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*a retrospective cohort study*

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**Title:**

# Transmission of Rheumatoid Arthritis through blood transfusion: A retrospective cohort study

**Authors:**

Søren Andreas Just[1], Klaus Rostgaard[2], Kjell Titlestad[3], Gustaf Edgren[4], Christian Erikstrup[5], Henrik Ullum[6], Ole B Pedersen[7], Kaspar Rene Nielsen[8], Johan Askling[9], Hanne Lindegaard[1], Henrik Hjalgrim[2,10]

[1]Department of Rheumatology, Odense University Hospital, Odense, Denmark

[2]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark

[3]Department of Clinical Immunology, Odense University Hospital, Odense, Denmark

[4]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, and Department of Cardiology, Södersjukhuset, Stockholm, Sweden

[5]Department of Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark

[6]Department of Clinical Immunology, The Blood Bank, Rigshospitalet, Copenhagen, Denmark

[7]Department of Clinical Immunology, Næstved Sygehus, Næstved, Denmark

[8]Department of Clinical Immunology, Aalborg University Hospital, Aalborg, Denmark

[9]Clinical Epidemiology Section, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden, and Department of Rheumatology, Karolinska University Hospital, Stockholm, Sweden

[10]Department of Hematology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

**Corresponding Author:** Søren Andreas Just, Department of Rheumatology

Odense University Hospital, Sdr. Boulevard 29, DK-5000 Odense C, Denmark

E-mail: soeren.andreas.just@rsyd.dk, Tel.: +45 26 71 45 67

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**Research (Letter)**

The long pre-clinical phase of Rheumatoid Arthritis (RA), where some factors involved in RA pathogenesis circulate peripherally, raises concern of RA transmissibility through blood transfusion.[1]

We used a large Danish-Swedish population-based research donations and transfusions database (SCANDAT2) with health register information on 1.5 million blood donors and 2.1 million recipients of their blood to investigate: (1) RA occurrence in recipients of blood from donors who later developed RA and (2) clustering of RA among recipients of blood from individual donors, regardless of the donor's RA status.[2 3 4]

We used two different approaches to analyze RA transmission. First, we identified all donors who developed RA after blood donation. For each of these index donors, we identified up to 10 donors matched on age, sex, county, date of first donation, number of donations, and ABO blood group, who were free of RA at the date of index donor diagnosis. We then identified all recipients of blood from the two donor populations, and followed them from date of transfusion originating in said donors until date of RA diagnosis, death, emigration, or end of 2012 (Sweden)/2013 (Denmark), whichever came first.

In the second approach, we investigated if RA clustered among recipients of blood from individual donors. Here, we used a modified time-dependent donor riskiness score by simply counting the RA occurrences among past recipients of each donor.

In both approaches, we used Cox regression with age as underlying time scale, with an exposure lag of 1 year and strata defined by sex and hospital. All analyses were adjusted for calendar period and number of transfusions as restricted cubic splines with 5 equally spaced knots and ABO blood group. Persons with RA were identified using contemporary national ICD 7, 8, 9 and 10 classifications. To reduce misclassification, we defined RA as having two registrations of RA

within the course of a two-year period. RA diagnoses were further sub-classified as seropositive RA or seronegative RA.

Among a total of 938,942 blood donors, 2412 were diagnosed with RA during follow-up. We identified 13,369 patients (exposed) who received at least one unit from donors with later RA, and 139,470 patients (unexposed) who received blood units from the matched donors who were free of RA at selection.

Analyses comparing RA occurrence in blood recipients to donors who did versus did not develop RA themselves showed that recipient RA risk did not vary by donor RA occurrence (HR = 1.04; 95% CI 0.80-1.35) (Table 1). Similarly, no association between donor and recipient RA was seen in analyses stratified according to RA serotype, donor age or interval between donation and donor RA diagnosis (Table 1).

**Table 1** Number of cases of rheumatoid arthritis (RA) overall and of seropositive RA and seronegative RA, respectively, observed among recipients whose blood donors were (exposed recipients) and were not (unexposed recipients) correspondingly diagnosed, with person-years of observation and hazard ratios (HR) with 95% confidence intervals (CI) for RA overall and in different strata.

| Recipient exposed to: | Recipient outcome | | | | |
|---|---|---|---|---|---|
| | Exposed | | Unexposed | | |
| | Events | Person-Years | Events | Person-Years | HR (95% CI) |
| | **Overall RA** | | | | |
| **Donor diagnosed with RA** | 63 | 82551 | 610 | 756275 | 1.04 (0.80-1.35) |
| **Shortest latency of donor RA[1]** | | | | | |
| **<10 years** | 46 | 59890 | 610 | 756275 | 0.99 (0.56-1.72) |
| **10+ years** | 17 | 22661 | 610 | 756275 | 1.05 (0.64-1.70) |
| **Lowest age at donor RA diagnosis** | | | | | |
| **< 65 years** | 51 | 69827 | 610 | 756275 | 0.80 (0.43-1.51) |
| **65+ years** | 12 | 12724 | 610 | 756275 | 1.24 (0.70-2.20) |
| | **Seropositive RA** | | | | |
| **Donor with seropositive RA** | 4 | 17030 | 27 | 186775 | 1.68 (0.58-4.84) |
| | **Seronegative RA** | | | | |
| **Donor with seronegative RA** | 9 | 39829 | 129 | 402138 | 0.72 (0.37-1.43) |

[1] Interval between donation and donor RA diagnosis.

Analyses of clustering of RA among recipients of blood from individual donors showed that recipient RA risk did not vary by RA occurrence in previous recipients of blood from the same donor, neither for all types of RA combined (HR per previous recipient with RA = 0.96; 95% CI 0.86-1.07) nor for specific RA subtypes.

The association between RA and blood transfusion history has previously been explored only in a small number of investigations, using self-reported transfusion history, which have arrived at opposite conclusions.[5 6] We restricted our analyses exclusively to transfused patients, and focused on the possible link between specific donor factors (e.g., donor RA diagnosis) and recipient RA risk.

In conclusion, we found no evidence that RA or RA risk is transmitted through blood transfusion. In light of study strengths, which include low likelihood of confounding and the large study size, ensuring meaningful statistical power, we believe it is unlikely that the possibility of RA transmission has any clinical relevance.

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**Competing Interests** The authors have no competing interests. JA has received grants from Abbvie, BMS, Merck, Pfizer, Roche, Samsung, UCB, mainly for safety monitoring via the Swedish ARTIS system.

**Contributors** All authors have contributed substantially in the process of completing this study, specified as follows: Conception of the study: SAJ, KR, JA, GE, HL, HH. Designing the study: SAJ, KR, JA, GE, HL, HH. Aggregation of data: KR, GE, HH, KT, CE, HU, OP, KRN. Interpretation of data: All authors. Drafting and revising, final approval and agreement to be accountable: All authors.

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**Ethics approval** The conduct of this study was approved by the regional ethics review board at Karolinska Institutet in Stockholm, Sweden (Reference Numbers 2009/1011, 2012/1233, 2013/37, and 2013/787) and by the Danish Data protection agency (Reference Number 2008-54-0472 and 2008-58-0035).

**Data sharing statement** The data from the Scandinavian Donations and Transfusions (SCANDAT2) database, constituting the basis for this study, cannot be shared due to Danish and Swedish law.

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