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ORIGINAL ARTICLE

RABBIT risk score and ICU admission due to infection in patients with rheumatoid arthritis

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Abstract Rheumatoid arthritis (RA) patients are at increased risk of infection. Aim of the present study was to investigate whether RA patients admitted to an intensive care unit (ICU) due to infection have higher Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) risk scores compared to control RA patients. Seventy-four RA patients (32.4% male) admitted to an ICU due to infection (from January 2002 to December 2013) and 74 frequency-matched control RA patients (16.2% male) were included in this cross-sectional study. There was strong evidence for a higher RABBIT risk score in ICU patients (median 2.0; IQR 1.3–3.2) as compared to controls (1.3; IQR 0.8–2.0; $p < 0.0001$). Traditional disease-modifying anti-rheumatic drugs (DMARDs) (82.4 vs 64.9%; $p = 0.015$) and biological DMARDs (28.4 vs 14.9%; $p = 0.012$) were more frequently given to RA patients without ICU admission. Glucocorticoid users were more frequently found in the ICU group (51.4 vs 31.1%; $p = 0.012$). In a multivariable analysis tDMARD use was associated with lower (OR 0.38; 95% CI 0.15–0.93; $p = 0.034$) and glucocorticoid use with borderline higher odds of ICU admission (OR 2.05; 95% CI 0.92–4.58; $p = 0.078$). Chronic obstructive pulmonary disease (OR 2.89; 95% CI 1.10–7.54; $p = 0.03$), chronic kidney disease (OR 16.08; 95% CI 2.00–129.48; $p = 0.009$), and age category (OR 2.67; 95% CI 1.46–4.87; $p = 0.001$) were strongly associated with ICU admission. There was a strong trend towards higher odds of ICU admission with increasing RABBIT risk score. Use of tDMARDs was associated with lower odds of ICU admission. In an adjusted analysis, bDMARDs were not associated with ICU admission. COPD, CKD, and age were strong risk factors for ICU admission.

Keywords Infection · Intensive care unit · RABBIT · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) patients have an increased risk of infection, which significantly contributes to morbidity and mortality in this particular group of patients [1, 2]. The increased infectious risk may be related to RA itself as well as to immunosuppressive/immunomodulatory effects of anti-rheumatic treatment [3]. Previously, several studies found an association between infections and the use of biological disease-modifying anti-rheumatic drugs (bDMARDs) [4–7]. A similar association has also been reported for methotrexate [5]. However, most importantly, glucocorticoids (GC) have been consistently shown to be a strong risk factor for infections [5, 8, 9]. Obviously, the infectious risk of an individual RA patient cannot be solely explained by anti-rheumatic treatment. Beside pharmacological therapies, factors such as age, co-morbidities, low functional capacity, and history of

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previous infections significantly increase the risk of infection [10]. In order to be able to estimate the probability of RA patients to acquire a serious infection during the next 12 months, the Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) risk score was developed [10, 11]. This risk score is a helpful tool in daily clinical practice to identify patients at risk for infection.

There is limited knowledge about RA patients admitted to an intensive care unit (ICU) due to infection. While some studies included patients with rheumatic diseases attending the ICU, these studies commonly included a mix of patients with quite different diseases, such as connective tissue diseases, vasculitis, spondyloarthritis, RA, and other autoimmune disorders [12–14]. In addition, reasons for ICU admission usually covered a wide spectrum of indications (e.g., cardiovascular disease, infections, worsening of underlying inflammatory rheumatic disease, etc.) [12, 15]. A population-based Canadian study found an overall increased risk of ICU admission for RA patients compared to the general population (HR 1.65; 95% CI 1.50–1.83) [14]. In general, ICU admissions are associated with significant burden for the critical ill. Mortality in patients with autoimmune diseases admitted to an ICU has been reported to be in the range of 17–55% [12].

While there are some data concerning the outcome of RA patients admitted to an ICU, there is substantial lack of knowledge on predictors for ICU admission of RA patients due to infection. Given the usefulness of the RABBIT risk score to estimate the 12-month risk of infection in RA patients, aim of the present study was to investigate whether a higher RABBIT risk score would also be associated with an increased risk for ICU admission due to infections. In addition, we were interested whether the use of GCs, bDMARDs, or tDMARDs is associated with ICU admission due to infection.

Methods

The study was approved by the local ethics committee (Land Oberösterreich; K-88-15) and is in accordance with the Helsinki Declaration. Data were retrieved retrospectively from the hospital's own electronic database.

Study design

This is a case-control study. Cases and controls were frequency matched (time period of admission).

Setting

The study was performed at the Kepler University Hospital, Med Campus 3, Linz, Austria (formerly: General Hospital Linz), a tertiary referral center. This hospital has a total of four ICUs: two ICUs at the Department of Anesthesiology and Operative Intensive Care Medicine and one at the 1st Department of Internal Medicine and one at the Department of Neurology.

Participants

Patients with RA admitted to one of these ICUs with an infection that required parenteral treatment with antibiotics were included as cases. The diagnosis of RA was registered when reported at the medical report from the ICU or other medical documents archived in our electronic database and verified by a rheumatologist (as long as the diagnosis was already established at the time point of admission to the ICU). Time of recruitment was from January 2002 to December 2013; according to our sample size calculations, this resulted in an adequate number of participants (see below). Patients were included independently of whether they received routine care at the hospital's Rheumatology Outpatient Clinic or elsewhere. For each patient admitted to the ICU, the first RA patient visiting the Rheumatology Outpatient Clinic after the time of admission of the index case at the ICU was selected as a control. In order to be able to investigate the impact of age and sex on the outcome variable, we did not match for these parameters. Of note, this might result in an unequal distribution of these variables, but matching for, e.g., age would preclude any further impact of age—a potential important risk factor—on ICU admission. Cases and controls were frequency matched by time period of admission (1:1 ratio).

Variables

Primary outcome was ICU admission due to infection. Main exposure variable was the RABBIT risk score [10]. Data were extracted from the electronic hospital records. Traditional disease-modifying anti-rheumatic drugs (tDMARDs) were defined as either one or a combination of the following drugs: methotrexate (MTX), leflunomide, sulfasalazine (SSZ), chloroquine, azathioprine, tacrolimus, or mycophenolate mofetil (MMF). Biological disease-modifying anti-rheumatic drugs (bDMARDs) were defined as: adalimumab, etanercept, infliximab, rituximab, abatacept, and tocilizumab (other biological agents were not used by the participants in the study).

Study size

We expected that the distribution of the RABBIT risk score would be positively skewed. This would make sample size calculations somewhat inaccurate, as these usually depend on normally distributed data. For sample size calculations, we therefore estimated means and added 15% to the total sample size [16]. We assumed a difference of mean scores of at least 1% and a standard deviation (SD) of 2 in each group.

With an allocation ratio of 1:1, alpha risk of 0.05, and 80% power (beta 0.20), we calculated a total sample size of $n = 128$ (64 in each group). As we expected data to depart from a normal distribution and we, therefore, considered a potential loss of power, we increased the sample size by 15%, which gives a total of $n = 148$ (74 in each group).

Quantitative variables

We used quantitative variables mainly as continuous parameters. Age (20-year age bands) and RABBIT risk score (0; 1; 2; 3; 5; > 5) were also transformed into ordered categorical variables to analyze a dose-response relationship.

Statistical methods

Primary outcome was the RABBIT risk score. The null hypothesis was that there is no difference in the RABBIT risk score between the ICU group and the control group. The alternative hypothesis was that there is a difference. Most continuous parameters, including the RABBIT risk score, were not normally distributed. Therefore, we used the Wilcoxon rank sum test for comparison of groups. The spread of continuous parameters is given as interquartile range (IQR). For the analyses of categorical data, we used the chi-square test and, if appropriate, a test for trend. In addition, we calculated odds ratios (OR) and 95% confidence intervals (CI). We used logistic regression for multivariable analyses (outcome: ICU admission). Due to conceptual considerations, the parameters "GC use," "bDMARD use," and "tDMARD use" were kept in the multivariable regression even if not statistically significant in the Wald test (see above). To compare different multivariable models, we used the likelihood-ratio-test (LRT). The linktest was used to investigate potential specification errors. The Hosmer-Lemeshow-test (with 10 groups) was used to analyze the goodness-of-fit of the model. Furthermore, we tested the variables in the model for collinearity. Initially, we used age category as a categorical parameter. However, according to the LRT, using age category as a continuous parameter did not result in departure from a linear trend and age category was, therefore, used as continuous parameter in a simplified model. This allowed the estimation of fewer parameters and gave more power for the parameters in the regression model. We classified individuals as cases if the predicted probability of ICU admission was equal or higher to 0.5 and calculated sensitivity, specificity, positive predictive value, and negative predictive value. In addition, we calculated the area under the curve (AUC) of the receiver operating characteristics (ROC) curve. We performed all analyses with Stata 13 IC (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

A total of 148 patients were included in the study: 74 RA patients had an ICU admission due to infection and 74 RA patients served as controls. Of those patients admitted to the ICU, 66 survived and 8 died, giving a mortality rate of 10.8%. The following infections were indications for ICU admission: 30 respiratory infections (40.5%), 13 postoperative infections (17.6%), 8 gastrointestinal tract infections (10.8%), 4 urinary tract infections (5.4%), 4 skin infections (5,4%), 3 endocarditis/pericarditis (4.1%), 1 gynecologic infection (1.4%), 1 meningitis (1.4%), 1 septic arthritis (1.4%), and 9 unknown origin (13.5%).

Table 1 summarizes the characteristics of RA patients with ICU admission and controls. Male RA patients were more likely in the ICU group (24/74; 32.4%) than in the control group (12/74, 16.2%; $p = 0.022$). Cases were older than controls: the median age in the ICU group was 71 years (IQR 63–77) and in the control group median age was 59.5 years (IQR 49–70; $p < 0.0001$). We found a strong trend for higher odds of ICU admission with increasing age category (Table 2). There was strong evidence for a higher RABBIT risk score in ICU patients (median 2.0; IQR 1.3–3.2) as compared to controls (1.3; IQR 0.8–2.0; $p < 0.0001$). As Table 3 shows, there was a strong trend towards higher odds of ICU admission with increasing RABBIT risk score. However, the power of the RABBIT risk score to discriminate between RA patients with and without ICU admission was low. Using logistic regression (exposure: RABBIT risk score; outcome: ICU admission) and classifying individuals as cases if the predicted probability of ICU admission was equal or higher to 0.5, the sensitivity of the RABBIT risk score was 59.5%, specificity 74.3%, positive predictive value 69.8%, and negative predictive value 64.7%. The area under the curve (AUC) of the receiver operating characteristics (ROC) curve was 0.70.

tDMARDs were more frequently given to RA patients without ICU admission than to patients in the ICU group: while 61/74 (82.4%) of control RA patients received treatment with tDMARDs, that group of anti-rheumatic drugs was given to only 48/74 (64.9%) in the ICU group ($p = 0.015$). This gave an OR of 0.39 (95% CI 0.18–0.86) for tDMARD use and ICU admission. Patients who received tDMARDs were younger (median age 63 years; IQR 52.0–72.0) than those not receiving tDMARDs (median age 71 years; IQR 62.0–76.0; $p = 0.027$). In univariable analysis, bDMARDS were more frequently prescribed to RA patients in the control group (21/74; 28.4%) than to RA patients in the ICU group (11/74; 14.9%; $p = 0.046$; OR 0.44, 95% CI 0.19–1.00). bDMARDs were more frequently prescribed to younger RA patients (bDMARD users median age 60.5 years (IQR 51–68) vs bDMARDs non-users median age 68 years (IQR 56–75); $p = 0.002$). In univariable analysis, there were more GC users in the ICU group (38/74; 51.4%) than in the control group (23/

Table 1 Characteristics of RA patients with and without ICU admission

	ICU no (n = 74)	ICU yes (n = 74)	Total (n = 148)	p value
RABBIT score (median)	1.3 (IQR 0.8–2.0)	2.0 (IQR 1.3–3.2)	1.3 (IQR 1.3–2.4)	< 0.0001
Age (years, median)	59.5 (IQR 49.0–70.0)	71.0 (IQR 63.0–77.0)	66.0 (IQR 54.0–74.5)	< 0.0001
Male	12 (16.2%)	24 (32.4%)	36 (24.3%)	0.022
GCs	23 (31.1%)	38 (51.4%)	61 (41.2%)	0.012
bDMARDs	21 (28.4%)	11 (14.9%)	32 (21.6%)	0.046
bDMARDs used in the ICU and control group				
None	53 (71.6%)	63 (85.1%)	116 (78.4%)	
Adalimumab	7 (9.5%)	5 (6.8%)	12 (8.1%)	
Etanercept	4 (5.4%)	3 (4.1%)	7 (4.7%)	
Infliximab	1 (1.4%)	1 (1.4%)	2 (1.4%)	
Rituximab	4 (5.4%)	2 (2.7%)	6 (4.1%)	
Abatacept	2 (2.7%)	0 (%)	2 (1.4%)	
Tocilizumab	3 (4.1%)	0 (%)	3 (2.0%)	
tDMARDs	61 (82.4%)	48 (64.9%)	109 (73.7%)	0.015
tDMARDs used in the ICU and control group				
None	13 (17.6%)	26 (35.1%)	39 (26.4%)	
MTX	50 (67.6%)	26 (35.1%)	76 (51.4%)	
Leflunomide	12 (16.2%)	13 (17.6%)	25 (16.9%)	
SSZ	8 (10.8%)	5 (6.8%)	13 (8.8%)	
Chloroquine	3 (4.1%)	6 (8.1%)	9 (6.1%)	
Azathioprine	0 (0%)	1 (1.4%)	1 (0.7%)	
Tacrolimus	0 (0%)	1 (1.4%)	1 (0.7%)	
MMF	0 (0%)	1 (1.4%)	1 (0.7%)	

bDMARD biological disease-modifying anti-rheumatic drugs, *GC* glucocorticoids, *MMF* mycophenolate mofetil, *MTX* methotrexate, *SSZ* sulfasalazine, *tDMARD* traditional disease-modifying anti-rheumatic drugs

74; 31.1%; p = 0.012). This gave an OR of 2.34 (95% CI 1.18–4.66) for GC use in the ICU group compared to the control group. There was a trend for higher age in GC users (median 68 years; IQR 55–75) compared to GC non-users (median 63 years; IQR 52–74), but this trend did not reach statistical significance (p = 0.17).

In an adjusted analysis, we calculated a logistic regression model to estimate the odds of ICU admission. Besides accounting for potential confounders, we also included the variables GC use, bDMARD use, and tDMARD use in the model in order to be able to evaluate the impact of these anti-rheumatic drug classes on ICU admission (Table 4). In a multivariable analysis, GC use was borderline associated with higher odds of ICU admission (OR 2.05; 95% CI 0.92–4.58; p = 0.078) and tDMARD use was associated with lower odds of ICU admission (OR 0.38; 95% CI 0.15–0.93; p = 0.034). For bDMARDs use, the multivariable analysis only gave a trend towards lower odds of ICU admission, but this was not statistically significant and the 95% CI was broad (OR 0.64; 95% CI 0.24–1.68; p = 0.360). Chronic obstructive pulmonary disease (COPD) (OR 2.89; 95% CI 1.10–7.54; p = 0.03), chronic kidney disease (CKD) (OR 16.08; 95% CI 2.00–129.48; p = 0.009), and age category (OR 2.67; 95% CI 1.46–4.87; p = 0.001) were strongly associated with ICU

Table 2 Admission to ICU: effect of increasing age category. There was a strong trend for higher odds of ICU admission with increasing age category. The category with the lowest risk is used as reference category

Age category (years)	ICU no	ICU yes	Total	OR (95%CI)
20- < 40	7 (9.5%)	1 (1.4%)	8 (5.4%)	1.0 (ref)
40- < 60	30 (40.5%)	10 (13.5%)	40 (27.0%)	2.3 (0.25–22.17)
60- < 80	33 (44.6%)	50 (67.6%)	83 (56.1%)	10.6 (1.1–99.4)
80-	4 (5.4%)	13 (17.6%)	17 (11.5%)	22.8 (1.1–473.1)
Total	74 (100.0%)	74 (100.0%)	148 (100.0%)	

Test of homogeneity p < 0.0001; test for trend of odds: p < 0.0001

Table 3 Admission to ICU: increasing RABBIT risk score. There was a strong trend for higher odds of ICU admission with increasing RABBIT risk score category. The category with the lowest risk is used as reference category

RABBIT score (points)	ICU no	ICU yes	Total	OR (95%CI)
0- < 1	23 (31.1%)	6 (8.1%)	29 (19.6%)	1.0 (ref)
1- < 2	32 (43.2%)	24 (32.4%)	56 (37.8%)	2.88 (0.98–8.43)
2- < 3	13 (17.6%)	21 (28.4%)	34 (23.0%)	6.19 (1.76–21.73)
3- < 5	5 (6.8%)	12 (16.2%)	17 (11.5%)	9.20 (1.86–45.59)
5-	1 (1.4%)	11 (14.9%)	12 (8.11%)	42.17 (2.11–844.49)
Total	74 (100.0%)	74 (100.0%)	148 (100.0%)	

Test of homogeneity $p = 0.0001$; test for trend of odds: $p < 0.0001$

admission. Sex was no longer significant in the multivariable analysis. Classifying individuals as cases if the predicted probability of ICU admission was equal or higher to 0.5, the sensitivity of the model was 73.0%, specificity 71.6%, positive predictive value 72.0%, and negative predictive value 72.6%. The AUC of the ROC curve was good with 0.82.

Discussion

The RABBIT risk score was higher in RA patients with ICU admission due to infection (median 2.0; IQR 1.3–3.2) as compared to controls (1.3; IQR 0.8–2.9.; $p < 0.0001$). We found a strong trend towards higher odds of ICU admission with increasing RABBIT risk score. Increasing age, which is used as a binary variable in the RABBIT risk score, also showed a strong trend towards higher odds of ICU admission. In univariable analysis, GC use was associated with increased odds of ICU admission, and tDMARDs as well as bDMARD use was associated with decreased odds of ICU admission. In multivariable analysis, tDMARDs remained statistically significant and was associated with a lower odds of ICU admission, and GC use was borderline significant. After adjustment bDMARDs were no longer associated with ICU admission. COPD, CKD, and age category were independently associated with ICU admission. For some of the analyses, we found broad 95% CIs. This results if the particular stratum contains only a few patients (e.g., age categories) or the outcome is rare (e.g., CKD). In addition, we defined the category with the lowest risk to be the reference category in those analyses describing a dose-response relationship (e.g., increasing risk of ICU admission with increasing age category). If the reference category is smaller than CIs also tend to be broader.

Table 4 Multivariable analysis of exposure variables and outcome ICU admissions (multivariable logistic regression)

Exposure variable	OR	(95% CI)	*p* value
tDMARD use	0.38	(0.15–0.93)	0.034
bDMARD use	0.64	(0.24–1.68)	0.360
GC use	2.05	(0.92–4.58)	0.078
COPD	2.89	(1.10–7.54)	0.030
CKD	16.08	(2.00–129.48)	0.009
Age category *	2.67	(1.46–4.87)	0.001

bDMARD biological disease-modifying anti-rheumatic drugs, *tDMARD* traditional disease-modifying anti-rheumatic drugs, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease

*Baseline is age category 20- < 40

In general, RA patients have an increased risk of infection [1, 2]. For instance, in a previous study, the adjusted HR for objectively confirmed infections and infections requiring hospitalization in RA patients were 1.70 (95% CI 1.42–2.03) and 1.83 (95% CI 1.52–2.21) compared to non-RA patients [3]. Infections are among the main reasons for ICU admission of patients with different inflammatory rheumatic diseases [12, 13, 15, 17]. Of note, there are limited data regarding ICU admission due to infection in RA patients. In the Canadian study mentioned above, the overall age- and sex-standardized 10-year cumulative incidence risk of ICU admission in RA patients was quite impressive: 7.68% of RA patients (95% CI 7.04–8.32) were admitted to an ICU within one decade. For the general population, the 10-year risk was 4.73% (95% CI 4.62–4.83). Most common reasons for ICU admission were ischemic heart disease (45.8%) and infections (19.8%). Compared to the general population, the adjusted OR for ICU admission was 1.74 (95% CI 1.30–2.31). According to the authors, immunomodulatory/immunosuppressive therapy was not associated with ICU admission due to infection, but GC use was (OR 1.97; 95% CI 1.53–2.52) [14]. ICU admission in patients with autoimmune diseases is associated with significant morality and is within the range of 17–55% [12]. In a previous study, more severe organ dysfunction, lung infection, acute exacerbation of the underlying rheumatic disease, as well as the need for vasopressive drugs were independent predictors of 30-day mortality in patients with systemic rheumatic diseases admitted to an ICU [15].

An important risk factor for infection in RA patients is GC use. While—in general—bDMARDs are associated with infection [4–7, 18], a deeper look into this matter reveals a more complex picture. Previous research indicated that the increased risk of hospitalization due to infection in RA patients treated with tumor necrosis factor (TNF)

antagonists is time dependent and diminishes with increasing treatment duration [19]. However, at least in part, this decline is explained by treatment termination or loss to follow-up in patients at increased risk as well as a risk reduction through decreasing GC doses and improvement in function [10].

While it is not uncommon to discontinue DMARDs in the case of severe infection, previous research could show that—compared to tDMARDs—the risk of developing sepsis was lower when patients were exposed to bDMARDs at the time of severe infection (OR 0.56, 95% CI 0.38–0.81). Patients treated with bDMARDs and those with better physical function had a significantly lower mortality. Compared to patients receiving < 5 mg daily steroid dose, those with >= 10 mg per day had an OR of 2.40 (95% CI 1.04–1.55) for death [20].

Our findings demonstrate that tDMARD and GC use in RA patients appear to be modifiable risk factors for infection requiring ICU admission. tDMARDs are associated with a decreased odds for ICU admission, while GC use seems to be associated with an increased risk. Of note, while one might feel that bDMARDs may be associated with an increased odds of ICU admission, this was not the case in our study. RA patients admitted to the ICU were older and tended to have a "more conservative" anti-rheumatic treatment regime with rather more GC use and rather less use of tDMARDs or bDMARDs. It might be the case that tDMARD/bDMARD use was previously stopped in patients having been hospitalized (especially in the case of infection) or those with significant co-morbidities (e.g., CKD). This might be due to the fear of increased risk of infection and, in turn, might lead to more frequent use of GCs and less frequent administration of DMARDs in older RA patients. However, also in elderly RA patients, GC use is a strong risk factor for infection, while bDMARD treatment does not seem to be [21, 22]. Of note, several studies report that elderly patients with RA often do not receive adequate therapy with DMARDs [23–26], despite the fact that efficacy is comparable to younger patients [27, 28]. These data are in line with our results. It should be stressed out that continuous GC use is not associated with sustainability of disease remission, but—as discussed above—is a risk factor for the development of infection [9]. In a previous US study, the prevalence of GC use in RA patients was reported to be 35.5%. Lifetime GC use was as high as 65.5%. While treatment with GCs was very dynamic, persistent use (> 5 years) was found in one third of patients [29]. Summing up all these points, with regard to infections, it seems reasonable to encourage the use of tDMARDs. As bDMARDs are not associated with ICU admission due to infection withholding those drugs (and probably favor GC use) due to fear of severe infection does not seem to be justified.

This study adds new information regarding risk factors for ICU admission of RA patients due to infection. Given the case-control design of the study, we were able to investigate different exposure variables at the same time. In order to be able to investigate the impact of age, sex, and co-morbidities on the outcome variable, we did not match for these parameters. That said, it was very likely from the beginning that a number of these factors will be distributed unequally between the groups. However, as these factors are exposures with regard to ICU, admission matching for these factors would preclude any further analyses. Adjustement for these factors has been done by multivariable analyses. We had sufficient power to detect a meaningful difference in the RABBIT risk score between the two groups. Our study has some limitations. First, due to its retrospective design, there might be measurement error, leading to misclassification. However, as this misclassification would most likely be non-differential, associations might be underestimated (i.e., no non-present associations can be found). That said, the effect of GCs or bDMARDs rather seems to be underestimated. Secondly, if the diagnosis of RA would not have been registered at the ICU (and at potential other visits in our hospital), these patients would have been missed. This could lead to selection bias. However, it is not clear how such patients might differ from RA patients with ICU admission included in our study. Third, as the number of available variables is limited, there might be residual confounding. In addition, we did not have detailed information in the ICU group concerning RA disease characteristics, first of all disease activity scores, which might have an influence on treatment strategy as well as the outcome. Fourth, our study was powered to detect differences in the RABBIT risk score. The study has not been powered for the analysis of secondary endpoints or multivariable analysis. For instance, the effect of bDMARD use was statistically significant in univariable analysis, but not in the multivariable logistic regression. It is possible that in a larger sample, the effect of bDMARDs on ICU admission might become statistically significant. Given the fact that our inclusion and exclusion criteria were very broad, we believe that data from this study are quite generalizable, even if the study was performed at a tertiary referral center.

In conclusion, the RABBIT risk score was higher in RA patients with ICU admission due to infection as compared to controls and there was a strong trend towards higher odds of ICU admission with increasing RABBIT risk score. Use of tDMARDs was associated with lower odds of ICU admission. In an adjusted analysis, bDMARDs were not associated with ICU admission. COPD, CKD, and age are strong independent and non-modifiable risk factors for ICU admission. Given the results of the present study, it appears reasonable to encourage the use of tDMARD and discourage use of GC also with regard to ICU admission due to infection. bDMARDs do not appear to be a risk factor for ICU admission. These points should also be considered in older RA patients with need for anti-rheumatic treatment.

There was no sponsor for this study. The authors have full control of all primary data and agree to allow the journal to review their data if requested.

Compliance with ethical standards

Disclosures None.

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