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TRANSFUSION MEDICINE

TRANSFUSION

Association between renal failure and red blood cell alloimmunization among newly transfused patients

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Abstract

Background: Renal failure and renal replacement therapy (RRT) affect the immune system and could therefore modulate red blood cell (RBC) alloimmunization after transfusion.

Study Design and Methods: We performed a nationwide multicenter case-control study within a source population of newly transfused patients between 2005 and 2015. Using conditional multivariate logistic regression, we compared first-time transfusion-induced RBC alloantibody formers (N = 505) with two nonalloimmunized recipients with similar transfusion burden (N = 1010).

Results: Renal failure was observed in 17% of the control and 13% of the case patients. A total of 41% of the control patients and 34% of case patients underwent acute RRT. Renal failure without RRT was associated with lower alloimmunization risks after blood transfusion (moderate renal failure: adjusted relative rate [RR], 0.82 [95% confidence interval (CI), 0.67-1.01]); severe renal failure, adjusted RR, 0.76 [95% CI, 0.55-1.05]). With severe renal failure patients mainly receiving RRT, the lowest alloimmunization risk was found in particularly these patients [adjusted RR 0.48 (95% CI 0.39-0.58)]. This was similar for patients receiving RRT for acute or chronic renal failure (adjusted RR, 0.59 [95% CI, 0.46-0.75]); and adjusted RR, 0.62 [95% CI 0.45-0.88], respectively).

Conclusion: These findings are indicative of a weakened humoral response in acute as well as chronic renal failure, which appeared to be most pronounced when treated with RRT. Future research should focus on how renal failure and RRT mechanistically modulate RBC alloimmunization.

KEYWORDS

blood transfusion, dialysis, red blood cell alloimmunization, renal failure, renal replacement therapy

Abbreviations: CVVH, continuous venovenous hemofiltration; eGFR, estimated glomerular filtration rate; HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy.

1 | INTRODUCTION

Red blood cell (RBC) transfusions can be complicated by the formation of RBC alloantibodies in more than 8% of intensively transfused patients.[1] It is known that changes in the recipient's immune system modulate its susceptibility for this alloimmune response.[2] The identification of factors that either increase or decrease the risk of transfusion-induced RBC alloimmunization could contribute to the development of patient-specific risk models and subsequent to more advanced matching strategies.

The innate and adaptive immune responses are altered in patients suffering from renal failure.[3–7] Both immune activation due to hyperinflammation and subsequent oxidative stress[8] and immune suppression characterized by quantitative and qualitative deficiencies of the T- and B-cell compartments hallmark this disease. Illustrating this, severe renal failure is associated with a higher susceptibility to both bacterial and viral infections, poorer responses to vaccination, and decreased antibody production to specific stimuli.[9–11]

In this respect, the general impaired cellular immunology may similarly modulate RBC alloimmunization. Previous studies have primarily focused on alloimmunization in non-Caucasian multitransfused patients with chronic renal failure undergoing hemodialysis and showed wide ranges of normal to elevated alloimmunization rates.[12–17] However, these studies were of small size and reported prevalences rather than incidence rates since they did not correct for cumulative exposure. In addition, the risk of transfusion-induced RBC alloimmunization in patients with acute renal failure undergoing renal replacement therapy (RRT) like continuous venovenous hemofiltration (CVVH) is yet to be researched but of high importance, since these clinical situations particularly depend on frequent RBC transfusions.

This study aims to quantify the association between renal failure, according to its degree and treatment with different renal replacement modalities, and transfusion-induced RBC alloimmunization in a newly transfused population with and without renal failure.

2 | METHODS

2.1 | Study design and setting

We performed a case-control study nested in the incident user cohort of the R-FACT (Risk Factors for Alloimmunization after red blood Cell Transfusions) study. The design of the R-FACT study has been described before.[2,18]

In brief, this cohort consisted of all nonalloimmmunized patients who received their first and subsequent blood transfusions in three university hospitals and three non-university hospitals between January 2005 and December 2015 in the Netherlands. Case patients were identified as patients with a first-time transfusion-induced alloimmunization against a clinically relevant RBC antigen (c, C, e, E, K, C^w, Fy^a, Fy^b, Jk^a, Jk^b, Le^a, Le^b, Lu^a, Lu^b, M, N, S, or s). Antibodies of other specificities were not included because they are not present on the standard screening panel that was used. Hence, including these nonroutinely measured antibodies would lead to selection bias in our results.

RBC alloimmunization was determined to be elicited by the last received transfusion containing the corresponding RBC antigen mismatch. In case of missing donor phenotypes, we assumed these to have expressed the nontested RBC antigens. If a case patient did not receive a verified or assumed antigen-mismatched transfusion, the patient was excluded from our analysis. Importantly, to avoid misclassifying booster reactions as primary alloimmunization events, patients with a first positive alloantibody screen within 7 days following the first and only mismatched transfusion were excluded from analysis.

In addition, patients with autoantibodies, hemoglobinopathies, age below 6 months, previous pregnancy-induced alloimmunization, or alloimmunizations detected in other hospitals were excluded from the study cohort. Each identified case patient was matched to two randomly selected nonalloimmunized control patients based on the hospital and on the (lifetime) cumulative number of RBC transfusions that the case patient had received at the time of alloimmunization. Subsequently, to investigate potential (clinical) confounders for RBC alloimmunization, an "alloimmunization risk period" was defined, stretching from 30 days before up to 7 days after the transfusion that was identified to have elicited alloantibody formation (Figure S1).

The study protocol was approved by the Ethical Review Board in Leiden and by the board of each participating center.

2.2 | Data collection

Routinely stored data of case and control patients from the hospitals' electronic laboratory information system were gathered, including sex, date of birth, RBC transfusion dates, product unique identification number, dates and results of antibody screening, and antibody specificity. In addition, the medical charts of all case and control patients were examined for the presence of various potential clinical risk factors during the alloimmunization risk period, including renal function and the presence of RRT.

Renal function was calculated using the Modification of Diet in Renal Diseases equation[19] and categorized as follows: "no renal failure" (estimated glomerular filtration rate [eGFR] >30 mL/min/1.73 m^2), "moderate renal failure" (eGFR ≥10-30 mL/min/1.73 m^2 for at least a continuous period of 7 days during the alloimmunization risk period), or "severe renal failure" (eGFR <10 mL/min/1.73 m^2 or use of any type of RRT during at least 1 day of the alloimmunization risk period). Furthermore, in case of RRT, type of modality (ie, hemodialysis [HD], CVVH, peritoneal dialysis [PD]), and whether it was used for an acute or chronic renal failure indication was recorded. Chronic severe renal failure was defined as at least 1 day of RRT before the alloimmunization risk period, and acute severe renal failure as the first time receiving RRT during the alloimmunization risk period. Finally, we studied the duration of RRT subdivided into four categories: 1 to 6 days, 6 to 11 days, 11 to 38 days, and more than 38 days.

2.3 | Statistical analyses

We studied the association between renal failure and the development of RBC alloimmunization using logistic regression analyses. All odds ratios were interpreted as relative rates (RRs).[20] Crude RRs were conditioned on the matching variables (ie, hospital and cumulative number of transfusions received). To adjust for potential confounding in multivariable analyses, we used the following strategy: First, we listed all measured potential confounders of the association between renal failure and RBC alloimmunization. Second, we identified actual confounders in our study based on a 3% or greater difference in covariate presence between control patients who did and did not have renal failure. Third, we used a multiple imputation model to handle missing data correctly. Fourth, we used logistic regression to estimate propensity scores for the determinants, with the confounders as predictors. Finally, these propensity scores, together with the matching variables, were put into multivariate logistic regression models with renal failure categories as determinants and RBC alloimmunization as outcome. To analyze a potential influence of RRT itself, patients with severe renal failure without RRT were compared to patients with RRT. In addition, we performed subgroup analyses for the different types, durations of, and indications for RRT.

3 | RESULTS

From a source population of 54 347 newly transfused patients, 24 063 met our inclusion criteria, of which 505 had formed RBC antibodies (Figure S2). Thirty-seven (7.3%) received RBC units with missing donor phenotypes; therefore, the last nontested unit preceding the first positive screen was selected to have elicited the alloimmunization. These case patients were matched to 1010 control patients. Baseline characteristics of our study population during the alloimmunization risk period are presented in Table 1.

3.1 | Presence of renal failure and RRT during alloimmunization risk period

Among all case and control patients, 78 were diagnosed with moderate renal failure and 158 with severe renal failure during the alloimmunization risk period (Table 2). Among the latter, 127 patients underwent RRT, including 79 CVVH, 26 HD, and 15 a combination of CVVH and HD. Seven patients underwent PD, or a combination of PD, CVVH, and/or HD. For one patient, the type of RRT could not be verified from the available records (Table S1). Median duration of RRT was 10.5 days (interquartile range, 6.0-32.5) and could not be verified for seven patients (Table S1). The majority of the patients (N = 93) received RRT because of acute renal failure (Table S1).

Based on a 3% difference between exposed and unexposed control patients with moderate or severe renal failure, confounders were identified in groups of (hemato)-oncologic malignancies and their treatments including immunosuppressants, (bacterial) infections, autoimmune diseases including diabetes mellitus type 1 and rheumatoid arthritis, (thoracic and abdominal) surgery, and admission to intensive care unit (Table S2).

3.2 | The association between renal failure, RRT, and RBC alloimmunization

Table 2 presents the number of case and control patients per different stage of renal failure and the presence or absence of RRT. Moderate and severe renal failure without RRT were associated with reduced risks of RBC alloimmunization (adjusted RR, 0.82 [95% CI, 0.67-1.01]; adjusted RR, 0.76 [95% CI, 0.55-1.05], respectively). Patients undergoing RRT showed the lowest alloimmunization risk (adjusted RR, 0.48 [95% CI, 0.30-0.59]). Different indications for RRT, that is, acute vs chronic renal failure, showed similar decreased alloimmunization risks (adjusted RR, 0.59 [95% CI, 0.46-0.75]; adjusted RR, 0.62 [95% CI, 0.45-0.88],

TABLE 1 Patient characteristics during the alloimmunization risk period

Characteristics	Cases (N = 505)	Controls (N = 1010)	Missing data
Male	237 (46.9)	568 (56.2)	
Age, y, median (IQR)	67 (55.0-75.9)	65.3 (51.6-75.1)	
Cumulative (lifetime) number of RBC units up to implicated transfusion, median (IQR)	4 (2–8)	4 (2-8)	
Single transfused	26 (5.1)	7 (0.7)	
Cumulative number of RBC units during risk period, median (IQR)	3 (2–6)	4 (2–8)	
Transfused in academic hospital	232 (45.9)	464 (45.9)	
ICU admission	175 (34.7)	363 (35.9)	
Days in ICU, median (IQR)	3.2 (2.6-3.8)	3.4 (3.0-3.8)	4
Surgery	267 (52.9)	457 (45.2)	2
Cardiothoracic, including CABG	61 (12.1)	143 (14.2)	
Abdominal	100 (19.8)	182 (18.2)	
Diabetes mellitus type 1	6 (1.2)	7 (0.7)	
Diabetes mellitus type 2	91 (18.0)	175 (17.3)	1
Atherosclerosis[a]	198 (39.5)	314 (31.5)	17
Chronic obstructive airway disease[b]	43 (8.5)	89 (9.0)	20
Splenectomy (in past or during risk period)	1 (0.2)	19 (1.9)	
Organ transplant (in past or during risk period)	4 (0.8)	11 (1.1)	
Liver cirrhosis	13 (2.6)	24 (2.4)	2
Hematologic malignancy	60 (11.9)	210 (20.8)	13
Carcinoma	112 (22.3)	183 (18.2)	7
Chemotherapy	66 (13.1)	219 (21.8)	6
Radiotherapy	15 (3.0)	37 (3.6)	
Hematopoietic stem cell transplantation (autologous or allogenic, in past or during risk period)	10 (2.0)	63 (6.2)	
Immunosuppressant medication[c]	154 (30.9)	423 (42.4)	20
Trauma	24 (4.8)	43 (4.3)	
Infection	169 (33.5)	357 (35.3)	94
Bacterial	142 (28.1)	275 (27.2)	72
Viral	15 (3.0)	38 (3.8)	9
Fungal	12 (2.4)	44 (4.4)	13
Autoimmune disease[d]	47 (9.3)	80 (7.9)	11

Note: Values are N (%), unless otherwise stated. Numbers of patients for whom data on certain diagnoses and/or treatment modalities were not documented are presented as missing.

Abbreviations: CABG, coronary artery bypass graft; ICU, intensive care unit; IQR, interquartile range.

[a]Systemic or coronary atherosclerosis.

[b]Chronic bronchial asthma or chronic obstructive pulmonary disease.

[c]Medication under subcategory H02 (corticosteroids) or L04 (other immunosuppressants) within the Anatomical Therapeutic Chemical classification index (World Health Organization Collaborating Centre for Drug Statistics Methodology, 2016).

[d]Graves disease, Sjögren syndrome, rheumatoid arthritis, aplastic anemia, autoimmune hemolytic anemia, immune thrombocytopenic purpura, psoriasis, sarcoidosis, other.

respectively]. Point estimates for alloimmunization risk in different durations and different types of RRT were the same, although numbers per subcategory were small (Table S3).

4 | DISCUSSION

We found lower incidences of transfusion-induced RBC alloimmunization in acute and chronic renal failure with

TABLE 2 Alloimmunization risk in different stages of renal failure including RRT

Stage of renal failure	Cases, N (%)	Controls, N (%)	RR (95% CI)[a]	Adjusted RR (95% CI)[b]
No renal failure	441 (87.3)	838 (83.0)	Ref.	Ref.
Moderate renal failure	24 (4.8)	54 (5.3)	0.90 (0.73-1.10)	0.82 (0.67–1.01)
Severe renal failure				
Total	40 (7.9)	118 (11.7)	0.62 (0.53-0.73)	0.53 (0.45-0.63)
Without RRT	10 (2.0)	21 (2.1)	0.85 (0.62-1.17)	0.76 (0.55–1.05)
With RRT [c]	30 (5.9)	97 (9.6)	0.57 (0.48-0.68)	0.48 (0.39-0.58)
Acute	22 (4.4)	71 (7.0)	0.57 (0.46-0.69)	0.59 (0.46-0.75)
Chronic	8 (1.6)	24 (2.4)	0.61 (0.44-0.85)	0.62 (0.45-0.88)

Abbreviations: CI, confidence interval; RR, relative risk; RRT, renal replacement therapy.

[a]Adjusted for number of transfused RBC units and hospital.

[b]Additionally adjusted for identified potential confounders (for details, see Table S2).

[c]Patients with at least 1 day of any form of renal replacement therapy during the implicated period.

or without RRT as compared with the incidences among patients without renal failure. These findings suggest a poorer humoral immune response in different stages of renal failure regardless of its treatment with RRT.

Previous observational studies evaluating alloantibody formation in renal failure primarily focused on chronically transfused (mostly Asian) patients undergoing HD and reported alloimmunization prevalences of 0% to 12.5%.[12–17] Importantly, these studies did not correct for important (clinical) confounders such as the cumulative number of RBC transfusions received. Finally, while ethnicity influences alloimmunization risk, the comparison of earlier studies with our mainly Caucasian population remains difficult.

The striking low alloimmunization risk in patients undergoing RRT raises an important question: To what extent is a worsened renal function responsible for a decreased alloimmunization risk, and to what extent does RRT play an additional (or even an independent) role in the patients' alloimmune response? General immunological changes and their effect on the (humoral) immune response in patients with renal failure as well as the enforcing role of RRT are well described and give several possible explanations that could contribute to a weaker alloimmune response in these patients.

First, specific to patients with acute renal failure, renal failure in our patient cohort was often caused by severe underlying conditions like sepsis with secondary acute tubular necrosis or multiple organ failure. Under these circumstances, renal failure itself in combination with the coexisting widespread (bacterial) infection leads to a hyperinflammatory state. Furthermore, specific RRT-related factors (eg, interactions with bio-incompatible solutions, catheter-related infections, and contamination of dialysis solutions)[7,21] may have coincided with the preexisting hyperinflammatory state, culminating in a reversible immune paralysis in which the patient's innate immune system is no longer able to properly respond to proinflammatory stimuli.[22,23] We hypothesize that such a reactive silencing of the immune system may have contributed to the observed weaker alloimmune response in our patients.

Second, in general, impaired renal filtration causes accumulation of toxins accompanied by uremia and oxidative stress, resulting in important immunological perturbations, that is, immunological aging. This condition has been characterized by a general immune dysfunction, including ineffective dendritic cell, B-cell, and T-cell responses,[3,24] all crucial for initiating a humoral response. This general effect of renal failure is illustrated by the poorer vaccination responses to hepatitis B observed among patients with chronic renal disease as compared to the general population.[9–11] These studies have also shown quantitative decreases in protective antibodies over time. In this respect, our findings for lower incidences of transfusion-induced RBC alloimmunization in patients with renal failure seem compatible.

Our study is important in several aspects. We performed our analyses in a large study cohort comprising all first-time transfused patients from six large hospitals with a 10-year follow-up period. In addition to a large set of transfusion data, we established an extensive clinical database of all included case and control patients, which allowed us to subsequently correct for a large set of known and potential risk-modulating factors. Finally, by the availability of data on RBC antigen phenotypes per RBC unit, we could adequately link a first alloantibody formation to the proper mismatched transfusion and its timing with respect to the diagnosis of renal failure.

To appreciate the relevance and validity of our findings better, several limitations of our study need to be considered.

First, and as indicated before, because of the low number of patients with severe renal failure without RRT, no direct comparison could be made between these patients and patients with moderate renal failure or with patients undergoing RRT. It therefore remains unclear to what extent the decrease in alloimmunization risk may have been caused by impairments in renal function and/or RRT itself. However, with the lowest alloimmunization risk in patients receiving RRT for both acute and chronic renal failure, RRT itself at least does not increase the alloimmunization risk. Interesting for this observation, but due to low sample sizes, we unfortunately could not further study duration and type of RRT in this regard. Notably, different types of RRT are reported to have their own specific effect on the immune system and its "aging."[21]

Second, while patients with renal failure are a heterogenic group of patients with different diagnoses and treatments (including medications, conditions, and complications), even our careful correction for confounding factors cannot rule out additional confounding to interfere with our results. Especially the underlying diagnosis for the renal disease was not accounted for and thereby neither was the large variety of the underlying pathophysiology surely affecting the immune response and, consequently, the risk for RBC alloimmunization. Future studies should therefore incorporate an even more detailed medical history of the patients.

Third, we could not account for possible time-dependent changes in practice in management of patients with renal failure, the use of RRT and transfusion medicine. Therefore, we cannot rule out that changes in management during our 10-year follow-up period might have affected the results.

Fourth, actual lag periods per specific RBC antigen are unknown. Thus, as posttransfusion antibody screening, direct antiglobulin tests, and subsequent elution studies are not routinely performed, we cannot completely exclude misclassification of primary RBC alloimmunizations despite all the safeguards taken. However, a sensitivity analysis excluding 91 cases (of which 40 were women) in whom alloantibodies were detected within the second week following their first antigen mismatched transfusion did not change our RRs (data not shown). Furthermore, reclassification of some of our alloimmunizations to in fact secondary boosting responses would bias our RRs toward the null effect and thus to an underestimation of true associations. Finally, because non-D alloantibodies are detected in only 0.33% of first-trimester pregnancies,[25] the impact of previous pregnancies seems limited. Taken together, we believe that potential bias due to our chosen lag period will be small and thus not influence our main conclusions.

Notwithstanding the above, our present data show significantly lower incidences of transfusion-induced RBC alloimmunization among patients with renal failure compared to patients without renal failure, which corroborates mechanistic and in vivo findings on the hampered immune response in patients with renal failure. The evident relevance of these findings lies in the fact that, in contrast to anemia in chronic renal failure, which can often be sufficiently handled with erythropoietin-stimulating agents, treatment of anemia in acute renal failure depends on RBC transfusions. Furthermore, patients with severe renal failure are more likely to receive future extensive treatments like a renal transplantation or shunting operations accompanied with additional blood transfusions. Therefore, prevention of RBC alloantibody formation in this specific patient group is of clear clinical relevance.

In conclusion, our data show an association between both acute and chronic renal failure and reduced RBC alloimmunization incidences after blood transfusion. Notably, patients undergoing RRT reported the lowest alloimmunization risks. Further research is needed to determine to what extent renal failure and RRT and its type and duration protect against RBC alloimmunization. Eventually, this will improve our understanding of the causal mechanisms and may benefit tailoring transfusion matching strategies.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

J.J.Z. and J.G.B. designed the study. D.E., K.M.K.V., D.K., O.V., N.C.V.P., and F.H. collected the data. J.A.O., D.E., R.A.M., J.J.Z., and J.G.B. analyzed and interpreted the data. J.A.O., D.E., R.A.M., J.J.Z., and J.G.B. wrote the

manuscript. All other authors revised and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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