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Short- and long-term mortality due to sepsis in patients with rheumatoid arthritis

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Abstract Severe infections and sepsis are common among patients with rheumatoid arthritis (RA) and are associated with increased morbidity and mortality risks. To determine whether RA is an independent risk factor for short- and long-term mortality in patients admitted to an Intensive Care Unit (ICU) with sepsis. A retrospective age- and sex-matched cohort study, based on data of the SEPSIS-ISR Registry, an ongoing study that collects data on all patients admitted with the diagnosis of sepsis to the ICUs of 7 large hospitals during the period 2002–2012. The primary outcomes of the study were the 30-day and 3-years survival rates. A total of 124 RA patients and 248 non-RA patients (mean age 71 years; 64.5% female) were included. Primary site of infection as well as pathogens distributions were similar between the two groups. Severe sepsis and septic shock were diagnosed in 92% vs. 84% ($p=0.03$) and 50% versus 39% ($p=0.06$) of the RA patients and non-RA, respectively. 30-day survival rates were similar between groups, whereas 3-year survival rate in 30-day survivors was significantly lower among RA patients (34.9%) compared to non-RA patients (55.7%) ($p=0.01$). In multivariate Cox proportional hazards regression, RA was found to be a significant independent risk factor for 3-year mortality in 30-day survivors (hazard ratio 1.63 95% confidence interval 1.03–1.63; $p=0.04$). RA is an independent risk factor for 3-year mortality, but not short-term mortality following ICU admission with sepsis.

Keywords Rheumatoid arthritis · Sepsis · Mortality infections

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by proliferative synovitis of diarthrodial joints, serositis, lymphocytic infiltration in various tissues, vasculitis of small vessels, and production of pathogenic autoantibodies. Patients with RA have an increased age- and sex-adjusted mortality rates compared to general population [1–4]. Severe infections, cardiovascular disease, and malignancies are the main causes for hospitalization, morbidity, and mortality among patients with RA [1–3]. Patients with RA are more susceptible to serious infectious disease, including pneumonia, genitourinary infections, septicemia, and septic arthritis. Infections in RA are characterized by a more complicated course and are associated with 4–6-fold increased risk for death compared to the general population [1, 5, 6] Rheumatoid arthritis-related risk factors for severe infections include, moderate to high diseases activity [7–10], smoking [11], elevated rheumatoid factor (RF), and the presence of extra articular manifestations [12]. In addition, leukopenia, advanced age, chronic lung or renal disease, alcoholism, diabetes mellitus, and functional limitations [9, 12–14] were also found to be associated with infection among patients with RA.

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The incidence rate of sepsis in the general population is increasing in the last three decades and it associated with mortality rate of 70% [15, 16]. The morbidity and mortality risk remains high up to 5 years after the survival of an episode of sepsis [17]. The literature regarding long-term sepsis survival in patients with RA is scarce.

In this study, we aimed to determine whether RA is an independent risk factor for short- and long-term mortality in patients admitted to the ICU with sepsis. Secondary aims of this study were to identify the characteristics and survival predictors of RA patients admitted to ICU with sepsis.

Patients and methods

Patients

SEPSIS-ISR collected the data on all patients admitted with the diagnosis of sepsis to the ICUs (General ICU, Internal ICU, Respiratory ICU, and Surgical ICU) of 7 tertiary hospitals during the period 2002–2012 [16] (total number of hospitalization beds 4271, total number of ICU beds 83). From this dataset, we identified all patients with RA diagnosed with sepsis. RA and non-RA Patients were age- and gender-matched at a ratio of 1:2. The data included sociodemographic status, a complete list of chronic diseases, and medical therapies used at the enrolment into the study. Data during hospitalization included site of infection, type of pathogens isolated, complete laboratory data, calculated Charlson's comorbidity index (CCI), an index used for predicting mortality by classifying or weighting 19 comorbid conditions [18], type of sepsis (severe sepsis or septic shock), and duration of hospitalization. The 30-day and 3-year survival rates were obtained from the electronic medical records of patients.

Outcome measures

The primary outcomes were 30-day and 3-year survival rates of all patients included in the study.

Statistical analyses

Baseline characteristics of the study population were summarized using descriptive statistics. Chi-square test was used for categorical variables with the use of Fisher's exact test when needed. Continuous variables were compared using t test for normally distributed variables and by Mann–Whitney U test for non-normally distributed variables. Results are presented as mean ± standard deviation (SD) for normally distributed continuous variables or as median and interquartile range (IQR) for non-normally distributed variables. Categorical data are presented as percentage. 30-day and 3-year survival analyses were assessed by Kaplan–Meier estimates. Log-rank test was used to assess the significance of difference in survival. Given the high mortality rates during the period adjacent to the event of sepsis, we used landmark analysis for the 3-year survival analysis in which we included only patients who survived the first 30 days after admission. Multivariate analysis was performed using logistic regression for evaluating the 30-day mortality and Cox proportional hazards regression for 3-year mortality. The selection of variables for inclusion into the multivariate analyses was based clinical and statistical significance (entry criteria $p < 0.10$ in univariate analysis). The results for the logistic regression are presented as odds ratio (OR) with 95% confidence interval (CI). The results of the survival models are presented as hazard ratios (HR) with 95% CI. For all analyses, a two-sided p value < 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS software (ver. 21.0 for Windows; SPSS Inc. Chicago, Illinois, USA).

Results

The study population comprised 124 RA patients and 248 matched non-RA patients. Table 1 shows the sociodemographic characteristics and comorbidities of the cohort. Mean age at admission to the ICU was 71.0 ± 11.5 years, with 64% of the patients being women. At the time of diagnosis of sepsis 72 (58.5%) of the RA patients were treated with Corticosteroids, 29 (23.6%) with methotrexate and 6 patients (4.9%) with biological therapy. Severe sepsis was diagnosed in 114 patients (91.9%) with RA and in 208 patients without RA (83.9%) ($p = 0.03$). Sixty-two (50%) of the patients with RA and 98 (39.5%) without RA fulfilled the diagnostic criteria of septic shock ($p = 0.06$).

Table 2 shows the site of the infection. Lungs were the most common site of infection with pneumonia being diagnosed in 44 (35.5%) patients with RA and 74 (29.8%) non-RA patients, ($p = 0.27$). Staphylococcus, Klebsiella, Escherichia Coli, and Pseudomonas were the most common pathogens (data not shown). The frequency of the various pathogens did not differ significantly among RA and non-RA patients. Median hospitalization length of stay in ICU was 5.0 days (IQR 2.0–14.0 days) and 6.0 days (IQR 2.0–14.0 days) for patients with and without RA, respectively ($p = 0.55$). Hospital admission duration was 19.0 days (IQR 9.0–36.0 days) 19.5 days (IQR 9.0–35.8 days) for the patients with and without RA ($p = 0.89$).

Figure 1 shows the 3-year survival curves of patients with RA and without RA, inpatients surviving the first 30 days of the acute sepsis episode. Kaplan–Meier 30-day survival rates were 51.2 and 56.5% for RA and non-RA

Table 1 Sociodemographic characteristics and baseline comorbidities of 124 RA patients and 248 non-RA patients

Characteristic	RA patients ($N=124$)	Non-RA patients ($N=248$)	P value
Age, years (Mean ± SD)	71.04 ± 11.51	71.05 ± 11.45	1
Gender—Female (*N*, %)	80 (64.5%)	180 (64.5%)	1
Origin—Jewish (*N*, %)	104 (83.9%)	222 (89.5%)	0.12
Socio economic status			0.51
Low (*N*, %)	53 (43.4%)	76 (37.6%)	
Intermediate (*N*, %)	49 (40.2%)	85 (42.1%)	
High (*N*, %)	20 (16.4%)	41 (20.3%)	
Chronic Ischemic heart disease (*N*, %)	39 (31%)	61 (24.8%)	0.17
Congestive heart failure (*N*, %)	43 (34.7%)	65 (26.4%)	0.10
Chronic renal failure (*N*, %)	43 (34.7%)	66 (26.8%)	0.12
Liver cirrhosis (*N*, %)	3 (2.4%)	3 (1.2%)	0.41
Essential hypertension (*N*, %)	95 (76.6%)	156 (63.4%)	0.01
Diabetes mellitus (*N*, %)	71 (57.3%)	128 (52.0%)	0.34
Cerebral vascular accident (*N*, %)	22 (17.7%)	42 (17.1%)	0.87
Chronic lung disease (*N*, %)	34 (27.4%)	52 (21.1%)	0.12
Smoker (*N*, %)	17 (13.7%)	46 (18.7%)	0.23
Leukemia (*N*, %)	1 (0.8%)	2 (0.8%)	1
Lymphoma (*N*, %)	5 (4.0%)	4 (1.6%)	0.17

Table 2 Confirmed infection site during sepsis in RA patients and non-RA patients

Infection site	RA	Non-RA	P value
Pneumonia (*N*, %)	44 (35.5%)	74 (29.8%)	0.27
Urinary tract infection (*N*, %)	11 (8.9%)	36 (14.5%)	0.12
Peritonitis (*N*, %)	14 (11.3%)	36 (14.5%)	0.39
Cellulitis (*N*, %)	9 (7.3%)	8 (3.2%)	0.08
Gastroenteritis (*N*, %)	4 (3.2%)	11 (4.4%)	0.58
Other sites (*N*, %)	19 (15.3%)	39 (15.7%)	0.92

patients, respectively ($p=0.38$), and a 3-year survival of 34.9% for RA patients versus 55.7% among non-RA patients ($p=0.01$). Univariate analysis of variables associated with 30-day mortality is shown in Table 3. In the adjusted multivariate analysis, RA was not associated with mortality at 30-days (OR 1.03; 95% CI 0.65–1.63).

Table 4 shows variables associated with mortality at 3-year after the diagnosis of sepsis (landmark analysis). In the adjusted landmark analysis of 3-year survival (Cox proportional regression model), RA was associated with increased hazard ratio of 3-year mortality (HR 1.63; 95% CI 1.03–2.57), (Table 5).

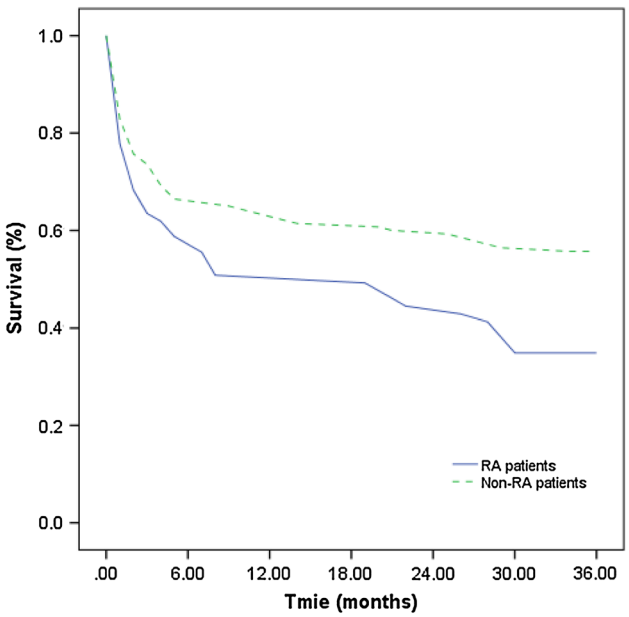

Fig. 1 Kaplan–Meier 3-year survival plots (landmark analysis) for RA patients and non-RA patients

Discussion

This retrospective matched cohort study included all RA patients with sepsis admitted to the ICU in 7 general hospitals from 2002 to 2012. We analyzed the type and causes of sepsis, carried out life table analyses, and conducted uni- and multivariate analyses to identify variables associated with death following sepsis and patient with RA and matched non-RA patients.

We have demonstrated that RA was not an independent risk factor for 30-day mortality, but was associated with a

Table 3 Univariate odds ratio for the relationship between 30-day mortality and clinical variables

Risk factor	Odds ratio	*P* value	95% CI
RA	1.22	0.377	0.79–1.87
Age	1.02	0.042	1.00–1.04
Cardiovascular dysfunction[b]	2.58	<0.001	1.68–3.95
Severe sepsis	2.98	0.002	1.50–5.90
Septic shock	2.78	<0.001	1.82–4.25
Multi-organ dysfunction[a]	1.35	0.004	1.10–1.57

[a]Multi-organ dysfunction = number of systems that were involved during severe sepsis (0, 1, 2)

[b]System involvement in severe sepsis during hospitalization

Table 4 Univariate hazard ratio for the relationship between 3-year* mortality and clinical variables

Risk factor	Hazard ratio	*P* value	95% CI
RA	1.65	0.013	1.11–2.44
Age	1.02	0.032	1.00–1.04
Congestive heart failure[†]	2.37	<0.001	1.59–3.52
Diabetes mellitus[†]	1.78	0.005	1.19–2.64
Charlson comorbidity index	1.31	<0.001	1.16–1.46
Intensive Care Unit days	1.01	0.003	1.00–1.02
Sever sepsis	2.00	0.024	1.09–3.65
Respiratory dysfunction[††]	2.20	<0.001	1.42–3.40
Multi-organ dysfunction*	1.33	0.003	1.10–1.61

Odds ratio for three-year mortality was performed using landmark analysis from 30 days after admission. Multi-organ dysfunction = number of systems that were involved during severe sepsis (0, 1, 2, 3)

[†]Comorbidity prior admission with sepsis

*Site of infection

[††]System involvement in severe sepsis during hospitalization,

Table 5 Independent risk factors for 36 months mortality after sepsis in multivariate analysis

Variable	Adjusted hazard ratio	*P* value	95% CI
RA	1.63	0.038	1.03–2.57
+	1.29	0.001	1.12–1.50

The model was adjusted for RA, age, Charlson Comorbidity Index, Congestive heart failure, diabetes mellitus, severe sepsis, number of ICU admission days, number of systems involved in multi-organ failure during the course of sepsis

more than 50% increase in mortality risk at 3 years in acute sepsis survivors. To the best of our knowledge, our study is the first to report 3-year survival of patients with RA admitted to ICU. Previous studies on sepsis in the general population reported long-term sequelae following sepsis. In Wang et al. study 1-year, 2-year, and 5-year survival among individuals with sepsis were 77, 71.2, and 56.2%, respectively [19]. Lemay et.al. study showed 1- and 2-year survival rates of 69 and 57%, respectively [20]. These rates are on par with the findings in non-RA cohort in our study. However, 3-year survival rate in patients with RA was 34.9%. The causes of the significantly increased 3-year mortality among RA patients after surviving the acute phase of sepsis are not clear. This could be related to long-term morbidity as a result of sepsis, in patients who fundamentally have a reduced immunological capacity, secondary to RA or the use of immunosuppressive medications, or it could be the result of the generally increased mortality seen among patients with RA due to increased rates of cardiovascular complications, malignancies, chronic lung diseases, and other causes.

The results of the study indicate that the site of infection and the pathogens of sepsis among patients with RA were similar to those of patients without RA. Lungs were the most common site of infection with pneumonia being diagnosed accounting for a third of the sepsis causes. Staphylococcus was the most common pathogen to be isolated in both groups. Similar data were reported by Vincent et.al [15]. Lungs were the predominant site of infection in patients admitted to the ICU with sepsis in several studies [21, 22]. In Sihvonen et al. study, pneumonia was the leading cause of infection site among RA patients [5].

In our study, the course of sepsis was more complicated among patients with RA compared to patients without RA. There was a trend suggesting a higher rate of severe sepsis and septic shock among RA patients compared to non-RA patients during ICU admission. The association between RA and serious infections including more complicated course requiring hospitalization was already reported in several RA studies [3, 4, 9], but the role of RA diagnosis on the course of sepsis was not reported previously.

In our study, more than half of the sepsis patients died within 30 days of the admission. Despite the higher prevalence of complicated severe forms of sepsis among the RA patients, the 30-day mortality was not significantly higher among the RA patients compared to the non-RA patients. Overall, this rate is higher than seen in other reports [19, 23]. Plausible explanations for the higher rates of in-hospital mortality in our study include low ratio of ICU-to-general medical beds which is estimated to be only 3%, resulting in selective admission of only very sick patients and early transfer of patients from the ICU to the medical wards. Moreover, our population was older than reported in other sepsis studies. Similar to our results, others also showed higher short-term mortality rates associated with advanced age [16, 17], septic shock, prior comorbidities, and number of organ systems affected by the septic event [15, 16, 24, 25]. The lack of association between RA

diagnosis and early mortality could be explained by the fact that the mortality in short term is a derivative of the severity of the acute disease and not of the underlying condition. This may suggest that the immune-suppression state as a result of corticosteroids, methotrexate, and biologic therapies has only marginal effect on short-term mortality from sepsis among patients with RA.

Limitation

Our study has several limitations: being a retrospective study, our study in inherently prone to various sources of bias and confounders. The use of ICD-codes to identify and evaluate the severity of sepsis is valid and has been previously used, but can lead to bias if the coding was incomplete or erroneous. Moreover, in 2016, sepsis definitions and clinical criteria have changed [26], posing a question of generalizability of our results in the current ICU climate. Yet, sepsis diagnosis in our study was in accordance with the well-validated diagnostic criteria that were in consensus at that time [23], while the applicability of the new definition for the use in administrative database analysis is yet to be established. Secondly, the use for the previous definition allows for the external comparison of the cohort characteristics and mortality rates to the previously published reports. Finally, our cohort included only patients admitted to the ICU with diagnosis of sepsis, thus we can assume that these critically ill patients would fulfill the new sepsis criteria.

Summary

In summary, our data suggest that patients with RA present with higher rates of severe sepsis and septic shock. Sepsis among patients with RA admitted to ICU is associated with very high in-hospital mortality and reduced survival up to 3 years after sepsis. RA is an independent risk factor for late mortality in acute sepsis survivors.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval The study was approved by the local ethics committee. All procedures performed in the participants were in accordance with ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was not required for this study (retrospective data).

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