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One-Year Outcome of Critically Ill Patients With Systemic Rheumatic Disease

A Multicenter Cohort Study

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BACKGROUND: Critically ill patients with systemic rheumatic disease (SRD) have benefited from better provision of rheumatic and critical care in recent years. Recent comprehensive data regarding in-hospital mortality rates and, most importantly, long-term outcomes are scarce.

RESEARCH QUESTION: The aim of this study was to assess short and long-term outcome of patients with SRD who were admitted to the ICU.

STUDY DESIGN AND METHODS: All records of patients with SRD who were admitted to ICU between 2006 and 2016 were reviewed. In-hospital and one-year mortality rates were assessed, and predictive factors of death were identified.

RESULTS: A total of 525 patients with SRD were included. Causes of admission were most frequently shock (40.8%) and acute respiratory failure (31.8%). Main diagnoses were infection (39%) and SRD flare-up (35%). In-hospital and one-year mortality rates were 30.5% and 37.7%, respectively. Predictive factors that were associated with in-hospital and one-year mortalities were, respectively, age, prior corticosteroid therapy, simplified acute physiology score II ≥ 50 , need for invasive mechanical ventilation, or need for renal replacement therapy. Knaus scale C or D and prior conventional disease modifying antirheumatic drug therapy was associated independently with death one-year after ICU admission.

INTERPRETATION: Critically ill patients with SRD had a fair outcome after an ICU stay. Increased age, prior corticosteroid therapy, and severity of critical illness were associated significantly with short- and long-term mortality rates. The one-year mortality rate was also associated with prior health status and conventional disease modifying antirheumatic drug therapy.

KEY WORDS: corticosteroid; ICU; outcome; systemic rheumatic disease

ABBREVIATIONS: DMARDs = disease modifying anti-rheumatic drugs; IQR = interquartile range; SAPS II = Simplified Acute Physiology Score II; SOFA = Sequential Organ Failure Assessment; SRD = systemic rheumatic disease

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Systemic rheumatic diseases (SRD), also known as connective tissue diseases, include various disorders, namely rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, primary Sjögren's syndrome, myositis, and systemic vasculitides.¹ All these diseases share common features such as difficult diagnosis, low incidence rate, multiorgan involvement, natural history of flare-up, treatment-induced immunosuppression, infectious, and cardiovascular complications. They remain associated with substantial morbidity and mortality rates.² Consequently, 10% to 25% of patients with SRD require a hospital admission during the course of their disease, and one-third of them will need ICU admission.²

Godeau et al,³ who studied 181 patients with SRD who were admitted to the ICU before 1990, reported a high in-hospital mortality rate (42.5%) and an estimated five-year survival of 69% for discharged patients. During

the last 20 years, survival in patients with SRD has improved due to advances in rheumatic care.⁴ At the same time, implementation of management bundles, especially for acute respiratory distress syndrome and septic shock, have also improved the outcome of ICU patients.^{5,6} Nonetheless, to date, it remains unclear whether the outcome of patients with SRD who have been admitted to the ICU has really changed. Most of the recent studies included a limited number of subjects and/or only investigated in-ICU deaths.⁷⁻¹¹ Obviously, recent comprehensive data regarding in-hospital deaths and, most importantly, long-term outcome of patients with SRD who were admitted to the ICU are scarce.

The aim of this study was therefore to assess short- and long-term outcome of patients with SRD who were admitted to an ICU in the era of advanced critical and rheumatic care and to determine prognostic factors.

Methods

Study Design and Settings

This observational retrospective cohort study was carried out from January 1, 2006, to December 31, 2016, in six French university hospital ICUs. An investigator on each site retrieved eligible patients by (1) screening SRD in ICU databases using the International Classification of Diseases, Tenth Revision, codes of SRD (in French: PMSI, programme de medicalisation des systemes d'information) and (2) reviewing all ICU discharge summaries. Patients were followed for at least one year after ICU admission. The Institutional Review Board of Montpellier University Hospital approved the study (No. 2018_IRB-MTP_07-12).

Patients

All consecutive patients with SRD who were admitted to ICUs during the study period were included. SRD was defined according to previously published classification criteria for each SRD.¹²⁻²⁶

Patients with SRD who were admitted to the ICU after scheduled surgery or trauma were excluded. Suicide attempts unrelated to neurologic involvement of SRD were excluded. We also excluded patients with SRD who had been treated for cancer with chemotherapy within a month before ICU admission. When a patient was admitted twice or more, only the first ICU admission was considered (Fig 1).

Data Collection

Demographic data and morbidities were collected retrospectively. Patients' prior health status was evaluated by the Knaus scale²⁷ and Charlson Comorbidity Index.²⁸ Characteristics and main treatment of SRD that included immunosuppressive therapy and corticosteroid (prednisone-equivalent daily-dose) within one month prior to ICU admission were also collected. Time elapsed from hospital to ICU admission was recorded and considered early if <24 hours. The main reason for ICU admission was classified as acute respiratory failure,⁶ septic shock and sepsis,⁵ other shock, acute kidney injury,²⁹ or neurologic dysfunction.³⁰ Severity of disease was assessed 24 hours after admission with the Simplified

Acute Physiology Score II (SAPS II)³¹ and Sequential Organ Failure Assessment (SOFA) score.³² Information on the treatment that was instituted during ICU stay was collected, as was occurrence of acute kidney injury,²⁹ severe acute respiratory distress syndrome,⁶ multidrug resistant bacteria colonization, or infection during ICU stay.

ICU diagnoses were classified into one of the following categories: infection, SRD flare-up, and other. All diagnoses (SRD, infection, and others) were confirmed retrospectively and blindly by two investigators (R. L. and M. P. de C.). Whenever a discrepancy between reviewers appeared, diagnosis was discussed with a third reviewer (K. K.) until a consensus was achieved.

Outcome

ICU and hospital length of stay and outcome that included ICU, in-hospital, and one-year deaths were collected. The survival state and date and cause of death, if applicable, were collected with the use of electronic medical records of each hospital or by phone call to the family doctor or the patient or his family. Death by limitation of care was informed. Predictive factors of hospital and one-year mortality rate were then identified.

Statistical Analysis

Categorical data are summarized as numbers and percentages; continuous data are given as mean with SD or median with interquartile range (IQR). Data of patients who died after one year after ICU admission and data of patients who are lost to follow up within one year after ICU admission are censored. Survival one year after ICU admission is presented with Kaplan-Meier curve. We performed a Cox regression model to identify variables that were associated with in-hospital death and one-year survival prognostic factors. For the multivariable analysis, we selected the variables according to their clinical relevance and statistical significance in univariate analysis ($P < .2$). Then a conditional stepwise regression was used to select the most informative variables to include in the multivariable analysis. The hypotheses of log-linearity and hazard proportionality were assessed respectively with the use of regression splines and Schoenfeld residues. In the case of non-log-linearity

(SAPS II, SOFA score), continuous covariates were discretized to the third quartile to select the most critically ill patients. Results of the Cox regression analysis are presented as hazard ratios and 95% CI.

All tests were two-tailed with a statistical significance level of 5%. The analyses are stratified by center and performed using R statistical software (version 3.3.5; Free Software Foundation).

Results

Population

Five hundred twenty-five patients (316 women; 60.2%) with a mean age of 56.1 years were included in the study (Fig 1). Mean Charlson index was at 3.7, and most patients had a Knaus scale of A or B (64.8%). The patients' characteristics are displayed in Table 1

Diagnosis of SRD was made during ICU stay in 75 patients (14.3%). In the remaining 450 patients, the median time elapsed from diagnosis to ICU admission

was 7.2 years (IQR, 2.6-16.3). SRD were mainly vasculitides (24.6%), systemic lupus erythematosus (20.8%), and rheumatoid arthritis (18.9%). Excluding joint and skin, SRD-related organ involvements were lung (35%), kidney (28.4%), and heart (18.9%). More than two-thirds of the patients (366; 69.7%) exhibited at least two organ involvements. A corticosteroid treatment with a median prednisone-equivalent daily dose of 10 mg (IQR, 5-30) was already instituted in 292 of the 450 patients (64.9%), and an immunosuppressive treatment (in association or not) was already instituted in 170 of them (37.8%). Immunosuppressive therapy

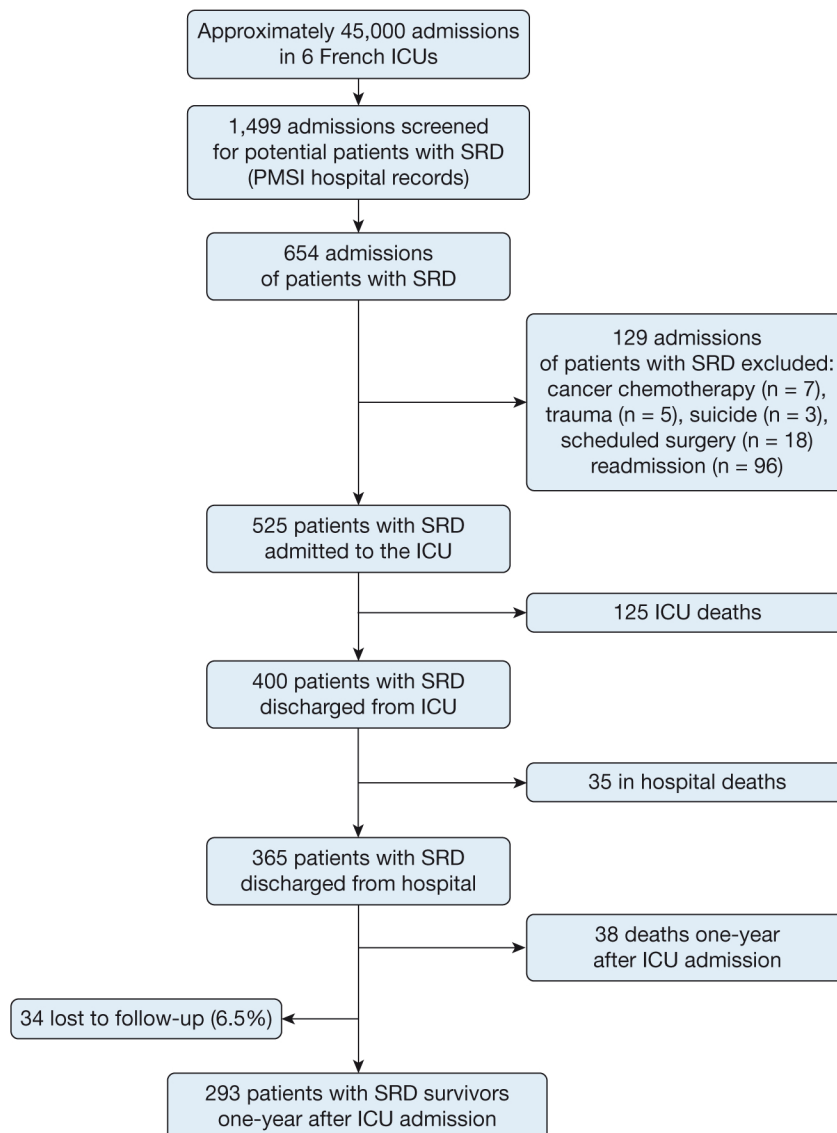


Figure 1 – Flow chart of the study population. SRD = systemic rheumatic disease.

TABLE 1] Characteristics of the Study Population, Reasons of ICU Admission, Clinical Variables at ICU Admission, and Organ Supports

Variables	Population (N = 525)
Characteristics	
Age, mean (SD), y	56.1 (18.6)
Female, No. (%)	316 (60.2)
Charlson comorbidity index, mean (SD)	3.7 (2.5)
Knaus scale, No. (%)	
A or B	340 (64.8)
C or D	185 (35.2)
SRD features	
SRD type,^a No. (%)	
Vasculitides ^b	129 (24.6)
Systemic lupus erythematosus	109 (20.8)
Rheumatoid arthritis	99 (18.9)
Systemic sclerosis	46 (8.8)
Myositis	27 (5.1)
Primary Sjogren's syndrome	13 (2.5)
Mixed connective tissue disease	8 (1.5)
Primary antiphospholipid syndrome	12 (2.3)
AA-amyloidosis	8 (1.5)
Miscellaneous ^c	74 (14.1)
SRD-related organ involvement, No. %	
Lung	184 (35.0)
Kidney	149 (28.4)
Heart	99 (18.9)
Nervous system	69 (13.1)
SRD diagnosed in ICU, No. (%)	75 (14.3)
SRD previously diagnosed, No. (%)	450 (85.7)
Time elapsed from SRD diagnosis to ICU admission, median [IQR], y	7.2 [2.6-16.3]
Rheumatic treatment	
None, No. (%)	120/450 (26.7)
Corticosteroids, No. (%)	292/450 (64.9)
Corticosteroid daily dose, median [IQR], mg	10.0 [5.0-30.0]
Immunosuppressive treatment, No. (%)	
Conventional DMARDs	134 (29.8)
Biologic DMARDs	51 (11.3)
IV immunoglobulins	11/450 (2.4)
ICU admission	
Reasons for admission	
Shock, No. (%)	214 (40.8)
Septic	97 (44.3)
Cardiogenic	77 (35.9)
Hypovolemic/hemorrhagic	33 (15.4)
Other	7 (3.3)
Acute respiratory failure, No. (%)	167 (31.8)
Neurologic dysfunction, No. (%)	60 (11.4)

(Continued)

TABLE 1] (Continued)

Variables	Population (N = 525)
Acute kidney injury, No. (%)	39 (7.4)
Sepsis/systemic inflammatory response syndrome, No. (%)	45 (8.6)
Scores, mean (SD)	
Simplified Acute Physiology Score II	45.5 (21.5)
Sequential Organ Failure Assessment	7.2 (4.7)
Glasgow	12 (4.5)
ICU management, No. (%)	
Vasoactive drugs	258 (49.1)
High flow nasal oxygen therapy	47 (8.9)
Mechanical ventilation	328 (61.3)
Noninvasive	100 (19.0)
Invasive	282 (53.7)
Renal replacement therapy	161 (30.6)
Extracorporeal membrane oxygenation	63 (12.0)
Venoarterial	39 (4.6)
Venovenous	24 (7.4)

Severity scores were calculated during the first 24 hours of ICU stay. DMARDs = disease modifying antirheumatic drugs (conventional: azathioprine, methotrexate, mycophenolate, anticalcineurin, cyclophosphamide, leflunomide, and biological: anti-tumor necrosis factor, tocilizumab, abatacept, anakinra, rituximab); IQR = interquartile range; SRD = systemic rheumatic diseases.

^aEach patient fulfilled SRD diseases classification criteria.

^b84 small vessels vasculitides (28 granulomatosis with polyangiitis, 11 eosinophilic granulomatosis with polyangiitis, 12 microscopic polyangiitis, 13 cryoglobulinemia, 9 Goodpasture diseases, 4 IgA vasculitides, 7 undifferentiated vasculitides), 6 medium vessels vasculitides (6 polyarteritis nodosa), 28 large vessels vasculitides (24 giant cell arteritis and 4 Takayasu arteritis) and 11 Behçet disease.

^c31 sarcoidosis, 30 spondylarthritis, 10 still disease, 3 relapsing polychondritis.

included mostly conventional disease-modifying antirheumatic drugs (DMARDs) in 78.8% and biologic DMARDs in 30%.

Reasons for ICU admission were shock (40.8%, mainly septic and cardiogenic) and acute respiratory failure (31.8%) (Table 1). Iatrogenic complications were involved in 14.9% of admissions (78 patients); 111 patients (21.1%) needed an early ICU admission.

Patients' Clinical Parameters at ICU Admission and Their ICU Management

As shown in Table 1, high mean SAPS II and SOFA scores at ICU admission underlined the severity of the patient's illnesses. During the ICU stay, 47 patients (8.9%) required high flow nasal oxygen therapy, and 328 patients (61.3%) required mechanical ventilation. Severe acute respiratory distress syndrome was diagnosed in 71 patients (13.5%) of which 23 required venovenous extracorporeal membrane oxygenation (4.4%). Also, 258 patients (49.1%) received vasoactive drugs, and 39 patients required venoarterial extracorporeal membrane oxygenation support for severe cardiogenic shock (7.4%). Acute kidney injury occurred in 232 patients, of whom 161 (69.4%) underwent renal replacement

therapy (Table 1). During the ICU stay, hospital-acquired infections occurred in 106 patients (20.1%), mostly ventilator-associated pneumonia. Seventy-one patients experienced a multidrug-resistant bacterial infection or carriage, and 42 patients had viral reactivation

ICU Diagnoses

Diagnoses of the event that led to ICU admission are displayed in Table 2. They were represented mainly by infection and SRD flare-up.

A diagnosis of SRD flare-up was determined in 184 patients (35%) that led to severe organ dysfunction that affected mainly lung (32.1%; 59 patients), heart (26.6%; 49 patients), and kidney (16.3%; 30 patients). SRD flare-up was treated with corticosteroids pulses in more than one-half of these patients (50.5%) associated or not with plasma exchange (28.8%), cyclophosphamide (24.5%), IV immunoglobulin therapy (9.8%), and rituximab (6.5%).

A severe infection was considered as a main diagnosis in 205 patients (39%) of whom more than one-half (105/205) experienced pneumonia. Infection was documented

TABLE 2] Diagnoses of the Acute Event That Led to ICU Admission and Outcomes

Variable	Population (N = 525), No. (%)
Infection	205 (39.0)
Pneumonia	105 (51.2)
Bloodstream infection	29 (14.1)
Intraabdominal infection	23 (11.2)
Urinary tract infection	11 (5.4)
Other	19 (9.3)
Sepsis of unknown origin	18 (8.8)
Documented infections	124 (60.5)
Bacteria	93 (75.0)
Virus	19 (15.3)
Fungus	12 (9.7)
Flare-up	184 (35.0)
Lung involvement	59 (32.1)
Heart involvement	49 (26.6)
Kidney involvement	30 (16.3)
Nervous system involvement	28 (15.2)
Other involvement	18 (9.8)
Other diagnosis	136 (26.0)
Cardiovascular event	60 (44.1)
Hemorrhage	33 (24.3)
Other	43 (31.6)
Outcomes	
In-ICU death	125 (23.8)
In-hospital death	160 (30.5)
One-year death	198 (37.7)

in almost two-thirds of them (124/205; 60.5%), mostly bacterial. It is noteworthy that 385 patients (73.3%) received antimicrobial treatment when only 205 of them had been diagnosed with infection.

Outcomes

The study population was followed for a median period of 486 days (IQR, 35-1,354] after ICU admission. Among 525 patients, 125 died in ICU, with a mortality rate at 23.8%. Thirty-five patients died before hospital discharge, which brought in-hospital mortality rate to 30.5% (Table 2; Fig 1). At ICU and hospital discharge, the survival probability was estimated at 76% (95% CI, 72-80) and 70% (95% CI, 65-74), respectively. Median ICU and hospital length-of-stay were 5 (IQR, 2-13) and 27 (IQR, 14-49) days. Of note, a limitation of life support was decided in 23.8% of deceased patients (e-Table 3).

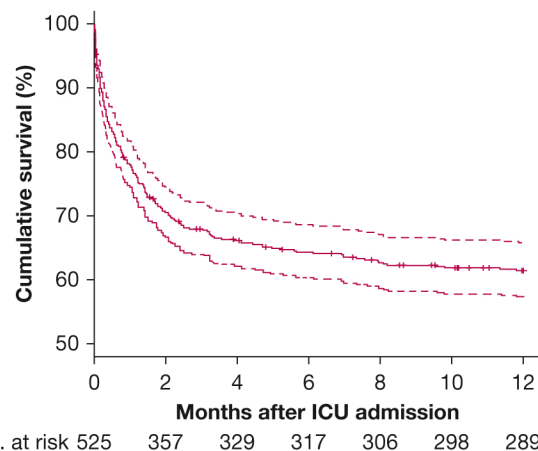


Figure 2 – Kaplan-Meier curve of one-year survival after ICU admission of critically ill patients with systemic rheumatic disease. The dashed lines represent the 95% CI.

Among the 365 patients who were discharged from the hospital, 38 died one-year after admission to ICU, which brings mortality rates to 37.7% (Table 2; Fig 1). The survival probability one-year after ICU admission was 61% (95% CI, 57-66) (Fig 2).

Predictive Factors of Death

By univariate analysis, in-hospital and one-year deaths were associated statistically with age, Knaus scale C or D, and prior corticosteroid treatment. SOFA score ≥ 10 ; a SAPS II ≥ 50 ; the need for vasoactive drugs, invasive mechanical ventilation, or renal replacement therapy; and diagnosis of infection were associated significantly with in-hospital and one-year mortality rates (Table 3). Moreover, a diagnosis of infection while in the ICU was associated with worse outcome as compared with SRD flare-up (e-Table 4).

Multivariable analysis showed that age and previous corticosteroid treatment were associated independently with in-hospital and one-year deaths. Moreover, a SAPS II ≥ 50 , the need for renal replacement therapy, or invasive mechanical ventilation were also associated factors with in-hospital and one-year mortality rates. In addition, multivariable analysis showed that Knaus scale C or D and prior treatment with conventional DMARDs were associated with the one-year mortality rate (Table 3). We failed to identify a cut-off value of corticosteroid dose associated with death.

Discussion

This study reports the results of a large multicenter cohort that included 525 patients with SRD who were admitted to the ICU during a recent ten-year period

TABLE 3] Factors Associated With In-hospital and One-Year Deaths

Predictive Factors of Death	Univariate Analysis With Strata (Center), Hazard Ratio [95% CI], <i>P</i> Value	Multivariable Analysis With Strata (Center), Hazard Ratio [95% CI], <i>P</i> Value
In hospital		
Age	1.02 [1.01-1.03], < .01	1.02 [1.01-1.03], < .01
Knaus scale C or D	1.52 [1.11-2.09], < .01	1.28 [0.91-1.78], .15
Prior corticosteroids	1.80 [1.29-2.53], < .01	1.93 [1.37-2.73], < .01
Sequential Organ Failure Assessment score ≥ 10	3.05 [2.21-4.21], < .01	...
Simplified Acute Physiology Score II ≥ 50	3.34 [2.39-4.66], < .01	2.03 [1.40-2.96], < .01
ICU diagnosis of severe acute event
Flare-up (Reference)
Infection	1.54 [1.05-2.26], .03	...
Other diagnosis	1.59 [1.03-2.44], .03	...
Vasoactive drugs	2.38 [1.67-3.39], < .01	...
Invasive mechanical ventilation	2.59 [1.75-3.81], < .01	1.76 [1.14-2.71], .01
Renal replacement therapy	2.41 [1.74-3.33], < .01	1.75 [1.23-2.48], < .01
One-year after ICU admission
Age	1.02 [1.01-1.03], < .01	1.02 [1.01-1.03], < .01
Knaus scale C or D	1.75 [1.32-2.31], < .01	1.35 [1.01-1.82], .04
Prior corticosteroids	1.64 [1.22-2.21], < .01	1.59 [1.16-2.16], .01
Prior conventional DMARDs	1.33 [0.98-1.82], .07	1.50 [1.09-2.07], < .01
Prior biologic DMARDs	0.96 [0.59-1.54], .86	...
Sequential Organ Failure Assessment score ≥ 10	3.41 [2.56-4.54], < .01	...
Simplified Acute Physiology Score II ≥ 50	3.42 [2.55-4.54], < .01	1.72 [1.24-2.39], < .01
Diagnosis in ICU
Flare-up (Reference)
Infection	1.72 [1.22-2.43], < .01	...
Other diagnosis	1.68 [1.14-2.47], < .01	...
Vasoactive drugs	2.67 [1.99-3.59], < .01	...
Invasive mechanical ventilation	2.95 [2.15-4.05], < .01	2.15 [1.52-3.04], < .01
Renal replacement therapy	2.87 [2.16-3.82], < .01	2.18 [1.60-2.97], < .01

See [Table 1](#) legend for the expansion of abbreviation.

(2006-2016) and describes their clinical features and outcome. We found in-hospital mortality rates at 30.5%. Long-term outcome was relatively favorable because the mortality rate one-year after ICU admission was 37.7%. Age, prior corticosteroid treatment, SAPS II ≥ 50 , and the need for renal replacement therapy or invasive mechanical ventilation were associated with short- and long-term outcome. In addition, Knaus scale C or D and prior conventional DMARDs treatment was also associated with one-year deaths.

We report herein the largest cohort of patients with SRD who would have benefited from improved life expectancy

of rheumatologic diseases and from recent advances in both immunosuppressive and life-sustaining therapies. Our population was comparable with those previously reported; most represented SRDs were vasculitides, systemic lupus erythematosus, and rheumatoid arthritis; most patients were treated with corticosteroids (65%) and with immunosuppressive therapy (38%).^{3,7-10} Yet, the patients were severely ill, which is reflected by high severity scores, and were treated aggressively in the early course of the event.^{3,7-9,33}

In critically ill patients with SRD, infection and flare-up were the two most common diagnosis in the ICU.^{3,7,9,33}

SRD flare-up affected more than one-third of patients, frequently involving the lungs.^{3,9,33} On the other hand, approximately 40% of patients were diagnosed with infection. However, differentiating infection and flare-up is challenging, and both SRD flare-up and infection may coexist, which was suggested by the large proportion (two-thirds) of patients with severe SRD flare-up who received antimicrobial therapy.³³ Opportunistic infections rarely were observed in our population, as previously reported.^{3,9}

One striking finding of this study was that in-hospital mortality rate was approximately 30%, approaching that of a general ICU population.¹¹ This short-term mortality rate had been previously and generally estimated at 20%-43%.^{3,8,11,33} Data are conflicting with some studies showing a decreased^{8,10} or an increased mortality rate.^{3,33,34} However, these studies included smaller cohorts and different case-mixes. Long-term mortality rates of critically ill patients with SRD were poorly or even not reported recently. Godeau et al³ reported a survival rate of 69% five years after hospital discharge in 1997. They observed the highest mortality rate the first year that decreased later on. Beil et al¹¹ reported, most recently, a 38.4% mortality rate at 180 days after admission. In our population, the survival probability at hospital discharge was at 70% and slightly decreased to 61% one-year after ICU admission. These results suggest that patients with SRD who survived would have a fair outcome after hospital discharge.^{35,36}

Our major concern in this study was the identification of prognosis predictive factors. Poor in-hospital and one-year outcomes were associated significantly with high illness severity scoring systems (SAPS II ≥ 50). Furthermore, a need for invasive mechanical ventilation or renal replacement therapy was also associated independently with in-hospital and one-year mortality rates. Previous studies showed comparable results, but only for short-term outcome.^{7-9,33} Our results would tend to suggest that the severity of the event leading to ICU admission determines not only short-term but also long-term outcome. Knaus scale C or D, increasing age, and previous corticosteroid or

conventional DMARDs treatment were associated with one-year mortality rates, which suggests that health status and level of immunosuppression may also affect long-term outcome.³ Previous data have suggested that, in general, elderly patients benefit poorly from admission to an ICU,³⁷ but this issue remains unresolved. Yet, physicians should be aware not only that ageing is risky in critically ill patients with SRD but also keep in mind that survival after hospital discharge remains satisfactory.

The present study has several limitations. First, the study is limited by its retrospective and not controlled design that may induce bias in data collection and results interpretation. However, it is the largest recent multicenter analysis on patients with SRD who were admitted to the ICU. Also, 34 patients were lost to follow up (6.5%), which may weaken our conclusions on long-term survival by inducing attrition bias. However, our statistical analysis has taken into account all censored data, unlike binary analysis in other studies. Finally, infection or flare-up diagnoses were sometimes not supported by robust evidence and might have been misclassified. To secure our data collection, three blinded investigators reevaluated all diagnoses that were reported in the medical chart. However, kappa agreement coefficient has not been calculated. Of note, almost two-thirds of suspected infections (60.5%) were documented, which is a higher rate than that previously reported (44%-57%).^{7,9,33} Last, functional status and quality of life that are important and relevant outcomes were not collected.

In conclusion, patients with SRD mostly require ICU admission for shock and acute respiratory failure related to infection or flare-up. In-hospital mortality rate was 30.5%, and one-year survival probabilities after ICU admission were encouraging, above 60%. Increased age, prior corticosteroid treatment, and illness severity were the main predictors of in-hospital and one-year death. Long-term outcome was also associated with Knaus scale C or D and prior conventional DMARDs treatment. Further studies are intended for improved ICU management in the era of new biologic DMARDs.

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