RhICU – A registry for patients with rheumatic diseases at the intensive care unit

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1. Summary

Despite tremendous advances in the treatment of patients suffering from systemic rheumatic diseases over the last two decades, affected patients have a high risk of admission to the ICU due to infections, disease related complications or drug side effects. Data concerning these critically ill patients are limited to few retrospective studies mainly focusing on epidemiologic and demographic descriptions. The lack of prognostic parameters in the context of the different therapeutic modalities sought us to establish a mulit-centre registry for patients with rheumatic diseases at the ICU.

2. Background

Systemic rheumatic diseases (SRD) are a heterogeneous group of autoimmune disorders characterized by systemic inflammation with multiple organ involvement. Better pathophysiological understanding and the introduction of new immunosuppressive and immunomodulatory drugs dramatically improved the outcome of patients suffering from SRD.[1] During the course of SRD, organ failure due to disease exacerbations, infections and drug-toxicities may necessitate the admission to the intensive care unit (ICU).[2] Despite all advances in critical care medicine over the last decade mortality of SRD patients referred to the ICU still remains poor.[3-5] However, data concerning critically ill SRD patients are limited and mostly focus on demographic and epidemiologic findings. Furthermore, existing studies often describe patient cohorts with different disease frequencies, which makes them difficult to compare. As a consequence of this heterogeneity, ICU mortality rates range across studies from 11% to 53%.[3, 6-13]

ICU admission of SRD patients is primarily required for acute exacerbation of the underlying rheumatic disease and infections.[12-14] Throughout the literature iatrogenic complications like drug related toxicities only accounted for 5-11%. Respiratory distress, acute kidney injury and shock are the main organ failures seen in SRD patients referred to the ICU.[12-14]

There are only a few studies analysing prognostic parameters for outcome in SRD patients admitted to ICU. Severity of the acute medical condition, mechanical ventilation, the necessity for vasopressor drugs and renal replacement therapy are all associated with higher mortality rates.[3,12-14] ICU admission due to infectious complications also represents a negative prognostic marker.[3,15] Data concerning treatment modalities for rheumatic diseases (e.g. use of immunosuppressive/immunomodulatory drugs) prior to or during ICU stay and differences in outcome are mainly lacking. In one study by Thong et al high doses of glucocorticoids and immunosuppressive drugs before ICU admission were associated with worse outcome.[15] However, the observations of this study are limited because of a small patient number (n=28) and the retrospective design of the study. Finally, also data on extra-corporal membrane oxygenation (ECMO) in case of diffuse alveolar haemorrhage as potential life-threatening complication of connective tissue diseases

and vasculitides is limited to few case series and has not been properly evaluated in case of SRD.[16]
Despite a considerable frequency of SRD patients referred to the ICU, this population still represents a neglected population in the context of prognostic parameters and therapeutic modalities. The Medical University of Vienna represents the largest centre for medical care of SRD patients in Austria with more than 4000 patients treated every year. With this project we aim to establish a single centre registry for patients with rheumatic diseases at the intensive care unit and to delineate the clinical features, potential prognostic variables and treatment modalities in our Viennese cohort. These data will serve as a starting point to generate new hypotheses and plan studies with a prospective design.

3. Objective

Identification of type and frequency of rheumatic diseases at the ICU, and determination of the outcome of those patients based on type of disease, initial presentation, and the results of initial examinations. This prospective study aims to:

1) make a detailed characterization of patients with SRD admitted to the ICU in terms of rheumatologic disease entity (diagnosis, stage of disease, therapy), comorbidities, reasons for ICU-admission, severity of acute illness and the use of life sustaining therapies (mechanical ventilation, vasopressive drugs, renal replacement therapy, plasma exchange, ECMO, e.g.) throughout the ICU stay.
2) evaluate ICU-, 1-year- and 2-year-mortality.
3) analyze potential predictive factors, which correlate with clinical outcome.
4) This descriptive study aims to lay the foundation for future prospective studies.

4. Patients

<u>Study population</u>
Inclusion criteria
- Age > 18 years
- Critically ill patients with newly diagnosed SRD during ICU stay
- Critically ill patients with known SRD

Exclusion criteria:
- Critically ill patients without SRD

Patients admitted to one of the ten ICU (medical, anesthesiologic and surgical) at the General Hospital of Vienna will be screened for the inclusion and exclusion criteria. All other participating centres, including the Medical University of Graz, the Medical University of Innsbruck, the Medical Centre Klagenfurt am Wörthersee, as well as the Kepler Medical University of Linz follow the same procedure. All Patients included in

this study will be studied and documented prospectively. An electronic case report form (CRF) will be used for documentation of each included patient (see section "methods" and supplement material).
Prior to the preparation of this study protocol we conducted a data collection of all relevant patients by diagnosis (based on ICD-10 coding) referred to the medical ICUs of the Medical University of Vienna from January 2012 to June 2018 (EK Nr.: 1976/2018). Over the last 6 years approximately 100 patients diagnosed with systemic rheumatic disease have been referred to the medical ICUs of the Medical University of Vienna. According to these numbers, it is feasible to expect that 100-150 patients will be included in our prospective registry over a time period of 5 years.

Control group

Inclusion criteria

- Age > 18 years
- Critically ill patients without SRD

Exclusion criteria:

- Critically ill patients with newly diagnosed or known SRD

To compare the group of critically ill patients with SRDs with the general ICU population, historical matches will be made 1:1 with non-SRD patients from the ICU. Matching algorithm will include sex (male / female), age (allowance ±1 year), SOFA score (concrete matching) and the reason for ICU admission (respiratory / hemodynamic / neurologic insufficiency).

5. Methods

5.1 RDA database

RhICU will be set up based on the RDA (Research, Documentation & Analysis) database, an established and regularly validated tool for the purpose of analyzing clinical and laboratory data.[17] This format allows a personally designed database and the implementation of specific patient and disease characteristics in an indirectly-anonymized way. Furthermore, laboratory tests can be transferred automatically in the database. Because of the options for remote access and secure transfer of data from outside the Medical University of Vienna/Vienna General Hospital, it is possible to also use it outside the campus of the Medical University of Vienna and is therefore the ideal tool for a multicentric registry.

5.2 PDMS patient charts

Since 2012, electronic patient charts are used at the ICUs at the Vienna General Hospital. Patient characteristics including diagnosis, physical examination, vital signs and laboratory tests as well as therapy and medication are documented prospectively

in those charts. Data will be extracted from PDMS and entered into the RhICU database.

5.3 Variables and definitions

For the characterization of our patients, the following variables will be extracted from the electronic patient charts. For the calculation of the specific ICU scores (see below) laboratory values will also be extracted from the electronic patient charts. A detailes list of parameters can be found as supplement.

Rheumatologic diseases
Diagnosis of the underlying rheumatologic disease in our patient cohort will be established according to internationally accepted and validated criteria, such as the classification criteria by European League against Rheumatism and the American College of Rheumatology.

ICU scores
To measure the severity of disease for patients admitted to the ICU following scores will be calculated for day 1 of admission: simplified acute physiology score (SAPS II)[18], sequential organ failure assessment score (SOFA)[19], acute physiology and chronic health evaluation score (APACHE III).[20]

Reasons for ICU admission
Cardiogenic shock[21], septic shock[22], acute kidney injury[23], diffuse alveolar hemorrhage[24], acute lung injury and acute respiratory distress syndrome[25] will be diagnosed based on previously published criteria.

SRD-related therapy / life sustaining therapy at ICU
In the context of specific SRD treatments, we will focus on immunosuppressive and immunomodulatory therapies prior to as well as during the ICU stay. Clinical data related to life sustaining therapies throughout the ICU stay will be extracted from the electronical medical charts of all patients.

6. Statistical analysis

Descriptive statistical analyses will be used to give an epidemiologic/demographic overview of all included patients with systemic rheumatic disease referred to the ICU. Quantitative parameters will be presented as median (interquartile range), qualitative parameters as numbers (%). Distribution of underlying diseases will be compared to previous publications.

In case of normal distribution, metric variables will be compared between the groups using T-test. To identify differences in baseline characteristics Pearson's Chi-square test for categorical variables and the Mann-Whitney U test for non-parametric variables will be used. ICU mortality will be analyzed as a major outcome variable. Correlations between mortality and ICU-scores (SOFA, SAPSII) will be evaluated using Chi-square test and Fisher's exact test, when applicable, and the Mann-Whitney U test for non-parametric variables. For mortality analyses comparing SRD with non-SRD patients, Kaplan-Meier curves will be conducted, log-rank testing will allow comparison with the control group.

As new hypotheses will arise with time its methods and statistical analyses will do as well. Nevertheless, first analyses will include the following:

a) Since the main goal of this project is to find variables which are associated with a better/worse outcome in patients with SRDs at the ICU, those patients will be compared with non-SRD patients from the ICU 13H1 (see matching algorithm under "4. Patients"). Here, we aim for a better understanding the nature of rheumatic diseases at the ICU and its differences compared to non-SRDs.

b) Furthermore, we will explore determinants of survival within SRD-patients by multiple univariate t-tests or chi²-tests (as appropriate) to understand which variables should be considered in a subsequent multivariable model. Here, we will decide against formal correction of significance level (α=0.05) in this approach merely using a significance level of α=0.10, since the purpose is to be sensitive in the identification of possible candidate predictors of survival. If several conceptually closely related variables are significant (e.g. C-reactive protein and ESR), only one representative variable from each group will promoted into the multivariable logistic regression analysis. The multivariable model allows the assessment of the effects of single variables independent of the effect of all other relevant ones using odds ratios.

c) Finally, we plan to construct a matrix risk model based on the identified risk factors from b). In the past, these models have been used to facilitate clinical interpretation of integrated risk coming from a combination of relevant risk factors. The matrix model presents the predicted probability level of survival (including the 95% confidence interval) for each combination of single risk factors as identified before (i.e. each "risk profile"). Statistically the probability of survival over death with each risk profile is calculated by logistic

regression analysis using the maximum likelihood method. We will perform an internal validation process of the matrix risk model by bootstrapping, with 50% sampling rate and 100-fold resampling.

7. Ethical and legal considerations

The study will be performed in accordance with the guidelines of the Declaration of Helsinki (1964) including current revisions, and the rules of Good Clinical Practice of the European Commission. This study will be conducted in keeping with local legal requirements.

8. Risk-Benefit Evaluation

This study is a prospective analysis of patients with rheumatic diseases referred to the intensive care unit. Therefore, incorporated patients do not gain any benefit out of the study nor will there be any risks. No additional blood sampling, besides routine laboratory assessment, will be conducted in course of this study. The aim of this study is a better characterization of these patients in order to improve their management and outcome at the ICU.

9. Data Protection

Data privacy will be assured by numbering patients and deletion of patient names, and birthdate before initiation of analyses during data export. Access to the RhICU-Database is password protected and reserved for authorized persons only, who are involved in this study. Exported data will only pseudonymized be processed at secured computers at the Medical University of Vienna.

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