Determination of the main causes, outcome, and prognostic factors of patients with rheumatologic diseases admitted to the medical intensive care unit in Southern Iran

Mojgan Arjmand1 · Reza Shahriarirad2 · Saeedeh Shenavandeh3 · Mohammad Javad Fallahi1,2,3

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Abstract

Background Systemic rheumatic diseases (SRD) are a heterogeneous group of diseases that can involve several organ systems and occasionally require intensive care unit (ICU) admission because of severe systemic disease, life-threatening organ involvement, or complication of treatment. The objective of this study is to determine the causes, outcome, and prognostic factors of patients with rheumatologic diseases admitted in teaching medical ICUs in southern Iran.

Methods A retrospective case review of all patients with rheumatologic diseases admitted in the academic medical ICUs in two referral hospitals in southern Iran, from March 2015 to January 2020. Patients’ data were documented from their hospital records and the cause of admission, in-hospital outcome, and prognostic factors was evaluated.

Results Ninety-one patients were included, of which 71.4% were female. Systemic lupus erythematosus (54.9%) was the most common disease. Nineteen (20.9%) patients were new cases of rheumatological disease. The most frequent symptom for admittance was dyspnea (54.9%) and hemoptysis (20.9%). The in-hospital mortality rate was 48%, and the leading cause of death was infection (29 patients; 65.5%) followed by disease activity (18 patients; 40.9%). Also, the death of 29.5% of patients was presumed due to both disease activity and infection. Factors associated with mortality included renal insufficiency ($p < 0.028$), infection ($p < 0.001$), pneumonia ($p < 0.042$), dyspnea ($p < 0.042$), loss of consciousness ($p < 0.046$), azathioprine consumption ($p < 0.004$) during 1 month before ICU admission, mechanical ventilation ($p < 0.001$), renal replacement therapy ($p < 0.001$), CNS involvement ($p < 0.009$), and ICU medications such as cyclosporine and azathioprine (0.03 and 0.03, respectively) or treatments such as plasmapheresis ($p < 0.018$).

Conclusion The ICU mortality rate of patients with SRD was high. Infection and disease exacerbation are the leading reasons for ICU admission in systemic rheumatic diseases. Intensivists must keep in mind that SRD exacerbation may require immunosuppressive agents along with lifesaving interventions, more particularly in newly diagnosed SRDs.

Key Points
- The ICU mortality rate of patients with SRD was high.
- Infection and disease exacerbation are the leading reasons for ICU admission in systemic rheumatic diseases.
- 63.8% of our patients fall into this category of new cases of rheumatologic disease and disease flare-up.

Keywords Intensive care units · Mortality · Systemic rheumatic diseases

Background

Systemic rheumatic diseases (SRDs) are a heterogeneous group of diseases that cause chronic inflammation, pain, tissue damage, spanning various types of arthritis, and systemic connective tissue diseases. The severity of these diseases ranges from mild systemic symptoms to severe organ or life-threatening manifestations that often need immunosuppressive treatments and sometimes lead...
to hospital admissions due to disease or medication complications [1].

The top three SRDs requiring admission to the intensive care unit (ICU) are rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic vasculitis (SV) [2–4]. Infection, renal failure, and disease flare-ups have been reported as the top 3 reasons for ICU admissions among SRDs patients [5]. Furthermore, the incidence of severe SRDs is approximately 3% [2], while it has been recently reported that SLE is the most frequent cause of ICU admission among SRDs [3, 6].

Several factors can affect the severity, mortality, and outcome of the diseases too, as a study by Portalatin et al. showed genetic predisposition to both SLE and chronic kidney disease in African Americans ancestry patients and their income inequality, education disparities, lack of support, health care access, and affordability can induce higher rates of progression of them to end stage renal disease (ESRD) and have a better access to healthcare and social support systems making new and alternative regimens more affordable and cost-effective [7]. In the era of the coronavirus disease (COVID-19), studies have also showed that patients with autoimmune disease had better outcomes with COVID-19 than controls [8, 9]. Higher creatinine and LDH levels were associated with death in the autoimmune disease group. SaO2 ≤ 88% and CO-RADS ≥ 4 were risk factors for in-hospital mortality and anticoagulant therapy was protective [8].

Few studies have examined the prognosis [10, 11] and prognostic factors [5] in patients with SRDs in ICU. Furthermore, in Iran, these studies are very limited and generally have been limited to single diseases [12]. Characteristics related to the underlying disease, prior chronic health condition, immunosuppressive therapy, infection, and acute physiology and chronic health assessment (APACHE II) have been shown to affect the prognosis and predict mortality in patients with SRDs admitted to the ICU [13]. Previous investigations into the outcome of patients with SRDs treated in ICU reported increased mortality compared to intensive care patients without rheumatic diseases [2, 14]. Given that patients with SRDs frequently require ICU treatment for their condition, this study aimed to determine the main causes, outcomes, and prognostic factors of rheumatologic diseases admitted to our medical ICU.

**Methods and materials**

This retrospective study was performed on all adult (> 18 years old) patients with known or new cases of rheumatic diseases who were hospitalized in the medical ICU of Shahid Faghihi and Namazi hospitals, both referral hospitals affiliated to Shiraz University of Medical Sciences from March 2015 to January 2020. The ethics committee of Shiraz University of Medical Sciences approved this study (Ethical code: IR.SUMS.MED.REC.1398.522). Patients’ information was anonymized before data analysis and confidentiality of patient information was guaranteed and protected.

Definition of individual rheumatic diseases was based on a new diagnosis by consultant rheumatologist according to American College of Rheumatology criteria or known case based on the previous diagnosis by a rheumatologist [15–17]. Demographic and clinical data of patients including signs and symptoms, disease severity on ICU admission based on APACHE II, hospitalization cause, comorbid diseases, duration of hospital stay, final diagnosis, and discharge status were collected. Also, the types of treatments they received during hospitalization along with their pre-admission medication regimens in the past month were recorded. The patient’s survival status, as well as the date and reason of death, were obtained via computerized medical data from each hospital or by calling the family doctor or the patient’s family.

Infection, either nosocomial or pre-hospital infection, was defined as either the documentation of a positive culture or the development of related signs or symptoms based on the judgment of the treating physician. In this study, the classification type of infections was based on the CDC/NHSN surveillance classification of healthcare-associated infection and criteria for specific types of infections in the acute care setting [18]. Sepsis diagnosis was based on the surviving sepsis campaign [19].

**Statistical analysis**

All variables were collected in a single database. Continuous data were computed as mean ± standard deviation (SD), whereas categorical variables were recorded as percentages. To investigate the impact of different variables on mortality, we performed univariate analyses, including independent sample t-test and χ². Also, statistically significant variables were included in the multivariable logistic regression analysis to adjust for confounding factors. The ability of the APACHE II scores to predict the 30-day mortality from all causes was assessed using the receiver operating characteristic (ROC) analysis. In addition, ROC analysis was used to evaluate the power of the APACHE II scores in predicting the 3, 6, 12, and 18-month mortality stratified according to the cause of mortality. In the univariate model, P-values were calculated and medications with a P-value of lower than 0.25 were included in the multivariate model to determine significant medications. A P-value of lower than 0.05 in the multivariate analysis was considered significant. All statistical analyses were carried out using SPSS version 22.0 software.
Results

During the study period (2015–2020), a total of 91 patients diagnosed with SRDs during hospitalization or before hospitalization were included; of them, 44 (48%) patients died in the ICU and 47 (52%) survived. Among the patients, sixty-five patients (71.4%) were female and the median age was 37 years (IQR 21–78). The baseline features of the patients in our study are shown in Table 1.

The most common SRD was SLE (55%), followed by granulomatosis with polyangiitis (GPA) (16.5%). Also, thirty-nine (43%) patients had comorbid diseases. The most frequent comorbidity was chronic kidney disease (CKD).

Regarding treatments and medications, 61 (67%) patients received immunosuppressive agents 1 month before their current hospital admission, with the majority being glucocorticoids 58 (63.7%) (Table 2). The most common presentations were dyspnea (50.4%) and hemoptysis (20.9%). The most frequent diagnoses were exacerbation of SRDs (49.5%) and infection (46.2%), followed by diffuse alveolar hemorrhage. Among the patients, 19 (20.9%) were new cases of SRDs, diagnosed for the first time during ICU admission, and SLE was the most common disease.

During ICU admission, the most frequent treatment and medications were glucocorticoids (93.4%), antibiotics (either therapeutic or empirical) (71.4%), plasmapheresis (34.1%), and cyclophosphamide (20.9%). The mean APACHE II score at admission was 15 ± 8.6, and the median length of ICU stay was 7 [3–15] days. Also, 56% underwent mechanical ventilation, and 29.7% underwent renal replacement therapy; among them, 26.4% were known cases of ESRD, and 3.3% were new cases of AKI.

The mortality rate was 48%, and the leading cause of death was infection (29 patients; 65.5%) followed by disease activity (18 patients; 40.9%). Also, the death of 13 patients was infection (29 patients; 65.5%) followed by disease activity (18 patients; 40.9%).

The most common site of infection was the respiratory system. The most frequent organisms in the blood, urine, and sputum cultures were Klebsiella sp., Acinetobacter, and Candida, respectively. Furthermore, Acinetobacter was the most common organism in our ICU.

Among the 19 new cases of rheumatologic disease, 11 (57.9%) were SLE, 4 (21.1%) granulomatosis with polyangiitis, 3 (15.8%) Eosinophilic granulomatosis with polyangiitis, and 1 (5.3%) Polymyositis.

Univariate analysis of the characteristics of survivors and non-survivors revealed some factors associated with poor outcome, including the older age (p < 0.003), presence of renal insufficiency (p < 0.028), diagnosis of infection (p < 0.0001), pneumonia (p < 0.028), dyspnea and loss of consciousness (p < 0.042 and 0.046), mechanical ventilation and renal replacement therapy (p < 0.0001 and 0.001), azathioprine consumption during 1 month before ICU admission (p < 0.004), CNS and lung involvement (p 0 < 0.0009 and 0 < 0.036 respectively), and ICU treatment/medications such as plasmapheresis, cyclophosphamide, and azathioprine (p < 0.018, 0.03, and 0.03, respectively) (Table 1).

Also, multivariate analysis did not show any independent prognostic factor.

We analyzed the APACHE II score by the roc curve for the prediction of hospital mortality (Fig. 1).

According to the ROC curve, an APACHE II score of above 9 during the first 24 h (HR: 16.95% CI, p < 0.0001) was strongly associated with reduced hospital mortality. Also, the mortality rate with an APACHE score above 9 was 96% (specificity 70.8, sensitivity 95.92) (Fig. 1).

Among our participants, 47 patients (51.65%) were discharged from the ICU, while 44 (48.35%) patients died during hospitalization, in which the causes of death of these patients is reported in Table 3. Unfortunately, among the 47 patients who were discharged, we could not access 18 (38.3%) patients due to loss in the follow-up. Thus, we followed the remaining 29 patients 18 months after hospital discharge. Twenty-four (82.7%) out of the 29 patients survived 18 months after hospitalization. During 3, 6, 12, and 18 months after hospital discharge, 2 (6.8%), 1 (3.4%), 0 (0%), and 2 (6.8%) of them died, respectively (Fig. 2).

Discussion

This study aimed to determine the main causes, outcomes, and prognostic factors of rheumatologic diseases admitted in the medical intensive care unit (ICU). In our study, systemic lupus erythematosus and granulomatosis with polyangiitis (Wegener’s granulomatosis) were the most frequent causes of ICU admission. Our findings are in line with those of a study by Bernal-Macías et al. in 2015 and Quintero et al. in 2013, which reported that systemic lupus erythematosus was the most common cause of ICU admission in SRDs [3, 6].

Infection was one of the most common causes of ICU mortality in SRD patients in our study. Furthermore, a French cohort study involving patients with SRDS demonstrated that infection and SRD exacerbation were the most common causes of ICU admission [20]. Godeau and Wang et al. also reported that infection was the most frequent cause of ICU admission and mortality [21, 22]. Barrett et al. in 2017 reported higher rates of severe sepsis and poorer prognosis in SRD patients than in the general population [14]. Patients with SRDs have an increased risk of infection [23, 24]. The most common site of infection in our study was the respiratory system, which was in line with other studies [5, 24, 25].
| Variable                                                      | Total; N=91 | Survivors; n=47 | Non-survivors; n=44 | P-value* |
|--------------------------------------------------------------|-------------|-----------------|--------------------|---------|
| **Age; mean ± SD**                                           | 40.7 ± 13.7 | 34 ± 11.7       | 44.5 ± 14.3        | 0.003   |
| **Gender; n (%)**                                             |             |                 |                    |         |
| Female                                                       | 65 (71.4)   | 35 (53.8)       | 30 (46.2)          | 0.507   |
| Male                                                         | 26 (28.6)   | 12 (46.2)       | 14 (53.8)          | 0.643   |
| **Immunosuppressive during one month before admission; n (%)**|             |                 |                    |         |
| Any immunosuppressive agent                                  | 61 (67)     | 32 (52.5)       | 29 (47.5)          | 0.95    |
| Glucocorticoid                                               | 58 (63.7)   | 29 (50)         | 29 (50)            | 0.45    |
| Hydroxychloroquine                                           | 20 (22)     | 9 (45)          | 11 (55)            | 0.59    |
| Azathioprine                                                 | 11 (12.1)   | 10 (90.9)       | 1 (9.1)            | 0.004   |
| Cyclophosphamide                                             | 10 (11)     | 5 (50)          | 5 (50)             | 1.00    |
| Mycophenolate mofetil                                        | 7 (7.7)     | 4 (57.1)        | 3 (42.9)           | 1.00    |
| Methotrexate                                                 | 6 (6.6)     | 2 (33.3)        | 4 (66.7)           | 0.16    |
| Tacrolimus                                                   | 4 (4.4)     | 3 (75)          | 1 (25)             | 1.00    |
| Methylprednisolone pulse                                     | 3 (3.3)     | 2 (66.7)        | 1 (33.3)           | 1.00    |
| Cyclosporine                                                 | 3 (3.3)     | 3 (100)         | 0                  | 0.10    |
| Intravenous immunoglobulin                                   | 2 (2.2)     | 2 (100)         | 0                  | 0.32    |
| **Clinical presentation; n (%)**                             |             |                 |                    |         |
| Dyspnea                                                      | 50 (54.9)   | 21 (42)         | 29 (58)            | 0.042   |
| Hemoptysis                                                   | 19 (20.9)   | 10 (52.6)       | 9 (47.4)           | 0.92    |
| Fever                                                        | 12 (13.2)   | 6 (50)          | 6 (50)             | 0.90    |
| Loss of consciousness                                        | 10 (11)     | 2 (20)          | 8 (80)             | 0.046   |
| Convulsion                                                   | 7 (7.7)     | 1 (14.3)        | 6 (85.7)           | 0.053   |
| Thrombocytopenia                                             | 6 (6.6)     | 5 (83.3)        | 1 (16.7)           | 0.20    |
| Gastrointestinal bleeding                                    | 5 (5.5)     | 2 (40)          | 3 (60)             | 0.67    |
| Weakness                                                     | 5 (5.5)     | 2 (40)          | 3 (60)             | 0.67    |
| Edema                                                        | 4 (4.4)     | 2 (50)          | 2 (50)             | 1.000   |
| Post cesarean section care                                   | 3 (3.3)     | 3 (100)         | 0                  | 0.24    |
| Abdominal pain                                               | 3 (3.3)     | 1 (33.3)        | 2 (66.7)           | 0.60    |
| Rise of creatinine                                           | 2 (2.2)     | 2 (100)         | 0                  | 0.49    |
| Blurred vision                                               | 1 (1.1)     | 1 (100)         | 0                  | 1.000   |
| Finger gangrene                                              | 1 (1.1)     | 1 (100)         | 0                  | 1.0000  |
| **Comorbid disease; n (%)**                                  |             |                 |                    |         |
| Chronic kidney disease                                       | 21 (23.1)   | 8 (40)          | 13 (65)            | 0.028   |
| Hypertension                                                 | 15 (16.5)   | 7 (46.7)        | 8 (53.3)           | 0.70    |
| Diabetes                                                     | 10 (11)     | 4 (40)          | 6 (60)             | 0.35    |
| Hypothyroidism                                               | 8 (8.8)     | 3 (37.5)        | 5 (62.5)           | 0.76    |
| Ischemic heart disease                                       | 7 (7.7)     | 3 (42.9)        | 4 (57.1)           | 1.00    |
| Convulsion                                                   | 5 (5.5)     | 3 (60)          | 2 (40)             | 0.32    |
| Congestive heart failure                                     | 3 (3.3)     | 1 (33.3)        | 2 (66.7)           | 1.00    |
| Cerebrovascular accident                                     | 2 (2.2)     | 1 (50)          | 1 (50)             | 1.00    |
| Tuberculosis                                                 | 2 (2.2)     | 1 (50)          | 1 (50)             | 1.00    |
| Thromboembolic events*                                        | 1 (1.1)     | 0               | 1 (100)            | 1.00    |
| Thalassemia intermedia                                       | 1 (1.1)     | 0               | 1 (100)            | 1.00    |
The most frequent organisms based on the study were gram-negative bacteria (mainly *Acinetobacter*), followed by fungi (mainly *Candida*). A study by Jin Min Peng et al. in China on patients with dermatomyositis and polymyositis in the ICU found that the most common organisms were fungi (mainly invasive pulmonary *Aspergillosis*) followed by gram-negative bacteria [26]. Treatment of these patients should be concerned regarding opportunistic infections and rapidly progressing disease.

In our study, there were 19 (20.9%) cases of new cases of rheumatologic disease and 39 (42.9%) cases of disease flare-up. Some studies have assigned new cases of rheumatological diseases as disease flare-ups [20]. With such an approach, 63.8% of our patients fall into this category. This is vital for internists and critical care physicians, who must retain a high level of suspicion for SRD aggravation as a differential diagnosis in unexplained systemic signs, especially in patients with renal and/or pulmonary impairments. Because SRD can lead to death due to significant organ failure, immunosuppressive treatment should be considered as soon as possible. As a result, ICU management should involve both organ support therapy and specialized treatment at the same time, as was the case in nearly 30% of our patients. This is especially true for people who have recently been diagnosed with SRD. Conversely, immunosuppression should be increased with caution in the event of shock or elderly individuals with a lower risk of SRD exacerbation [20].

Two previous studies have shown that the use of corticosteroids for the treatment of SRDs leads to a poorer prognosis as a result of short-term hospitalization in the ICU [22, 27]. Patients with SRDs often have multiple comorbid conditions such as pulmonary dysfunction, renal dysfunction, and hypertension that can affect the prognosis of ICU admission [20]. In our study, 43% had a comorbid disease. There was no significant relationship between death and the presence of comorbid diseases, except renal insufficiency, which was associated with a higher mortality rate.

Our data indicated that the leading cause of death was infection (29; 65.5%) followed by disease activity (18; 40.9%). Previous studies have also reported that in SRD patients, both disease exacerbation and infection are the leading reasons for ICU admission [2, 20, 28]. A study carried out in 2018 by Meiying Wang considered multi-organ involvement as the most important cause of death in these
Table 2 Clinical and hospital course features of patient admitted to the intensive care unit due to rheumatological disease

| Variable                                                                 | Total, N=91 | Survivors; n=47 | Non-survivors; n=44 | P-value* |
|-------------------------------------------------------------------------|-------------|-----------------|---------------------|----------|
| ICU length of stay; median [Q1–Q1]                                      | 7 [3–15]    | 7 [4–14]        | 6 [3–18.25]        | 0.388    |
| APACHE II; mean ± SD                                                   | 15 ± 8.6    | 9 ± 5.3         | 20 ± 8.2           | < 0.001  |
| Diagnosis at ICU admission; n (%)                                       |             |                 |                     |          |
| Infection                                                              | 42 (46.2)   | 14 (33.3)       | 28 (66.7)          | < 0.001  |
| Diffuse alveolar hemorrhage                                            | 20 (22)     | 7 (35)          | 13 (65)            | 0.09     |
| New case of rheumatologic disease                                      | 19 (20.9)   | 12 (63.2)       | 7 (36.8)           | 0.53     |
| Acute kidney injury                                                    | 19 (20.9)   | 7 (36.8)        | 12 (63.2)          | 0.14     |
| Thrombotic thrombocytopenic purpura                                    | 10 (11)     | 4 (40)          | 6 (60)             | 0.43     |
| Intestinal tract disease                                               | 9 (9.9)     | 4 (44.4)        | 5 (56.5)           | 0.73     |
| Shock                                                                  | 8 (8.8)     | 2 (25)          | 6 (75)             | 0.201    |
| Gastrointestinal bleeding                                              | 6 (6.6)     | 2 (33.3)        | 4 (66.7)           | 0.42     |
| Acute heart failure                                                    | 5 (5.5)     | 1 (20)          | 4 (80)             | 0.19     |
| Pulmonary thromboembolism                                              | 4 (4.4)     | 2 (50)          | 2 (50)             | 1.00     |
| Intracranial hemorrhage                                                | 3 (3.3)     | 0               | 3 (100)            | 0.10     |
| Cytomegalovirus infection                                              | 2 (2.2)     | 1 (50)          | 1 (50)             | 1.00     |
| Tracheal stenosis                                                      | 2 (2.2)     | 1 (50)          | 1 (50)             | 1.00     |
| Pneumothorax                                                           | 2 (2.2)     | 1 (50)          | 1 (50)             | 1.00     |
| CNS vasculitis                                                         | 2 (2.2)     | 0               | 2 (100)            | 0.23     |
| Bowel ischemia                                                         | 1 (1.1)     | 0               | 1 (100)            | 0.48     |
| Pulmonary artery aneurysm                                              | 1 (1.1)     | 1 (100)         | 0                   | 1.00     |
| Warfarin toxicity                                                      | 1 (1.1)     | 1 (100)         | 0                   | 0.48     |
| Guillain barre syndrome                                                | 1 (1.1)     | 1 (100)         | 0                   | 1.00     |
| Sinus vein thrombosis                                                  | 1 (1.1)     | 1 (100)         | 0                   | 1.00     |
| Right-sided heart failure                                              | 1 (1.1)     | 0               | 1 (100)            | 0.48     |
| Supportive treatment; n (%)                                            |             |                 |                     |          |
| Mechanical ventilation                                                 | 51 (56)     | 7 (14.9)        | 44 (100)           | 0.001    |
| Renal replacement therapy                                              | 27 (29.7)   | 6 (22.2)        | 21 (77.7)          | 0.001    |
| Organ involvement; n (%)                                               |             |                 |                     |          |
| Lung                                                                   | 64 (70.3)   | 28 (43.8)       | 36 (56.2)          | 0.036    |
| Kidney                                                                 | 43 (47.3)   | 18 (42.9)       | 25 (57.1)          | 0.07     |
| Hematologic                                                            | 25 (27.5)   | 13 (52)         | 12 (48)            | 0.96     |
| Brain                                                                  | 22 (24)     | 6 (27.3)        | 16 (72.7)          | 0.009    |
| Heart                                                                  | 20 (22)     | 8 (40)          | 12 (60)            | 0.23     |
| Skin                                                                   | 7 (7.7)     | 4 (57.1)        | 3 (42.9)           | 0.62     |
| Joint                                                                  | 6 (6.6)     | 4 (66.7)        | 2 (33.3)           | 0.68     |
| Sinus                                                                  | 4 (4.4)     | 4 (100)         | 0                   | 0.143    |
| Eye                                                                    | 1 (1.1)     | 1 (100)         | 0                   | 1.00     |
| Treatment during ICU admission; n (%)                                   |             |                 |                     |          |
| Glucocorticoid                                                         | 85 (93.4)   | 45 (52.9)       | 40 (47.1)          | 1.00     |
| Antibiotics                                                            | 65 (71.4)   | 30 (46.2)       | 35 (53.8)          | 0.11     |
| Methylprednisolone pulse                                               | 60 (65.5)   | 31 (51.7)       | 29 (48.3)          | 0.9      |
| Plasmapheresis                                                         | 31 (34.1)   | 11 (35.5)       | 20 (64.5)          | 0.018    |
| Cyclosporine                                                           | 19 (20.9)   | 4 (100)         | 0                   | 0.03     |
| Cyclophosphamide                                                       | 19 (20.9)   | 13 (68.4)       | 6 (31.6)           | 0.63     |
| Intravenous Immunoglobulin                                             | 10 (11)     | 6 (60)          | 4 (40)             | 0.27     |
| Azathioprine                                                           | 9 (9.9)     | 8 (88.9)        | 1 (11.1)           | 0.03     |
| Hydroxychloroquine                                                     | 9 (9.9)     | 5 (55.6)        | 4 (44.4)           | 0.76     |
| Rituximab                                                              | 6 (6.6)     | 3 (50)          | 3 (50)             | 1.00     |
| Tacrolimus                                                             | 4 (4.4)     | 3 (75)          | 1 (25)             | 1.00     |
| Mycophenolate mofetil                                                  | 1 (1.1)     | 0               | 1 (100)            | 1.00     |
| Site of infection                                                      |             |                 |                     |          |
| Lung                                                                   | 36 (39.6)   | 10 (27.8)       | 26 (72.2)          | 0.032    |
| Urinary tract                                                          | 7 (7.7)     | 3 (42.9)        | 4 (57.1)           | 0.805    |
| Brain                                                                  | 3 (3.3)     | 3 (100)         | 0                   | 0.725    |

*Fisher’s exact/chi-square test or independent sample t-test, bold values indicate significant association

SD, standard deviation; ICU, intensive care unit
Yael Haviv-Yadid also reported respiratory and renal failure as the cause of death of SRD patients [10]. Furthermore, our data showed that patients who require mechanical ventilation and renal replacement therapy had a poorer prognosis. Previous studies by KaoC-C and Hilbert Gin in 2017 reported that organ replacement therapies, including mechanical ventilation and vasopressors, were associated with higher mortality in the ICU population [30, 31]. This can be due to the severity of the disease and the involvement of vital organs.

In this study, the median APACHE II score at admission was 15, and an APACHE II score > 9 was strongly associated with reduced long-term survival. The mortality rate with APACHE II score above 9 was 96%. Previously, studies have also supported that the APACHE II score is a predictive factor of ICU mortality in the general population, while it is also capable of predicting ICU mortality in SRDs patients [32]. In a study by Camargo et al. [33] despite having high activity scores and expected mortality, only two SLE patients in our study passed away while receiving ICU care, while also disease activity (i.e., SLEDAI) appeared to have a low prognostic value among their ICU-admitted SLE patients. These findings concur with those made by Alzeer et al. [34], who noted that mortality was associated with APACHE II score equal to or greater than 20, but not SLEDAI score. Although disease activity was not recorded in our study, we demonstrated similar cutoff point of APACHE II of above 9 as a prognostic value. However, further studies regarding the comparison of this scale with disease activity scores are required to achieve a better understanding and management of rheumatological diseases.

Some studies have reported that the prognostic factors of ICU mortality in patients with SRDs included high APACHE II, serious infection, mechanical ventilation,

![Fig. 1 ROC curve for APACHE II score for prediction of hospital mortality](image)

Table 3 Causes of death among hospitalized intensive care unit rheumatologic patients

| Cause of death                                      | Frequency (%) | N = 44 |
|----------------------------------------------------|---------------|--------|
| Overall                                            |               |        |
| Respiratory failure                                | 31 (70.5)     |        |
| Disease flare-up/activity                           | 18 (40.9)     |        |
| Infection                                          | 29 (65.9)     |        |
| Gastrointestinal bleeding                          | 3 (6.8)       |        |
| Tamponade                                          | 2 (4.5)       |        |
| Brain death                                        | 1 (2.3)       |        |
| Detailed                                           |               |        |
| Disease flare-up/activity, respiratory failure, and infection | 9 (20.5)   |        |
| Disease flare-up/activity and respiratory failure   | 1 (2.3)       |        |
| Disease flare-up/activity and infection             | 4 (9.1)       |        |
| Disease flare-up/activity                           | 4 (9.1)       |        |
| Respiratory failure, infection, and gastrointestinal bleeding | 2 (2.2)  |        |
| Respiratory failure, infection, and brain death     | 1 (1.1)       |        |
| Respiratory failure and infection                   | 11 (25.0)     |        |
| Respiratory failure                                | 7 (15.9)      |        |
| Infection                                          | 2 (4.5)       |        |
| Gastrointestinal bleeding                          | 1 (2.3)       |        |
| Tamponade                                          | 2 (4.5)       |        |
vasopressor drugs, renal replacement therapy, and corticosteroids dose [30, 35]. This data supports the findings from previous reports by Biscotti et al. on mixed cohorts of patients with SRDs [5], in which the mortality rate of SRD patients was 48.4%. Also, Godeau et al. reported ICU mortality rates of 33% [27]. On the contrary, in a large-scale study of 149 critically ill patients with SRD, Faguer et al. found a 28-day mortality rate of 16% [36]. Beil et al. in one study on SRDs patients in ICU in Germany reported mortality rates ranging from 23% in the ICU to 32% in the hospital [37]. One possible explanation of the wide variation of ICU mortality is the difference in patients underlying disease and severity and ICU admission criteria.

Few studies have looked at the prognosis of patients with systemic rheumatic diseases admitted to the ICU in terms of prior medical conditions and treatments. According to Godeau et al. [38], factors linked to in-hospital mortality include severity score, prior health condition, corticosteroid use, and ICU admission for an infectious complication. The main prognostic factors, according to Bouachour et al. [39], were severity score, the number of acute organ system failures, and iatrogenic complications. Poor prior health status, APACHE II score, and admission for infection were identified in Moreels study [13] as prognostic factors for in-hospital mortality; however, prior use of corticosteroids or other immunosuppressive medications was not linked to mortality, in contrast to the data of Godeau et al. [38].

One of the strengths of our study was that, unlike other studies, we included all types of rheumatological diseases. Among the limitations of this study is that the retrospective nature of our study, which accounts for the inability to determine causation, and only association. Also, another limitation was the missing data and incomplete documentation, such as the definite cause of death, disease activity and indices, drug adherence, laboratory data such as platelet to lymphocyte ratio, and pre-admission factors such as unattended comorbidities and clinical reactivation. Another limitation is that we could not differentiate infection based on hospital-acquired or prehospitalization infection. Although our settings were referral centers, the total sample size and frequencies among some variables were relatively low. Therefore, further multicentric studies are recommended. Also, some laboratory tests for diseases such as Pneumocystis jirovecii or cytomegalovirus were not routinely available. Also, our study was conducted before the onset of the COVID-19 pandemic and future studies are warranted about changes in the pattern of admission causes.

Conclusion

In summary, in SRD patients, our study demonstrated that both infection and disease exacerbation were the leading reasons for ICU admission. SLE was the most common SRDs admitted to the ICU. Also, the ICU mortality rate was high. Further studies are recommended to improve ICU management and therapeutic regimen evaluations.

Abbreviations APACHE II: Acute physiology and chronic health assessment; CKD: Chronic kidney disease; GPA: Granulomatosis with polyangiitis; ICU: Intensive care unit; IQR: Interquartile range; RA: Rheumatoid arthritis; ROC: Receiver operating characteristic; SD: Standard deviation; SLE: Systemic lupus erythematosus; SRD: Systemic rheumatic diseases; SV: Systemic vasculitis

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Author contribution M. J. F. and S. S. conceived the study; M. A. collected the data; R. S wrote the first draft of the manuscript; S. S. and M. J. F. proofread the manuscript. All authors read and approved the final version before submission.

Data availability All data generated or analyzed during this study are included in this manuscript. Please write to the corresponding author for further information.

Compliance with ethical standards

Ethics approval and consent to participate The ethics committee of Shiraz University of Medical Sciences approved this study (Ethical code: IR.SUMS.MED.REC.1398.522). Patients’ information was anonymized before data analysis and confidentiality of patient information was guaranteed and protected.

Consent for publication Not applicable.

Disclosures None.

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