Mortality and long-term survival prognostic factors of patients with systemic autoimmune diseases admitted to an intensive care unit: a retrospective study

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Abstract

Objectives

To determine mortality and long-term survival factors in patients with systemic autoimmune diseases (SAD) admitted to the intensive care unit (ICU).

Methods

Retrospective observational study including all consecutive patients with a diagnosis of any systemic autoimmune disease admitted to the medical ICU in a tertiary hospital between 1999 and 2007. Factors associated with reduced survival were identified by means of log rank test and backward stepwise Cox regression.

Results

Thirty-seven patients (26 females) were included with median age being 44.3 years (interquartilic range [IQR]: 31.3). Sixteen (43.2%) patients had systemic lupus erythematosus, 9 (24.3%) had systemic vasculitis, 4 (10.8%) had systemic sclerosis and 4 (10.8%) had primary antiphospholipid syndrome. The main reason for ICU admission was autoimmune disease flare-up in 20 (54.0%) patients, followed by infections in 12 (32.4%). Median APACHE II at admission was 17 (IQR 7). At the end of follow-up, 15 (40.5%) patients died, 10 (27%) during hospitalisation (7 in the ICU) and 5 after hospital discharge. Factors associated with reduced long-term survival were: APACHE II score ≥18 (HR 6.02, 95% CI 1.76–20.62), age <45 years (HR 6.54, 95% CI 1.84–23.29), presence of any previous chronic disease (HR 18.20, 95% CI 3.72–88.96), and increase of corticosteroid therapy during ICU stay (HR 22.87, 95% CI 4.31–121.30).

Conclusion

The long-term survival of patients with systemic autoimmune diseases admitted to the ICU was related with age, higher APACHE II score, previous chronic diseases, and an increase in corticosteroids dose when comparing with previous ICU admissions.

Key words

intensive care units, mortality, autoimmune diseases, systemic lupus erythematosus, antiphospholipid syndrome, vasculitis

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Introduction

Systemic autoimmune diseases (SAD) are a group of immune-mediated illnesses associated with high morbidity. In some patients, they may lead to devastating end-organ damage. Furthermore, corticosteroid and other immunosuppressive drugs required to treat these patients can be associated with complications (especially infections) that may cause severe organ dysfunction. Thus, admission to the intensive care unit (ICU) may be necessary as a result from disease flare-up or infection associated to immunosuppression.

The outcome of patients with systemic autoimmune diseases admitted to an ICU was previously analysed in several studies (1-16). They showed ICU and in-hospital mortality rates and identified different mortality predictor factors according to the systemic autoimmune disease – *i.e.* systemic lupus erythematosus (SLE) (1-5), necrotising vasculitis (6,7), systemic sclerosis (8), dermatomyositis (9), and rheumatoid arthritis (10-16). Among predictor factors influencing the survival of ICU patients, infection as a cause of ICU admission, previous health status, corticosteroid administration, and severity scores as Acute Physiology and Chronic Health Evaluation (APACHE II) score, are regularly identified. However, to our knowledge long-term predictors of outcome in these patients have been poorly studied (13, 15). The estimated 5-year survival rate ranged from 35% (13) to 69% (15). Only age over 60 years was a prognostic factor significantly associated with an increase in long-term mortality (15).

The main objective of our study was to describe a cohort of critically ill patients with systemic autoimmune diseases admitted to a medical ICU, to analyse their short and long-term survival at 1 and 3 years and identify which patient characteristics may influence this long-term prognosis.

Patients and methods

Patients

A retrospective observational descriptive study was performed. All the patients with any systemic autoimmune disease requiring admission to the medical ICU of the Hospital Clinic of Barcelona (Barcelona, Catalonia, Spain) from January 1999 to June 2007 were initially included in the study. In general, patients were admitted to ICU at demand, *i.e.* when the responsible physician thought that a specific patient needed critical care. In any case, there have not been any changes in admission criteria in our ICU in this period of time. The ICU register was used to identify any patient with a diagnosis of autoimmune disease. Only patients with the diagnosis of systemic autoimmune disease according to accepted criteria made prior to ICU admission or during hospitalisation were selected. For patients with SLE, systemic sclerosis, and vasculitis, we used the American College of Rheumatology criteria (17-19) whereas those with inflammatory myopathies were classified according to recent reviews (20, 21). The patients with antiphospholipid syndrome (APS) fulfilled the Sidney preliminary classification criteria (22). Patients with short-term irreversible disease and those with an ICU stay less than 48 hours were finally excluded. Eligible study patients were identified and data were collected retrospectively from ICU notes, physiological data charts, hospital notes, death certificates, and laboratory data. The protocol was approved by the institutional review board of the Hospital Clinic of Barcelona that allowed waivering the need for informed consent.

Data collection

Demographic data, previous chronic pathologies (chronic obstructive pulmonary disease, interstitial lung disease, heart failure, ischaemic heart disease, stroke, chronic renal failure, and nephrotic syndrome), diagnosis and duration of autoimmune disease, reason for ICU admission, and length of ICU stay were recorded. Clinical follow-up, the immunosuppressive treatment received six months before ICU admission, the mean corticosteroid dose in the last year and in the previous 3 months and one month, and corticosteroid dosage prior to ICU admission were also assessed.

The diagnoses for ICU admission were identified according to the following definitions: clinical infections were

defined according to the Centres for Diseases Control and Prevention criteria (23), autoimmune disease flare-up was defined as an exacerbation of the autoimmune disease condition, an episode of catastrophic APS was diagnosed according to accepted criteria (24); finally, we also considered as cause of ICU admission acute serious illness that were not directly related to the autoimmune process, including the adverse effect of drugs.

Clinical features on admission were obtained. Severe sepsis and septic shock were defined according to SCCM/ESICM/ACCP/ATS/SIS consensus conference (25). Respiratory failure was defined as PaO2 of less than 60 mmHg and/or the need for ventilatory support. Renal insufficiency was defined by a serum creatinine ≥150 mmol/L. Finally, the administration of immunosuppressive drugs or anticoagulation, and the need for supportive therapies (mechanical ventilation, renal replacement therapy or sympathomimetic amines) were also recorded.

Severity of illness at ICU admission and predicted in-hospital mortality were determined from the APACHE II score (26). The APACHE II score is a well validated and widely used tool for the assessment of severity of illness, weighted for age, sex, and previous morbidity. It was obtained from ICU charts, or, if absent, calculated from worst physiological data and laboratory tests in the first 24 hours from admission.

Occurrences of death during ICU and hospital stay were recorded, along with ICU and hospital discharge date. Long-term follow-up was ascertained from clinical records.

Data analyses

We studied long-term survival as survival time from the admission to ICU. Kaplan and Meier survival curves were calculated for clinical variables (previous chronic illness, diagnosis of autoimmune disease, physiological variables at ICU admission, diagnosis at ICU admission) and treatment (prior to and during ICU admission) and compared by means of log rank test. The variables identified by log rank test with $p<0.20$ were entered into a backward stepwise regression model, using the Cox proportional hazard model, to determine predictor factors associated with survival. Hazard ratio (HR) and 95% confidence intervals (95% CI) were reported. Differences among clinical groups were compared using the χ^2 test (categorical variables) and the Mann-Whitney U-test (quantitative variables). A *p*-value less than 0.05 was regarded as significant. Data are expressed as median (interquartilic range [IQR]). All analyses were performed using Statistical Package for Social Sciences (SPSS) programme version 12.0 (Chicago, IL).

Table I. Demographic and clinical characteristics of 37 patients with systemic autoimmune diseases admitted to the intensive care unit.

Gender (female)	26	(70.3%)
Age (years)	44.3	(31.3)
Systemic autoimmune disease		
Systemic lupus erythematosus (SLE)*	16	(43.2%)
Vasculitis	9	(24.3%)
Systemic sclerosis	4	(10.8%)
Primary antiphospholipid syndrome (APS)	4	(10.8%)
Primary Sjögren's syndrome†	3	(8.1%)
Dermatomyositis	1	(2.7%)
Time from diagnosis of systemic autoimmune disease to ICU admission (years)	4.5	(11.6)
Treatment received before ICU admission		
Corticosteroids	26	(70.3%)
Dosage in previous year (mg/day)	12	(45.0)
Dosage at ICU admission (mg/day)	8	(17.5)
Any immunosuppressant/immunomodulating agent‡	11	(29.7%)
Azathioprine	6	(16.2%)
Cyclophosphamide	4	(10.8%)
Mycophenolic acid	4	(10.8%)
Intravenous immunoglobulins	1	(2.7%)
Comorbid diseases		
Any comorbid condition	21	(56.8%)
Chronic renal failure	10	(27.0%)
Interstitial lung disease	7	(18.9%)
Nephrotic syndrome	7	(18.9%)
Stroke	4	(10.8%)
Ischaemic heart disease	3	(8.1%)
Chronic pulmonary obstructive disease	2	(5.4%)
Chronic heart failure	1	(2.7%)

*Six SLE patients had APS associated; †one patient with Sjögren's syndrome had APS associated; ‡referred as the use of any immunosupressant agent in the last six months before ICU admission. Quantitative variables are presented as median (interquartilic range).

Results

Thirty-nine patients, accounting for 51 ICU admissions, were identified as having a diagnosis of systemic autoimmune disease prior to ICU admission or during hospitalisation. Two patients having short uncomplicated postoperative admissions were excluded from the study. Finally, 37 patients with a total of 49 ICU admissions were included (5 patients were admitted twice, 2 patients three times and one patient four times), representing the 1.3% of the 2890 patients admitted to the ICU in the mentioned period.

General characteristics

Demographic and clinical characteristics of these patients are shown in Table I. Four (10.8%) patients were diagnosed of systemic autoimmune disease during hospitalisation. Fourteen (37.8%) patients had positive antiphospholid antibodies (lupus anticoagulant and/or anticardiolipin antibodies), but only eleven of them met diagnostic criteria for APS, 6 associated to SLE, 4 of primary APS, and one was diagnosed as having Sjögren's syndrome. Nine (24.3%) patients had a diagnosis of systemic vasculitis (cryoglobulinaemia, polyarteritis nodosa and leucocytoclastic vasculitis, two cases each, and there were single cases of Wegener's granulomatosis, microscopic polyangeitis, and giant cell arteritis).

Co-existing chronic diseases were present in 21 (56.8%) patients at ICU admission. The most frequent was chronic damage of autoimmune disease

in form of chronic renal failure, present in 10 (27.0%) patients (6 SLE, 2 primary APS, one systemic sclerosis, and one cryoglobulinaemia, respectively), followed by interstitial lung disease in 7 (18.9%) (3 systemic sclerosis, 2 SLE, one primary Sjögren's syndrome, and one dermatomyositis, respectively), and nephrotic syndrome in 7 (18.9%) (6 SLE and one cryoglobulinemia). In SLE patients with chronic renal failure or nephrotic syndrome, active lupus nephritis was rejected with renal biopsy. In addition, stroke present in 4 patients, myocardial infarction in 3, chronic pulmonary obstructive disease in 2, and chronic heart failure in one patient were the comorbidities not directly related with autoimmune disease.

Clinical characteristics, treatment and outcome of ICU admissions

Clinical features, treatment and outcome of the first time ICU admissions of the 37 patients are shown in Table II. The main primary diagnoses at ICU admission included classic autoimmune disease flare-up in 16 (43.2%) patients, four of them in form of catastrophic APS. The 7 SLE patients who were admitted to the ICU due to flare-up had an activity of disease of 12 (7) measured as SLEDAI (SLE disease activity index) activity score. In addition, four patients presented with a complication derived from autoimmune disease but not in form of classic flare-up. Specifically, two of them had systemic sclerosis and were admitted because of mesenteric ischaemia and respiratory insufficiency due to pulmonary hypertension. The remaining two patients suffered from lupus nephritis with renal insufficiency and secondary cardiac insufficiency, and from hemorrhagic shock due to thrombocytopenia in the context of APS (27), respectively. Twelve (32.4%) patients had an infection leading their admission to ICU. Five (13.5%) patients had an acute serious illness unrelated to autoimmune disease. Specifically, two patients had an adverse effect of drugs (paracetamol-induced hepatotoxicity and intravenous immunoglobulin-induced anaphylaxis, respectively) and the remaining three had a non-ST-segment elevation myocardial infarction, a diabetic ketoacidosis, and a perirenal hematoma complicating a kidney biopsy, respectively.

Table II. Clinical characteristics, treatment and outcome of the first time admission of 37 patients with systemic autoimmune diseases admitted to the intensive care unit.

Primary diagnosis for ICU admission	
Autoimmune disease flare	20 (54.0%)
Catastrophic antiphospholipid syndrome*	4 (10.8%)
Infection	12 (32.4%)
Acute serious illness unrelated to autoimmune disease	5 (13.5%)
Adverse effect of drugs*	2 (5.4%)
Clinical presentation at ICU admission	
Respiratory failure	23 (62.2%)
SLE 8, vasculitis 6, systemic sclerosis 4, APS 2, Sjögren's syndrome 2, dermatomyositis 1	
Acute renal failure	18 (48.6%)
SLE 8, vasculitis 4, APS 3, systemic sclerosis 2, Sjögren's syndrome 1	
Sepsis	14 (37.8%)
SLE 5, vasculitis 5, systemic sclerosis 3, Sjögren's syndrome 1	
Disseminated intravascular coagulation	4 (10.8%)
SLE 2, APS 2	
APACHE II	17 (7)
Supportive treatment	17 (45.9%)
Mechanical ventilation	13 (35.1%)
Vasopressor drugs	12 (32.4%)
Renal replacement therapy	4 (10.8%)
Administration of glucocorticoids	
No	6 (16.2%)
Higher dose than previously	18 (48.6%)
Same dose as previously	10 (27.0%)
Started glucocorticoid therapy in the ICU	3 (8.1%)
Administration of immunosuppressant/immunomodulating agents	12 (32.4%)
Plasma exchange	9 (24.3%)
Cyclophosphamide	8 (21.6%)
IVIg	8 (21.6%)
Rituximab	3 (8.1%)
Administration of anticoagulant drugs	10 (27%)
Patients with ICU readmission	8 (21.6%)
Length of ICU stay (days)	6 (6)
ICU mortality	7 (18.9%)
In-hospital mortality	10 (27.0%)

APS: antiphospholipid syndrome; ICU: intensive care unit; IVIg: intravenous immunoglobulins; SLE: systemic lupus erythematosus.
*Patients with catastrophic antiphospholipid syndrome are included as a part of the total of patients with autoimmune disease flare-ups. Patients with adverse effects are included as a part of the patients with acute illnesses unrelated to autoimmune disease.
Quantitative variables are presented as median (interquartilic range).

The 4 patients in whom systemic autoimmune disease was diagnosed during hospitalisation were admitted because of autoimmune disease flare-up. Furthermore, there was a trend towards autoimmune disease flare-up being a more frequent cause of ICU admission in those patients with a time from autoimmune disease diagnosis to ICU admission lower than 1 year (64.2% *vs.* 30.4%, p=0.086).

The median APACHE II score was 17 (IQR 7; range, 6–31). Length of ICU stay for first ICU admission was highly variable, with a median of 6 days (IQR 6, range, 0–49). The median length of hospital stay before ICU admission was 1 day (range 0–180).

On the whole series, 15 (40.5%) patients had died at the time of last follow-up on July 2007. Five (13.5%) patients died after hospital discharge. Median time from ICU admission to death was 1.1 months (range, 0–21). The mean (standard deviation) risk of hospital death, as calculated from APACHE II score, was 26.3% (15.5%). Hospital death rate was 27.0% (10/37), whereas ICU mortality rate was 18.9% (7/37). Five of these patients had SLE, one patient had primary APS and the other

had dermatomyositis. The main causes of ICU mortality were septic shock and multiorgan failure (3 cases each one) and alveolar haemorrhage. Interestingly, hospital death rate and ICU mortality of patients with non-rheumatic diseases admitted to the ICU within the same period were 7% and 15%, respectively, without significant differences with rheumatic disease patients. Unfortunately, we have not provided data of their long-term survival rate.

Eight (21.6%) patients suffered from 12 ICU readmissions. Eight of them were due to infections, two by complications derived from the underlying autoimmune disease (acute respiratory insufficiency due to interstitial lung disease and pulmonary hypertension, respectively), and the remaining due to a drug-induced renal toxicity and a postoperative course of bowel perforation. Hospital death rate of patients with ICU readmissions was 75% (6/8), whereas their ICU mortality rate was 12.5% (1/8). In the majority of them, the treating physicians in accordance with their relatives, decided to withdraw life-sustaining treatment. The septic shock was the leading cause of mortality in this group of patients.

When differences between survivors and non-survivors were analysed (Table III), we found that the median dosage ± IQR (mg/day) of corticosteroids in the year before the ICU admission was higher in non-survivors (12.0±52.0 mg/day *versus* 6.5±15.0 mg/day) (p=0.009). Conversely, we did not find differences in median dosage of corticosteroids in the 3 months (12.0±52.0 mg/day *versus* 10.0±22.5 mg/day) (p=0.381) and the month (12.0±50.0 mg/day *versus* 10.0±30.0 mg/day) (p=0.419) previous to ICU admission. Moreover, patients who died in ICU were more likely to need renal replacement therapy, to suffer from respiratory failure and to have an increase of corticosteroid therapy during ICU stay (p<0.05). Multivariable analysis identified renal replacement therapy (p=0.015; HR 7.3 95%CI 1.5–36.3) and a high median dosage of corticosteroids in the year before the ICU admission (p=0.02, HR 1.03 95%CI 1.002–1.08) as significant prognostic factors for in-ICU mortality.

Table III. Comparison of the characteristics between survivors and non-survivors patients with autoimmune diseases admitted to the intensive care unit.

	Non-survivors (n=7)	Survivors (n=30)	*p*-value
Sex (female)	6 (85.7%)	20 (66.7%)	NS
Age at ICU admission (years)	37.7 ± 14.9	49.8 ± 33.8	NS
Time from autoimmune disease diagnosis to ICU admission (days)	6.2 ± 18.4	4.5 ± 11.05	NS
Length stay in ICU	6.0 ± 22.0	5.5 ± 5.3	NS
APACHE score at ICU admission	19.0 ± 12.0	17.0 ± 7.5	NS
Dosage of corticosteroids in previous year (mg/day)	12.0 ± 52.0	6.5 ± 15.0	0.009
Increase of corticosteroid therapy during ICU admission	6 (85.7%)	12 (40.0%)	0.042
Immunosuppressive treatment in ICU			
Cyclophosphamide	2 (28.6%)	6 (20.0)	NS
Plasma exchange	3 (42.9%)	6 (20.0)	NS
IVIg	3 (42.9%)	5 (16.7)	NS
Supportive treatment in ICU	5 (71.4%)	12 (40)	NS
Mechanical ventilation	5 (71.4%)	8 (26.7)	NS
Vasopresor drugs	4 (57.1%)	8 (26.7)	NS
Renal replacement therapy	3 (42.9%)	1 (3.3)	0.016
Any previous comorbid disease	6 (85.7%)	15 (50.0)	NS
Primary diagnosis at ICU admission			
Flare-up of autoimmune disease	5 (71.4%)	15 (50.0%)	NS
Infection	2 (28.6%)	10 (33.3%)	NS
Clinical presentation at ICU admission			
Respiratory failure	7 (100%)	16 (53.3%)	0.031
Acute renal failure	5 (71.4%)	13 (43.3%)	NS
Sepsis	2 (28.6%)	12 (40.0%)	NS
Readmission at ICU	1 (14.3%)	6 (20.0%)	NS

ICU: intensive care unit; IVIg: intravenous immunoglobulins; NS: not significant.
Quantitative variables are presented as median (interquartilic range).

Long-term survival

The 1-year and 3-year survival rates from first ICU admission were 58.8% and 54.6%, respectively, with a median follow-up of 4.1 months (26.19). Eight patients (21.6%) were followed up for more than three years. In the multivariable analysis, APACHE II score ≥18 (HR 6.04, 95%CI 1.78–20.64), age below 45 years (HR 6.56, 95%CI 1.85–23.27), the presence of any chronic disease (HR 18.23, 95%CI 3.71–88.94) and an increase of corticosteroid therapy during ICU stay (HR 22.84 95%CI 4.33–121.32) were related to a lower long-term survival from ICU admission.

Discussion

Our study suggested that APACHE II score ≥18, age below 45 years, the presence of any chronic disease and an increase of corticosteroid therapy during ICU stay were related to a lower long-term survival from ICU admission among patients with autoimmune diseases. Moreover, the need for renal replacement therapy and a high median dosage of corticosteroids in the year before the ICU admission were identified as significant prognostic factors for in-ICU mortality of these patients.

There is a paucity of data on prognostic factors relating to critically ill patients with systemic autoimmune diseases compared to other illness. In studies focused on patients with different systemic autoimmune diseases (10-16), the ICU mortality rate ranges from 17% (10) to 56% (12). Our result (18.9%) is amongst the lowest recorded for these groups of patients. This fact may be a result of the improvement in the diagnostic and specific therapies in critically ill patients in recent years. Furthermore, the wide experience dealing with these patients from our department of autoimmune diseases and the ICU of our hospital identifying critical clinical situations may also explain, in part, this low mortality, similar to the expected in patients without autoimmune diseases. In this sense, the patients were prematurely admitted to the ICU as indicated by the short median length of hospital stays before ICU admission. Unfortunately, we were not able to study prog-

nostic factors for in-hospital mortality due to the low number of events.

In accordance with previous studies (10, 13, 15), the main causes of ICU admission were autoimmune disease flare-up and infections. The APACHE II score in our series is also similar to those previously reported. Interestingly, APACHE II-predicted in-hospital mortality was 26.3% for our cohort, and actual mortality was 27%. In other words, APACHE II may be a very accurate tool to estimate in-hospital mortality in patients with autoimmune diseases. Probably it reflects improved survival in these patients, with mortality rates approaching those of other ICU patients (15). In a recent retrospective study performed in patients with SLE admitted to the ICU, high APACHE score was an independent prognostic factor on in-ICU death in the multivariable analysis (28). However, it was unable to accurately predict in-ICU mortality (28).

In accordance with previous studies reporting these data, infection has been detected as the main cause of ICU mortality among patients with autoimmune diseases (13, 15). Regarding prognostic factors associated with in-ICU mortality, severity score, prior health condition, corticosteroids use, and ICU admission secondary to infectious complication were identified in previous studies (10, 11, 13-15). In our study, renal replacement therapy and the increase of corticosteroid therapy during ICU stay were the significant prognostic factors for in-ICU mortality. However, this later prognostic factor should be interpreted with caution. The value found for the 95% CI 1.002–1.08 indicates that a significant difference may exist but with an unlikely clinical relevance. The wide heterogeneity of the autoimmune diseases of the patients included in the previous studies and the different epidemiological design of these studies may explain these differences. Regarding renal replacement therapy, it is a well-known prognostic factor of ICU patients with acute renal failure (29).

To our knowledge, long-term predictors of outcome in these patients have been poorly studied (13, 15). The estimated 5-year survival rate ranged from 35% (13) to 69% (15). Only age over 60 years was a prognostic factor significantly associated with an increase in long-term mortality (15). In contrast with this data, we found that an APACHE II score ≥18 and age below 45 years were related to lower long-term survival from ICU admission. Taking into account that APACHE II score is a well validated tool for the assessment of severity of illness, weighted for age, sex and previous morbidity (26), with a similar APACHE II score value, younger patients will present with more severe clinical manifestations. This is relevant because half of patients in our series were under 45 years at ICU admission.

The most prominent shortcomings of the present study are its retrospective design, its sample size, and, in particular, the heterogeneity of the systemic autoimmune diseases from the patients finally included. First, we have to recognise that the low number of patients with specific diagnosis made it impossible to find prognostic factor for individual diseases and this is a major limitation of our study. In addition, there was no control data of SLE patients not admitted to the ICU. Second, although we have excluded patients that were admitted for less than 48 hours, the lack of specific inclusion criteria may lead to overestimate survival since older patients with comorbidities or those with a long course of disease may have been not considered for ICU admission in spite of the severity of their disease. However, the mean APACHE of patients admitted in this study showed that they were critically ill and there were no pre-emptive admissions. Despite these potential limitations, our study offers a realistic picture of patients with systemic autoimmune diseases admitted to the ICU.

The in-ICU mortality of patients with systemic autoimmune diseases in our hospital was amongst the lowest recorded for these groups of patients. The APACHE II score ≥18, age below 45 years, the presence of any chronic disease and an increase of corticosteroid therapy during ICU stay were related to a reduced long-term survival from ICU admission among patients with systemic autoimmune diseases.

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