66 cases dying from pulmonary infection during January 2006 to March 2012, there were 39 patients infected with definite pathogens, including 16 cases of single pathogen, and 23 cases of mixed infections, accounting for 39.5 and 60.5 %, respectively.

The most frequent causative pathogen of single pathogen infection was fungal infection ($n=10$, 62.5 %), followed by common bacterial infection ($n=4$, 25.0 %), and tuberculosis infection ($n=2$, 12.5 %) (Table 5). *Pneumocystis carinii* and *Aspergillus fumigates* were the most common pathogens in single pathogen infection. Mixed infection included common bacteria, fungal infection, and cytomegalovirus (Table 6).

Pathogens of extrapulmonary infection in SLE death cases

Table 7 shows pathogens of extrapulmonary infection in SLE death cases. Pathogens diagnosis of disseminated fungal infection, blood stream infection, and tuberculous peritonitis were based on blood culture and clinical manifestations. Tubercular meningitis was proved by cerebrospinal fluid test and

Table 3 Causes of death in SLE patients

Cause of death	^3 years (%)	>3 years (%)	Total	P
Events caused by SLE disease activity	70 (50.7)	68 (49.3)	138	0.932
Lupus encephalopathy	32 (64.0)	18 (36.0)	50	0.065
Renal involvement	12 (33.3)	24 (66.7)	36	0.065
Diffuse alveolar hemorrhage	7 (53.8)	6 (46.2)	13	1.000
Severe pulmonary hypertension	2 (15.4)	11 (84.6)	13	0.022*
Events caused by complications of the disease and/or its treatment but not disease activity	62 (49.2)	64 (50.8)	126	0.929
Infections	49 (48.5)	52 (51.5)	101	0.842
Acute cardiovascular events	3 (30.0)	7 (70.0)	10	0.227
Cancer	0 (0.0)	6 (100.0)	6	0.031*
Events unrelated to SLE disease	0 (0.0)	4 (100.0)	4	0.125
Total	132 (49.3)	136 (50.7)	268	0.855

*$p<0.05$

Table 4 Infection sites of SLE death cases

	Number	%
Infection	101	37.7
Pulmonary infection	66	24.6
Generalized infection	19	7.1
Blood stream infection	8	3.0
Purulent peritonitis	2	0.7
Purulent meningitis	4	1.5
The left lower limb gangrene	1	0.4
Extra-pulmonary tuberculosis	4	1.5
Disseminated fungal infection	1	0.4
Chickenpox	1	0.4
Urinary tract infection	1	0.4
Brain abscess	1	0.4
Fungal endocarditis	1	0.4
Non-infection	167	62.3

Table 5 Single pathogen of pulmonary infection in SLE death cases from 2006 to 2012

Pulmonary infection	Number
Fungal infection	10
Pneumocystis Carinii	4
A. fumigatus	3
Fusarium	1
Tropical *Candida albicans* (C. tropical)	1
Cryptococcus	1
Common bacterial infection	4
Methicillin-resistant Staphylococcus aureus (*MRSA*)	2
Klebsiella pneumonia (*K. pneumonia*)	1
Pseudomonas aeruginosa (*P. aeruginosa*)	1
Tuberculosis	2

magnetic resonance imaging, while intracerebral abscess of *Nocardiosis* was confirmed by autopsy.

Table 6 Pathogens of pulmonary mixed infection in SLE death cases from 2006 to 2012

Mixed infection	23
Common bacteria	3
Acinetobacter baumannii (*A. baumannii*) + *Paeruginosa*	1
Enterococcus faecium + *Escherichia coli* (*E. coli*)	1
P. aeruginosa + *K. pneumoniae*	1
Fungal infection	3
Pneumocystis carinii + *Aspergillus flavus*	1
A. fumigatus + *Candida albicans* (*C. albicans*)	2
Fungal mixed with common bacterial infections	11
Enterococcus faecium + *C. tropical* + *Biomphalaria*	1
A. fumigatus + *Terreus* + *A. baumannii*	1
A. fumigatus + *Enterococcus faecalis* + *Enterobacter cloacae*	1
Paeruginosa + *A. baumannii* + *C. tropical*	1
A. fumigatus + *E. coli*	1
MRSA + *C. albicans*	1
K. pneumoniae + *C. tropical*	1
K. pneumoniae + *Candida krusei* + *C. tropical*	1
A. fumigatus + *Aspergillus flavus* + *E. coli* + *A. baumannii*	1
Pneumocystis carinii + *A. baumannii*	1
Pneumocystis carinii + *MRSA*	1
Cytomegalovirus (CMV) + fungus/bacteria	6
A. baumannii + *CMV*	1
A. fumigatus + *CMV*	1
Aspergillus flavus + *CMV*	1
Klebsiella pneumonia + *C. albicans* + *CMV*	1
Aspergillus flavus + *Pneumocystis carinii* + *A. baumannii* + *CMV*	1
MRSA + *CMV*	1

Table 7 Pathogens of extrapulmonary infection

Pathogens	Infection sites	Number
Aspergillus	Disseminated fungal infection	1
Common bacterial infection	Blood stream infection	9
MRSA (*2*), *Paeruginosa*, *A. baumannii* (*2*), *E. coli*, *Enterococcus* (*2*), *Salmonella*		
Nocardiosis	Intracerebral abscess	1
Mycobacterium	Tubercular meningitis	1
Tuberculosis	Tuberculous peritonitis	1

Discussion

The primary value of this study is its description of death causes change in lupus patients in a developing country. In previous studies, although aggressive therapy has effectively reduced the mortality related to disease activity, it has led to the occurrence of complications that can be related to disease itself or to almost unavoidable drug side effects, especially infections [1–8]. Iriya et al. reported that 58 % of Brazilian lupus patients had infections as the major cause of death after studying 113 autopsies [9].

Although a retrospective hospital based report on mortality remained inferior to a report of a cohort, the percentages reported in this study suggested that the death rate decreased gradually before 2005 (from 12.7 to 5.3 %), while it increased since then (from 5.3 to 5.7 %, $P=0.671$). In addition, there was a great change of constituent ratio of specific death causes in SLE patients during the past 26 years. It seems clear that certain types of deaths, primarily related to lupus activity, have decreased over time, whereas infections, often attributed to the use of corticosteroid and immunosuppressant medications, have increased gradually and changed to the most frequent death causes of SLE. From 1986 to 1995, death of SLE patients was most commonly caused by severe nephritis, whereas there were only three SLE patients dying from renal involvement during 2006 to 2012. In addition to aggressive therapy which has effectively reduced the mortality related to disease activity, the significant decline of death rate in lupus nephritis also attributed to renal replacement therapy, which was widely applied on patients with end-stage renal disease after 1995. Besides, lupus nephritis, other events caused by SLE disease activity, have also decreased markedly.

It has been reported that consequent to the advent of effective immunosuppressive treatment and the prolongation of patient survival, cardiovascular disease had emerged as an important long-term complication. Previous work has shown a very high incidence of cardiac events (specifically, myocardial infarction and angina) in SLE patients compared with the general population [10–12]. The role that corticosteroid therapy plays in the development of clinical and subclinical atherosclerosis has

become more evident [13]. In our study, we observed only ten death cases attributable to acute cardiovascular events caused by atherosclerosis, accounting for 3.7 % of death cases, despite the increasing frequency of cardiovascular events as cause of death in industrialized countries. It is worth noting that 50 % of the patients who died of cardiac events were males, whereas the female-to-male ratio for the death cases was 238:30.

In this study, half of deaths were the result of active disease manifestations, such as lupus encephalopathy, renal involvement, and diffuse alveolar hemorrhage, etc., including cases with low response to therapy or low compliance. Moreover, patients who died of active disease manifestations were much younger than those who died from infection, acute cardiovascular events, and cancer. Because SLE is a disease that commonly occurs before the age of 40 years, it is not surprising that the patients who died of active disease manifestations were young.

In previous report, early mortality, defined as a death occurring within 5 years of disease onset, is mainly related to disease activity or infections. Late mortality, occurring beyond 5 years disease duration, is frequently due to malignancy or cardiovascular disease [14, 15]. In our study, early death due to lupus encephalopathy occurred more commonly in early stage (<3 years), while late death (>3 years) happened more frequently in patients dying from cardiovascular events and cancer (Table 3).

Infections remained the most common immediate cause of death now. *Escherichia coli* and *Staphylococcus aureus* were the leading pathogens of bloodstream infections in SLE patients [16]. Invasive fungal disease is a life-threatening and opportunistic infection, usually occurring in the immunocompromised host [17]. In a previous study, *Cryptococcus neoformans* infection accounted for most fatalities in SLE patients with fungal infections [18]. It has also been reported that *Aspergillus* spp. infection is the most frequently indentified opportunistic invasive fungal infection in SLE patients, followed by *Cryptococcus* spp. and *Candida* spp. [19]. In the present study, we found that mixed infections were more frequent than single pathogen infection in SLE death cases (60.5 vs. 39.5 %). The most frequent causative pathogen of single pathogen infection was fungal infection, in which *P. carinii* was the most common pathogen, followed by *A. fumigatus*. Among 11 cases of fungal mixed with common bacterial infections, *A. fumigatus* and *P. carinii* were the two most commonly infected pathogens. Besides the common bacteria and fungi, *cytomegalovirus* was a frequent pathogen of mixed infection.

Consequently, adequate and prompt recognition and proper treatment of the infected patient are imperative, especially when patients receiving high doses of corticosteroids and immunosuppressive therapy. Early use of broad-spectrum antifungal therapy should be considered when SLE patients have severe infection.

Disclosures None.

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