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Definition and Risk Factors of Rapidly Declining Residual Renal Function in Peritoneal Dialysis: An Observational Study

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Key Words

End-stage renal disease · Glomerular filtration rate · Peritoneal dialysis · Residual renal function · Risk factors · Urine output

Abstract

Background: It is critical to preserve residual renal function (RRF) in peritoneal dialysis (PD), as RRF is associated with lower morbidity and mortality. There is no uniform definition of RRF, and rapidly declining RRF has rarely been studied and predominately limited to single factor analysis and not corrected for lead-time bias. ***Methods:*** An observational study in 71 incident PD patients. RRF was defined as urine output (UO) ≥500 ml/day and renal glomerular filtration rate (rGFR) ≥2 ml/min/1.73 m^2, rapid declining RRF as UO <500 ml/day and rGFR <2 ml/min/1.73 m^2 occurring within 6 months which were separately evaluated. Independent risk factors associated with rapid RRF decline were identified while correcting for lead-time bias. ***Results:*** RRF declined rapidly by both definitions in 65% patients 2.5 years after PD start. Both definitions of RRF decline were consistent in 96%. Nephrotoxic drugs, renal transplant failure and absent angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) were independent risk factors associated with rapidly declining RRF defined both by definitions, intravascular radiocontrast additionally for UO decline. ***Conclusions:*** Most PD patients demonstrated rapid RRF decline, independent of its definition. Both definitions are highly consistent and interchangeable. Nephrotoxic drugs and radiocontrast were identified as risk factors of acute, absent ACEI or ARB, and renal transplant failure of chronic renal injury.

Introduction

Previous studies have well established that the contribution of residual renal function (RRF) and peritoneal small solutes clearance are not equivalent in peritoneal dialysis (PD) [1–3]. In PD, preserved RRF is associated with lower morbidity and mortality, and higher quality of life [1–3], largely explained by better control of malnutrition and hypertension, less ventricular hypertrophy, overhydration and microinflammation, and lower rates of infection and hospitalization [4–6]. These data suggest that it may be critical to preserve RRF in PD patients. Among the proposed prophylactic strategies are the use of continuous ambulatory PD instead of automated PD [7, 8], avoidance of underhydration when using icodextrin-containing PD solutions [9], administration of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) [10–12], use of pH

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neutral, bicarbonate-buffered dialysis solutions with low levels of glucose degradation products [13, 14], prevention of peritonitis, and avoiding the use of nephrotoxic drugs and radiocontrast media [15–18], although the effects of these protective strategies to preserve RRF are not undisputed [18–25].

Despite the current knowledge on RRF in PD, there remain unresolved issues. First, there is no uniform definition of RRF at present. While most authors currently consider renal glomerular filtration rate (rGFR) as the measure of RRF [1–4, 6–9, 12, 14–16, 18–22, 24–27], others use urine output (UO) [28], or both rGFR and UO [5, 7, 10, 11, 17, 29]. As UO determines water and sodium removal which again are independently related to survival in PD, it makes perfect sense to consider UO as an important measure of RRF [7]. Secondly, most previous reports studies have described a slow, continuous decline of RRF [1, 3, 5, 7, 13, 15–17, 19, 21]. However, radiocontrast, nephrotoxic drugs, hypotension and other factors exert acute, adverse effects on renal function with an abrupt RRF decline. Thirdly, those studies looking at rapidly declining RRF have limited the analysis to single risk factors disregarding other potentially important factors [8, 10, 11, 18, 20]. Finally, when analyzing risk factors of rapid RRF decline, the effect of lead-time bias needs to be taken into account which was only done in a minority of previous studies [10, 11]. In this context, lead-time is the interval between initiation of PD and RRF decline. Risk factors may simply be identified in one cohort due to higher RRF and longer follow-up of these patients, that is, by recording a longer lead-time [30]. This confounding is called lead-time bias. Purpose of this study in incident PD patients was, (i) to evaluate 2 different definitions of rapid RRF decline based on UO and rGFR, and (ii) to analyze various factors to identify independent risk factors associated with rapid RRF decline while correcting for lead-time bias.

Patients and Methods

Patients and PD Treatment

In this retrospective cohort study, we screened all 131 consecutive adult PD patients who started PD treatment in our institution from 1993 to 2003. We included those 71 patients who were treated for more than 12 months in our institution, who had complete data on UO every 6 months from the initiation of PD and had UO $\geq$500 ml/day and rGFR $\geq$2 ml/min/1.73 m^2 at least at initiation and after the first 12 months of PD. Patients treated for less than 12 months in our institution (transfer to another PD facility or to hemodialysis, technical failure of PD, renal transplantation, death) (n = 12), those with incomplete data on 6-monthly UO and/or rGFR (n = 25) and with UO <500 ml/day and/or with rGFR <2 ml/min/1.73 m^2 during the first 12 months of PD were excluded (n = 23). All patients received conventional glucose-containing, lactate-buffered PD solutions, and some in addition icodextrin solutions during the long dwell. Patients' demographic, clinical and laboratory data, and medication were obtained from their records. rGFR was calculated as the average of 24 h renal creatinine and urea clearance, and normalized to 1.73 m^2 body surface area. As part of our clinical routine, patients underwent clinical evaluations including a complete history, physical examination and 24 h urine collection at the initiation of PD and every 6 months afterwards. rGFR measurements and peritoneal equilibrium tests were performed 1 month after PD initiation and every 6 months afterwards. A subgroup analysis of 32 included patients was performed. Complete 3-monthly data on both UO and rGFR were available for these patients.

Definitions of RRF Decline and Variables

Rapid decline of RRF was defined either as (i) decrease of UO <500 ml/day, or (ii) decrease of rGFR <2 ml/min/1.73 m^2, both occurring within two 6-monthly measurements and persistent thereafter. In the subgroup described above, rapid RRF decline was defined either as (i) decrease of UO <500 ml/day, or (ii) decrease of rGFR <2 ml/min/1.73 m^2, both occurring within two 3-monthly measurements and persistent thereafter. These cut-off values were chosen by consensus applying the Delphi technique on clinical relevance and the basis of data from previous studies [3, 4, 9, 10, 18, 20]. The Delphi technique is a structured, written consensus process whereby documents are anonymously circulated within an expert group, with each round of the document incorporating the feedback from the previous round until consensus has been achieved. This process has the advantage that no specific expert can dominate the process. Experts in our study were all nine board-certified nephrologists from our division. In patients with rapid decline of RRF, those 6 months prior to the measurement of UO <500 ml or of rGFR <2 ml/min/1.73 m^2 were studied with regard to the presence of potential risk factors for the decline. We included those variables which were identified in previous studies as risk factors of RRF decline (gender, age, body mass index, baseline RRF, diabetic nephropathy, renal transplant failure as cause of anew dialysis therapy, peritonitis, nephrotoxic medication, continuous administration of ACEI/ARB for at least 12 months prior to the rapid decline of RRF or the equivalent time-point in control patients, intravascular radiocontrast, icodextrin solution, automated PD, peritoneal membrane transporter type, microinflammation) and added other factors which were most proposed to be associated with it. By our institution's protocol, patients with renal transplant failure receive a dual immunosuppressive regime with prednisone $\leq$7.5 mg/day, and trough levels of cyclosporine A <60 ng/ml or of tacrolimus <2 ng/ml until they are anuric. Diagnosis of PD-associated, microbial-induced peritonitis required abdominal pain, turbid dialysate with a leukocyte count >100/μl and more than 50% polymorphonuclear cells, and detection of microorganisms by Gram staining or culture of the dialysate. Nephrotoxic medication was analyzed as non-steroidal anti-inflammatory drugs (NSAIDs) and the intraperitoneal or intravenous administration of aminoglycosides and vancomycin separately and pooled, and in combination with radiocontrast. High-dose loop diuretics were defined as furosemide doses $\geq$250 mg/day. Radiocontrast included the intravascular ap-

plication of non-ionic, iso- and low-osmolar contrast agents, and the volume of radiocontrast was determined. Automated PD was continuous cyclic PD as only this was applied during the study period in our institution. Adequate control of blood pressure was defined <140/90 mm Hg, adequate hydration status as no clinical and radiological signs of peripheral and pulmonary edema. Cardiovascular diseases were defined as coronary heart disease, congestive heart failure in NYHA stages II–IV, cerebrovascular and/or peripheral arterial disease diagnosed by history, physical examination and the appropriate diagnostic tests. Global patient comorbidity was stratified according to the Khan index into low, medium and high risk [31]. Microinflammation was defined by C-reactive protein >10 mg/l [6]. Sepsis was defined by the detection of microorganisms in normally sterile tissues or fluids by Gram staining or culture together with two or more of the following criteria: temperature >38 or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min, and leukocytes >12,000 or <4,000/μl [32]. Severe infections were defined as any infection except peritonitis requiring hospital admission and intravenous antimicrobial treatment.

Data Analysis

The primary end-point was the rapid decline of RRF, defined by UO in the analysis of the entire cohort and by rGFR in the separate analysis of a subgroup of 52 patients (73%). To analyze the same period prior to RRF decline, patients with rapidly declining RRF were retrospectively standardized with regard to time of decline. The 6-, 12-, etc. month intervals prior to the decline were termed '-6' and '-12'. Patients without rapid RRF decline were matched to those with RRF decline according to length of PD treatment and matched pairs standardized to the time of PD initiation. The 6-month interval preceding the rapid decline of RRF was analyzed with regard to the presence of potential risk factors of declining RRF. This period was compared to the equivalent 6-month interval in patients without rapid RRF decline. As both groups demonstrated similar UO and rGFR at this time period, we successfully corrected for lead-time. Both periods are termed 'observation period'. In a subgroup, the identical analysis was performed comparing the 3-month interval prior to and after rapid decline of RRF, or a matched time interval in patients without rapid RRF decline. Continuous data are presented as mean ± SD, discrete data as absolute counts and percentages. After testing for normal distribution, continuous data were compared by Student's t test or Mann-Whitney rank-sum test, categorical data either by χ^2 or Fisher's exact test. Multiple testing was performed by two-way ANOVA with subsequent Student-Newman-Keuls test. Potential risk factors associated with RRF decline were coded as present or absent and assessed by bivariate analysis either as single (radiocontrast) or combined factors (nephrotoxic drugs ± radiocontrast). Variables with a $p < 0.10$ were included in the multivariate, logistic regression analysis. A two-sided p value <0.05 was considered to be statistically significant. Due to the small patient number in the subgroup, only those variables identified as statistically significant in the multivariate analysis of the entire cohort were included to avoid overfitting of the statistical model in this subgroup. Approval of the study was waived by the local institutional review board and informed consent was not required due to the retrospective nature of the study. The study protocol is in accordance with the Declaration of Helsinki.

Results

We identified 46 patients with a rapid decline of UO <500 ml/day (group 1; 65%). The remaining 25 patients did not demonstrate a rapid decline of UO (group 2). Baseline characteristics of the patients are summarized in table 1. The mean time from PD initiation to the observation period did not differ between groups 1 and 2 (2.1 ± 0.7 vs. 2.2 ± 0.8 years; p = 0.41). There was a moderate, continuous decline of UO over time in both groups during the period of PD treatment preceding the observation period (fig. 1). In group 1, the slope of this continuous UO decline tended to be steeper until the observation period compared to group 2. There was neither a statistical difference between UO at all studied time-points within each group nor between the slopes of continuously declining UO in groups 1 and 2. As demonstrated in figure 1, UO rapidly declined in group 1 by 79 ± 28% and remained almost constant in group 2 (decline of 8 ± 17%; $p < 0.001$ vs. group 1) thereafter. In the subgroup of 52 patients with complete data for rGFR, 34 patients demonstrated a rapid decline of rGFR <2 ml/min/1.73 m^2 (group 1a; 65%). The remaining 18 patients demonstrated rGFR of at least 2 ml/min/1.73 m^2 (group 2a). The time from PD initiation to the observation period did not differ between groups 1a and 2a (2.0 ± 0.8 vs. 1.9 ± 0.6 years; p = 0.79). In parallel to UO, rGFR moderately declined in both groups during the period of PD treatment preceding the observation period (fig. 2). As for UO, there was a trend towards a steeper slope of continuous rGFR decline in group 1a compared to group 2a. However, rGFR was neither statistically different at all studied time-points within each group nor between groups 1a and 2a. Finally, rGFR markedly declined in group 1a by 68 ± 20% and remained almost constant in group 2a (decline of 6 ± 11%; $p < 0.001$ vs. group 1a). In 96% of patients the definitions of the rapid RRF decline by UO and by rGFR were consistent.

Patients with rapidly declining RRF defined either by UO or by rGFR did not differ with regard to age, gender, body mass index, diabetic nephropathy as primary renal disorder, rates of cardiovascular disease, high Khan comorbidity index, use of loop diuretics and adequacy of both blood pressure control and hydration status (table 1). Additionally, neither characteristics of PD as its mode, use of icodextrin solutions or high transporter type nor the rate of sepsis, of other severe infections or of peritonitis, the administration of aminoglycosides, NSAIDs, vancomycin or the combination of nephrotoxic drugs with radiocontrast differed markedly between pa-

Table 1. Patients' characteristics and distribution of potential risk factors for declining RRF

Characteristics	RRF defined by UO			RRF defined by rGFR		
	<500 ml/day (group 1; n = 46)	≥500 ml/day (group 2; n = 25)	p	<2 ml/min/1.73 m^2 (group 1a; n = 34)	≥2 ml/min/1.73 m^2 (group 2a; n = 18)	p
Age, years	53 ± 13	55 ± 12	0.59*	57 ± 10	54 ± 11	0.25*
Male gender	27 (59%)	13 (52%)	0.77‡	16 (47%)	9 (50%)	0.93‡
Body mass index	23 ± 4	24 ± 4	0.24*	24 ± 4	24 ± 4	0.78*
Diabetic nephropathy	9 (20%)	4 (16%)	1.00†	5 (15%)	4 (22%)	0.70†
Renal transplant failure	16 (35%)	2 (8%)	0.02†	12 (35%)	2 (11%)	0.08†
Cardiovascular disease	16 (35%)	11 (44%)	0.61‡	15 (44%)	4 (22%)	0.14†
Khan comorbidity high risk	16 (35%)	5 (20%)	0.28†	9 (26%)	4 (22%)	1.00†
Automated PD	11 (24%)	4 (16%)	0.35†	6 (18%)	3 (17%)	1.00†
High transporter type	10 (22%)	5 (20%)	1.00†	8 (24%)	4 (22%)	1.00†
Icodextrin use for long dwells	8 (17%)	2 (8%)	0.48†	4 (12%)	2 (11%)	1.00†
Sepsis/severe infection	15 (33%)	5 (20%)	0.29†	9 (26%)	3 (17%)	0.51†
Peritonitis	9 (20%)	2 (8%)	0.31†	5 (15%)	2 (11%)	1.00†
Nephrotoxic medication, combined	17 (37%)	2 (8%)	0.01†	13 (38%)	2 (11%)	0.05†
Aminoglycosides	4 (9%)	0	0.29†	3 (9%)	0	0.54†
NSAIDs	1 (2%)	0	1.00†	0	0	1.00†
Vancomycin	12 (26%)	2 (8%)	0.12†	10 (29%)	2 (11%)	0.18†
Radiocontrast	17 (37%)	3 (12%)	0.03†	11 (32%)	2 (11%)	0.11†
Volume of radiocontrast, ml	156 ± 85	172 ± 79	0.78*	163 ± 74	158 ± 96	0.93*
Radiocontrast + nephrotoxic drugs	11 (24%)	1 (4%)	0.05†	10 (29%)	1 (6%)	0.07†
No ACEI/ARB use	29 (63%)	9 (36%)	0.04‡	21 (62%)	5 (28%)	0.04‡
No high-dose loop diuretic use	10 (22%)	3 (12%)	0.36†	5 (15%)	2 (11%)	1.00†
Adequate blood pressure control	22 (48%)	10 (40%)	0.62†	16 (47%)	7 (39%)	0.77†
Adequate hydration status	43 (93%)	23 (92%)	1.00†	32 (94%)	16 (89%)	0.60†
C-reactive protein, mg/l	11.0 ± 9.6	4.4 ± 3.4	<0.001*	7.3 ± 4.6	4.2 ± 2.7	0.16*

* Rank-sum test; ‡ χ^2 test; † Fisher's exact test.

tients with or without rapid declining RRF by both definitions (table 1). Nephrotoxic medication as a pooled variable, however, and absent ACEI/ARB in the observation period, as well as renal transplant failure were independent risk factors associated with rapidly declining RRF defined both by UO <500 ml/day and by rGFR <2 ml/min/1.73 m^2 (tables 2, 3). Intravascular radiocontrast in the observation period was identified as an additional independent risk factor of rapidly declining UO. The volume of radiocontrast did not differ between patients with or without rapidly declining RRF by both definitions. In bivariate analysis, significant differences were found for microinflammation and UO <1,000 ml/day at the last measurement preceding RRF decline in patients with and without rapidly declining RRF defined by UO, and for rGFR <4 ml/min/1.73 m^2 at the last measurement preceding RRF decline in patients with and without rapidly declining RRF defined by rGFR. However, these differences were not statistically independent, as summarized in tables 2 and 3. In the subgroup of patients with 3-monthly data available, these risk factors were affirmed for the most part. Rapidly declining RRF defined by UO was independently associated with renal transplant failure, nephrotoxic medication and radiocontrast, defined by rGFR with absent ACEI/ARB and nephrotoxic medication (table 4).

Discussion

Our data indicate that the majority of incident PD patients with adequate RRF at PD initiation demonstrate a rapid decline of RRF, corrected for lead-time bias. This rapid decline occurred approximately 2.5 years after PD initiation for both RRF criteria, in addition to a moderate, continuous loss of RRF observed in all patients.

Table 2. Potential risk factors associated with an acute decline of UO <500 ml/day in PD

	Bivariate analysis			Multivariate analysis		
	odds ratio	95% confidence limits	p	odds ratio	95% confidence limits	p
Age >60 years	0.9	0.3–2.4	0.98	–	–	–
Male gender	1.3	0.5–3.5	0.77	–	–	–
Diabetic nephropathy	1.3	0.4–4.7	1.00	–	–	–
Renal transplant failure	6.1	1.3–29.4	0.01	4.7	1.3–22.1	0.02
Cardiovascular disease	0.7	0.3–1.8	0.61	–	–	–
Khan comorbidity high risk	2.1	0.7–6.8	0.28	–	–	–
UO predecline <1.0 liters/day	7.5	2.2–25.3	<0.001	4.0	0.8–30.2	0.31
Automated PD	1.7	0.5–5.9	0.35	–	–	–
High transporter type	1.1	0.3–3.7	1.00	–	–	–
Icodextrin use for long dwells	2.4	0.5–12.4	0.48	–	–	–
Sepsis/severe infection	1.9	0.6–6.2	0.29	–	–	–
Peritonitis	2.8	0.6–14.1	0.31	–	–	–
Nephrotoxic medication	6.7	1.4–32.2	0.01	2.6	1.0–7.6	0.04
Intravascular radiocontrast	4.3	1.1–16.5	0.03	3.2	1.1–12.7	0.03
No ACEI/ARB use	3.0	1.1–8.3	0.04	2.0	1.2–6.4	0.02
No high-dose loop diuretic use	2.0	0.5–8.2	0.36	–	–	–
Adequate blood pressure control	1.4	0.5–3.7	0.62	–	–	–
Adequate hydration status	1.2	0.2–8.0	1.00	–	–	–
Microinflammation	4.5	1.1–22.0	0.04	2.9	0.6–14.4	0.20

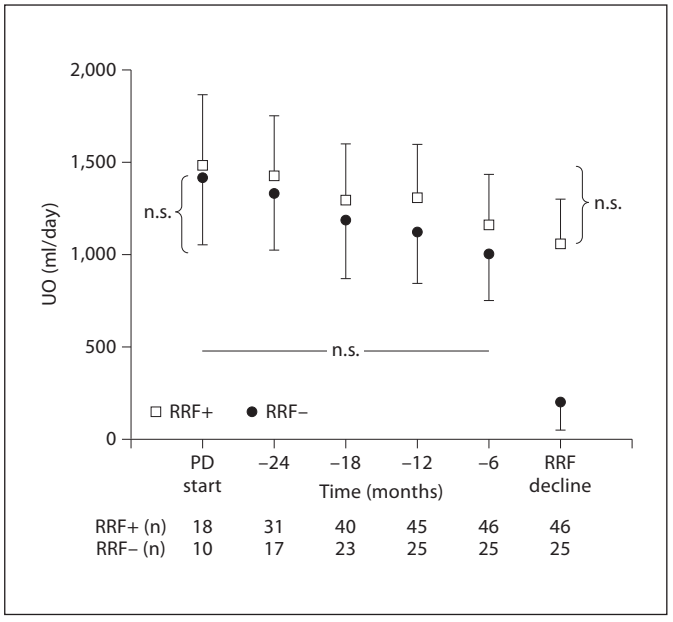

Fig. 1. Course of UO in PD patients with (RRF+) and without (RRF–) rapid decline of RRF defined by UO ≥500 ml/day. –6 depicts the 6 months prior to RRF decline, –12 depicts the 12 months prior to RRF decline, etc. The number of patients in both groups available for analysis is presented below the figure.

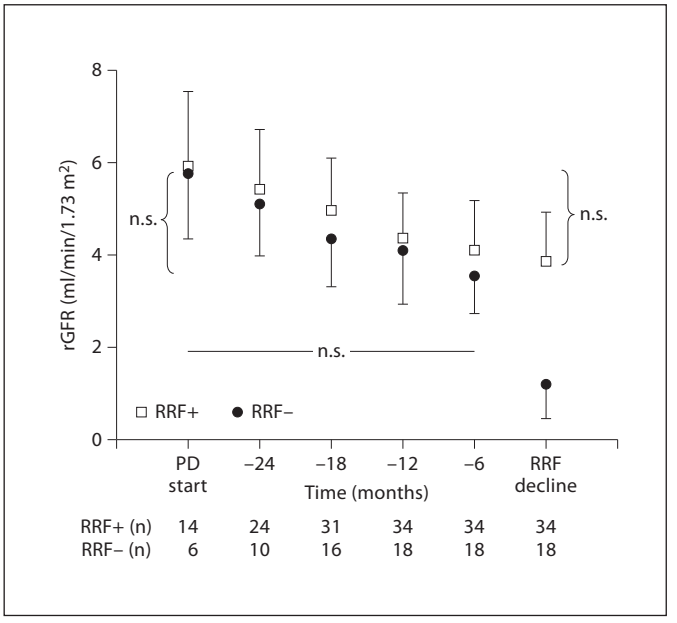

Fig. 2. Course of rGFR in PD patients with (RRF+) and without (RRF–) rapid decline of RRF defined by rGFR ≥2 ml/min/1.73 m^2. –6 depicts the 6 months prior to RRF decline, –12 depicts the 12 months prior to RRF decline, etc. The number of patients in both groups available for analysis is presented below the figure.

Table 3. Potential risk factors associated with an acute decline of rGFR <2 ml/min/1.73 m^2 in PD

	Bivariate analysis			Multivariate analysis		
	odds ratio	95% confidence limits	p	odds ratio	95% confidence limits	p
Male gender	1.1	0.4–3.5	0.93	–	–	–
Age >60 years	1.2	0.4–4.1	0.96	–	–	–
Diabetic nephropathy	0.6	0.2–2.6	0.70	–	–	–
Renal transplant failure	4.4	0.9–22.3	0.08	4.9	1.2–25.1	0.04
Cardiovascular disease	2.8	0.8–10.2	0.14	–	–	–
Khan comorbidity high risk	1.3	0.3–4.8	1.00	–	–	–
rGFR predecline <4 ml/min/1.73 m^2	4.4	1.2–16.3	0.04	4.2	0.8–23.0	0.09
Automated PD	1.1	0.2–4.9	1.00	–	–	–
High transporter type	1.1	0.3–4.2	1.00	–	–	–
Icodextrin use for long dwells	1.1	0.2–6.5	1.00	–	–	–
Sepsis/severe infection	1.8	0.4–7.7	0.51	–	–	–
Peritonitis	1.4	0.2–7.9	1.00	–	–	–
Nephrotoxic medication	5.0	1.0–25.1	0.05	3.3	1.1–14.7	0.04
Intravascular contrast media	3.8	0.7–19.6	0.11	–	–	–
No ACEI/ARB use	4.2	1.2–14.5	0.04	6.5	1.3–31.5	0.02
No high-dose loop diuretic use	1.4	0.2–7.9	1.00	–	–	–
Adequate blood pressure control	1.4	0.4–4.5	0.77	–	–	–
Adequate hydration status	5.0	0.3–15.5	0.60	–	–	–
Microinflammation	2.1	0.5–8.8	0.50	–	–	–

Table 4. Potential risk factors associated with an acute decline of RRF in PD patients with 3-monthly data

	Bivariate analysis			Multivariate analysis		
	odds ratio	95% confidence limits	p	odds ratio	95% confidence limits	p
Acute decline of RRF defined as UO <500 ml/day						
Renal transplant failure	2.9	1.5–6.8	0.009	2.5	1.3–5.2	0.01
Nephrotoxic medication	3.9	1.4–11.7	0.007	2.0	1.2–6.9	0.03
Intravascular contrast media	1.8	1.2–5.6	0.03	1.7	1.1–7.5	0.04
No ACEI/ARB use	2.7	1.3–7.1	0.01	2.3	0.8–11.5	0.11
Acute decline of RRF defined as rGFR <2 ml/min/1.73 m^2						
Renal transplant failure	2.8	1.4–6.7	0.008	2.1	1.0–7.8	0.06
Nephrotoxic medication	5.3	2.6–12.5	0.05	4.2	1.5–15.0	0.008
Intravascular contrast media	2.0	1.3–5.8	0.003	2.9	0.9–8.4	0.08
No ACEI/ARB use	3.2	1.2–8.8	0.04	2.7	1.3–7.5	0.03

These findings were independent of the definition of RRF by UO of 500 ml/day or rGFR of 2 ml/min/1.73 m^2. Risk factors of declining RRF may be categorized into those causing chronic and acute renal injury as recently proposed [33]. Renal transplant failure requiring repeat dialysis and absent ACEI/ARB treatment were identified as independent risk factors of the first category whether rapidly declining RRF was defined by UO or rGFR. Nephrotoxic drugs were found to be risk factors of the second category for rapidly declining RRF defined by both UO and rGFR, intravascular radiocontrast for rapidly declining RRF defined by UO.

Most previous studies have applied rGFR to define RRF [1–4, 6–9, 12, 15, 16, 18–22, 26, 27]. This is plausible

as GFR is acknowledged as the best overall variable to quantify renal function. Recently, adequate endogenous renal water and sodium removal were demonstrated to be independently associated with lower mortality in PD [7]. As UO is a major determinant for water and sodium removal in PD, there is a strong rationale for its use as a measure of RRF [5, 7, 10, 11, 17, 28]. The high consistency of UO and rGFR in our study with regard to their trend of RRF loss, rapid decline and risk factors suggest their interchangeable use to detect rapid RRF decline. As UO can be measured more frequently and easily in the typical home-based setting of PD, this marker permits early detection of RRF decline by the patients themselves. This may result in immediate avoidance of nephrotoxic drugs and other causes of acute renal injury, and timely changes of the PD regime to avoid harmful overhydration. Additionally, cut-off values compared to slopes are more easily applied and to work with in clinical routine.

Previous reports have predominately described a gradual continuous decline of RRF or slope and analyzed risk factors of this without applying cut-off values to characterize RRF [1, 3, 5, 7, 15–17, 19, 21]. As frequent and sequential RRF measurements have rarely been reported, rapid RRF decline may have been unrecognized. The majority of those studies which reported frequent and sequential data on rGFR and UO detected a rapid decline as the principal component in RRF loss which is consistent with our findings [3, 5, 7, 10, 11]. The trend toward a steeper slope of continuous RRF decline preceding the rapid decline may be rated as a more extensive preexisting chronic renal injury in these patients. Both renal transplant failure and the lack of inhibition of the renin-angiotensin-aldosterone system (RAAS) could account for this increasing susceptibility and decreasing compensatory capacity to acute renal insults but not primarily for the rapid RRF decline.

Little data has been reported on the effect of renal transplant failure as cause of repeat PD therapy on RRF. Our findings are supported by previous studies which identified renal transplant failure as risk factors of early RRF decline [26, 34]. Consistent with this, RRF in PD patients with renal transplant failure was shown to profit from continued immunosuppression by prolonging graft function, a therapeutic strategy which we also applied [26, 34, 35]. However, these findings are not undisputed [27]. A large body of evidence shows that RAAS activation is critical in chronic irreversible renal injury leading to glomerulosclerosis and tubulointerstitial fibrosis. The RAAS-mediated injury progresses further even after the initiation of PD and is likely to contribute to RRF decline. This is the potential rationale for the benefit of RAAS inhibition by ACEI and ARB in the preservation of RRF in PD patients which we could confirm in our study [10–12]. On the basis of renal transplant failure and lack of RAAS inhibition, it seemed plausible that we also identified nephrotoxic medication and radiocontrast as additional risk factors of rapid RRF decline which are typically known to acutely impair renal function. Nephrotoxic medication and intravascular radiocontrast have previously been described as risk factors of RRF decline [16, 17, 36]. This has only been challenged in randomized controlled studies which exclusively concentrated on aminoglycosides or radiocontrast, and meticulously applied preventative strategies as hydration, administration of the minimal volume of radiocontrast, and serial serum aminoglycoside levels [18–20, 22]. However, we advise caution to interpret the latter results as an argument for the liberal use of nephrotoxic medication and contrast media in PD patients with adequate RRF. Avoidance of such nephrotoxic agents as NSAIDs, aminoglycosides and radiocontrast agents still seems a rational approach to preserve RRF, as precautions taken in randomized controlled trials may not always apply to clinical routine. We did not detect other risk factors which were previously described including female gender, diabetes, automated PD and use of icodextrin solutions, or have a strong biological rationale as dehydration [7–9, 21, 28]. The impact of these factors on RRF in PD is still controversial though [15, 16, 24, 37]. The benefit of biocompatible compared to conventional solutions on RRF preservation could not be investigated as none of our patients were dialyzed with solutions with higher pH and reduced glucose degradation products. However, previous studies on effects of biocompatible fluids have provided inconsistent results with some demonstrating RRF preservation [13, 14], while others did not [25].

The strengths of this study are its longitudinal design with complete data on RRF, compliance with the STROBE guidelines, incorporation of a wide spectrum of potential risk factors, and the correction for lead-time bias to prevent false lower mortality rates. This study is limited by its observational and retrospective design with potential confounding, information and selection bias. To reduce confounding, a comprehensive search and inclusion of potential confounders as factors in the statistical analyses were performed. Furthermore, we made every effort to reduce confounding by indication, selection or information bias on the outcome presented as (i) demographic and clinical characteristics of patients with and without RRF decline were well balanced, (ii) follow-up data were

complete for all patients, and (iii) frequency and mode of RRF measurement were identical in all patients to avoid underestimation of rapidly declining RRF. Although widely adopted in the literature and endorsed by the Delphi technique, further limitations are the use of not uniformly accepted definitions of RRF and its rapid decline, and the dichotomous nature of the definitions. As a consequence, our findings may not generally apply, especially to patients with initially low RRF, but our results are broadly comparable to previous publications. Finally, we performed a small single-center study. Despite providing a typical cross section of PD patients in Germany and Europe, our results require validation in larger multicenter studies.

In conclusion, our data indicate that the majority of incident PD patients with initial RRF demonstrate a rapid decline of RRF which occurs approximately 2–3 years after the initiation of PD. RRF may be defined by UO $\geq$500 ml/day or by rGFR $\geq$2 ml/min/1.73 m^2. Independent risk factors associated with the rapid RRF decline by UO and rGFR definitions are renal transplant failure, absent ACEI/ARB treatment and nephrotoxic drugs, additionally intravascular radiocontrast for rapidly declining RRF defined by UO.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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